EVOLVING PARADIGMS IN THE TREATMENT OF HEPATITIS B

by

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Abstract

Hepatitis B is a serious global health problem with over 2 billion people infected worldwide and 350 million suffering from chronic hepatitis B (CHB) infection. Infection can lead to chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC) accounting for 320,000 deaths per year. Numerous treatments are available, but with a growing number of therapies each with considerable trade-offs, the optimal treatment strategy is not transparent.

This dissertation investigates the relative efficacy of treatments for CHB and estimates the health related quality of life (HRQOL) and health utilities of mild to advanced CHB patients.

A systematic review of published randomized controlled trials comparing surrogate outcomes for the first year of treatment was performed. Bayesian mixed treatment...
comparison meta-analysis was used to synthesize odds ratios, including 95% credible intervals and predicted probabilities of each outcome comparing all currently available treatments in HBeAg-positive and/or HBeAg-negative CHB patients. Among HBeAg-positive patients, tenofovir and entecavir were most effective, while in HBeAg-negative patients, tenofovir was the treatment of choice.

Health state utilities and HRQOL for patients with CHB stratified by disease stage were elicited from patients attending tertiary care clinics at the University Health Network in Toronto. Respondents completed the standard gamble, EQ5D, Health Utilities Index Mark 3 (HUI3), Short-Form 36 version-2 and a demographics survey in their preferred language of English, Cantonese or Mandarin. Patient charts were accessed to determine disease stage and co-morbidities.

The study included 433 patients of which: 294 had no cirrhosis, 79 had compensated cirrhosis, 7 had decompensated cirrhosis, 23 had HCC and 30 had received liver transplants. Mean standard gamble utilities were 0.89, 0.87, 0.82, 0.84 and 0.86 for the respective disease stages. HRQOL in CHB patients was only impaired at later stages of disease. Neither chronic infection nor antiviral treatment lowered HRQOL. Patients with CHB do not experience lower HRQOL as seen in patients with hepatitis C.

The next step in this area of research is to incorporate the estimates synthesized by the current studies into a decision model evaluating the cost-effectiveness of treatment to provide guidance on the optimal therapy for patients with HBeAg-positive and HBeAg-negative CHB.
Acknowledgements

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I will persist until I succeed.

So long as there is breath in me, that long will I persist. For now I know one of the greatest principles of success; if I persist long enough I will win.

I will persist. I will win.

Og Mandino
The Greatest Salesman in the World
The Scroll Marked III
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LIST OF ABBREVIATIONS AND ACRONYMS

ALT - alanine aminotransferase
anti-HBs – anti hepatitis B surface antigen
CHB – chronic hepatitis B
Crl –credible interval
EASL – European Association for the Study of the Liver
HBeAg – hepatitis B e antigen
HBsAg – hepatitis B surface antigen
HBV – hepatitis B virus
HCC – hepatocellular carcinoma
HRQOL – health related quality of life
HUI –Health Utility Index
HUI3 – Health Utility Index Mark 3
IgM – Immunoglobulin M
MCS – mental component summary
MTC – mixed treatment comparison
PCS – physical component summary
QALY – quality adjusted life year
SF36 – Short Form 36
SF36v2 – Short Form 36 version 2
VAS – visual analogue scale
CHAPTER 1

INTRODUCTION AND STUDY OBJECTIVES

The purpose of this chapter is to:

1. Provide an outline of the dissertation
2. Provide the rationale for the study
3. Present the study objectives

1.1 Outline of Thesis

Chapter 1 provides the rationale for this study, introduces the study research question and presents the study objectives.

Chapter 2 reviews the literature surrounding chronic hepatitis B (CHB) provides a summary of the natural history of the disease, its epidemiology and the currently available treatments. It outlines the limitations of the current literature and provides a justification for this research study.

Bayesian mixed treatment comparison (MTC) meta-analysis methods are also be introduced, as it was the approach that was taken to synthesize summary estimates for the efficacy of current treatments for CHB. That chapter also provides a review of the methods used for eliciting health utilities and health related quality of life (HRQOL).
Chapter 3 addresses the first study goal. It presents the Bayesian MTC meta-analysis of the current treatments for CHB. The study question is introduced and the methods and results of the analysis are provided. The conclusions and directions for future studies are also summarized.

Chapter 4 addresses the second research goal. It comprises of a study of the HRQOL and health utilities of patients with CHB and related disease states. This chapter outlines the methods that were used to gather the comprehensive listing of utility and HRQOL scores elicited using the standard gamble, EQ5D, Health Utility Index Mark 3 (HUI3) and Short-Form 36 version 2 (SF36v2). It also presents the comparison between the current study and previously published literature in patients with CHB and in patients with chronic hepatitis C. In addition, the study presents a comparison between scores from patients who are taking and those who are not taking antiviral treatment for hepatitis B.

Chapter 5 contains a summary of the main findings of these analyses. It provides a discussion of the methodological considerations of taking a Bayesian approach to meta-analysis and the methodological considerations of eliciting patient preferences and utilities. It ends with an outline of future research to be undertaken.

1.2 Rationale

The treatment of hepatitis B is evolving quickly; clinicians have been presented with various paradigms. The old paradigm was to treat patients solely on serum alanine aminotransferase (ALT) levels and clinical or histological disease once the virus had already progressed and caused liver damage [1]. The new paradigm is to prevent the progression of the disease by monitoring viral DNA and suppressing the virus to prevent liver damage. Treatment is aimed at causing the loss of hepatitis B surface antigen (HBsAg).
Clinicians must also determine which diagnostic factors are clinically relevant as a basis for initiating treatment. Should therapy be started, treatment may be short-term, long-term or possibly lifelong viral suppression. To complicate this decision further, new treatments are becoming available with good short-term effectiveness but limited data on long-term outcomes. Since the initiation of treatment may result in lifelong therapy, drug induced viral resistance becomes an increasingly important factor to consider when choosing a treatment. However, with the lack of long-term data, clinicians must make decisions based on imperfect information.

Depending on the type of oral antiviral treatment used, between 0-3% of patients become negative for HBsAg within the first year of therapy. In those with hepatitis B e antigen (HBeAg)-positive CHB, between 16 and 24% of patients may have sustained loss of HBeAg which allows the patient to enter the ‘inactive’ phase of CHB. However, the majority of patients, particularly those who have HBeAg-negative hepatitis, will relapse when treatment is stopped. Relapse following cessation of therapy with oral agents may be associated with severe exacerbation of disease on the rare occasion leading to hepatic decomposition and even death [2-4]. Thus, once oral antiviral treatment has been started and the individual fails to clear HBsAg, it is often difficult to stop and the reasonable alternative is long-term treatment. However, with long-term treatment, issues such as safety (e.g. in pregnancy), side effects, drug fatigue, resistance and increased costs become critical. Suppression of viral replication and the consequent improvement of hepatitis is both cost-effective and it can be assumed to improve the quality of life of patients if it prevents further progression of the disease. But to date, the endpoint for drug therapy in those who do not lose HBsAg on oral antiviral agents remains unknown [2].

Head-to-head clinical trials of treatments for hepatitis B provide information on the relative effectiveness of the therapies used in the trial. However, trials that include treatment arms for the new more potent therapies for hepatitis B have not been performed [3]. Therefore, a need exists to quantitatively summarize the available
evidence regarding the relative efficacy of all licensed treatments for CHB. In this thesis, a systematic review of published randomized controlled trials of treatments for patients with CHB was performed. Using a Bayesian MTC meta-analytic model, the relative efficacy of each treatment was determined.

In the published literature to date, there is limited information available on patient preferences and utilities of different disease states in the progression of hepatitis B [3]. In the past, utility values for hepatitis C patients were used as surrogates thus assuming they were similar to those for CHB. Consequently, studies addressing the quality of life of patients with hepatitis B are required for accurate cost-effectiveness analysis of treatment options for CHB. The utility and HRQOL of patients with CHB were elicited in patients attending liver clinics in downtown Toronto using the standard gamble, HUI3, EQ5D and SF36v2. This thesis therefore bridges the knowledge gap in these areas.

Cost-effectiveness analysis is a tool that can be used to help clinicians determine the optimal treatment option for a disease. Chronic hepatitis B is a complicated disease with many different clinical treatment outcomes of interest and numerous available treatments. Due to the possibility of lifelong therapy, the cost of treatment becomes an increasingly important factor to consider when initiating therapy. In addition, the quality of life of patients is also a chief concern when therapy may be long-term. Cost-effectiveness analysis is a powerful tool since it can bring together the concerns of drug efficacy, costs and quality of life quantitatively to determine the optimal therapy considering each of those factors. Although this dissertation does not include a cost-effectiveness analysis of the treatment of CHB, the results of the meta-analysis and quality of life study were performed to synthesize the information required for a future cost-effectiveness decision model to be created.
1.3 Study Goals

The goals of the study were as follows:

1) To determine using a variety of markers of outcome, the most efficacious treatment for patients with HBeAg-positive and HBeAg-negative chronic hepatitis B.

2) To estimate the utilities and health related quality of life of patients with chronic hepatitis B in disease stages ranging from non-cirrhotic hepatitis to post liver transplantation.
CHAPTER 2

BACKGROUND

The purpose of this chapter is to review the following:

1. Natural history of hepatitis B infection
2. Epidemiology and burden of disease for hepatitis B
3. Different genotypes of the hepatitis B virus
4. Current treatments used for chronic hepatitis B
5. Meta-analytic techniques
6. Patient preferences and utility measurement tools

2.1 Natural History of Hepatitis B infection

Hepatitis B is a disease caused by the hepatitis B virus which infects liver cells causing liver inflammation (hepatitis), liver damage and hepatocellular carcinoma. The routes of transmission for hepatitis B are: percutaneous – injection drug use and other inadvertent exposure to blood or bodily fluids; sexual – heterosexual or male homosexual activities; vertical – from mother to infant; and horizontal – among children and household contacts [4, 5]. Adult percutaneous transmissions from injection drug use or sexual activity are the major risk factors associated with the transmission of hepatitis B amongst adults in Canada [6-8]. Multiple sexual partners, sex with those with CHB both heterosexual or homosexual activities, or sharing equipment, living with a HBsAg carrier and a past (prior 1970) history of blood transfusion are all risk factors for of hepatitis B virus (HBV) infection among Canadians [9].
2.1.1 Acute Hepatitis B Infection

The incubation period of the hepatitis B virus following exposure to the virus is 2-6 weeks. Only then does HBsAg become detectable in the serum and the IgM antibody forms against the hepatitis B core antigen [10]. The virus replicates within the host and as a consequence both HBV DNA is detected in the serum as well as the viral protein HBeAg is detected in the serum [11]. Subsequently, ALT levels (a marker of inflammation causing destruction of hepatocytes) increase as the immune system responds to the virus with specific cytotoxic T lymphocytes targeted against infected hepatocytes. Individuals who recover from acute hepatitis B infection acquire protective levels of anti-hepatitis B surface antigen (anti-HBs) and lifelong immunity. However, in some individuals CHB infection ensues. The long-term outcome of acute hepatitis infection is determined by age and immunocompetence [12, 13]. When transmission occurs in neonates and infants, 90% will develop CHB infection while chronic infection will develop in 30% of children between the ages of 1-5. In adults, acute HBV infection normally resolves without any intervention or antiviral treatment however fulminant chronic hepatitis may develop in 0.1-0.5% [14]. Approximately 1-5% of immunocompetent adults become chronically infected [12].

2.1.2 Chronic Hepatitis B Infection

Individuals who do not clear an acute infection thus become chronically infected. CHB is a state characterized by persistence of detectable HBsAg, HBeAg and HBV DNA in serum for more than 6 months [15]. This infection if acquired vertically is characterised by 4 phases: immunotolerant, HBeAg positive immunoactive, HBeAg negative (inactive) and HBeAg negative hepatitis. The four phases are described in detail below:

Immunotolerant phase - This phase is characterised by very high levels of circulating HBV DNA due to a high rate of viral replication from the host’s failure of immune control of the virus. Normal ALT and detectable HBeAg and HBsAg are also observed. This phase is only
seen in patients following vertical infection and this immunotolerant phase often lasts for decades. During this phase, the virus is not directly cytopathic as the infant has been ‘tolerised’ in utero by passage of HBeAg across the placenta. Only once immune recognition of the virus develops does it cause liver disease. Thus, minimal histological activity is seen on liver biopsy during the immunotolerant phase [16, 17].

Immune Clearance Phase - Once the host’s immune system begins to recognize the HBV (i.e. the virus is no longer ‘tolerated’) immune mediated hepatocellular injury ensues [18, 19]. This phase is characterized by the presence of HBeAg, high but falling levels of HBV DNA, elevation of serum ALT levels, and histological findings of active inflammation which if left untreated, leads to progressive fibrosis of the liver [20, 21]. Patients in this phase are referred to as having HBeAg-positive chronic hepatitis B. Although viral replication continues, the serum HBV DNA levels decline as the immune system begins to lyse infected hepatocytes thereby causing liver damage. Only when an infant is infected during childbirth does the immunotolerant phase start and the transition to the immune clearance phase typically occurs in the second or third decade of life [21]. The immune clearance phase is variable in length from months to years. A patient in this phase usually remains asymptomatic; however, some may present with symptomatic flares of hepatitis that mimic that of acute hepatitis B. Rarely, this can lead to hepatic decompensation [22, 23]. In some cases, the flare may precede disappearance of HBeAg and the development of antibody against it (HBeAg seroconversion) resulting in remission of hepatitis activity and progression to the HBeAg-negative phase [24].

Spontaneous HBeAg seroconversion eventually occurs in all patients regardless of route of transmission but the longer it takes for sustained immune control to occur the more severe the underlying liver disease [25-30]. Factors associated with a higher rate of spontaneous seroconversion include older age [30], higher ALT levels (a surrogate marker for immune activity) [31, 32] and the infecting genotypes [33, 34]. Between 12-20% of
these patients will develop serious liver injury within 5 years depending on the duration of chronic hepatitis and the frequency and severity of hepatic flares [28, 35-38].

Inactive CHB generally follows HBeAg seroconversion and is characterized by a low or non replicative phase, normalization of ALT levels, decreases in HBV DNA to low (<1000 copies/ml) or undetectable levels and resolution of liver necroinflammation and fibrosis [39]. Patients in this phase can have several possible outcomes: sustained remission, HBeAg reversion or development of HBeAg negative chronic hepatitis B. Approximately two thirds of patients in the inactive phase will remain in remission, 50% of whom lose HBsAg and develop anti-HBs with a good long-term prognosis [40]. Although many patients can remain in remission for a lifetime, a proportion may undergo subsequent spontaneous or drug induced (immunosuppressive agents) reactivation of HBV replication with reappearance of high HBV DNA levels with or without HBeAg seroconversion and a rise in ALT levels [39]. HBeAg reversion occurs in 5-10% of inactive carriers [40]. Patients may show fluctuations between seroconversion and seroreversion having 2-3 reversions over 7 years [41]. Seroreversion is often accompanied by a hepatic flare [42]. In 20-30% of inactive carriers, hepatitis B will reactivate without HBeAg in the serum resulting in HBeAg-negative chronic hepatitis B.

 Reactivation/HBeAg-negative chronic hepatitis B – One third of inactive carriers may develop CHB without reversion of HBeAg [43-45]. This phase is characterized by chronic persistent HBeAg negativity with anti-HBe positivity, detectable serum HBV DNA (10^5-10^6 copies/ml), ALT elevation and liver necroinflammation. These carriers have undergone mutation of the core gene of HBV so that, although viral replication is ongoing, the mutation does not allow expression of HBeAg [46, 47]. Individuals may progress directly from HBeAg positive hepatitis or from an inactive carrier state to HBeAg negative hepatitis [40]. In general, these patients are typically older and infected with genotypes B or C and have more advanced disease with lower serum HBV DNA levels in comparison to their HBeAg-positive counterparts and the majority are male [25, 48]. The recurrent flares of
hepatitis that occur with relapses of the disease have a lower chance of remission for patients with HBeAg negative CHB in comparison to patients with HBeAg positive CHB. Flares of hepatitis may be severe and cause progression to cirrhosis and its end stage complications [49]. Periods of remission where there are normal ALT levels and lower serum HBV DNA (<10^5 copies/ml) may be long lasting. However, the disease usually recurs [50]. Overall in those with CHB, especially those with HBeAg-negative hepatitis, spontaneous HBsAg clearance is rare at a rate of 0.5-1.0% per year [40, 51].

2.1.3 Cirrhosis

The annual incidence of cirrhosis is higher among patients with HBeAg negative hepatitis (8-10%) compared to those with HBeAg-positive hepatitis (2-5%) [37, 52-54]. This difference is likely in part due to patients’ being older with more prolonged ongoing HBV replication [35, 37, 49]. Once cirrhosis has been established, the yearly incidence of hepatic decompensation (failure) is approximately 3% [36, 55]. Only at this stage do symptoms become apparent in those with CHB. The most common symptoms are ascities, jaundice, variceal bleeding and hepatic encephalopathy. The 5-year cumulative incidence of hepatic decompensation in untreated cirrhotics is 20% [38] and the 5-year survival rates without treatment are very low at 15% [56]. As expected, the risk factors associated with cirrhosis are older age and persistent HBV replication [35, 37].

2.1.4 Hepatocellular Carcinoma

Hepatitis B is a known carcinogen and particularly in patients with cirrhosis, it is a known risk factor for hepatocellular carcinoma (HCC). In patients with cirrhosis, the incidence of HCC is 100 times that of uninfected persons [57]. The annual incidence for HCC is estimated as 1% for those with non-cirrhotic CHB and 2-3% in carriers with cirrhosis [40, 58]. The overall 5-year cumulative incidence of HCC is 9% in those with CHB infection [58]. The risk factors for HCC include older age, HBeAg-positive status, persistent and high levels of HBV replication, abnormal ALT levels, long duration of infection, male sex, co-
infection with hepatitis C or D, alcohol abuse, aflatoxin, cigarette exposure and certain HBV genotypes [59-61]. Surprisingly, regular consumption of coffee is associated with a lower rate of cirrhosis and HCC in patients with CHB [62, 63].

2.1.5 Mortality

Each year 1 million people in the world die due to HCC and/or liver failure as a result of CHB infection [64]. In inactive carriers followed over 18 years, none died of liver-related causes [40, 65]. The 5-year survival rates for chronic hepatitis or compensated cirrhosis are 99-100% [35, 66] and 80-86% [38, 56, 58], respectively. The causes of death or need for liver transplantation include HCC (35%), liver failure (53%) and nonhepatic causes (12%) [58]. The strongest predictors of survival are younger age, sustained viral suppression and indicators of maintained hepatic function and absence of portal hypertension. Ongoing active HBV replication is a negative prognostic factor while viral clearance, ALT normalization and seroconversion from HBeAg-positive to HBeAg-negative and HBsAg loss is associated with better survival [56, 67].

2.2 Epidemiology and modes of infection for hepatitis B

2.2.1 Epidemiology

Globally, over 2 billion individuals have been infected with hepatitis B at some point in their life, of whom 450 million remain chronically infected [64, 68]. The distribution of individuals with hepatitis B varies considerably across different countries. In Asian and Western Pacific countries, the prevalence is over 10% while in the North America and northern European countries, the prevalence is under 0.5% [69, 70]. The estimated prevalence of CHB across Canada is 0.5-1% but it is much higher among immigrants from countries with a high prevalence [71].
The number of new HBV cases in Canada increased from 1971 peaking in 1989 with approximately 3378 cases, varied from 1990-1995 and has since been declining [72]. The estimated rates of infection are currently around 2.3/100,000 in the general population per year for symptomatic patients presenting to physicians. Since new infections can be asymptomatic, it has been estimated that as much as 50% or more of cases are not reported. Therefore, a precise estimate of new infections remains unknown. The incidence rate of new chronic infections has also not been established.

Data on those with CHB is poorly reported and collected and is not uniformly distributed across populations within Canada. The general population has low prevalence whereas attendees of sexually transmitted disease clinics and residents of long term care facilities have prevalence which are higher at 0.4% and 0.6% respectively [7, 73-75]. The Aboriginal population also has intermediate prevalence with 11.3% who have evidence of previous infection and 0.3% who are HBsAg positive carriers [76]. The highest prevalence is among the Inuit population where 26.4% have evidence of previous HBV infection and 6.9% are HBsAg positive [77]. Hepatitis B is also highly prevalent among immigrant populations from Southeast Asia and Africa where the prevalence of HBV infection ranges from 8%-20%. 7.4% of pregnant women born in Asia versus 0.1% of those born in Canada are carriers [78, 79].

2.2.2 Burden of Disease

Although a highly effective HBV vaccine has been available for more than 20 years, HBV related disease burden is still a major public health problem. There are approximately 450 million people worldwide who have been chronically infected resulting in 1 million HBV related deaths per year [80]. It has been estimated that 54.4% of liver cancers worldwide are attributed to HBV and 89% of HBV-related HCC are reported from developing countries [81]. Individuals infected with HBV are 20 times the risk of HCC development in comparison to the general population (relative risk 100-2000) [82]. The current anti-
virals for CHB delay the progression of liver disease. However, a large proportion of individuals with CHB live in developing countries where there are limited health care resources that may prevent them from receiving treatment. To date there is no convincing evidence that antiviral therapy reduces HCC. This may be due to the potency of therapies used until recently.

The financial burden of CHB varies significantly depending on stage of the disease. Within Canada, estimates of the annual cost (in 2001 Canadian dollars) of treatment for disease states related to hepatitis B range from $2191 for non-cirrhotic CHB to $99,066 for liver transplantation (Table 2.1). In the earlier stages of disease, medications contribute most to the overall cost of treatment. In later stages, which develop mostly in those who have never received treatment, hospitalizations comprise the largest cost component.

Although the overall rate of CHB infection is low among Canadians in the general population, approximately 280,000 individuals with CHB reside in Canada [83]. The annual cost of treatment for CHB varies significantly between $1778 to 22,000 Canadian dollars for the year 2008 (Table 2.2). Considering the number of carriers that remain in Canada, the large annual costs and a focus towards lifelong therapy, hepatitis B remains a great financial burden in Canada.
Table 2.1 Annual health care costs per patient by disease state for chronic hepatitis B for Canada and the United States.

<table>
<thead>
<tr>
<th>Disease state</th>
<th>Canada (2001 CAD) [83]</th>
<th>United States (2000 USD) [84]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hepatitis B</td>
<td>$2191</td>
<td>$761</td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>$2987</td>
<td>$227</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>$11,228</td>
<td>$11,459</td>
</tr>
<tr>
<td>Liver transplant</td>
<td>$99,066</td>
<td>$86,552</td>
</tr>
<tr>
<td>Transplant care after first year</td>
<td>$38,242</td>
<td>$12,560</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>$13,350</td>
<td>$7533</td>
</tr>
</tbody>
</table>

Abbreviations: CAD, Canadian dollars; USD, American dollars
Table 2.2 Annual treatment costs per patient for chronic hepatitis B in Canada

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Dosage</th>
<th>Treatment Costs (2008 CAD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegylated interferon</td>
<td>100 µg/week</td>
<td>$22,000</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>100 mg /day</td>
<td>$1778</td>
</tr>
<tr>
<td>Adefovir</td>
<td>10 mg/day</td>
<td>$9201</td>
</tr>
<tr>
<td>Entecavir</td>
<td>0.5 mg or *1.0 mg/day</td>
<td>$9201 or *$18,402</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>300 mg/day</td>
<td>$6796</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>600 mg/day</td>
<td>$7110</td>
</tr>
</tbody>
</table>

Note: Costs of drugs were obtained from the Toronto General Pharmacy at Toronto’s University Health Network for 2008.

* Using entecavir following prior treatment with lamivudine requires doubling the dosage
2.3 HBV Genotypes

There is increasing evidence to suggest HBV genotype may affect clinical and treatment outcomes. Eight genotypes (A-H) categorized by divergence in the entire HBV genome sequence of >8% have become recognized to date [85-88]. The genotypes have distinct geographical distributions: B and C are prevalent in Asia, A and D most frequently occur in Africa, Europe and India, E is restricted to West Africa, F is found in Central and South America, G is found in Europe, and North America and H in Central America [89, 90].

The literature on the clinical relevance of viral genotype is limited to certain parts of the world. Most studies have been performed in Asian countries where genotypes B and C predominate. As most patients from these areas typically contract hepatitis B in the perinatal period (either vertically or horizontally), these studies help to understand the relationships of genotype B and C on the rate of progression of liver disease. Within genotypes B and C, studies indicate that there are more serious outcomes in Asia with genotype C in comparison to B.

Studies of Japanese and Chinese patients suggest that genotype C is associated with more abnormal ALT levels, higher histologic activity scores, faster progression to cirrhosis, more active liver disease, older age for spontaneous HBeAg seroconversion and is less likely to remain in remission after HBeAg seroconversion in comparison to genotype B [91, 92]. Three studies of Japanese and Chinese patients found that cirrhosis and thus HCC was more prevalent in patients with genotype C versus genotype B [93-95]. One study performed in the US showed that genotype B patients with compensated cirrhosis were less likely to develop decompensation [96].
There is conflicting evidence regarding the effects of genotype on the incidence of HCC. A study of Japanese patients found that HCC occurred less frequently in patients with genotype B than C while studies in Taiwan and India found that patients with genotype B were more likely to have HCC [93, 95].

Information on the clinical course of patients with genotypes other than B and C is lacking. A study performed in India reported that genotype D was associated with ALT elevation, core antigen positivity and negative anti-HBe in patients 25 years of age and above. A study performed in Spain reported similar HBeAg seroconversion rates of genotypes A and D however following HBeAg seroconversion, a sustained biochemical and virological response was not common in patients with genotype A [97]. Progression from acute to chronic hepatitis is also more likely in genotype A than with D [98].

Research has shown that genotype influences response to interferon treatment. Clinical trials of interferon show higher levels of HBeAg seroconversion in those treated who are infected with genotypes A and B in comparison to C and D [93, 99, 100] and the rate of HBsAg seroconversion with interferon treatment is higher among those infected with genotype A than D [99, 101].

In two trials of lamivudine, one showed comparable virological and biochemical outcomes of treatment among genotypes A and D [102] while one study reported that those infected with genotype D were more likely to have sustained virological response [103]. Among genotypes B and C, one study suggested better virological response [104] to lamivudine in genotype B while other studies suggest no difference [105, 106]. Another trial investigated the responses of different genotypes to treatment with adefovir and found no
differences [107]. Overall, there is little effect of genotype on response to treatment with oral nucleos(t)ide analogues in contrast to that observed with interferon.

These studies suggest that genotyping prior to treating may help in the selection of treatment that provides the best clinical outcomes. However, further examination of the association between genotype and treatment outcomes needs to be performed.

2.4 Treatments for chronic hepatitis B

2.4.1 Goals of hepatitis B therapy

“The goal of therapy for hepatitis B is to improve quality of life by improving survival by preventing progression of disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC and death” [1] as stated in the European Association of the Study of Liver (EASL) 2009 guidelines. This goal can be reached through sustained suppression of HBV replication which leads to an improvement in the activity of the disease and thereby (if sustained) lessens the risk of liver failure and possibly HCC [108]. The endpoints of therapy as stated by the most recent EASL guidelines are as follows:

1. In HBeAg-positive and HBeAg-negative patients, sustained HBsAg loss with or without seroconversion to anti-HBs. This outcome has been associated with complete and definitive remission of chronic hepatitis B and an improved long-term outcome.

2. In HBeAg-positive patients, durable HBe seroconversion. HBe seroconversion has been associated with improved prognosis.

3. In HBeAg-positive patients who do not achieve HBe seroconversion, and in HBeAg-negative patients, a sustained undetectable HBV DNA level on treatment with oral
anti-virals or a sustained undetectable HBV DNA level following interferon therapy [1].

There are several therapies available for the treatment of CHB. There are two main categories of treatments: immune modulators (interferons) and oral anti-viral agents (nucleoside and nucleotide analogues): lamivudine, adefovir, entecavir, telbivudine and tenofovir.

2.4.2 Interferon (Peg-intron™, Pegasys™)

Interferons are cytokines which are efficient in the treatment of some infectious diseases. Pegylated forms have replaced standard interferon as they have a less demanding injection schedule and their efficacy is either comparable or perhaps improved [109, 110]. Interferons have anti-viral activity, anti-proliferative and immunomodulation properties. They function by increasing expression of major histocompatibility antigens, increasing natural killer and cytotoxic T cell activity and increasing cytokine induction and the stimulation of endogenous interferon pathways. Treatment with interferon has been limited because its side effect profile is greater than that of oral agents although efficacy particularly in terms of loss of HBsAg is often better (depending on the infecting genotype).

