A NEW ERA FOR SCREENING AND TREATMENT OF HEPATITIS C: A PUBLIC HEALTH CHALLENGE.

Viral Hepatitis Prevention Board Meeting
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This pre-meeting document contains 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.

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Pubmed MEDLINE search on \{Healthcare workers OR HCW) AND (vaccine* OR Immuni*)\} in all fields and published from 2007 on, was performed. In End-note the relevant references were selected and classified in the different meeting subjects.

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List of publications achieved via speakers form when this form was not available a Pubmed MEDLINE search was performed on Name of the speaker in [Author] and [hepatitis*]. If more than 10 references only the most recent articles are shown.
1. Meeting subjects

Session 2: Hepatitis C situation

*Presentation Erika Duffel – Presentation on epidemiology of hepatitis C in Europe - incidence, risk population, prevalence, disease burden (cirrhosis, HCC) and mortality*

ECDC Hepatitis B and C surveillance in Europe 2006-2011. Document available on

Summary

This is the first report from the European Centre for Disease Prevention and Control (ECDC) on the enhanced surveillance of hepatitis B and C viral infections. It aims to describe basic trends and epidemiological features of both diseases across countries in the European Union and European Economic Area (EU/EEA) for the years 2006 to 2011. Enhanced surveillance of hepatitis B and C in Europe provides important information to help monitor the distribution of the diseases and to evaluate the public health response to control the transmission of infections.

Data were collected on a range of demographic and specific epidemiological variables for both infections. Data completeness varied considerably across variables and countries, and a small proportion of countries were not able to provide data as defined by the new EU 2012 case definitions1. Nevertheless, this first data collection is an important step towards the harmonisation of hepatitis B and C surveillance across countries to enable a better understanding of the distribution of these infections across Europe.

In 2011, 17,025 cases of hepatitis B were reported from 28 EU/EEA Member States; 2,812 (16.5%) of these cases were reported as acute, 11,557 (67.9%) of cases were chronic and 2,312 (13.6%) were classified as ‘unknown’. Rates in acute cases declined over time which is likely to be related to vaccination programmes. Rates of chronic infection varied widely between countries and aside from differences in surveillance systems they are most likely attributed to different levels of screening and diagnostic testing.

Hepatitis B was more often reported in men than women, with an overall rate of 4.1 cases per 100,000 for men and 2.7 for women. The most affected age group were those between 25 and 34 years old, accounting for 32.9% of cases, followed by those younger than 25 years (16.7%).

For hepatitis B, there was a striking difference between reported modes of transmission by disease status. For acute infection, heterosexual transmission and nosocomial transmission were the most commonly reported routes of transmission. For chronic infections, mother-to-child transmission was the most common reported transmission route, most likely due to a high proportion of ‘imported’ cases.

In terms of absolute numbers, hepatitis C represents a greater disease burden than hepatitis B.

In 2011, 29,896 cases of hepatitis C were reported from 26 EU/EEA Member States, representing an overall notification rate of 7.8 cases per 100,000 population. Of these cases, 398 cases (1.3%) were reported as ‘acute’, 2,913 (9.7%) as ‘chronic’ and 24,337 (81.4%) as ‘unknown’. Although some countries only report acute viral hepatitis C cases, the majority of reported cases were classified as chronic or ‘unknown’. In countries able to report all viral hepatitis C cases, it is likely that most of these ‘unknown’ cases are chronic cases as acute hepatitis C is difficult to diagnose clinically or serologically. There was marked variation between countries in the reported cases of acute, chronic or ‘unknown’ hepatitis C. This variation is related to several factors including differences in surveillance systems as well as variations in national screening and testing practices across countries.

The most affected age group for the reported hepatitis C cases were those between 25 and 34 years old which account for 28.2% of the total number of cases in 2011. There were more male cases reported than female cases resulting in a male-to-female rate ratio of 2:1. Injecting drug use was the most commonly reported route of transmission.

The enhanced surveillance of hepatitis B and C across Europe has highlighted the significant burden of these infections as well as considerable differences in the epidemiology of these infections. The comparability of data across countries is impaired by differences in surveillance systems. Improvements in the quality and completeness of the data over time will further improve the usefulness of the data.

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Other recent publications on Hepatitis C available on the ECDC website

**Surveillance and prevention of hepatitis B and C in Europe**

**Hepatitis B and C in the EU neighbourhood: prevalence, burden of disease and screening policies**

**Annual Epidemiological Report 2012**

Anti-HCV prevalence among pregnant women


### Hepatitis C

<table>
<thead>
<tr>
<th>Reported Acute (New) Cases of Hepatitis C Virus (HCV)</th>
<th>Estimated Actual New Cases of HCV (range) in 2011*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 2006 2007 2008 2009 2010 2011</td>
<td>2011 (estimated)*</td>
</tr>
<tr>
<td>694  802  849  878  781  853  1,229</td>
<td>16,500 (7,200- 43,400)</td>
</tr>
</tbody>
</table>

* Actual acute cases estimated to be 13.4 times the number of reported cases in any year

<table>
<thead>
<tr>
<th>Est. No. of Chronic Cases In the United States</th>
<th>No. of Death Certificates listing HCV as a Cause of Death, 2010*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.7- 3.9 million</td>
<td>16,627†</td>
</tr>
</tbody>
</table>

* Underlying or contributing cause of death in most recent year available (2010)  
†Current information indicates these represent a fraction of deaths attributable in whole or in part to chronic hepatitis C
Surveillance for Viral Hepatitis – United States, 2011 available from CDC website


Summary hepatitis C:

**Hepatitis C**

HCV is transmitted primarily through percutaneous (parenteral) exposure that can result from injection-drug use, needle-stick injuries, and inadequate infection control in health-care settings. Much less often, HCV transmission occurs among HIV-positive persons, especially MSM, as a result of sexual contact with an HCV-infected partner (27, 28), among persons who received non-professionally applied tattoos (28) and among infants born to HCV-infected mothers (29). With an estimated 3.2 million chronically infected persons nationwide, HCV infection is the most common blood-borne infection in the United States (15).

