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Overview of viral hepatitis treatment research in China

Final report

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PREFACE

Background

China is facing a major challenge in treating a large population infected with hepatitis B virus and hepatitis C virus. There has been documented successes in the introduction of a nationwide strategy of hepatitis B vaccination in 1992, after which the prevalence of hepatitis B surface antigen (HBsAg) decreased substantially in child populations (and to a less extent in adult populations) [1, 2]. Despite this, the absolute numbers of people with chronic infection remains high. There are an estimated 93 million people with chronic hepatitis B among China's 1.3 billion population, and 300,000 deaths every year in China as result of chronic hepatitis B including liver cirrhosis and hepatocellular carcinoma (HCC)[3].

The prevalence of hepatitis C in the general Chinese population has been estimated to be 0.43% in 2008, amounting to more than 7 million infected individuals [4]. Before the introduction of hepatitis C screening during blood donation, the prevalence of HCV infection was 12.9% among paid blood donors [5]. This has decreased to 1.7% however a large number of other populations remain at high risk of hepatitis C infection, such as people who require haemodialysis (positive rate of anti-HCV in 2013: 6.0%) and people who inject drugs (positive rate of anti-HCV in 2013: 38.4%) [4-6].

Chronic hepatitis B and C infection is associated with considerable healthcare costs and morbidity and mortality. Each year about 280,000 people die from hepatitis related diseases [7]. Hepatitis B and hepatitis C are leading causes of end-stage liver disease and hepatocellular carcinoma (HCC). China alone accounts for 55% of HCC cases worldwide with approximately 85% of HCC cases related to hepatitis B and 10% related to hepatitis C [8].

Research funding for hepatitis

The Chinese Government plans to invest 3 billion RMB (US$390 million) in hepatitis research, 2009-2018. In 2013 alone, China's Ministry of Science and Technology invested 300 million RMB (US$50 million) towards research focussed on prevention, elimination, clinical treatment, surveillance and intervention of viral hepatitis and liver cancer [9].

The World Health Organization (WHO) is committed to developing a comprehensive regional action plan for the prevention and control of viral hepatitis in high burden countries of the Western Pacific Region. According to the WHO Country Cooperation Strategy for China, it will continue to support China in the prevention and control of priority infectious diseases [10].

Purpose of this report

Burnet Institute was commissioned by WHO to provide an overview of China's research efforts in the developing area of hepatitis treatment within the following objectives:

1. Describe the accessibility and cost of viral hepatitis treatment and monitoring of patients in China
2. Report on Chinese clinicians' awareness and compliance to existing national treatment guidelines
3. Provide an inventory of existing Chinese research efforts to simplify diagnostics and treatment

This report documents China's recent and current viral hepatitis treatment research, with a focus on hepatitis B and hepatitis C. China's considerable experience in hepatitis B and hepatitis C treatment will help to inform the development and regular update of diagnosis and treatment guidelines and the development of a public health approach to the management of viral hepatitis in China.

Review findings are reported in three distinct sections; each section addressing the objectives listed above.

EXECUTIVE SUMMARY

Background

China is facing a major challenge in treating a large population infected with hepatitis B virus (HBV) and hepatitis C virus (HCV). It is estimated that 93 million people live with chronic hepatitis B, 7 million people live with chronic hepatitis C in China and 300,000 deaths occur every year from hepatitis related diseases.

Chronic hepatitis B and C infection is associated with considerable healthcare costs for the Chinese health system, individuals and the society at large. As a result the Chinese Government has planned very large investment towards research focussed on the elimination, clinical treatment, surveillance and management of viral hepatitis and liver cancer.

The World Health Organization (WHO) is also committed to China's health system reforms and development of a comprehensive action plan for the surveillance, prevention and management of viral hepatitis including treatment. WHO commissioned the Burnet Institute to provide an overview of China's research efforts in the developing area of hepatitis treatment. This would be used to inform updates of screening, diagnosis and treatment guidelines as well as the development of a public health approach to the management of viral hepatitis in China. The objectives of the review were to:

1. Describe the accessibility and cost of viral hepatitis treatment and monitoring of patients in China
2. Report on Chinese clinicians' awareness and compliance to existing national treatment guidelines
3. Provide an inventory of existing Chinese research efforts to simplify diagnostics and treatment

Methods

The Burnet Institute conducted a document and literature review of published and unpublished literature, surveyed 27 key informants identified as experts in epidemiology, virology and treatment of hepatitis B and hepatitis C infection in China and interviewed two leading experts in viral hepatitis clinical research, Professor Lai Wei from Peking University and Professor Jinlin Hou from Southern Medical University, to explore their experience and knowledge around diagnostics, treatment and current research efforts.

Findings

Treatment for chronic hepatitis is expensive regardless of insurance schemes and drug reimbursements. The authors note that the medical costs of hepatitis pose a significant financial burden on patients and their families in China. This would be more pronounced in China's rural populations, as reimbursement is insufficient under the rural health insurance scheme and many patients in rural areas cannot afford to access adequate medical treatment. In addition to medication, other components of health care provision such as diagnostic testing can be considered by decision makers to offset the high costs involved for patients.

Hepatitis C treatment: Published literature on hepatitis C treatment shows that the results of PEG-INF and RBV treatment for chronic HCV infection are effective in China due to the pre-dominant HCV genotype I b. More equitable access to such treatment would decrease risks of disease progression

and subsequent mortality. Treatment of hepatitis C with direct-acting antiviral agents (DAA) is likely to improve uptake of and adherence to treatment but antivirals are expensive and a consideration of resources is required to assess which treatments are most suitable for the situation in China. Many individual countries are negotiating lower prices of DAAs and generic formulations of these medications will become available in some countries. It is likely that these highly effective therapies will become increasingly available in China.

Hepatitis B treatment: The cost of treating hepatitis B varied for individuals for many reasons: their type of health insurance; whether they were hospitalised in a tertiary hospital; or had more comorbidities. Cost was also dependant on the choice of antiviral drugs used for treatment. The estimated disease cost burden is high and can exceed individuals' earning capacity with the costs to treat hepatitis B increasing as the disease progresses. This is of major concern when considering strategies for treatment in a population with considerable prevalence.

Treatment with recently approved nucleoside analogues will decrease cost as well as reduce the risk of drug resistance, disease progression and subsequent mortality. According to the latest literature entacavir (ETV) and tenofovir (TDF) are both highly effective with minimal resistance. TDF monotherapy has been shown to be cost-effective for rescue therapy in generous economic conditions whereas ADV/3TC combination treatment was more cost-effective in health care systems with limited resources such as the majority of mainland China.

Chinese clinicians' awareness and compliance to existing national treatment guidelines: Clinicians in China thought viral hepatitis treatment was still expensive for most patients. Infectious disease specialists, gastroenterologists and hepatologists who were interviewed were aware of the existence of the national guidelines but most thought the guidelines were outdated or unsuitable to China's current situation, but they were not necessarily familiar with the latest version.

Existing Chinese research efforts to simplify diagnostics and treatment: Treatments for viral hepatitis are changing rapidly worldwide. The review found over 20 planned and progressing studies in China researching treatments for hepatitis B and C.

The identified key research centres in China were (in no order): Southern Medical University, Beijing Friendship Hospital, Renji Hospital in Shanghai, Shanghai Dongfang Liver and Gall Bladder Hospital, Shanghai Zhongshan Hospital, Peking University First Hospital, Shenzhen Third People's Hospital, The Third Affiliated Hospital, Sun Yat-Sen University in Guangzhou and National Taiwan University Hospital.

Large sponsors funding China's research in these areas were Johnson & Johnson, Xiamen Amoytop Biotech, Bristol-Myers Squibb, Hoffmann-La Roche, Janssen R&D Ireland, New Discovery LLC and Gilead Sciences.

METHODS

Information was gathered from a range of existing data sources to inform both the data collection process and mapping of current and ongoing research efforts in China in the areas of viral hepatitis detection and treatment.

A detailed methodology can be found in *Appendix 1* of this report however below is a brief summary and description of the methods used.

Document and literature review

A literature review of published and unpublished literature from key research groups was conducted. This work informed the discussions with experts and provided the basis of the inventory of Chinese research. Relevant documents were identified via an internet search, publications databases, conference abstracts and informants within WHO China. Details of the search methods used can be found in Appendix 1, however to address objectives 1 and 2 of this review and in the interest of presenting only recent research efforts, Chinese and English peer reviewed literature selected were published from 2009 to date.

Clinician surveys

A total of 27 key informants identified as experts in epidemiology, virology and treatment of hepatitis B and hepatitis C infection in China were shortlisted (*Appendix 2*). All key informants were approached by an initial email (*Appendix 3*) and a further email reminder (*Appendix 4*). Information about their involvement and a link to a web-based questionnaire (*Appendix 5*) were included in the email. In total, seven informants completed the questionnaire. These respondents include Professor Lai Wei from Peking University, Professor Jinlin Hou from Southern Medical University, Dr Yanfang Jiang from Jilin University and four others who chose to remain anonymous.

Engagement with key experts

Information was gathered from key informants via email and telephone from relevant government and non-government organisations that work in areas of hepatitis testing and treatment. Brief interviews were conducted with two leading experts in viral hepatitis clinical research, Professor Lai Wei from Peking University and Professor Jinlin Hou from Southern Medical University, to explore their experience and knowledge around diagnostics, treatment and current research efforts.

FINDINGS

1 Cost and accessibility of viral hepatitis treatment and monitoring of patients in China

This section provides background to China's health care system and summarises the published Chinese and English literature around cost and accessibility of treatment in China for hepatitis C followed by B. **Published literature on the cost and accessibility of hepatitis C treatment in China is scarce.**

1.1 China's health care system

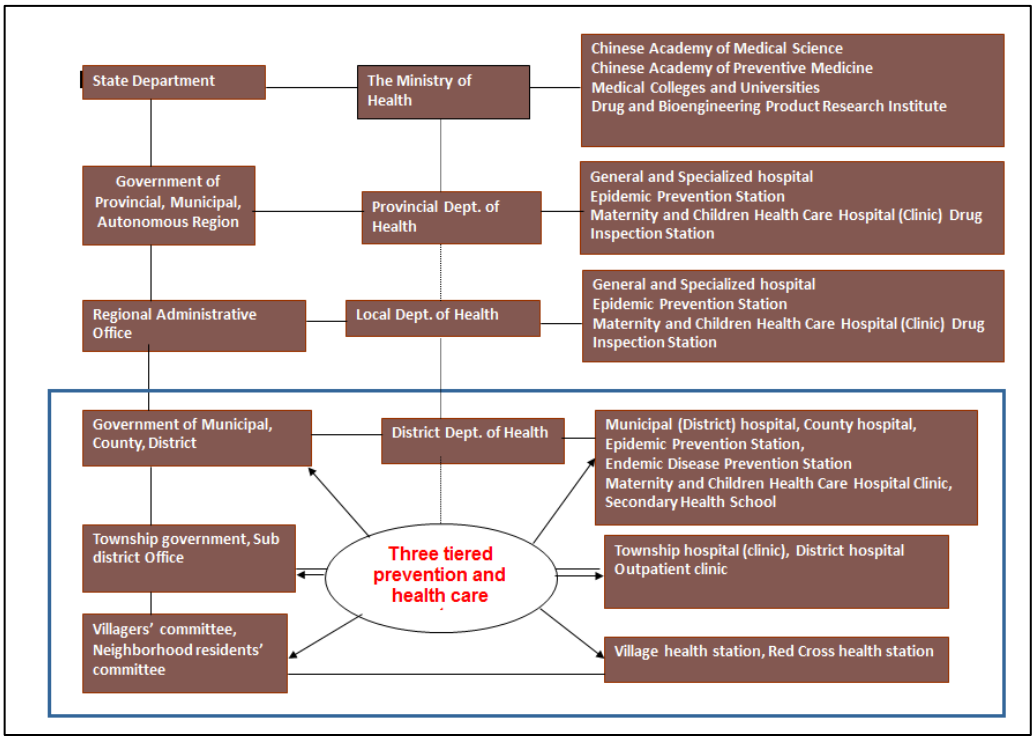
To understand the cost of hepatitis treatment and patient management in China, it is important to be familiar with China's healthcare organizational and funding structure. It is a complex health

system required to service the needs of over 1.3 billion people and provide equitable access to healthcare for an estimated 640 million rural residents [11]. A three tiered structure exists where health care is provided through public facilities at three levels: primary care given by village doctors and workplace clinics, secondary care at rural township hospitals and urban district hospitals; and tertiary care through county and city hospitals[12] (Figure 1).

