

**“Identification and Management of
persons with chronic viral hepatitis
in Europe”**

Viral Hepatitis Prevention Board Meeting
Budapest, Hungary, 18-19 March 2010.

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Content

This pre-meeting document is a list of selected abstracts/ references from a Pubmed MEDLINE search on different search terms. The references are ranged by publication year (most recent first) and for each year in alphabetical order of the first author's name.

1. Screening and Management of persons with chronic hepatitis.....pag. 3

Pubmed MEDLINE search1 on '**Management of chronic viral hepatitis**' search 2 '**screening AND chronic AND viral hepatitis**' only review papers, search 3 : '**identification chronic viral hepatitis**'. Of these 3 search only the **English** publication **since 2008** were selected. In total (411 + 151+104) 666 article were transferred to one library in End Note. In this the library a search was performed { **NOR Bloodbank NOR Alcoholic NOR Brazil NOR liver transplant NOR case reports NOR HIV co-infections** } resulting in 174 articles. Manually the publications were selected related to '**Recommendation**' and '**strategies**' and '**control**'. 36 references are arranged by publication year (most recent first) and for each year in alphabetical order of the first author's name.

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Pubmed MEDLINE search1 on {((**Cost effectiveness AND hepatitis**) AND (**Viral OR virus OR antiviral OR chronic**) AND (**management OR treatment OR identification OR screening**))} combined with search 2 '**screening AND chronic AND viral hepatitis**' were only the **English** publication **since 2008** were selected resulted in 49 articles. Manually the publications were selected related to '**Cost effectiveness of treatment, diagnosis, control and screening**'.

25 references are arranged by publication year (most recent first) and for each year in alphabetical order of the first author's name.

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1. Screening and Management of persons with chronic hepatitis

Pubmed MEDLINE search1 on 'Management of chronic viral hepatitis' search 2 'screening AND chronic AND viral hepatitis' only review papers, search 3 : 'identification chronic viral hepatitis'. Of these 3 search only the English publication since 2008 were selected. In total (411 + 151+104) 666 article were transferred to one library in End Note. In this the library a search was performed { NOR Bloodbank NOR Alcoholic NOR Brazil NOR liver transplant NOR case reports NOR HIV co-infections } resulting in 174 articles. Manually the publications were selected related to 'Recommendation' and 'strategies' and 'control'. 36 references are ranged by publication year (most recent first) and for each year in alphabetical order of the first author's name.

Beasley RP.

Rocks along the road to the control of HBV and HCC.

Ann Epidemiol 19: 231-234, 2009.

Hepatitis B vaccine is one of the best human vaccines ever developed; it is safe, cheap, and highly immunogenic, stimulates long lasting protective efficacy, and is the first human cancer vaccine. Remarkably, HBV vaccine works even when administered to newborns, timing which is necessary because of mother to infant transmission. Countrywide HBV immunization programs were initiated in Taiwan and Thailand in the 1980s. HBV vaccine has been part of the WHO global immunization since 199x and with at-birth immunization programs in xxx countries resulting in major declines in acute sequelae of HBV infection. Of far greater significance, HBV vaccination prevents hepatocellular carcinoma (HCC) and its use is reducing mother to infant transmission, the driving force behind the HBV carrier state worldwide. These benefits are just being realized since decades elapse between perinatal transmission at birth and the onset of HCC decades later. Studies in Taiwan and Thailand are showing declines in HCC incidence as a result of country wide at-birth HBV immunization programs initiated in the 1980s. Many investigators from many countries have contributed to the understanding of HBV and its role as the major cause of HCC. This article briefly summarizes the work of my University of Washington laboratory in Taipei, Taiwan where I lived and worked from 1972 and 1986 because of the very high HBV carrier rates of HBV in Taiwan. During those 14 years we discovered vertical transmission, its timing and mechanism, and the predictive value of HBeAg. We went on to establish the efficacy of HBIG for prevention of vertical transmission. In later studies we established the efficacy and timing of HBV vaccine and HBIG and HBV vaccine in combination for optimum preventive efficacy. Of greatest significance, our studies showed that chronic HBV infection is the commonest cause of HCC. Worldwide, mothers are the driving force behind the infections that lead to HCC because the HBV carrier state is inversely proportional to the age of the infant when infected. We were able persuade WHO to adopt HBV as the 7th immunogen in the EPI, its global infant immunization program. In some ways enormous progress has been made but measured against its potential, progress in most countries, including the United States has been far too slow.

Dakhil N, Junaidi O, and Befeler AS.

Chronic viral hepatitis.
Mo Med 106: 361-365, 2009.

Chronic liver disease is the tenth leading cause of death in the United States. The economic burden of liver disease is approximately 1% of the total national health care expenditure. Chronic hepatitis C is the most common cause of chronic liver disease in the United States, and chronic hepatitis B is the leading cause of liver disease worldwide. This article provides a brief overview of the evaluation and treatment of chronic hepatitis B and C infection.

Dusheiko GM, and Jacobs MG.

Perspectives on the management of chronic hepatitis B and C.
Expert Rev Anti Infect Ther 7: 243-247, 2009.

European Association For The Study Of The L.

EASL Clinical Practice Guidelines: management of chronic hepatitis B.
J Hepatol 50: 227-242, 2009.

Gupta S, and Altice FL.

Hepatitis B virus infection in US correctional facilities: a review of diagnosis, management, and public health implications.
J Urban Health 86: 263-279, 2009.

Among the blood-borne chronic viral infections, hepatitis B virus (HBV) infection is one that is not only treatable but also preventable by provision of vaccination. Despite the availability of HBV vaccine for the last 15 years, more than 1.25 million individuals in the USA have chronic HBV infection, and about 5,000 die each year from HBV-related complications. From a societal perspective, access to treatment of chronic viral infections, like HIV and viral hepatitis, is highly cost-effective and has lasting benefits by reducing risk behaviors, morbidity, mortality, as well as disease transmission in the community. Individuals in correctional facilities are specially predisposed to such chronic viral infections because of their high-risk behaviors. The explosion of incarceration in the USA over the last few decades and the disproportionate burden of morbidity and mortality from chronic infections among the incarcerated have put incredible strains on an overcrowded system that was not originally designed to provide comprehensive medical care for chronic illnesses. Recently, there has been a call to address medical care for individuals with chronic medical conditions in correctional settings, including those with infectious diseases. The economic and public health burden of chronic hepatitis B and its sequelae, including cirrhosis and hepatocellular carcinoma, is felt most prominently in managed care settings with limited budgets, like correctional facilities. Prevalence of HBV infection among the incarcerated in the USA is fivefold that of the general population. We present a review of diagnosis, prevention, and the recently streamlined treatment guidelines for management of HBV infection in correctional settings, and discuss the implications and public health impact of these measures.

Haber BA, Block JM, Jonas MM, Karpen SJ, London WT, McMahon BJ, Murray KF, Narkewicz MR, Rosenthal P, and Schwarz KB.

Recommendations for screening, monitoring, and referral of pediatric chronic

hepatitis B.

Pediatrics 124: e1007-1013, 2009.

Most children with chronic hepatitis B virus infection (persistent hepatitis B surface antigen-positive for >6 months) are asymptomatic and do not generally require treatment. These children are, however, at increased risk for severe complications later in life, including advanced liver disease and liver cancer. On November 11, 2008, the Hepatitis B Foundation, a nonprofit research and disease advocacy organization, convened a panel of nationally recognized North American pediatric liver specialists to consider and recommend an approach for the screening, monitoring, initial management, and referral of children with chronic hepatitis B. The panel developed recommendations to provide guidance to practitioners on determining what additional tests to conduct, how often to monitor on the basis of test results, and when to refer to a pediatric liver specialist to build a partnership between the practitioner and liver specialist to enhance the success of management of children with this lifelong infection.

Janssen HL, and Buster EH.

Comments on the EASL practice guidelines for the management of chronic hepatitis B: controversies in interferon-based therapy.

J Hepatol 51: 224-226, 2009.

Morgan M, and Keeffe EB.

Diagnosis and treatment of chronic hepatitis B: 2009 update.

Minerva Gastroenterol Dietol 55: 5-22, 2009.

The diagnosis of chronic hepatitis B (CHB) is made using a combination of serological, virologic, biochemical, and histologic markers. The natural history of hepatitis B virus (HBV) infection can be divided into four phases: immune tolerance, immune clearance (HBeAg-positive chronic hepatitis B), inactive HBsAg carrier, and reactivation (HBeAg-negative chronic hepatitis B). Patients in the immune clearance and reactivation phases, with elevated alanine aminotransferase (ALT) and HBV DNA levels, are candidates for antiviral therapy. The primary determinant of treatment outcomes for CHB is suppression of serum HBV DNA, and long-term suppression of viral replication is likely to reduce progression to cirrhosis and hepatocellular carcinoma. Current antiviral treatment options for CHB include interferon alfa-2b, peginterferon alfa-2a, lamivudine, adefovir, entecavir, telbivudine, and tenofovir. In patients with HBeAg-positive CHB, antiviral treatment is indicated when the serum HBV DNA level is 20 000 IU/mL and the ALT level is elevated. For HBeAg-negative patients, the threshold for initiation of therapy is lower, i.e., a serum HBV DNA level 2 000 IU/mL in association with an elevated ALT level. The presence of at least moderate necroinflammation and the presence of fibrosis on liver biopsy may be useful in supporting the decision to initiate therapy, particularly in patients with normal ALT levels. While undergoing therapy, patients require monitoring every 3 to 6 months to ensure adherence to therapy, confirm that the response to therapy is optimal, and survey for the development of resistance if an oral agent is used. Issues that remain controversial or need to be studied further are the necessity of a baseline liver biopsy, the HBV DNA and ALT thresholds for initiation of therapy, the optimal duration of antiviral therapy, selection of one agent over another, response to suboptimal suppression of viral replication, and the role of combination therapy.

Pan JJ, and Firpi RJ.

The management of hepatitis C.

Minerva Gastroenterol Dietol 55: 23-35, 2009.

Hepatitis C is a serious public health problem with more than 170 million chronic carriers worldwide. Although hepatitis C infection can be cured in up to 40% of patients, current treatment is not ideal and is associated with a wide spectrum of side effects and complications. Therefore, emerging evidence suggests that patients can receive tailored therapy based on their viral kinetic changes during treatment. With better knowledge of hepatitis C viral genome and life cycle, compounds so called "Specifically Targeted Antiviral Therapy for HCV or STAT-C" are under development. This review will discuss current therapies and recent advances in new therapies for hepatitis C.

Papathodoridis GV, and Manolakopoulos S.

EASL clinical practice guidelines on the management of chronic hepatitis B: the need for liver biopsy.

J Hepatol 51: 226-227, 2009.

Shah U, Kelly D, Chang MH, Fujisawa T, Heller S, Gonzalez-Peralta RP, Jara P, Mieli-Vergani G, Mohan N, and Murray KF.

Management of chronic hepatitis B in children.

J Pediatr Gastroenterol Nutr 48: 399-404, 2009.

Hepatitis B virus (HBV) infection is a worldwide problem and can cause acute liver failure, acute hepatitis, chronic hepatitis, liver cirrhosis, and liver cancer. In areas of high prevalence such as in Asia, Africa, southern Europe, and Latin America, the hepatitis B surface antigen positive rate ranges from 2% to 20%. In endemic areas, HBV infection occurs mainly during infancy and early childhood. Mother-to-infant transmission accounts for approximately half of the chronic HBV infections. In contrast to infection in adults, HBV infection during early childhood results in a much higher rate of persistent infection and long-term serious complications such as liver cirrhosis and HCC. Three phases of chronic hepatitis B have been identified: the immune-tolerant phase, the immune-active phase, and the inactive hepatitis B phase. These phases of infection are characterized by variations in viral replication, hepatic inflammation, spontaneous clearance, and response to antiviral therapy. The optimal goal of antiviral therapy for chronic HBV infection is to eradicate HBV and to prevent its related liver complications. However, due to the limited effect of available therapies in viral eradication, the goal of treatment is to reduce viral replication, to minimize liver injury, and to reduce infectivity. In this review the current recommendations for monitoring and treating chronic HBV infection in children are reviewed.

Shamliyan TA, MacDonald R, Shaukat A, Taylor BC, Yuan JM, Johnson JR, Tacklind J, Rutks I, Kane RL, and Wilt TJ.

