Population Health Impact and Cost-Effectiveness of Monitoring Inactive Chronic Hepatitis B and Treating Eligible Patients in Shanghai, China

Mehlika Toy,1,2 Joshua A. Salomon,1 Hao Jiang,3 Honglian Gui,3 Hui Wang,3 Jiangshe Wang,4 Jan Hendrik Richardus,2 and Qing Xie3

Inactive chronic hepatitis B (CHB) carriers make up the largest group of hepatitis B virus-infected patients, and China bears the largest total CHB burden of any country. We therefore assessed the population health impact and cost-effectiveness of a strategy of lifelong monitoring for inactive CHB and treatment of eligible patients in Shanghai, China. We used a computer simulation model to project health outcomes among a population cohort of CHB based on age-specific prevalence of hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and cirrhosis. Using a Markov model we simulated patients’ progression through a discrete series of health states, and compared current practice to a monitor and treat (M&T) strategy. We measured lifetime costs and quality-adjusted life years (QALYs) (both discounted at 3% per year), incremental cost-effectiveness ratios (ICERs), and clinical outcomes such as development of hepatocellular carcinoma (HCC). We estimated that there are 1.5 million CHB-infected persons in Shanghai. The M&T strategy costs US$20,730 per patient and yields a discounted QALY of 15.45, which represents incremental costs and health benefits of US$275 and 0.10 QALYs compared to current practice, and an ICER of US$2,996 per QALY gained. In the base case, we estimated that the M&T strategy will reduce HCC and CHB-related mortality by only around 1%. If variables such as adherence to monitoring and treatment could be substantially improved the M&T strategy could reduce HCC by 70% and CHB-related mortality by 83%. Conclusion: Lifelong monitoring of inactive CHB carriers is cost-effective in Shanghai according to typical benchmarks for value for money, but achieving substantial population-level health gains depends on identifying more CHB-infected cases in the population, and increasing rates of treatment, monitoring, and treatment adherence. (HEPATOLOGY 2014;60:46-55)

Every year, an estimated 500,000 people die from hepatitis B virus (HBV)-related diseases in China, including hepatocellular carcinoma (HCC) and hepatic failure.1,2 Approximately 60% of the population has a history of HBV infection, and an estimated 7%-10% of persons in China are chronically infected with HBV and at risk of premature death from liver diseases.3 Even though the availability of universal vaccination against hepatitis B has resulted in a reduction in the rate of chronic hepatitis B (CHB) infection in children in China,4 the enormous reservoir of persons already infected remains a major health problem. Many chronically infected persons do not know that they are infected due to the asymptomatic nature of the disease.5

Without monitoring or treatment, an estimated one in four CHB-infected persons will eventually die of liver cancer or liver failure.6 Antiviral therapy is the
only currently available option to prevent progression of disease in patients with active CHB. Recent cohort studies underscore the need for stringent monitoring of the levels of HBV replication in addition to alanine aminotransferase (ALT) to distinguish active from inactive cases.\textsuperscript{7} Inactive carriers make up the largest group in CHB-infected patients, defined as hepatitis B surface antigen (HBsAg)-positive, hepatitis B e antigen (HBeAg)-negative, normal levels of ALT ≤ 40 U/L and HBV DNA ≤ 10,000 copies/mL.\textsuperscript{8,9} Treatment is not recommended for this group, since there is not enough evidence whether therapy affects HBsAg status in the long term.\textsuperscript{9} Patients transition from inactive to active CHB at a rate of ~0.9%-2% annually,\textsuperscript{10} either by experiencing a reversion from anti-HBe to HBeAg or by having flares of anti-HBe CHB characterized by episodes of elevated HBV DNA levels followed by flares of ALT elevation.\textsuperscript{11} Patients can move from active back to inactive CHB by clearing HBsAg, which occurs at a rate of ~0.7%-1.8% annually.\textsuperscript{10}

In light of these potential transitions, international guidelines suggest that inactive CHB should be monitored by ALT and serum HBV DNA levels over a period of at least 1 year following detection and confirmation of an inactive case.\textsuperscript{9} Despite these recommendations, lifelong monitoring of ALT and HBV DNA in inactive, untreated patients with CHB is not current practice in China. High costs, absence of a structured surveillance system for CHB infected patients, not being aware of the risk of developing HCC and limited access to highly effective antiviral drugs are several possible contributors to the lack of a lifelong monitoring system for these patients.\textsuperscript{3,12} The aim of this study was to assess the population health impact and cost-effectiveness of a strategy of lifelong monitoring for inactive CHB, and treatment upon transition to active disease, in Shanghai, China.