Township health centres and county hospitals are owned by the government, and there are seldom private health institutions at these two levels. However, there are many privately owned village level clinics which are an important complement to the provision of primary health care services in rural China[13].

The healthcare system in China has undergone many reforms in the past 40 years and the government continues to fund improvements with the aim of universal health coverage and the reduction of health risk, morbidity and mortality from major diseases[10]. To meet these objectives the government is investing in county-level hospitals and community primary care facilities as well as the country's health insurance programs[14, 15].

Figure 1: The organization structure of the Chinese health care system



Source: Jesse Huang, Professor of Epidemiology, Chinese Academy of Medical Sciences, Peking Union Medical College. http://www.bibalex.org/supercourse/SupercoursePPT/37011-38001/37901.ppt

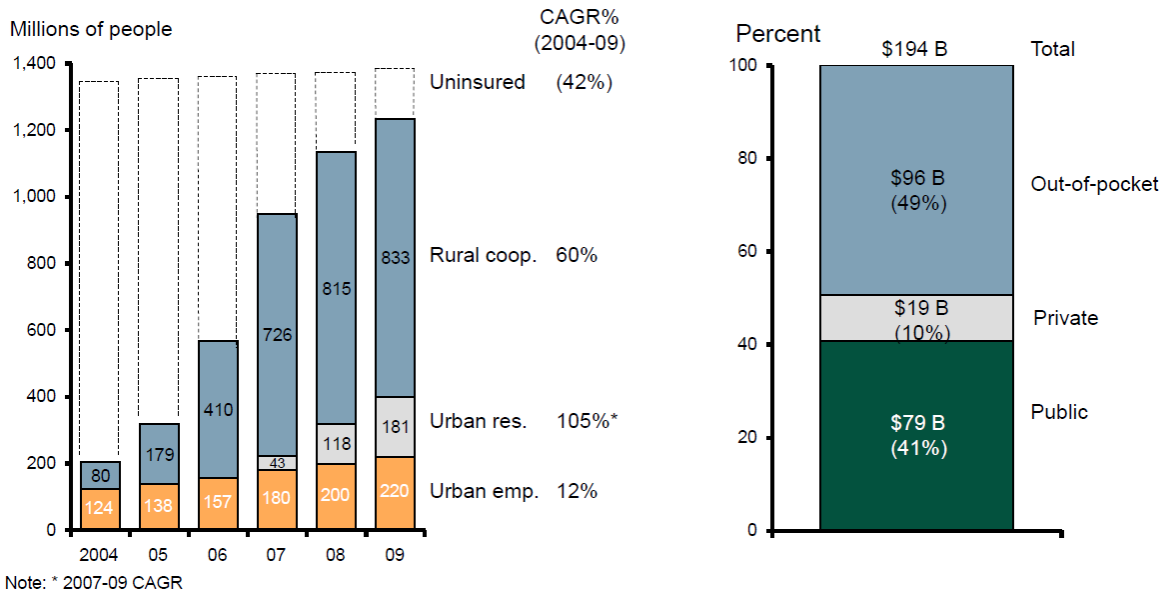
There are three major health insurance programs operating in China that cover specific groups: rural residents under the New Rural Cooperative Medical Scheme (NCMS), urban employees under the Urban Employees Basic Medical Insurance (UE-BMI) and unemployed urban residents under the Urban Residents Basic Medical Insurance (UR-BMI). China's levels of health insurance coverage in 2009 reached over 85%, significantly higher than what they were just a few years earlier, but despite this there remains a substantial amount of out-of-pocket spend by the patient [15] (Figure 2). This is

likely due to the medical assistance programme which helps poorer rural residents enrol in the NCMS rather than covering more of their costs [16, 17].

Despite the continued efforts of the Chinese government to improve access to healthcare and the many health gains achieved, China has also experienced growing health inequalities. A number of evaluations concluded that the increased investment toward individual medical care has shifted the focus from public health and preventive treatment toward curative treatment and increased utilization of expensive care [16-19]. For example it is not uncommon for patients who could be appropriately seen on an outpatient basis to be hospitalised for inpatient care because the insurance schemes cover only inpatient services or offer higher rebates for inpatient services. High deductibles and co-payments were introduced to reduce unnecessary services but providers receive strong incentives to dispensing drugs and perform procedures that require high-tech equipment, leading to overuse of some services[16]. There has been increased outpatient and inpatient utilization and increased ownership of expensive equipment among central township health centres but this has had no impact on cost per case or out-of-pocket expenses [17].

Private supplemental health insurance is also available and encouraged for urban residents, although is not affordable to most people and hence implementation has been slow [20].

Figure 2: Chinese social insurance coverage by type, 2004-09 (L) and China healthcare expenditure by payer type, 2008 (R)



Source: EIU, WHO, China Ministry of Human Resources and Social Security, L.E.K. Consulting Limited http://www.lek.com/sites/default/files/LEK_China_pharma__December_2011.pdf

1.2 China's hepatitis treatment guidelines

1.2.1 Hepatitis C

At the time of this review, the most recent guidelines relevant to China were the *Asian Pacific Association for the Study of the Liver (APASL) consensus statements on the diagnosis, management and treatment of hepatitis C virus infection* (2007) of which Chinese authorship was contributed[21]. These were revised in 2012[22]. Prior to these, the *Guidelines for the Prevention and Treatment of Hepatitis C* were developed by the China Medical Association, Chinese Society of Hepatology and Chinese Society of Infectious Diseases and Parasitic Diseases in 2004[23, 24].

In April 2014, WHO released its first hepatitis C treatment guidelines, primarily targeted at ministries of health working in low- and middle-income countries to assist officials as they develop national hepatitis C treatment plans and guideline documents[25]. These guidelines could also be useful for clinicians who manage HCV-infected persons but are not specific to China in terms of the availability of drugs and resources.

According to all guidelines however, the goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, by the achievement of virologic cure as evidenced by sustained virological response (SVR). SVR is indicated by non-detectability of HCV RNA in serum 24 weeks after completing treatment.

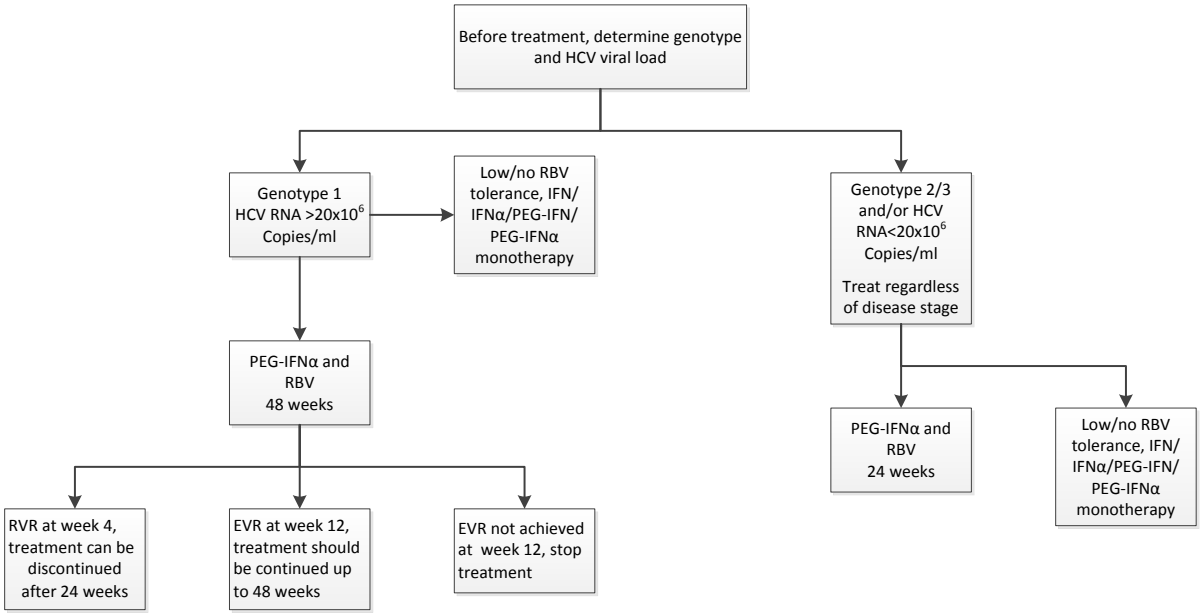
Until the recent advent of direct-acting antiviral drugs (DAAs), pegylated interferon alfa (PEG-IFNα) combined with ribavirin (RBV) has had the highest rate of SVR and according to the 2004 guidelines should always be used in treatment of HCV if there are no counter indications [24]. The recommended duration of treatment varies, depending on the genotype, stage of disease and initial response to treatment (Figure 3).

For treatment of chronic hepatitis C, combination of once a week injection of long acting PEG-IFNα and daily oral RBV for 48 weeks is currently the standard of care in China, especially for patients infected with HCV genotype 1[24]. Genotype 1 is the most common strain of HCV in China with subtype 1b being the most prevalent [26, 27]. Asian patients have higher SVR rates than non-Asian patients with standard therapy and this trend applies across all genotypes (GT1 61-79%, GT2/3 74-94%, GT6 60-79%)[28]. Clinical trials have associated 48 weeks of PEG-IFNα-2a plus RBV in treatment-naive Asian patients with genotype 1 infection with a higher SVR rate, compared with 24 weeks of the same[29]. For those with delayed virological response (genotype 1), treatment can be extended to 72 weeks[25].

Treatment of hepatitis C in the acute stage has resulted in better SVR rates than treatment in the chronic stage and can significantly reduce the progression to chronic hepatitis C[26, 30]. Diagnosis of acute HCV is problematic however as it relies on testing before and after exposure or the presence of clinical signs or symptoms, which only occurs in one-third of cases. In these cases, it is recommended by APASL that that treatment be delayed for 8-16 weeks to allow for spontaneous resolution which occurs in up to 50% of patients.

By early 2014 there were four DAAs licenced for use boceprevir, telaprevir, simeprevir and sofosbuvir. With the introduction of DAA it is not clear how RBV is positioned but early clinical studies provide strong evidence for a benefit of RBV in combination with DAAs for regimens with or without IFN. DAAs are very expensive and the effects of long term use are not yet known [25]. Also at the time of this review none of these were being marketed in China.

Figure 3: Flow chart of treatment regimen guidelines for chronic hepatitis C



Source: Based on APASL Consensus Statements: Treatment of HCV infection (2007)
EVR, RVR= early, rapid virological response

1.2.2 Hepatitis B

At the time of this review, the most recent guidelines relevant to China were the *Guideline on prevention and treatment of chronic hepatitis B in China (2005), Chinese Society of Hepatology and Chinese Society of Infectious Diseases* [31]. These were translated to English in 2007. There also exists the *Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update* [32]. This was again updated in 2012 and China contributed to authorship on both published statements[33].