Antiviral therapy for adults with chronic hepatitis B: a systematic review for a National Institutes of Health Consensus Development Conference.

Ann Intern Med 150: 111-124, 2009.

BACKGROUND: Chronic hepatitis B infection can lead to liver failure, hepatocellular carcinoma, and death. PURPOSE: To evaluate the effectiveness of antiviral therapy

for adults with chronic hepatitis B infection. DATA SOURCES: Randomized, controlled trials (RCTs) of interferon (alpha2b and pegylated alpha2a), lamivudine, adefovir, entecavir, and telbivudine published from 1990 to 2008. STUDY SELECTION: Randomized, controlled clinical trials of adults with chronic hepatitis B published in English after 1989 that reported death; incidence of hepatocellular carcinoma or liver failure; prevalence and incidence of cirrhosis; presence or seroconversion of hepatitis B e antigen (HBeAg) or surface antigen (HBsAg), viral load of hepatitis B virus DNA; aspartate aminotransferase and alanine aminotransferase (ALT) levels; or fibrosis scores after therapy with interferon-alpha2b, pegylated interferon-alpha2a, lamivudine, adefovir, entecavir, and telbivudine. DATA EXTRACTION: Data extracted with standard protocols to calculate risk difference for clinical outcomes, viral load, HBeAg and HBsAg, ALT, histologic scores, and adverse events. DATA SYNTHESIS: In 16 RCTs (4431 patients), drug treatment did not improve clinical outcomes of chronic hepatitis B infection, but the trials were underpowered. In 60 RCTs that examined intermediate outcomes, no single treatment improved all intermediate outcomes. Low-quality evidence suggested HBsAg clearance after interferon-alpha2b (2 RCTs; 211 patients). Moderate-quality evidence suggested ALT normalization at follow-up after treatment with adefovir (2 RCTs; 600 patients) and HBeAg loss with lamivudine (2 RCTs; 318 patients). With interferon-alpha2b, moderate-quality evidence suggested HBeAg loss (3 RCTs; 351 patients), seroconversion (2 RCTs; 304 patients), and ALT normalization (2 RCTs; 131 patients). Pegylated interferon-alpha2a versus lamivudine improved HBeAg seroconversion (1 RCT; 814 patients) and ALT normalization (2 RCTs; 905 patients) off treatment. Pegylated interferon-alpha2a combined with lamivudine versus lamivudine improved HBeAg loss (1 RCT; 543 patients) and ALT normalization (2 RCTs; 905 patients). Adverse events during antiretroviral therapy occurred in more than 50% of patients but were not associated with increased treatment discontinuation. However, most studies excluded patients with hepatic or renal insufficiency or other serious comorbid conditions. Limitation: Marked heterogeneity in study samples, interventions, and measured outcomes preclude definitive conclusions. CONCLUSION: Evidence was insufficient to assess treatment effect on clinical outcomes or determine whether inconsistent improvements in selected intermediate measures are reliable surrogates. Future research is needed to provide evidence-based recommendations about optimal antiviral therapy in adults with chronic hepatitis B infection.

Slavenburg S, Lamers MH, Roomer R, de Knegt RJ, van Oijen MG, and Drenth JP.

Current clinical care compared with new Dutch guidelines for hepatitis C treatment.

Neth J Med 67: 177-181, 2009.

BACKGROUND: Recently, the Dutch Association of Gastroenterology and Hepatology issued new guidelines for the treatment of chronic hepatitis C virus (HCV). These guidelines reflect the current standard of care. Before these guidelines were published and implemented we (1) studied the current clinical care of HCV patients among Dutch physicians, and (2) identified areas for future refinement in the current treatment. METHODS: We conducted a non-targeted survey among Dutch medical specialists in Gastroenterology, Hepatology and Internal Medicine who actively treat HCV patients. The questionnaire contained items about facility, duration and dosing of treatment, and side effect management using clinical vignettes followed by short questions. RESULTS: We received 49 questionnaires from treating HCV specialists. The majority (65%) of respondents treat HCV patients during regular outpatient clinics, while 35% treat these patients in a separate setting dedicated to the care of HCV patients. The majority of physicians follow the

stipulated dosage regimens of pegylated interferon (88%) and ribavirin (83%). A minority (13%) exceed the advised dosage of ribavirin. Side effects such as neutropenia are mostly managed by decreasing the interferon dosage (42%). Some 35% of physicians reduce ribavirin if haemoglobin levels drop below 5.4 mmol/l, and 41% initiate erythropoietin treatment. CONCLUSION: Dutch clinical practice reflects the recently issued HCV guidelines. An important area of refinement in treatment of HCV is the management of side effects.

Tran TT.

Management of hepatitis B in pregnancy: weighing the options.
Cleve Clin J Med 76 Suppl 3: S25-29, 2009.

Maternal screening and active and passive immunoprophylaxis have reduced the perinatal, or vertical, transmission of hepatitis B virus (HBV) dramatically. Without immunoprophylaxis, chronic HBV infection occurs in up to 90% of children by age 6 months if the mother is positive for both hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg). Even with immunoprophylaxis, perinatal transmission is possible when the mother is highly viremic and HBeAg positive. Antiviral therapy during the third trimester of pregnancy in high-risk women with chronic HBV infection reduces viral load in the mother and may decrease the risk of perinatal transmission, although data are lacking. Safety data in pregnancy are most robust with lamivudine and tenofovir compared with other therapies. Careful discussion with the patient regarding the risks and benefits of therapy is warranted. Prophylaxis remains the best method of prevention of perinatal transmission.

Weinbaum CM, Mast EE, and Ward JW.

Recommendations for identification and public health management of persons with chronic hepatitis B virus infection.
Hepatology 49: S35-44, 2009.

Early identification of persons with chronic HBV infection enables infected persons to receive necessary care to prevent or delay onset of liver disease, and enables the identification and vaccination of susceptible household contacts and sex partners, interrupting ongoing transmission. Testing has been recommended previously to enable primary prevention of HBV infection among close contacts for pregnant women, household contacts and sex partners of HBV-infected persons, persons born in countries with hepatitis B surface antigen (HBsAg) prevalence of more than 8%, persons who are the source of blood or body fluid exposures that might warrant postexposure prophylaxis (e.g., needlestick injury to a healthcare worker or sexual assault), and to enable appropriate treatment for infants born to HBsAg-positive mothers and persons infected with human immunodeficiency virus. Recently, with the increasing availability of efficacious hepatitis B treatment, the Centers for Disease Control and Prevention published new recommendations for public health evaluation and management for chronically infected persons and their contacts and extended testing recommendations to include persons born in geographic regions with HBsAg prevalence of greater than 2%, men who have sex with men, and injection drug users. Patient and provider education, developing partnerships between health departments and community organizations, and other resources will be needed to assure appropriate populations are tested and care provided for persons newly identified as HBsAg-positive.

NIH consensus development statement on management of hepatitis B.
NIH Consensus State Sci Statements 25: 1-29, 2008.

OBJECTIVE: To provide health care providers, patients, and the general public with a responsible assessment of currently available data on the management of hepatitis B. **PARTICIPANTS:** A non-DHHS, nonadvocate 12-member panel representing the fields of hepatology and liver transplantation, gastroenterology, public health and epidemiology, infectious diseases, pathology, oncology, family practice, internal medicine, and a public representative. In addition, 22 experts from pertinent fields presented data to the panel and conference audience. **EVIDENCE:** Presentations by experts and a systematic review of the literature prepared by the Minnesota Evidence-based Practice Center, through the Agency for Healthcare Research and Quality. Scientific evidence was given precedence over anecdotal experience. **CONFERENCE PROCESS:** The panel drafted its statement based on scientific evidence presented in open forum and on published scientific literature. The draft statement was presented on the final day of the conference and circulated to the audience for comment. The panel released a revised statement later that day at <http://consensus.nih.gov>. This statement is an independent report of the panel and is not a policy statement of the NIH or the Federal Government. **CONCLUSIONS:** The most important predictors of cirrhosis or hepatocellular carcinoma in persons who have chronic HBV are persistently elevated HBV DNA and ALT levels in blood. Other risk factors include HBV genotype C infection, male sex, older age, family history of hepatocellular carcinoma, and co-infection with HCV or HIV. The major goals of anti-HBV therapy are to prevent the development of progressive disease, specifically cirrhosis and liver failure, as well as hepatocellular carcinoma development and subsequent death. To date, no RCTs of anti-HBV therapies have demonstrated a beneficial impact on overall mortality, liver-specific mortality, or development of hepatocellular carcinoma. Most published reports of hepatitis therapy use changes in short-term virologic, biochemical, and histologic parameters to infer likelihood of long-term benefit. Approved therapies are associated with improvements in intermediate biomarkers, including HBV DNA, HBeAg loss or seroconversion, decreases in ALT levels, and improvement in liver histology (Table). Although various monitoring practices have been recommended, no clear evidence exists for an optimal approach. The most important research needs include representative prospective cohort studies to define the natural history of the disease and large RCTs of monotherapy and combined therapies, including placebo-controlled trials, that measure the effects on clinical health outcomes. Table. **Criteria Useful in Determining for Whom Therapy is Indicated:** Patients for whom therapy is indicated: Patients who have acute liver failure, cirrhosis and clinical complications, cirrhosis or advanced fibrosis and HBV DNA in serum, or reactivation of chronic HBV after chemotherapy or immunosuppression; Infants born to women who are HBsAg-positive (immunoglobulin and vaccination). Patients for whom therapy may be indicated: Patients in the immune-active phase who do not have advanced fibrosis or cirrhosis. Patients for whom immediate therapy is not routinely indicated: Patients with chronic hepatitis B in the immune-tolerant phase (with high levels of serum HBV DNA but normal serum ALT levels or little activity on liver biopsy); Patients in the inactive carrier or low replicative phase (with low levels of or no detectable HBV DNA in serum and normal serum ALT levels); Patients who have latent HBV infection (HBV DNA without HBsAg). We recommend routine screening for hepatitis B of newly arrived immigrants to the United States from countries where the HBV prevalence rate is greater than 2%. Screening will facilitate the provision of medical and public health services for infected patients and their families and provide public health data on the burden of disease in immigrant populations. The screening test should not be used to prohibit immigration.

Ayoub WS, and Keeffe EB.

Review article: current antiviral therapy of chronic hepatitis B.
Aliment Pharmacol Ther 28: 167-177, 2008.

BACKGROUND: The long-term goals of therapy for chronic hepatitis B are to reduce serum HBV DNA to low or undetectable levels and ultimately reduce or prevent the development of cirrhosis and hepatocellular carcinoma. **AIM:** To review the current treatment of chronic hepatitis B, with a focus on diagnosis and management of resistance and active management of suboptimal responses. **METHODS:** A systematic review of the literature, with a focus on recent guidelines, was undertaken. **RESULTS:** Among the six drugs licensed for the treatment of chronic hepatitis B in the US, the preferred agents in 2008 will include entecavir, peginterferon alfa-2a, possibly telbivudine, and tenofovir following licensure. When using an oral agent, a major focus of management is on the selection of a drug with high potency and low rate of resistance, and active on-treatment management to optimize therapy. Preventing the sequelae of antiviral drug resistance and appropriate management when resistance is initially detected are also the major focus of current management. The addition of an antiviral agent that is not cross-resistant is critical to restore suppression of viral replication. **CONCLUSIONS:** Newer agents and modified treatment strategies, especially using combination therapy, hold promise to optimize the management of patients with chronic hepatitis B by achieving the high potency and the lowest rate of resistance.

Chevaliez S, and Pawlotsky JM.

Diagnosis and management of chronic viral hepatitis: antigens, antibodies and viral genomes.
Best Pract Res Clin Gastroenterol 22: 1031-1048, 2008.

Virological tools, including serological and molecular tools, are needed to diagnose chronic hepatitis B and C infections. They may also be useful to establish their prognosis, but they have found their principal application in guiding treatment decisions and assessing the virological responses to therapy. The goal of chronic hepatitis B therapy is to prevent progression of liver disease. This is achieved if HBV replication is durably abolished or significantly reduced. In HBeAg-positive patients, HBeAg clearance followed by the HBe seroconversion phase can be achieved. In HBeAg-negative patients, long-term antiviral suppression of viral replication is needed. The loss of HBsAg, eventually associated with an HBs seroconversion, is the most desirable endpoint of therapy but is rarely achieved. The efficacy endpoint of chronic hepatitis C treatment is the sustained virological response, defined by an undetectable HCV RNA in serum with a sensitive assay 24 weeks after the end of treatment. The HCV genotype and on-treatment viral kinetics can be used to tailor treatment dosages and duration.