**Materials and Methods**

**Overview.** We used a computer simulation model to project health outcomes among a population cohort of people known to have inactive CHB in Shanghai based on age-specific prevalence of HBsAg, HBeAg, and cirrhosis. Using a Markov model we simulated patients’ progression through a discrete series of health states, and compared current practice to a monitor and treat (M&T) strategy. Outcomes from the model included clinical endpoints (cirrhosis, HCC, CHB-related mortality), summary measures of lifetime costs (2010 U.S. dollars and Chinese Yuan Renminbi [RMB]) and quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs) expressed as the additional costs per QALY gained for the M&T strategy compared to current practice. Simulations were undertaken separately for the age groups 0-14, 15-24, 25-34, 35-44, 45-54, 55-64, 65+ years, and overall estimates were made by combining the age-specific results into weighted averages for lifetime costs and QALYs and then taking the ratios of the average.

**Strategies.** In the current practice strategy, we assumed that there is no monitoring of HBsAg-positive inactive cases. In the (M&T) strategy, we assumed that there is regular monitoring of inactive cases, which entails twice-yearly monitoring of HBV DNA and ALT levels.\textsuperscript{9} In both strategies treatment for known cases of active CHB uses entecavir, which is known for its potency,\textsuperscript{13} and has been found to be cost-effective in a recent comparative assessment of antiviral therapy options in China.\textsuperscript{14}

Treatment guidelines often recommend a finite period of therapy with oral nucleoside analogs for patients with HBeAg-positive CHB who undergo HBeAg seroconversion, in contrast to the recommendation to consider prolonged therapy for those patients with evolving HBeAg-negative CHB and active HBV DNA replication (>log\textsuperscript{4} IU/mL) and patients with cirrhosis.\textsuperscript{9} More recent publications\textsuperscript{15} suggest continuation of long-term nucleos(t)ide analog treatment, irrespective of the occurrence of HBeAg seroconversion in HBeAg-positive patients. Following these recent findings, our model assumes continued antiviral therapy for HBeAg-positive patients even if seroconversion occurs. For HBeAg-negative patients, we also assume long-term or indefinite treatment.\textsuperscript{16}

**Model.** We developed a Markov model to simulate the long-term trajectories for patients under each of the two strategies evaluated in this study (Fig. 1). Depending on the strategy, patients begin the simulation in one of seven different states: 1) inactive CHB, HBsAg-positive; 2) active CHB, HBeAg-negative,
untreated; 3) active CHB, HBeAg-negative, treated; 4) active CHB, HBeAg-positive, untreated; 5) active CHB, HBeAg-positive, treated; and 6) cirrhosis, untreated; and 7) cirrhosis, treated. Active CHB, signifying potentially progressive disease, was defined as HBV DNA >10^5 copies/mL and ALT 2× upper limit of normal. Treated states are further stratified in the model according to whether patients are in the first year of treatment or subsequent years, and whether patients are drug-sensitive or drug-resistant. From these initial states, patients in the model may transition to other states, reflecting viral suppression (response to treatment), seroconversion (defined as HBe antigen loss and development of anti-HBe), seroclearance (defined as loss of serum HBsAg), decompensated cirrhosis, and liver transplantation. The model does not take newly diagnosed patients into account.

We defined the size of the starting cohort for the simulations, and the distribution of the cohort across different clinical states, based on the age-specific prevalence of HBsAg measured in a recent sero-survey study in China. Pediatric patients from ages 0-14 were included in the population projections, but were not included in the model analysis for treatment; since the guidelines to treat children are different, we decided to exclude this age group from our analysis. Active CHB cases were categorized by age-specific HBeAg status and the presence of cirrhosis, based on our analysis of data from 1,014 newly diagnosed CHB patients, collected at the Jiaotong University, Rui Jin Hospital, Shanghai.