2.4.3 Lamivudine (Heptovir™)

Lamivudine was the first registered nucleoside analogue for the treatment of chronic HBV. It was approved in 1998 by the FDA for the treatment of CHB infections. It is a cytosine analogue, which has to be phosphorylated to its active metabolite. Lamivudine works by
directly inhibiting the viral polymerase by competing with natural triphosphates for incorporation into the viral DNA thus terminating the DNA polymerase chain [111]. The efficacy rates of lamivudine and other oral anti-virals are summarized in Table 2.3
Table 2.3 Comparison of clinical data for approved medical treatments for chronic hepatitis B at 1 year of therapy [112-127]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Interferon-α</th>
<th>Peg interferon-α-2a</th>
<th>Lamivudine</th>
<th>Adefovir dipivoxil</th>
<th>Entecavir</th>
<th>Telbivudine</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg+ CHB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate of HBeAg seroconversion (%)</td>
<td>~18</td>
<td>27</td>
<td>16-18</td>
<td>12</td>
<td>21</td>
<td>17-22</td>
<td>21</td>
</tr>
<tr>
<td>Rate of HBsAg loss (%)</td>
<td>7.8</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>HBeAg- CHB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate of HBV DNA undetectability (%)</td>
<td>60-70</td>
<td>63</td>
<td>50-70</td>
<td>51</td>
<td>90</td>
<td>85-88</td>
<td>96</td>
</tr>
<tr>
<td>Duration of Therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg+ CHB</td>
<td>4-6 months</td>
<td>1 year</td>
<td>&gt;1 year</td>
<td>&gt;1 year</td>
<td>&gt;1 year</td>
<td>&gt;1 year</td>
<td>&gt;1 year</td>
</tr>
<tr>
<td>HBeAg- CHB</td>
<td>12 months</td>
<td>1 year</td>
<td>Indefinite</td>
<td>Indefinite</td>
<td>Indefinite</td>
<td>Indefinite</td>
<td>Indefinite</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Subcutaneous</td>
<td>Subcutaneous</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Many</td>
<td>Many</td>
<td>Negligible</td>
<td>Negligible</td>
<td>Negligible</td>
<td>Negligible</td>
<td>Negligible</td>
</tr>
<tr>
<td>Contraindications</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Drug resistance (%)</td>
<td>None</td>
<td>None</td>
<td>~20 at year 1</td>
<td>0 at year 1</td>
<td>0 at year 1</td>
<td>~4 at year 1</td>
<td>0 at year 1</td>
</tr>
<tr>
<td></td>
<td>~70 at year 5</td>
<td>~18 at year 4</td>
<td>7 in Lam-R</td>
<td>~22 at year 2</td>
<td>0 at year 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B s antigen; Lam-R, lamivudine resistant patients, ++ indicates contraindications for usage; - indicates no contraindications for usage
2.4.4 Adefovir (Hepsera TM)

Adefovir dipivoxil is an oral prodrug of adefovir that contains a phosphate group that requires a final phosphorylation before competing for integration into the HBV DNA strand causing chain termination [128-130]. It was approved in Canada in 2002 for the treatment of CHB. When it first came to market, it had an advantage over lamivudine because it has a lower rate of viral resistance. However, since it was approved, newer anti-viral agents have become available with both improved efficacy and potency in comparison to adefovir.

2.4.5 Entecavir (Baraclude TM)

Entecavir is a nucleoside analogue that affects multiple functions of HBV polymerase, including priming, reverse transcription, and DNA elongation [131]. It is one of the most potent anti-HBV drugs available with a low resistance rate. It is in the same class of drugs as lamivudine; therefore, patients previously treated with lamivudine who are lamivudine-resistant show cross-resistance to entecavir [122, 132]. Rates of resistance in treatment naïve patients were zero at one year but unfortunately the phase 3 trial was designed in such a way that an intention to treat analysis was no possible after on year. However, the rates of resistance at one year are significantly lower than in patients treated with either lamivudine or adefovir (Table 2.3).

2.4.6 Tenofovir (Viread TM)

Tenofovir is an antiviral drug that has a similar molecular structure to adefovir with a similar mechanism of action but it is more potent and to date resistance to tenofovir has not been described but in the phase 3 trial, those individuals with HBV DNA > 400 copies/ml were offered Truvada (emtricitabine and tenofovir) [133-136]. It is one of the most potent agents available and like adefovir, it is effective against lamivudine-resistant virus [136, 137]. At this time, there have been no cases of tenofovir resistance in
treatment-naive patients [121]. It may also be efficacious against adefovir resistant mutations but with reduced efficacy [138].

2.4.7 Telbivudine (*Tyzeka™*)

Telbivudine is an antiviral that shares a similar molecular structure to lamivudine. It exerts its antiviral effect by preventing DNA synthesis by acting as a chain terminator during replication [139]. It has a somewhat lower resistance profile than lamivudine but higher than that for entecavir and tenofovir.

2.4.7 Comparison across treatments

Currently, no head-to-head clinical studies have been undertaken that compare all of these treatments. Due to the numerous treatments available, changing treatment target outcomes and the high variability in the cost of different treatments, the optimal treatment option for CHB is not clear. Traditionally, meta-analyses are used to bring together a number of trials comparing two different interventions to synthesize a single treatment effect. However, there are multiple therapies available for the treatment of CHB and these traditional techniques are not sufficient to provide an indication of the relative treatment efficacy of all currently available therapies. In this dissertation, Bayesian meta-analytic techniques are used to compare all of these treatments as monotherapies and combination therapies simultaneously to present a clearer picture of the relative efficacy for each of these treatments for each clinical target outcome.
2.5 Meta-analysis

2.5.1 Introduction to meta-analysis

Meta-analysis is a statistical tool that can be used to combine the results of several studies to address a shared research hypothesis regarding a drug’s treatment effect. Just as individual studies summarize data collected from many participants in order to answer a specific research question (i.e., each participant is a separate data point in the analysis), a meta-analysis summarizes data from individual studies that concern a specific research question (i.e., each study is a separate data-point in the analysis [140]. This synthesis is normally done by expression of a common measure of effect size (e.g., odds ratio, relative risk, risk difference or difference in change from baseline). Meta-analysis uses the magnitude of the effect and the degree of its uncertainty from each study to produce a weighted mean. Because the net effect of pooling studies is to increase the sample size, the resulting overall average, when controlling for study characteristics, can be considered a more precise estimate of the true effect size than those derived from individual studies [140].

A meta-analysis answers multiple questions. First, what is the effect size of the relationship of two variables and is it statistically significant? Second, is the heterogeneity between individual studies greater than what one would expect from chance alone? Third, can meta-regression be used to determine the variables that may affect the relationship between X and Y? [141]

The advantages of meta-analysis versus that of classical systematic reviews or simple averages of effect sizes are: i) they derive a statistical test of the effect size in the related studies; ii) they make the results generalizable to the population that is included in the studies; iii) they allow for control of between study variation; and iv) they provide greater statistical power than a single study [140, 141].
The weakness of meta-analysis is that the data entered into the meta-analysis controls the results of the analysis. A meta-analysis with poor methodological quality will result in inaccurate results, just as would happen in a randomized controlled trial with poor quality. Thus, before including a specific trial, a grading system is often used to determine its acceptability [141]. Furthermore, publication bias often occurs as most published data show an effect whereas studies that show small or no effect are less likely to be published [142]. Consequently, including published studies in a meta-analysis may be a biased subset of all studies which may result in an upwardly biased estimate of the effect size.

2.5.2 Fixed versus random effects meta-analysis

There are two main models used for meta-analysis, fixed effect models and random effect models. A fixed effect model assumes a single common underlying true treatment effect for every trial and consequently allows for within study variability of an estimate around its true value but no between study variability in the true values [141]. Any differences between estimates from different studies are assumed to be solely due to patient-level sampling variation. A study’s observed effect is equal to a fixed effect common to all studies plus a sampling error. There are various methods for calculating the effect size. However, the most commonly used technique for estimating the true treatment effect is to calculate the weighted average of study specific effects where the weights are equal to the inverse variance of each study. Using this method, the variance of the pooled effect is calculated as the reciprocal of the sum of the weights [140].

A random effect model assumes that the true effects vary across studies due to heterogeneity between studies (in the implementation of the treatment, follow-up duration, patient population, etc.) and thus allows for both within study sampling variability and between study variability in the true effect. In this model, it is commonly assumed that the true effects vary around a common mean according to a normal
distribution [143]. The variance across studies in the true underlying effect is called the random-effects variance. Like the fixed effect model, the true treatment effect can be calculated as the weighted average of study specific effects. However, the weights are based on a combination of both the variance of each study and the random-effects variance. The variance of the pooled estimate is again calculated as the reciprocal of the sum of the weights [140]. The random effects model will provide wider confidence intervals in comparison to the fixed effect model since it is a function of both sampling error of the individual studies and the between study variance.

A random effects model was chosen for the current study since it takes into consideration the differences that may exist between studies. In the Bayesian meta-analysis that follows, the subjects included in the trials came from different samples recruited from clinic centers across the globe. A random effects model takes into consideration the heterogeneity in study populations that may exist and is the more appropriate model for this analysis.

2.5.3 Frequentist versus Bayesian meta-analysis

There are two main schools of statistical inference, classical or frequentist inference and Bayesian inference. There are fundamental differences between the two schools on the interpretation of probability, the use of information outside a given set of data and the focus of parametric statistical analysis. The “frequentist” sees probability as the expected frequency of an occurrence over a long period of time. \( P(A) = \frac{n}{N} \), where \( n \) is the number of times event \( A \) occurs in \( N \) opportunities. The Bayesian view of probability is related to degree of belief. It is a measure of the plausibility of an event given incomplete knowledge [144]. Using a frequentist approach to meta-analysis, a point estimate and 95% confidence intervals are calculated whereas a Bayesian approach to meta-analysis will calculate a posterior probability distribution of the pooled effect with 95% credible intervals.
Consider a simple situation, the estimation of a mean based on a sample of observations where the observations are assumed to come from a normal distribution. A frequentist believes that a population mean is real but unknown and unknowable and can only be estimated from the data. The usual confidence interval is constructed using the sample mean as the center and with upper and lower limits based on statistical theory relating to the behaviour of repeated samples. For a frequentist, the true mean either lies within the interval or not since the mean is a fixed value and does not have a distribution; the interval is random, being just one possible sample that could have been observed. Thus a frequentist interprets probability as a long-run fraction having this characteristic. The 95% confidence interval is thus interpreted as having the property that 95% of similar intervals would contain the true mean if each of the intervals were constructed from a different random sample like this one (Figure 2.1) [144].
Figure 2.1 Frequentist interpretation of 95% confidence intervals.

Note: Each vertical line represents a 95% confidence interval for a sample. The horizontal line reflects the true mean.
A Bayesian 95% credible interval is constructed by combining any prior information about the value of the mean with information contained in the sample. The interpretation is that there is a 95% probability (degree of belief) that the interval contains the mean. The credible interval is centered near the sample mean but is influenced by both the data and prior beliefs. Bayesians believe that only the data is accurate and the prior beliefs make some values of the true effect more believable than others.

One difference in interpretation between confidence intervals and credible intervals is in what the ‘95%’ refers to. It is correct to say that there is a 95% probability that the mean lies between the lower and upper ends of a credible interval. The 95% refers to the particular interval just calculated. With a confidence interval, the correct word is ‘coverage’ – there is a 95% probability that intervals constructed in such a way will cover the true value. The Bayesian analysis also produces an output that has no analog in the frequentist analysis – the posterior distribution. A 95% credible interval is simply a range that has 95% probability but the posterior distribution gives us the relative probabilities of any values of the true mean. While it makes sense to sample values of the true mean from its posterior distribution, there is no statistical justification for sampling values of the mean from a confidence interval – it is not a distribution.

The advantages of a Bayesian approach to meta-analysis include the ability to make predictions of the probability of an outcome and incorporate different sources of uncertainty [140, 145]. In our study, the results of the meta-analysis will be used in cost-effectiveness analyses assessing the different treatments used for CHB. The decision models used in cost-effectiveness analysis can thus easily incorporate the estimates synthesized from this study as inputs to determine the optimal treatment option for CHB.
2.5.4 Bayesian meta-analysis

A Bayesian framework for analysis consists of prior distributions (beliefs) and likelihoods (trial data) that when entered into a model, result in posterior distributions for the pooled treatment effect and any other unknowns. The prior distributions represent the beliefs regarding the plausibility of all of the different possible values for the treatment effect, excluding evidence from trial data. The trial data is the support of the plausibility of each of the different values of the treatment effect. A model is used to bring together the prior distributions (beliefs) and the data from actual trials (likelihoods) to produce a posterior distribution for the pooled treatment effect and its heterogeneity [146]. From the posterior distribution, we can obtain the mean, the median, and a 95% credible interval for the pooled treatment effect and its heterogeneity.

The simple Bayesian random effects meta-analysis model for continuous outcomes is written below [145]:

\[ \text{diff}_i \sim N(\delta_i, \sigma_i^2) \]  
Data for each study \( i \) (Likelihood): \( \text{diff}_i \) are the observed values and they vary around their true values due to within-study sampling variability.

\[ \delta_i \sim N(d, \sigma_\delta^2) \]  
Random effects model: true values \( \delta_i \) vary around the pooled effect \( d \) with standard deviation \( \sigma_\delta \).

\[ d \sim [-, -] \]  
Prior distribution for the pooled treatment effect.
\[ \sigma_\delta \sim [-, -] \]  

Prior distribution for the heterogeneity of the pooled treatment effect

The object of a meta-analysis is to estimate the pooled treatment effect \( d \) and its heterogeneity \( \sigma_\delta^2 \). Prior distributions for both \( d \) and \( \sigma_\delta^2 \) are used to reflect the prior belief of the believability of estimates for each of parameters. \([-, -]\) symbolizes arbitrary prior distributions for these parameters. If \( \sigma_\delta^2 \) were set to 0, the model would not allow for between study heterogeneity and would describe a fixed effect model.

The value \( \text{diff}_i \) represents the observed treatment effect of treatment A versus treatment B in study \( i \). In this case, \( \text{diff}_i \) is given a normal distribution \( N \), and described by the study specific true effect \( \delta_i \) and the sampling error standard deviation \( \sigma_i \). The data for each study enter the analysis through the likelihood. A model is used to describe how the true study specific effects \( \delta_i \) are distributed. The model also describes how the parameters \( d \) and \( \sigma_\delta^2 \) relate to the data. Prior distributions are updated according to the data to result in a posterior distribution for \( d \) and \( \sigma_\delta^2 \) [147].

2.5.5. Bayesian mixed treatment comparison meta-analysis

There are numerous therapeutic options for the treatment of CHB. However, head-to-head trials do not exist for pair wise comparisons for all of the available treatments. Furthermore, clinical trials assessing the efficacy of new treatments for CHB are no longer compared to placebo but instead an active control. Lamivudine is the first oral antiviral therapy that was made available for the treatment of CHB and given its proven efficacy against the virus, it is no long ethical to use placebo as the control group in trials of patients with active CHB. In order to identify the most effective treatment and rank each relative to the alternative, a Bayesian mixed treatment comparison (MTC) meta-analysis model was employed. The random effects MTC model is written below:
\[
\text{diff}_i \sim N(\delta_i, \sigma_i^2) \quad \text{Data for each study (Likelihood)}
\]

The value \text{diff}_i is the observed relative treatment effect data of in study i. It is given a normal distribution, with mean equal to the true relative effect \delta_i for that study and the sampling error standard deviation \sigma_i.

\[
\delta_{i,b,k} \sim N(d_{b,k}, \sigma_\delta^2) \sim N(d_{P,k} - d_{P,b}, \sigma_\delta^2) \quad \text{Random effects MTC model}
\]

Here, \(P\) refers to the placebo intervention, \(k\) refers to the active intervention (e.g., lamivudine), and \(b\) is the comparator intervention. This says that the true mean effect for study i, which compares interventions \(b\) and \(k\) is equal to the effect of \(k\) vs. placebo minus \(b\) vs. placebo

\[d_{b,k} = d_{P,k} - d_{P,b}\]

Notice that any comparison of two interventions is based on the difference of the two comparisons back to placebo, so with \(K\) treatments, we need \(K-1\) values \(d_{P,k}\). We allow that the true effect for a study varies with a mean equal to the average effect for studies making that comparison and a variance of \(\sigma_\delta^2\).

Finally, in the MTC model, priors are required to describe the distribution of the \(K-1\) effects comparing back to placebo and the heterogeneity of the effects around their true value.
Prior distribution for the true relative effect of $P$ to $k$

Prior distribution for the heterogeneity of the true relative effect

The model defines how the true study and comparison-specific relative effects $\delta_{i,b,k}$ are distributed. The prior distributions are updated according to the data entered into the model to result in posterior distributions for the $d_{P,k}$ values and $\sigma_\delta^2$. The values of $d_{P,k}$ can be used to compute the effect for any two treatments and can also be used to compute estimates of the probability of an outcome following treatment. In the following chapter, this model will be used to determine the relative efficacy and rank of the various treatments available for CHB.

### 2.6 Patient preferences and utilities

#### 2.6.1. Health related quality of life

Health related quality of life, as defined by Patrick and Erickson, “is the value assigned to the duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment or policy” [148]. HRQOL scoring systems provide utility (preference) scores for defined health states on a generic scale where dead = 0 and perfect health = 1. The quality adjusted life year (QALY) is essentially a health index where the time spent in ill health (measured in years) is multiplied by a weight measuring the relative desirability of the illness state to yield a number that represents the equivalent number of years with full health. QALYs provide a common unit of measure that allows comparisons across programs [149].
HRQOL can be separated into preference and non-preference based quality of life each of which can be quantified and provided a unit of measurement. Preference based assessment yields either utilities or values depending on the instrument used to elicit HRQOL. Preference is a term that encompasses the overall concept and utilities and values are types of preferences [150]. There are two major categories of preference-based measures: direct and multi-attribute (indirect). In the direct approach, respondents can be asked to value health states. The health states evaluated in the direct approach may be hypothetical health states or the respondent’s subjectively defined current health state. In the latter case, respondents reflect on their own state of health, and then value it. The direct approach not only evaluates an individual’s multi-dimensional health state but also captures an individual’s risk attitude, as the method usually requires a choice between two alternatives. In the multi-attribute approach, respondents complete a questionnaire based on a health-status classification system that is a component of a multi-attribute system. A multi-attribute system categorizes health into different parts such as mental status or physical functioning and creates a single score by compiling the individual attributes together using a mathematical scoring function [151]. The scoring functions for some instruments are derived from standard gamble utilities taken from large studies of the community.

The methods used to measure preferences will determine whether one elicits patient values or utilities. Utilities are a unit of measuring quality of life that can be elicited using the method in which a question is framed under uncertainty and the respondent is asked to choose from two alternatives, one of which contains an unknown outcome. Patient values are also measures of health. However, unlike a utility; they are elicited by asking patients to choose between alternatives with certain known outcomes. The standard gamble is a method that elicits utilities directly and is preferred and over other methods as it captures a subject’s risk attitude and frames the question under uncertainty which are concepts patients face when choosing whether or not to proceed with a medical intervention.
2.6.2 Direct utility measurement – Standard Gamble

The standard gamble was described by von Neumann and Morgenstern [152]. It is based on a paired comparison in which the subjects choose one of the two strategies. One strategy has two possible outcomes: perfect health with probability p and death with probability 1-p. The other strategy leads to a chronic health state which is intermediate in desirability between perfect health and dead and is defined by the research study. The probability p is varied until the respondent registers indifference to the two strategies, at which point the utility value is p.

The most commonly used approach to measure standard gamble utilities for health states is the face-to-face interview using visual aids and an iterative approach [153]. Patients are offered an option (e.g. a hypothetical pill) that will confer upon them perfect health or death [154]. The risk of death is titrated to find the point of indifference to the alternative scenario of chronic illness. The reliability of the standard gamble is generally very good with a test-retest reliability of 0.80 [155-157], and adult patients generally understand it. Because it involves uncertainty, a characteristic of almost all medical decisions, it is a true utility assessment method [158, 159]. It is the only method consistent with the von Neumann and Morgenstern axioms of decision theory, and the only utility measure for which the expected value is meaningful [160-162].

A disadvantage of the standard gamble method is the expense associated with its measurement and the cognitive skill required of the respondent [163]. Most contemporary assessments involve face-to-face interaction with trained interviewers or sophisticated computer software [156]. Generally, utility assessment involves travel by either the patient or facilitator. The standard gamble is infrequently used because of its complexity and cost of administration. While questionnaire-based utility assessment in general is desirable, using the computerized standard gamble is also particularly attractive [164].
2.6.3 Direct utility measurement – Rating Scale/Visual Analogue Scale

The rating scale or visual analogue scale consists of a 10 cm long line with zero at one end, equivalent to dead, and 1 at the other, equivalent to perfect health. The subjective health status, i.e., preference, is placed on the line between zero and one in such a way that the distance from zero to the placement corresponds to the degree of preferences for the defined state as perceived by the subject. Measurement of the distance between zero and the mark placed for the health state is the utility. The visual analogue scale is simple to use and easy for patients to understand. However, it is often subject to measurement bias since patients tend to shy away from the ends of the scale [150]. The scales can be translated into standard gamble scores using a power curve function.

2.6.4 Indirect utility measurement – EQ5D and Health Utility Index

Multi-attribute measurement instruments are also used to assess generic HRQOL. The most commonly used tools are the EQ5D [165] and Health Utility Index (HUI) [151].

The EQ5D defines health in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is divided into three levels: no problem/some or moderate problems/extreme problems. According to this classification system, 243 potential health states are defined in addition to these two further states specified as, ‘dead’ and ‘unconscious’, giving a total of 245 health states.

The Health Utility Index is a preference-based system that is used to measure health status, that reports HRQOL to produce utility scores [166]. The HUI3 captures 8 attributes: Vision, Hearing, Speech, Ambulation, Dexterity, Emotion, Cognition and Pain, each with 5 or 6 levels of ability/disability. The HUI3 defines 972,000 unique health states for a utility interval of -0.36 to 1.00. Negative scores represent states considered worse
than death [166]. The HUI3 was used to generate population norms in the 1996-1997 National Population Health Survey conducted by Statistics Canada [167]. The survey found that scores decline with age and were lower for institutionalized subjects relative to community-dwelling subjects [167].

### 2.6.5 Non-preference based HRQOL assessment

The Short Form 36 (SF36) questionnaire measures three aspects of health: functional ability, well-being and overall health [168]. It provides scores on eight areas of functioning and well being, and generates summary scores for physical health and mental health. It is a 36 item questionnaire that measures eight multi-item dimensions of health: physical functioning (10 items), social functioning (2 items), role limitations due to physical problems (4 items), role limitations due to emotional problems (3 items), mental health (5 items), energy/vitality (4 items), pain (2 items) and general health perception (5 items). For each dimension, the item scores are coded, summed and transformed on to a scale from 0 (worst possible health) to 100 (best health).

Chapter 4 of this dissertation describes the study performed to elicit health utilities and HRQOL of patients with CHB. In this study the EQ5D, HUI3, SF36v2 and the standard gamble were used to determine the quality of life of patients attending tertiary care liver clinics in downtown Toronto. Multiple instruments were used in the study since prior studies of the HRQOL of patients with CHB used one or two of the instruments and found conflicting results [169-171]. By using a variety of methods, the current research study is able to provide a comprehensive list of utilities and HRQOL scores as measured by each of the instruments as well as determine if differences exist between the measurement tools.
CHAPTER 3

BAYESIAN MIXED TREATMENT COMPARISONS

The objectives of this chapter are to:

1. Provide an overview of the study methods used in the systematic review and meta-analysis

2. Describe the trials included in the meta-analysis with attention to eligibility criteria, the search strategy, quality of trials and definition of efficacy measurements and outcomes.

3. To describe the methods of the data extraction process and Bayesian statistical methods

4. Present the literature search results and describe the characteristics of the studies found in the systematic review and included in the meta-analysis

5. Present the results for direct and indirect comparisons of treatments in HBeAg-positive patients

6. Present the results for direct and indirect comparisons of treatments in HBeAg-negative patients

7. Describe the severe adverse events from treatment of chronic hepatitis B

8. Discuss the main findings of the meta-analysis

9. Discuss the major limitations of the meta-analysis

10. State the clinical controversies surrounding this meta-analysis
3.1 Overview of study methods for a systematic review and Bayesian meta-analysis

An extension of traditional systematic review and frequentist meta-analysis was used to examine the efficacy of treatments for chronic hepatitis B. Literature databases were searched from their dates of inception to Oct 30, 2009 for published studies on all currently available treatments. Because there is no cure for hepatitis B, surrogate outcomes were used out of necessity to assess the efficacy of treatments: serum HBV viral levels, normalization of liver enzymes (alanine transaminase/ALT), HBeAg seroconversion and loss, HBsAg loss, histologic improvement of the liver and severe adverse events at one year following initiation of treatment. It was expected that that newer treatments would result in better outcomes.

Bayesian Mixed Treatment Comparison (MTC) methods were used to:

1. Compare the treatments and combination of treatments available for chronic hepatitis B
2. Determine the probability of an outcome following treatment
3. Rank the treatments to determine the most efficacious treatment for chronic hepatitis B

3.2 Assessment of randomized controlled trials

3.2.1 Eligibility Criteria

To be included, studies must have examined adults with HBeAg-positive and/or HBeAg-negative CHB in randomized phase 3 controlled trials comparing new drug treatments with either placebo or already licensed drugs. The drugs evaluated included pegylated interferon, lamivudine, adefovir, entecavir, telbivudine or tenofovir as monotherapy or combination therapy administered for a one-year period (48-52 weeks). Trials that
employed standard interferon therapy were not included in the analysis. The trials that
used pegylated interferon were conducted for 48 weeks and measurements of treatment
efficacy were taken 24 weeks after cessation of therapy in comparison to oral antiviral
therapies whose measurements were taken at 48 weeks while on treatment. Treatment
with pegylated interferon is limited to 24 weeks of therapy while discontinuations of oral
antivirals are often associated with a flare up of hepatitis. Hence, measurements of oral
antiviral treatments were taken while on treatment. The analysis was limited to results
from the first 12 months of treatment since published long-term data were not available
for the newer treatments. Furthermore, an intention-to-treat approach was not taken for
all drug trials past the first year of treatment.

Excluded were studies: (i) of patients who were coinfected with HIV, hepatitis C or D, (ii)
not reporting any efficacy measures and (iii) of patients with lamivudine resistance due to
mutations in the YMDD motif of the reverse transcription polymerase gene. When several
publications pertaining to one study were identified, the primary publication was used.

3.2.2 Literature search

MEDLINE, EMBASE, Cochrane Systematic Reviews and Web of Science Databases were
searched using MeSH terms and keywords describing CHB, pegylated interferon,
lamivudine, adefovir, entecavir, telbivudine, tenofovir, RCT and surrogate treatment
outcome. The search was limited to the English language and started from the date of
inception of each database until October 30, 2009. The search strategy is described in
greater detail in Appendix A. Initial screening of abstracts was performed for each article
by two reviewers; a third party arbiter addressed disagreements. Full papers for all
potentially relevant trials were obtained; and the reference list of each article was
searched for other potential studies. Clinical experts were consulted to determine if any
published studies were missing. Meeting abstracts, unpublished data, or theses were not
reviewed.
3.2.3 Quality of randomized controlled trials

Methodological quality was independently assessed by two reviewers using the Cochrane risk of bias tool, an established tool based on assessing: sequence generation for the randomization of subjects, allocation concealment of treatment, blinding, reporting of data and other sources of bias. Where discrepancies arose, a third party was consulted.

3.2.4 Efficacy measures and definitions

All outcome measurements were surrogates and were taken 12 months following initiation of therapy. Measurements for oral antivirals were taken while patients were still receiving therapy, whereas measurements for pegylated interferon were taken from results obtained 24 weeks after completing therapy, except in the case of one study where pegylated interferon was used for 48 weeks and off treatment outcomes were not reported [114]. Data extracted included rates of virological and biochemical response, HBeAg loss, HBeAg seroconversion, HBsAg loss, histological improvement and serious adverse events. Virologic response was defined as attainment of undetectable levels of HBV DNA as determined by the PCR test for the particular study. Threshold values for undetectable DNA levels according to method of technique used for measurement were documented as they could be a source of heterogeneity. Only studies where the threshold of detection was ≤1,000 copies/millilitre were used in the analysis of undetectable HBV DNA levels [172]. Biochemical responses were defined as normalization of alanine aminotransferase (ALT) levels to below the upper limit of normal for that study. In HBeAg-positive patients, seroconversion was defined as undetectable HBeAg and presence of anti-HBeAg. HBeAg loss and HBsAg loss were defined as undetectable, using the threshold of detection used in each corresponding study. Histological improvement of the liver was defined as a two point improvement on the Knodell inflammation score without an increase in fibrosis. Treatment safety was assessed using the occurrence of serious adverse events requiring withdrawal from treatment or reduction in treatment dosage.
3.2.5 Data extraction

Two authors independently extracted the data using a standard form. Discrepancies were resolved between the reviewers with the assistance of an arbiter when necessary. The following data were recorded: (i) number of patients in the study, (ii) details of the study design, (iii) treatment doses and duration, (iv) patient characteristics, and v) outcome measures as described above.