Davison SM, and Kelly DA.

Management strategies for hepatitis C virus infection in children.
Paediatr Drugs 10: 357-365, 2008.

Chronic hepatitis C virus (HCV) infection is a major cause of morbidity and mortality worldwide. Progression to cirrhosis and hepatocellular carcinoma occurs in 20% of infected adults. The natural history following childhood infection is less well defined, although cirrhosis in children is described. Since blood product screening for HCV infection was introduced in 1990, most children who acquire HCV do so by vertical

transmission from an infected mother. Transmission to offspring occurs in approximately 5%. Most children with HCV infection are asymptomatic. Diagnosis is made by testing those at risk for HCV RNA by polymerase chain reaction (PCR) and HCV antibody (anti-HCV) by enzyme immunoassay (EIA). The clinical impact of HCV infection is assessed by monitoring symptoms and signs, blood testing of liver enzymes, ultrasound imaging, and by liver biopsy. Improved efficacy and tolerability of treatment strategies in adults have had a significant impact on the management of children with HCV infection. The emphasis is now on promoting awareness, early diagnosis, and treatment. Treatment strategies have evolved from monotherapy with interferon alfa (IFNalpha), to combination therapy with ribavirin. Pegylated IFNalpha is superior to conventional IFNalpha, and forms the basis of current recommendations. The genotype of HCV influences treatment efficacy. Treatment is generally well tolerated in children, although adverse effects are common. Preparation and support throughout treatment for the whole family is needed. A proportion of children with HCV infection have co-morbidity, including viral co-infection or hematologic disease. Although treatment may be contraindicated, risks and benefits must be considered before denying treatment. Anemia is more common in those with HIV co-infection, renal insufficiency, thalassemia, or cirrhosis, and may be aggravated by treatment. Children with thalassemia may have iron overload, and transfusion requirements may increase during treatment. Further refinements of combination therapy and development of new drugs are in progress. Vaccine candidates are undergoing phase I and II treatment trials.

Keeffe EB, Dieterich DT, Han SH, Jacobson IM, Martin P, Schiff ER, and Tobias H.

A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update.

Clin Gastroenterol Hepatol 6: 1315-1341; quiz 1286, 2008.

Chronic HBV infection is an important public health problem worldwide and in the United States. A treatment algorithm for the management of this disease, published previously by a panel of U.S. hepatologists, has been revised on the basis of new developments in the understanding of the disorder, the availability of more sensitive molecular diagnostic tests, and the licensure of new therapies. In addition, a better understanding of the advantages and disadvantages of new treatments has led to the development of strategies for reducing the rate of resistance associated with oral agents and optimizing treatment outcomes. This updated algorithm was based primarily on available evidence by using a systematic review of the literature. Where data were lacking, the panel relied on clinical experience and consensus expert opinion. The primary aim of antiviral therapy is durable suppression of serum HBV DNA to low or undetectable levels. Assays can now detect serum HBV DNA at levels as low as 10 IU/mL and should be used to establish a baseline level, monitor response to antiviral therapy, and survey for the development of drug resistance. Interferon alfa-2b, lamivudine, adefovir, entecavir, peginterferon alfa-2a, telbivudine, and tenofovir are approved as initial therapy for chronic hepatitis B and have certain advantages and disadvantages. Although all of these agents can be used in selected patients, the preferred first-line treatment choices are entecavir, peginterferon alfa-2a, and tenofovir. Issues for consideration for therapy include efficacy, safety, rate of resistance, method of administration, and cost.

Keeffe EB, Dieterich DT, Pawlotsky JM, and Benhamou Y.

Chronic hepatitis B: preventing, detecting, and managing viral resistance.

Clin Gastroenterol Hepatol 6: 268-274, 2008.

Licensed oral agents for antiviral therapy in patients with chronic hepatitis B virus (HBV) infection include lamivudine, adefovir, entecavir, and telbivudine. Emtricitabine, tenofovir, and the combination of tenofovir plus emtricitabine in 1 tablet, which are licensed for the treatment of human immunodeficiency virus infection, are additional off-label options for treating HBV infection. Preventing HBV antiviral drug resistance to nucleoside/nucleotide analogues and appropriate management when resistance occurs has become a major focus in the management of chronic hepatitis B. HBV antiviral drug resistance may be best prevented by using an agent or combination of agents with a high genetic barrier to resistance, and 2 potent nucleoside and nucleotide drugs with different resistance profiles may prove to be the optimal first-line treatment for chronic hepatitis B. Frequent assessment of quantitative serum HBV DNA remains the best approach to early detection of resistance, and antiviral therapy should be modified as soon as resistance is detected. Results from several clinical trials have shown that the addition or substitution of newer antiviral agents can restore suppression of viral replication, normalize alanine aminotransferase levels, and reverse histologic progression in patients with resistance to lamivudine, but little information exists regarding the long-term benefits of second-line treatment regimens. Despite the substantial advances in treatment made to date, new agents with novel viral targets will be needed for patients who ultimately may fail second- or third-line therapy.

Kennedy PT, Lee HC, Jeyalingam L, Malik R, Karayiannis P, Muir D, Main J, Thursz M, Goldin R, Smith B, Brown A, and Thomas HC.

NICE guidelines and a treatment algorithm for the management of chronic hepatitis B: a review of 12 years experience in west London.

Antivir Ther 13: 1067-1076, 2008.

BACKGROUND: Treatment strategies in chronic hepatitis B (CHB) are evolving as more potent oral antivirals become available. However, drug resistance remains a major challenge and policy guidelines on management are limited by the evidence base. This study aims to review the implications of the National Institute for Health and Clinical Excellence (NICE) guidelines in a cohort of unselected CHB patients in the United Kingdom and to evolve a management algorithm for their treatment. **METHODS:** In total, 783 unselected hepatitis B surface antigen-positive patients, were assessed of whom 212 (27%) underwent liver biopsy. Age, alanine aminotransferase, hepatitis B virus DNA and necroinflammatory score were analysed to determine their value as predictors of fibrosis. Patients with biopsy evidence of fibrosis were offered treatment and followed longitudinally. Six-month on-treatment virologic response was evaluated to determine the validity of this strategy in predicting the early emergence of resistance. **RESULTS:** Age, gender and necroinflammatory score were predictors of fibrosis in CHB patients, whereas age > 40 years was a predictor of cirrhosis in both hepatitis B e antigen (HBeAg)-positive ($P < 0.03$) and HBeAg-negative patients ($P < 0.003$). A total of 81% of HBeAg-positive and 65% of HBeAg-negative CHB patients who required adefovir add-on therapy were identifiable after 6 months of lamivudine monotherapy, by continuing HBV DNA positivity ($P < 0.002$ and $P < 0.0001$, respectively). **CONCLUSIONS:** Advanced liver disease was present in patients falling outside current treatment guidelines, highlighting the importance of liver histology in identifying fibrosis and the need for antiviral therapy. While 6 month on-treatment virologic response as a trigger for instituting add-on therapy may be an improvement on the current recommendations, such a strategy should be integrated into any new treatment algorithm, likely to consist of entecavir and tenofovir.

Lavanchy D.

Chronic viral hepatitis as a public health issue in the world.
Best Pract Res Clin Gastroenterol 22: 991-1008, 2008.

This article will focus on the impact caused by chronic viral hepatitis B and C globally and will discuss public health measures that have to be implemented in order to prevent and control these diseases. Chronic viral hepatitis is a major global public health problem, an important cause of morbidity and mortality from sequelae which include chronic hepatitis, cirrhosis and primary liver cancer. Being a 'silent' disease, the contribution of chronic hepatitis to global morbidity and mortality is generally underestimated. Hepatitis B and C prevention and control should seek to reduce both the incidence of new infections and the risk of chronic liver disease. A comprehensive public health prevention programme should include the prevention and detection of HBV and HCV infections, the diagnosis and control of viral hepatitis related chronic liver disease, conducting surveillance and monitoring the effectiveness of prevention activities, and setting up a research agenda.

Liaw YF, Leung N, Kao JH, Piratvisuth T, Gane E, Han KH, Guan R, Lau GK, and Locarnini S.

Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update.
Hepatol Int 2: 263-283, 2008.

Large amounts of new data on the natural history and treatment of chronic hepatitis B virus (HBV) infection have become available since 2005. These include long-term follow-up studies in large community-based cohorts or asymptomatic subjects with chronic HBV infection, further studies on the role of HBV genotype/naturally occurring HBV mutations, treatment of drug resistance and new therapies. In addition, Pegylated interferon alpha2a, entecavir and telbivudine have been approved globally. To update HBV management guidelines, relevant new data were reviewed and assessed by experts from the region, and the significance of the reported findings were discussed and debated. The earlier "Asian-Pacific consensus statement on the management of chronic hepatitis B" was revised accordingly. The key terms used in the statement were also defined. The new guidelines include general management, special indications for liver biopsy in patients with persistently normal alanine aminotransferase, time to start or stop drug therapy, choice of drug to initiate therapy, when and how to monitor the patients during and after stopping drug therapy. Recommendations on the therapy of patients in special circumstances, including women in childbearing age, patients with antiviral drug resistance, concurrent viral infection, hepatic decompensation, patients receiving immune-suppressive medications or chemotherapy and patients in the setting of liver transplantation, are also included.

Mallette C, Flynn MA, and Promrat K.

Outcome of screening for hepatitis C virus infection based on risk factors.
Am J Gastroenterol 103: 131-137, 2008.

OBJECTIVES: Screening for hepatitis C virus (HCV) infection in individuals at increased risk is currently recommended by most, but not all, health authorities. This study identifies outcomes of individuals diagnosed through a screening program targeting high-risk patients. **METHODS:** Veterans presenting for care in VA facilities are assessed for HCV risk factors by a questionnaire. Those with a risk factor are

offered anti-HCV testing. Between October 1998 and May 2004, 25,701 patients were assessed and 8,471 patients had a risk factor for HCV. Patients diagnosed through the screening program were assessed per study protocol. RESULTS: The prevalence of a positive HCV antibody in veterans who identified a risk factor was 7.3% (95% CI 6.6-8.0%). Among those diagnosed through the screening program (N = 260), 47% had chronic hepatitis C. Among patients with chronic HCV, 18% had evidence of advanced liver disease (stage III/IV on biopsy or clinical cirrhosis) while 34% had persistently normal alanine aminotransferase (ALT). Two-thirds of individuals who underwent liver biopsy had minimal or no fibrosis. About half (47%) of the screen-detected patients with chronic HCV were treatment candidates. Forty-four percent were not immediate candidates secondary to medical or psychiatric comorbidities or active substance abuse. Twenty-two patients (8%) had died after a median follow-up of 911 days. Two were liver-related deaths. CONCLUSION: Screening for hepatitis C in persons at high risk can lead to early identification of individuals at risk for progressive liver disease who may benefit from antiviral therapy and counseling to reduce HCV-related liver injury.

Nguyen T, Locarnini S, and Desmond P.

Changing landscape of antiviral resistance management in chronic hepatitis B. *J Gastroenterol Hepatol* 23: 1314-1317, 2008.

Papatheodoridis GV, Manolakopoulos S, and Archimandritis AJ.

Current treatment indications and strategies in chronic hepatitis B virus infection. *World J Gastroenterol* 14: 6902-6910, 2008.

The optimal approach to the management of several marginal cases with chronic hepatitis B virus (HBV) infection is controversial. Serum HBV DNA and aminotransferase levels, and the degree of necroinflammation and fibrosis determine the therapeutic decisions. All patients with elevated aminotransferase (>twice the upper limit of normal) and serum HBV DNA above 20000 IU/mL should be treated. Liver biopsy is important for therapeutic decisions in cases with mild aminotransferase elevations and serum HBV DNA below 20000 IU/mL. Chronic HBV patients who do not receive treatment should be followed for life. There are seven agents licensed for chronic hepatitis B: standard and pegylated interferon-alpha, lamivudine, adefovir, entecavir, telbivudine and tenofovir. One-year courses with pegylated interferon-alpha induce sustained off-therapy remission in 30%-32% of patients with HBeAg-positive chronic hepatitis B and in a smaller proportion of patients with HBeAg-negative chronic hepatitis B. Oral antivirals achieve initial on-therapy responses in the majority of patients, but are intended as long-term therapies. Viral suppression has favourable effects on patients' outcome and modifies the natural course of the disease. Viral resistance, however, is the major drawback of long-term oral antiviral therapy. Lamivudine monotherapy is associated with the highest and entecavir monotherapy with the lowest resistance rate so far. There has been no resistance to tenofovir, but after only 18 mo of treatment to date. The optimal first-line anti-HBV therapy with the best long-term cost/benefit ratio remains unclear. If oral antiviral agents are used, compliance should always be ascertained and HBV DNA levels should be regularly tested.