In order to determine the proportion of active CHB patients in untreated and treated states at the initiation of the Markov model, we accounted for the probabilities of being tested, receiving follow-up of test results, initiating treatment, and adhering to treatment. Based on data from a recent survey study in the Hong Kong adult Chinese population, we assumed that 58% of people out of the 1.5 million cohort were ever tested for HBsAg and 41% of those ever tested who were HBsAg-positive had no follow-up, despite being aware of their disease. According to the findings of a retrospective study based on review of patients’ medical records, only 33% of active patients eligible for treatment according to the treatment guidelines actually
receive treatment in China. We assumed that out of the 53% of active cases that are being treated, only 65% adhere to the treatment; this rate was chosen to fall between the general estimate from the World Health Organization (WHO) for adherence in developing country patient populations to therapies for chronic illness and the reported treatment adherence among active CHB patients in the United States. International CHB treatment guidelines recommend that inactive carriers should be monitored for ALT and HBV DNA levels over the course of their lifetime. Studies on adherence outcomes for monitoring inactive CHB patients show that only 65% adhere to the treatment, which falls between the general estimate from the WHO for adherence in developing country patient populations to therapies for chronic illness and the reported treatment adherence among active CHB patients in the United States. International CHB treatment guidelines recommend that inactive carriers should be monitored for ALT and HBV DNA levels over the course of their lifetime. Studies on adherence outcomes for monitoring inactive CHB patients show that only 65% adhere to the treatment, which falls between the general estimate from the WHO for adherence in developing country patient populations to therapies for chronic illness and the reported treatment adherence among active CHB patients in the United States.
transitions in the Markov model are governed by disease progression parameters (Table 1) and treatment effectiveness parameters (Table 2). Disease progression estimates were derived from recent age-specific cohort studies on inactive and active CHB in Asia. Treatment effectiveness estimates were expressed as reductions in progression risks and are shown in Table 2. When progression rates were reported, these were transformed into annual probabilities using an exponential model. Other causes of death not related to liver disease were included in the model, based on age-specific mortality rates from the National Bureau of Statistics of China. Annual probabilities of receiving a liver transplant for decompensated cirrhosis and HCC (12% and 4.7%, respectively) were calculated based on data from China Liver Transplant Registry.

The Markov model was calculated using a 1-year time step, and implemented with TreeAge Pro 2009 (TreeAge Software, Williamstown, MA).

Cost and Utility Estimates. We used medical management costs for CHB and other related costs from a recent multinational study on CHB. Costs and QALYs were discounted at a rate of 3% per year. Following guidelines for benchmarking cost-effectiveness estimates from the WHO, we regarded incremental cost-effectiveness ratios of less than one times GDP per capita for each healthy life year (QALY) gained as signifying a cost-effective intervention, and incremental cost-effectiveness ratios between one and three times GDP per capita per QALY as signifying a potentially cost-effective intervention. The GDP per capita in China in 2010 was USD $5,445 (34,848 RMB).

Age-specific utility estimates (Table 3) were obtained from a recent multinational study on CHB. Costs and QALYs were discounted at a rate of 3% per year. Following guidelines for benchmarking cost-effectiveness estimates from the WHO, we regarded incremental cost-effectiveness ratios of less than one times GDP per capita for each healthy life year (QALY) gained as signifying a cost-effective intervention, and incremental cost-effectiveness ratios between one and three times GDP per capita per QALY as signifying a potentially cost-effective intervention. The GDP per capita in China in 2010 was USD $5,445 (34,848 RMB).

Sensitivity Analysis. We examined the sensitivity of the results to variation in key parameters and assumptions in the model, including the percentage of HBV cases ever tested, the proportion of patients who are followed up, the adherence to monitoring therapy of 50%, reported by Liaw et al. 2004 [35].
recommendations, the percentage of active CHB treated, treatment adherence, and the cost of entecavir. We conducted additional sensitivity analyses in which we assumed the low and high values in the ranges of estimates for transition probabilities (Tables 1, 2). Specifically, we defined a best-case scenario based on applying the high ranges of progression to spontaneous virological response in the natural history model, and for sustained virological response in the treatment model, and applying the low ranges of the estimates of disease progression. A worst-case scenario was defined by the application of the low progression rates to spontaneous virological response and the sustained virological response, and by the application of the high ranges of the disease progression estimates.

Results

The age-group specific distribution of CHB in Shanghai by HBeAg and stage of liver disease is shown in Table 4. Around 1.5 million adults were estimated to be HBsAg carriers, of whom 63% were HBeAg-positive. The number of active CHB cases among adults, who are those considered eligible for treatment, included 258,139 (17%) in the HBeAg-positive group, and 152,384 (10%) in the HBeAg-negative group, with 235,342 (15%) of cirrhosis cases at baseline. Table 5 shows the patient characteristics of the CHB database from the Ruijin hospital. The patient population was predominantly male (72.5%) with a median age of 37 years (range, 1-90). The median ALT was 170 U/L (range, 0-2690) and the median HBV DNA level was 3.8 log, copies/mL.