3.3 Statistical analysis

There were ten different treatment combinations, and data were available for only thirteen of the 45 possible pairs of comparisons. Standard methods of meta-analysis would give an incomplete picture of the relative benefits of the treatment regimens as they only evaluate two treatments at a time. Therefore, our primary analysis used Bayesian mixed treatment comparisons (MTC). This method can be used to perform direct (head-to-head) comparisons, as well as indirect comparisons of treatments not compared directly within any of the individual trials. The indirect comparison of two treatments requires a common comparator or a link between them by a chain of comparisons. For example, an indirect comparison of treatments A and C can be made if head-to-head data for the comparisons A vs. B and B vs. C are available (Figure 3.1). MTC analysis preserves the within-trial randomized treatment comparisons (e.g., A vs. B and B vs. C); it does not directly compare the single arms A and C, but rather combines all chains of evidence to provide unbiased treatment effect estimates [173, 174].
Figure 3.1 Bayesian mixed treatment comparison method

Abbreviations: T1, trial 1; T2, trial 2; xA, number of responders on treatment A; nA, number of patients on treatment A; xB, number of responders on treatment B; nB, number of patients on treatment B; xC, number of responders on treatment C; nC, number of patients on treatment C; OR, odds ratio; PA, probability of a response from treatment A; PB, probability of response from treatment B; Rx, treatment effect; vs., versus
Lamivudine was used as the common comparator since it is the most commonly used treatment for CHB and the first antiviral oral therapy to be licensed. We ran the MTC model to calculate the odds ratio (OR) comparing each of the treatments. Using the same data, we ran a Bayesian random effects meta-analysis of pairs compared directly in trials. We reported the median of the posterior probability distribution and 95% credible interval (CrI) for each OR. When the OR 95% CrI did not include 1, the OR was considered statistically significantly different from the comparator.

As the predicted probabilities of an outcome with a given treatment are more readily understood than the OR comparing treatments, we used the MTC model to estimate these probabilities. This required that we run in parallel a separate meta-analysis to estimate the probability of an outcome for lamivudine, the baseline comparator. The estimate of the response probability for lamivudine was then combined with the results of the MTC model to obtain the probability of a therapeutic effect for each treatment. The analysis was carried out using a Bayesian random effects logistic model using WinBUGS software Version 1.4.3 [146] (Appendix B). For example, if the probability of a virological response for lamivudine is $P_{\text{lam}}$ and the odds ratio for successful treatment comparing pegylated interferon to lamivudine is $OR_{\text{peg-lam}}$, the estimated probability of a virological response under treatment with pegylated interferon would be:

$$P_{\text{peg}} = OR_{\text{peg-lam}} \times P_{\text{lam}} / [1 + P_{\text{lam}}(OR_{\text{peg-lam}}-1)].$$

To fit the model, we used three sets of starting values sampled from uniform and normal prior distributions and 5000 burn-in iterations. Convergence was assessed using the Gelman-Rubin-Brooke statistic [175]. A further 20,000 Markov Chain Monte Carlo iterations were run and the sampled values were used to estimate posterior means, medians and credible intervals for response probabilities and odds ratios.
The treatments were then ranked for each of the surrogate outcomes on the basis of their predicted probabilities. Since there was some uncertainty in the rankings due to uncertainty in the estimation of the treatment OR, we also present the probability that each treatment was ranked first among the ten treatments. For each surrogate outcome, heterogeneity was assessed through calculation of the between-study standard deviation in log-odds ratios, the range of odds ratios and the median ratio of random pairs of odds ratios [176].

3.4 Search results and study characteristics

3.4.1 Study selection

3,338 potentially eligible citations were identified. After evaluating these citations and their bibliographies, we included 20 trials [114, 116-119, 122-127, 177-184] (FIGURE 3.2); 15 in HBeAg-positive patients, eight in HBeAg-negative patients. Three of these studies evaluated both HBeAg-positive and HBeAg-negative patients.
Figure 3.2 Study selection and disposition.
3.4.2 Characteristics of the studies included in the meta-analysis

Tables 3.1 and 3.2 provide a summary of the characteristics of the 20 studies that met our inclusion criteria. Double blinding was described fully in 12, partially in 2, 4 were open label studies, and two studies did not report blinding. As assessed by the Cochrane Risk of Bias tool, inadequate sequence generation provided the largest risk of bias followed by inadequate allocation concealment (Figure 3.3).

The doses of pegylated interferon varied (100 or 180 µg per week or 1.5 µg/kg per week) while standard doses of lamivudine, adefovir, entecavir, tenofovir were 100 mg, 10 mg, 0.5 mg and 300 mg, respectively. Findings from studies with doses of telbivudine of 400 and 600 mg were pooled together as these doses have been found to be pharmacodynamically equivalent [126].
Figure 3.3  Cochrane risk of bias tool results
3.5 Results of direct and indirect Bayesian meta-analysis in HBeAg-positive patients

3.5.1 Lamivudine

For the treatment of CHB, there were ten trials with 1,540 individuals treated with lamivudine, the common comparator used for our analysis (Table 3.1). In direct comparisons, lamivudine was significantly more effective in inducing ALT normalization (OR=0.11, 95% CrI: 0.03-0.38) and improving liver histology (OR=0.27, 95% CrI: 0.09-0.84) compared to placebo. In indirect comparisons, lamivudine was superior to placebo for all surrogate outcomes except inducing HBsAg loss.
<table>
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<th>Study Design</th>
<th>No.</th>
<th>Medication</th>
<th>Outcomes</th>
</tr>
</thead>
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<td>358</td>
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<td>1998</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>LAM:100mg daily</td>
<td>27/66</td>
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<td></td>
<td></td>
<td></td>
<td>ADV:10mg daily</td>
<td>36/171</td>
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<td></td>
<td></td>
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<tr>
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<td>100</td>
<td>LAM:100mg daily</td>
<td>2/50</td>
</tr>
<tr>
<td>[179]</td>
<td></td>
<td></td>
<td></td>
<td>LAM+PEG: 100mg daily + 1.5µg/kg weekly</td>
<td>5/50</td>
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<td>Janssen,</td>
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<td>LAM+PEG: 100mg daily + 100µg weekly</td>
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<td></td>
<td></td>
<td></td>
<td>LdT: 400/600mg daily</td>
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<td>Design</td>
<td>Follow-up and Withdrawal</td>
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<td>LdT: 600 mg daily</td>
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<td>LdT: 600 mg daily 26/45 35/45 12/45 13/45 0/45</td>
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<td>ETV: 0.5 mg daily 15/21 18/21 3/21</td>
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<td>LdT: 600 mg 67/147 87/147 25/147 31/147 0/147</td>
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<td>Follow-up and withdrawal described</td>
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<td>LAM + ADV: 100 mg + 10 mg daily</td>
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</tbody>
</table>

Abbreviations: PLA, placebo; LAM, lamivudine; PEG, pegylated interferon; LdT, telbivudine; ETV, entecavir; ADV, adefovir; TDF, tenofovir; HBV DNA, undetectable HBV DNA levels; ALT norm, normalization of serum alanine aminotransferase levels; HBeAg sero, hepatitis B e antigen seroconversion; HBeAg loss, hepatitis B e antigen loss; HBsAg loss, hepatitis B surface antigen loss; Histo Improv, histological improvement of the liver

*a In studies with pegylated interferon, partial blinding was used as placebo injections were not administered*
Table 3.2 Randomized Controlled Studies Reporting the Use of Anti-Viral Agents in HBeAg-Negative Patients

<table>
<thead>
<tr>
<th>Source</th>
<th>Duration (wks)</th>
<th>Study Design</th>
<th>No.</th>
<th>Medication</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hadziyannis, [182] 2003</td>
<td>48</td>
<td>Double-blind; follow-up and withdrawal described</td>
<td>185</td>
<td>PLA: daily</td>
<td>0/61</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ADV: 10mg daily</td>
<td>63/123</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ALT norm</td>
<td>84/116</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HBsAg loss</td>
<td>77/121</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Histo Improv</td>
<td></td>
</tr>
<tr>
<td>Marcellin, [116] 2004</td>
<td>48</td>
<td>Partially double-blind; follow-up and withdrawal described</td>
<td>537</td>
<td>LAM: 100mg daily</td>
<td>133/181</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PEG: 180 µg weekly</td>
<td>112/177</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PEG + LAM: 180µg weekly + 100mg daily</td>
<td>156/179</td>
</tr>
<tr>
<td>Lai, [183] 2006</td>
<td>52</td>
<td>Double-blind; follow-up and withdrawal described</td>
<td>648</td>
<td>LAM: 100mg daily</td>
<td>225/313</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ETV: 0.5mg daily</td>
<td>293/325</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ALT norm</td>
<td>253/325</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HBsAg loss</td>
<td>1/325</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Histo Improv</td>
<td>208/296</td>
</tr>
<tr>
<td>Kaymakoglu, [184] 2007</td>
<td>48</td>
<td>Open-label; follow-up and withdrawal described</td>
<td>48</td>
<td>PEG: 1.5µg/kg weekly</td>
<td>5/19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PEG + LAM: 1.5µg/kg weekly + 100mg daily</td>
<td>7/29</td>
</tr>
<tr>
<td>Lai, [117] 2007</td>
<td>52</td>
<td>Double-blind; follow-up and withdrawal described</td>
<td>1370</td>
<td>LAM: 100mg daily</td>
<td>160/224</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LdT: 600mg daily</td>
<td>196/222</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ALT norm</td>
<td>177/224</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HBsAg loss</td>
<td>148/224</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Histo Improv</td>
<td></td>
</tr>
<tr>
<td>Hou, [118] 2008</td>
<td>52</td>
<td>Double-blind; follow-up and withdrawal described</td>
<td>42</td>
<td>LAM: 100 mg</td>
<td>17/22</td>
</tr>
<tr>
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<td></td>
<td>LdT: 600 mg</td>
<td>17/20</td>
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<tr>
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<td></td>
<td></td>
<td>ALT norm</td>
<td>20/20</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>HBsAg loss</td>
<td>20/20</td>
</tr>
<tr>
<td>Marcellin, [121] 2008</td>
<td>48</td>
<td>Double-blind; follow-up and withdrawal described</td>
<td>375</td>
<td>ADV: 10mg daily</td>
<td>79/125</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TDF: 300mg daily</td>
<td>233/250</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ALT norm</td>
<td>91/118</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HBsAg loss</td>
<td>0/125</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Histo Improv</td>
<td>86/125</td>
</tr>
<tr>
<td>Papadopoulos, [187] 2009</td>
<td>48</td>
<td>Blinding unknown; follow-up, withdrawal described</td>
<td>123</td>
<td>PEG: 1.5µg/kg weekly</td>
<td>24/35</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PEG + LAM: 1.5µg/kg weekly + 100mg daily</td>
<td>73/88</td>
</tr>
</tbody>
</table>

**Abbreviations:** PLA, placebo; LAM, lamivudine; PEG, pegylated interferon; LdT, telbivudine; ETV, entecavir; ADV, adefovir; TDF, tenofovir; HBV DNA, undetectable HBV DNA levels; ALT norm, normalization of serum alanine aminotransferase levels; HBsAg loss, hepatitis B surface antigen loss; Histo Improv, histological improvement of the liver

*a* In studies with pegylated interferon, partial blinding was used as placebo injections were not administered
Table 3.3 Odds ratios outcome results of direct and indirect comparisons for HBeAg-Positive patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LAM</th>
<th>PEG</th>
<th>ADV</th>
<th>ETV</th>
<th>LTif</th>
<th>TDF</th>
<th>Placebo</th>
<th>LAM+PEG</th>
<th>LAM+LTif</th>
<th>LAM+ADV</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA</td>
<td>0.53 (0.34-0.95)</td>
<td>0.11 (0.02-0.53)</td>
<td>1.34 (0.62-2.70)</td>
<td>1.26 (0.62-2.36)</td>
<td>1.15 (0.03-35.79)</td>
<td>1.30 (0.12-8.99)</td>
<td>1.54 (1.05-2.26)</td>
<td>7.33 (1.58-87)</td>
<td>3.87 (3.64-4.10)</td>
<td>0.27 (0.09-0.84)</td>
</tr>
<tr>
<td>HBeAg Sero</td>
<td>1.53 (0.84-1.36)</td>
<td>0.87 (0.40-1.83)</td>
<td>0.65 (0.24-1.63)</td>
<td>0.65 (0.19-2.16)</td>
<td>0.58 (0.23-1.40)</td>
<td>0.73 (0.14-36.1)</td>
<td>3.64 (0.91-17.33)</td>
<td>1.35 (0.62-2.16)</td>
<td>0.11 (0.03-0.38)</td>
<td>0.96 (0.12-10.69)</td>
</tr>
<tr>
<td>HBeAg loss</td>
<td>1.50 (0.81-16.66)</td>
<td>1.50 (0.81-16.66)</td>
<td>1.50 (0.81-16.66)</td>
<td>1.50 (0.81-16.66)</td>
<td>1.50 (0.81-16.66)</td>
<td>1.50 (0.81-16.66)</td>
<td>1.50 (0.81-16.66)</td>
<td>1.50 (0.81-16.66)</td>
<td>1.50 (0.81-16.66)</td>
<td>1.50 (0.81-16.66)</td>
</tr>
<tr>
<td>HbsAg loss</td>
<td>3.01 (0.63-14.48)</td>
<td>3.01 (0.63-14.48)</td>
<td>3.01 (0.63-14.48)</td>
<td>3.01 (0.63-14.48)</td>
<td>3.01 (0.63-14.48)</td>
<td>3.01 (0.63-14.48)</td>
<td>3.01 (0.63-14.48)</td>
<td>3.01 (0.63-14.48)</td>
<td>3.01 (0.63-14.48)</td>
<td>3.01 (0.63-14.48)</td>
</tr>
<tr>
<td>Histo Improv</td>
<td>1.56 (1.12-2.19)</td>
<td>1.56 (1.12-2.19)</td>
<td>1.56 (1.12-2.19)</td>
<td>1.56 (1.12-2.19)</td>
<td>1.56 (1.12-2.19)</td>
<td>1.56 (1.12-2.19)</td>
<td>1.56 (1.12-2.19)</td>
<td>1.56 (1.12-2.19)</td>
<td>1.56 (1.12-2.19)</td>
<td>1.56 (1.12-2.19)</td>
</tr>
</tbody>
</table>
| Abbreviations: OR, median odds ratio; 95% CrI, 95% credible interval; PLA, placebo; LAM, lamivudine; PEG, pegylated interferon; LdT, telbivudine; ETV, entecavir; ADV, adefovir; TDF, tenofovir; HBV DNA, undetectable HBV DNA levels; ALT norm, normalization of serum alanine aminotransferase levels; HBeAg sero, hepatitis B e antigen seroconversion; HBeAg loss, hepatitis B e antigen loss; HBsAg loss, hepatitis B surface antigen loss; Histo Improv, histological improvement of the liver.

Note: Direct comparisons values are above the diagonal while indirect comparison values are below the diagonal. For values above the diagonal, values above 1 reflect increased efficacy by the treatment specified in the first column. For values below the diagonal, values above 1 reflect an increased efficacy by the treatment specified in the first column.

Bolded numbers denote statistical significant difference in efficacy of one treatment.
<table>
<thead>
<tr>
<th>Rank</th>
<th>Treatment</th>
<th>% Best</th>
<th>(95% CrI)</th>
<th>Treatment</th>
<th>% Best</th>
<th>(95% CrI)</th>
<th>Treatment</th>
<th>% Best</th>
<th>(95% CrI)</th>
<th>Treatment</th>
<th>% Best</th>
<th>(95% CrI)</th>
<th>Treatment</th>
<th>% Best</th>
<th>(95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TDF</td>
<td>98.9</td>
<td>(0.69-0.97)</td>
<td>TDF</td>
<td>39.02</td>
<td>(0.41-0.91)</td>
<td>TDF</td>
<td>25.65</td>
<td>(0.07-0.43)</td>
<td>LAM+PEG</td>
<td>52.20</td>
<td>(0.10-0.63)</td>
<td>TDF</td>
<td>47.90</td>
<td>(0.05-0.54)</td>
</tr>
<tr>
<td>2</td>
<td>ETV</td>
<td>0.79</td>
<td>(0.36-0.80)</td>
<td>ETV</td>
<td>28.94</td>
<td>0.70</td>
<td>PEG</td>
<td>24.75</td>
<td>0.23</td>
<td>LdT</td>
<td>19.56</td>
<td>0.34</td>
<td>LAM+PEG</td>
<td>13.87</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>LAM+PEG</td>
<td>0.20</td>
<td>(0.34-0.77)</td>
<td>LAM+PEG</td>
<td>23.15</td>
<td>0.64</td>
<td>LAM+PEG</td>
<td>23.15</td>
<td>0.23</td>
<td>PEG</td>
<td>9.68</td>
<td>0.33</td>
<td>ETV</td>
<td>12.87</td>
<td>0.01</td>
</tr>
<tr>
<td>4</td>
<td>LdT</td>
<td>0.00</td>
<td>(0.30-0.70)</td>
<td>LdT</td>
<td>5.99</td>
<td>0.65</td>
<td>LdT</td>
<td>12.28</td>
<td>0.21</td>
<td>ADV</td>
<td>7.28</td>
<td>0.28</td>
<td>PEG</td>
<td>10.38</td>
<td>0.01</td>
</tr>
<tr>
<td>5</td>
<td>LAM+LdT</td>
<td>0.00</td>
<td>(0.17-0.73)</td>
<td>LAM+LdT</td>
<td>1.20</td>
<td>0.54</td>
<td>ETV</td>
<td>6.29</td>
<td>0.19</td>
<td>ETV</td>
<td>6.49</td>
<td>0.28</td>
<td>LAM+LdT</td>
<td>5.69</td>
<td>0.01</td>
</tr>
<tr>
<td>6</td>
<td>ADV</td>
<td>0.00</td>
<td>(0.11-0.66)</td>
<td>ADV</td>
<td>0.70</td>
<td>0.58</td>
<td>LAM+ADV</td>
<td>3.09</td>
<td>0.12</td>
<td>LAM+LdT</td>
<td>2.69</td>
<td>0.19</td>
<td>ADV</td>
<td>5.09</td>
<td>0.02</td>
</tr>
<tr>
<td>7</td>
<td>LAM</td>
<td>0.00</td>
<td>(0.16-0.48)</td>
<td>LAM+ADV</td>
<td>0.50</td>
<td>0.39</td>
<td>LAM+LdT</td>
<td>2.70</td>
<td>0.11</td>
<td>LAM+ADV</td>
<td>1.78</td>
<td>0.17</td>
<td>LAM</td>
<td>2.70</td>
<td>0.00</td>
</tr>
<tr>
<td>8</td>
<td>LAM+ADV</td>
<td>0.00</td>
<td>(0.10-0.36)</td>
<td>LAM+ADV</td>
<td>0.20</td>
<td>0.61</td>
<td>ADV</td>
<td>1.90</td>
<td>0.33</td>
<td>LAM</td>
<td>0.04</td>
<td>0.28</td>
<td>LAM</td>
<td>0.90</td>
<td>0.00</td>
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<tr>
<td>9</td>
<td>PEG</td>
<td>0.00</td>
<td>(0.09-0.36)</td>
<td>PEG</td>
<td>0.00</td>
<td>0.39</td>
<td>LAM</td>
<td>0.00</td>
<td>0.18</td>
<td>PLA</td>
<td>0.00</td>
<td>0.11</td>
<td>LdT</td>
<td>0.60</td>
<td>0.00</td>
</tr>
<tr>
<td>10</td>
<td>PLA</td>
<td>0.00</td>
<td>(0.00-0.04)</td>
<td>PLA</td>
<td>0.00</td>
<td>0.20</td>
<td>PLA</td>
<td>0.00</td>
<td>0.06</td>
<td>PLA</td>
<td>0.00</td>
<td>0.06</td>
<td>PLA</td>
<td>0.00</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Abbreviations: PLA, placebo; LAM, lamivudine; PEG, pegylated interferon; LdT, telbivudine; ETV, entecavir; ADV, adefovir; TDF, tenofovir; HBV DNA, undetectable HBV DNA levels; ALT norm, normalization of serum alanine aminotransferase levels; HBeAg sero, hepatitis B e antigen seroconversion; HBeAg loss, hepatitis B e antigen loss; HBsAg loss, hepatitis B surface antigen loss; Histol Improv, histological improvement of the liver; 95% CrI, 95% credible interval

* Percentage of iterations for which the treatment is ranked first

* Posterior probability of an outcome
3.5.2 Pegylated interferon

Pegylated interferon (n=407) was evaluated as monotherapy in two trials. Studies of standard interferon were omitted as they are no longer considered by most as the standard of care. Direct comparisons suggested that it is significantly more effective than lamivudine monotherapy in inducing decreases in HBeAg loss and HBsAg loss. Pegylated interferon ranked among the top four treatments for HBeAg seroconversion (predicted probability (PP)=0.23, 95% CrI: 0.14-0.35), HBeAg loss (PP=0.33, 95% CrI: 0.15-0.54), HBsAg loss (PP=0.01, 95% CrI: 0-0.07) and histological improvement of the liver (PP=0.52, 95% CrI: 0.06-0.95) (Table 3.3).

3.5.3 Adefovir

Adefovir (n=337) was evaluated in four trials and was not significantly better than lamivudine. Adefovir did not rank above fourth place for any outcome.

3.5.4 Entecavir

Entecavir (n=408) was a comparator in three trials. In direct comparisons, it had increased efficacy in comparison to lamivudine in improving liver histology (OR=1.56, 95% CrI: 1.12-2.19). Entecavir consistently ranked in the top five treatments for all surrogate outcomes and was ranked first with regard to improving liver histology (PP=0.56, 95% CrI: 0.12-0.94).

3.5.5 Telbivudine

Telbivudine (n=684) was a comparator in four trials. In direct comparisons, it had improved efficacy compared to lamivudine in inducing undetectable HBV DNA (OR=2.34,
95% CrI: 1.31-5.36) and histological improvement of the liver (OR=1.41, 95% CrI: 1.09-1.84). Indirect comparisons confirmed the results of the direct comparison of HBV DNA undetectability. Telbivudine’s rankings ranged from second for HBeAg loss to last for HBsAg loss.

3.5.6 Tenofovir

Tenofovir (n=176) was a comparator in one study. In indirect comparisons, tenofovir demonstrated improved efficacy compared to lamivudine in inducing undetectable HBV DNA levels (OR=23.34, 95% CrI: 6.19-76.39). Tenofovir was consistently ranked in the top three treatments for all surrogate outcomes except HBeAg loss where no data were available. It was ranked first for inducing undetectable HBV DNA (PP=0.88, 95% CrI: 0.69-0.97) normalization of ALT levels (PP=0.66, 95% CrI: 0.41-0.91), HBeAg serconversion (PP=0.20, 95% CrI: 0.07-0.43) and HBsAg loss (PP=0.05, 95% CrI: 0-0.54).

3.5.7 Combination therapy

Three combination strategies were assessed in this analysis, lamivudine plus pegylated interferon (n=451), lamivudine plus telbivudine (n=41) and lamivudine plus adefovir (n=53). In indirect comparisons, lamivudine plus pegylated interferon was more effective in inducing undetectable HBV DNA than to lamivudine alone (OR=3.08, 95% CrI: 1.88-4.91). In overall rankings, this combination was first in inducing HBeAg loss (PP=0.39, 95% CrI: 0.18-0.63) and third for HBeAg seroconversion and second for HBsAg loss. In neither direct nor indirect comparisons were significant improvements found with combination therapy of two oral therapies (i.e., lamivudine plus telbivudine or lamivudine plus adefovir) relative to lamivudine monotherapy.

The all oral antiviral combinations of lamivudine plus telbivudine and lamivudine plus adefovir were ranked low in comparison to other therapies.
The between-study standard deviations of log-odds ratios for the surrogate outcomes, undetectable HBV DNA, ALT normalization, HBeAg seroconversion, HBeAg loss, HBsAg loss and histological improvement had posterior medians of 0.14, 0.29, 0.16, 0.27, 0.58 and 0.30 respectively, Table 3.7.

For all but HBsAg loss, the degree of heterogeneity was considered reasonable [176].