Papatheodoridis GV, Manolakopoulos S, Dusheiko G, and Archimandritis AJ.

Therapeutic strategies in the management of patients with chronic hepatitis B virus infection.

Lancet Infect Dis 8: 167-178, 2008.

Currently available options for the treatment of chronic hepatitis B virus (HBV) infection include standard and pegylated interferon alfa and four oral antiviral agents (lamivudine, adefovir, entecavir, and telbivudine). These treatment strategies are either therapies of finite duration that aim to achieve sustained off-therapy responses, or long-term treatments that aim to maintain on-therapy remission. Pegylated interferon alfa may offer higher sustained off-therapy responses after 1 year, but most patients do not respond. Oral antivirals are the only candidates for long-term treatment of patients with chronic HBV infection. Viral suppression has favourable effects on patients' outcome and modifies the natural history of the disease. Viral resistance is the main drawback of long-term antiviral therapy. Lamivudine monotherapy is associated with higher resistance (year 1, 10-27%; year 2, 37-48%; year 4, 60-65%) than adefovir (year 1, 0%; year 2, 3%; year 5, 29%) or telbivudine (year 1, 3-4%; year 2, 9-22%). Entecavir resistance is rare in naive individuals (year 4, <1%), but increases over time in lamivudine-resistant patients (year 4, 43%). The best strategy for long-term therapy in chronic HBV infection has yet to be established.

Pellicelli AM, Barbaro G, Barbarini G, and Soccorsi F.

Management of chronic hepatitis in drug addicts: a systematic review.
Clin Ter 159: 41-49, 2008.

Injection drug users constitute the largest group of person at high risk for acquiring chronic hepatitis C, B and Delta. In particular viral, host and environmental factors all seem to favour rapid spread of these infections among drugs addicts. Host factors include behaviours that expose individuals to hepatitis virus such as the shared use of drug preparation, injection equipment and not protected sexual relationship with other drugs users. While in some clinical studies adherence to treatment regimens was often poor and to treat chronic hepatitis in injection drug users was stated as futile, in other controlled clinical studies adherence and sustained biological response to antiviral treatment was slightly lower or similar to that reported in other groups of patients. In this review we describe the epidemiology, diagnosis and treatment of chronic hepatitis C, B and Delta in intravenous drug users.

Rockstroh JK, Bhagani S, Benhamou Y, Bruno R, Mauss S, Peters L, Puoti M, Soriano V, and Tural C.

European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults.
HIV Med 9: 82-88, 2008.

OBJECTIVES: With the decline in HIV-associated morbidity and mortality following the introduction of highly active antiretroviral therapy (HAART), liver disease has emerged as a major cause of death in HIV/hepatitis B virus (HBV) and HIV/hepatitis C virus (HCV) coinfecting persons. Therefore, screening for underlying viral hepatitis coinfection and the provision of management and treatment recommendations for patients with chronic viral hepatitis are of great importance in preventing, as far as possible, the development of liver disease. With the introduction of new agents for the treatment of hepatitis B and increased knowledge of how best to manage hepatitis C, an update of current guidelines for management of HBV and HCV coinfection with HIV is warranted. **SUMMARY:** Clearly, all HIV-infected patients should be screened for hepatitis A, B and C, taking into account shared pathways of transmission. Patients who are seronegative for hepatitis A and B should be

considered for vaccination. In HIV-infected patients with chronic hepatitis B, the first important differentiation is whether HAART is required or not. In the setting of stable HIV infection, with no need for HAART, several treatment options are available, namely treatment with interferon, early initiation of HAART, or selective non-HIV active anti-HBV nucleoside therapy, with the aim of achieving undetectable HBV DNA levels. In most cases, undetectable HBV DNA can only be achieved with combination therapy. With regard to hepatitis C, individualized tailoring of the duration of HCV therapy is advisable, taking into account rapid or delayed virological response. In patients who do not achieve at least a 2 log drop in HCV RNA at week 12, treatment can be terminated because of the low probability of achieving sustained virological response. Overall, with the currently available treatment algorithms, HCV can be eradicated in over 50% of patients. Therefore, HCV therapy should be considered and discussed with the patient if an indication for HCV therapy (elevated liver enzymes, positive HCV RNA and >F1 fibrosis) is present.

CONCLUSIONS: Management of underlying hepatitis B and/or C in patients with HIV infection is of great importance in preventing liver disease-associated morbidity and mortality.

Weinbaum CM, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, Neitzel SM, and Ward JW.

Recommendations for identification and public health management of persons with chronic hepatitis B virus infection.

MMWR Recomm Rep 57: 1-20, 2008.

Serologic testing for hepatitis B surface antigen (HBsAg) is the primary way to identify persons with chronic hepatitis B virus (HBV) infection. Testing has been recommended previously for pregnant women, infants born to HBsAg-positive mothers, household contacts and sex partners of HBV-infected persons, persons born in countries with HBsAg prevalence of $\geq 8\%$, persons who are the source of blood or body fluid exposures that might warrant postexposure prophylaxis (e.g., needlestick injury to a health-care worker or sexual assault), and persons infected with human immunodeficiency virus. This report updates and expands previous CDC guidelines for HBsAg testing and includes new recommendations for public health evaluation and management for chronically infected persons and their contacts. Routine testing for HBsAg now is recommended for additional populations with HBsAg prevalence of $\geq 2\%$: persons born in geographic regions with HBsAg prevalence of $\geq 2\%$, men who have sex with men, and injection-drug users. Implementation of these recommendations will require expertise and resources to integrate HBsAg screening in prevention and care settings serving populations recommended for HBsAg testing. This report is intended to serve as a resource for public health officials, organizations, and health-care professionals involved in the development, delivery, and evaluation of prevention and clinical services.

Wilt TJ, Shamliyan T, Shaikat A, Taylor BC, MacDonald R, Yuan JM, Johnson JR, Tacklind J, Rutks I, and Kane RL.

Management of chronic hepatitis B.

Evid Rep Technol Assess (Full Rep) 1-671, 2008.

OBJECTIVES: Synthesize evidence of the natural history of chronic hepatitis B (CHB) and effects and harms of antiviral drugs on clinical, virological, histological, and biochemical outcomes. **DATA SOURCES:** MEDLINE, electronic databases, and manual searches of systematic reviews. **REVIEW METHODS:** We included original observational studies to assess natural history and randomized controlled trials

(RCTs) of adults with CHB published in English to assess treatment effects and harms if they reported mortality, incidence of hepato-cellular carcinoma (HCC), cirrhosis or failure, HBeAg or HBsAg, viral load (HBV DNA), alanine aminotransferase (ALT) levels, histological necroinflammatory and fibrosis scores, and adverse events after interferon alfa-2b, pegylated interferon alfa 2-a, lamivudine, adefovir, entecavir, tenovir or telbivudine. We excluded pregnant women, transplant patients, and individuals undergoing cancer chemotherapy. We calculated relative risk or absolute risk differences at end of treatment and post-treatment. RESULTS: Observational studies (41 publications) suggested that male gender, coinfection with hepatitis C, D, or HIV, increased HBV DNA, and cirrhosis were associated with increased risk of HCC and death. Drugs did not reduce death, liver failure, or HCC in 16 RCTs not designed to test long-term clinical outcomes. Evidence from 93 publications of 60 RCTs suggested drug effects on viral load or replication, liver enzymes, and histology at end of treatment and lasting from 3 to 6 months off treatment. No one treatment improved all outcomes and there was limited evidence on comparative effects. Two RCTs suggested interferon alfa-2b increased CHB solution versus placebo. Interferon alfa-2b or lamivudine improved off treatment HBV DNA and HBeAg clearance and seroconversion and ALT normalization. Adefovir improved off treatment ALT normalization and HBV DNA clearance. Pegylated interferon alfa 2-a versus lamivudine improved off-treatment HBV DNA and HBeAg clearance and seroconversion, ALT normalization and liver histology. Lamivudine combined with interferon alfa-2b versus lamivudine improved off treatment HBV DNA clearance and HBeAg seroconversion and reduced HBV DNA mutations. Pegylated interferon alfa 2-a plus lamivudine improved off treatment HBV DNA and HBeAg clearance and seroconversion and ALT normalization compared to lamivudine but not pegylated interferon alfa 2-a monotherapy. Adverse events were common but generally mild and did not result in increased treatment discontinuation. Longer hepatitis duration, male gender, baseline viral load and genotype, HBeAg, and histological status may modify treatment effect on intermediate outcomes. Adefovir and pegylated interferon alfa 2-a with lamivudine improved off treatment viral clearance in HBeAg negative patients. There was insufficient evidence to determine if biochemical, viral, or histological measures are valid surrogates of treatment effect on mortality, liver failure, or cancer. CONCLUSION: Adults with CHB have an increased risk of death, hepatic decompensation, and HCC. Mono or combined drug therapy improves selected virological, biochemical, and histological markers with no consistent effects on all examined outcomes. Patient and disease characteristics may modify treatment-induced intermediate outcomes. Evidence was insufficient to assess treatment effect on clinical outcomes, predict individualized patient response, or determine if intermediate measures are reliable surrogates. Future research should assess long-term drug effects on clinical outcomes and among patient subpopulations.

Bihl F, Alaei M, and Negro F.

The new EASL guidelines for the management of chronic hepatitis B infection adapted for Swiss physicians.

Swiss Med Wkly.

Since the arrival of several new antivirals and due to the growing molecular and clinical knowledge of hepatitis B virus (HBV) infection, therapy of hepatitis B has become complex. Clinical guidelines aim at streamlining medical attitudes: in this respect, the European Association for the Study of the Liver (EASL) recently issued clinical practice guidelines for the management of chronic hepatitis B. Guidelines made by international experts need however to be adapted to local health care systems. Here, we summarise the EASL guidelines with some minor modifications in

order to be compatible with the particular Swiss situation, while discussing in more detail some aspects. Chronic hepatitis B is a complex disease with several phases where host and viral factors interact: the features of this continuous interplay need to be evaluated when choosing the most appropriate treatment. The EASL guidelines recommend, as first-line agents, using the most potent antivirals available with the optimal resistance profile, in order to abate HBV DNA as rapidly and as sustainably as possible. Once therapy has been started, the infection evolves and resistant viral strains may emerge. Rescue therapy needs to be started early with more potent agents lacking cross-resistance.

Maheshwari A, and Thuluvath PJ.

Management of acute hepatitis C.

Clin Liver Dis 14: 169-176; x.

The World Health Organization estimates that about 170 million people are infected with hepatitis C virus (HCV). Blood transfusions from unscreened donors and unsafe therapeutic procedures are the major modes of HCV transmission in the developing world, and injection drug use accounts for most newly diagnosed HCV infections in the developed countries. Acute infection with HCV leads to symptomatic hepatitis in only a minority of patients, and recent studies suggest that spontaneous clearance of virus is higher in symptomatic acute hepatitis C infection. Pooled data from various studies suggest that higher sustained viral clearance rates could be achieved with a shorter course of antiviral treatment in the early stages of chronic HCV infection. This article examines the diagnosis of acute infection and critically appraises the various treatment regimens.

Mitchell AE, Colvin HM, and Palmer Beasley R.

Institute of Medicine recommendations for the prevention and control of hepatitis B and C.

Hepatology 51: 729-733.