We estimated that the M&T strategy would cost US$20,730 (132,672 RMB), and result in 15.45 QALYs per patient, compared to US$20,455 (130,912 RMB) and 15.35 QALYs for current practice. In the current practice scenario, we estimated that over their lifetime, 20% of the cohort would develop cirrhosis, 19% develop HCC, and 36% of cases die due to CHB-related causes. With addition of lifelong monitoring for inactive cases, assuming 35% adherence, we estimated that the M&T strategy would be associated with 1% reductions in cirrhosis, HCC, and CHB-related death, compared to the current practice (Table 6). The ICER for M&T strategy compared to the current practice was US$2,996 (19,174 RMB).

Age group-specific QALYs for the M&T strategy declined from 20.79 to 7.70 as age increased, and the ICER ranged across age groups between US$1,119-5,224 (7,161-33,433 RMB) (Fig. 2).
**Sensitivity Analysis.** Increasing the percentage of HBV-tested persons to 80% in the population (compared to the base-case estimate of 58%) reduced the ICER for the M&T strategy compared to current practice by about 50% (to $1,540, or 9,856 RMB). If we also assumed that the proportion of people in follow-up who would be tested was 80% rather than 58.7% in the base-case analysis, the ICER decreased further, to $1,112 (7,116 RMB). Increasing the percentage of monitoring adherence, percentage of active CHB-treated, and percentage of treatment adherence to 50%, 65%, and 85%, respectively, lowered the ICER to $808 (5,171 RMB), with a reduction in CHB-related death by almost 10%, compared to the current practice as reported in Table 6. If we were to increase monitoring adherence, adherence to treatment and percentage of treated all to 85%, we estimate that the associated reductions in HCC, cirrhosis, and CHB-related death would be 70%, 84%, and 83%, respectively. The most influential assumption identified in sensitivity analyses was the entecavir drug cost. If this cost were reduced by 50%, the M&T strategy would cost less per patient than the current practice, which makes the M&T program cost-saving. The multivariate sensitivity analysis (best case, worst case) for treatment effectiveness and disease progression in natural history showed QALY and ICER estimates ranging from 14.00 and $3,413 (21,843 RMB), respectively, for the worst case, to 17.93 and $11,886 (76,070 RMB) for the best case. Age group-specific ICERs for each sensitivity analysis strategy tested are shown in Fig. 2.

### Table 5. Demographic and Laboratory Data for Overall Patients

| Parameters                   | Results                          |
|------------------------------|----------------------------------|
| Total number, N              | 1,014                            |
| Age, years, median (range)   | 37 (1-90)                        |
| Males, number (%)            | 735 (72.5%)                      |
| HBeAg positive, number (%)   | 642 (63)                         |
| Liver biochemistry            |                                  |
| ALT (range)                  | 170 (0-2690)                     |
| HBV DNA, copies/ml (range)   | $3.8 \times 10^9$ ($60-3.0 \times 10^{12}$) |

Continuous variables are expressed as median values (range).

### Table 6. Cost-Effectiveness Outcomes of Monitoring Inactive Chronic Hepatitis B Carriers

| Program                                          | % HBV Ever Tested | % of Follow-up | Total Cost per Patient (US$) | Incr. Cost | Incr. QALYs | Incr. QALYs Gained (ICER) | % HCC | % Cirrhosis | % CHB-Related Deaths |
|--------------------------------------------------|-------------------|----------------|-----------------------------|------------|-------------|--------------------------|-------|-------------|--------------------|
| Current practice                                 | 58%               | 58.7%          | $20,455                     | –          | 15.35       | –                        | 20%   | 19%         | 36%                |
| Monitor & treat base-case                        | 35%               | 58.7%          | $20,730                     | $275       | 15.45       | 0.10                     | $2,996 | 19%         | 18%                |
| Monitor & treat sensitivity analyses             | 50%               | 58.7%          | $21,051                     | $596       | 15.93       | 0.58                     | $1,040 | 16%         | 17%                |
| 50% reduction in entecavir drug cost             | 58%               | 58.7%          | $19,912                     | –          | 15.45       | –                        | Cost-saving | –           | –                 |