Currently a single positive anti-HCV result cannot distinguish between acute and chronic (past or present) HCV infection, and making this distinction requires a health department to follow-up with a provider to determine if there were symptoms. Laboratory criteria in the 2011 case definition for past or present HCV infection require one or more of the following: anti-HCV positive (repeatedly reactive) by EIA, verified by at least one more specific assay, or HCV RIBA positive, or HCV nucleic acid test (NAT) positive, or anti-HCV screening-test positive with an assay-specific signal-to-cutoff ratio predictive of a true. No clinical symptoms are required; however, the case must be known to not be an acute case. Approximately 75%-85% of newly infected persons develop chronic infection (30).

Because of the high burden of chronic HCV infection in the United States and because no vaccine is available for preventing infection, national recommendations (31) emphasize other primary prevention activities, including screening and testing blood donors, inactivating HCV in plasma-derived products, testing persons at risk for HCV infection and providing them with risk-reduction counseling, and consistently implementing and practicing infection control in health-care settings. In 2010, the FDA approved point-of-care tests for HCV infection, which meant that patients could receive HCV test results within the same visit and faster referral to care (32). In 2012, CDC augmented existing risk-based recommendations for HCV testing by recommending one-time screening for HCV infection among all those born during 1945-1965 (33). It is estimated that persons born during these years have a 3% prevalence of HCV antibodies, which is five times higher than the prevalence seen in adults born in other years. Of all persons living with HCV infection, about 75% were born during 1945-1965; a similar percentage of HCV-associated deaths can be attributed to this birth cohort (33). The goal of the new birth-cohort approach to HCV testing is to identify unrecognized infections among the segment of the population with the largest risk of HCV associated morbidity and mortality, thereby increasing opportunities for persons infected with HCV to benefit from appropriate care and treatment. Implementation of the birth cohort screening recommendation and point of care testing for HCV infection will facilitate testing, notification of results, post-test counseling and referral to care.
Linkage to care and treatment is critical to improving health outcomes for persons found to be infected with HCV. Such linkage is particularly important in light of the major advancements that have been made in HCV treatments. For patients infected with HCV, treatment has previously consisted of pegylated interferon combined with oral doses of ribavirin, a regimen that has improved health outcomes for many infected persons. Approximately 40% of HCV-infected patients receiving this therapy clear their infection. New direct acting agents against HCV (telaprevir, boceprevir) were licensed by the FDA in 2011 and are now standard-of-care. These agents, when given in combination with current therapy, can increase virologic cure rates to 80% while decreasing duration of therapy (34). Several drugs are now administered orally (a major advancement in how treatments are administered for this infection), leading to viral suppression in 90% of patients taking one of these new oral medications (35, 36).


BACKGROUND: The increasing health burden and mortality from hepatitis B virus (HBV) and hepatitis C virus (HCV) in the United States are underappreciated.

OBJECTIVE: To examine mortality from HBV; HCV; and, for comparison, HIV.


MEASUREMENTS: Age-adjusted mortality rates from HBV, HCV, and HIV. Logistic regression analyses of 2007 data generated 4 independent models per
outcome (HCV- or HBV-related deaths) that each included 1 of 4 comorbid conditions and all sociodemographic characteristics. RESULTS: Between 1999 and 2007, recorded deaths from HCV [corrected] increased significantly to 15,106, whereas deaths from HIV declined to 12,734 by 2007. Factors associated with HCV-related deaths included chronic liver disease, HBV co-infection, alcohol-related conditions, minority status, and HIV co-infection. Factors that increased odds of HBV-related death included chronic liver disease, HCV co-infection, Asian or Pacific Islander descent, HIV co-infection, and alcohol-related conditions. Most deaths from HBV and HCV occurred in middle-aged persons. LIMITATION: A person other than the primary physician of the decedent frequently completed the death certificate, and HCV and HBV often were not detected and thus not reported as causes of death. CONCLUSION: By 2007, HCV had superseded HIV as a cause of death in the United States, and deaths from HCV and HBV disproportionately occurred in middle-aged persons. To achieve decreases in mortality similar to those seen with HIV requires new policy initiatives to detect patients with chronic hepatitis and link them to care and treatment. PRIMARY FUNDING SOURCE: Centers for Disease Control and Prevention.


Hepatitis C virus (HCV) is the most common blood-borne infection in the United States. HCV infection is a leading cause of chronic liver disease, end-stage liver disease, and liver transplantation. Newly available therapies can clear HCV in most infected persons who receive treatment. However, many persons living with HCV infection are unaware of their infection status, including those born during 1945-1965 (a population at increased risk for chronic hepatitis C in the United States). This review highlights the epidemiology of hepatitis C and the importance of HCV testing and linkage to care in an era of more effective antiviral therapies.


Society faces an immense burden of hepatitis C virus (HCV) infection-related morbidity and mortality. Transmission of HCV is ongoing, and the incidence of HCV infection has been increasing in recent years. New therapies for treating HCV infection hold considerable promise for increasing cure rates and thus reducing HCV transmission. However, many persons with HCV infection in the United States are unaware of their infection status. The Centers for Disease Control and Prevention (CDC) recently expanded its HCV testing recommendations to include 1-time HCV testing for individuals born between 1945 and 1965, a population with a 3% prevalence of infection. Linkage to care and treatment for those identified with infection through testing would have a profound impact in reducing HCV disease burden. Coordinated efforts by public health agencies, clinical care providers, laboratories, and payers are necessary to improve primary and secondary prevention of HCV disease. This article summarizes a presentation by John W. Ward, MD, at the IAS-USA live continuing medical education program held in Atlanta, Georgia, in October 2012.
In total 24 were selected:


An important proportion of hepatitis C virus patients in Europe are unaware of their condition with substantial discrepancies between European countries in terms of hepatitis C virus screening. Factors contributing to low screening rates likely include limited physician awareness, reluctance of patients to admit to unsafe past behaviours, and lack of efficient public health policy for HVC screening. It becomes urgent to define innovative public health policy to improve hepatitis C virus screening that is the only choice allowing non-tested hepatitis C virus patients access to therapy as hepatitis C virus patients remain undiagnosed until they develop advanced liver disease. European health authorities should encourage innovative approaches to increase the proportion of hepatitis C virus persons aware of their condition, such as those proposed recently by the Centers for Disease Control and Prevention. Antiviral treatment will impact on hepatitis C virus-related morbidity and mortality with marked differences between European countries. In genotype 1 patients, protease inhibitors-based triple therapy would considerably impact the hepatitis C virus-related incidence of cirrhosis and deaths. There is an urgent need for the reinforcement of hepatitis C virus screening and access to therapy when considering their major impact on hepatitis C virus-related morbidity and mortality. In Europe, although clinicians from different countries are using the same therapies, impact on morbidity and mortality across countries will significantly vary.