Despite federal, state, and local public health efforts to prevent and control hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, these diseases remain serious health problems in the United States. About 1%-2% of the U.S. population has chronic HBV or HCV infections, and each year about 15,000 people die from liver cancer or liver disease related to these preventable infections. The Institute of Medicine formed an expert committee to determine ways to reduce new HBV and HCV infections and the morbidity and mortality related to chronic viral hepatitis and released its findings in a report. The major factor found to impede current efforts to prevent and control HBV and HCV is lack of knowledge and awareness about these diseases among healthcare and social-service providers, members of the public, and policy makers. Because the extent and seriousness of this public health problem is not appreciated, inadequate resources are being allocated to prevention, control, and surveillance programs. This situation has led to continued transmission of HBV and HCV and inadequate identification of and medical management for chronically infected people. Conclusion: To address the situation, the Institute of Medicine report makes recommendations in four areas: improved surveillance for HBV and HCV; improved knowledge and awareness among healthcare and social-service providers and the public, especially at-risk people; improved HBV vaccine coverage; and improved viral hepatitis services and access to those services. HEPATOLOGY, 2010.

Yeung LT, and Roberts EA.

Current issues in the management of paediatric viral hepatitis.

Liver Int 30: 5-18.

Viral hepatitis poses important problems for children. In preschoolers, hepatitis A virus (HAV) infection frequently causes acute liver failure. Vaccinating toddlers against HAV in countries with high endemicity is expected to decrease mortality. HAV vaccine demonstrates efficacy (comparable to immunoglobulin) as post-exposure prophylaxis. A recently developed vaccine against hepatitis E virus (HEV) may benefit fetal health, because pregnant women are most prone to acute liver failure as a result of HEV. Hepatitis B vaccine continues to demonstrate value and versatility for preventing serious liver disease. With chronic infection, undetectable levels of serum HBV DNA complement e-seroconversion as the preferred outcome measure; suppressed viral load correlates with long-term complications better than HBeAg status. Among Taiwanese children, low pretreatment HBV DNA ($<2 \times 10^8$) copies/ml strongly predicted response to interferon-alpha. Future paediatric studies must incorporate HBV DNA levels. The rationale for routine treatment of immunotolerant hepatitis B during childhood remains uncertain. Any treatment of chronic hepatitis B in childhood requires consideration of the risks and benefits. Childhood hepatitis C virus (HCV) infection results mainly from mother-to-infant transmission. Babies of HCV-infected women should be tested for serum HCV RNA at 1 month of age. If negative, confirmatory anti-HCV antibody testing may be performed between 12 and 15 months of age. Children with chronic hepatitis C may develop progressive fibrosis/cirrhosis, particularly in the setting of obesity and insulin resistance. Treatment of children chronically infected with genotype 2 or 3 is highly successful: combination therapy of pegylated interferon-alpha and ribavirin is well tolerated and superior to pegylated interferon-alpha alone.

2. Cost effectiveness of screening and management of chronic hepatitis

Pubmed MEDLINE search1 on {{{(Cost effectiveness AND hepatitis) AND (Viral OR virus OR antiviral OR chronic) AND (management OR treatment OR identification OR screening)}}} combined with search 2 ' screening AND chronic AND viral hepatitis' were only the **English** publication **since 2008** were selected resulted in 49 articles. Manually the publications were selected related to '**Cost effectiveness of treatment, diagnosis, control and screening**'. 25 references are arranged by publication year (most recent first) and for each year in alphabetical order of the first author's name.

Alswaidi FM, and O'Brien SJ.

Premarital screening programmes for haemoglobinopathies, HIV and hepatitis viruses: review and factors affecting their success.

J Med Screen 16: 22-28, 2009.

This literature review is a comprehensive summary of premarital (prenuptial) screening programmes for the most prevalent hereditary haemoglobinopathies, namely thalassaemia and sickle cell disease, and the important infections HIV (human immunodeficiency virus) and hepatitis viruses B and C (HBV and HCV). It describes the background to premarital screening programmes and their value in countries where these diseases are endemic. The use of premarital screening worldwide is critically evaluated, including recent experiences in Saudi Arabia, followed by discussion of the outcomes of such programmes. Despite its many benefits, premarital testing is not acceptable in some communities for various legal and religious reasons, and other educational and cultural factors may prevent some married couples following the advice given by counsellors. The success of these programmes therefore depends on adequate religious support, government policy, education and counselling. In contrast to premarital screening for haemoglobinopathies, premarital screening for HIV and the hepatitis viruses is still highly controversial, both in terms of ethics and cost-effectiveness. In wealthy countries, premarital hepatitis and HIV testing could become mandatory if at-risk, high-prevalence populations are clearly identified and all ethical issues are adequately addressed.

Buti M, Brosa M, Casado MA, Rueda M, and Esteban R.

Modeling the cost-effectiveness of different oral antiviral therapies in patients with chronic hepatitis B.

J Hepatol 51: 640-646, 2009.

BACKGROUND/AIMS: Chronic hepatitis B (CHB) is a common disease associated with high morbidity, mortality and impact on healthcare costs. Several oral antiviral therapies can lead to complete virologic response, which is associated with prevention of disease progression. The aim of this study was to estimate the cost-effectiveness of the oral antiviral treatments lamivudine, adefovir, telbivudine, entecavir and tenofovir, in patients with CHB. **METHODS:** A Markov model was used to project the lifetime complications and costs in cohorts of both HBeAg-positive and HBeAg-negative CHB patients treated with one of the above drugs or no treatment. Rescue therapy with two different combination therapies (adefovir plus lamivudine or tenofovir plus entecavir) with their corresponding costs and efficacy rates was also

considered. The probabilities of disease progression were based on serum HBV DNA levels. Disease and complication costs were assessed using the perspective of the Spanish National Health System. RESULTS: The highest rate of virologic response was obtained with tenofovir, and this translated to its higher life years saved (LYS) and quality adjusted life years (QALY) compared with the rest of the alternatives in HBeAg-positive and HBeAg-negative patients. Tenofovir is associated with lower costs and higher efficacy over entecavir, telbivudine and adefovir in HBeAg-positive patients, and telbivudine and entecavir in HBeAg-negative patients. The incremental cost-effectiveness ratios with respect to the rest of the alternatives are below the common reference efficiency threshold of 30,000 euro per LYS/QALY. CONCLUSION: In chronic HBV infected patients, tenofovir is a cost-effective or even cost-saving strategy compared with other available treatment options for CHB.

Colombo M.

Screening and diagnosis of hepatocellular carcinoma.
Liver Int 29 Suppl 1: 143-147, 2009.

Early diagnosis of hepatocellular carcinoma (HCC) is feasible because HCC develops in the background of well-known, readily identifiable and potentially avoidable environmental risk factors. According to the American Association for the Study of the Liver Diseases and the European Association for the Study of the Liver, patients with cirrhosis and carriers of chronic viral hepatitis are the target of surveillance to be investigated with abdominal ultrasounds (US) every 6 or 12 months. The diagnostic confirmation of a $>$ or $=$ 2 cm nodule in patients with cirrhosis detected during surveillance is possible with any imaging technique among second-generation contrast US, contrast computed tomography and gadolinium-contrast magnetic resonance imaging. HCC shows an early hyperenhanced arterial vascularization, followed by enhanced hypoattenuation (wash-out) in the late phase of imaging. In patients with a $<$ or $=$ 2 cm nodule, two imaging techniques are required for the final diagnosis, which, however, have a relatively low diagnostic sensitivity (33%). Nodules with negative imaging findings need to be investigated further with an echo-guided liver biopsy or enhanced follow-up with imaging (every 3 months) to reach a final diagnosis. The cost-effectiveness ratio of surveillance depends on multiple factors, like HCC incidence, the cost and accuracy of diagnostic tests and the costs and outcome of the therapeutic interventions.

Dusheiko GM.

Cost-effectiveness of oral treatments for chronic hepatitis B.
J Hepatol 51: 623-625, 2009.

Kretzschmar M, Mangen MJ, van de Laar M, and de Wit A.

Model based analysis of hepatitis B vaccination strategies in the Netherlands.
Vaccine 27: 1254-1260, 2009.

We used a mathematical model for the transmission of hepatitis B infection to compare the effectiveness of different vaccination strategies in the Netherlands. Vaccination of children of immigrants from high and medium endemic countries is an effective strategy in countries with substantial immigration of carriers from high and medium endemic countries. A targeted vaccination programme for sexually highly active risk groups has a moderate additional effect if continued over a long time period. Universal vaccination has the largest effect on the incidence of new infections

at the cost of having to vaccinate many more individuals than in targeted programmes. The impact on the prevalence of chronic hepatitis B infection, however, remains limited.

Liaw YF.

On-treatment outcome prediction and adjustment during chronic hepatitis B therapy: now and future.

Antivir Ther 14: 13-22, 2009.

Studies published to date regarding on-treatment outcome prediction during chronic hepatitis B therapy were reviewed. Studies have shown that initial virological responses in terms of week 24 serum hepatitis B virus (HBV) DNA levels are associated with therapeutic outcomes of 1-year pegylated interferon-alpha and entecavir therapy, and weeks 52 or 104 of lamivudine and telbuvudine therapy. HBV DNA levels at week 48 are also associated with long-term adefovir therapy outcomes. Conceptual on-treatment adjustment and strategies have been proposed; however, this approach seems only necessary during therapy with nucleos(t)ide analogues with substantial risk of drug resistance. In addition, studies are needed to decide whether switching to or adding on a second drug, and with which drug, is the most cost-effective strategy.

Massad E, Coutinho FA, Chaib E, and Burattini MN.

Cost-effectiveness analysis of a hypothetical hepatitis C vaccine compared to antiviral therapy.

Epidemiol Infect 137: 241-249, 2009.

We propose a mathematical model to simulate the dynamics of hepatitis C virus (HCV) infection in the state of Sao Paulo, Brazil. We assumed that a hypothetical vaccine, which cost was taken to be the initial cost of the vaccine against hepatitis B exists and it is introduced in the model. We computed its cost-effectiveness compared with the anti-HCV therapy. The calculated basic reproduction number was 1.20. The model predicts that without intervention a steady state exists with an HCV prevalence of 3%, in agreement with the current epidemiological data. Starting from this steady state three interventions were simulated: indiscriminate vaccination, selective vaccination and anti-HCV therapy. Selective vaccination proved to be the strategy with the best cost-effectiveness ratio, followed by indiscriminate vaccination and anti-HCV therapy.

Robotin MC, Kansil M, Howard K, George J, Tipper S, Dore GJ, Levy M, and Penman AG.

Antiviral therapy for hepatitis B-related liver cancer prevention is more cost-effective than cancer screening.

J Hepatol 50: 990-998, 2009.

BACKGROUND/AIMS: In Australia, Asian-born populations are 6-12 times more likely to develop hepatocellular cancer (HCC) than Australian-born individuals. We therefore, modelled the consequences of different management strategies for chronic hepatitis B (CHB) in Asian-born adults aged > or = 35 years. METHODS: A Markov model compared (1) enhanced surveillance for HCC alone (HCC surveillance), or (2) enhanced HCC surveillance coupled with CHB treatment (HCC prevention) to the current practice, of low CHB treatment uptake. Patients were stratified and managed according to risk categories, based upon hepatitis B virus (HBV) viral load and

alanine aminotransferase (ALT) levels. We measured costs, health outcomes [cases of HCC and deaths averted, quality-adjusted life-years (QALYs) gained] and incremental cost-effectiveness ratios (ICERs). RESULTS: HCC surveillance would cost on average AU\$8479 per person, compared to AU\$2632 with current clinical practice and result in a gain of 0.014 QALYs (AU\$401,516/QALY gained). A HCC prevention strategy would cost on average AU\$14,600 per person, result in 0.923 QALYs gained (AU\$12,956/QALY gained), reduce cases of cirrhosis by 52%, HCC diagnoses by 47% and CHB-related deaths by 56%, compared to current practice. CONCLUSIONS: HCC prevention appears to be a cost-effective public health strategy in at-risk populations in Australia and is preferable to HCC surveillance as a cancer control strategy.

Siebert U, Sroczynski G, Aidelsburger P, Rossol S, Wasem J, Manns MP, McHutchison JG, and Wong JB.

Clinical effectiveness and cost effectiveness of tailoring chronic hepatitis C treatment with peginterferon alpha-2b plus ribavirin to HCV genotype and early viral response: a decision analysis based on German guidelines.

Pharmacoeconomics 27: 341-354, 2009.