Abbreviations: CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; Incr, incremental.
Discussion

Implementing lifelong monitoring for inactive CHB carriers in Shanghai, China, assuming adherence levels of ~35%, consistent with current observed patterns, appears cost-effective, with an estimated cost-effectiveness ratio of US$2,996 (19,174 RMB) per QALY gained compared to current practice, but such a strategy would not produce a substantial reduction in HCC or CHB-related deaths. The costs and QALYs for the M&T strategy and the current practice are similar because the majority of the costs are incurred when complications such as decompensated cirrhosis or HCC occur or the need for liver transplantation due to these complications. A significant impact on rates of HCC, cirrhosis, and CHB-related mortality would be realized only if the proportion of patients tested and then followed up were increased, and if the rate of treating active patients was also increased. Moreover, to attain cost savings compared to current practice, we estimate that the price of entecavir would need to be reduced by around 50% (US$934) compared to its current price of US$1,869. In other countries the costs of monitoring, physician visits, imaging, and antiviral drugs could make this difference much greater.

According to a population survey study by Wah et al.,18 used in this study to inform our assumption about the rate of testing and follow-up, the 58% of patients who were ever tested for CHB infection tended to have higher education and family income than patients who were never tested. Out of those who were ever tested, 12% were found to be HBsAg-positive. Not all patients with CHB are identified, and out of those who are, an inadequate proportion receives management and follow-up. Among the 41% of patients who were ever tested but had no follow-up, it is likely that many do not know that they are at risk for developing HCC, and therefore will not be able to benefit from highly effective drugs that could reduce this risk.

To our knowledge this is the first cost-effectiveness analysis assessing costs and cost-effectiveness of monitoring inactive CHB patients. Various studies have examined the cost-effectiveness of antiviral therapy for CHB and have concluded that treatment is cost-effective compared to the counterfactual of no treatment.14,29,42 Lifelong antiviral therapy costs for a 30-year-old CHB patient with entecavir are estimated to be US$46,600, or US$1,083 per year according to a recent cost-effectiveness study.14

A limitation of our study is the lack of data to support the assumptions regarding the rate of being tested, or the rate of awareness of infection in the population. A survey study from Hong Kong18 was the only study we found that assessed community awareness about CHB in China. Use of these studies may lead to overestimation of the proportion of patients ever tested in current practice, as this study, originating from Hong Kong might not be generalizable to the current practice in Shanghai. Another limitation was the lack of data to support estimates of the probability of adherence to monitoring and treatment. The only study we found in the literature that assessed adherence to monitoring of patients who are not receiving antiviral therapy was a study from the U.S. by Juday et al.,21 which found that HBV DNA monitoring rates were lower than rates of ALT monitoring. This finding is perhaps unsurprising, as liver function tests are a quick and inexpensive mode of monitoring, although patients with advanced liver disease may have normal liver function and therefore may not receive appropriate treatment if HBV DNA levels are not monitored as well. Although some studies43 suggest that antiviral therapy for CHB would appear to possess a profile favoring high adherence rates, given the once daily dosing of a single nucleos(t)ide analog, which is usually well tolerated with minimal side effects, it is also suggested that this should be explored further in various settings.

Another area that needs further assessment is whether enough resources are available for those who are eligible for treatment, but do not have access to or who cannot afford the current price of a highly effective drug. Although China recently became the second largest economy in absolute terms and is increasingly playing an important and influential role in the global economy, in 2011 China’s gross national income per capita of $4,940 ranked 114th in the world, and over 170 million people still live below the $1.25-a-day international poverty line, with an average disposable income of US$3,000 per year.41 In a recent survey study44 from Shandong province, the authors reported that direct costs for CHB and liver cancer exceeded the average annual incomes for 78% and 297% of households, respectively. High costs of antiviral therapy, and the absence of a structured surveillance system, could explain the low rate of patients being treated, and the low adherence rate to antiviral therapy as well as the loss to follow-up.