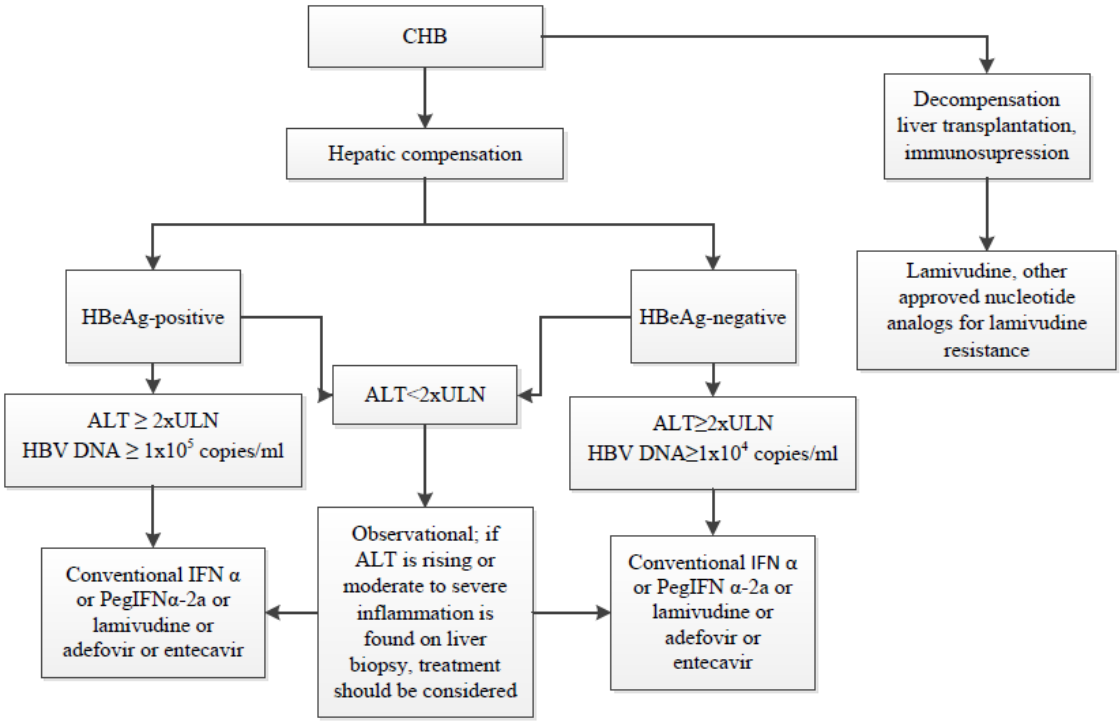
In chronic hepatitis B patients, the long term objective of treatment is to permanently suppress HBV replication as viral eradication is not feasible with current drug therapy. This will decrease the infectivity and pathogenicity of HBV, reduce or prevent liver disease progression, reduce the likelihood of a HCC and prolong survival. Clinically, the short-term goal of treatment is to achieve HBeAg seroconversion and/or HBV-DNA suppression and alanine transaminase (ALT) normalization[33].

The 2005 guidelines distinguish between chronic HBV carriers and inactive HBsAg carriers and makes recommendations for the treatment of each separately (Figure 4). Chronic HBV carriers are HBsAg positive with active viral replication but normal transaminase levels. Inactive HBsAg carriers are HBsAg positive without active viral replication and significant liver disease[34].

In the 2005 guidelines, the mainstay first-line treatment for viral hepatitis in China included conventional IFN or PEG-IFNα-2a and/or nucleoside analogs(NA): lamivudine (LAM or 3TC); adefovir dipivoxil (ADV); and entecavir (ETV)[31]. PEG-IFNα-2b and telbivudine (TBV or LdT) were not included in those guidelines and more recently have been included for treating chronic hepatitis B in the revised Asia-Pacific statement[33, 34].

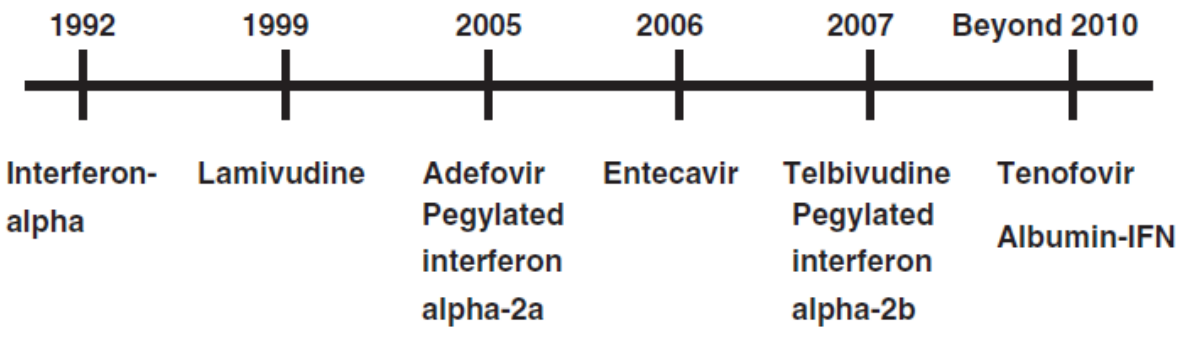
Tenofovir (TDF) is an antiviral used for treatment of HIV and was approved by the Chinese State Food and Drug Administration for chronic hepatitis B treatment in China[35] in recent years therefore not included in the 2005 Chinese guidelines (Figure 5). TDF is generally well tolerated, even in patients with decompensated liver disease and no TDF resistance has been reported during treatments of up to 3 years. TDF has been discussed and included in the 2012 revision of the consensus statement however which also recommends for patients who develop drug resistance while on 3TC, add-on ADV therapy or switch to TDF [33].

Figure 4: Flow chart for chronic hepatitis B antiviral treatment



Source: Guideline on prevention and treatment of chronic hepatitis B in China (2005)

Figure 5: Timeline of the State Food and Drug Administration (SFDA)-approved therapy for chronic hepatitis B in China



Source: Sun J, et al. Journal of Viral Hepatitis, 2010

1.3 Cost and accessibility of hepatitis treatment in China

1.3.1 Hepatitis C

1.3.1.1 The cost of drug treatments for hepatitis C

According to the key informants for this review, IFNα is manufactured domestically at approximately 60-110 RMB per dose and patients are given three doses weekly. PEG-IFN manufactured by Roche and Merck costs approximately 1100 RMB per dose and 1 dose per week are used to treat hepatitis C for 24-48 weeks depending on hepatitis C genotype (Figure 6) .

Figure 6: Cost of antiviral medication per individual treatment for hepatitis C
(Exchange rate of USD/CYR=6.2)

Drugs	Price（Yuan）	Cost/yr (Yuan)
PEG IFNa-2a （Pegasys 180 ug）	1124 / W	58448.00
PEG IFNa-2b （Pegintron 50 ug）	708 / W	36816.00
IFNa-2b （Anfulong 5 MU）	60.18 / ampule	10982.85
IFNa-2b （Anfulong 3 MU）	41.57 / ampule	7586.53
Ribavirin （for HCV only）	32.43 / month	389.16

Source: Jidong Jia, Beijing Friendship Hospital, Capital Medical University. Presented at WHO technical meeting, Beijing, Feb 21, 2014

1.3.1.2 The influence of the healthcare system on the costs of hepatitis C treatment to patients

Treatment of hepatitis C is available in medical facilities above county level in China and patients are able to claim higher rebates when treated in tertiary hospitals than when treated in secondary or primary healthcare services. Also, the cost of hepatitis C treatment can be fully reimbursed for inpatient treatments and partially rebated for outpatient services with percentages ranging from 50% to 80% depending on the individual's health insurance policy. Despite subsidies, hepatitis C treatment is still a big financial burden for patients who are required to pay out-of-pocket costs for laboratory tests, examinations and other hospital related inpatient services and medication[36].

To alleviate the financial burden on patients and hospitals, PEG-IFNα was included on the Essential Drugs List in some provinces from 1 February 2008. Since then, out-of-pocket expenditures for hepatitis C infected patients decreased significantly (Table 1). Fewer patients underwent inpatient treatment to receive free medication once outpatients were no longer required to pay for them. This contributed to the decrease in the total cost of treatment to patients and hospitals [36].

Table 1: Costs of PEG-IFNα before and after government subsidies introduced in China

	Average monthly medical cost (CYR)	Average subsidized payment (CYR)
Before Mar 2008	13,360	8,362
Mar - Aug 2008	4,803	3,283
Feb - Jul 2009	4,420	2,936

Note: Exchange rate of USD/CYR=6.2 at time of report, http://www.xe.com.
Source: Liu Y, et al. Chinese Health Economics, 2011

1.3.1.3 Other considerations that impact on accessibility and cost of treatment

China is experiencing low HCV treatment rates which can impact on China's disease burden[37]. There are many reasons for poor uptake of HCV treatment, including toxicity of interferon-based therapy, cost to patients and the prolonged course of treatment (24–48 weeks and potentially 72 weeks for some). Poor HCV treatment uptake can impact on disease burden and infection control. DAAs are a way of moving away from IFN based therapy and toward short duration and high efficacy. These are not yet available in China but are being trialled there currently (see Section 3).

1.3.2 Hepatitis B

1.3.2.1 The influence of the healthcare system on the costs of hepatitis B treatment to patients

The estimated costs of hepatitis B care are a significant proportion of the average annual wage in China. An analysis of data from six hospitals in Shandong showed the average hospitalisation costs of urban hepatitis B patients were 46%-60% of their annual per capita net income, and at least 104% of the annual per capita net income for their rural counterparts [38]. Antiviral drugs contributed 50%-60% of total medical costs of hepatitis B treatment [39-42].

Patients with UE-BMI could get 70% rebates for their total medical costs while patients insured under the UR-BMI and NCMS programs could only claim 45% and 21% rebates, respectively [38]. The direct costs of hepatitis B related diseases (except acute hepatitis B) exceeded 40% of household income in China, demonstrating again the large economic burden of viral hepatitis. The median cost for chronic hepatitis B in secondary hospitals was higher than in tertiary hospitals possibly suggesting hospital inefficiency as an issue[43]. Key Chinese decision makers may need to take this into account when addressing the direct economic burden of hepatitis B.

Within China's healthcare structure the government subsidizes medicines on the Essential Drugs List under the National Reimbursement Drugs List (NRDL) program [44]. However, it is common in China to use a combination of multiple therapies to treat hepatitis B by including hepatic protectors and in some cases complementary medications which are out-of-pocket costs for the patients [45, 46].

The health system results in inequitable access to treatment among patients and can create heavier financial burdens to patients if they do not have health insurance; have rural health insurance; are hospitalised in a tertiary hospital; have more comorbidities; or depend on antiviral drugs[47]. Therefore despite hepatitis B treatments being widely available, only a small proportion of people diagnosed with chronic hepatitis B will access them[37].

1.3.2.2 Accessibility and compliance in long term monitoring and surveillance of Hepatitis B

The high cost of treatment to patients has been linked to poor levels of follow-up and compliance in China. Reasons for non-compliance with follow-up included various health care system barriers such

as patient income, out-of-pocket expenditures for outpatient visits, increasing health care costs, fragmented services and no choice of physician[48]. Further, social barriers such as existing stigma and discrimination against people with chronic hepatitis B in addition to the perceptions of patients themselves, contributed to such poor outpatient follow-up[49]. It is recommended that these factors be addressed when key decision makers look to revise and implement future guidelines [48].

1.3.2.3 Economic cost burden of hepatitis B

The total economic burden of chronic hepatitis B related diseases in Beijing and Guangzhou has been calculated by measuring direct and indirect economic costs to patients per year by disease (Table 2) [50]. Despite slight differences in utilisation and costs between Beijing and Guangzhou, the findings can be generalised to most large cities in China with similar population density and economy.