To survey the burden of liver disease in Europe and its causes 260 epidemiological studies published in the last five years were reviewed. The incidence and prevalence of cirrhosis and primary liver cancer are key to understand the burden of liver disease. They represent the end-stage of liver pathology and thus are indicative of the associated mortality. About 0.1% of Hungarian males will die of cirrhosis every year compared with 0.001% of Greek females. WHO estimate that liver cancer is responsible for around 47,000 deaths per year in the EU. Harmful alcohol consumption, viral hepatitis B and C and metabolic syndrome related to overweight and obesity are the leading causes of cirrhosis and primary liver cancer in Europe. Chronic hepatitis B affects 0.5-0.7% of the European population. In the last decade the prevalence of chronic hepatitis C was 0.13-3.26%. It is of great concern that about 90% of people in Europe infected by viral hepatitis are unaware of their status. Available data suggest the prevalence rate of NAFLD is 2-44% in the general European population (including obese children) and 42.6-69.5% in people with type 2 diabetes. Each of these four major causes of liver disease is amenable to prevention and treatment, reducing the burden of liver disease in Europe and saving lives. Further surveys are urgently needed to implement cost-effective prevention programmes and novel treatments to tackle this problem.

Hepatocellular carcinoma (HCC) is increasing in incidence and has a very high fatality rate. Cirrhosis due to chronic hepatitis B or hepatitis C is the leading risk factor for HCC. Global epidemiology of HCC is determined by the prevalence of dominant viral hepatitis and the age it is acquired in the underlying population. Upcoming risk factors include obesity, diabetes, and related nonalcoholic fatty liver disease. This review discusses the latest trends of HCC globally and in the United States. It also provides an evidence-based commentary on the risk factors and lists some of the preventive measures to reduce the incidence of HCC.


We are entering an important new chapter in the story of hepatitis C virus (HCV) infection. There are clear challenges and opportunities. On the one hand, new HCV infections are still occurring, and an estimated 185 million people are or have previously been infected worldwide. Most HCV-infected persons are unaware of their status yet are at risk for life-threatening diseases such as cirrhosis and hepatocellular carcinoma (HCC), whose incidences are predicted to rise in the coming decade. On the other hand, new HCV infections can be prevented, and those that have already occurred can be detected and treated--viral eradication is even possible. How the story ends will largely be determined by the extent to which these rapidly advancing opportunities overcome the growing challenges and by the vigor of the public health response.


BACKGROUND: The Chronic Hepatitis Cohort Study (CHeCS), a dynamic prospective, longitudinal, observational cohort study, was created to assess the clinical impact of chronic viral hepatitis in the United States. This report describes the cohort selection process, baseline demographics, and insurance, biopsy, hospitalization, and mortality rates. METHODS: Electronic health records of >1.6 million adult patients seen from January 2006 through December 2010 at 4 integrated healthcare systems in Detroit, Michigan; Danville, Pennsylvania; Portland, Oregon; and Honolulu, Hawaii were collected and analyzed. RESULTS: Of 2202 patients with chronic hepatitis B virus (HBV) infection, 50% were aged 44-63 years, 57% male, 58% Asian/Pacific Islander, and 13% black; and 5.1% had Medicaid, 16.5% Medicare, and 76.3% private insurance. During 2001-2010, 22.3% had a liver biopsy and 37.9% were hospitalized. For the 8810 patients with chronic hepatitis C virus (HCV) infection, 75% were aged 44-63 years, 60% male, 23% black; and 12% had Medicaid, 23% Medicare, and 62% private insurance. During 2001-2010, 38.4% had a liver biopsy and 44.3% were hospitalized. Among persons in care, 9% of persons with HBV and 14% of persons with HCV infection, mainly those born during 1945-1964, died during the 2006-2010 five-year period. CONCLUSIONS: Baseline demographic, hospitalization, and mortality data from CHeCS highlight the substantial US health burden from chronic viral hepatitis, particularly among persons born during 1945-1964.

Ward, J. W. "The hidden epidemic of hepatitis C virus infection in the United States:
Society faces an immense burden of hepatitis C virus (HCV) infection-related morbidity and mortality. Transmission of HCV is ongoing, and the incidence of HCV infection has been increasing in recent years. New therapies for treating HCV infection hold considerable promise for increasing cure rates and thus reducing HCV transmission. However, many persons with HCV infection in the United States are unaware of their infection status. The Centers for Disease Control and Prevention (CDC) recently expanded its HCV testing recommendations to include 1-time HCV testing for individuals born between 1945 and 1965, a population with a 3% prevalence of infection. Linkage to care and treatment for those identified with infection through testing would have a profound impact in reducing HCV disease burden. Coordinated efforts by public health agencies, clinical care providers, laboratories, and payers are necessary to improve primary and secondary prevention of HCV disease. This article summarizes a presentation by John W. Ward, MD, at the IAS-USA live continuing medical education program held in Atlanta, Georgia, in October 2012.

Worldwide eradication of hepatitis C virus (HCV) is possible through a combination of prevention education, universal clinical and targeted community screening, effective linkage to care and treatment with promising new direct-acting antiviral drug regimens. Universal screening should be offered in all healthcare visits, and parallel community screening efforts should prioritize high-prevalence, high-transmission populations including injection drug users, prison inmates and those with HIV/HCV co-infection. Increasing awareness of HCV infection through screening, improving treatment uptake and cure rates by providing linkage to care and more effective treatment, and ultimately combining education efforts with vaccination campaigns to prevent transmission and reinfection can slow and eventually stop the 'silent epidemic'.