BACKGROUND: Recently developed German guidelines for antiviral treatment in patients with chronic hepatitis C recommend basing drug dosage, intended treatment duration and early stopping rules on the genotype of the hepatitis C virus and early viral responses to treatment. OBJECTIVES: To evaluate effectiveness and cost effectiveness of different antiviral treatment strategies including the German guidelines, for chronic hepatitis C. METHODS: A validated lifetime Markov model was used to project life expectancy, QALYs and lifetime costs for the following strategies: (i) no antiviral therapy (NoAVT); (ii) interferon-alpha-2b plus ribavirin for 48 weeks (IFN + R); (iii) peginterferon-alpha-2b plus weight-based ribavirin for 48 weeks (PEG + R); (iv) peginterferon-alpha-2b plus ribavirin according to German guidelines with genotype-dependent treatment duration, dosage and 12-week viral response evaluation (GUIDE). Clinical and resource utilization data were derived from a clinical trial, the published literature and a survey of German hepatologists. Incremental cost-effectiveness ratios (ICERs) were calculated adopting the German societal perspective. Costs (in euro, year 2005 values) and health outcomes were discounted at 3% annually. Uncertainty was assessed using deterministic and probabilistic sensitivity analyses. RESULTS: Compared with NoAVT, PEG + R increased undiscounted life expectancy by 5.0 life-years (5.2 QALYs) and GUIDE increased undiscounted life expectancy by 4.9 years (5.1 QALYs). Compared with PEG + R, GUIDE saved 13% of hepatitis C virus-related lifetime costs per patient. GUIDE dominated IFN + R. Compared with NoAVT, discounted ICERs were euro1500 per QALY for GUIDE and euro3200 per QALY for PEG + R. CONCLUSION: Administering GUIDE should allow tailoring treatment efficiently to genotype, bodyweight and early viral response in patients with chronic hepatitis C, and appears cost effective compared with other well accepted medical interventions.

Sroczynski G, Esteban E, Conrads-Frank A, Schwarzer R, Muhlberger N, Wright D, Zeuzem S, and Siebert U.

Long-term effectiveness and cost-effectiveness of screening for hepatitis C virus infection.

Eur J Public Health 19: 245-253, 2009.

BACKGROUND: Hepatitis C virus (HCV) infection is an emerging problem in public health. In most countries, the majority of HCV infected people are yet undiagnosed.

Early detection and treatment may result in better health outcomes and save costs by preventing future advanced liver disease. The evidence for long-term effectiveness and cost-effectiveness of HCV screening was systematically reviewed. **METHODS:** We performed a systematic literature search on long-term health-economic effects of HCV screening and included Health Technology Assessment (HTA) reports, systematic reviews, long-term clinical trials, full health economic and decision-analytic modelling studies with a sufficiently long time horizon and patient-relevant long-term outcomes such as life-years gained (LYG) or quality-adjusted life years (QALY) gained. Economic results were converted to 2005 Euros. **RESULTS:** Seven studies were included. Target population, HCV prevalence, study perspective, discount rate, screening and antiviral treatment mode varied. The incremental effectiveness of HCV screening and early treatment compared to no screening and standard care varied from 0.0004 to 0.066 LYG, and from 0.0001 to 0.072 QALY. Incremental cost-effectiveness and cost-utility ratios of HCV screening vs. no screening were 3900-243,700 euro/LYG and 18,300-1,151,000 euro/QALY. HCV screening seems to be cost-effective in populations with high HCV prevalence, but not in low HCV prevalence populations. **CONCLUSIONS:** HCV screening and early treatment have the potential to improve average life-expectancy, but should focus on populations with elevated HCV prevalence to be cost-effective. Further research on the long-term health-economic impact of HCV screening when combined with appropriate monitoring strategies in different European health care systems is needed.

Barreto AM, Takei K, E CS, Bellesa MA, Salles NA, Barreto CC, Nishiya AS, and Chamone DF.

Cost-effective analysis of different algorithms for the diagnosis of hepatitis C virus infection.

Braz J Med Biol Res 41: 126-134, 2008.

We compared the cost-benefit of two algorithms, recently proposed by the Centers for Disease Control and Prevention, USA, with the conventional one, the most appropriate for the diagnosis of hepatitis C virus (HCV) infection in the Brazilian population. Serum samples were obtained from 517 ELISA-positive or -inconclusive blood donors who had returned to Fundacao Pro-Sangue/Hemocentro de Sao Paulo to confirm previous results. Algorithm A was based on signal-to-cut-off (s/co) ratio of ELISA anti-HCV samples that show s/co ratio $>$ or $=95\%$ concordance with immunoblot (IB) positivity. For algorithm B, reflex nucleic acid amplification testing by PCR was required for ELISA-positive or -inconclusive samples and IB for PCR-negative samples. For algorithm C, all positive or inconclusive ELISA samples were submitted to IB. We observed a similar rate of positive results with the three algorithms: 287, 287, and 285 for A, B, and C, respectively, and 283 were concordant with one another. Indeterminate results from algorithms A and C were elucidated by PCR (expanded algorithm) which detected two more positive samples. The estimated cost of algorithms A and B was US\$21,299.39 and US\$32,397.40, respectively, which were 43.5 and 14.0% more economic than C (US\$37,673.79). The cost can vary according to the technique used. We conclude that both algorithms A and B are suitable for diagnosing HCV infection in the Brazilian population. Furthermore, algorithm A is the more practical and economical one since it requires supplemental tests for only 54% of the samples. Algorithm B provides early information about the presence of viremia.

Holbrook ML.

Cost-effective pharmacologic therapies to treat chronic hepatitis B: how far have we

really come?

J Manag Care Pharm 14: 65-69, 2008.

Lacey L, Chien RN, Chuang WL, and Pwu RF.

Economic evaluation of chronic hepatitis B treatments in Taiwan.

J Gastroenterol Hepatol 23: 571-579, 2008.

BACKGROUND AND AIMS: Chronic hepatitis B (CHB) and its sequelae are major health problems in Taiwan. The purpose of the present study was the economic evaluation of short-duration treatments of CHB and longer duration antiviral treatment for up to 5 years. **METHODS:** Ten-health state CHB disease progression Markov models were used for hepatitis B e antigen (HBeAg)-positive and HBeAg-negative CHB patients, respectively, that included the emergence of antiviral resistance. The perspective of this economic evaluation was the Taiwan health-care system. Costs and benefits were discounted at 3% per annum. **RESULTS:** Short-course therapies of up to 1-year treatment had limited impact on improving patient survival. Long-term viral suppression with lamivudine and adefovir sequential rescue therapies (including add-on therapies) for up to 5 years were found to be highly cost-effective by international standards (estimated to be NT\$580,000 per quality adjusted life year [QALY] for Taiwan). When Taiwan-specific model inputs were used for HBeAg-positive CHB, the cost per QALY for lamivudine plus adefovir sequential antiviral therapy increased by approximately 100% over the base-case estimate, but was still well within the estimated NT\$580,000 per QALY threshold. **CONCLUSIONS:** In Taiwan, treatment of CHB patients with lamivudine and adefovir sequential antiviral therapies for up to 5 years results in survival benefits and is highly cost-effective.

Miriti MK, Billah K, Weinbaum C, Subiadur J, Zimmerman R, Murray P, Gunn R, and Buffington J.

Economic benefits of hepatitis B vaccination at sexually transmitted disease clinics in the U.S.

Public Health Rep 123: 504-513, 2008.

OBJECTIVE: This study assessed the long-term economic implications of a national program to vaccinate all adults treated at sexually transmitted disease (STD) clinics in a single year. **METHODS:** A model was developed to track the long-term disease outcomes and costs among a hypothetical cohort of 2 million STD clinic clients accessing services in one year, using data from published sources and demonstration projects at STD clinics in San Diego (California), Illinois, and Denver (Colorado). The model estimated net economic benefits of a routine hepatitis B vaccination policy at STD clinics nationwide compared with no vaccination. **RESULTS:** Without a vaccination program, an estimated 237,021 new hepatitis B virus (HBV) infections would occur over the lifetimes of the 2 million STD clinic clients seen in a single year. HBV-related medical costs and productivity losses would be \$1.6 billion. In a national program for routine vaccination at STD clinics, 1.3 million adults would be expected to receive at least one vaccine dose, and an estimated 45% of the new HBV infections expected without vaccination would be prevented. The vaccination program would cost \$138 million, HBV infections occurring despite the program would cost \$878 million, and clients' time and travel would cost \$45 million. The net economic benefit (savings) of routine vaccination would be \$526 million. If the indirect costs of lost productivity due to HBV infection are not considered, routine vaccination would have a net cost of \$28 million. **CONCLUSIONS:** Estimates from this model suggest a national program for routine

hepatitis B vaccination of adults at STD clinics would be a cost saving to society.

Nakamura J, Terajima K, Aoyagi Y, and Akazawa K.

Cost-effectiveness of the national screening program for hepatitis C virus in the general population and the high-risk groups.

Tohoku J Exp Med 215: 33-42, 2008.

In Japan, the national screening for the hepatitis C virus (HCV) has been started for both the general population and the high-risk groups. Our cost-effectiveness analysis was based on the result of the screening program including 99,001 people among the general population and 42,538 people among the high risk group from 2003 to 2006. The screening was performed using the three steps of the semi-quantitative HCV antibody test, the HCV core antigen test and the HCV-PCR test. A Markov model for HCV infected patients was constructed to estimate the future clinical benefits and the lifetime cost and the cost-effectiveness analysis was performed considering the recent treatment with peginterferon plus ribavirin. In the cost-effectiveness analysis, the cohort, in which the screening was implemented (= screening strategy), was compared with the similar cohort without the screening (= no-screening strategy) in both the general population and the high-risk group, stratified by age. The infection rates of the general population and the high-risk group were 0.36% and 0.81%, respectively. The incremental cost-effectiveness ratio (ICER), a measure of cost-effectiveness, of the general population and the high-risk group was calculated to be from 848 to 4,825 and --749 to 2,297 \$/life expectancy gained, respectively. The treatment effectiveness, transition probabilities and the infection rate varied in the one-way sensitivity analyses, but the superiority of the screening strategy regarding the cost-effectiveness was unchanged. In conclusion, the screening strategy in both the general population and the high-risk group therefore appears to be more cost-effective than a no-screening strategy.

Papatheodoridis GV, Manolakopoulos S, and Archimandritis AJ.

Current treatment indications and strategies in chronic hepatitis B virus infection.

World J Gastroenterol 14: 6902-6910, 2008.

The optimal approach to the management of several marginal cases with chronic hepatitis B virus (HBV) infection is controversial. Serum HBV DNA and aminotransferase levels, and the degree of necroinflammation and fibrosis determine the therapeutic decisions. All patients with elevated aminotransferase (>twice the upper limit of normal) and serum HBV DNA above 20000 IU/mL should be treated. Liver biopsy is important for therapeutic decisions in cases with mild aminotransferase elevations and serum HBV DNA below 20000 IU/mL. Chronic HBV patients who do not receive treatment should be followed for life. There are seven agents licensed for chronic hepatitis B: standard and pegylated interferon-alpha, lamivudine, adefovir, entecavir, telbivudine and tenofovir. One-year courses with pegylated interferon-alpha induce sustained off-therapy remission in 30%-32% of patients with HBeAg-positive chronic hepatitis B and in a smaller proportion of patients with HBeAg-negative chronic hepatitis B. Oral antivirals achieve initial on-therapy responses in the majority of patients, but are intended as long-term therapies. Viral suppression has favourable effects on patients' outcome and modifies the natural course of the disease. Viral resistance, however, is the major drawback of long-term oral antiviral therapy. Lamivudine monotherapy is associated with the highest and entecavir monotherapy with the lowest resistance rate so far. There has been no resistance to tenofovir, but after only 18 mo of treatment to date. The optimal first-line anti-HBV therapy with the best long-term cost/benefit ratio

remains unclear. If oral antiviral agents are used, compliance should always be ascertained and HBV DNA levels should be regularly tested.

Smith VE, and Bruno CJ.

The search for cost-effective treatment of chronic hepatitis B.
J Manag Care Pharm 14: 61-64, 2008.

Spackman DE, and Veenstra DL.

A cost-effectiveness analysis of currently approved treatments for HBeAg-positive chronic hepatitis B.
Pharmacoeconomics 26: 937-949, 2008.