In addition uninsured inpatients had almost no self-treatment costs and the direct economic burden of hepatitis B was found to increase as disease progressed; with the need for other treatments including transplants then becoming a necessity in some cases. Self-treatment expenditures among insured inpatients were highest for primary liver cancer and severe hepatitis B [43].

The high costs and economic burden associated with chronic hepatitis B highlight the importance of disease prevention and treatment. Successful prevention of HBV infection and the prevention or delay of disease progression will offer considerable socioeconomic savings in the future[34].

Table 2: Cost of economic burden in Beijing and Guangzhou

Beijing		**Guangzhou**	
Economic Burden type	Annual Cost (US$)	Economic Burden type	Annual Cost (US$)
Direct economic burden= direct medical+ non-medical costs			
CHB	1380	CHB	1355
Compensated cirrhosis	2282	Compensated cirrhosis	1875
Decompensated cirrhosis	3870	Decompensated cirrhosis	3816
HCC	6084	HCC	5472
Indirect economic burden= work loss from sick days			
CHB	256	CHB	97
Compensated cirrhosis	440	Compensated cirrhosis	190
Decompensated cirrhosis	741	Decompensated cirrhosis	474
HCC	531	HCC	582
Total Economic burden= Direct economic burden + Indirect economic burden			
CHB	1636	CHB	1452
Compensated cirrhosis	2722	Compensated cirrhosis	2065
Decompensated cirrhosis	4611	Decompensated cirrhosis	4290
HCC	6615	HCC	6054

Source: Hu M, et al. Value in Health 2009

1.3.2.4 Economic cost of drug treatments for hepatitis B

A 2012 study comparing the cost of entacavir (ETV) versus 3TC in chronic hepatitis B patients found that by reducing hepatitis B viral load and initiating treatment early, using ETV was both cost effective and favourable compared with 3TC, which demonstrated high antiviral resistance [51, 52]. The model did not account for indirect medical costs and loss of productivity but it determined that

short term and long term use of ETV is both clinically effective and economically viable for treatment of CHB.

Similarly, a cost-effectiveness study from 2010 had examined NA therapy and showed that ETV was the most cost-effective NA for hepatitis B in China compared with ADV, TBV and 3TC[53]. ETV treatment achieved the best health outcomes in both the HBeAg positive and negative groups, with a gain of 11.8 and 12.7 QALY respectively and decreased incidences of cirrhosis, hepatocellular carcinoma (HCC) and death. The least cost-effective treatment was ADV; it had the highest drug cost and relatively few health benefits (Table 3).

Table 3: Base case results of treatment strategies: costs, quality-adjusted life years (QALY) gained and incidences of cirrhosis hepatocellular carcinoma and death

Treatment type	No treatment		Lamivudine (3TC)		Adefovir (ADV)		Telbevudine (TBV)		Entecavir (ETV)	
HBeAG status	positive	negative	positive	negative	positive	negative	positive	negative	positive	negative
Cumulative costs (US$)	84000	87000	34200	33100	51300	47000	38000	36300	46600	45100
Cumulative QALYs	8.8	8.8	10.5	10.9	10.4	11.0	11.0	11.6	11.8	12.7
Cumulative incidence of cirrhosis (%)	45.6	45.9	35.2	22.8	35.4	31.7	32.5	27.5	23.8	16.8
Cumulative incidence of HCC (%)	26.7	26.8	20.8	13.0	21.0	18.9	19.3	16.6	14.8	11.0
Cumulative incidence of death (%)	43.7	44.1	32.7	43.7	33.1	29.3	29.9	25.1	23.0	16.8

**No treatment was the baseline strategy compared with other treatment strategies*
Source: Wu B, et al. Value in Health 2010

Mathematical modelling based on clinical trial data from 2006 found for a treatment duration of five years and a follow-up period of 30 years, ETV treatment was translated into specific patient benefit of an estimated cost saving of $2.69 per day compared with no treatment. In addition, long-term usage of ETV resulted in daily $2.33 and $1.73 cost saving compared with short-term usage (1-year and 2-year, respectively). Among available treatment options in China at the time, ETV treatment exhibited about $0.90 to $1.81 daily cost saving versus the comparators. The detailed daily cost saving of ETV is summarized as follows: ETV versus 3TC: $1.81, ETV versus TBV: $0.90, ETV versus ADV: $2.02, and ETV versus generic ADV: $1.37[54]. In addition, studies indicated the defined daily dose cost (DDDc) of ETV has not had major changes from 2006 to 2010, but it has increased 5-8 times over time which apparently led to much more expense for this drug [55, 56].

More recent studies have modelled the cost-effectiveness of rescue therapies for 3TC-resistant chronic hepatitis B in China which included TDF [51]. Combination ADV/3TC was found to be most cost effective with lowest total cost and TDF was the most expensive rescue therapy in HBeAg positive and HBeAg negative groups. Cost-effectiveness analysis demonstrated that it would cost US$6,531.7 to gain an additional quality-adjusted life year for HBeAg positive or a 3TC-resistant patient [57]. TDF did demonstrate a positive health benefit with QALY gained in both HbeAg positive and HbeAg negative groups (Table 4).

When combination ADV/3TC therapy was compared with TDF monotherapy based on incremental cost-effectiveness ratio (ICER) the authors interpreted that TDF monotherapy was a cost-effective choice for 3TC resistant rescue treatment in generous economic conditions (Shanghai) whereas ADV/3TC combination treatment was more cost-effective in health care systems with limited resources such as the majority of mainland China [57].

Table 4: Modelled lifetime clinical outcomes of rescue therapies in 3TC resistant CHB patients

Treatment type	No treatment		Adefovir (ADV)		Adefovir/Lamivudine ADV/3TC		Entecavir (ETV)		Tenofovir (TDF)	
HBeAG status	positive	negative	positive	negative	positive	negative	positive	negative	positive	negative
Total cost (US$)	9748	13097.2	13011.9	16229.5	21284.9	25552.8	25387	27556.3	27556.3	32270.9
QALYs	8.77	7.76	9.25	8.64	10.58	10.48	9.43	8.51	11.17	10.36
Incremental cost (US$)^	-	-	3533.8	3132.3	11806.9	12455.6	15908.9	14459.2	22452.4	19173.8
Incremental QALYs ^	-	-	0.47	0.88	1.81	2.72	0.66	0.75	2.4	2.6
ICER*	-	-	7468	3552.6	6531.7	4571.7	24268.9	19157.1	9359.8	7370.4
Cumulative incidence of compensated cirrhosis %	0.51	0.8	0.49	0.76	0.39	0.59	0.47	0.76	0.31	0.53
Cumulative incidence of decompensated cirrhosis %	0.2	0.33	0.19	0.3	0.14	0.22	0.18	0.31	0.12	0.21
Cumulative incidence of HCC %	0.19	0.25	0.18	0.23	0.15	0.18	0.18	0.23	0.13	0.17
Cumulative mortality# %	0.41	0.64	0.38	0.58	0.3	0.42	0.37	0.59	0.25	0.41

*# Death is associated with hepatitis B, * ICER= Incremental cost/Incremental QALY, ^ As compared to no treatment baseline*

Source: Wu B, et al. BMC Health Services Research, 2012

1.3.2.5 Other considerations that impact on accessibility and cost of treatment

Despite cost, TDF 300 mg daily has been shown to have superior HBV DNA suppression than ADV 10 mg daily in both HBeAg positive and HBeAg negative patients[58]. TDF treatment for 3 years was associated with 72% undetectable HBV DNA and 26% HBeAg seroconversion in HBeAg positive patients, and 87% undetectable HBV DNA in HBeAg negative patients (Figure 7). The HBsAg clearance rate is unknown in Chinese patients. In other populations, TDF treatment for 5 years was associated with sustained viral suppression (2.8 % remained viremic) and significant regression of fibrosis (44%)/cirrhosis (76 %), and no resistance to TDF was detected [58].

Since the recent approval of TDF for CHB treatment in China, it is not known how widely it is being used. In the case of HIV, ART prices have dropped from more than US$10,000 per person per year in 2000 to less than US$65 in many countries. In China, the price of TDF has been successfully negotiated at RMB 113 per month for the HIV public health program but its price is still RMB 1,470

per month for hepatitis patients (Figure 6). There is also a Free ART Program which has made considerable progress in providing the necessary care and treatment for HIV-infected people in China and has strong government support for continued improvement and expansion [59]. A similar strategy could be considered for the fight against hepatitis B in China [60].

Figure 6: The cost of nucleoside analogs for CHB

Drugs	Cost /28 d (Yuan/)	Cost/yr （Yuan）
Lam（Heptidin）	360.00	4692.86
Lam（generic）	280.00	3650.00
ADV（Hepsera）	441.74	5758.40
ADV（Generic）	262.62	3423.44
LdT（Sebivo）	537.60	7008.00
ETV（Baraclude）	834.80	10882.21
ETV（generic）	587.84	7662.91
TDF（Viread）	1300.00 （30d）	15600.00

Source: Jidong Jia, Beijing Friendship Hospital, Capital Medical University. Presented at WHO technical meeting, Beijing, Feb 21, 2014

Figure 7: Comparison of viral responses among five direct antiviral agents in treatment-naive patients with chronic hepatitis B

	LAM		ADV		ETV		LdT		TDF	
HBeAg	+	−	+	−	+	−	+	−	+	−
HBV DNA undetectable (%)										
Year 1	36–40	71–72	13–21	63–71	67–71	88–90	60	88	76	93
Year 2	39	57	NA	71	80–83	96	56	82	NA	NA
Year 3	20	40	36	73	83–89	98	77	83	72	87
Year 4	NA	NA	38	62	91	NA	NA	NA	NA	NA
Year 5	NA	NA	39	53	94	NA	NA	NA	NA	NA
HBeAg seroconversion (%)										
Year 1	15–22	NA	12–18	NA	21–22	NA	23	NA	21	NA
Year 2	25–29	NA	29	NA	31	NA	30	NA	26	NA
Year 3	35–40	NA	37	NA	44[a]	NA	37[b]	NA	26	NA
Year 4	46–47	NA	35	NA	NA	NA	NA	NA	NA	NA
Year 5	44	NA	30	NA	NA	NA	NA	NA	NA	NA
Genotypic resistance (%)										
Year 1	12–24	6	0	0	0	0	5	2	0	0
Year 2	40–50	26	NA	3	0	NA	25	11	0	0
Year 3	53–71	NA	NA	11	1.2		+3.6	+6.2	0	0
Year 4	67–70	NA	NA	18	1.2		NA	NA	0	0
Year 5	71	NA	NA	29	1.2		NA	NA	0	0

NA not available

[a] Cumulative

[b] Excluding those with resistance at year 2

Source: APASL consensus statement, 2012, data from RCTs and long-term follow-up cohorts

1.4 Summary

1.4.1 Hepatitis C

Published literature on hepatitis C treatment shows that the results of PEG-INF and RBV treatment for chronic HCV infection are effective in China due to the pre-dominant HCV genotype I b. More equitable access to such treatment would decrease risks of disease progression and subsequent mortality.

Also, it is important to note that over the next five years, the introduction of PEG-free DAA regimes will change the treatment landscape of hepatitis C globally. Treatment of hepatitis C with DAAs is likely to improve uptake of and adherence to treatment but antivirals are expensive and a consideration of resources is required to assess which treatments are most suitable for the situation in China. Many individual countries are negotiating lower prices of DAAs and generic formulations of these medications will become available in some countries. It is likely that these highly effective therapies will become increasingly available in China.

1.4.2 Hepatitis B

It is well documented that treatment of hepatitis B with oral nucleoside analogues will strongly decrease risks of disease progression and subsequent mortality. According to the latest Asia-Pacific consensus statement ETV and TDF are both highly effective with minimal resistance but TDF is a lot more expensive at around twice the cost per annum.