HCV infection is a major public health problem worldwide. Several studies reported that HCV infection might cluster in families or households. Horizontal intrafamilial transmission of the virus has been demonstrated previously. Whether horizontal transmission makes any significant contribution to the global burden of HCV infection is still controversial and data about epidemiology and routes of transmission are uncertain. The certain diagnosis of horizontal intrafamilial transmission of HCV is based on the simultaneous presence of specific laboratory criteria, the temporal association between intrafamilial exposure and infection and the exclusion of all the potential extrafamilial routes of transmission of the infection. This review summarizes the current knowledge of epidemiology, risk factors and molecular biology of horizontal intrafamilial transmission of HCV infection.

In efforts to inform public health decision makers, the Global Burden of Diseases, Injuries, and Risk Factors 2010 (GBD2010) Study aims to estimate the burden of disease using available parameters. This study was conducted to collect and analyze
available prevalence data to be used for estimating the hepatitis C virus (HCV) burden of disease. In this systematic review, antibody to HCV (anti-HCV) seroprevalence data from 232 articles were pooled to estimate age-specific seroprevalence curves in 1990 and 2005, and to produce age-standardized prevalence estimates for each of 21 GBD regions using a model-based meta-analysis. This review finds that globally the prevalence and number of people with anti-HCV has increased from 2.3% (95% uncertainty interval [UI]: 2.1%-2.5%) to 2.8% (95% UI: 2.6%-3.1%) and >122 million to >185 million between 1990 and 2005. Central and East Asia and North Africa/Middle East are estimated to have high prevalence (>3.5%); South and Southeast Asia, sub-Saharan Africa, Andean, Central, and Southern Latin America, Caribbean, Oceania, Australasia, and Central, Eastern, and Western Europe have moderate prevalence (1.5%-3.5%); whereas Asia Pacific, Tropical Latin America, and North America have low prevalence (<1.5%).

Conclusion: The high prevalence of global HCV infection necessitates renewed efforts in primary prevention, including vaccine development, as well as new approaches to secondary and tertiary prevention to reduce the burden of chronic liver disease and to improve survival for those who already have evidence of liver disease.


The only hope for a cure from hepatocellular carcinoma (HCC) rests on early diagnosis as it can be attained through semiannual surveillance with abdominal ultrasound (US) of patients at risk. While the strategy of semiannual screening rests on the growth rate of the tumor that in cirrhotic patients takes 6 months to double its volume, on average, the noninvasive radiological diagnosis of HCC is possible in cirrhotic patients with a de novo HCC and patients with chronic hepatitis B. More recently, metabolic diseases related to insulin resistance, including diabetes and obesity, have been recognized to be causally related to HCC as well, in most patients bridging HCC to the histopathological diagnosis of non-alcoholic steatohepatitis (NASH). While the endpoint of an early diagnosis is achieved quite easily in most patients with >1 cm HCC by computed tomography (CT) or magnetic resonance imaging (MRI) demonstrating the specific pattern of an intense contrast uptake during the arterial phase (wash-in) and contrast wash-out during the venous/delayed phase, nodules <1 cm in size are more difficult to diagnose, almost invariably requiring an enhanced follow up with three monthly examinations with US until they grow in size or change their echo pattern. Owing to the lack of robust controlled evidence demonstrating a clinical benefit of surveillance, the real support for screening for liver cancer comes from the striking differences in response to therapy between screened populations in whom HCC is diagnosed and treated at early stages and patients with more advanced, incidentally detected tumors. This notwithstanding, numerous barriers work against screening effectiveness, including limited or outdated knowledge, lack of financial incentives, and limited access to appropriate testing and treatment. Though strengthening prediction in individual patients is expected to improve the cost-effectiveness ratio of screening, the benefits of approaches like pretreatment patient stratification by clinical, histologic, and genetic scores remain uncertain, while the worthiness of excluding patients with severe comorbidities and aged individuals is still debated.


Hepatitis C virus (HCV), first recognized as a cause of transfusion-associated acute
and chronic hepatitis in 1989, plays a major role as a cause of chronic liver injury, with potential for neoplastic degeneration. It is mainly transmitted by the parenteral route. However, although with lower efficiency, it may be also transmitted by sexual intercourses and by the mother-to-child route. Epidemiological evidence shows that a wave of infection occurred in the 1945-65 period (baby boomers) in western countries. After acute infection, as many as 50-85% of the patients fail to clear the virus resulting in chronic liver infection and/or disease. It is estimated that, on a global scale, about 170 million people are chronically infected with HCV, leading to about 350,000 deaths yearly. Among western countries southern Europe, and particularly Italy, is among the most affected areas. The impact on the public health systems is noteworthy, with high number of hospitalizations due to chronic liver disease, cirrhosis or hepatocellular carcinoma. While waiting for a safe and effective vaccine to be made available, new promising direct-acting antiviral (DAA) drugs offer a better therapeutic scenario than in the past even for the poor responder genotypes 1 and 4, provided that effective screening and care is offered. However, the long and aspecific prodromic period before clinical symptoms develop is a major obstacle to early detection and treatment. Effective screening strategies may target at-risk groups or age specific groups, as recently recommended by the CDC.


The global risk of hepatocellular carcinoma (HCC) has been largely driven by hepatitis B virus (HBV) infection for the past century, along with hepatitis C virus (HCV), aflatoxin, excessive alcohol consumption, and obesity/diabetes. The dominant effect of HBV on global HCC risk should decline as the population vaccinated against HBV grows older. Infection with HCV is also expected to decline. Projections of HCV-related HCC rates remaining high for another 30 years may be overly pessimistic. Alcohol may be less of a factor in HCC in coming years. However, obesity and diabetes may become even more important risk factors for HCC.


BACKGROUND AND AIM: Decisions on public health issues are dependent on reliable epidemiological data. A comprehensive review of the literature was used to gather country-specific data on risk factors, prevalence, number of diagnosed individuals and genotype distribution of the hepatitis C virus (HCV) infection in selected European countries, Canada and Israel. METHODOLOGY: Data references were identified through indexed journals and non-indexed sources. In this work, 13,000 articles were reviewed and 860 were selected based on their relevance. RESULTS: Differences in prevalence were explained by local and regional variances in transmission routes or different public health measures. The lowest HCV prevalence (</= 0.5%) estimates were from northern European countries and the highest (>/= 3%) were from Romania and rural areas in Greece, Italy and Russia. The main risk for HCV transmission in countries with well-established HCV screening programmes and lower HCV prevalence was injection drug use, which was associated with younger age at the time of infection and a higher infection rate among males. In other regions, contaminated glass syringes and nosocomial infections continue to play an important role in new infections. Immigration from endemic countries was another factor impacting the total number of infections and the genotype distribution. Approximately 70% of cases in Israel, 37% in Germany and 33% in Switzerland were not born in the country. In summary, HCV epidemiology shows a high variability
across Europe, Canada and Israel. CONCLUSION: Despite the eradication of
transmission by blood products, HCV infection continues to be one of the leading
blood-borne infections in the region.