Another reason why large proportion of patients are not being followed up, even though they are aware of their infection, might be due to their healthcare providers who may be unaware of the natural history of HCC, and the need for lifelong monitoring of inactive CHB. According to a survey study among healthcare
professionals in various regions in China, 33% of the healthcare workers were unaware of the asymptomatic nature of CHB infection, as well as the endpoints of the disease, such as cirrhosis, HCC, and premature death; about 18% of the health professionals surveyed said that they do not report a positive HBsAg screening test result directly to the patient.45

We present the health impact and cost-effectiveness of a lifelong M&T strategy at the population level. Monitoring of inactive cases can achieve substantial health gains, but these gains will depend critically on the ability to identify more HBsAg-positive cases and to improve rates of treatment and adherence to monitoring. Consequently, methods and/or programs to increase CHB detection, e.g., systematic and opportunistic screening of the general population, access to treatment, adherence to monitoring and treatment with CHB antivirals should be investigated, toward the end of developing a well-organized and effective surveillance system for inactive carriers. A national initiative is strongly needed to deliver effective and affordable care to those who are eligible, to train and instruct healthcare providers, and to inform and support patients about prevention and control of CHB.

References

1. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat 2004;11:97-107.
2. Chen JG, Zhang SW. Liver cancer epidemic in China: past, present and future. Semin Cancer Biol 2011;21:59-69.
3. Liu J, Fan D. Hepatitis B in China. Lancet 2007;369:1582-1583.
4. Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, et al. Epidemiological serosurvey of hepatitis B in China—declining HBV prevalence due to hepatitis B vaccination. Vaccine 2009;27:6550-6557.
5. Lee W. Hepatitis B virus infection. N Engl J Med 1997;337:1733-1745.
6. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012;142:1264-1273 e1261.
7. Tai DI, Lin SM, Sheen IS, Chu CM, Lin DY, Liaw YE. Long-term outcome of hepatitis B e antigen-negative hepatitis B surface antigen carriers in relation to changes of alanine aminotransferase levels over time. Hepatology 2009;49:1859-1867.
8. Hadiyannis SJ. Unrevealing the natural course of the so-called "inactive HBsAg or HBV carrier state." Hepatol Int 2007;1:281-284.
9. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. HEPATOLOGY 2009;50:661-662.
10. Chu CM, Liaw YE. HBsAg seroconversion in asymptomatic carriers of high endemic areas: appreciably high rates during a long-term follow-up. HEPATOLOGY 2007;45:1187-1192.
11. Lok AS, Lai CL. Acute exacerbations in Chinese patients with chronic hepatitis B virus (HBV) infection. Incidence, predisposing factors and etiology. J Hepatol 1990;10:29-34.
12. Wang L, Wang Y, Jin S, Wu Z, Chin DP, Koplan JP, et al. Emergence and control of infectious diseases in China. Lancet 2008;372:1598-1605.
13. Woo G, Tomlinson G, Nishikawa Y, Kowgier M, Sherman M, Wong DK, et al. Tenofir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. Gastroenterology 2010;139:1218-1229.
14. Wu B, Li T, Chen H, Shen J. Cost-effectiveness of nucleoside analog therapy for hepatitis B in China: a Markov analysis. Value Health 2010;13:592-600.
15. Reijnders JG, Penquin MJ, Zhang N, Hansen BE, Jansen HL. Nucleos(t)ide analogues only induce temporary hepatitis B e antigen seroconversion in most patients with chronic hepatitis B. Gastroenterology 2010;139:491-498.
16. Shouval D, Lai CL, Chang TT, Cheinquer H, Martin P, Carosi G, et al. Relapse of hepatitis B in HBeAg-negative chronic hepatitis B patients who discontinued successful entecavir treatment: the case for continuous antiviral therapy. J Hepatol 2009;50:289-295.
17. Haber BA, Block JM, Jonas MM, Karpen SJ, London WT, McMahon BJ, et al. Recommendations for screening, monitoring, and referral of pediatric chronic hepatitis B. Pediatrics 2009;124:e1007-1013.
18. Wib CP, Hung SS, Ka CO, Hsi LT, Yeung LT. Awareness and knowledge of hepatitis B infection and prevention and the use of hepatitis B vaccination in the Hong Kong adult Chinese population. Chin Med J 2012;125: 422-427.