The estimated disease cost burden is high and can exceed individuals' earning capacity with the costs to treat hepatitis B increasing as the disease progresses. This is of major concern when considering strategies for treatment in a population with considerable prevalence. Decreasing the price of TDF to the same level as for HIV is one way that would greatly decrease expenditures for HBV treatment. While other less expensive drugs can be used to treat hepatitis B, drug resistance is another major barrier for widespread effective treatment and reduction of disease burden and cost.

TDF monotherapy has been shown to be cost-effective for rescue therapy in generous economic conditions whereas ADV/3TC combination treatment was more cost-effective in health care systems with limited resources such as the majority of mainland China.

2 Chinese clinicians' awareness and compliance to existing national treatment guidelines

Section 2 provides a summary of Chinese published literature on clinicians' awareness and compliances with existing national guidelines. As well it includes the results of the online survey administered to Chinese clinicians and feedback from key informants.

2.1 From the Chinese literature

No literature was identified assessing clinicians' knowledge and awareness of the Hepatitis C Guidelines.

2.1.1 Hepatitis B

The Chinese Society of Hepatology and the Chinese Society of Infectious Diseases first published the Guideline of Prevention and Treatment for Chronic Hepatitis B [61] in 2005 and it was updated in 2010 [62]. Whilst not a mandatory clinical standard, the guideline has played a major role in the current clinical practice among clinicians [63]. Increasing numbers of clinicians are using the guidelines as a practical reference and this trend can also be seen in some analyses of drugs used in hospitals [55, 56]. In the Guideline, LAM, ADV dipivoxil, ETV and TBV are recommended for antiviral treatment besides IFN, and as a result the amount of prescription of these drugs have increased significantly since the Guidelines publication.

Despite the increasing use of the Guidelines there may be variation in their uptake and implementation across China. For example, a study showed there was 151% increase of antiviral nucleoside drugs prescribed in a hospital in Beijing in 2006 with an annual growth of over 20% for these prescriptions since then [55]. A similar sharp surge occurred in 2009 in a hospital in Guangxi province which is less developed than Beijing [56].

In China, even though 3TC is still the most prescribed drug to treat hepatitis B, due to resistance and other factors, 3TC is gradually loosing popularity but ETV is gradually gaining popularity[37]. The popularity of antiviral nucleoside drugs in clinics may not only be driven by the application of the Guideline and the increasing number of patients accessing treatment, but related to doctors' decision to prescribe more medications in order to receive incentives from drug companies [41].

There is a gap between the understanding and practice of hepatitis B treatment guidelines among clinicians[49]. Of 411 Chinese physicians surveyed regarding their understanding of CHB treatment, 99% understood that patients should continue oral anti-viral for at least 2 years, but more than half reported that their patients continued treatment for less than 2 years. Also, 88% agreed to the importance of anti-viral of high potency and low drug resistance, but in real practice over 70% patients use anti-viral of low potency and high drug resistance rate. Finally, almost all the physicians surveyed inform their patients of the danger of using anti-viral of low potency and high drug resistance rate, but in real practice, 86% of physicians find patients with drug resistance very common[64].

It is also important to consider patient perspectives. Of over 15000 patients surveyed from 11 cities around China, the majority were suspicious of and pessimistic about anti-viral treatment with only one-third believing that anti-viral therapies may help them return to a normal life. Of the total patients, 43% were most worried about treatment efficacy and 33% worried about the burden of treatment cost[64].

2.2 From key informants

2.2.1 Hepatitis C

According to informants, the current national guidelines have standard treatment regimens for hepatitis C infection that include PEG-IFN combined with RBV or IFN combined with RBV. The newer, first generation protease inhibitors bocepravir, telapravir, simeprevir, and sofosbuvir are not available in China.

The seven respondents held positions with multiple responsibilities: Of the seven key informants, six are clinical doctors who currently treat hepatitis patients and one is conducting research about hepatitis diagnosis and treatment, five on the efficacy of antiviral treatment, three on diagnosis and laboratory testing of viral hepatitis, three in hepatitis virology, two work in new drug research and development and two in hepatitis epidemiology (Appendix 6). Of the 7 key informants, 6 are clinical doctors who current treat hepatitis patients and 1 is doing research about hepatitis so they have the expertise to comment the treatment guidelines. It is also important to know if clinicians in lower levels know the guidelines but this was not captured within this project.

2.2.2 Hepatitis B

All seven were aware of the latest 2010 hepatitis B treatment guidelines of the Chinese Hepatic Society but only four provided the name and year of the guidelines. Two thought the latest hepatitis B treatment guidelines was published in 2010, one thought it was in 2011 and another one thought it was in 2013.

All seven were aware of the latest hepatitis C treatment guidelines (2004) but only four provided the name and year of the guidelines. Two thought the latest hepatitis C treatment guidelines was published in 2004, one thought it was in 2006 and another one thought it was in 2011.

Opinion of the current hepatitis B and hepatitis C treatment guidelines varied among respondents: three believed they were suitable for the current medical practice in China and four believed they were not up-to-date and should be changed according to the unique socio-demographic characteristics of hepatitis B and hepatitis C patients in China.

Six out of the seven respondents thought clinicians in China were aware of the existing hepatitis B and hepatitis C treatment guidelines, of whom four thought these clinicians apply them into their clinical practice, two thought clinicians only used them as a reference rather than as guidelines, and one thought clinicians are not aware of the guidelines. Six out of the seven respondents treat hepatitis B and hepatitis C patients in a clinic, of whom five applied the guidelines in their own clinical practice and one only used them as a reference rather than guidelines.

Five out of seven respondents thought viral hepatitis treatment expensive or very expensive for most of their patients. Five thought antiviral agents were easy to access via doctors or over the counter (OTC) for most of patients.

2.3 Summary

Clinicians in China thought viral hepatitis treatment was still expensive for most patients. Whilst the clinicians were aware of the existence of the guidelines released by the Chinese Society for Hepatology there appeared to be a lack of familiarity with the details of the guidelines. Most of the clinicians expressed concern that the guidelines were either out of date or not suitable to China's current situation.

3 Inventory of existing Chinese research efforts to simplify diagnostics and treatment for viral hepatitis

Section 3 reports on Chinese research efforts in diagnostics and treatment. It includes information from consultations with key informants and the results from published and unpublished literature and internet searches that included https://clinicaltrials.gov.

Key informants Jin-Lin Hou, Director and Professor of the Hepatology Unit and Department of Infectious Diseases, Nanfang Hospital, Southern Medical University and Professor Lai Wei, Director and Professor at Peking University People's Hospital provided the information below on current research in China and this was supplemented by the document review.

3.1 Non-invasive method for assessment of liver fibrosis

The key informants reported that the available modalities for non-invasive assessment of liver fibrosis in China are ultrasound-based transient elastography (FibroScan, made by Echosens) and the indirect test, aminotransferase/platelet ratio index (APRI). Physicians use FibroScan more commonly. There were 216 FibroScan machines throughout China as of October 2013.

Informants identified the following researchers in this area:

- Professors Yong-Peng Chen and Jin-Lin Hou from Southern Medical University have been working in this area for many years and in 2013 published a literature review on non-invasive methods of assessment of liver fibrosis[65].
- Professor Ji-Dong Jia, Hepatologist and Director of the Liver Research Centre at the Beijing Friendship Hospital, Capital University is collaborating with Tsinghua University in Beijing to produce FibroTouch which is similar to Fibroscan.
- JL Hou also identified Mingde Zeng at Renji Hospital in Shanghai as working in this area, however details of the work were not found by the document review.

The document review identified the following recent and ongoing research:

- Guiqiang Wang, Peking University First Hospital is leading a prospective cohort study that aims to construct and validate a non-invasive model consisting biochemical markers, FibroScan, and radiological parameters for evaluating liver fibrosis caused by hepatitis B virus in mainland China. (http://clinicaltrials.gov/ct2)
- YX Liu, CF Dong, GL Yang, et al from Shenzhen Institute of Hepatology, Shenzhen Third People's Hospital, Shenzhen presented at the 2013 International Liver Congress organized of the European Association for the Study of the Liver (EASL). They reported on the diagnostic accuracy of Virtual Tissue Quantification for a non-invasive assessment of liver fibrosis in patients with chronic hepatitis B. This is a relatively novel technology with high diagnostic accuracy and convenience.

3.2 Most cost effective methods for early detection of hepatocellular carcinoma

According to the informants, ultrasound scan and the serum maker, alpha-fetoprotein (AFP) are commonly used to screen for HCC in China. Computed tomography (CT) and magnetic resonance imaging (MRI) are used for diagnosis of HCC. The serum markers, AFU and GP-73 are not commonly

used. Both informants identified Shanghai Dongfang Liver and Gall Bladder Hospital as leading research in this area:

- Professor Hongyang Wang's, laboratory at Shanghai Dongfang Liver and Gall Bladder Hospital screened and charactered MXR7(GPC-3) as a novel marker of HCC. Combination measurement of MXR7 and AFP markedly improved diagnostic sensitivity. Her team found p28 to be a potential therapeutic target for HCC. They also found that DKK1 could complement measurement of AFP in the diagnosis of HCC and improve identification of patients with AFP-negative HCC and distinguish HCC from non-malignant chronic liver diseases [66].
- JL Hou also identified Professor Zhaoyou Tang's team at Shanghai Zhongshan Hospital who found a plasma microRNA panel that has considerable clinical value in diagnosing early-stage HCC. Thus, patients who would have otherwise missed the curative treatment window can benefit from optimal therapy [67].

3.3 Criteria for treatment start

The current criteria for antiviral treatment initiation are based on the national guidelines [24, 62] . At present, there are three standard IFNs (IFNα-1b, -2a and -2b), two PEG-IFNs (PEG -IFNα-2a and -2b) and four NAs (3TC, ADV, ETV and LdT) licenced and launched in China. TDF is registered in China for hepatitis treatment since the end of 2013. Apart from the PEG-IFNs, all of the antiviral agents are manufactured in China by patents [34]. No new research was identified by the informants.

No current or recent research in China was identified on when to start patients on hepatitis B and hepatitis C treatment in the document review.

One recent publication however by Li S, et al from Zhoushan Hospital, Wenzhou Medical College Zhoushan, Zhejiang, provides evidence for the clinical and economic benefits of early detection of active CHB through monitoring and treatment of eligible patients. A monitor and treat strategy applied in this cohort study showed a reduction in the risk of cirrhosis and HCC as well as cost-effectiveness in all risk categories. The authors suggested the next step should be to find out how much a screening program will cost, and whether it continues to be cost-effective in combination with the proposed monitor and treat strategy [68].

3.4 Efficacy and safety of new antiviral treatments in Chinese populations

Treatments for viral hepatitis are changing rapidly worldwide, in particular for hepatitis C. Although the new DAA therapies are not currently available for treating patients, some clinical trials are being conducted on these new drugs.

3.4.1 Hepatitis C

- Bristol-Myers Squibb are directing a Phase 3, study with daclatasvir and asunaprevir (dual) for subjects with genotype 1b chronic hepatitis C infection who are intolerant or ineligible to interferon alfa therapies with or without ribavirin. This trial has been conducted in 27 locations around China (ClinicalTrials.gov identifier: NCT01995266).
- Janssen R&D Ireland completed a phase 3 study in multiple sites around China and Hong Kong to investigate the efficacy, pharmacokinetics, safety and tolerability of TMC435 vs. placebo as part

of a treatment regimen including PEG-IFN α -2a and RBV in treatment-naïve, genotype 1 hepatitis C-infected subjects (ClinicalTrials.gov Identifier: NCT01725529).