Sievert, W., I. Altraif, H. A. Razavi, A. Abdo, E. A. Ahmed, A. Alomair, D. Amarpurkar, C.
BACKGROUND: The hepatitis C pandemic has been systematically studied and
characterized in North America and Europe, but this important public health problem
has not received equivalent attention in other regions. AIM: The objective of this
systematic review was to characterize hepatitis C virus (HCV) epidemiology in
selected countries of Asia, Australia and Egypt, i.e. in a geographical area inhabited
by over 40% of the global population. METHODOLOGY: Data references were
identified through indexed journals and non-indexed sources. In this work, 7770
articles were reviewed and 690 were selected based on their relevance. RESULTS:
We estimated that 49.3-64.0 million adults in Asia, Australia and Egypt are anti-HCV
positive. China alone has more HCV infections than all of Europe or the Americas.
While most countries had prevalence rates from 1 to 2% we documented several with
relatively high prevalence rates, including Egypt (15%), Pakistan (4.7%) and Taiwan
(4.4%). Nosocomial infection, blood transfusion (before screening) and injection drug
use were identified as common risk factors in the region. Genotype 1 was common in
Australia, China, Taiwan and other countries in North Asia, while genotype 6 was
found in Vietnam and other Southeast Asian countries. In India and Pakistan
genotype 3 was predominant, while genotype 4 was found in Middle Eastern
countries such as Egypt, Saudi Arabia and Syria. CONCLUSION: We recommend
implementation of surveillance systems to guide effective public health policy that
may lead to the eventual curtailment of the spread of this pandemic infection.


More than 20 years after the discovery of the hepatitis C virus (HCV), it is now well
established that HCV is of global importance affecting all countries, leading to a
major global health problem that requires widespread active interventions for its
prevention and control. Chronic hepatitis C was linked to the development of
cirrhosis and hepatocellular carcinoma in many areas of the world. Current
epidemiological assessments have identified complex patterns with highly variable
local prevalence rates between countries and within countries. HCV infection patterns
have not significantly changed in most parts of the world since 1997, when first
analyzed, partly due to the lack of new and more accurate data. The assessment of the
national HCV prevalence and transmission modes should be completed to enable
national authorities to prioritize preventive measures and to make the most
appropriate use of available resources. The 'patchy' epidemiological situation in some
areas will continue to complicate the task of the establishment of global, regional and
national base line data. The present assessment finds a global prevalence of 2.35%,
affecting 160 million chronically infected individuals. There is an urgent need for
more accurate Information on the costs and burden of HCV to society. Twenty-one
year after the discovery of HCV, the assessment is far from being complete and little
progress has been made in the past 10 years in many countries. In some countries
significant increases have been reported and this may also apply to countries were
insufficient data exist. A safe and efficient vaccine against HCV is urgently needed.


BACKGROUND: Injecting drug use is an important risk factor for transmission of viral hepatitis, but detailed, transparent estimates of the scale of the issue do not exist. We estimated national, regional, and global prevalence and population size for hepatitis C virus (HCV) and hepatitis B virus (HBV) in injecting drug users (IDUs).

METHODS: We systematically searched for data for HBV and HCV in IDUs in peer-reviewed databases (Medline, Embase, and PsycINFO), grey literature, conference abstracts, and online resources, and made a widely distributed call for additional data. From 4386 peer-reviewed and 1019 grey literature sources, we reviewed 1125 sources in full. We extracted studies into a customised database and graded them according to their methods. We included serological reports of HCV antibodies (anti-HCV), HBV antibodies (anti-HBc), or HBV surface antigen (HBsAg) in studies of IDUs with more than 40 participants (<100% HIV-positive) and sampling frames that did not exclude participants on the basis of age or sex. With endorsed decision rules, we calculated prevalence estimates with anti-HCV and anti-HBc as proxies for exposure and HBsAg as proxy for current infection. We combined these estimates with IDU population sizes to calculate the number of IDUs with positive HBV or HCV statuses.

FINDINGS: We located eligible reports with data for prevalence of anti-HCV in IDUs for 77 countries; midpoint prevalence estimates suggested 60-80% of IDUs had anti-HCV in 25 countries and more than 80% of IDUs did so in 12 countries. About 10.0 million (range 6.0-15.2) IDUs worldwide might be anti-HCV positive. China (1.6 million), USA (1.5 million), and Russia (1.3 million) had the largest such populations. We identified eligible HBsAg reports for 59 countries, with midpoint prevalence estimates of 5-10% in 21 countries and more than 10% in ten countries. Worldwide, we estimate 6.4 million IDUs are anti-HBc positive (2.3-9.7 million), and 1.2 million (0.3-2.7 million) are HBsAg positive.

INTERPRETATION: More IDUs have anti-HCV than HIV infection, and viral hepatitis poses a key challenge to public health. Variation in the coverage and quality of existing research creates uncertainty around estimates. Improved and more complete data and reporting are needed to estimate the scale of the issue, which will inform efforts to prevent and treat HCV and HBV in IDUs. FUNDING: WHO and US National Institutes of Health (NIDA R01 DA018609).


BACKGROUND: Hepatitis C virus (HCV) transmission is mainly due to parenteral exposure; however, in absence of such risk factor, there are reports of intrafamilial spread of HCV and observational studies suggest an increased risk for households of infected subjects. The aim of our study was to systematically review and meta-analyse studies about HCV prevalence among households of HCV patients in Italy.