3.6 Results of direct and indirect Bayesian meta-analysis in HBeAg-negative patients

3.6.1 Lamivudine

In indirect comparisons, lamivudine (n=740) was more effective in comparison to placebo in inducing undetectable HBV DNA levels (Table 3.5). In comparison with other treatments, it was ranked in the bottom two treatments for all outcomes measured (Table 3.6).
Table 3.5 Odds ratios outcome results of direct and indirect comparisons for Chronic HBsAg-Negative patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LAM</th>
<th>PEG</th>
<th>ADV</th>
<th>ETV</th>
<th>LdT</th>
<th>TDF</th>
<th>Placebo</th>
<th>LAM + PEG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>(95% CrI)</td>
<td>OR</td>
<td>(95% CrI)</td>
<td>OR</td>
<td>(95% CrI)</td>
<td>OR</td>
<td>(95% CrI)</td>
</tr>
<tr>
<td>LAM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV DNA</td>
<td>0.62</td>
<td>(0.40-0.98)</td>
<td>3.53</td>
<td>(2.30-5.55)</td>
<td>2.75</td>
<td>(1.65-9.60)</td>
<td>0.35</td>
<td>(0.23-0.55)</td>
</tr>
<tr>
<td>ALT norm</td>
<td>0.23</td>
<td>(0.15-0.35)</td>
<td>1.44</td>
<td>(1.00-2.06)</td>
<td>2.14</td>
<td>(0.30-5.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histo Improv</td>
<td></td>
<td></td>
<td>1.53</td>
<td>(1.09-2.16)</td>
<td>1.03</td>
<td>(0.70-1.52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG</td>
<td>0.77</td>
<td>(0.33-2.74)</td>
<td>5.42</td>
<td>(0.11-231)</td>
<td>7.75</td>
<td>(0.56-1.61)</td>
<td>0.01</td>
<td>(0.00-0.06)</td>
</tr>
<tr>
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<td>(0.04-2.28)</td>
<td>7.63</td>
<td>(0.10-507)</td>
<td>1.19</td>
<td>(0.09-2.13)</td>
<td></td>
<td>(0.08-0.31)</td>
</tr>
<tr>
<td>ALT norm</td>
<td></td>
<td></td>
<td>5.74</td>
<td>(0.28-101)</td>
<td>4.31</td>
<td>(0.74-19.38)</td>
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</tr>
<tr>
<td>Histo Improv</td>
<td>1.63</td>
<td>(0.07-26.42)</td>
<td>0.78</td>
<td>(0.01-39.51)</td>
<td>1.03</td>
<td>(0.01-23.19)</td>
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<tr>
<td>ADV</td>
<td>4.38</td>
<td>(0.10-171)</td>
<td>4.45</td>
<td>(0.52-20.03)</td>
<td>0.35</td>
<td>(0.01-17.98)</td>
<td>0.47</td>
<td>(0.02-11.88)</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>1.84</td>
<td>(0.04-94.89)</td>
<td>5.74</td>
<td>(0.28-101)</td>
<td>0.81</td>
<td>(0.12-4.82)</td>
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<td>(0.02-4.85)</td>
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<tr>
<td>ALT norm</td>
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<td>(0.04-2.28)</td>
<td>0.78</td>
<td>(0.01-39.51)</td>
<td>2.76</td>
<td>(0.01-39.51)</td>
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<td>(0.02-3.28)</td>
</tr>
<tr>
<td>Histo Improv</td>
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<td>(0.07-26.42)</td>
<td>0.9</td>
<td>(0.05-20.51)</td>
<td>1.19</td>
<td>(0.09-507)</td>
<td></td>
<td>(0.08-0.31)</td>
</tr>
<tr>
<td>ETV</td>
<td>3.37</td>
<td>(0.74-12.90)</td>
<td>3.51</td>
<td>(0.64-142)</td>
<td>0.81</td>
<td>(0.12-4.82)</td>
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<td>(0.02-4.85)</td>
</tr>
<tr>
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<td>(0.16-12.76)</td>
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<td>(0.28-101)</td>
<td>2.94</td>
<td>(0.01-39.51)</td>
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<td>5.74</td>
<td>(0.01-39.51)</td>
<td></td>
<td>(0.02-3.28)</td>
</tr>
<tr>
<td>Histo Improv</td>
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<td></td>
<td>0.9</td>
<td>(0.05-20.51)</td>
<td>1.44</td>
<td>(0.01-39.51)</td>
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<td>(0.02-3.28)</td>
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<td>LdT</td>
<td>2.68</td>
<td>(0.83-7.75)</td>
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<td>(0.64-142)</td>
<td>0.81</td>
<td>(0.12-4.82)</td>
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<td>(0.02-4.85)</td>
</tr>
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<td>HBV DNA</td>
<td>1.64</td>
<td>(0.32-19.63)</td>
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<td>(0.28-101)</td>
<td>2.94</td>
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<td>(0.02-3.28)</td>
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<td>ALT norm</td>
<td>1.04</td>
<td>(0.18-6.83)</td>
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<td>(0.01-39.51)</td>
<td>5.74</td>
<td>(0.01-39.51)</td>
<td></td>
<td>(0.02-3.28)</td>
</tr>
<tr>
<td>Histo Improv</td>
<td></td>
<td></td>
<td>0.9</td>
<td>(0.05-20.51)</td>
<td>1.44</td>
<td>(0.01-39.51)</td>
<td></td>
<td>(0.02-3.28)</td>
</tr>
<tr>
<td>TDF</td>
<td>29.40</td>
<td>(0.69-1407)</td>
<td>36.38</td>
<td>(0.73-1850)</td>
<td>9.47</td>
<td>(0.15-475)</td>
<td></td>
<td>(0.02-4.85)</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>1.55</td>
<td>(0.03-94.68)</td>
<td>6.30</td>
<td>(0.05-515)</td>
<td>1.08</td>
<td>(0.01-88.49)</td>
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<td>ALT norm</td>
<td>1.93</td>
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<td>0.88</td>
<td>(0.08-9.07)</td>
<td>2.86</td>
<td>(0.04-28.45)</td>
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<td>(0.02-4.85)</td>
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<td>Histo Improv</td>
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<td></td>
<td>1.19</td>
<td>(0.09-19.27)</td>
<td>1.28</td>
<td>(0.04-28.45)</td>
<td></td>
<td>(0.02-4.85)</td>
</tr>
<tr>
<td>Placebo</td>
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<td>(0.00-0.89)</td>
<td>0.02</td>
<td>(0.00-0.92)</td>
<td>0.01</td>
<td>(0.00-0.89)</td>
<td>0.01</td>
<td>(0.00-0.89)</td>
</tr>
<tr>
<td>HBV DNA</td>
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<td>(0.01-18.45)</td>
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<td>(0.02-102)</td>
<td>0.22</td>
<td>(0.00-2.20)</td>
<td>0.01</td>
<td>(0.00-0.89)</td>
</tr>
<tr>
<td>ALT norm</td>
<td>0.47</td>
<td>(0.02-11.80)</td>
<td>0.29</td>
<td>(0.02-4.85)</td>
<td>0.22</td>
<td>(0.00-2.20)</td>
<td>0.01</td>
<td>(0.00-0.89)</td>
</tr>
<tr>
<td>Histo Improv</td>
<td></td>
<td></td>
<td>0.36</td>
<td>(0.01-7.37)</td>
<td>0.36</td>
<td>(0.01-7.37)</td>
<td>0.01</td>
<td>(0.00-0.89)</td>
</tr>
<tr>
<td>LAM + PEG</td>
<td>1.01</td>
<td>(0.61-1.58)</td>
<td>2.38</td>
<td>(0.70-5.28)</td>
<td>0.42</td>
<td>(0.01-17.98)</td>
<td>0.06</td>
<td>(0.00-3.00)</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>0.38</td>
<td>(0.06-2.85)</td>
<td>1.50</td>
<td>(0.19-1258)</td>
<td>0.22</td>
<td>(0.01-15.12)</td>
<td>0.28</td>
<td>(0.02-22.54)</td>
</tr>
<tr>
<td>ALT norm</td>
<td></td>
<td></td>
<td>0.53</td>
<td>(0.01-4.67)</td>
<td>0.68</td>
<td>(0.01-13.19)</td>
<td>0.28</td>
<td>(0.02-22.54)</td>
</tr>
<tr>
<td>Histo Improv</td>
<td>0.27</td>
<td>(0.01-4.67)</td>
<td>0.24</td>
<td>(0.01-2.46)</td>
<td>0.28</td>
<td>(0.02-22.54)</td>
<td>1.24</td>
<td>(0.01-107)</td>
</tr>
</tbody>
</table>

**Abbreviations:** OR, median odds ratio; 95% CrI, 95% credible interval; PLA, placebo; LAM, lamivudine; PEG, pegylated interferon; LdT, telbivudine; ETV, entecavir; ADV, adefovir; TDF, tenofovir; HBV DNA, undetectable HBV DNA levels; ALT norm, normalization of serum alanine aminotransferase levels; HBsAg sero, hepatitis B e antigen seroconversion; HBsAg loss, hepatitis B e antigen loss; HBsAg loss, hepatitis B surface antigen loss; Histo Improv, histological improvement of the liver

**Note:** Direct comparisons values are above the diagonal while indirect comparison values are below the diagonal. For values above the diagonal, values above 1 reflect increased efficacy by the treatment specified in the top row. For values below the diagonal, values above 1 reflect increased efficacy by the treatment specified in the first column.

**Bolded numbers denote statistical significant difference in efficacy of one treatment.**
Table 3.6 Rank order of treatments for 3 outcomes for HBeAg-Negative Patients

<table>
<thead>
<tr>
<th>Rank</th>
<th>Treatment</th>
<th>Outcomes 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Outcomes 2&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Outcomes 3&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBV DNA</td>
<td>ALT norm</td>
<td>Histo Improv</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>TDF</td>
<td>81.04 (0.56-1.00)</td>
<td>27.25 (0.47-0.99)</td>
<td>33.43 (0.01-1.00)</td>
</tr>
<tr>
<td>2</td>
<td>ETV</td>
<td>11.08 (0.65-0.97)</td>
<td>23.55 (0.07-1.00)</td>
<td>23.15 (0.01-1.00)</td>
</tr>
<tr>
<td>3</td>
<td>LdT</td>
<td>6.59 (0.67-0.96)</td>
<td>22.55 (0.11-1.00)</td>
<td>20.46 (0.01-1.00)</td>
</tr>
<tr>
<td>4</td>
<td>LAM+PEG</td>
<td>0.70 (0.56-0.93)</td>
<td>20.96 (0.25-0.98)</td>
<td>14.77 (0.00-1.00)</td>
</tr>
<tr>
<td>5</td>
<td>ADV</td>
<td>0.50 (0.15-1.00)</td>
<td>1.99 (0.15-0.93)</td>
<td>5.09 (0.00-1.00)</td>
</tr>
<tr>
<td>6</td>
<td>PEG</td>
<td>0.00 (0.41-0.89)</td>
<td>1.70 (0.02-0.98)</td>
<td>3.09 (0.01-1.00)</td>
</tr>
<tr>
<td>7</td>
<td>LAM</td>
<td>0.00 (0.65-0.81)</td>
<td>1.40 (0.54-0.89)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>PLA</td>
<td>0.00 (0.00-0.71)</td>
<td>0.60 (0.09-0.89)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PLA, placebo; LAM, lamivudine; PEG, pegylated interferon; LdT, telbivudine; ETV, entecavir; ADV, adefovir; TDF, tenofovir; HBV DNA, undetectable HBV DNA levels; ALT norm, normalization of serum alanine aminotransferase levels; Histo Improv, histological improvement of the liver; 95%CrI, 95% credible interval

<sup>a</sup> Percentage of iterations for which the treatment is ranked first

<sup>b</sup> Posterior probability of an outcome

Note: No post pegylated interferon liver biopsies were performed as the effect may continue to change following discontinuation since interferon is both an antiviral and an immune stimulant.
3.6.2 Monotherapies

In direct comparisons, pegylated interferon was less effective than lamivudine in inducing undetectable HBV DNA levels and ALT normalization one year following the initiation of therapy. In pair-wise comparisons to lamivudine, neither adefovir, telbivudine nor tenofovir were more efficacious. However, treatment with entecavir was more efficacious for all outcomes. Entecavir was ranked among the top four treatments for all outcomes, HBV DNA (PP=0.88, 95% CrI: 0.65-0.97), ALT normalization (PP=0.76, 95% CrI: 0.25-0.98) and histological improvement (PP=0.64, 95% CrI: 0.01-1.00). Tenofovir ranked first for HBV DNA suppression (PP=0.94, 95% CrI: 0.56-1.00) and histological improvement (PP=0.65, 95% CrI: 0.01-1.00) and second for ALT normalization (PP=0.73, 95% CrI: 0.07-1.00).

3.6.3 Combination therapy

Lamivudine plus pegylated interferon (n=296) was more effective than lamivudine alone in inducing HBV DNA levels (OR=2.40, 95% CrI: 1.41-4.19). However, it was less effective in inducing ALT normalization (OR=0.35, 95% CrI: 0.23-0.55) at one year.

The standard deviation for the surrogate outcomes, undetectable HBV DNA, ALT normalization and histological improvement were 0.48, 0.83 and 0.48, respectively (Table 3.7).
<table>
<thead>
<tr>
<th></th>
<th>HBV DNA</th>
<th>ALT norm</th>
<th>HBeAg sero</th>
<th>HBeAg loss</th>
<th>HBsAg loss</th>
<th>Histo improv</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg-positive patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>0.1399</td>
<td>0.278</td>
<td>0.1647</td>
<td>0.2667</td>
<td>0.5827</td>
<td>0.2988</td>
</tr>
<tr>
<td>exp(3.92sd)</td>
<td>1.73</td>
<td>2.97</td>
<td>1.91</td>
<td>2.84</td>
<td>9.82</td>
<td>3.23</td>
</tr>
<tr>
<td>exp(1.09sd)</td>
<td>1.16</td>
<td>1.35</td>
<td>1.20</td>
<td>1.34</td>
<td>1.89</td>
<td>1.38</td>
</tr>
<tr>
<td><strong>HBeAg-negative patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>0.48</td>
<td>0.83</td>
<td></td>
<td></td>
<td></td>
<td>0.49</td>
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<tr>
<td>exp(3.92sd)</td>
<td>6.53</td>
<td>25.48</td>
<td></td>
<td></td>
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<td>6.71</td>
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<tr>
<td>exp(1.09sd)</td>
<td>1.68</td>
<td>2.46</td>
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<td></td>
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<td>1.70</td>
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</table>

Abbreviations: HBV DNA, undetectable HBV DNA levels; ALT norm, normalization of serum alanine aminotransferase levels; HBeAg sero, hepatitis B e antigen seroconversion; HBeAg loss, hepatitis B e antigen loss; HBsAg loss, hepatitis B surface antigen loss; Histo improv, histological improvement of the liver; exp(3.92sd), standard deviation range of odds ratio at two standard deviations; exp(1.09sd), median ratio of a random pair of odds ratios.

Note: Values of SD from 0.1 to 0.5 appear reasonable, from 0.5-1.0 are considered fairly high and above 1.0 represent extreme heterogeneity.[176]
3.7 Severe adverse events from treatment

Severe adverse events were inconsistently documented and had varied definitions for each study which prevented quantitative analysis. The greatest number of events occurred with monotherapy and combination therapies involving pegylated interferon [123, 179]. Most events resolved following a decrease in dosage of pegylated interferon, withholding of dosages for a short period of time or termination of therapy [179].

Depression was reported as the main concern in patients treated with pegylated interferon [114, 116]. The rate of depression on pegylated interferon therapy was 5%; combination therapy of lamivudine plus pegylated interferon was associated with similar rates (6-7%) [114, 116]. The reported average rates of discontinuation of therapy were: pegylated interferon, <5%; lamivudine, 2.8%; adefovir, 1.0%; entecavir, 1.8%; and tenofovir 1.0% respectively. The most common adverse events reported while on treatment with oral antivirals were: headache, upper respiratory infection, nasopharyngitis, cough, fatigue, upper abdominal pain, back pain and diarrhea, most of which were mild-to-moderate in severity as reported by each of the studies [121, 178, 180, 181, 185]. There was inconsistent documentation for those following discontinuation of therapy. All treatments caused low rates of grade 3 or 4 changes in clinical laboratory values of liver tests (serum ALT, creatine kinase) and the rates were similar for each treatment [118, 121, 185]. The rates of hepatic flares on therapy were as follows: lamivudine (4% [181]), pegylated interferon (8% [116]), adefovir (2% [116]), entecavir (1% [183]), telbivudine (1% [121]), tenofovir (6% [121]) and combination therapy with lamivudine plus adefovir (7% [181]).

3.8 Major findings of a meta-analysis of treatments for chronic hepatitis B

Many new antiviral treatments for CHB have become available within the last two decades. The first drug approved was interferon, an immune modulator and antiviral. Following its
inception, there has been a shift towards focusing on oral antiviral drugs, nucleos(t)ide analogues. RCTs comparing these treatments have been limited to comparing 2-3 drugs or drug combinations at a time while traditional meta-analytic techniques are limited to comparing two interventions. This has left clinicians to make their own judgments about the relative efficacy of treatments where head-to-head trials are not available.

In our study, we utilized Bayesian MTC to evaluate the relative efficacy of all available treatments across six surrogate clinical outcomes. We consolidated the information of all RCTs that included the treatments of interest to provide, for the first time, the probability of an outcome at the end of one year of treatment as well as a rank for all treatments. The results of our analysis suggest that in treatment naïve individuals, entecavir and tenofovir are most effective at the end of the first year of therapy in HBeAg-positive patients while tenofovir is most effective in HBeAg-negative patients based on an overall assessment of all surrogates outcomes.

Our study focused on assessing surrogate clinical outcomes at the end of the first year of treatment. In recent years, there has been a shift towards evaluating outcomes that will reflect long-term improvements in the prognosis of those with CHB. Two authors (Fattovich [188] and Hui [189]) have suggested that loss of HBsAg is the optimal goal of treatment and is the only surrogate marker of successful immunological control and is associated with lower incidence of cirrhosis and HCC and improved survival rates. Loss of HBsAg was not seen in those on oral antiviral treatment for one year but in some patients who received pegylated interferon at one year following the initiation of treatment in the studies we reviewed. Though useful as an initial comparison of the various drugs, the utility of this review is limited for standard clinical practice where the nucleos(t)ide analogue polymerase inhibitors are rarely used for just one year. Rather, long term, perhaps life-long, suppressive therapy may be required. Important treatment issues such as long term drug cost and drug toxicity, treatment failure due to inadequate patient
adherence and/or drug resistance have not been addressed. Finally, the change in biomarker status examined in this review, such as loss of HBeAg or suppression of HBV DNA to undetectable levels, were determined while continuing antiviral therapy and the durability of this response on stopping therapy is not well known, particularly for the newer agents, tenofovir and entecavir.

3.9 Limitations of the meta-analysis

This study had limitations. First, the number of studies included for each pairwise comparison was small. There was only one study evaluating the efficacy of tenofovir, one of the recommended treatments. The quality of reporting for this study was optimal however the power of the comparison was limited as expressed in the wide credible intervals. Our review was also limited to fully published studies in the English language. A number of clinical studies of CHB have been conducted in non-English speaking countries.

Other limitations include variation in definitions, measurements, patient characteristics and protocols across studies and the quality of reported data. For example, the threshold values for undetectable HBV DNA varied significantly thus earlier studies with higher thresholds tended to have higher proportions of subjects with undetectable HBV DNA. There were too few studies with any given threshold value to determine its effect on the OR for each pairwise comparison; any variation in treatment effect due to the threshold became part of the random between-study variance. We chose a threshold of (<1000 copies/ml) as studies have shown that for treatment with lamivudine, telbivudine and adefovir, subsequent resistance is low for those whose viral load is maintained below 1000 copies/mL [190]. In addition, the error of the diagnostic test is approximately 0.5 log copies so that a viral load of 300 to 1000 copies/mL is within the error of the test and the majority of studies that used PCR to detect HBV DNA levels were below that of 1000 copies/mL.
This study offers some insight into the relative benefits of current drugs at one year. Because many of these treatments will be taken for much longer perhaps for a lifetime, these data are not sufficient to definitively resolve the question of optimal treatment choice. Although hard outcomes such as HCC, liver failure and death are the most important clinical end points, these are rare events when observation times are only 1-2 years. There is presently no consensus regarding the most appropriate surrogate markers of a long-term outcome or even the validity of ‘on treatment’ measurements.

### 3.10 Clinical controversies

The controversy about which drug to use is dwarfed by the controversy about who should be treated. Patients with cirrhosis and ongoing viral replication appear to benefit from treatment in terms of rate of progression of liver disease. The only randomized trial conducted in patients with advanced liver disease was stopped prematurely because of a dramatic reduction in rates of liver failure and liver cancer [191]. Any potential long term benefits of treatment are unclear among patients with earlier stage disease.

Chronic infection with hepatitis B occurs predominantly in those who acquired infection as a neonate or young infant. Neonatal infection induces an early immune tolerant phase of the disease. Only when the infected individual enters the phase of active HBeAg-positive hepatitis is loss of HBeAg and seroconversion to anti-HBe possible reducing the risk of developing significant chronic liver disease [189]. This seroconversion when followed by sustained immune control has been shown, in recent publications of such individuals followed for a 20-30 year period, to have a 50% chance of spontaneously losing HBsAg. Those who lose HBsAg before the age of 50 years have a reduced likelihood of HCC [192]. On the other hand, individuals with HBeAg-positive hepatitis who fail to seroconvert within 3-6 months or who subsequently develop HBeAg-negative hepatitis may warrant lifelong antiviral therapy because they are at the greatest risk of progressive liver disease and HCC.
An impetus toward earlier treatment has been provided by the “REVEAL” study. This large, population-based study from Taiwan which recruited men over the age of 30 years showed that elevation of HBV DNA was associated with a high nine-year risk of hepatoma [61]. In this study, liver biopsy data were not available at baseline, so cirrhosis may have been present in some patients. This study also noted that the risk of HCC was greatest in those who were older and who remained HBeAg-positive. The generalizability of this study’s findings to females and to young persons who are often in the immune tolerant phase is lacking. Nevertheless the REVEAL study indicates that prolonged viral replication in men approaching middle age with evidence of ongoing liver injury are at risk of liver cancer. It is unknown whether prolonged drug induced viral suppression reduces this risk.

Finally, we do not know when and if it is appropriate to stop antiviral therapy once started if the individual has not undergone HBeAg loss or seroconversion for HBeAg-positive hepatitis. We only know that individuals who spontaneously achieve sustained immune control and who lose HBsAg (particularly if this occurs under the age of 50 years), do secure a better chance of survival. Because treatment may continue for many years, the potential benefits of antiviral therapy on liver-related morbidity and mortality must be carefully weighed against the possibility of future drug resistance, high lifetime costs, and adverse effects.

3.11 Conclusions

This systematic review and Bayesian MTC analysis shows that for patients with HBeAg-positive CHB, entecavir and tenofovir are the most effective treatments while for HBeAg-negative patients, tenofovir is the most effective treatment as measured by our defined surrogate clinical outcomes.
CHAPTER 4

PATIENT PREFERENCES AND UTILITIES

The objectives of this chapter are to:

1. Provide an overview of the study methods

2. To described the patient sample recruited for the utility study

3. Detail the statistical methods used to examine patient preferences and utilities

4. Present the sociodemographic features of the patient population enrolled in the utility study

5. Present results of HRQOL scores from the Short Form 36 version 2

6. Present results of direct and indirect utility measurements

7. Provide the predictors of utility and HRQOL in patients with hepatitis B

8. Compare the results derived from different measurement tools

9. Compare the quality of life of patients with hepatitis B to quality of life scores reported by patients with hepatitis C

10. Discuss the main findings of the study

11. Outline the study’s limitations

12. State the conclusions of the study and outline directions for future research
4.1 Overview of study methodology

In this study five independent quality of life measurement tools were applied to examine patient preferences and utilities in individuals with chronic hepatitis B and related health states. Patient charts were used to identify individuals who had previously attended tertiary care liver clinics due to infection with hepatitis B. The disease of the patients was stratified by disease stages: non-cirrhotic chronic hepatitis B, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and post-liver transplantation. The Short Form 36 version 2, EQ5D, visual analogue scale, Health Utility Index Mark 3 and the standard gamble were used to obtain quality of life measurements from these patients. We used multiple instruments as previous studies using one or two instruments have provided conflicting results. Furthermore, an identical study was previously performed in patients with hepatitis C attending the same clinics. The current study population was compared to the study of patients with hepatitis C to determine the differences in quality of life of patients with hepatitis B to patients with hepatitis C.

The goals of this study were:

1. To determine the health related quality of life scores for patients with chronic hepatitis B.

2. To assess the quality of life scores of patients in different stages of chronic hepatitis B.

3. To compare the quality of life scores of patients with hepatitis B to the general Canadian population.

4. To compare the quality of life scores of patients with chronic hepatitis B to quality of life scores from patients with chronic hepatitis C.

5. To determine if patients on or off oral antiviral treatment have different health related quality of life scores in patients with chronic hepatitis B.
4.2 Patient population of hepatitis B utility study

4.2.1 Patient sample and setting

Consecutive patients with hepatitis B related illness attending liver clinics between the dates of July 2, 2007 and March 11, 2009 were included in the study. Patients were recruited from liver clinics at the Toronto General Hospital, Toronto Western Hospital, Princess Margaret Hospital and the liver transplant clinic at the Toronto General Hospital. These hospitals make up the University Health Network, a tertiary care referral center in Toronto, ON Canada. Included were consecutive outpatients who: i) had documented HBV infection; ii) were age ≥16 years; and iii) were fluent in either in English, Cantonese or Mandarin. This study was approved by the University Health Network Research Ethics Board, Toronto, ON and the University of Toronto Research Ethics Board. Copies of the ethics approvals appear in Appendix C. As well, all patients were required to provide written informed consent (Appendix D). Copies of the instruments used appear in Appendix E. Each of the forms was translated into Cantonese and Mandarin and verified using University Health Network’s translation services.

4.2.2 Patient preferences and utility tools

Once written consent was obtained, patients with CHB attending the clinics were provided a booklet of the non-preference based instruments (SF36v2) and preference based instruments (EQ5D, VAS and HUI3) to complete during their visit. The time taken for patients to complete the array of instruments ranged from 30-45 minutes. The SF36v2 is a non-preference based quality of life instrument that has eight dimensions of health: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, energy/vitality, pain and general health perception to make up a physical component score (PCS) and mental component score (MCS). The EQ5D questionnaire characterizes health in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression on 3 levels to define HRQOL values for 245 health states. The VAS scale used in the EQ5D is a vertical line on a page
with a zero at one end representing worst possible health and a one at the other end representing best possible health. The HRQOL score is the measurement of the distance between zero and the mark made by respondents indicating their current health state. The HUI3 characterizes health using eight attributes, including vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain on 5-6 levels to define 972,000 health states scored between -0.37 (worst possible health) and 1 (best possible health). The negative values represent health states worse than being dead. Validated versions of each of these instruments in English, Cantonese and Mandarin have been developed [166, 193-195]. These instruments have also been used to measure HRQOL in patients with chronic hepatitis B infection [170, 171, 196-198].

Following completion of the surveys, a chance board was employed as a prop to elicit patients’ standard gamble utilities using two practice scenarios and the patient’s current health state. Respondents were asked to choose between two options: 1) remain in their current health state without improvement; or 2) take a hypothetical medication that would result in either full health or immediate death. The probability of death in the latter option was changed until the respondent reached a point of indifference between the two options. The utility weight was calculated as 1 minus the probability of death at the point of indifference.

4.2.3 Baseline patient data

In addition to the quality of life questionnaires, participants completed a set of questionnaires regarding their sociodemographic characteristics, including gender, age, ethnicity, education level and income as well as risk factors for HBV. We also performed a systematic chart review to extract the following data: coexisting illnesses categorized using the Charlson Index [199], liver enzyme levels, liver biopsy reports, radiology reports and treatment history and current medications.
The disease of each patient with CHB was classified into one of five stages: 1) chronic hepatitis in the absence of cirrhosis (n=294), 2) compensated cirrhosis - cirrhosis based on liver biopsy results or cirrhosis reported on ultrasound imaging (n= 79); 3) decompensated cirrhosis – cirrhosis with a history of either ascites, variceal bleeding, or hepatic encephalopathy as reported in the chart review (n= 7); 4) HCC – patients having disease with features typical of hepatocellular carcinoma demonstrated by a liver biopsy or triphasic computed tomography (n= 23) and 5) post liver transplantation (n = 30).

4.3 Statistical analysis of patient preferences and utility estimates

The means and corresponding 95% confidence intervals were calculated for the scores for each health state obtained using each instrument. Analysis of variance (ANOVA) and Tukey’s post-hoc test were performed on the scores derived from each measurement tool to determine if differences existed across disease stages, between languages of response or from responses given by patients with chronic hepatitis C in the same clinic population. In order to compare scores across disease stage groups, an adjustment was made for age using linear regression for each disease stage. The utility scores were the dependent variables, which were regressed on age, which was the independent variable. Scores were standardized to the age of 50 years.

The SF36v2, EQ5D, VAS and HUI3 scores were compared with population norms using student t-tests after adjusting the means and standard deviations to match the age distribution of the different disease stages. The SF36v2 norms were based on a survey mailed to 4843 US residents [200]. The EQ5D and VAS norms were based on a mailed general population survey conducted in Alberta, Canada [201] of 1555 respondents. The HUI3 norms were based on a survey of 7946 Canadians with no chronic conditions [167]. The scores obtained from the current study were also compared to scores obtained from a previous study of patients with hepatitis C (n=193) who were recruited from the same liver clinics [202].
To determine which clinical and demographic factors might be associated with differences in quality of life, general linear models were constructed for each instrument. Variables significantly related (p < 0.05) to HRQOL scores in univariate analyses were then used in a multivariate general linear model for each quality of life instrument. Statistical analysis was completed using SAS 9.2 (SAS Institute, Cary, NC).

4.4 Sociodemographic features of patients enrolled in the utility study

Among the 486 sequential clinic patients approached, 40 declined to participate and 13 failed to complete the study. Thus, 433 persons completed the study for an overall participation rate of 89.1%. There were 294 patients with non-cirrhotic CHB, 79 with compensated cirrhosis, 7 patients with decompensated cirrhosis, 23 with HCC and 30 who had previously undergone a liver transplant (Table 4.1).