BACKGROUND: A variety of pharmaceuticals are currently approved for the treatment of hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB), but their relative economic value is unclear. The goal of this analysis was to compare the cost effectiveness of adefovir, entecavir, lamivudine, pegylated interferon and telbivudine. **METHODS:** We conducted a cost-utility analysis from a US payer perspective over a lifetime time horizon using a Markov model, in a hypothetical population with HBeAg-positive CHB and a mean age of 35 years. Disease progression probabilities, costs and quality-of-life data were derived from the literature. We assumed a treatment duration of 4 years, with the use of combination therapy for drug resistance. Nonresponders to pegylated interferon were assumed to receive entecavir in years 3-4. Sensitivity analyses, including probabilistic sensitivity analysis, were conducted to evaluate uncertainty in the results. All costs were valued in \$US, year 2008 values. Costs and outcomes were discounted at 3% per annum. **RESULTS:** The 10-year cumulative incidence of cirrhosis for no treatment was 26.1%, and ranged from 19.7% to 23.8% with treatment; undiscounted life-years were 36.2 for no treatment, or ranged from 36.82 to 37.54 with treatment. Initiation with entecavir (18.70 QALYs) and pegylated interferon (18.64 QALYs) provided the largest treatment benefits overall, followed by telbivudine (18.55 QALYs). The probabilities of the interventions being cost effective at a threshold of USD 50,000 per QALY were 57%, 37% and 2% for initiation with entecavir, pegylated interferon and telbivudine, respectively. The results were dependent on baseline seroconversion rate and the effect of viral suppression on cirrhosis risk. **CONCLUSIONS:** Initiation of treatments for HBeAg-positive CHB with a favourable combination of seroconversion, viral suppression and resistance profile appear to offer the greatest clinical and economic value.

Sutton AJ, Edmunds WJ, Sweeting MJ, and Gill ON.

The cost-effectiveness of screening and treatment for hepatitis C in prisons in England and Wales: a cost-utility analysis.
J Viral Hepat 15: 797-808, 2008.

Prisoners have a high prevalence of hepatitis C virus (HCV) infection compared with the general population in England and Wales and in many locations throughout the world. This is because of large numbers of injecting drug users that engage in behaviours likely to transmit HCV being present within prison populations. It is, therefore, suggested that prison may be an appropriate location for HCV screening and treatment to be administered. Using cost-utility analysis, this study considers the costs and benefits of administering a single round of screening on reception into prison to all individuals followed by possible later screening in the community and

comparing this to individuals who may only be tested and treated in the community at a later date. The cost/QALY of one round of prison testing and treatment was found to be 54,852 pounds sterling, although probabilistic sensitivity analysis showed extensive uncertainty about this estimate. One-way sensitivity analysis revealed the importance of the parameters describing the progression of chronic HCV and the discount rates. While the results presented here at baseline would suggest that screening and treatment for HCV in prisons is not cost-effective, these results are subject to much uncertainty. The importance of the rates describing the progression of chronic HCV on the cost-effectiveness of this intervention has been demonstrated and this suggests that future work should be undertaken to gain further insight into the rates that individuals progress to the later stages of chronic HCV infection.

Tan JA, Joseph TA, and Saab S.

Treating hepatitis C in the prison population is cost-saving.
Hepatology 48: 1387-1395, 2008.

The prevalence of chronic hepatitis C infection in U.S. prisons is 12% to 31%. Treatment of this substantial portion of the population has been subject to much controversy, both medically and legally. Studies have demonstrated that treatment of chronic hepatitis C with pegylated interferon (PEG IFN) and ribavirin is a cost-effective measure in the general population; however, no study has addressed whether the same is true of the prison population. The aim of this study was to determine the cost-effectiveness of hepatitis C treatment with PEG IFN and ribavirin in the U.S. prison population. Cost-effectiveness was determined via a decision analysis model employing Markov simulation. The cohort of prisoners had a distribution of genotypes and stages of fibrosis in accordance with prior studies evaluating inmate populations. The probability of transitioning from one health state to another, reinfection rates, in-prison and out-of-prison mortality rates, sustained viral response rates, costs, and quality of life weights were also obtained from the literature. Sensitivity analysis was performed. In a strategy without a pretreatment liver biopsy, treatment was cost-effective for all ages and genotypes. This model was robust to rates of disease progression, mortality rates, reinfection rates, sustained viral response rates, and costs. In a strategy employing a pretreatment liver biopsy, treatment was also cost-saving for prisoners of all ages and genotypes with portal fibrosis, bridging fibrosis, or compensated cirrhosis. Treatment was not cost-effective in patients between the ages of 40 and 49 with no fibrosis and genotype 1. CONCLUSION: Treatment of chronic hepatitis C with PEG IFN and ribavirin in U.S. prisons results in both improved quality of life and savings in cost for almost all segments of the inmate population. If the decision to treat hepatitis C is based on pharmaco-economic measures, this significant proportion of infected individuals should not be denied access to therapy.

Tramarin A, Gennaro N, Compostella FA, Gallo C, Wendelaar Bonga LJ, and Postma MJ.

HCV screening to enable early treatment of hepatitis C: a mathematical model to analyse costs and outcomes in two populations.
Curr Pharm Des 14: 1655-1660, 2008.

Early treatment of acute hepatitis C virus (HCV) infections reflects a new clinical paradigm and a significant option to reduce the socioeconomic burden of HCV. Therefore, this approach seems suitable as a new strategy to face HCV and prevent end stage liver diseases and premature deaths due to progressed chronic HCV-infections. The main limitation of this approach is that the majority of acute infections

show an asymptomatic course and do thus not present to the health-care settings. Screening for HCV has already been extensively studied in the literature. This paper offers further insights in screening for HCV using cost effectiveness analysis for the impact of screening in two cohorts: Injecting Drug Users (IDUs) and Individuals With Surgery (IWSs). The setting of the cost effectiveness simulation is the Veneto Region in the North-east of Italy. Using a Markov model of the natural history of HCV infection we derive costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness related to screening vs. no-screening strategies. In the IDUs cohort, the screening strategy can result in a substantial difference in premature deaths and dominates (less costs better outcomes) the no-screening one. The overall outcomes of the screening strategy are mostly affected by the prevalence of HCV and of genotypes that are more relatively more difficult to treat (above 10% of prevalence for its cost effectiveness). The number of premature deaths prevented in the IWSs cohort is lower and there seems to be an unacceptable incremental cost per QALY gained, which may be unsustainable for society.

Veenstra DL, Spackman DE, Di Bisceglie A, Kowdley KV, and Gish RG.

Evaluating anti-viral drug selection and treatment duration in HBeAg-negative chronic hepatitis B: a cost-effectiveness analysis.

Aliment Pharmacol Ther 27: 1240-1252, 2008.

BACKGROUND: Several anti-viral treatments are now available for HBeAg-negative chronic hepatitis B (CHB), but the clinical and economic outcomes of potential treatment strategies and durations are unclear. **AIM:** To examine the clinical and economic outcomes of potential treatment strategies and durations for HBeAg-negative CHB. **METHODS:** We conducted a cost-utility analysis from a payer perspective over a lifetime time horizon. Disease progression probabilities, costs and quality of life data were derived from the literature. We evaluated 5-year, 10-year, lifetime and 5 on-1 off treatment durations. For each of these treatment durations, we evaluated initial therapy with entecavir, lamivudine or adefovir, with addition of adefovir or entecavir for patients who developed virological breakthrough because of resistance (12 strategies total). **RESULTS:** Increasing treatment duration improved quality-adjusted life-years (QALYs) and was generally cost-effective for all three drugs. However, a 5 on-1 off strategy was the most cost-effective: lifetime vs. 5 on-1 off entecavir had an ICER of \$148,200/QALY. In probabilistic sensitivity analyses, entecavir 5 on-1 off was the preferred strategy over the range of commonly reimbursed cost-effectiveness thresholds. Lifetime treatment was preferred to a 5 on-1 off strategy, if treatment durability was < 10%. **CONCLUSION:** The results of our analysis suggest that in HBeAg-negative CHB infection, a 5 on-1 off treatment strategy with entecavir improves health outcomes in a cost-effective manner compared to alternative strategies.

Armbruster B, and Brandeau ML.

Cost-effective control of chronic viral diseases: finding the optimal level of screening and contact tracing.

Math Biosci 224: 35-42.

Chronic viral diseases such as human immunodeficiency virus (HIV) and hepatitis B virus (HBV) afflict millions of people worldwide. A key public health challenge in managing such diseases is identifying infected, asymptomatic individuals so that they can receive antiviral treatment. Such treatment can benefit both the treated individual (by improving quality and length of life) and the population as a whole (through reduced transmission). We develop a compartmental model of a chronic, treatable

infectious disease and use it to evaluate the cost and effectiveness of different levels of screening and contact tracing. We show that: (1) the optimal strategy is to get infected individuals into treatment at the maximal rate until the incremental health benefits balance the incremental cost of controlling the disease; (2) as one reduces the disease prevalence by moving people into treatment (which decreases the chance that they will infect others), one should increase the level of contact tracing to compensate for the decreased effectiveness of screening; (3) as the disease becomes less prevalent, it is optimal to spend more per case identified; and (4) the relative mix of screening and contact tracing at any level of disease prevalence is such that the marginal efficiency of contact tracing (cost per infected person found) equals that of screening if possible (e.g., when capacity limitations are not binding). We also show how to determine the cost-effective equilibrium level of disease prevalence (among untreated individuals), and we develop an approximation of the path of the optimal prevalence over time. Using this, one can obtain a close approximation of the optimal solution without having to solve an optimal control problem. We apply our methods to an example of hepatitis B virus.

Sroczyński G, Esteban E, Conrads-Frank A, Schwarzer R, Muhlberger N, Wright D, Zeuzem S, and Siebert U.

Long-term effectiveness and cost-effectiveness of antiviral treatment in hepatitis C. *J Viral Hepat* 17: 34-50.

We systematically reviewed the evidence for long-term effectiveness and cost-effectiveness of antiviral treatment in patients with chronic hepatitis C. We performed a systematic literature search on the long-term effectiveness and cost-effectiveness of AVT in hepatitis C (1990-March 2007), and included health technology assessment (HTA) reports, systematic reviews, long-term clinical trials, economic studies conducted alongside clinical trials and decision-analytic modelling studies. All costs were converted to 2005euro. Antiviral therapy with peginterferon plus ribavirin in treatment-naïve patients with chronic hepatitis C was the most effective (3.6-4.7 life years gained [LYG]) treatment and was reasonably cost-effective (cost-saving to 84 700euro/quality adjusted life years [QALY]) when compared to interferon plus ribavirin. Some results also suggest cost-effectiveness (below 8400euro/(QALY) of re-treatment in nonresponders/relapsers. Results for patients with persistently normal alanine aminotransferase (ALT) levels or with special co-morbidities (e.g. HIV) or risk profiles were rare. We conclude that antiviral therapy may prolong life, improve long-term health-related quality-of-life and be reasonably cost-effective in treatment-naïve patients with chronic hepatitis C as well as in former relapsers/nonresponders. Further research is needed in patients with specific co-morbidities or risk profiles.

Veldhuijzen IK, Toy M, Hahne SJ, De Wit GA, Schalm SW, de Man RA, and Richardus JH.

Screening and early treatment of migrants for chronic hepatitis B virus infection is cost-effective.

Gastroenterology 138: 522-530.

BACKGROUND & AIMS: Persons with chronic hepatitis B virus (HBV) infection are at risk of developing cirrhosis and hepatocellular carcinoma. Early detection of chronic HBV infection through screening and treatment of eligible patients has the potential to prevent these sequelae. We assessed the cost-effectiveness in The Netherlands of systematically screening migrants from countries that have high and intermediate HBV infection levels. **METHODS:** Epidemiologic data of the expected numbers of patients with active chronic HBV infection in the target population and

information about the costs of a screening program were used in a Markov model and used to determine costs and quality-adjusted life years (QALY) for patients who were and were not treated. RESULTS: Compared with the status quo, a 1-time screen for HBV infection can reduce mortality of liver-related diseases by 10%. Using base case estimates, the incremental cost-effectiveness ratio (ICER) of screening, compared with not screening, is euros (euro) 8966 per QALY gained. The ICER ranged from euro7936 to euro11,705 based on univariate sensitivity analysis, varying parameter values of HBV prevalence, participation rate, success in referral, and treatment compliance. Using multivariate sensitivity analysis for treatment effectiveness, the ICER ranged from euro7222 to euro15,694; for disease progression, it ranged from euro5568 to euro60,418. CONCLUSIONS: Early detection and treatment of people with HBV infection can have a large impact on liver-related health outcomes. Systematic screening for chronic HBV infection among migrants is likely to be cost-effective, even using low estimates for HBV prevalence, participation, referral, and treatment compliance.