METHODS: PubMed and Embase were searched to identify Italian studies about HCV intrafamilial transmission. Keywords used were: 'HCV', 'Hepatitis C', 'intrafamilial', 'family' and 'Italy'. Selected studies were reviewed to assess the quality and meta-analysed using StatsDirect software. RESULTS: 25 studies were selected. The pooled overall prevalence was 9% (95% CI 7.1% to 11.1%). The highest pooled prevalence was found among sexual partners of index cases: 14.7% (95% CI 10.7% to 19.2%) globally and 9.9% (95% CI 3.6% to 18.8%) and 17.6% (95% CI 12.1% to
...24%) in northern and central-southern regions, respectively. The meta-analysis of high-quality studies yielded the lowest HCV prevalence. CONCLUSION: To be a HCV patient household is a risk factor for HCV and counselling for these households should be provided.


This article reviews the prevalence, disease burden, genotype distribution, and transmission patterns of hepatitis B virus (HBV) and hepatitis C virus in the 6 World Health Organization regions. The global epidemiology of hepatitis B and C demonstrates a predominantly declining prevalence of the diseases. Improvement in the control of hepatitis B has been largely achieved with implementation of a more universal HBV vaccine program, although a large gap still remains in the effort toward global prevention of hepatitis B. The transmission of hepatitis C has been greatly impacted by mandatory screening of blood donors in most countries in the world, although intravenous drug use continues to be a major source of infection. Public education regarding the risks of exposure to infected paraphernalia as well as household items such as razors is necessary in the continuing effort to curb this disease.


Hepatocellular carcinoma (HCC) is a global health problem, although developing countries are disproportionately affected: over 80% of HCCs occur in such regions. About three-quarters of HCCs are attributed to chronic HBV and HCV infections. In areas endemic for HCV and HBV, viral transmission occurs at an early age, and infected individuals develop HCC in mid-adulthood. As these are their most productive years of life, HCC accounts for a substantial burden on the health-care system and drain of productive capacity in the low-income and middle-income countries most affected by HCV and HBV infections. Environments with disparate resource levels require different strategies for the optimal management of HCC. In high-resource environments, guidelines from the American Association for the Study of Liver Diseases or European Association for the Study of the Liver should be applied. In intermediate-resource or low-resource environments, the fundamental focus should be on primary prevention of HCC, through universal HBV vaccination, taking appropriate precautions and antiviral treatments. In intermediate-resource and low-resource environments, the infrastructure and capacity for abdominal ultrasonography, percutaneous ethanol injection, radiofrequency ablation and surgical resection should be established. Programs to provide targeted therapy at low cost, similar to the approach used for HIV therapy in the developing world, should be pursued.


Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide, and the burden of this devastating cancer is expected to increase further in coming years. The collection and analysis of epidemiologic HCC data will play a critical role in guiding future disease prevention strategies and optimizing patient management. Previous epidemiologic studies have highlighted striking global variations in the incidence of HCC, which is particularly high in much of east Asia and sub-Saharan Africa, and lower, but on the increase, in North America and most of
Europe. This variation appears to be related to the complex etiology of HCC, with different risk factors, primarily infection with hepatitis B or hepatitis C virus, responsible for driving HCC incidence rates in different regions. Although previous studies have contributed considerably to the knowledge of HCC epidemiology, there are limitations associated with the currently available data, which arise from studies performed at different times in the past, using varying methodologies, and with diverse patient populations. A new and global approach to the study of HCC epidemiology is required if HCC disease prevention and treatment strategies are to be adequately directed and supported in coming years.


Hepatitis C is of concern both to industrialized and developing countries. Preliminary unpublished estimates of the global burden of disease (GBD) attributable to HCV-related chronic liver disease seem to be substantial. Therefore, the reduction of global mortality and morbidity related to chronic hepatitis C should be a concern to public health authorities, and primary, secondary and tertiary prevention activities should be implemented and monitored in each country, with precise targets set to be reached. In order to decide on national health policies, there is a need to estimate the burden of disease, globally, regionally and nationally. To evaluate the GBD, three components have to be assessed: 1) The global, regional and national burden of morbidity and mortality associated with HCV infection, based on prevalence, incidence, transmission and economics; 2) The natural history of HCV infection, including 'healthy individuals'; and 3) The areas for which more research is needed. A working group was created to assist the World Health organization (WHO) in estimating the GBD associated with HCV infection.


Hepatitis C continues to be a major public health problem affecting approximately 3% of the global population. According to the World Health Organization, an estimated 170 million people have chronic hepatitis C. Ten percent to 20% of those who are chronically infected with hepatitis C will progress to cirrhosis and 5% will develop hepatocellular carcinoma. Although the safety and efficacy of hepatitis C therapies have been studied extensively in patients between the ages of 18 and 65, patients who are older than 65 still remain an understudied and difficult-to-treat population. This review discusses the epidemiology, natural history, and treatment of chronic hepatitis C in older adults.


BACKGROUND: Hepatitis C virus (HCV) is a leading cause of chronic liver disease, end-stage cirrhosis, and liver cancer, but little is known about the burden of disease caused by the virus. We summarised burden of disease data presently available for Europe, compared the data to current expert estimates, and identified areas in which better data are needed. METHODS: Literature and international health databases were systematically searched for HCV-specific burden of disease data, including incidence, prevalence, mortality, disability-adjusted life-years (DALYs), and liver transplantation. Data were collected for the WHO European region with emphasis on 22 countries. If HCV-specific data were unavailable, these were calculated via HCV-attributable fractions. RESULTS: HCV-specific burden of disease data for Europe are scarce. Incidence data provided by national surveillance are not fully comparable and
need to be standardised. HCV prevalence data are often inconclusive. According to available data, an estimated 7.3-8.8 million people (1.1-1.3%) are infected in our 22 focus countries. HCV-specific mortality, DALY, and transplantation data are unavailable. Estimations via HCV-attributable fractions indicate that HCV caused more than 86000 deaths and 1.2 million DALYs in the WHO European region in 2002. Most of the DALYs (95%) were accumulated by patients in preventable disease stages. About one-quarter of the liver transplants performed in 25 European countries in 2004 were attributable to HCV. CONCLUSION: Our results indicate that hepatitis C is a major health problem and highlight the importance of timely antiviral treatment. However, data on the burden of disease of hepatitis C in Europe are scarce, outdated or inconclusive, which indicates that hepatitis C is still a neglected disease in many countries. What is needed are public awareness, co-ordinated action plans, and better data. European physicians should be aware that many infections are still undetected, provide timely testing and antiviral treatment, and avoid iatrogenic transmission.
Session 3: New hepatitis C era: changing therapy landscape

Presentation Jake Liang Overview of current developments in treatment of hepatitis C


Presentation Benjamin Maasoumy Hepatitis C therapy: lessons learned from the first experience in a real world setting.