- Gilead Sciences is currently funding a phase 3 intervention trial in 80 sites around the world, one in Hong Kong to evaluate the efficacy, safety, and tolerability of sofosbuvir /GS-5816 fixed dose combination for 12 weeks in adults with chronic genotype 1, 2, 4, 5, or 6 hepatitis C infection (ClinicalTrials.gov Identifier:NCT02201940).
- Hoffmann-La Roche completed a phase 2 study to evaluate safety, tolerability, pharmacokinetics, and antiviral activity of ritonavir-boosted danoprevir in combination with PEG-IFNα-2a plus RBV in treatment-naïve patients of Asian origin who have chronic hepatitis C genotype 1 with or without compensated cirrhosis. China is not one of the locations however (ClinicalTrials.gov Identifier: NCT01749150).
- Our search identified three studies ongoing in China that involved IFN/PEG or a biological version: phase 3 of new bio-product peg recombinant consensus IFN variant (PEG-IFN-SA) (NCT01903278); phase 2 YPeg-IFN vs pegasys (Xiamen) (NCT01140997); observational study of HCV treatment and outcomes (ClinicalTrials.gov Identifier: NCT01594554).

3.4.2 Hepatitis B

Global studies have found that the treatment of HBeAg positive patients who have high viral load and normal ALT with highly potent antiviral drugs such as TDF is safe, efficacious, and does not promote viral resistance [69, 70]. Studies to optimize the efficacy of such treatments are ongoing in China.

- New Discovery LLC and Gilead Sciences are conducting a randomized control trial in China of Tenofovir Disoproxil among HBeAg positive CHB pregnant women to determine its tolerability and safety during late pregnancy and its efficacy in the reduction of hepatitis B vertical transmission rate. Principal investigators: S Zhang, Hepatobiliary Disease Hospital of Jilin Province; B Zhu, The Fifth Hospital of Shijiazhuang; G Han, The Second Affiliated Hospital of the Southeast University, Nanjing; Y Zhai, Nanyang Central Hospital; and Y Wang, Southwest Hospital, Chongqing.
- Professor G Han, a collaborator in the study above, has also published on the success of TBV in the prevention of vertical transmission from HBeAg positive women with chronic hepatitis B (Clin Gastro Hep 10(5) 520-526, 2012)
- Professor Jinlin Hou, at Southern Medical University is examining the efficacy and safety of PEG-IFNα -2a (40KD) in HBeAg-positive chronic hepatitis B patients participating in a response-guided therapy study.
- J Hou, H Ma, J Sun, et al presented at an international liver conference in 2013 on efficacy and safety of PEG-IFNα-2a (40KD) in HBeAg positive chronic hepatitis B patients participating in a response-guided therapy study. An interim analysis at week 72 found early decline of HBsAg following the commencement of treatment was associated with sustained response post-treatment, and HBV-DNA levels may improve prediction. This study in HBeAg positive chronic hepatitis B patients aimed to identify how response to Peg-IFN α-2a can be optimised through treatment extension or combination with nucleotide analogues using a response-guided treatment strategy.

- Southern University China has conducted a prospective study of pregnant women with chronic hepatitis B to trial the efficacy, safety and tolerability of telbivudine treatment. Initial findings from 88 women recruited 2008/2009 – prevention of mother to child transmission (ClinicalTrials.gov Identifier: NCT01337791) [71]
- Southeast University China is currently enrolling pregnant women for another trial by invitation only (phase 4). The purpose of this study is to evaluate the efficacy and safety of telbivudine in pregnancy for the prevention of HBV perinatal transmission in highly viraemic mothers (ClinicalTrials.gov Identifier: NCT00939068).
- A collaboration between Taixing People's Hospital and Zhenjiang Fourth People's Hospital, China. This study aims to determine whether telbivudine among both hepatitis B surface antigen (HBsAg) and HBeAg positive pregnant women during the third trimester, in addition to standard immunoprophylaxis in infants, will be more effective than standard immunoprophylaxis alone at preventing HBV infections in these infants (ClinicalTrials.gov Identifier: NCT01637844).
- China CDC is recruiting for a phase 2 intervention trial. The purpose of this study is to compare a regimen of TDF/3TC/lopinavir-ritonavir to the WHO-recommended and locally practiced standard of care regimen consisting of zidovudine/lamivudine/lopinavir-ritonavir during the second and third trimesters of pregnancy in HIV and HBV co-infected women. This is a phase II study evaluating the safety of the test regimen in pregnant women and their newborns. While the study is not powered to examine efficacy, preliminary estimates of transmission of HIV and HBV to the infants and of the rate of resistance development will be obtained (ClinicalTrials.gov Identifier: NCT01125696).
- New Discovery LLC and Gilead Sciences are recruiting pregnant women from five Chinese hospitals for a randomized intervention trial to prospectively evaluate two aspects on TDF use in pregnancy: its tolerability and safety in HBeA positive pregnant women with HBV DNA > 6log10 copies/mL during late pregnancy and infants; and its efficacy in the reduction of HBV vertical transmission rate (ClinicalTrials.gov Identifier: NCT01488526).

3.5 Cost effectiveness of PEG-IFN versus IFN

L Wai suggested that patient response should be considered when conducting research in this area. For example hepatitis C patients treated with PEG-IFN combined with RBV are more likely to have a SVR to treatment than those treated with standard IFN alone. Multi-center RCTs have shown that the use of PEG-IFN combined with RBV can result in significantly less recurrence over 6 months.

No studies have been identified.

3.6 Optimal combination therapy to enhance efficacy

3.6.1 Hepatitis C

The document review identified the following studies in China.

- Patients with chronic hepatitis genotype 1b, who are intolerant or ineligible to IFN alfa therapy with or without Ribavirin, will be treated for 24 weeks with daclatasvir (DCV) Dual regimen (= daclatasvir + asunaprevir) and followed for an additional 24 weeks post-treatment in order to determine the safety and efficacy of the DCV dual regimen.

- The purpose of this study is to provide confirmatory efficacy and safety data of TMC435 as part of a treatment regimen including PEG-IFNα-2a and RBV in patients with genotype 1 hepatitis C infection to evaluate the efficacy and safety of PEG-IFNα-2b (40kD, Y Shape) in combination with RBV in Chinese chronic hepatitis C patients.

3.6.2 Hepatitis B

- One hepatitis B study was identified via informants is a prospective study investigating the optimization of LDT and ADV combination treatment, the EFFORT study [37].
- Another identified by the review - Yuehua Huang from The Third Affiliated Hospital, Sun Yat-Sen University is conducting a clinical trial to study whther hepatitis B vaccine activated-DCs combined with PEG-IFN or NAs has more efficacy than PEG-IFNs or NAs alone in chronic hepatitis B treatment. This is being done in collaboration with Ruijin Hospital Affiliated to Shanghai Jiaotong University School of Medicine and The Second People's Hospital of Yunnan province (ClinicalTrials.gov NCT01935635).

3.7 Impact of antiviral treatment on long term prognosis of hepatitis in China

It seems from both informants and the document review that China is involved in many longitudinal studies assessing the impact of long term treatment on individuals with chronic hepatitis B and C and China's Twelfth Five Year Plan supports key research in this area.

3.7.1 Hepatitis C

- Professor Wei Lai is currently leading two observational clinical studies on hepatitis C
  1. A joint program between University of Michigan and Peking University involving over 1000 hepatitis C infected patients in Beijing and 1000 hepatitis C infected patients in Michigan, followed for 5 years (2012-2019), is investigating the progression of inpatients in treatment and patients not in treatment.
  2. A 5-year observational follow-up study to describe treatment patterns and outcomes in real world clinical practice for 600 adult patients of newly confirmed HCV infection in China (2012-2016).
- Beijing 302 Hospital is currently recruiting for an observational study on hepatitis C patients aged <19 years. The aim of this study is to investigate the relationships between interleukin 28B genetic variants and the response to treatment of chronic hepatitis C in Chinese children (ClinicalTrials.gov Identifier: NCT01607021)
- In addition, an extension, observational protocol to evaluate the long term effects of PEG-IFNα -2a plus RBV for chronic hepatitis C/B co-infection was conducted recently at National Taiwan University Hospital, sponsored by Hoffmann-La Roche. The principal investigator is Dr Pei-Jer Chen (ClinicalTrials.gov Identifier: NCT00361179)

3.7.2 Hepatitis B

- China is part of multi-centre international clinical trial led and sponsored by Bristol-Myers Squibb (BMS) in 290 locations in 24 countries around the world. It is referred to as the REALM Study and is a randomized, observational study which will prospectively assess the long-term benefits and risks associated with ETV therapy as compared to other antivirals approved for the treatment of chronic HBV infection (ClinicalTrials.gov Identifier: NCT00388674). For the China sub study, patients randomized to ETV will have safety and efficacy assessments performed during the first year of the study. The only data published from this study has been by Professor Jinlin Hou (J Viral Hepat, 20(11):811-20, 2013)
- A retrospective-prospective observational study to evaluate the effect of anti-viral treatment on the long-term outcome in patients with chronic hepatitis B (SEARCH-B Study) is being developed by Nanfang Hospital of Southern Medical University (NCT02167503). Participants are currently being recruited from multiple locations throughout China.

In the near future more important data, focussing on optimization of the efficacy of antiviral agents, will be released from China, based on the newly launched National Twelfth Five Year Plan Project on Hepatitis Research.

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APPENDICES

Appendix 1: Detailed methodology

Methodology for literature review

In December 2013, we searched the China National Knowledge Infrastructure (CNKI 中国知网 www.cnki.net) for Chinese literature. CNKI collects 99.6% of all academic journals in China. We limited literature search to journal articles published in the past five years (2009-2013) in order to avoid outdated and other irrelevant literature. We used the following key words ("乙型肝炎 (Hepatitis B)" OR "乙肝(Hep B)" OR "丙型肝炎 (Hepatitis C)" OR "丙肝 (Hep C)") AND ("费用 (Cost)" OR "可及性 (Accessibility)") in title/abstract. A total of 30 papers were found and after reading the abstract 18 papers were shortlisted of which full-text papers obtained. After reading full-text papers, * papers were referenced in this report. We collected the following information from all referenced papers: author, title, journal title, year of publication, issue, pages.

From the PubMed inventory search initially 13 articles were identified as relating to the accessibility and cost of viral hepatitis in China. Following close evaluation of these articles through reading of their abstracts it was found that one article was more about accessibility of ultrasound for diagnosis [72] rather than the specified treatments and monitoring. We also excluded another article as it was a Non-Chinese researcher [73]. In addition, it was discovered that one of the other articles from our list of 13 was actually published in Chinese [74]. It was therefore excluded from the English inventory and sent for inclusion in Chinese inventory. After the full text articles were obtained further reading eliminated another two articles as one was focussed on diagnosis of hepatitis B rather than monitoring and treatment [75] and the other article whilst initially discussing the economic burden of hepatitis B treatments was mainly discussing the efficacy of antiviral treatments through drug trials done in the China context[76]

All research was undertaken throughout mainland China with many studies also naming authors from International centres outside of China. Institutions where Chinese authors were located included: Division of Clinical Immunology Tongji Hospital, Shandong Center for Disease Control and Prevention Jinan Shandong, Department of Pharmacy Clinical Outcomes and Economics Group Renji Hospital, School of Public health, Fudan University Shanghai, Hepatology Unit and Key Lab for Organ Failure Research, Nanfang Hospital, Southern Medical University, Guangzhou, Clinical Immunology Research Center, Jin An District Hospital, Department of Clinical Epidemiology and Evidence-Based Medicine, Chinese Evidence-Based Medicine Center, West China Hospital and First Affiliated Hospital, Beijing University.

Of the narrowed down eight articles, one related to accessibility and compliance with long term monitoring and surveillance of hepatitis [48], three were relating to the overall economic burden for hepatitis B[43, 50, 77] [43, 50, 76, 77], four related to economic implications of hepatitis medications specifically the nucleoside analogues [51, 53, 78, 79].