3. Relevant abstracts per meeting session

SESSION 2 SCREENING FOR PERSONS WITH UNDERLYING CHRONIC DISEASE

Presentation:

Revisiting Wilson and Jungner in the genomic age: a Review of screening criteria over the past 40 years.

Anne Andermann

- **Wilson JMG, Jungner G.** *Principles and practice of screening for disease.* Geneva: WHO; 1968

-Andermann A, Blancquaert I, Beauchamp S, Dery V. **Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years.** *Bull World Health Organ* 2008,86:317-319.

Abstract : Almost 40 years ago, WHO commissioned a report on screening from James Maxwell Glover Wilson, then Principal Medical Officer at the Ministry of Health in London, England, and Gunner Jungner, then Chief of the Clinical Chemistry Department of Sahlgren's Hospital in Gothenburg, Sweden. The report¹, published in 1968, was entitled: *Principles and practice of screening for disease* and it has since become a public health classic.

Presentation:

Screening for Chronic Kidney disease: Where does Europe go?

Paul E de jong

de Jong PE, van der Velde M, Gansevoort RT, and Zoccali C.

Screening for chronic kidney disease: where does Europe go?
Clin J Am Soc Nephrol 3: 616-623, 2008.

This review discusses various screening approaches for chronic kidney disease that are used in Europe. The criterion for defining chronic kidney disease in the various programs differs but is frequently limited to estimated glomerular filtration rate, thus offering only data on chronic kidney disease stages 3 and higher; however, screening should not be limited to measuring only estimated glomerular filtration rate but should also include a measure of microalbuminuria, because this will offer identification of chronic kidney disease stages 1 and 2. Defining these earlier stages is of importance because the risk for developing end-stage renal disease that is associated with stages 1 and 2 is nearly equal to the risk that is associated with stage 3. Moreover, the risk for cardiovascular events in stages 1 and 2 is equal to that in stage 3. Various reports argue that costs of screening programs in general practitioner or outpatient offices are high and that they are cost-effective only for preventing end-stage renal disease when they are limited to target groups, such as patients with diabetes or hypertension and elderly. The benefits of screening programs, however, should not be evaluated only with respect to the prevention of renal events but should also include the benefits of preventing cardiovascular events. The use of preselection based on either an

impaired estimated glomerular filtration rate or on protein-dipstick positivity or elevated albuminuria in a morning urine void has been found effective in various European countries as an alternative for targeted screening.

Presentation:

Long-term effectiveness and cost-effectiveness of screening for hepatitis C virus infection

Uwe Siebert

-Sroczynski G, Esteban E, Conrads-Frank A, Schwarzer R, Muhlberger N, Wright D, Zeuzem S, and Siebert U.

Long-term effectiveness and cost-effectiveness of screening for hepatitis C virus infection.

Eur J Public Health 19: 245-253, 2009.

BACKGROUND: Hepatitis C virus (HCV) infection is an emerging problem in public health. In most countries, the majority of HCV infected people are yet undiagnosed. Early detection and treatment may result in better health outcomes and save costs by preventing future advanced liver disease. The evidence for long-term effectiveness and cost-effectiveness of HCV screening was systematically reviewed. **METHODS:** We performed a systematic literature search on long-term health-economic effects of HCV screening and included Health Technology Assessment (HTA) reports, systematic reviews, long-term clinical trials, full health economic and decision-analytic modelling studies with a sufficiently long time horizon and patient-relevant long-term outcomes such as life-years gained (LYG) or quality-adjusted life years (QALY) gained. Economic results were converted to 2005 Euros. **RESULTS:** Seven studies were included. Target population, HCV prevalence, study perspective, discount rate, screening and antiviral treatment mode varied. The incremental effectiveness of HCV screening and early treatment compared to no screening and standard care varied from 0.0004 to 0.066 LYG, and from 0.0001 to 0.072 QALY. Incremental cost-effectiveness and cost-utility ratios of HCV screening vs. no screening were 3900-243,700 euro/LYG and 18,300-1,151,000 euro/QALY. HCV screening seems to be cost-effective in populations with high HCV prevalence, but not in low HCV prevalence populations. **CONCLUSIONS:** HCV screening and early treatment have the potential to improve average life-expectancy, but should focus on populations with elevated HCV prevalence to be cost-effective. Further research on the long-term health-economic impact of HCV screening when combined with appropriate monitoring strategies in different European health care systems is needed.

Siebert U, and Sroczynski G.

Effectiveness and cost-effectiveness of initial combination therapy with interferon/peginterferon plus ribavirin in patients with chronic hepatitis C in Germany: a health technology assessment commissioned by the German Federal Ministry of Health and Social Security.

Int J Technol Assess Health Care 21: 55-65, 2005.

OBJECTIVES: The purpose of this health technology assessment (HTA), commissioned by the German Federal Ministry of Health and Social Security, was to systematically review the evidence for the effectiveness and cost-effectiveness of antiviral treatment (AVT) with interferon (INF) or peginterferon (PegIFN) in combination with ribavirin (RBV) in treatment-naive patients with chronic hepatitis C (CHC) and to apply these data in the context

of the German health-care system. **METHODS:** We performed a systematic literature search on effectiveness and cost-effectiveness of AVT and summarized results using meta-analysis and evidence tables. We applied the German Hepatitis C Model (GEHMO), a decision-analytic Markov model, to determine long-term clinical effectiveness, costs, and incremental cost-effectiveness ratios (ICER) of the examined treatment strategies. Model parameters were derived from German databases, published international randomized clinical trials (RCT), and a Cochrane Review. **RESULTS:** Overall, nine RCTs, two HTA reports, one Cochrane review, two meta-analyses, and seven economic evaluations met the inclusion criteria. These studies indicate that PegIFN + RBV achieved the highest sustained virological response rates (SVR) (54-61 percent), followed by IFN + RBV (38-54 percent) and IFN monotherapy (11-21 percent). Based on our meta-analysis, PegIFN + RBV reduced cases without SVR by 17 percent compared with INF + RBV. International cost-effectiveness studies indicate that INF+ RBV is cost-effective when compared with INF monotherapy. For PegIFN + RBV, our decision analysis yielded an ICER of 9,800 Euros per quality-adjusted life-year gained. **CONCLUSIONS:** This HTA suggests that initial combination therapy prolongs life, improves quality of life, and is cost-effective in

SESSION 4 ONGOING ACTIVITIES TO RAISE AWARENESS AND GATHER INFORMATION ABOUT CHRONIC VIRAL HEPATITIS AND ORGANIZATIONS' VISION ON SCREENING

Presentation:

IOM (institute of Medicine)

Brian Mc Mahon

[Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C](#) Released: January 11, 2010

This IOM report concludes that the current approach to the prevention and control of chronic hepatitis B and hepatitis C is not working and that new actions must be taken to reduce illnesses and deaths related to these preventable diseases.

<http://www.iom.edu/Reports.aspx>

Mitchell AE, Colvin HM, and Palmer Beasley R.

Institute of Medicine recommendations for the prevention and control of hepatitis B and C.

Hepatology 51: 729-733.

Despite federal, state, and local public health efforts to prevent and control hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, these diseases remain serious health problems in the United States. About 1%-2% of the U.S. population has chronic HBV or HCV infections, and each year about

15,000 people die from liver cancer or liver disease related to these preventable infections. The Institute of Medicine formed an expert committee to determine ways to reduce new HBV and HCV infections and the morbidity and mortality related to chronic viral hepatitis and released its findings in a report. The major factor found to impede current efforts to prevent and control HBV and HCV is lack of knowledge and awareness about these diseases among healthcare and social-service providers, members of the public, and policy makers. Because the extent and seriousness of this public health problem is not appreciated, inadequate resources are being allocated to prevention, control, and surveillance programs. This situation has led to continued transmission of HBV and HCV and inadequate identification of and medical management for chronically infected people. Conclusion: To address the situation, the Institute of Medicine report makes recommendations in four areas: improved surveillance for HBV and HCV; improved knowledge and awareness among healthcare and social-service providers and the public, especially at-risk people; improved HBV vaccine coverage; and improved viral hepatitis services and access to those services. HEPATOLOGY, 2010.

SESSION 5 MANAGEMENT OF IDENTIFIED PERSONS WITH CHRONIC VIRAL HEPATITIS

Presentation:

Need for long term evaluation of therapy

Solko Schalm

Toy M, Veldhuijzen IK, de Man RA, Richardus JH, and Schalm SW.

Potential impact of long-term nucleoside therapy on the mortality and morbidity of active chronic hepatitis B.

Hepatology 50: 743-751, 2009.

The potential impact of long-term antiviral therapy on the burden of chronic hepatitis B has hardly been documented. The aim of this study was to estimate the effects of prolonged antiviral therapy and antiviral resistance on the mortality and morbidity of active chronic hepatitis B patients. A population cohort of chronic hepatitis B patients in the Netherlands was constructed and stratified according to 10-year age groups, prevalence of hepatitis B surface antigen, hepatitis B virus DNA level, alanine aminotransferase level, hepatitis B e antigen status, and presence of cirrhosis. A Markov model was created to mathematically simulate the cohort's progression through a finite series of health states. The analysis was performed on the basis of four scenarios: natural history, long-term therapy with a high-resistance profile drug without or with salvage, and therapy with a low-resistance profile drug. It has been estimated that there were 64,000 people (0.4%) suffering from chronic hepatitis B infection in the Netherlands in 2005, with 6521 (10%) of them having high viremia and elevated alanine aminotransferase levels. Within a 20-year period, 1725 (26%) of the 6521 patients in the active chronic hepatitis B cohort will die because of liver-related causes. Of the 5685 without cirrhosis at entry, 1671 (29%) will develop cirrhosis. Of those 836 with cirrhosis at entry, 619 (74%) will die within a 20-year period. If this active chronic hepatitis B cohort is fully detected and treated, mortality related to liver disease can be reduced by 80% if a low-resistance profile drug is chosen from the start. The

effect is due to both the reduction in complications of cirrhosis and the prevention of the development of cirrhosis. Conclusion: Long-term antiviral therapy with a strategy that minimizes or controls resistance will have a major preventive effect on liver-related mortality and morbidity.

Presentation:

Economic evaluation of treatment of chronic hepatitis B and hepatitis C

John Wong

Rajendra A, and Wong JB.

Economics of chronic hepatitis B and hepatitis C.

J Hepatol 47: 608-617, 2007.

Although not all patients develop progressive liver disease, chronic hepatitis B and chronic hepatitis C infections cause substantial morbidity and mortality worldwide. To address this need, many new antiviral treatments have become available over the past 10 years. While safety, efficacy, and therapeutic indications have been well established for these agents, the economics of antiviral treatment have become increasingly a focus of discussion for physicians, policymakers, and health payers. In this paper, we will elucidate some economic principles using examples from the treatment of hepatitis B and C. In particular, we will examine the considerations in estimating drug costs, methods for performing economic analyses and lastly summarize published cost-effectiveness analyses for antiviral treatments of chronic hepatitis B and chronic hepatitis C. This review should help clinicians understand economic issues regarding new drugs and answer questions about whether the clinical benefit provided by a medication justifies its expense.

Session 5 Country sessions

Presentation:

Migrant screening

Manuel Carballo – replaced by Rowan Cody

ECDC Technical report

Migrant health series: Background note to the ECDC Report on migration and infectious diseases in the EU

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4. Bibliography of the Speakers

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Anne Andermann

Woodrow Wilson School of Public and International Affairs, Princeton University, USA

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Caroline Semaille -Safar (10/14)

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Paul E de jong (11/40)

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Heiner Wedemeyer (extra search in pubmed: 'Full name' AND 'hepatitis', only English papers were selected) (10/74)

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Angelos Hadzakis (extra search in pubmed: 'Full name' AND 'hepatitis', only English papers were selected) (10/15)

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John Wong (extra search in pubmed: 'Full name' AND 'hepatitis') (10/27)
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Manuel Carballo (extra search in pubmed: 'Full name' AND 'migrants')
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Replaced by **Rowan Cody**

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William Irving (10/18)

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Irene Veldhuijzen (10/34)

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