Table 4.1 presents the sociodemographic and clinical characteristics of the study sample. The mean age of the cohort was 50 years; patients with non-cirrhotic hepatitis B were younger than those with compensated cirrhosis, HCC and or a liver transplant (p < 0.05). Patients with non-cirrhotic hepatitis B also had fewer comorbidities in comparison to patients with decompensated cirrhosis and those post-transplantation. A large proportion of patients were either from East Asia (64% from Mainland China, Hong Kong, Japan, Macau, Mongolia, North Korea, South Korea or Taiwan) or Southeast Asia (11% from Brunei, Burma, Cambodia, East Timor, Indonesia, Laos, Malaysia, Philippines, Singapore, Thailand, Vietnam). Nevertheless, seventy percent of the participants completed the study in English. The study sample was predominantly male (70.5%) two-thirds of whom were married/common-law/engaged. Nearly half (47%) reported an annual income of over CDN $40,000.
<table>
<thead>
<tr>
<th></th>
<th>Non-cirrhotic CHB (n = 294)</th>
<th>Compensated Cirrhosis (n = 79)</th>
<th>Decompensated Cirrhosis (n = 7)</th>
<th>HCC (n = 23)</th>
<th>Post-transplant (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>47 (0.72)</td>
<td>55 (1.3)</td>
<td>54 (5.1)</td>
<td>54 (2.2)</td>
<td>58 (2.1)</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>185 (63)</td>
<td>68 (86)</td>
<td>5 (71)</td>
<td>19 (83)</td>
<td>25 (83)</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>East Asian</td>
<td>196 (66)</td>
<td>47 (59)</td>
<td>3 (43)</td>
<td>12 (52)</td>
<td>19 (63)</td>
</tr>
<tr>
<td>Southeast Asian</td>
<td>35 (12)</td>
<td>6 (8)</td>
<td>1 (14)</td>
<td>4 (17)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Marital Status (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married or common-law</td>
<td>201 (72)</td>
<td>49 (66)</td>
<td>5 (83)</td>
<td>14 (67)</td>
<td>16 (57)</td>
</tr>
<tr>
<td>Employment (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-time</td>
<td>181 (66)</td>
<td>42 (56)</td>
<td>2 (33)</td>
<td>13 (62)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Annual income (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$C 20,000</td>
<td>68 (26)</td>
<td>21 (30)</td>
<td>1 (17)</td>
<td>7 (35)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>$C 20 000–40 000</td>
<td>70 (27)</td>
<td>16 (23)</td>
<td>2 (33)</td>
<td>6 (30)</td>
<td>6 (24)</td>
</tr>
<tr>
<td>$C 40 000–60 000</td>
<td>60 (23)</td>
<td>14 (20)</td>
<td>2 (33)</td>
<td>4 (20)</td>
<td>7 (28)</td>
</tr>
<tr>
<td>$C 60 000–100 000</td>
<td>43 (17)</td>
<td>12 (17)</td>
<td>0 (0)</td>
<td>2 (10)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>&gt; $C 100 000</td>
<td>19 (7)</td>
<td>7 (10)</td>
<td>1 (17)</td>
<td>1 (5)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Charlson (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>251 (86)</td>
<td>61 (77)</td>
<td>4 (67)</td>
<td>16 (73)</td>
<td>14 (47)</td>
</tr>
<tr>
<td>1</td>
<td>26 (9)</td>
<td>13 (17)</td>
<td>0 (0)</td>
<td>4 (18)</td>
<td>13 (43)</td>
</tr>
<tr>
<td>&gt;1/2</td>
<td>14 (7)</td>
<td>5 (5)</td>
<td>2 (33)</td>
<td>2 (10)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Language of response (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>English</td>
<td>207 (70)</td>
<td>53 (67)</td>
<td>5 (71)</td>
<td>14 (63)</td>
<td>22 (76)</td>
</tr>
<tr>
<td>Cantonese</td>
<td>41 (14)</td>
<td>16 (20)</td>
<td>1 (14)</td>
<td>5 (23)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Mandarin</td>
<td>46 (16)</td>
<td>10 (13)</td>
<td>1 (14)</td>
<td>3 (14)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>On treatment (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>179 (61)</td>
<td>27 (34)</td>
<td>1 (14)</td>
<td>4 (17)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>40 (14)</td>
<td>26 (33)</td>
<td>3 (42)</td>
<td>13 (57)</td>
<td>21 (70)</td>
</tr>
<tr>
<td>Adefovir</td>
<td>16 (5)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Entecavir</td>
<td>17 (6)</td>
<td>4 (5)</td>
<td>0 (0)</td>
<td>2 (9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>3 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>18 (6)</td>
<td>7 (9)</td>
<td>0 (0)</td>
<td>2 (9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lamivudine + adefovir</td>
<td>13 (4)</td>
<td>9 (11)</td>
<td>3 (42)</td>
<td>1 (4)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Lamivudine + tenofovir</td>
<td>8 (3)</td>
<td>4 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Entecavir + tenofovir</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Abbreviations: $C =$Canadian dollars; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; SD, standard deviation
4.5 Short-form 36 version 2 health related quality of life scores

The scores elicited using the SF36v2 are presented in Table 4.2. Among all of the disease groups, patients with non-cirrhotic CHB had the highest scores across all domains. Patients with cirrhosis had lower scores in comparison to non-cirrhotic patients with the lowest scores observed in patients with decompensated cirrhosis for all domains. The scores for the different domains for patients with hepatocellular carcinoma were higher than non-cirrhotic patients for some while lower for others. For those individuals who underwent liver transplantation, scores were higher than patients with decompensated cirrhosis while similar to patients with hepatocellular carcinoma.

Patients without cirrhosis had similar scores to the general population. Of interest was that physical functioning, role physical, bodily pain and vitality attributes, which make up the PCS score, were all higher among patients with non-cirrhotic CHB in comparison to general population norms.
Table 4.2 Non preference-based QOL: SF-36v2 scores (and SEs) for HBV Patients at different disease stages compared with US population norms [200]

<table>
<thead>
<tr>
<th></th>
<th>Physical Functioning</th>
<th>Role Physical</th>
<th>Bodily Pain</th>
<th>General Health</th>
<th>Vitality</th>
<th>Social Functioning</th>
<th>Role Emotional</th>
<th>Mental Health</th>
<th>PCS</th>
<th>MCS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US general population</strong></td>
<td>50.0 (0.14)</td>
<td>50.0 (0.14)</td>
<td>50.0 (0.14)</td>
<td>50.0 (0.14)</td>
<td>50.0 (0.14)</td>
<td>50.0 (0.14)</td>
<td>50.0 (0.14)</td>
<td>50.0 (0.14)</td>
<td>50 (0.14)</td>
<td>50 (0.14)</td>
</tr>
<tr>
<td><strong>Non-cirrhotic CHB</strong></td>
<td>52.5 (0.55)</td>
<td>51.8 (0.42)</td>
<td>55.3 (0.47)</td>
<td>48.4 (0.57)</td>
<td>54.6 (0.58)</td>
<td>50.6 (0.51)</td>
<td>49.3 (0.52)</td>
<td>50.9 (0.60)</td>
<td>53.1 (0.35)</td>
<td>50.1 (0.41)</td>
</tr>
<tr>
<td><strong>Compensated cirrhosis</strong></td>
<td>48.6 (1.2)*</td>
<td>48.6 (1.1)*</td>
<td>54.5 (1.0)</td>
<td>46.7 (1.1)</td>
<td>53.8 (1.01)</td>
<td>48.84 (1.0)</td>
<td>47.12 (1.3)</td>
<td>49.6 (1.1)</td>
<td>50.4 (0.87)*</td>
<td>49.2 (0.92)</td>
</tr>
<tr>
<td><strong>Decompensated cirrhosis</strong></td>
<td>39.3 (5.3)*</td>
<td>33.7 (6.4)*</td>
<td>41.2 (4.3)*</td>
<td>39.4 (5.7)*</td>
<td>40.9 (5.1)*</td>
<td>38.9 (7.1)*</td>
<td>32.5 (8.1)*</td>
<td>41.2 (6.6)</td>
<td>39.4 (4.3)*</td>
<td>38.5 (3.4)*</td>
</tr>
<tr>
<td><strong>HCC</strong></td>
<td>47.3 (2.4)</td>
<td>48.2 (2.1)</td>
<td>51.3 (2.5)</td>
<td>46.9 (2.1)</td>
<td>55.4 (1.9)</td>
<td>49.6 (2.4)</td>
<td>49.2 (2.5)</td>
<td>54.9 (2.3)</td>
<td>47.2 (2.0)*</td>
<td>53.5 (2.0)</td>
</tr>
<tr>
<td><strong>Post-transplant</strong></td>
<td>47.0 (2.1)*</td>
<td>47.5 (2.2)</td>
<td>50.7 (2.2)</td>
<td>47.2 (2.0)</td>
<td>53.2 (1.9)</td>
<td>47.6 (2.1)</td>
<td>47.3 (2.1)</td>
<td>51.3 (2.1)</td>
<td>47.7 (2.0)*</td>
<td>50.6 (2.1)</td>
</tr>
</tbody>
</table>

Abbreviations: SE, standard error; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PCS, physical component summary; MCS, mental component summary

* denotes statistically significant differences in scores for the disease group in comparison to the non-cirrhotic CHB disease group (p < 0.05)
4.6 Direct and indirect utility estimates

Utility scores are reported in Table 4.3. The results from the utility scoring instruments were similar to those of the SF36v2. Non-cirrhotic patients had the highest scores which were similar to those of the general population. Patients with cirrhosis had a consistent trend of reporting lower utility scores as liver disease stage severity increased from non-cirrhotic CHB to compensated cirrhosis and then to decompensated cirrhosis. As was determined by the SF36v2, patients with hepatocellular carcinoma had lower utility scores in comparison to non-cirrhotic patients. However, they were not as low as patients with decompensated cirrhosis. Patients who underwent a liver transplant had higher utility than did patients with decompensated cirrhosis and hepatocellular carcinoma; however those scores were not comparable to those from non-cirrhotic patients as was found by the SF36v2. As was observed in the physical attributes of the SF36v2, the EQ5D scores of non-cirrhotic patients were higher in comparison to those of the general population.
<table>
<thead>
<tr>
<th>Measurement Instruments</th>
<th>SG</th>
<th>HUI3</th>
<th>VAS</th>
<th>EQ5D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian population norms</td>
<td>0.93 (0.85-1.01)[167]</td>
<td>0.81 (0.80-0.82)[201]</td>
<td>0.86 (0.85-0.87)[201]</td>
<td></td>
</tr>
<tr>
<td>Non-cirrhotic CHB (n = 294)</td>
<td>0.89 (0.87-0.91)</td>
<td>0.87 (0.85-0.88)</td>
<td>0.80 (0.79-0.82)</td>
<td>0.92 (0.91-0.94)</td>
</tr>
<tr>
<td>Compensated cirrhosis (n=79)</td>
<td>0.87 (0.83-0.91)</td>
<td>0.81 (0.75-0.86)</td>
<td>0.78 (0.74-0.82)</td>
<td>0.88 (0.85-0.92)</td>
</tr>
<tr>
<td>Decompensated cirrhosis (n = 7)</td>
<td>0.82 (0.60-1.00)</td>
<td>0.49 (0.22-0.75)*</td>
<td>0.63 (0.29-0.83)*</td>
<td>0.73 (0.39-1.00)*</td>
</tr>
<tr>
<td>HCC (n = 23)</td>
<td>0.84 (0.77-0.92)</td>
<td>0.85 (0.76-0.95)</td>
<td>0.77 (0.67-0.88)</td>
<td>0.81 (0.67-0.94)*</td>
</tr>
<tr>
<td>Post-transplant (n = 30)</td>
<td>0.86 (0.79-0.93)</td>
<td>0.72 (0.60-0.83)*</td>
<td>0.80 (0.75-0.87)</td>
<td>0.84 (0.77-0.91)</td>
</tr>
</tbody>
</table>

Abbreviations: CHB, chronic hepatitis; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HUI3, Health Utilities Index Mark 3; SG, standard gamble; VAS, visual analogue scale

* denotes statistically significant differences in scores for the disease group in comparison to the non-cirrhotic CHB disease group (p ≤ 0.05)
4.7 Predictors of utility and HRQOL

General linear models were created to identify the set of variables that were significantly associated with HRQOL in patients chronically infected with hepatitis B (p ≤ 0.05). The adjusted R² values were low and ranged between 0.048 and 0.251. Three factors consistently were associated with utility scores were: age, number of comorbidities and marital status (Table 4.4). A one year increase in age was associated with lower HRQOL as measured across all instruments except the MCS score of the SF36v2. As expected, patients with a greater number of comorbidities as measured by the Charlson Index had lower HRQOL scores. Patients who reported themselves as in a relationship (married/engaged/common-law) had higher scores in comparison to patients who did not.

Risk factors for hepatitis B were not consistently associated with a difference in utility. ALT levels showed no consistent correlation to HRQOL across instruments. In the present study, there were too few patients who had undergone a liver biopsy to assess the association with HRQOL scores. With respect to the effect of antiviral therapy on quality of life, there was no statistically significant difference in adjusted scores between patients on and off treatment regardless of disease severity (p > 0.05).
Table 4.4 Results of regression models

<table>
<thead>
<tr>
<th>Variable</th>
<th>PCS</th>
<th></th>
<th>MCS</th>
<th></th>
<th>Standard Gamble</th>
<th></th>
<th>HUI</th>
<th></th>
<th>VAS</th>
<th></th>
<th>EQ5D</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B*</td>
<td>95% CI</td>
<td>B*</td>
<td>95% CI</td>
<td>B*</td>
<td>95% CI</td>
<td>B*</td>
<td>95% CI</td>
<td>B*</td>
<td>95% CI</td>
<td>B*</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age†</td>
<td>-0.09</td>
<td>-0.03, -0.15</td>
<td>0.08</td>
<td>0.16, 0.00</td>
<td>0.00</td>
<td>0.00, 0.00</td>
<td>0.00</td>
<td>0.00, 0.00</td>
<td>0.00</td>
<td>0.00, 0.00</td>
<td>0.00</td>
<td>0.00, 0.00</td>
</tr>
<tr>
<td>Gender‡</td>
<td>-0.84</td>
<td>0.76, -2.43</td>
<td>-1.99</td>
<td>0.22, -4.20</td>
<td>0.04</td>
<td>0.03, 0.07</td>
<td>-0.05</td>
<td>-0.01, -0.09</td>
<td>0.00</td>
<td>0.03, -0.04</td>
<td>-0.01</td>
<td>0.02, -0.05</td>
</tr>
<tr>
<td>ALT</td>
<td>-1.40</td>
<td>-0.33, -2.46</td>
<td>0.27</td>
<td>1.75, -1.21</td>
<td>-0.04</td>
<td>-0.02, -0.06</td>
<td>-0.04</td>
<td>-0.01, -0.06</td>
<td>-0.02</td>
<td>0.01, -0.04</td>
<td>-0.04</td>
<td>-0.01, -0.06</td>
</tr>
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<td>Charlson</td>
<td>0.78</td>
<td>2.49, -0.92</td>
<td>0.07</td>
<td>2.45, -2.31</td>
<td>0.02</td>
<td>0.05, -0.02</td>
<td>0.03</td>
<td>0.28, -0.21</td>
<td>0.02</td>
<td>0.06, -0.02</td>
<td>0.01</td>
<td>0.04, -0.03</td>
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<td>HBeAg status</td>
<td>-1.53</td>
<td>0.01, -3.06</td>
<td>-2.66</td>
<td>-0.55, -4.78</td>
<td>0.00</td>
<td>0.04, -0.03</td>
<td>-0.05</td>
<td>-0.01, -0.09</td>
<td>-0.04</td>
<td>0.00, -0.07</td>
<td>-0.05</td>
<td>-0.02, -0.08</td>
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<td>Marital Status§</td>
<td>0.07</td>
<td>1.56, -1.41</td>
<td>1.76</td>
<td>3.90, -0.37</td>
<td>-1.66</td>
<td>1.59, -4.92</td>
<td>0.02</td>
<td>0.06, -0.02</td>
<td>-0.15</td>
<td>3.21, -3.51</td>
<td>0.02</td>
<td>0.05, -0.01</td>
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<td>Men having sex with men</td>
<td>5.88</td>
<td>11.19, 0.56</td>
<td>5.24</td>
<td>12.67, -2.19</td>
<td>0.17</td>
<td>0.28, 0.05</td>
<td>0.24</td>
<td>0.38, 0.11</td>
<td>0.07</td>
<td>0.19, -0.05</td>
<td>0.06</td>
<td>0.17, -0.05</td>
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<td>Lives with hepB</td>
<td>0.30</td>
<td>1.96, -1.36</td>
<td>0.98</td>
<td>3.29, -1.34</td>
<td>-0.02</td>
<td>0.02, -0.05</td>
<td>0.01</td>
<td>0.06, -0.03</td>
<td>0.00</td>
<td>0.04, -0.03</td>
<td>0.92</td>
<td>0.95, 0.89</td>
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<tr>
<td>Injection drugs</td>
<td>2.74</td>
<td>6.66, -1.19</td>
<td>-5.93</td>
<td>-0.47, -11.38</td>
<td>0.02</td>
<td>0.11, -0.07</td>
<td>0.00</td>
<td>0.10, -0.10</td>
<td>-0.04</td>
<td>0.04, -0.13</td>
<td>0.02</td>
<td>0.10, -0.06</td>
</tr>
<tr>
<td>In prison</td>
<td>1.44</td>
<td>4.20, -1.32</td>
<td>1.67</td>
<td>5.53, -2.19</td>
<td>0.04</td>
<td>0.10, -0.02</td>
<td>0.04</td>
<td>0.12, -0.03</td>
<td>0.05</td>
<td>0.11, -0.01</td>
<td>0.24</td>
<td>0.29, 0.18</td>
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<td>Tattoo</td>
<td>0.83</td>
<td>6.17, -4.50</td>
<td>0.65</td>
<td>8.09, -6.79</td>
<td>0.02</td>
<td>0.14, -0.09</td>
<td>-0.09</td>
<td>0.04, -0.23</td>
<td>0.14</td>
<td>0.25, 0.02</td>
<td>-0.02</td>
<td>0.08, -0.13</td>
</tr>
<tr>
<td>Body piercing</td>
<td>-2.23</td>
<td>-4.60, 0.14</td>
<td>0.56</td>
<td>5.59, -4.47</td>
<td>0.01</td>
<td>0.08, -0.07</td>
<td>0.04</td>
<td>0.13, -0.05</td>
<td>0.05</td>
<td>0.13, -0.02</td>
<td>0.01</td>
<td>0.09, -0.06</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>0.57</td>
<td>2.77, -1.64</td>
<td>2.00</td>
<td>5.06, -1.06</td>
<td>-0.01</td>
<td>0.04, -0.05</td>
<td>0.03</td>
<td>0.09, -0.02</td>
<td>0.01</td>
<td>0.06, -0.03</td>
<td>0.02</td>
<td>0.07, -0.02</td>
</tr>
</tbody>
</table>

* Unstandardized coefficient
† Age was calculated using the birth date and date of study completion
‡ Gender was coded as 1=male, 2=female
§ Marital status is a binary variable with, 1=married, common-law or engaged and 2=not married, common-law or engaged
|| On antiviral treatment is a binary variable with, 1=no treatment and 2=on an oral anti-viral treatment

Abbreviations: ALT, alanine transaminase; HBeAg, hepatitis B e antigen; PCS, physical component summary; MCS, mental component summary; HUI3, Health Utilities Index Mark 3; VAS, visual analogue scale
4.8 Comparison of measurement tools

The difference in utility estimates for each disease stage varied in the same direction for each instrument; patients with non-cirrhotic hepatitis B had the highest scores and as the stage of liver damage severity increased, the utilities decreased as measured by the EQ5D, VAS and SG. However, the scores obtained from the HUI3 differed from those derived using other instruments as the HUI3 scores were higher for patients with HCC in comparison to those post-transplant (Figure 1). As expected, VAS scores were lower than EQ5D, SG and HUI3 scores by 0.106, 0.086 and 0.043, respectively (p < 0.001). Scores obtained from the EQ5D and SG were higher than those elicited using the HUI3 by 0.061 and 0.038, respectively (p < 0.0006). There was no significant difference between the EQ5D and SG scores.
Figure 4.1 Mean utilities and HRQOL scores stratified by disease stage of patients with chronic hepatitis B.

Abbreviations: HCC, hepatocellular carcinoma; VAS, visual analogue scale; SG, standard gamble; HUI3, Health Utilities Index Mark 3.
Table 4.5 Comparison of patient-elicited utilities with published utilities in HBV-specific populations.

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-cirrhotic CHB</td>
<td>SG 0.89 HUI3 0.87 EQ5D (median) 0.92 (1) VAS (median) 0.80 (0.80)</td>
<td>SG 0.68 HUI2 0.87 HUI2 0.78</td>
<td>EQ5D 1.0 VAS 0.82 SF6D 0.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>0.87 0.81 0.88 (1) 0.78 (0.80) 0.69</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>0.82 0.49 0.73 (0.85) 0.63 (0.65) 0.35</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>0.84 0.85 0.81 (1) 0.77 (0.85) 0.38</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-transplant</td>
<td>0.86 0.72 0.84 (0.85) 0.80 (0.85) 0.67</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SG, standard gamble; HUI2, health utilities index mark 2; HUI3, health utilities index mark 3; VAS, visual analogue scale; SF6D, short form 6D

*Ong et al. scores are reported as median and not mean values

†Scores for Bondini et al. and Dan et al. derived from patients from all disease states and not only non-cirrhotic patients
Table 4.6 Comparison of Patient-Elicited SF36v2 Mean Physical Component Score (PCS) and Mean Mental Component Score (MCS) with Published Studies in HBV-Specific Populations

<table>
<thead>
<tr>
<th></th>
<th>Patient Elicited</th>
<th>Published SF36v2 Summary Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic HBV</td>
<td>53.09 (54.38)</td>
<td>50.08 (52.81)</td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>50.43 (53.18)</td>
<td>49.18 (53.03)</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>39.46 (37.72)</td>
<td>38.51 (34.23)</td>
</tr>
<tr>
<td>HCC</td>
<td>47.17 (48.42)</td>
<td>53.91 (56.21)</td>
</tr>
<tr>
<td>Post-transplant</td>
<td>47.73 (52.41)</td>
<td>50.57 (50.96)</td>
</tr>
</tbody>
</table>

Note: Ong et al. reports median scores
Scores for Bondini et al.[171] reflect patients from all disease states and not only non-cirrhotic patients
4.9 Comparisons of chronic hepatitis B and hepatitis C sample populations

We compared our data to an identical study performed in hepatitis C infected patients attending the same liver clinics at the University Health Network [202]. There was a similar trend observed with regard to the relative scores between disease states; patients in a non-cirrhotic chronic state had the highest scores and patients with more progressive liver disease had the lower scores. Overall, hepatitis C infected patients had lower utility scores than patients with hepatitis B, as measured by every utility instrument (p<0.05). In addition, both PCS and MCS scores from the SF36v2 for hepatitis C patients were lower than those in our study population (p <0.05).

4.10 Major findings from utility and patient preferences study

4.10.1 In patients with HBV, QOL is impaired only among those who have developed late stage liver disease

The aim of the present study was to determine the HRQOL of patients with CHB using the SF36v2, EQ5D, VAS, HUI3 and standard gamble. Lower HRQOL scores were not associated with hepatitis B infection itself, but rather with presence of cirrhosis causing liver failure and/or hepatocellular carcinoma (Figure 4.1). Increased age, number of comorbidities and not being in a long-term relationship were associated with lower HRQOL.

This study provides standard gamble utilities for patients assessing their own HRQOL in the different stages of CHB. Ong et al. [169] stratified 432 patients into respective disease stages and assessed their HRQOL using the SF36v2, EQ5D and VAS. They found no difference in HRQOL between non-cirrhotic CHB and non infected individuals. Lower HRQOL was only observed in those with cirrhosis with or without liver failure. Although the present study used a historical control group for comparison of scores and not a parallel control group, it corroborates the findings of Ong et al. [169], suggesting that non-cirrhotic patients do not have impaired HRQOL in comparison to the general population.
4.10.2 Antiviral treatment does not affect HRQOL

The present study shows that patients with more severe liver disease had a larger proportion of patients on oral antiviral treatment (Table 4.1). Lamivudine was the most widely used oral antiviral as this is the first line of therapy supported by government funding in the province of Ontario. Only a small proportion of patients were on newer more potent treatments such as entecavir or tenofovir. None of the patients were being treated with interferon. Overall, there was no difference in the HRQOL of patients on and off oral antiviral treatment regardless of stage of disease or measurement instrument, suggesting that daily oral antiviral treatment is not associated with lower or higher HRQOL as measured by both preference and non-preference based instruments. However, this study did not follow patients prospectively, (i.e. evaluated before and after administration of antiviral treatment) or investigate patients who may have started treatment but failed to continue due to adverse events.

4.10.3 Significant differences between patients with HBV and HCV

Patients infected with HBV and hepatitis C virus (HCV) do not experience the same changes in HRQOL as assessed in the current study. Prior to 2008, all cost-effectiveness studies assessing treatment options for CHB used utilities from studies of patients with HCV since data were not available for patients with HBV [204-207]. Those studies assumed that patients with CHB had the same HRQOL as patients with HCV infection. The current study shows differences between these two patient groups.

A study with a similar design and identical setting to the present one was performed in the year 2000 on 193 patients with hepatitis C attending the same liver clinics in downtown Toronto [202]. Chong et al., suggested that HRQOL was significantly diminished in patients with HCV both in those with or without cirrhosis. We compared our results with those of Chong et al. Patients with HCV had lower HRQOL in comparison to patients with HBV (p≤0.05). The patient groups in the Chong study differed from ours in that they had higher
rates of prior use of injection drugs, rates of previous incarceration and homosexual activity and also had differences in ethnicity and age. All of these differences may have been the reason for the disparity in HRQOL observed between studies. Kanwal and associates [205] performed a cost-effectiveness analysis for patients with CHB. As inputs, they used the utilities of patients with HCV collected by Chong et al. using the standard gamble method. The ranges for those utility estimates used by Kanwal and associates were lower than those elicited from the current study of patients with hepatitis B. By using the utilities of patients with HCV in decision models assessing the cost-effectiveness of CHB, the lower utility estimates over estimates the burden of the disease from hepatitis B.

4.10.4 Different methods provide different answers

Disease severity of patients with CHB varies substantially even within the same phase of disease. As a result, health utilities should be solicited from individual patients to reflect their health states and the real burden of disease since a single description of a health state may not capture the variability of this patient group. Levy et al. [170] measured the health utility from study participants which included infected and non-infected individuals using descriptions of health states related to HBV. The use of hypothetical descriptions yielded much lower utility scores compared to our results. This is most likely because the current study population actually experienced the health state. This is quite different in comparison to Levy’s study that presented hypothetical scenarios to patients who may or may not have been experiencing the health state that they were evaluating. Patients typically provide higher HRQOL values when evaluating their current health state in comparison to a description of the same health state [208]. For example, the average utility reported by patients with non-cirrhotic CHB and compensated cirrhosis from the current study was 0.89 and 0.87, respectively. The corresponding average utilities reported by participants infected with HBV evaluating descriptions of non-cirrhotic CHB and compensated cirrhosis were 0.68 and 0.69 (Table 4.5). The direction in the latter averages suggests that potentially the descriptions could not fully capture the variation in HBV and its prognosis. The results from the present study are consistent with Ong and
associates [169] in which health utility measures were solicited from patients with HBV who assessed their current health states.

### 4.11 Study Limitations

This study had several limitations. First, subjects were recruited from tertiary care centers of patients returning for follow-up visits related to CHB. This sample may not reflect the full patient population as individuals in tertiary care clinics are those who are either known to have more severe liver disease and/or to have symptoms. However, as non-cirrhotic patients showed no difference in HRQOL compared to the general population, it is unlikely that those not seeking care for hepatitis B would have HRQOL that is different from the group of non-cirrhotic patients. Nevertheless studies of patients with hepatitis B not attending tertiary care clinics may provide a more comprehensive reflection of the affects of hepatitis B on HRQOL. Another major limitation of this study is the number of patients with advanced liver disease. Convenience patient sampling was used during our period of recruitment and few patients were found with decompensated cirrhosis attending the clinics for follow-up of their CHB infection. The small number of patients is likely attributable to improved management with treatments available to prevent liver failure such as antiviral therapy [191]. In locations where these treatments are not readily available, more patients with decompensated cirrhosis may be available for study. The result of a small sample size was a limitation of the statistical power of this study. Also, this study did not contain a control group of non-infected individuals. Historical published general population norms for Canada and the United States were used in place of a control group for comparison. As each of those studies contained over a thousand subjects, they were adequate representations of general population norms. Finally, the design was cross-sectional, which impeded our ability to determine the causal relationships between health state and quality of life. Another possible limitation was respondent burden due to the array of instruments used which may have affected the accuracy of responses.
4.12 Conclusions and future recommendations

This study’s aim was to provide a comprehensive list of values from the most common measurement tools. In this analysis, the scores obtained from all instruments suggested that patients with non-cirrhotic CHB do not have lower HRQOL and the impairment to the quality of life of patients is a result of cirrhosis or hepatocellular carcinoma. Another finding was that oral antiviral therapy does not seem to affect HRQOL however those who might have benefited most (i.e. patients with decompensated cirrhosis) were very few in number and only one had not been treated at the time of the study. Consequently these results may have been confounded by treatment of patients with cirrhosis since antiviral treatment has almost eliminated this patient group. Furthermore, the HRQOL of patients with CHB appears to be better than for patients with HCV. In the future, longitudinal studies with larger samples could thoroughly investigate the effects of viral resistance on HRQOL as well as differences in HRQOL that may exist for patients on different antiviral treatments.
CHAPTER 5
GENERAL DISCUSSION

The objectives of this chapter are to:

1. Discuss the main findings of the analysis
2. Discuss methodological considerations of Bayesian mixed treatment comparison meta-analysis
3. Discuss the methodological considerations of eliciting patient preferences and utilities
4. Outline directions for future research

5.1 General Discussion

There were two main aims of this thesis. First, to determine the optimal treatment for patients with chronic hepatitis B using a Bayesian mixed treatment comparison meta-analytic approach. Second, to determine the health related quality of life of patients with chronic hepatitis B and disease states resulting from infection. This thesis describes the findings from the literature in a systematic way. Furthermore, the treatments of choice for both patients with HBeAg-positive and HBeAg-negative chronic hepatitis B are presented. In addition patient derived health utilities and health related quality of life scores for patients with chronic hepatitis B are provided. Also, the quality of life from patients on and off oral antiviral treatment is presented. In this general discussion, the main findings and methodological issues are discussed. Finally, implications for future research are considered.
5.2 Main findings

The face of treating hepatitis B is rapidly changing. New measures of treatment efficacy and new therapies are quickly evolving. Therefore, it is not surprising that clinicians are inundated with new studies comparing treatments and with changing target outcomes, they are uncertain of the optimal treatment option for their patients.