Identification of publications in the English literature

To-date we have used the CNKI database to search Chinese literature in the areas of hepatitis B and C treatments in China and PubMed database to search English literature in the areas of hepatitis B and C treatments in China. The publications found are tabled in a supplementary document of existing Chinese research efforts to simplify diagnostic and treatment. In the inventory of English

language literature we also include systematic review and meta-analysis on viral hepatitis treatment in China and herbal complementary alternative medicines used in viral hepatitis treatment in China.

1. Accessibility and cost of viral hepatitis monitoring and treatment (all drugs)
2. Clinicians awareness and compliance to existing national treatment guidelines
3. Best non-invasive method for assessment of liver fibrosis (APRI vs fibro test)
4. Most cost effective methods for early detection of HCC
5. Criteria for treatment start
6. Efficacy and safety of new antiviral treatments in China
7. New hepatitis C drugs (first generation protease inhibitors (BOC or TPV)
8. Telbuvidine and TDF efficacy studies in HbeAg + pregnant women
9. Cost effectiveness of PEG interferon versus interferon
10. Optimal combination therapy to enhance efficacy
11. Influence of antiviral on long term prognosis in China
12. Systematic review and meta-analysis
13. Herbal complementary alternative medicine

Methodology of searching for key Chinese informants

The Chinese Medical Association (CMA) is the most prestigious academic organisation in China formed by Chinese medical science and technology professionals. Two specialty societies of CMA are closely associated with hepatitides, Society of Infectious Diseases and Society of Hepatology. According to the committee members of the Society of Infectious Diseases on its website (http://www.infectcma.org.cn/intro.php?type=zzjg), a list of experts in hepatitides were selected based on their speciality on their profiles. No information of the committee members is available on the website of the other society (http://www.heporg.com). Although there are lists of committee members of the Society of Hepatology on the website of CMA (http://www.cma.org.cn/hyzq/zzgl/20111028/1319766019002_1.html), there is no information about their expertise. Therefore, this search was mainly focused on doctors from the Society of Infectious Diseases. The names of these key informants were used as key words searching on Pubmed (http://www.ncbi.nlm.nih.gov/pubmed) for their English publications, particularly for the papers that they are the corresponding authors as there are always contact information of the corresponding authors on English publications. For those Chinese experts who have not had any English publications or have had some English publications but not the corresponding authors, Google search was used to search their contact information, and the key words included their Chinese names, '肝炎'(hepatitis), and 'pdf' or 'email' or '电邮'. Chinese journal articles were the reliable sources to look for their contact information; however, author's contact information was sometimes missed on Chinese journals. Although it is easy to find the switchboard number of the institutions which these informants work for, it is impossible to get the informants personal contact information through that. Accordingly, email has been the major way to contact these informants.

Conference abstracts from China were discovered through internet search on various established International hepatitis/liver Conference websites. A basic Google search was conducted to find websites for European Association for the Study of the Liver (EASL), American Association for the Study of Liver Disease (AASLD), Conferences on Retroviruses and Opportunistic Infections (CROI), International Society for Antiviral Research (ISAR) and Asia Pacific Association for the Study of the Liver (APASL). From EASL website http://www.easl.eu/_the-international-liver-congress/general-information a link for the International Liver Congress was available and a PDF abstract book for International Liver Conference 2013 was obtained through the website. Likewise, other 2013 conference abstract books were obtained from AASLD http://www.aasld.org/Pages/Default.aspx and ISAR http://www.isar-icar.com/ websites. To search for other conference abstracts before 2013 a preliminary internet search was conducted on google using keyword phrases like "Conference abstracts from 2012 International Liver Conference" and "Conference abstracts from International Liver Congress 2008-2012." This led to different individual web pages specific for the conference from that year been found. Subsequently posters and abstracts could be located and downloaded into a word document from each specific conference from that year. The internet based google search also brought up online version of Journal Hepatology available from http://www.journal-of-hepatology.eu/issues# where it was disclosed that the supplemental issues held abstracts from previous International Liver Congresses. From each of the conferences spanning a 5 year period (2008-2013) the titles of the papers and posters were canvassed to narrow down publications from

China. This was done by looking at Author's names, work institutions they were from and context of where study was done (eg. If title described research been done in China), they would be included. Note only researchers, abstracts and posters from mainland China were included, those from Taiwan or Hong Kong were excluded from the review. In some cases it was hard to determine if the research or researchers were Chinese, so these posters and abstracts were compiled into a separate document. Further internet searches were then conducted on Google and Pubmed databases using the primary researchers name as the keyword, to determine if the primary researchers were from China and therefore relevant to the scope of our work.

Methodology of searching for key Chinese informants

A total of 27 key informants who are experts in the epidemiology, virology and treatment of hepatitis B and hepatitis C in China were shortlisted (Table 1). All key informants were approached by an initial email (Appendix 1) and a further reminder email (Appendix 2). Information about the consultancy and a link to a web-based questionnaire was included in the email. Seven out of 27 completed the questionnaire. These responding experts include three named professionals, Prof. Lai Wei, Prof. Jinlin Hou and Dr. Yanfang Jiang; and four who chose to remain anonymous. Detailed comments from key informants on the awareness and compliance to existing national treatment guidelines are summarised in Table 2. In addition we conducted a 30-minute telephone interview to collect Prof. Lai Wei and Prof. Jinlin Hou's opinions in the following topics:

1. Best non-invasive method for assessment of liver fibrosis (APRI vs fibro test)
2. Most cost effective methods for early detection of HCC
3. Criteria for treatment start (routine use of viral load, hepatitis B and hepatitis C genotyping before starting treatment ? access ? alternatives ?)
4. Efficacy and safety of new antiviral treatments in Chinese populations
   4.1 New hepatitis C drugs (first generation protease inhibitors (BOC or TPV)
   4.2 TBV and TDF efficacy studies in HbeAg + pregnant women
   4.3 cost effectiveness of PEG interferon versus interferon
   4.4 optimal combination therapy to enhance efficacy
5. Influence of antiviral on long term prognosis in China

Appendix 2: Key Informants of Viral Hepatitis Treatment in China

Name 姓名	Organisation 就职机构	Postal Address 通信地址	Phone 联系电话	Email 电子邮件	Affiliation 所属学术机构
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Wang Yuming 王宇明	Institute of Infectious Diseases, Southwest Hospital Affiliated to the Third Military Medical University 第三军医大学附属西南医院感染病专科医院	重庆市沙坪坝区高滩岩正街 30 号	023-68754858	wym417@163.com	Society of Infectious Diseases, CMA 中华医学会感染病学会委员会（第九届）
Zhang Lunli 张伦理	Departments of Infectious Diseases, the First Hospital Affiliated to Nanchang University 南昌大学第一附属医院感染科	江西省南昌市东湖区永外正街 17 号			Society of Infectious Diseases, CMA 中华医学会感染病学会委员会（第九届）

Name 姓名	Organisation 就职机构	Postal Address 通信地址	Phone 联系电话	Email 电子邮件	Affiliation 所属学术机构
Jiang Heqing 江河清	Department of Infectious Diseases, First Affiliated Hospital of Zhengzhou University 郑州大学第一附属医院感染科	河南省郑州市建设东路 1 号			Chinese Society of Hepatology, CMA 中华医学会肝病学分会（第四届） Society of Infectious Diseases, CMA 中华医学会感染病学会委员会（第七届）
Zhao Yingren 赵英仁	Department of Infectious Diseases, The First Affiliated Hospital of the Medical College of Xi'an Jiaotong University 西安交通大学第一附属医院传染科	陕西省西安市雁塔区雁塔西路 277 号		zhaoyingren@mail.xjtu.edu.cn zyr@mail.xjtu.edu.cn zhaoyingren@sohu.com	Society of Infectious Diseases, CMA 中华医学会感染病学会委员会（第九届）
Y.-F. Jiang 姜艳芳	女 1971 年研究员消化内科 2003 年 10 月吉林大学第一医院 ... 省长春市新民大街 71 号 86-431- 85612729			yanfangjiang@hotmail.com	
X.-B. Pan.	Tel.: +86 10 88325566; fax: +86 10 68322662. E-mail addresses: pxbdxq@hotmail.com (X.-B. Pan)			pxbdxq@hotmail.com	

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L Wei 魏来	Director and Professor. Peking University People's Hospital		010 88325566 13601281862	weilai@pkuph.edu.cn	
B. Wang	Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China			bjwang73@yahoo.com	
X.F. Chen	ZhongShan III Road, Guangzhou, Guangdong, China. Telephone: +86 13711568011			chenxuefu@yahoo.com.cn	
X. Duan	Liver Failure Treatment and Research Center, 302 Hospital of PLA, Beijing 100039, China			duanxuezhang2006@163.com	
J. Hou 候金林	Phone: 86-20-61641941. Fax: 86-20-87714940 中华医学会感染病学分会候任主任委员，南方医科大学南方医院感染病科主.任。 ... 手机：13802727354			jlhou@fimmu.com	

Name 姓名	Organisation 就职机构	Postal Address 通信地址	Phone 联系电话	Email 电子邮件	Affiliation 所属学术机构
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Q. Li 李强	Medical College, Shandong University, Jinan 250012, China Corresponding author: LI Qiang, Email: doctorliqiang@yahoo.com.cn, Jinan Infectious Diseases Hospital, Jinan 250021, China			doctorliqiang@yahoo.com.cn	
B.-F. Wu	Bang-FU Wu， 1 Southern Medical University Renkang Hospital, Gastroenterology and Hepatology Center, China 2 Guangzhou Pubang Bio-Immunological Tech Research Institute, China			bangfu.wu@163.com	
X.X. Zhang. 张欣欣	xin-xin-zhang@163.com 上海市瑞金二路 197 号瑞金医院感染科 200025			zhangxinxin@rjh.com.cn	

Name 姓名	Organisation 就职机构	Postal Address 通信地址	Phone 联系电话	Email 电子邮件	Affiliation 所属学术机构
J. Liu	The Third Affiliated Hospital of Sun Yat-sen University			diudiu1203@yahoo.com.cn	
Z.-Y.J. Zhan	Zannan Pharma Ltd, 4299 Jindu Rd., Bldg 3, FL 3, Shanghai, 201108, China			zzhan@zannan.com	
Li Taisheng 李太生	北京协和医院感染科主任，教授			litsh@263.net	

Appendix 3: Email to key informants

邹华春博士

伯内特医学研究所

澳大利亚，墨尔本

电话：+61 3 8506 2382

电邮： huachun.zou@burnet.edu.au

日期：2014 年 1 月 7 日

Dr. Huachun Zou

Burnet Institute

Melbourne, Australia

Phone: +61 3 8506 2382

Email: huachun.zou@burnet.edu.au

Date: 7 January, 2014

Dear Professor ***,

尊敬的***教授：

RE: WHO Consultancy on Viral Hepatitis Treatment in China (WHO project No. APW-200901912-2013/379977)

关于：世界卫生组织中国病毒性肝炎治疗现状研究 (项目编号 APW-200901912-2013/379977)

On behalf of WHO China Office, Burnet Institute in Australia is conducting a consultancy on viral hepatitis treatment in China. The report from this consultancy will help update contextualised national hepatitis B and hepatitis C treatment guidelines in China. You are an expert in the treatment for viral hepatitis in China. We would like to know your opinions about the following question in order to better understand the current situation of China's current hepatitis B and C treatment.

澳大利亚伯内特医学研究所代表世界卫生组织驻中国办事处，目前正开展一项有关病毒性肝炎在中国治疗现状的调查研究。这项咨询研究报告将会为修订全国乙肝丙肝防治指南提供参考。您是中国在病毒性肝炎治疗领域的专家，因此，我们希望就以下问题了解一下您的看法，以便我们更好地掌握中国目前治疗乙肝和丙肝的现状。

Your answers will be confidential. If you do not mind, your name can also appear on our final report. Your expertise, participation and contributions will be sincerely appreciated.