19. Zhiqiang G, Zhaohui D, Qinhuan W, Dexian C, Yunyun F, Hongtao L, et al. Cost of chronic hepatitis B infection in China. J Clin Gastroenterol 2004;38:S175-178.
20. Lok AS. Does antiviral therapy for hepatitis B and C prevent hepatocellular carcinoma? J Gastroenterol Hepatol 2011;26:221-227.
21. Juday T, Tang H, Harris M, Powers AZ, Kim E, Hanna GJ. Adherence to chronic hepatitis B treatment guideline recommendations for laboratory monitoring of patients who are not receiving antiviral treatment. J Gen Intern Med 2011;26:239-244.
22. Karwal F, Farid M, Martin P, Chen G, Gralnek IM, Dulai GS, et al. Treatment alternatives for hepatitis B cirrhosis: a cost-effectiveness analysis. Am J Gastroenterol 2006;101:2076-2089.
23. Lin X, Robinson NJ, Thures M, Rosenberg DM, Weidl A, Pimenta JM, et al. Chronic hepatitis B virus infection in the Asia-Pacific region and Africa: review of disease progression. J Gastroenterol Hepatol 2005;20:833-845.
24. Chen YC, Chu CM, Liaw YE. Age-specific prognosis following spontaneous hepatitis B e antigen seroconversion in chronic hepatitis B. HEPATOLOGY 2010;51:435-444.
25. Yuen MF, Wong DK, Fung J, Ip P, But D, Hung I, et al. HBsAg Seroconversion in chronic hepatitis B in Asian patients: replicative level and risk of hepatocellular carcinoma. Gastroenterology 2008;135:1192-1199.
26. Chu CM, Liaw YE. Incidence and risk factors of progression to cirrhosis in inactive carriers of hepatitis B virus. Am J Gastroenterol 2009;104:1693-1699.
27. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65-73.
28. Chen JD, Yang HI, Iloeje UH, You SL, Lu SN, Wang LY, et al. Carriers of inactive hepatitis B virus are still at risk for hepatocellular carcinoma and liver-related death. Gastroenterology 2010;138:1747-1754.
29. Karwal F, Gralnek IM, Martin P, Dulai GS, Farid M, Spigel BM. Treatment alternatives for chronic hepatitis B virus infection: a cost-effectiveness analysis. Ann Intern Med 2005;142:821-831.
30. Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. J Hepatol 2008;48:335-352.
31. Shouval D, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med 2006;354:1001-1010.
32. Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2006;354:1011-1020.
33. Colombo RJ, Rose RE, Pokorski K, Baldick CJ, Eggers B, Xu D, et al. Four year assessment of entecavir resistance in nucleoside-naive and lamivudine refractory patients. J Hepatol 2007;46:5294.
34. Tenney DJ, Rose RE, Baldick CJ, Pokorski KA, Eggers BJ, Fang J, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naive patients is rare through 5 years of therapy. HEPATOLOGY 2009;49:1503-1514.
35. Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, et al. Lami-
vudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004;351:1521-1531.
36. Fleurence RL, Hollenbeak CS. Rates and probabilities in economic
modeling: transformation, translation and appropriate application. Pharmacoeconomics 2007;25:3-6.
37. National Bureau of Statistics of China. Available from: www.stats.
gov.cn/english.
38. China Liver Transplant Registry. Available from: www.cltr.org.
39. Levy AR, Kowdlely KV, Iloeje U, Tafesse E, Mukherjee J, Gish R, et al. The impact of chronic hepatitis B on quality of life: a multinational
study of utilities from infected and uninfected persons. Value Health
2008;11:527-538.
40. World Health Organization. WHO guide to cost-effectiveness; 2003.
Geneva, Switzerland: WHO.
41. World Bank. China overview. 2012. Available from: http://www.world
bank.org/en/country/china.
42. Yuan Y, Iloeje U, Li H, Hay J, Yao GB. Economic implications of entecavir treatment in suppressing viral replication in chronic hepatitis
B (CHB) patients in China from a perspective of the Chinese Social
Security program. Value Health 2008;11(Suppl 1):S11-S22.
43. Chotiyaputta W, Peterson C, Ditah FA, Goodwin D, Lok AS. Persist-
ence and adherence to nucleos(t)ide analogue treatment for chronic
hepatitis B. J Hepatol 2011;54:12-18.
44. Lu J, Xu A, Wang J, Zhang L, Song L, Li R, et al. Direct economic
burden of hepatitis B virus related diseases: evidence from Shandong,
China. BMC Health Serv Res 2013;13:37.
45. Chao J, Chang ET, So SK. Hepatitis B and liver cancer knowledge and
practices among healthcare and public health professionals in China: a
cross-sectional study. BMC Public Health 2010;10:98.