BACKGROUND: HCV protease inhibitors (PIs) boceprevir and telaprevir in combination with PEG-Interferon alfa and Ribavirin (P/R) is the new standard of care in the treatment of chronic HCV genotype 1 (GT1) infection. However, not every HCV GT1 infected patient is eligible for P/R/PI therapy. Furthermore phase III studies did not necessarily reflect real world as patients with advanced liver disease or comorbidities were underrepresented. The aim of our study was to analyze the eligibility and safety of P/R/PI treatment in a real world setting of a tertiary referral center.

METHODS: All consecutive HCV GT1 infected patients who were referred to our hepatitis treatment unit between June and November 2011 were included. Patients were evaluated for P/R/PI according to their individual risk/benefit ratio based on 4 factors: Treatment-associated safety concerns, chance for SVR, treatment urgency and nonmedical patient related reasons. On treatment data were analyzed until week 12. RESULTS: 208 patients were included (F3/F4 64%, mean platelet count 169/nl, 40% treatment-naive). Treatment was not initiated in 103 patients most frequently due to safety concerns. 19 patients were treated in phase II/III trials or by local centers and a triple therapy concept was initiated at our unit in 86 patients. Hospitalization was required in 16 patients; one patient died due to a gastrointestinal infection possibly related to treatment. A platelet count of <110/nl was associated with hospitalization as well as treatment failure. Overall, 128 patients were either not eligible for therapy or experienced a treatment failure at week 12. CONCLUSIONS: P/R/PI therapies are complex, time-consuming and sometimes dangerous in a real world setting, especially in patients with advanced liver disease. A careful patient selection plays a crucial role to improve safety of PI based therapies. A significant number of patients are not eligible for P/R/PI, emphasizing the need for alternative therapeutic options.

Maasoumy, B., K. Port, B. Calle Serrano, A. A. Markova, L. Sollik, M. P. Manns, M.
BACKGROUND: Drug-drug interactions (DDIs) in the treatment of chronic hepatitis C infection became a potential challenge with the introduction of direct-acting antivirals (DAAs). Both currently approved DAAs, the protease inhibitors (PIs) telaprevir (TVR) and boceprevir (BOC), are substrates and inhibitors of P-glycoprotein and the cytochrome P450 3A4, which are regularly involved in DDIs. AIM: To analyse the risk for DDIs in patients with chronic HCV genotype 1 infection considered for PI treatment at a tertiary referral centre. METHODS: The first 115 consecutive patients selected for a PI therapy at Hannover Medical School were included. All changes to co-medication before and during PI treatment were documented. Drugs were checked for DDIs with TVR and BOC using DDI websites and the respective prescribing information. RESULTS: Out-patient medication contained 116 different drugs. Median number of drugs/patient was 2 (range 0-11). The risk for DDIs was substantial for 38% of the drugs affecting 49% of patients. Only 4% of the drugs were strictly contraindicated. DDIs between a PI and drugs newly prescribed during antiviral therapy were considerable in 42% of the patients. Suspected DDIs were managed by dose adjustments and discontinuation of co-medication in 7% and 21% of the patients respectively. CONCLUSIONS: Many patients with chronic HCV genotype 1 infection are affected by potential DDIs if treated with a protease inhibitor, but only in a minority of cases co-medication is strictly incompatible. Overall, the challenge of DDIs is time-consuming, but well manageable by a careful review of the patient's drug chart and monitoring during treatment.

Presentation  Homie Razavi  Market access and uptake of new antiviral drugs for the treatment of hepatitis.


Emerging data indicate that all-oral antiviral treatments for chronic hepatitis C virus (HCV) will become a reality in the near future. In replacing interferon-based therapies, all-oral regimens are expected to be more tolerable, more effective, shorter in duration and simpler to administer. Coinciding with new treatment options are novel methodologies for disease screening and staging, which create the possibility of more timely care and treatment. Assessments of histologic damage typically are performed using liver biopsy, yet noninvasive assessments of histologic damage have become the norm in some European countries and are becoming more widespread in the United States. Also in place are new Centers for Disease Control and Prevention (CDC) initiatives to simplify testing, improve provider and patient awareness and expand recommendations for HCV screening beyond risk-based strategies. Issued in 2012, the CDC recommendations aim to increase HCV testing among those with the greatest HCV burden in the United States by recommending one-time testing for all persons born during 1945-1965. In 2013, the United States Preventive Services Task Force adopted similar recommendations for risk-based and birth-cohort-based testing. Taken together, the developments in screening, diagnosis and treatment will likely increase demand for therapy and stimulate a shift in delivery of care related to chronic HCV, with increased involvement of primary care and infectious disease specialists. Yet even in this new era of therapy, barriers to curing patients of HCV will exist. Overcoming such barriers will require novel, integrative strategies and investment of resources at local, regional and national levels.

BACKGROUND/AIMS: Peginterferon plus ribavirin is the state-of-the-art antiviral therapy for prevention of serious complications of hepatitis C. Our aim was to compare market uptake of and access to these drugs across Europe. METHODS: We collected launch and sales data for peginterferons for 21 countries in the WHO European region and compared country-specific sales rates. Additionally, we converted sales figures into patient numbers and related those to country-specific hepatitis C prevalence, taking into account genotype distribution, patient characteristics and practice patterns. RESULTS: Peginterferon sales rates differed considerably across countries. The earliest, most rapid and highest adoption rates were in EU founder states, followed by EU members that joined after foundation, and EU non-member states. Most new member states showed a marked increase in sales. By the end of 2005, approximately 308,000 patients had been treated with peginterferons in the 21 countries evaluated. The number of patients ever treated ranged from 16% of prevalent cases in France to less than 1% of cases in Romania, Poland, Greece and Russia. CONCLUSIONS: Peginterferon market uptake and access differed considerably across Europe, suggesting unequal access to optimised therapy. Besides budget restrictions, national surveillance and treatment policies should be considered as reasons for market access variation.