您的反馈将完全保密。如果您不介意的话，我们也很乐意在最终报告中提及您的姓名。我们真诚地感谢您的专业见解、参与和支持。

Please click the following link and answer the questions online

请点击下面的 链接在线回答上述问题。

http://survey.burnet.edu.au/index.php?sid=11642&newtest=Y&lang=zh-Hans

Burnet is an Australian, not-for-profit, unaligned and independent medical research organisation. While based in Melbourne, the Burnet Institute is also actively involved in various research and project activities in other Asia and Pacific countries. Burnet has a strong track record of working in China.

伯内特医学研究所是澳大利亚的一所非盈利性、独立的医学研究机构。我们座落在墨尔本，但积极参与了在亚太地区的各种研究和项目，我们与中国有着长期的研究合作。

In addition, we hope we can have a phone interview with you regarding the above questions. If it is OK for you, please simply reply this email and tell us your number and prefer time and date. We will contact with you as soon as possible.

此外，我们希望能有机会就上述问题通过电话采访您。如果可行的话，麻烦您回复此邮件并告之您的号码和方便的时间点和日期。我们将会及时与您取得联系。

If you could get back to us by Thursday, January 16, 2014, that would be appreciated!

如果您能够在 2014 年 1 月 16 日周四前回复，我们将不胜感激！

Please feel free to contact me if you have any question.

有任何疑问，请与我联系。

Kind Regards!

谨致问候！

Dr. Huachun Zou

邹华春 博士

Dr Huachun Zou
MD, MS, PhD
Research Assistant
Centre for Population Health
Working days: Tuesday, Thursday and every other Wednesday

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Appendix 4: Reminder email to key informants

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Melbourne, Australia

Phone: +61 3 8506 2382

Email: huachun.zou@burnet.edu.au

日期：2014 年 1 月 7 日

Date: 7 January, 2014

Dear Professor ***,

尊敬的***教授：

RE: WHO Consultancy on Viral Hepatitis Treatment in China (WHO project No. APW-200901912-2013/379977)

关于：世界卫生组织中国病毒性肝炎治疗现状研究 (项目编号 APW-200901912-2013/379977)

On behalf of WHO China Office, Burnet Institute in Australia is conducting a consultancy on viral hepatitis treatment in China. The report from this consultancy will help update contextualised national hepatitis B and hepatitis C treatment guidelines in China. You are an expert in the treatment for viral hepatitis in China. We would like to know your opinions about the following question in order to better understand the current situation of China's current hepatitis B and C treatment.

澳大利亚伯内特医学研究所代表世界卫生组织驻中国办事处，目前正开展一项有关病毒性肝炎在中国治疗现状的调查研究。这项咨询研究报告将会为修订全国乙肝丙肝防治指南提供参考。您是中国在病毒性肝炎治疗领域的专家，因此，我们希望就以下问题了解一下您的看法，以便我们更好地掌握中国目前治疗乙肝和丙肝的现状。

Three weeks ago we contacted you for your professional opinions. We are currently preparing a report for WHO China Office. If you could kindly fill the questionnaire by February 1 that would be very much appreciated.

三周前我们通过电子邮件联系过您。目前我们正在准备一份报告提交给世界卫生组织驻中国办事处。如果您可以在 2 月 1 日前通过以下链接完成这份简短的问卷，我们将不胜感谢！

If you have already participated in the questionnaire, please disregard this email.

如果您已经完成问卷，请忽略此邮件。

Please click the following link and answer the questions online

请点击下面的 链接在线回答上述问题。

http://survey.burnet.edu.au/index.php?sid=11642&newtest=Y&lang=zh-Hans

Kind Regards!

谨致问候！

Dr. Huachun Zou

邹华春 博士

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EMAIL huachun.zou@burnet.edu.au **WWW** http://burnet.edu.au

Appendix 5: Questionnaire on clinicians' awareness of hepatitis B and C treatment guidelines

WHO Consultancy on Viral Hepatitis Treatment in China

世界卫生组织关于中国病毒性肝炎治疗现状研究

On behalf of WHO China Office, Burnet Institute is conducting a consultancy on viral hepatitis treatment in China. The report from this consultancy will help update contextualised national hepatitis B and hepatitis C treatment guidelines in China.

伯内特医学研究所代表世界卫生组织驻中国办事处，目前正开展一项有关病毒性肝炎在中国治疗现状的调查研究。这项研究报告将为修订全国乙肝丙肝防治指南提供参考。

You are an expert in the treatment for viral hepatitis in China. We would like to know your opinions about the following question.

您是中国在病毒性肝炎治疗领域的专家，因此，我们希望就以下问题了解一下您的看法。

本调查包括 10 个问题。

WHO Consultancy on Viral Hepatitis Treatment in China

世界卫生组织关于中国病毒性肝炎治疗现状研究

1. Is viral hepatitis treatment expensive for most of patients?

对大多数病人来说，病毒性肝炎的治疗很昂贵吗？

请只选择下面的一项：

Very expensive 非常昂贵

- Expensive 有一些贵
- Acceptable cost 可以承受的花费
- Not expensive 不算昂贵
- I am not sure about this question 我不太了解这个问题

请为您的选择做个评论：

2. Are antiviral agents accessible for most of patients? (Multi-answers available)

对大多数病人来说，容易得到抗病毒药物吗？(可多选)

请选择所有符合条件的：

Difficult to get them because of the cost 因为价格问题不容易获得

Difficult to get them because of shortage 因为供应问题不容易获得

Easy to get them through doctor 容易从医生那里开到

Easy to buy them over the counter 方便从药店买到

I am not sure about this question 我不太了解这个问题

其它:

3. Do you know the national treatment guidelines of hepatitis B?

您是否知道全国乙肝防治指南？ *

请只选择下面的一项：

Yes 我知道。（请在下面的评论栏里写出您知晓的乙肝防治指南名称和发表年份）
No 我不知道
请为您的选择做个评论：
4. Do you know the national treatment guidelines of hepatitis C?
您是否知道全国丙肝防治指南？ *
请只选择下面的一项：
Yes 我知道。（请在下面的评论栏里写出您知晓的丙肝防治指南名称和发表年份）
No 我不知道
请为您的选择做个评论：
5. Do you think these guidelines are suitable for the current medical practice in China?
您认为这些指南是否符合当前中国医疗实际情况？ *
请只选择下面的一项：
Yes 符合
No 不符合
I am not sure about this question 我不太了解这个问题
其它
6. How are you practicing the national treatment guidelines for hepatitis B and C?
您对目前的全国乙肝和丙肝防治指南是如何执行的？ *
请只选择下面的一项：
I apply them into my clinical practice 我在临床中贯彻这些指南
I generally follow the local guidelines rather than the national one 我在临床治疗中一般遵循当地的指南而不是全国的
I only use the guidelines as a reference rather than guidance 我在临床治疗中只是把指南当作一个参考，并不会当作一个准则
I treat patients following my own plans 我在临床治疗中一般按照自己的方案治疗病人
I am not treating hepatitis patients 我不治疗肝炎患者
其它
7. Are Chinese clinicians aware of the existing national treatment guidelines for hepatitis B and C?
中国医生对目前的全国乙肝和丙肝防治指南知晓如何？ *
请只选择下面的一项：
Yes, and apply them into their clinical practice 知道，并应用到临床上
Yes, but they generally follow the local guidelines rather than the national one 知道，但是他们一般遵循当地的指南而不是全国的
Yes, but the guidelines are just used as a reference rather than guidance 知道，但只是把指南当作一个参考，并不会当作一个准则
Not really, doctors treat patients following their own plans 不那么知晓，医生安装自己的方案治疗病人
I am not sure about this question 我不太了解这个问题
其它

8 Do you want to be acknowledged in the final report? (Your name will not be linked to your answers)

您希望在最终报告中提及您的名字吗？(您的名字不会与您提供的信息关联起来)

请只选择下面的一项：

No 不希望

Yes 可以 (请在下面评论栏填入您的姓名，职务和单位名称)

请为您的选择做个评论：

9. What are the key areas of your research group in hepatitis B or/and C? (Multi-answers available)

请问您的研究团队从事乙肝或/和丙肝什么方面的研究？(可多选) *

请选择所有符合条件的：

Epidemiology 流行病学研究

Diagnostics and laboratory detection 诊断技术和实验室检查研究

Virology 病毒学研究

Efficacy of clinical treatments 临床治疗疗效研究

New drugs development 新药物开发研究

其它:

10. Are you treating patients with hepatitis B or hepatitis C at moment?

您目前是否正治疗乙肝或丙肝病人？ *

请只选择下面的一项：

Yes 是的

No, but I had these patients before 没有，但我前一段时间治疗过这些病人

No, I am mainly doing research rather than clinical work 没有，我主要做研究而非临床工作

I am not sure about this question 我不太了解这个问题

其它

Thank you for your time!

谢谢您的参与！

请按提交 01.02.2014 – 00:00

提交您的问卷.

感谢您完成此项调查。

Appendix 6: Key informants' comments on the awareness and compliance to existing national treatment guidelines

	Informant 1	Informant 2	Informant 3	Informant 4	Informant 5	Informant 6	Informant 7
Background of key informants	Not treating hep B/C patients	Treating hep B/C patients	Treating hep B/C patients	Treating hep B/C patients	Treating hep B/C patients	Treating hep B/C patients	Treating hep B/C patients
1. What are the key areas of your research group in hepatitis B or/and C? (Multi-answers available)							
Epidemiology				√			√
Dx and lab detection	√	√					√
Virology	√	√					√
Efficacy of Tx		√	√	√	√		√
New drugs R&D		√			√		
2. Is viral hepatitis treatment expensive for most of patients?							
Very expensive							√
Expensive	√		√	√	√		
Acceptable cost		√				√	
Not expensive							
3. Are antiviral agents accessible for most of patients? (Multi-answers available)							
Difficult, high cost				√			√
Difficult, short of supply							

Easy to access via doctors	√	√	√		√	√	
Easy to purchase OTC			√		√		
4. Do you know the national treatment guidelines of hepatitis B?							
Yes	√ <Guideline of Prevention and Treatment for Chronic Hepatitis B updated in 2011>	√ <Guideline of Prevention and Treatment for Chronic Hepatitis B 2010>	√ Did not enter	√ <Guideline of Prevention and Treatment for Chronic Hepatitis B 2010>	√ Did not enter	√ <Guideline of Prevention and Treatment for Chronic Hepatitis B 2013>	√ Did not enter
No							
5. Do you know the national treatment guidelines of hepatitis C?							
Yes	√ <Guideline of Prevention and Treatment for Chronic Hepatitis C 2011>	√ <Guideline of Prevention and Treatment for Chronic Hepatitis B 2004>	√ Did not enter	√ <Guideline of Prevention and Treatment for Chronic Hepatitis B 2004>	√ Did not enter	√ <Guideline of Prevention and Treatment for Chronic Hepatitis B 2006>	√ Did not enter
No							
6. Do you think these guidelines are suitable for the current medical practice in China?							
Yes		√	√			√	
No	√			√	√		√
Other							

7. How are you practicing the national treatment guidelines for hepatitis B and C?							
I apply them in my clinical practice		√	√	√		√	√
I generally follow the local guidelines rather than the national ones							
I only use the guidelines as a reference rather than guidance					√		
I follow my own plans							
I am not treating hepatitis patients	√						
8. Are Chinese clinicians aware of the existing national treatment guidelines for hepatitis B and C?							
Yes, and apply them into their clinical practice			√	√		√	√
Yes, but they generally follow the local guidelines rather than the national ones							
Yes, but the guidelines are just used as a reference rather than guidance		√			√		
Not really, doctors follow their own plans	√						