Hepatitis B is a life-threatening virus that causes end stage liver disease and hepatocellular carcinoma. Despite widespread vaccination programs which have decreased the incidence of new infections, there remain over 400 million individuals worldwide who remain infected. Since 1998, oral antiviral treatments have become available and are an important alternative to interferon therapy.

Since the introduction of oral antivirals, the goal of treatment for patients with chronic hepatitis B has changed. Due to fewer side effects and an easier to manage route of administration in comparison to interferon, most physicians are more likely to administer oral antivirals instead of interferon therapy even though sustained efficacy off treatment may be less. In patients on interferon therapy, their rates of HBsAg loss (which is now equated to curing hepatitis B infection) are higher than many of the older antiviral treatments particularly with longer follow up off treatment (5 years at 11% in HBeAg-positive and 12% in HBeAg-negative CHB) Furthermore, interferon therapy is limited to six months of treatment whereas following the initiation of antiviral therapy, there is no clear indication for terminating treatment if HBsAg loss does not occur. Viral resistance from oral antiviral therapy is also not a concern of patients who receive interferon treatment.

Published studies comparing interferon and/or oral antivirals as monotherapies or combination therapies in the first year of treatment for patients with either HBeAg-positive or HBeAg-negative chronic hepatitis B were systematically evaluated. Following
the first year of treatment, entecavir and tenofovir were the most effective treatments in HBeAg-positive patients while tenofovir was the most effective treatment in HBeAg-negative patients.

In this review we assessed six different surrogate markers for treatment efficacy for patients with HBeAg-positive chronic hepatitis B. HBsAg loss is a strong indicator of a cure of hepatitis B infection. This analysis found that both tenofovir and entecavir were ranked first and third most efficacious for HBsAg loss however combination therapy including pegylated interferon and pegylated interferon itself were ranked second and fourth respectively. These results indicate that along with tenofovir and entecavir, pegylated interferon is an attractive treatment if a defined period of treatment is a concern for a patient. Pegylated interferon combination therapy and monotherapy also ranked second and third for HBeAg seroconversion which is another important surrogate outcome of successful treatment of HBeAg-positive chronic hepatitis B.

Of the three surrogate outcomes that were assessed in patients with HBeAg-negative chronic hepatitis B, tenofovir provided a clear advantage over other treatments. Combination therapy with pegylated interferon did not rank highly as was observed in HBeAg-positive patients. These results suggest that pegylated interferon still has a place for treating chronic hepatitis B if HBsAg loss and HBeAg seroconversion are the target surrogate outcomes of interest. However, overall, the current study suggests that if all outcomes are considered, treatment with tenofovir and entecavir are preferred.

Health related quality of life is used in the assessment of the cost-effectiveness of treating chronic hepatitis B. It has often been thought that patients with non-cirrhotic chronic hepatitis B do not have a decrease in HRQOL in comparison to the general population as many individuals remain unaware of their infection and only seek medical care when symptoms of cirrhosis or hepatocellular carcinoma arise. However, until the past few
years, there were no published studies assessing the HRQOL of patients infected with chronic hepatitis B. The limited literature currently available has assessed HRQOL using different instruments and methods for eliciting HRQOL and thus provided conflicting results. In the present study, a comprehensive battery of HRQOL instruments was used to assess the HRQOL of patients with chronic hepatitis B assessing their own current health.

The current study showed that patients with non-cirrhotic chronic hepatitis B did not have lower HRQOL in comparison to the general population as measured by the HUI3, EQ5D and SF36v2. These results are not surprising as many people remain asymptomatic for decades with chronic hepatitis B infection. As expected, impairment of HRQOL was observed in patients with cirrhosis and hepatocellular carcinoma. Patients post liver transplantation showed significantly higher HRQOL scores in comparison to patients with decompensated cirrhosis. However, post liver transplant patients showed insignificantly higher scores than patients with hepatocellular carcinoma.

Oral antiviral treatments are now the most common form of therapy for chronic hepatitis B. Although treatment is effective in preventing progression of liver disease, with often lifelong treatment following the initiation of therapy, its effects on HRQOL become increasingly important. In clinical trials, the rates of severe adverse events and dropouts were low which would indicate a highly tolerable therapy. The results of the present study suggest that patients on oral antiviral therapy did not have lower HRQOL than those thought not to require treatment.

This same study was previously performed in patients with chronic hepatitis C attending the same liver clinics. A comparison of the chronic hepatitis B population to that of patients with chronic hepatitis C found that patients with hepatitis C had lower HRQOL in comparison to patients with hepatitis B when stratified into the same disease stages. The comorbidities for CHB and chronic hepatitis C are very different and likely are in part,
responsible for the differences observed in measurements of HRQOL. In addition, patients with non-cirrhotic chronic hepatitis C had lower HRQOL in comparison to the general population which was not observed in patients with non-cirrhotic chronic hepatitis B. These results stress the importance of using HRQOL scores elicited specifically from the disease of interest in decision models assessing the cost-effectiveness of treatments.

5.3 Methodological considerations

To determine the relative efficacy of treatments, a head-to-head randomized controlled trial is the recommended study design. However, there are rarely trials including treatment arms of all available therapies. Consequently, indirect comparisons must be made where head-to-head trials do not exist.

In the systematic review, only published studies that were randomized controlled trials, the highest level of evidence were included. By including only published studies, the analysis is likely prone to bias of reporting positive results as often negative results are not published. Consequently, the results are likely to overestimate the efficacy of treatments however since the methods assess the relative efficacy and not the absolute values, all treatments are prone to the same bias.

Using Bayesian mixed treatment comparison meta-analysis, the relative efficacy of all available treatments was determined. In this model, the results of the analysis borrow strength from each of the studies that includes a treatment arm with a therapy of interest. However, as is often the case with meta-analytic studies, there are limited numbers of studies being input into the model. In the analysis, only one study included tenofovir, the most recently approved treatment available. This was simply due to few studies having been published since it is a newer antiviral agent. However, it is also the treatment of choice for patients with HBeAg-positive and HBeAg-negative chronic hepatitis B. The limited number of studies resulted in wide credible intervals.
An advantage of using Bayesian mixed treatment comparisons is the ability to provide the probability of a treatment outcome which is not possible with traditional meta-analysis. However, the current study is limited to the first year of treatment. Treatment for chronic hepatitis B can often be lifelong as there is no indication to take patients off oral antiviral therapy. Consequently, to provide a more complete idea of the efficacy of various treatments, studies with long-term data must be included when it becomes available.

The current study included a number of HRQOL measurement instruments. In previous HRQOL studies, one or two instruments are most often used. However, in published studies of HRQOL of patients with chronic hepatitis B, different instruments have provided conflicting results. The present research had consistent results across four measurement tools.

However, the current study used patients infected with chronic hepatitis B and not the general public. There is an ongoing debate on who should be asked: the general public or patients experiencing the disease. In present study included only patients currently in the health state and consequently was limited in the number of patients that had decompensated cirrhosis as a result of hepatitis B infection. In the past, decompensated cirrhosis due to chronic hepatitis B occurred more frequently, however antiviral therapies have been successful in preventing the progression of cirrhosis. This resulted in a small sample size of patients with decompensated cirrhosis and decreased the statistical power of the disease group.

Furthermore, by including a battery of instruments, one is now faced with the decision of which scores should be used. The standard gamble is often thought of as the gold standard since it is the only instrument that provides a true utility value. However, standard gamble utility scores are not available for the general population and since no control arm of
uninfected respondents was included in the study, the difference in health utility in comparison to the general population cannot be assessed.

Also, the results of the current study are limited to patients attending tertiary care clinics in the downtown Toronto area. Although there is a large patient population in the Greater Toronto Area where a high proportion of patients are of East or South East Asian descent, the results of this study may not be transferable to patients currently living in these areas where there is the highest proportion of patients living with chronic hepatitis B.

5.4 Future directions

Based on the surrogate markers used to measure the outcomes of treatment for chronic hepatitis B, more research on long-term and hard outcomes seems justified. It should be noted, however, that such an analysis can only be performed as long-term data becomes available.

The results of the current study suggest that newer antiviral therapies are more effective than older treatments however analysis on important outcomes such as viral resistance could not be performed as it is rarely observed in the first year of treatment. Furthermore, rates of surrogate outcomes following multiple years of treatment should be evaluated to determine if the relative efficacy of the treatments remains constant.

In addition, more research focused on which outcomes should be selected to determine treatment efficacy needs to be performed. In this study, multiple clinical surrogate outcome markers were assessed to provide the probability of an outcome following treatment. A single treatment did not rank first for all surrogate outcomes of effectiveness and in the case of patients with HBeAg-positive chronic hepatitis B, two treatments were
found to be highly effective. Future head-to-head trials for these two treatments should be performed to directly compare the efficacy of these therapies.

Furthermore, a prospective trial of tenofovir and entecavir that includes ongoing measurement of HRQOL is recommended. The current study was not designed in a way that would allow the measurement of a causal effect of antiviral treatment on changes in clinical measures of health. This study was a cross-sectional study admitting all patients with documented chronic hepatitis B infection. Cost-effectiveness studies are rapidly becoming more important for decisions on the reimbursement of medications. To improve the HRQOL data for decision models used for cost-effectiveness analysis, HRQOL measurements are needed to go alongside randomized clinical trials since they can provide information of the effects of treatment on HRQOL.

The recommended study design for future research is a randomized controlled trial comparing the leading therapies for chronic hepatitis B with ongoing monitoring of HRQOL. This study should be done in both HBeAg-positive and HBeAg-negative patient groups with sample sizes large enough to assess these patient groups separately as they have different target treatment outcomes. However, whatever study that is undertaken, the generalizability and time horizon especially in treatments that may be life-long are limitations to be dealt with. Nevertheless, especially in a disease where new treatments are rapidly becoming available, it should be questioned whether a randomized controlled trial is the optimal method for performing research since the current relevance of the research may be limited.

Decision analytic models are used to evaluate the cost-effectiveness of interventions. In these models, assumptions are often made when data is not available. Prior to the initiation of the current research studies, the data available regarding the relative efficacy of the treatments for chronic hepatitis B was limited. In addition, HRQOL scores were not
available for this patient group. The current studies were performed to bridge these knowledge gaps by providing current estimates that could be used in decision analytic models evaluating the cost-effectiveness of interventions for chronic hepatitis B. The landscape for treatment options for hepatitis B is divided into two main streams, interferon therapy and oral antivirals. Due to the significant differences in the costs of these treatments, durations of therapy, the considerable trade-offs with regard to side effects and the shift towards long-term viral suppression to prevent liver damage instead of treatment upon presentation of biochemical markers following liver damage, the optimal treatment option is not transparent. Thus, cost-effectiveness analysis can be used to help guide clinicians through this complex problem by bringing together all available evidence while taking the above concerns into consideration to provide a single. The next step in this research area is to build such a model including the evidence synthesized from this dissertation.

Whereas this dissertation focuses on the treatments that suppress the hepatitis B virus in those already infected, it is always better to focus on prevention of infection and cure of disease. Promotion of universal vaccination of neonates is the optimal method of reducing the morbidity and mortality associated with CHB. This is the first and foremost approach to prevention of this disease [209]. Furthermore, research regarding the cure of hepatitis B should be taken into account. A recent study by Fattovich and associates [210] has equated HBsAg loss to a cure of hepatitis B infection. This research highlights the need for therapies that promote HBsAg loss instead of long-term suppression of the virus. Furthermore, the probability of the most gain in HRQOL of patients with chronic hepatitis B can be obtained with HBsAg loss. Previously the goal of treatments was to suppress the effects of the virus and thus prevent the need for liver transplantation. Fortunately within the Canada, there is universal access to the health care system so there are few individuals who present with decompensated liver disease de novo; so much that recruitment of this patient group is difficult. However the next advance is to cure patients and remove the need for ongoing therapy.
In summary, the results of this thesis demonstrate that newer oral antivirals are most effective in the treatment of chronic hepatitis B. With the current knowledge, it seems justified to treat patients with newer oral antiviral treatments in comparison to older treatments to enhance HBeAg and HBsAg loss. Further research in the area is needed and should concentrate on long-term (more than first year) clinical effectiveness and the effects of treatment on HRQOL. In addition, the consensus of a single clinical outcome measure to determine the effectiveness of treatments is an ongoing process. Therefore further updating of this analysis is encouraged.
REFERENCES


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145. Spiegelhalter D and a.j.M. Abrams K, Bayesian Approaches to Clinical Trials and Health-Care Evaluation. 2004, West Sussex: John Wiley and Sons Ltd.


Appendix A: Details of Search Method

Summary:

Databases searches were run in OVID MEDLINE (1950 to 2009), EMBASE (1980 to 2009) and Web of Science (1945 to 2009). All of the searches used available subject headings, text words and were limited to human studies and randomized control trials.

MEDLINE search

The MEDLINE search strategy used a combination of MeSH terms and text word combinations for pegylated interferons, anti-virals and Hepatitis B. The base set was limited to RCTs and humans. The complete strategy is listed below

(((interferon alfa-2a/ or interferon-alpha/ or interferon alfa-2b/ or interferon alfa-2c/) and ((peg or pegylated).mp.)) or ((peg adj5 interferon adj5 alpha) or (peginterferon adj5 alpha) or (pegylated adj5 interferon adj5 alpha:) or (peg adj5 ifn) or (pegylated adj5 ifn)).mp. or (LAMivudine/ or LAMIVUDINE (nm) or ("gr 103665" or gr103665 or heptodin or hepivir or "nsc 620753 nsc6207533" or zefix or 3tc or epivir or (bch189 or "bch 189") or (gr109714x or "gr 109714x") or (hepitec or heptovir or trizivir or zeffix or zidovudine or lamivudine)).mp. or (adefovir or hepsera or preveon or pmea or adv or phoshonymethoxyethyl: or ("gs 0393" or gs0393 or gs840 or "gs 840" or gs0840 or "gs 0840")).mp. or (142217-69-4 or 209216-23-9).rn. or (entecavir or baraclude or etv or "bms 200475" or bms200475 or "sq 34676" or sq34676).mp. or (Telbivudine or Epavudine or "LdT 600" or LdT600 or "Nv 02b Nv02b" or Sebivo).mp. or 3424-98-4.rn. or tenofovir:.mp. or 147127-19-3.rn. or 147127-20-6.rn. or pmpa.ti,ab. AND Hepatitis B Antibodies/ or hepatitis b/ or hepatitis b, chronic/ or Hepatitis B Antibodies/ or hepatitis b antigens/ or hepatitis b core antigens/ or hepatitis b e antigens/ or hepatitis b surface antigens/ or Hepatitis B virus/ or ("hep b" or "hepatitis b" or "type b hepatitis" or "hbv" or (chronic adj2 homologous adj2 serum adj2 jaundice) or (chronic adj2 diffuse adj2 hepatocellular adj2 inflamm:)).mp. AND (randomized controlled trial.pt. or controlled
clinical trial.pt. or randomized controlled trials/ or Controlled Clinical Trials/ or (((rct or rcts or random: or (singl: or doubl: or tripl: or trebl:) and (blind: or mask:)) or control:adj5 trial:)).mp.limit 11 to (humans and (randomized controlled trial or controlled clinical trial)) or randomized controlled trials/ or Controlled Clinical Trials/ or (((rct or rcts or random: or (singl: or doubl: or tripl: or trebl:) and (blind: or mask:)) or control:adj5 trial:)).mp. AND human

EMBASE search

The EMBASE search strategy used a combination of MeSH terms and text word combinations for pegylated interferons, anti-virals and Hepatitis B. The base set was limited to RCTs and humans. The complete strategy is listed below

(198153-51-4 or 215647-85-1).rn. or peginterferon/ or peginterferon alpha2a/ or peginterferon alpha2b/ or ((peg adj5 interferon adj5 alpha) or (peginterferon adj5 alpha) or (pegylated adj5 interferon adj5 alpha:) or (peg adj5 ifn) or (pegylated adj5 ifn)).mp. or 134680-32-3.rn. or lamivudine/ or lamivudine plus nevirapine plus stavudine/ or lamivudine plus zidovudine/ or ("gr 103665" or gr103665 or heptodin or hepivir or "nsc 6207533 nsc6207533" or zefix or 3tc or epivir or (bch189 or "bch 189") or (gr109714x or "gr 109714x") or (hepitec or heptovir or trizivir or zeffix or zidovudine or lamivudine)).mp. or (106941-25-7 or 142340-99-6).rn. or adefovir/ or adefovir dipivoxil/ or (adefovir or hepsera or preveon or pmea or adv or phoshonomethoxyethyl: or ("gs 0393" or gs0393 or gs840 or "gs 840" or gs0840 or "gs 0840")).mp. or (142217-69-4 or 209216-23-9).rn. or entecavir/ or (entecavir or baraclude or etv or "bms 200475" or bms200475 or "sq 34676" or sq34676).mp.or peginterferon/ct or peginterferon alpha2a/ct or peginterferon alpha2b/ct or lamivudine/ct or lamivudine plus nevirapine plus stavudine/ct or lamivudine plus zidovudine/ct or adefovir/ct or adefovir dipivoxil/ct or entecavir/ct AND hepatitis b antibody/ or hepatitis b core antibody/ or "hepatitis b(e) antibody"/ or hepatitis b surface antibody/ or hepatitis b antigen/ or hepatitis b core antigen/ or "hepatitis b(e) antigen"/ or hepatitis b surface antigen/ or hepatitis b virus/ or Hepatitis B/ or hepatitis gb virus b/. AND ct. fs.randomized controlled trial/ or Clinical
Trial/ or (((rct or rcts or random: or (singl: or doubl: or tripl: or trebl:)) and (blind: or mask:)) or control:adj5 trial:).mp. AND human

**Web of Science search**

The Web of Science database is not indexed with subject headings, only textwords were used. The complete strategy is listed below

```
((TS=interferon alfa-2a OR TS=interferon-alpha OR TS=interferon alfa-2b OR TS=interferon alfa-2c) and =(TS=peg OR TS=pegylated)) OR TS=((peg NEAR interferon adj5 alpha) OR TS=(peginterferon NEAR alpha) OR TS=(pegylated NEAR interferon adj5 alpha:) OR TS=(peg NEAR ifn) OR TS=(pegylated NEAR ifn)) AND =(TS=peg OR TS=pegylated) OR =(TS=LAMivudine OR TS=hepivir OR TS=zefix OR TS=3tc OR TS=epivir OR TS=hepitec OR TS=heptovir OR TS=trizivir OR TS=zeffix OR TS=zidovudine OR TS=lamivudine) OR =(TS=adefovir OR TS=hepsera OR TS=preveon OR TS=pmea OR TS=adv OR TS=phoshonymethoxyethyl*) OR =(TS=entecavir OR TS=baraclude OR TS=etv) AND TS=Hepatitis B Antibodies OR TS=hepatitis b OR TS=hepatitis b, chronic OR TS=Hepatitis B Antibodies OR TS=hepatitis b antigens OR TS=hepatitis b core antigens OR TS=hepatitis b e antigens OR TS=hepatitis b surface antigens OR TS=Hepatitis B virus OR TS=("hep b" OR TS="hepatitis b" OR TS="type b hepatitis" OR TS="hbv" OR TS=(chronic NEAR homologous NEAR serum NEAR jaundice) OR TS=(chronic NEAR diffuse NEAR hepatocellular NEAR inflammm:))) AND (TS=(((rct or rcts or random* OR (singl* OR doubl* OR tripl* OR trebl*)) AND (blind* OR mask*)) OR (control*NEAR trial*)) OR TI=(((rct or rcts or random* OR (singl* OR doubl* OR tripl* OR trebl*)) AND (blind* OR mask*)) OR (control*NEAR trial*)) OR ((TS=random* trial*) AND (TI=random* trial*)))
```
Appendix B: Models and Computations Used for Meta-Analytic Estimates

Winbugs code for direct comparisons

For one study
model {
  rA ~ dbin (pA, nA)  # like for Lam
  rcom ~ dbin (pcom, ncom)  # like for comparator
  pA ~ dunif(0,1)
  pcom ~ dunif(0,1)
  OR <- (pcom/(1-pcom))/(pA/(1-pA))
}

For more than one study
model {
  for(i in 1: NS){
    rA[i] ~ dbin (pA[i], nA[i])
    rcom[i] ~ dbin (pcom[i], ncom[i])
    logit(pA[i]) <- mu[i]
    logit(pcom[i]) <- mu[i] + del[i]
    mu[i] ~ dnorm(0.0, 0.000001)
    del[i] ~ dnorm(d, prec)
  }  
  #priors for odds ratios
  d ~ dnorm (0.0, 0.000001)
  tau ~ dt(0.0, 1, 2)I(0,)
  # half (positive half) t prior for random effect standard deviation
  prec <- 1/pow(tau,2)
  # precision is 1/sd^2
  OR <- exp(d)
}

WinBUGS code for indirect comparisons
model{
  for(i in 1:N) {
    r[i] ~ dbin(p[i], n[i])
    logit(p[i]) <- mu[s[i]] + delta[i]*(1-equals(t[i], b[i]))
    delta[i] ~ dnorm(md[i], tau)
    md[i] <- d[t[i]] - d[b[i]]

    # measuring the goodness of fit
    # expected value of the numerators
    rhat[i] <- p[i] * n[i]
    dev[i] <- -2 * (r[i] * (log(r[i])-log(rhat[i])) +
                    (n[i]-r[i]) * (log(n[i]-r[i])- log(n[i]-rhat[i])))
  }
}
```r
# Priors for study-specific baselines
for(j in 1:NS) {
    mu[j] ~ dnorm(0, 0.1)
}

#reference group has logOR=0 compared to itself
d[1] <- 0

#priors for other log-odds ratios
for(k in 2:NT) {
    d[k] ~ dnorm(0, 0.1)
}

# Total Deviance should be approximately N if the model fits well
# look at individual values dev[i] to see which observations do not fit well if resdev >> N
resdev <- sum(dev[])

#code for calculation of rate in LAM (baseline) group
for (k in 1:NB) {
    rlam[k] ~ dbin(plam[k], nlam[k])
    logit(plam[k]) <- mulam[k]
    mulam[k] ~ dnorm(mu0lam, taulam)
}

sd ~ dt(0, 1, 2)I(0, )
tau <- 1/pow(sd, 2)

# these are the priors and calculations for the baseline probability model
mu0lam ~ dnorm(0, 0.00001)
taulam <- 1/pow(sigmalam, 2)
sigmalam ~ dunif(0,10)
logit(plam0) <- mu0lam
prob[1] <- cut(plam0)
b1ODDS <- prob[1] / (1-prob[1])

# Calculate the probability of the treatment being a success
for (q in 2:NT) {
    logit(prob[q]) <- mu0lam+d[q]
}

# Calculate the rank for each treatment
for(g in 1:NT) {
    rk[g] <- NT+1-rank(prob[,g])
    best[g] <- equals(rk[g], 1)
}
```
Note:
The model was run with a 5000 iteration burn-in followed by 20,000 monitored iterations. Convergence was assessed through the Brooks-Gelman-Rubin statistic.
Appendix C: Letters of Approval from the University of Toronto Office of Research and the University Health Network Research Ethics Board
UNIVERSITY OF TORONTO
Office of the Vice-President, Research and Associate Provost
Ethics Review Office

PROTOCOL REFERENCE #19935

March 23, 2007

Dr. Murray Krahm
Toronto General Hospital
200 Elizabeth St.
Toronto, ON M5G 2C4

Ms. Gloria Woo
Faculty of Pharmacy
144 College St.
Toronto, ON M5S 3M2

Dear Dr. Krahm and Ms. Woo:

Re: Administrative Approval of your research protocol entitled, "Health-state utilities and quality of life in hepatitis B patients"

We are writing to advise you that the Ethics Review Office has granted administrative approval to the above-named research study. The level of approval is based on the following role of the University, as you have identified with your submission:

- Graduate Student research – hospital-based only

This approval does not substitute for ethics approval, which has been obtained from your hospital Research Ethics Board. Should the status (i.e. University involvement) of the project change, please contact the Ethics Review Office to determine whether a new review (administrative or ethics) may be required.

Best wishes for the successful completion of your project.

Yours sincerely,

Jenny Peto
Ethics Review Coordinator
Notification of REB Initial Approval

Date: March 13, 2007

To: Dr. Murray Krahn
EN 14-207, TGH

Re: 06-0931-AE
Health-state Utilities and Quality of Life in Hepatitis B Patients

Sponsor: Gilead Sciences
REB Review Type: Expedited
REB Initial Approval Date: March 6, 2007
REB Expiry Date: March 6, 2008

Documents Approved:
Protocol and Appendices C-G, I & J (received December 4, 2006)
Consent Form (dated March 5, 2007)
Appendix B (received March 6, 2007)
Appendix H (received March 6, 2007)

The above named study has been reviewed and approved by the University Health Network Research Ethics Board. If, during the course of the research, there are any serious adverse events, any confidentiality concerns, changes in the approved protocol or consent form, or any new information that must be considered with respect to the project, these should be brought to the immediate attention of the REB. In the event of a privacy breach, you are responsible for reporting the breach to the UHN REB and the UHN Corporate Privacy Office (in accordance with Ontario health privacy legislation – Personal Health Information Protection Act, 2004). Additionally, the UHN REB requires reports of inappropriate/unauthorized use of the information.

If the study is expected to continue beyond the expiry date, you are responsible for ensuring the study receives re-approval. The REB must be notified of the completion or termination of this study and a final report provided. As the Principal Investigator, you are responsible for the ethical conduct of this study.

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement, ICH GCP Guidelines and Part C, Division 5 of the Food and Drug Regulations of Health Canada.

Sincerely,

Ronald Heselgrave, Ph.D.
Chair, University Health Network Research Ethics Board

RH/11
Notification of REB Amendment Approval

Date: July 4, 2007

To: Dr. Murray Krahn
EN 14-207, TGH

Re: 06-0931-AE
Health-state Utilities and Quality of Life in Hepatitis B Patients

REB Review Type: Expedited
REB Amendment Approval Date: June 28, 2007
REB Initial Approval Date: March 6, 2007
REB Expiry Date: March 6, 2008

Documents Approved:
Amendment to add Dr. A. Chan & M. Ho Sites (dated April 18, 2007)
Toronto Western Informed Consent Form (ICF) Version #3 (dated June 14, 2007)
Toronto General ICF Version #3 (dated June 14, 2007)
Community ICF Version #3 (dated June 14, 2007)


Best wishes for the successful completion of your project.

Sincerely,

Alex Kerr BSc.
Research Ethics Coordinator

For: Ronald Heslegrave, Ph.D.
Chair, University Health Network Research Ethics Board

AK/cp
Notification of REB Continued Approval***

Date: November 19th, 2009
To: Dr. Murray Krahn
Rm 14E207, Eaton, TGH

Re: 06-0931-AE
Health-state Utilities and Quality of Life in Hepatitis B Patients

REB Review Type: Expedited
REB Initial Approval Date: March 6th, 2007
REB Expiry Date: April 2nd, 2009

***The purpose of this letter is to confirm the REB approval status of the aforementioned study.

The above-named study has received continued approval from the University Health Network Research Ethics Board until the expiry date noted above. If the study is expected to continue beyond the expiry date, you are responsible for ensuring the study receives re-approval. The REB must also be notified of the completion or termination of this study and a final report provided.

If, during the course of the research, there are any serious adverse events, confidentiality concerns, changes in the approved project, or any new information that must be considered with respect to the project, these should be brought to the immediate attention of the REB. In the event of a privacy breach, you are responsible for reporting the breach to the UHN REB and the UHN Corporate Privacy Office (in accordance with Ontario health privacy legislation Personal Health Information Protection Act, 2004). Additionally, the UHN REB requires reports of inappropriate/unauthorized use of the information. As the Principal Investigator, you are responsible for the ethical conduct of this study.

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement, ICH/GCP Guidelines, the Ontario Personal Health Information Protection Act (2004), and Part C, Division 5 of the Food and Drug Regulations of Health Canada.

Sincerely,

Ajay Pillai
Research Ethics Coordinator

For: Ronald Heslegrave, Ph.D.
Chair, University Health Network Research Ethics Board
Appendix D: Patient Consent Forms in English, Cantonese and Mandarin
CONSENT FORM

Title: Health state utilities and quality of life in hepatitis B patients.

Co-Principal Investigators: Dr. Jenny Heathcote
Toronto Western Hospital
399 Bathurst Street
6B Fell Pavillion, Room 154
Toronto, Ontario M5T 2S8
Tel: 416-603-5914

Dr. Murray Krahn
Toronto General Hospital
200 Elizabeth Street
EN 14-207
Toronto, Ontario M5G 2C4
Tel: 416-340-4800 ext. 4155

Co-Investigators: Dr. Morris Sherman
Dr. David Wong
Dr. Alex Chan
Dr. Michael Ho
Ms. Colina Yim

Sponsor: Gilead Sciences

You are being asked to take part in a research study. Before agreeing to participate in this study, it is important that you read and understand the proposed study procedures. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Please ask the study doctor or study staff to explain any words you don’t understand and make sure all your questions have been answered to your satisfaction before signing this document.

Background

The main purpose of this study is to evaluate new methods of measuring quality of life in patients with hepatitis B. The study results will be used to help understand how hepatitis B affects quality of life and to determine which methods are most useful to help doctors and patients make decisions about which treatments are best for hepatitis B patients. The value and cost-effectiveness of new medications for hepatitis B also will be studied.

Purpose

You have been asked to participate in a study because you have been diagnosed with hepatitis B. This study is designed to investigate patient “preferences and utilities” for individuals in the different stages of hepatitis B infection.

Procedures
If you agree to participate in this study, you will be asked to complete a series of surveys and be interviewed by one of the members of the study team. The surveys will ask you about your general health status and about various aspects of your hepatitis B treatments. The surveys should take about 30 minutes while the interview will take about 10 minutes. The survey and interview will be conducted at the same time and can be done while you are waiting for your clinic appointment.

Also, the study team will look at your medical record in order to obtain information about your health status, when you were diagnosed with hepatitis B, the medications that you are taking, your last blood test results that were taken with regard to hepatitis B, any other health conditions that you may have and any information regarding previous liver transplantation due to hepatitis B.

Once you have completed the surveys and interview, your participation in the study will be complete.

Risks
There are no known risks to participating in this study.

Benefits
You may not receive any benefit from your participation in this study. Information learned from this study may help us understand how patients with hepatitis feel about their current health state. This may benefit patients infected with hepatitis B as it could provide evidence to improve access to new medicines for the treatment of hepatitis B.

Confidentiality
If you agree to join this study, the study doctor and his/her study team will look at your personal health information and collect only the information they need for the study. Personal health information is any information that could be used to identify you and includes your:
• name,
• address,
• date of birth,
• new or existing medical records, or
• types, dates and results of medical tests or procedures,

The information that is collected for the study will be kept in a locked and secure area by the study doctor for two years after the study results are published. Only the study team or the people or groups listed below will be allowed to look at your records. Your participation in this study also may be recorded in your medical record at this hospital.

Employees of the University Health Network Research Ethics Board may look at the study records and at your personal health information to check that the study information is correct and to make sure the study followed proper laws and guidelines.

All information collected during this study, including your personal health information, will be kept confidential and will not be released to anyone outside the study unless
required by law. You will not be named in any reports, publications, or presentations that may come from this study.

Participation
Your participation in this study is voluntary. You can choose not to participate or you may withdraw at any time without affecting your medical care.

Questions
If you have any questions about the study, please call Dr. Jenny Heathcote at 416-603-5914.

If you have any questions about your rights as a research participant, please call Dr. R. Heslegrave, Chair of the University Health Network Research Ethics Board at (416) 340-4557.

Consent
I have had the opportunity to discuss this study and my questions have been answered to my satisfaction. I consent to take part in the study with the understanding I may withdraw at any time without affecting my medical care. I understand that I will receive a signed copy of this consent form. I voluntarily consent to participate in this study.

_________________________             ______________________    ____________
Study Subject’s Name  (Please Print)          Study Subject’s Signature     Date

I confirm that I have explained the nature and purpose of the study to the subject named above. I have answered all questions.

_________________________ ______________________      _____________
Name of Person                    Signature          Date

Obtaining Consent

IF THIS CONSENT HAS BEEN VERBALLY TRANSLATED:

I confirm that I have verbally translated this consent form for the study subject noted above, and in my opinion the study subject has understood what I have explained to them.

_________________________                     ________________        ____________
Name of Translator                Signature                   Date

Language of Translation            Relationship to Subject (if applicable)
同意書

研究課題：乙型肝炎患者健康狀況感受及生活質素

共同主要調查人員：Jenny Heathcote 醫生
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Murray Krahn 醫生
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共同調查人員：Morris Sherman 醫生
David Wong 醫生
Alex Chan 醫生
Michael Ho 醫生
Colina Yim 女士

贊助者：Gilead Sciences

我們特此邀請您參加一項研究。在參與這個研究項目前，您有必要閱讀和了解該研究的程序和步驟。在決定是否參加這項研究前，您應該對它的風險和益處有足夠的了解，以便作出明智的決定。這就是所說的先了解，再同意的過程。如果您有不明白的詞句，請找研究醫生或研究職員加以解釋，以確保所有的問題都有了令您滿意的答案，您才簽署這份同意書。

背景
這項研究的主要目標，是對衡量乙型肝炎病人生活質素的新方法作出考量。研究成果將會用來幫助更好地了解乙型肝炎如何影響生活質素，以及確定哪些方法能最有效地幫助醫生和病人找出最佳的治療方案。治療乙型肝炎的新藥物的價值和成本效益，也將是研究的對象。

目的
我們請您參加這項研究，是因為您已被診斷患有乙型肝炎。該研究的目的是調查病人在乙型肝炎不同階段的「偏好及感受」。

程序
如果您同意参加此项研究，您将需要完成一系列的问卷调查，并与我们研究小组的某一成员作双向交谈。问卷将询问您的整体健康状况，以及您所接受的乙型肝炎治疗的各方面情况。问卷调查大概需要30分钟，交谈大概需要10分钟。问卷及交谈将同时进行，并可在您候诊的时间进行。

同时，研究人员也会查阅您的病历，以便获取有关您健康状况的资讯，您何时被诊断患有乙型肝炎，您正在服用的药物，您上次有关乙型肝炎的检验报告，您可能有的任何医疗症状，以及任何有关从前因乙型肝炎引起肝移植的资料。

在您完成问卷及交谈后，您参与该项研究的义务就完成了。

风险
目前所知参与此项研究没有任何风险。

得益
您参加此项研究也许不会得到任何益处。该研究所获得的信息可能帮助我们了解乙型肝炎病人对他们的现有健康状况的感受。这可能对乙型肝炎病人有益，因为它能够提供有关证据，使病人获得治疗乙型肝炎的新药物更加便利。

保密
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- 名字，
- 地址，
- 出生日期，
- 新的或既有的病历，或
- 体检或医疗手术的类型、日期及结果。

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参与
您参与该项研究是自愿行为。您可以选择不参与或随时退出，这对您的就医没有影响。

问题
如果您對此研究有任何疑問，請致電Jenny Heathcote 醫生，電話號碼416-603-5914。

如果您對您作為研究參與者的權利有任何疑問，請致電R. HESLEGRAVE 醫生，他是大學健康網絡研究操守委員會的主席，電話號碼416 340-4557。

同意
有關人員已與我探討過這項研究，並令我滿意地解答了我的所有問題。我同意參與這項研究，但我清楚我可以隨時退出而不會影響我的就醫。我明白我將保留一份經過簽名的同意書副本。我自願同意參與這項研究。

研究對象姓名(請工整書寫)        研究對象簽名        日期

我確認我已向上述研究對象解釋過該研究的性質和目的。我已解答所有的問題。

征求同意的職員姓名        職員簽名        日期

如果這份同意書經過口頭傳譯：

我確認我已經向上述研究對象口頭傳譯了以上同意書，我個人認為研究對象已經明白我所解释的內容。

傳譯員姓名        傳譯員簽名        日期

傳譯語言        傳譯員與研究對象的關係(如適用)
同意书

研究课题：乙型肝炎患者健康状况感受及生活质素

共同主要调查人员：Jenny Heathcote 医生
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Toronto General Hospital
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Toronto, Ontario M5G 2C4
电话：416-340-4800 内线. 4756

David Wong 医生
Alex Chan 医生
Michael Ho 医生
Colina Yim 女士

赞助者：Gilead Sciences

我们特此邀请您参加一项研究。在参与这个研究项目前，您有必要阅读和了解该研究的程序和步骤。在决定是否参加这项研究前，您应该对它的风险和益处有足够的了解，以便作出明智的决定。这就是所说的先了解，再同意的过程。如果您有不明白的词句，请找研究医生或研究职员加以解释，以确保所有的问题都有了令您满意的答案，您才签署这份同意书。

背景
这项研究的主要目标，是对衡量乙型肝炎病人生活质素的新方法作出考量。研究成果将会用来帮助更好地了解乙型肝炎如何影响生活质素，以及确定哪些方法能最有效地帮助医生和病人找出最佳的治疗方案。治疗乙型肝炎的新药物的价值和成本效益，也将是研究的对象。

目的
我们请您参加这项研究，是因为您已被诊断患有乙型肝炎。该研究的目的是调查病人在乙型肝炎不同阶段的 「偏好及感受」。

程序
如果您同意参加此项研究，您将需要完成一系列的问卷调查，并与我们研究小组的某一成员作双向交谈。问卷将询问您的整体健康状况，以及您所接受的乙型肝炎治疗的各方面情况。
问卷调查大概需要30分钟，交谈大概需要10分钟。问卷及交谈将同时进行，并可在您候诊的时间进行。

同时，研究人员也会查阅您的病历，以获取有关您健康状况的资讯，您何时被诊断患有乙型肝炎，您正在服用的药物，您上次有关乙型肝炎的验血报告，您可能有的任何医疗症状，以及任何有关从前因乙型肝炎引起肝移植的资料。

在您完成问卷及交谈后，您参与该项研究的任务就完成了。

风险
目前所知参与此项研究没有任何风险。

得益
您参加该项研究也许不会得到任何益处。该研究所获得的信息可能帮助我们了解乙型肝炎病人对他们现有健康状况的感受。这可能对乙型肝炎病人有益，因为它能够提供有关证据，使病人获得治疗乙型肝炎的新药物更加便利。

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问题
如果您对此研究有任何疑问，请致电Morris Sherman 医生，电话号码416-340-4800，内线4756。
如果您对您作为研究参与者的权利有任何疑问，请致电R. HESLEGRAVE医生，他是大学健康网络研究操守委员会的主席，电话号码416 340-4557。

同意
有关人员已与我探讨过这项研究，并令我满意地解答了我的所有问题。我同意参与这项研究，但我清楚我可以随时退出而不会影响我的就医。我明白我将保留一份经过签名的同意书副本。我自愿同意参与这项研究。

研究对象姓名(请工整书写)        研究对象签名        日期

我确认我已向上述研究对象解释过该研究的性质和目的。我已解答所有的问题。

征求同意的职员姓名        职员签名        日期

如果这份同意书经过口头传译：

我确认我已经向上述研究对象口头传译了以上同意书，我个人认为研究对象已经明白我所解释的内容。

传译员姓名        传译员签名        日期

传译语言        传译员与研究对象的关系(如适用)
Appendix E: Quality of Life Assessment Tools
EQ - 5D

Health Questionnaire

(Canadian English version)
By placing a check-mark in one box in each group below, please indicate which statements best describe your own state of health today.

**Mobility**
- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

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

**Usual Activities (e.g. work, study, housework, family or leisure activities)**
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

**Pain/Discomfort**
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

**Anxiety/Depression**
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed
To help people say how good or bad their state of health is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your state of health is today.
This questionnaire contains a set of questions which ask about various aspects of your health. When answering these questions please think about your health and your ability to do things on a day-to-day basis, during the past 2 weeks. To define the 2 week period, please think about what the date was 2 weeks ago and recall the major events that you have experienced during this period. Please focus your answers on your abilities, disabilities and how you have felt during the past 2 weeks.

You may feel that some of these questions do not apply to you, but it is important that we ask the same questions of everyone. Also, a few questions are similar; please excuse the apparent overlap and answer each question independently.

Please read each question and consider your answers carefully. For each question, please select one answer that best describes your level of ability or disability during the past 2 weeks. Please indicate the selected answer by circling the letter (a, b, c, …) beside the answer.

All information you provide is confidential. There are no right or wrong answers; what we want is your opinion about your abilities and feelings.

1. Which one of the following best describes your ability, during the past 2 weeks, to see well enough to recognize a friend on the other side of the street?
   a. Able to see well enough without glasses or contact lenses.
   b. Able to see well enough with glasses or contact lenses.
   c. Unable to see well enough even with glasses or contact lenses.
   d. Unable to see at all.

2. Which one of the following best describes your ability, during the past 2 weeks, to hear what was said in a group conversation with at least three other people?
   a. Able to hear what was said without a hearing aid.
   b. Able to hear what was said with a hearing aid.
   c. Unable to hear what was said even with a hearing aid.
   d. Unable to hear what was said, but did not wear a hearing aid.
   e. Unable to hear at all.

3. Which one of the following best describes your ability, during the past 2 weeks, to hear what was said
in a group conversation with at least three other people?

a. Able to hear what was said without a hearing aid.
b. Able to hear what was said with a hearing aid.
c. Unable to hear what was said even with a hearing aid.
d. Unable to hear what was said, but did not wear a hearing aid.
e. Unable to hear at all.

4. Which one of the following best describes your ability, during the past 2 weeks, to hear what was said in a conversation with one other person in a quiet room?

a. Able to hear what was said without a hearing aid.
b. Able to hear what was said with a hearing aid.
c. Unable to hear what was said even with a hearing aid.
d. Unable to hear what was said, but did not wear a hearing aid.
e. Unable to hear at all.

5. Which one of the following best describes your ability, during the past 2 weeks, to be understood when speaking your own language with people who do not know you?

a. Able to be understood completely.
b. Able to be understood partially.
c. Unable to be understood.
d. Unable to speak at all.

6. Which one of the following best describes your ability, during the past 2 weeks, to be understood when speaking with people who know you well?

a. Able to be understood completely.
b. Able to be understood partially.
c. Unable to be understood.
d. Unable to speak at all.

7. Which one of the following best describes how you have been feeling during the past 2 weeks?

a. Happy and interested in life.
b. Somewhat happy.

c. Somewhat unhappy.

d. Very unhappy.

e. So unhappy that life was not worthwhile.

8. Which one of the following best describes the pain and discomfort you have experienced during the past 2 weeks?

   a. Free of pain and discomfort.
   
   b. Mild to moderate pain or discomfort that prevented no activities.
   
   c. Moderate pain or discomfort that prevented some activities.
   
   d. Moderate to severe pain or discomfort that prevented some activities.
   
   e. Severe pain or discomfort that prevented most activities.

9. Which one of the following best describes your ability, during the past 2 weeks, to walk?

   Note: Walking equipment refers to mechanical supports such as braces, a cane, crutches or a walker.

   a. Able to walk around the neighbourhood without difficulty, and without walking equipment.
   
   b. Able to walk around the neighbourhood with difficulty; but did not require walking equipment or the help of another person.
   
   c. Able to walk around the neighbourhood with walking equipment, but without the help of another person.
   
   d. Able to walk only short distances with walking equipment, and required a wheelchair to get around the neighbourhood.
   
   e. Unable to walk alone, even with walking equipment. Able to walk short distances with the help of another person, and required a wheelchair to get around the neighbourhood.
   
   f. Unable to walk at all.
10. Which one of the following best describes your ability, during the past 2 weeks, to use your hands and fingers? **Note:** Special tools refers to hooks for buttoning clothes, gripping devices for opening jars or lifting small items, and other devices to compensate for limitations of hands or fingers.

   a. Full use of two hands and ten fingers.

   b. Limitations in the use of hands or fingers, but did not require special tools or the help of another person.

   c. Limitations in the use of hands or fingers, independent with use of special tools (did not require the help of another person).

   d. Limitations in the use of hands or fingers, required the help of another person for some tasks (not independent even with use of special tools).

   e. Limitations in the use of hands or fingers, required the help of another person for most tasks (not independent even with use of special tools).

   f. Limitations in the use of hands or fingers, required the help of another person for all tasks (not independent even with use of special tools).

11. Which one of the following best describes your ability, during the past 2 weeks, to remember things?

   a. Able to remember most things.

   b. Somewhat forgetful.

   c. Very forgetful.

   d. Unable to remember anything at all.

12. Which one of the following best describes your ability, during the past 2 weeks, to think and solve day to day problems?

   a. Able to think clearly and solve day to day problems.

   b. Had a little difficulty when trying to think and solve day to day problems.

   c. Had some difficulty when trying to think and solve day to day problems.

   d. Had great difficulty when trying to think and solve day to day problems.

   e. Unable to think or solve day to day problems.
13. Which one of the following best describes your ability, during the past 2 weeks, to perform basic activities?
   a. Eat, bathe, dress and use the toilet normally.
   b. Eat, bathe, dress or use the toilet independently with difficulty.
   c. Required mechanical equipment to eat, bathe, dress or use the toilet independently.
   d. Required the help of another person to eat, bathe, dress or use the toilet.

14. Which one of the following best describes how you have been feeling during the past 2 weeks?
   a. Generally happy and free from worry.
   b. Occasionally fretful, angry, irritable, anxious or depressed.
   c. Often fretful, angry, irritable, anxious or depressed.
   d. Almost always fretful, angry, irritable, anxious or depressed.
   e. Extremely fretful, angry, irritable, anxious or depressed; to the point of needing professional help.

15. Which one of the following best describes the pain or discomfort you have experienced during the past 2 weeks?
   a. Free of pain and discomfort.
   b. Occasional pain or discomfort. Discomfort relieved by non-prescription drugs or self-control activity without disruption of normal activities.
   c. Frequent pain or discomfort. Discomfort relieved by oral medicines with occasional disruption of normal activities.
   d. Frequent pain or discomfort; frequent disruption of normal activities. Discomfort required prescription narcotics for relief.
   e. Severe pain or discomfort. Pain not relieved by drugs and constantly disrupted normal activities.
16. Overall, how would you rate your health during the past 2 weeks?
   a. Excellent.
   b. Very good.
   c. Good.
   d. Fair.
   e. Poor.

17. How did you complete the questionnaire? Please select the one answer that best describes your situation.
   a. By myself, without any help from anyone else.
   b. By myself, except someone else circled the answers on the questionnaire form for me.
   c. With the help of someone else.
   d. This questionnaire was completed by a family member, without help from the subject or patient.
   e. This questionnaire was completed by a nurse or other health professional, without help from the subject or patient.
      Please specify type of health professional: ________________________________
   f. This questionnaire was completed by another person, without help from the subject or patient.
      Please specify relationship to subject or patient: ________________________

Thank you.
That ends this set of questions.
Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please mark an ✑ in the one box that best describes your answer.

1. In general, would you say your health is:

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>□₁</td>
<td>□₂</td>
<td>□₃</td>
<td>□₄</td>
<td>□₅</td>
</tr>
</tbody>
</table>

2. Compared to one year ago, how would you rate your health in general now?

<table>
<thead>
<tr>
<th>Much better now than one year ago</th>
<th>Somewhat better now than one year ago</th>
<th>About the same as one year ago</th>
<th>Somewhat worse now than one year ago</th>
<th>Much worse now than one year ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
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<tr>
<td>□₁</td>
<td>□₂</td>
<td>□₃</td>
<td>□₄</td>
<td>□₅</td>
</tr>
</tbody>
</table>
3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

<table>
<thead>
<tr>
<th>Activity</th>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>c Lifting or carrying groceries</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>d Climbing several flights of stairs</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>e Climbing one flight of stairs</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>f Bending, kneeling, or stooping</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>g Walking more than a mile</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>h Walking several hundred yards</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>i Walking one hundred yards</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>j Bathing or dressing yourself</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

a. Cut down on the amount of time you spent on work or other activities ........................................... □1 □2 □3 □4 □5

b. Accomplished less than you would like .................................. □1 □2 □3 □4 □5

c. Were limited in the kind of work or other activities .......................................................... □1 □2 □3 □4 □5
d. Had difficulty performing the work or other activities (for example, it took extra effort) ........... □1 □2 □3 □4 □5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

a. Cut down on the amount of time you spent on work or other activities ........................................... □1 □2 □3 □4 □5

b. Accomplished less than you would like .................................. □1 □2 □3 □4 □5

c. Did work or other activities less carefully than usual .......................................................... □1 □2 □3 □4 □5
6. During the **past 4 weeks**, to what extent has your **physical health** or **emotional problems** interfered with your normal social activities with family, friends, neighbors, or groups?

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>□₃</td>
<td>□₄</td>
<td>□₅</td>
</tr>
</tbody>
</table>

7. How much **bodily** pain have you had during the **past 4 weeks**?

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Very mild</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
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<td>□₅</td>
<td>□₆</td>
</tr>
</tbody>
</table>

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>□₂</td>
<td>□₃</td>
<td>□₄</td>
<td>□₅</td>
</tr>
</tbody>
</table>
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- Did you feel full of life? ..........................................
- Have you been very nervous? ........................................
- Have you felt so down in the dumps that nothing could cheer you up? ................................
- Have you felt calm and peaceful? ................................
- Did you have a lot of energy? .......................................
- Have you felt downhearted and depressed? ........................
- Did you feel worn out? ...............................................
- Have you been happy? ..................................................
- Did you feel tired? ....................................................
10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
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<td>□2</td>
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<td>□4</td>
<td>□5</td>
</tr>
</tbody>
</table>

11. How TRUE or FALSE is each of the following statements for you?

<table>
<thead>
<tr>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don't know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

a. I seem to get sick a little easier than other people ........................................... □1 ............ □2 ............ □3 ............ □4 ............ □5

b. I am as healthy as anybody I know ........................................... □1 ............ □2 ............ □3 ............ □4 ............ □5

c. I expect my health to get worse ........................................... □1 ............ □2 ............ □3 ............ □4 ............ □5

d. My health is excellent ........................................... □1 ............ □2 ............ □3 ............ □4 ............ □5

THANK YOU FOR COMPLETING THESE QUESTIONS!
EQ - 5D

健康問卷

供香港地區使用之版本

(Chinese version for Hong Kong)
請在下列各組選項中，指出哪一項敘述最能描述您今天的健康狀況，並在空格內填寫。

**行動**

我可以四處走動，沒有任何問題。 □

我行動有些不便。 □

我臥病在床。 □

**自我照顧**

我能照顧自己，沒有任何問題。 □

我在盥洗、洗澡或穿衣方面有些問題。 □

我無法自己盥洗、洗澡或穿衣。 □

**平常活動（如工作、讀書、家事、家庭或休閒活動）**

我能進行平常活動，沒有任何問題。 □

我在進行平常活動方面有些問題。 □

我無法進行平常活動。 □

**疼痛 / 不舒服**

我沒有任何疼痛或不舒服。 □

我覺得中度疼痛或不舒服。 □

我覺得極度疼痛或不舒服。 □

**焦慮 / 沮喪**

我不覺得焦慮或沮丧。 □

我覺得中度焦慮或沮喪。 □

我覺得極度焦慮或沮喪。 □
為了幫助一般人事述健康狀況的好壞，我們畫了一個刻度尺（有點像溫度計），在這刻度尺上，100 代表您心目中最理想的狀況，0 代表您心目中最差的狀況。

我們希望就您的看法，在這個刻度尺上標出您今天健康狀況的好壞。請從下面方格中畫出一條線，連到刻度尺上最能代表您今天健康狀況好壞的那一點。

您今天的
健康狀況
HUI23S2Cl.15Q
HEALTH UTILITIES INDEX MARK 2 和 MARK 3 (HUI2/3)

15題問卷，由受訪人自填，自我評估過去「二個星期」健康狀況之測量

答題說明：

本問卷包含一系列問題，要請教您健康的各方面狀況。當回答這些問題時，請您回想過去2個星期中，每一天您的健康以及您進行日常活動的能力。過去的2個星期是指，14天之前的日期到今天，請回顧這段期間您所經歷的主要事件與活動。在選擇問卷答案時，請將重點放在過去2個星期中，您整體的能力，喪失的能力，以及您的感受。

您可能會覺得，下面一些問題中所涉及的事情，是您沒有經歷過的，但請原諒我們要對每一個人問相同的問題。另外，有幾個問題可能會很相似，也請您包涵這些重複的問題，請您針對每一個問題單獨個別地回答。

請您仔細閱讀和回答每一個問題。對每一題，請選擇一個答案來最適當地描述您在過去2個星期中，能力的大小或能力喪失的程度。您的答案請以圈選各題選項前的字母 (a、b、c等等) 來表示。

您提供的所有資訊都會被保密的。這裡面沒有正確或錯誤的答案；我們想知道的是您對於自己能力和感覺的看法。

1. 下列哪一項能最適當地描述您在過去2個星期中，看清楚一般報紙的能力？
   a. 能夠看清楚，不需要戴眼鏡或隱形眼鏡。
   b. 能夠看清楚，但需要戴眼鏡或隱形眼鏡。
   c. 看不清楚，即使戴眼鏡或隱形眼鏡也不行。
   d. 完全看不見東西。

2. 下列哪一項能最適當地描述您在過去2個星期中，看清楚而認出馬路對面朋友的能力？
   a. 能夠看清楚，不需要戴眼鏡或隱形眼鏡。
   b. 能夠看清楚，但需要戴眼鏡或隱形眼鏡。
   c. 看不清楚，即使戴眼鏡或隱形眼鏡也不行。
   d. 完全看不見東西。
3. 下列哪一项能最适当地描述您在过去2个星期中，与其他人至少三人一起谈话时，听清楚谈话内容的能力？
   a. 能够听清楚谈话内容，不需要助听器具。
   b. 能够听清楚谈话内容，但需要助听器具。
   c. 聆听不清楚谈话内容，使用助听器具也不行。
   d. 聆听不清楚谈话内容，但没有戴助听器具。
   e. 完全听不到。

4. 下列哪一项能最适当地描述您在过去2个星期中，与另一人在一个安静的房间内交谈时，听清楚交谈内容的能力？
   a. 能够听清楚谈话内容，不需要助听器具。
   b. 能够听清楚谈话内容，但需要助听器具。
   c. 聆听不清楚谈话内容，使用助听器具也不行。
   d. 聆听不清楚谈话内容，但没有戴助听器具。
   e. 完全听不到。

5. 下列哪一项能最适当地描述您在过去2个星期中，使用您常用的语言与陌生人谈话时，让对方听得懂的能力？
   a. 能够让对方完全地听懂我所说的话。
   b. 能够让对方部分地听懂我所说的话。
   c. 无法让对方听懂我所说的话。
   d. 我完全不能说话。
6. 下列哪一項能最適當地描述您在過去2個星期中，與熟人談話時，讓對方聽懂的能力？
   a. 能夠讓對方完全地聽懂我說的話。
   b. 能夠讓對方部份地聽懂我說的話。
   c. 無法讓對方聽懂我說的話。
   d. 我完全不能說話。

7. 下列哪一項能最適當地描述您在過去2個星期中的感覺？
   a. 快樂，認為生活有樂趣。
   b. 有點快樂。
   c. 有點不快樂。
   d. 很不快樂。
   e. 非常不快樂，覺得活著沒什麼意思。

8. 下列哪一項能最適當地描述您在過去2個星期中，所經歷的疼痛和不舒服？
   a. 沒有疼痛和不舒服。
   b. 有輕微至中等程度的疼痛或不舒服，但不影響從事任何活動。
   c. 有中等程度的疼痛或不舒服，以致少數活動不能執行。
   d. 有中等至嚴重程度的疼痛或不舒服，以致不能從事某些活動。
   e. 有嚴重的疼痛或不舒服，以致不能從事大多數活動。
9. 下列哪一項能最適當地描述您在過去2個星期中，走路的能力？
   說明：「走路設備」是指機械支持物，譬如：支架、拐杖或助行器。
   a. 能夠在住所附近地方走動，沒有任何困難，不需要走路設備。
   b. 能夠在住所附近地方走動，有些困難，但不需要走路設備或別人幫助。
   c. 能夠在住所附近地方走動，需要走路設備，但不需要別人幫助。
   d. 使用走路設備也只能走很短的距離，需要輪椅才能在住所附近地方活動。
   e. 即使使用走路設備也無法自己走路，有人幫助時能走很短的距離，需要輪椅才能在住所附近地方活動。
   f. 完全不能走路。

10. 下列哪一項能最適當地描述您在過去2個星期中，使用手和手指的能力？
    說明：「特殊工具」是指繫衣服鈕扣的勾子、開廣口罐或舉起小物品的抓握器具，以及其他協助克服手或手指殘障的工具。
    a. 能夠完全自如地使用兩隻手和十隻手指。
    b. 手或手指的功能不健全，但不需要特殊工具或別人幫助。
    c. 手或手指的功能不健全，使用特殊工具時，可以自己做好事情 (不需要別人幫助)。
    d. 手或手指的功能不健全，做某些事情時，需要別人幫助 (即使使用特殊工具，也不能自己做好)。
    e. 手或手指的功能不健全，做大多數事情時，需要別人幫助 (即使使用特殊工具，也不能自己做好)。
    f. 手或手指的功能不健全，做所有的事情時，都需要別人幫助 (即使使用特殊工具，也不能自己做好)。
11. 下列哪一項能最適當地描述您在過去2個星期中的記憶力？
   a. 能夠記住大多數的事情。
   b. 有點健忘。
   c. 非常健忘。
   d. 無法記住任何事情。

12. 下列哪一項能最適當地描述您在過去2個星期中，思考和解決日常生活問題的能力？
   a. 能夠清楚地思考和解決日常生活中的問題。
   b. 當嘗試去思考和解決日常生活中的問題時，有一點點困難。
   c. 當嘗試去思考和解決日常生活中的問題時，有較多困難。
   d. 當嘗試去思考和解決日常生活中的問題時，有很大困難。
   e. 無法思考或解決日常生活中的問題。

13. 下列哪一項能最適當地描述您在過去2個星期中，進行一些基本活動的能力？
   a. 能夠正常地吃東西，洗澡，穿衣服和上廁所。
   b. 能夠自行吃東西，洗澡，穿衣服，或上廁所，但有些困難。
   c. 能夠自行吃東西，洗澡，穿衣服，或上廁所，但需要機械工具幫助。
   d. 需要別人幫助才能吃東西，洗澡，穿衣服，或上廁所。
14. 下列哪一項能最適當地描述您在過去2個星期中的感覺？
   a. 整體上快樂，沒有什麼煩惱。
   b. 偶爾煩躁、生氣、易怒、憂慮或沮喪。
   c. 經常煩躁、生氣、易怒、憂慮或沮喪。
   d. 總是煩躁、生氣、易怒、憂慮或沮喪。
   e. 極度煩躁、生氣、易怒、憂慮或沮喪，達到需要看醫生的程度。

15. 下列哪一項能最適當地描述您在過去2個星期中，所經歷的疼痛或不舒服？
   說明：「非處方藥物」是指不需經由醫師開立處方即可購買的藥品。
   a. 沒有疼痛和不舒服。
   b. 偶爾疼痛或不舒服。使用非處方藥物或自我調適後，可以解除不舒服現象，
      不會妨礙正常的活動。
   c. 經常疼痛或不舒服。使用口服藥物，可解除不舒服現象，但偶爾會妨礙正常的活動。
   d. 經常疼痛或不舒服，且經常妨礙正常的活動，需要使用麻醉止痛藥才能止痛。
   e. 非常嚴重的疼痛或不舒服。藥物根本無法止痛，持續地妨礙正常的活動。

16. 整體來說，您認為在過去2個星期中，您的健康狀況如何？
   a. 極好
   b. 很好
   c. 好
   d. 一般
   e. 差
17. 您是如何完成這份問卷的？請選出一個最能描述您狀況的答案。

a. 我自己完成的，沒有其他任何人的幫助。

b. 我自己完成的，但問卷上的答案是請別人幫我圈的。

c. 有別人的幫助。

d. 這份問卷是由一位家屬完成的，被調查的(病)人沒有參與。

e. 這份問卷是由一位護士或其他醫務人員完成的，被調查的(病)人沒有參與。
   請說明醫務人員的類別：______________________________________

f. 這份問卷是由另一人完成的，被調查的(病)人沒有參與。
   請說明回答問卷的人與被調查的(病)人的關係：___________________

謝謝您！問卷到此結束。
您的身心健康狀況

這項調查是詢問您對自己健康狀況的了解。此項資料記錄您的自我感覺和日常生活的情況。謝謝您回答這份問卷!

敬請回答下列各問題並在最適當的答案畫一個(□)。

1. 總括來說，您認為您的健康狀況是:

<table>
<thead>
<tr>
<th>極好</th>
<th>很好</th>
<th>好</th>
<th>一般</th>
<th>差</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
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<td>□3</td>
<td>□4</td>
<td>□5</td>
</tr>
</tbody>
</table>

2. 和一年前相比較，您認為您目前全面的健康狀況如何?

<table>
<thead>
<tr>
<th>比一年前好多了</th>
<th>比一年前好一些</th>
<th>和一年前差不多</th>
<th>比一年前差一些</th>
<th>比一年前差多了</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
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<td>□4</td>
<td>□5</td>
</tr>
</tbody>
</table>
3. 下列問題是關於您日常生活中可能進行的活動。以您目前的健康狀況，您在進行這些活動時，有沒有受到限制？如果有的話，程度如何？

<table>
<thead>
<tr>
<th>活動描述</th>
<th>有很大限制</th>
<th>有一點限制</th>
<th>沒有任何限制</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. 創烈活動，比如跑步、搬重物或參加劇烈的體育活動</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>b. 中等強度的活動，比如搬桌子、使用吸塵器清潔地面、玩保齡球或打太極拳</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>c. 提起或攜帶蔬菜、食品或雜貨</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>d. 上幾層樓梯</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>e. 上一層樓梯</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>f. 彎腰、跪下或俯身</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>g. 步行一公里以上</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>h. 步行幾百米</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>i. 步行一百米</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>j. 自己洗澡或穿衣服</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>
4. 在過去四個星期裏，您在工作或其它日常活動中，有多少時間會因為身體健康的原因而遇到下列的問題？

<table>
<thead>
<tr>
<th>常常</th>
<th>大部分</th>
<th>有時</th>
<th>偶爾</th>
<th>從來</th>
</tr>
</thead>
<tbody>
<tr>
<td>如此</td>
<td>時間</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- a. 減少了工作或其它活動的時間 ........................................... □ 1 .............. □ 2 ............ □ 3 .............. □ 4 ............ □ 5
- b. 實際做完的比想做的要少 ........................................... □ 1 .............. □ 2 ............ □ 3 .............. □ 4 ............ □ 5
- c. 工作或其它活動的種類受到限制 ........................................... □ 1 .............. □ 2 ............ □ 3 .............. □ 4 ............ □ 5
- d. 進行工作或其它活動時有困難（比如覺得更為吃力） ........................................... □ 1 .............. □ 2 ............ □ 3 .............. □ 4 ............ □ 5

5. 在過去的四個星期裏，您在工作或其它日常活動中，有多少時間由於情緒方面的原因（比如感到沮喪或焦慮）遇到下列的問題？

<table>
<thead>
<tr>
<th>常常</th>
<th>大部分</th>
<th>有時</th>
<th>偶爾</th>
<th>從來</th>
</tr>
</thead>
<tbody>
<tr>
<td>如此</td>
<td>時間</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- a. 減少了工作或其它日常活動的時間 ........................................... □ 1 .............. □ 2 ............ □ 3 .............. □ 4 ............ □ 5
- b. 實際做完的比想做的要少 ........................................... □ 1 .............. □ 2 ............ □ 3 .............. □ 4 ............ □ 5
- c. 工作時或從事其它活動時不如往常細心了 ........................................... □ 1 .............. □ 2 ............ □ 3 .............. □ 4 ............ □ 5
6. 在過去四個星期裏，您的身體健康或情緒問題在多大程度上妨礙了您與家人、朋友、鄰居或社團的日常社交活動？

<table>
<thead>
<tr>
<th>毫無妨礙</th>
<th>有很少妨礙</th>
<th>有一些妨礙</th>
<th>有較大妨礙</th>
<th>有極大妨礙</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

1 2 3 4 5

7. 在過去四個星期裏，您的身體有沒有疼痛？如果有的話，疼痛到什麼程度？

<table>
<thead>
<tr>
<th>完全沒有疼痛</th>
<th>很輕微</th>
<th>輕微</th>
<th>有一些</th>
<th>剎烈</th>
<th>非常劇烈</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

1 2 3 4 5 6

8. 在過去四個星期裏，您身體上的疼痛對您的日常工作（包括上班和家務）有多大影響？

<table>
<thead>
<tr>
<th>毫無影響</th>
<th>有很少影響</th>
<th>有一些影響</th>
<th>有較大影響</th>
<th>有極大影響</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

1 2 3 4 5
9. 下列問題是有關您在過去四個星期裏您覺得怎樣和您其它的情況。針對每一個問題，請選擇一個最接近您的感覺的答案。在過去四個星期裏，有多少時間：

常 常
大 部 分
時 間
有 時
偶 爾
從 經

a. 您覺得充滿活力？.......................... □ 1 ................ □ 2 ................ □ 3 ................ □ 4 ................ □ 5
b. 您覺得精神非常緊張？....................... □ 1 ................ □ 2 ................ □ 3 ................ □ 4 ................ □ 5
c. 您覺得情緒低落，以至於沒有任何事能使您高興起來？........ □ 1 ................ □ 2 ................ □ 3 ................ □ 4 ................ □ 5
d. 您感到心平氣和？.......................... □ 1 ................ □ 2 ................ □ 3 ................ □ 4 ................ □ 5
e. 您感到精力充足？.......................... □ 1 ................ □ 2 ................ □ 3 ................ □ 4 ................ □ 5
f. 您覺得心情不好，悶悶不樂？......... □ 1 ................ □ 2 ................ □ 3 ................ □ 4 ................ □ 5
g. 您感到筋疲力盡？.......................... □ 1 ................ □ 2 ................ □ 3 ................ □ 4 ................ □ 5
h. 您感到快樂？.............................. □ 1 ................ □ 2 ................ □ 3 ................ □ 4 ................ □ 5
i. 您覺得疲倦？.............................. □ 1 ................ □ 2 ................ □ 3 ................ □ 4 ................ □ 5

10. 在過去四個星期裏，有多少時間由於您的身體健康或情緒問題妨礙了您的社交活動（比如探親，訪友等）？

常 常
大 部 分
時 間
有 時
偶 爾
從 經

□ 1 □ 2 □ 3 □ 4 □ 5
11. 如果用下列的句子来形容您，您认为有多正确？

<table>
<thead>
<tr>
<th>肯定对</th>
<th>大致对</th>
<th>不知道</th>
<th>大致不对</th>
<th>肯定不对</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

a. 您好像比别人更容易生病 ........................................... 1 .............. 2 ............ 3 ............... 4 ............ 5

b. 您好像所有您认识的人一样
   健康 ................................................................ 1 .............. 2 ............ 3 ............... 4 ............ 5

c. 您觉得自己的身体状况会
   变坏 ................................................................ 1 .............. 2 ............ 3 ............... 4 ............ 5

d. 您的健康极好 ...................................................... 1 .............. 2 ............ 3 ............... 4 ............ 5

谢谢您回答这些问题！
EQ - 5D

健康问卷

供中国地区使用之中文版

Chinese version for China
请在下列各组选项中，指出哪一项最能反映您的健康状况，并在空格内打勾(✓)。

**行动**
- 我可以四处走动，没有任何困难。
- 我行动有些不方便。
- 我不能下床活动。

**自己照顾自己**
- 我能自己照顾自己，没有任何困难。
- 我在洗脸、刷牙、洗澡或穿衣方面有些困难。
- 我无法自己洗脸、刷牙、洗澡或穿衣。

**日常活动（如工作，学习，家务事，家庭或休闲活动）**
- 我能进行日常活动，没有任何困难。
- 我在进行日常活动方面有些困难。
- 我无法进行日常活动。

**疼痛 / 不舒服**
- 我没有任何疼痛或不舒服。
- 我觉得中度疼痛或不舒服。
- 我觉得极度疼痛或不舒服。

**焦虑（如紧张、担心、不安等等）/ 抑郁（如做事情缺乏兴趣、没乐趣、提不起精神等等）**
- 我不觉得焦虑或抑郁。
- 我觉得中度焦虑或抑郁。
- 我觉得极度焦虑或抑郁。
为了帮助您反映健康状况的好坏，我们画了一个刻度尺（有点像温度计），在这刻度尺上，
100 代表您心目中的最好的状况，0 代表您心目中最差的状况。

请在右边的刻度尺上标出您今天的健康状况。
请从下面方格中画出一条线，连到刻度尺上
最能代表您今天健康状况好坏的那一点。

您今天的
健康状况
答题说明：

此问卷包含一组问题，要询问您各方面的健康状况。当回答这些问题时，请您回想一下在过去的2个星期中的健康状况，以及进行日常活动的能力。过去的2个星期是指，自14天之前的日期到今天，请回顾一下您在这段时间所经历的主要活动。在选择答案时，请集中考虑在过去2个星期中，您整体的能力、丧失的能力，和您的感觉。

您可能会觉得下面一些问题中所涉及的事情，是您没有经历过的，但请原谅我们要对每一个人问相同的问题。另外，有几个问题可能会很相似，请您原谅这些重复的提问，对每一个问题单独个别地回答。

请您仔细阅读和回答每一个问题。对每一个问题，请选择一个最恰当的答案来描述您在过去2个星期中能力的大小或能力丧失的程度。请圈出所选答案前面的字母(a、b、c、等等)，来表示您的答案。

您提供的所有信息将被保密。答案没有正确或错误之分。我们想知道的是您对自己的能力和感觉的看法。

1. 下列哪一项最恰当地描述您在过去2个星期中，看清楚普通报纸的能力？
   a. 能够看清楚，不需要戴眼镜或隐形眼镜。
   b. 能够看清楚，但需要戴眼镜或隐形眼镜。
   c. 看不清楚，即使戴眼镜或隐形眼镜也不行。
   d. 完全看不见东西。

2. 下列哪一项最恰当地描述您在过去2个星期中，看清楚而认出马路对面的朋友的能力？
   a. 能够看清楚，不需要戴眼镜或隐形眼镜。
   b. 能够看清楚，但需要戴眼镜或隐形眼镜。
c. 看不清楚，即使戴眼镜或隐形眼镜也不行。

d. 完全看不见东西。

3. 下列哪一项最恰当地描述您在过去2个星期中，和其他至少三个人一起谈话时，听清楚谈话内容的能力？

   a. 能够听清楚谈话内容，不需要助听器具。
   
   b. 能够听清楚谈话内容，但需要助听器具。
   
   c. 听不清楚谈话内容，即使用助听器具也不行。
   
   d. 听不清楚谈话内容，但没用过助听器具。
   
   e. 完全听不到。

4. 下列哪一项最恰当地描述您在过去2个星期中，和另外一个人在安静的房间谈话时，听清楚谈话内容的能力？

   a. 能够听清楚谈话内容，不需要助听器具。
   
   b. 能够听清楚谈话内容，但需要助听器具。
   
   c. 听不清楚谈话内容，即使用助听器具也不行。
   
   d. 听不清楚谈话内容，但没用过助听器具。
   
   e. 完全听不到。

5. 下列哪一项最恰当地描述您在过去2个星期中，使用您常用的语言与陌生人谈话时，让对方听懂的能力？
6. 下列哪一项最恰当地描述您在过去2个星期中，和熟悉您的人谈话时，让对方听懂的能力？
   a. 能够让对方完全地听懂我说的话。
   b. 能够让对方部份地听懂我说的话。
   c. 无法让对方听懂我说的话。
   d. 我完全不会说话。

7. 下列哪一项最恰当地描述您在过去2个星期中的感觉？
   a. 快乐，觉得生活有乐趣。
   b. 有点快乐。
   c. 有点不快乐。
   d. 很不快乐。
   e. 非常不快乐，觉得活着没什么意思。

8. 下列哪一项最恰当地描述您在过去2个星期中，所经历的疼痛和不舒服？
a. 没有疼痛和不舒服。

b. 有轻微至中等程度的疼痛或不舒服，但不影响进行任何活动。

c. 有中等程度的疼痛或不舒服，以致不能进行少数活动。

d. 有中等程度至严重的疼痛或不舒服，以致不能进行某些活动。

e. 有严重的疼痛或不舒服，以致不能进行大多数活动。
9. 下列哪一项最恰当地描述您在过去2个星期中走路的能力？
说明："走路设备"指机械支持物，例如：支架、拐杖或助行器。

   a. 能够在住所附近地方走动，没有任何困难，不需要走路设备。
   b. 能够在住所附近地方走动，有些困难，但不需要走路设备或别人帮助。
   c. 能够在住所附近地方走动，需要走路设备，但不需要别人帮助。
   d. 使用走路设备也只能走很短的距离，需要轮椅才能在住所附近地方活动。
   e. 即使使用走路设备也无法自己走路，有人帮助时能走很短的距离，需要轮椅才能在住所附近地方活动。
   f. 完全不能走路。

10. 下列哪一项最恰当地描述您在过去2个星期中，使用手和手指的能力？
说明："特殊工具"指系衣服钮扣的勾子、打开罐子或举起小物品的抓握工具、以及其他用来克服手或手指残障的工具。

   a. 能够完全自如地使用两只手和十个手指。
   b. 手或手指的功能不健全，但不需要特殊工具或别人帮助。
   c. 手或手指的功能不健全，使用特殊工具，可以自己做好事情(不需要别人帮助)。
   d. 手或手指的功能不健全，某些事情需要别人帮助(即使使用特殊工具，也不能自己做好)。
   e. 手或手指的功能不健全，大多数事情需要别人帮助(即使使用特殊工具，也不能自己做好)。
   f. 手或手指的功能不健全，所有的事情都需要别人帮助(即使使用特殊工具，也不能自己做好)。

11. 下列哪一项最恰当地描述您在过去2个星期中的记忆力？
   a. 能够记住大多数的事情。
b. 有点健忘。
c. 非常健忘。
d. 无法记住任何事情。

12. 下列哪一项最恰当地描述您在过去2个星期中，思考和解决日常生活问题的能力？

a. 能够清楚地思考和解决日常生活中的问题。
b. 在尝试去思考和解决日常生活中的问题时，有一点点困难。
c. 在尝试去思考和解决日常生活中的问题时，有一些困难。
d. 在尝试去思考和解决日常生活中的问题时，有很大困难。
e. 无法思考或解决日常生活中的问题。

13. 下列哪一项最恰当地描述您在过去2个星期中，进行一些基本活动的能力？

a. 能够正常地吃东西、洗澡、穿衣服、和上厕所。
b. 能够独立地吃东西、洗澡、穿衣服、或上厕所，但有些困难。
c. 能够独立地吃东西、洗澡、穿衣服、或上厕所，但需要机械工具帮助。
d. 需要别人帮助才能吃东西、洗澡、穿衣服、或上厕所。

14. 下列哪一项最恰当地描述您在过去2个星期中的感觉？

a. 大体上快乐，没有什么烦恼。
b. 偶尔烦躁、生气、易怒、焦虑、或忧郁。
c. 经常烦躁、生气、易怒、焦虑、或忧郁。
d. 总是烦躁、生气、易怒、焦虑、或忧郁。

e. 极度烦躁、生气、易怒、焦虑、或忧郁，达到需要看医生的程度。

15. 下列哪一项最恰当地描述您在过去2个星期中，所经历的疼痛或不舒服？

说明：“非处方药”是指不需要经过医生开处方即可自己购买的药物。

a. 没有疼痛和不舒服。

b. 偶尔疼痛或不舒服。通过使用非处方药或自我调整，不舒服减轻了，没有妨碍正常的活动。

c. 经常疼痛或不舒服。通过吃药，不舒服减轻了，偶尔妨碍正常的活动。

d. 经常疼痛或不舒服，经常妨碍正常的活动，需要使用麻醉止痛药才能止痛。

e. 非常严重的疼痛或不舒服。药物无法止痛，疼痛持续地妨碍正常的活动。

16. 总的来说，您如何评价您在过去2个星期中的健康状况？

a. 极好

b. 很好

c. 好

d. 一般

e. 差

17. 您是如何完成这份问卷的？请选出最适合您情况的答案。

a. 我自己完成的，没有其他任何人的帮助。

b. 我自己完成的，但别人帮我在问卷上圈出答案。

c. 有别人的帮助。
d. 这份问卷是由一位家属完成的，被调查的(病)人没有参与。

e. 这份问卷是由一位护士或其他医务人员完成的，被调查的(病)人没有参与。
   请说明医务人员的类别：__________________________________________

f. 这份问卷是由别人完成的，被调查的(病)人没有参与。
   请说明您和被调查的(病)人的关系：______________________________

谢谢您！问卷到此结束。
您的身体健康与精神状态

这项调查询问您对自己健康状况的评估。您所提供的信息有助于了解您的自我感觉和从事日常生活能力的情况。谢谢您回答这份问卷!

回答下列每一个问题时，请在最适当答案的方格内画一个(☐)。

1. 总的来说, 您认为您的健康状况是:

<table>
<thead>
<tr>
<th>极好</th>
<th>很好</th>
<th>好</th>
<th>一般</th>
<th>差</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼ 1</td>
<td>▼ 2</td>
<td>▼ 3</td>
<td>▼ 4</td>
<td>▼ 5</td>
</tr>
</tbody>
</table>

2. 和一年前相比较，您认为您目前的健康状况大致如何？

<table>
<thead>
<tr>
<th>比一年前好多了</th>
<th>比一年前好一些</th>
<th>和一年前差不多</th>
<th>比一年前差一些</th>
<th>比一年前差多了</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼ 1</td>
<td>▼ 2</td>
<td>▼ 3</td>
<td>▼ 4</td>
<td>▼ 5</td>
</tr>
</tbody>
</table>
3. 下列几个问题是关于您在一天的日常生活中可能进行的活动。您目前的健康状况是否会限制您从事这些活动？如果限制的话，限制到什么程度？

<table>
<thead>
<tr>
<th>活动</th>
<th>有很大限制</th>
<th>有一点限制</th>
<th>没有任何限制</th>
</tr>
</thead>
<tbody>
<tr>
<td>剧烈活动，比如跑步、搬重物或参加剧烈的体育活动</td>
<td>▼1 □2 □3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>中等强度的活动，比如搬桌子、使用吸尘器清洁地面、玩保龄球或打太极拳</td>
<td>△1 □2 □3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>提起或携带杂货</td>
<td>△1 □2 □3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>上几层楼梯</td>
<td>△1 □2 □3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>上一层楼梯</td>
<td>△1 □2 □3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>弯腰、跪下或俯身</td>
<td>△1 □2 □3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>步行一公里以上</td>
<td>△1 □2 □3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>步行几百米</td>
<td>△1 □2 □3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>步行一百米</td>
<td>△1 □2 □3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>自己洗澡或穿衣服</td>
<td>△1 □2 □3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4. 在过去四个星期里，您在工作或其它日常活动中，有多少时间会因为身体健康的原因而遇到下列的问题？

<table>
<thead>
<tr>
<th>常常</th>
<th>大部分</th>
<th>有时</th>
<th>偶尔</th>
<th>从来</th>
</tr>
</thead>
<tbody>
<tr>
<td>常常如此</td>
<td>大部分时间</td>
<td>有时</td>
<td>偶尔</td>
<td>从来</td>
</tr>
</tbody>
</table>

a. 减少了工作或其它活动的时间 ........................................... \[\] 1 ... \[\] 2 ... \[\] 3 ... \[\] 4 ... \[\] 5

b. 实际做完的比想做的要少 ........................................... \[\] 1 ... \[\] 2 ... \[\] 3 ... \[\] 4 ... \[\] 5

c. 工作或其它活动的种类受到限制 ........................................... \[\] 1 ... \[\] 2 ... \[\] 3 ... \[\] 4 ... \[\] 5

d. 进行工作或其它活动时有困难 （比如觉得更为吃力） ........................................... \[\] 1 ... \[\] 2 ... \[\] 3 ... \[\] 4 ... \[\] 5

5. 在过去的四个星期里，您在工作或其它日常活动中，有多少时间会因为情绪方面的原因（比如感到沮丧或焦虑）而遇到下列的问题？

<table>
<thead>
<tr>
<th>常常</th>
<th>大部分</th>
<th>有时</th>
<th>偶尔</th>
<th>从来</th>
</tr>
</thead>
<tbody>
<tr>
<td>常常如此</td>
<td>大部分时间</td>
<td>有时</td>
<td>偶尔</td>
<td>从来</td>
</tr>
</tbody>
</table>

a. 减少了工作或其它日常活动的时间 ........................................... \[\] 1 ... \[\] 2 ... \[\] 3 ... \[\] 4 ... \[\] 5

b. 实际做完的比想做的要少 ........................................... \[\] 1 ... \[\] 2 ... \[\] 3 ... \[\] 4 ... \[\] 5

c. 工作或从事其它活动时不如往常细心了 ........................................... \[\] 1 ... \[\] 2 ... \[\] 3 ... \[\] 4 ... \[\] 5
6. 在过去四个星期里，您的身体健康或情绪问题在多大程度上妨碍了您与家人、朋友、邻居或社团的日常社交活动？

<table>
<thead>
<tr>
<th>毫无妨碍</th>
<th>有很少妨碍</th>
<th>有一些妨碍</th>
<th>有较大妨碍</th>
<th>有极大妨碍</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>

7. 在过去四个星期里，您在身体上有多大程度的疼痛？

<table>
<thead>
<tr>
<th>完全没有</th>
<th>很轻微</th>
<th>轻微</th>
<th>有一些</th>
<th>剧烈</th>
<th>非常剧烈</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
</tbody>
</table>

8. 在过去四个星期里，您身体上的疼痛对您的日常工作（包括上班和家务）有多大影响？

<table>
<thead>
<tr>
<th>毫无影响</th>
<th>有很少影响</th>
<th>有一些影响</th>
<th>有较大影响</th>
<th>有极大影响</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>

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9. 下列几个问题是有关您在过去四个星期里的自我感觉和其它一些情况。回答每一个问题时，请选择一个最接近您的感觉的答案。
在过去四个星期里，有多少时间:

<table>
<thead>
<tr>
<th>常常如此</th>
<th>大部分时间</th>
<th>有时</th>
<th>偶尔</th>
<th>从来没</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

a. 您觉得充满活力? ........................................... □ 1 □ 2 □ 3 □ 4 □ 5
b. 您觉得精神非常紧张? ................................. □ 1 □ 2 □ 3 □ 4 □ 5
c. 您觉得情绪低落，以至于没有任何事能使您高兴起来? □ 1 □ 2 □ 3 □ 4 □ 5
d. 您感到心平气和? ................................. □ 1 □ 2 □ 3 □ 4 □ 5
e. 您感到精力充沛? ................................. □ 1 □ 2 □ 3 □ 4 □ 5
f. 您觉得心情不好，闷闷不乐? ................................ □ 1 □ 2 □ 3 □ 4 □ 5
g. 您感到筋疲力尽? ........................................... □ 1 □ 2 □ 3 □ 4 □ 5
h. 您感到快乐? ........................................... □ 1 □ 2 □ 3 □ 4 □ 5
i. 您觉得疲倦? ........................................... □ 1 □ 2 □ 3 □ 4 □ 5

10. 在过去四个星期里，有多少时间您的身体健康或情绪问题妨碍了您的社交活动（比如探亲、访友等）?

<table>
<thead>
<tr>
<th>常常有妨碍</th>
<th>大部分时间有妨碍</th>
<th>有时有妨碍</th>
<th>偶尔有妨碍</th>
<th>从来没 有妨碍</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>

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11. 如果用下列的句子来形容您，您认为有多正确？

<table>
<thead>
<tr>
<th></th>
<th>肯定对</th>
<th>大致对</th>
<th>不知道</th>
<th>大致不对</th>
<th>肯定不对</th>
</tr>
</thead>
<tbody>
<tr>
<td>您好像比别人更容易生病</td>
<td>▲</td>
<td>▲</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>您和所有您认识的人一样健康</td>
<td>▲</td>
<td>▲</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>您觉得自己的身体状况会变坏</td>
<td>▲</td>
<td>▲</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>您的健康极好</td>
<td>▲</td>
<td>▲</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

谢谢您回答完这些问题！