RELATED Abstracts session 3

Pubmed MEDLINE search on {(Hepatitis C OR Hep C OR HCV) AND (treatment OR therapy) AND (new OR development)} in all fields and filters used on this search ‘2013,2012’ and ‘Review’ on, was performed. ] The reference were sorted by publication year and first author

In total 52 were selected


Opportunities to treat infection with hepatitis C virus (HCV) are evolving rapidly. From the introduction of interferon-alpha monotherapy in 1992 to the approval of telaprevir- and boceprevir-based triple therapies with pegylated interferon-alpha and ribavirin in 2011, the chances of curing patients infected with HCV genotype 1 have improved from <10% to approximately 70%. Significant further improvements are on the horizon, which may well cure virtually all hepatitis C patients with an all-oral, interferon-free regimen in the very near future. These exciting developments are reviewed in the present article.


The first-generation Protease Inhibitors Boceprevir and Telaprevir administered in
triple therapy regimens with Peg-interferon alpha and Ribavirin have been proven effective in increasing the rate of Sustained Virological Response in both naive and treatment-experienced patients with chronic genotype-1 hepatitis C. However, at the individual level, the therapeutic advantage of triple therapy is highly variable and results from the combination of multiple factors related to the characteristics of patient, viral status and liver disease. The recommendations presented are promoted by the Italian Association for the Study of the Liver, with the aim to help the physician in the decision-making process as well as to manage patients during treatment with triple therapy.


Emerging data indicate that all-oral antiviral treatments for chronic hepatitis C virus (HCV) will become a reality in the near future. In replacing interferon-based therapies, all-oral regimens are expected to be more tolerable, more effective, shorter in duration and simpler to administer. Coinciding with new treatment options are novel methodologies for disease screening and staging, which create the possibility of more timely care and treatment. Assessments of histologic damage typically are performed using liver biopsy, yet noninvasive assessments of histologic damage have become the norm in some European countries and are becoming more widespread in the United States. Also in place are new Centers for Disease Control and Prevention (CDC) initiatives to simplify testing, improve provider and patient awareness and expand recommendations for HCV screening beyond risk-based strategies. Issued in 2012, the CDC recommendations aim to increase HCV testing among those with the greatest HCV burden in the United States by recommending one-time testing for all persons born during 1945-1965. In 2013, the United States Preventive Services Task Force adopted similar recommendations for risk-based and birth-cohort-based testing. Taken together, the developments in screening, diagnosis and treatment will likely increase demand for therapy and stimulate a shift in delivery of care related to chronic HCV, with increased involvement of primary care and infectious disease specialists. Yet even in this new era of therapy, barriers to curing patients of HCV will exist. Overcoming such barriers will require novel, integrative strategies and investment of resources at local, regional and national levels.


BACKGROUND: The stability and propagation of hepatitis C virus (HCV) is dependent on a functional interaction between the HCV genome and liver-expressed microRNA-122 (miR-122). Miravirsen is a locked nucleic acid-modified DNA phosphorothioate antisense oligonucleotide that sequesters mature miR-122 in a highly stable heteroduplex, thereby inhibiting its function. METHODS: In this phase 2a study at seven international sites, we evaluated the safety and efficacy of miravirsen in 36 patients with chronic HCV genotype 1 infection. The patients were randomly assigned to receive five weekly subcutaneous injections of miravirsen at doses of 3 mg, 5 mg, or 7 mg per kilogram of body weight or placebo over a 29-day period. They were followed until 18 weeks after randomization. RESULTS: Miravirsen resulted in a dose-dependent reduction in HCV RNA levels that endured beyond the end of active therapy. In the miravirsen groups, the mean maximum
reduction in HCV RNA level (log10 IU per milliliter) from baseline was 1.2 (P=0.01) for patients receiving 3 mg per kilogram, 2.9 (P=0.003) for those receiving 5 mg per kilogram, and 3.0 (P=0.002) for those receiving 7 mg per kilogram, as compared with a reduction of 0.4 in the placebo group. During 14 weeks of follow-up after treatment, HCV RNA was not detected in one patient in the 5-mg group and in four patients in the 7-mg group. We observed no dose-limiting adverse events and no escape mutations in the miR-122 binding sites of the HCV genome. CONCLUSIONS: The use of miravirsen in patients with chronic HCV genotype 1 infection showed prolonged dose-dependent reductions in HCV RNA levels without evidence of viral resistance. (Funded by Santaris Pharma; ClinicalTrials.gov number, NCT01200420.)


OBJECTIVE: Despite the remarkable improvements in pharmacologic treatment efficacy for hepatitis C (HCV) reported in published clinical trials, published research suggests that, in "real-world" patient care, these medical outcomes may be difficult to achieve. This review was undertaken to summarize recent experience in the treatment of HCV in clinical settings, examining the course of patients through the stages of treatment and barriers to treatment encountered. METHOD: A comprehensive and representative review of the relevant literature was undertaken to examine HCV treatment experience outside of clinical trials in the last decade. This review found 25 unique studies with data on course of treatment and/or barriers to treatment in samples of patients with HCV not preselected for inclusion in clinical trials. RESULTS: Results were examined separately for samples selected for HCV infection versus HCV/HIV coinfection. Only 19% of HCV-selected and 16% of HCV/HIV-coinfection selected patients were considered treatment eligible and advanced to treatment; even fewer completed treatment (13% and 11%, respectively) or achieved sustained virologic response (3% and 6%, respectively). Psychiatric and medicalineligibilities were the primary treatment barriers. CONCLUSION: Only by systematically observing and addressing potentially solvable medical and psychosocial barriers to treatment will more patients be enrolled in and complete HCV therapy.


Vaccination is possible to prevent infections with some viruses: hepatitis B virus (HBV), varicella-zoster virus (VZV), influenza A and B viruses, Yellow fever virus and poliovirus; but not for others: human immunodeficiency virus (HIV), hepatitis C virus (HCV), herpes simplex virus (HSV), cytomegalovirus (CMV), and most hemorrhagic fever viruses (HFV) (except for Yellow fever virus). Antiviral therapy is obviously needed to control those infections that are not amenable to prophylaxis by vaccination, but is also highly desirable for those infections where vaccination has not been implemented or did not fulfill its premises for complete protection.


Prominent in the current stage of antiviral drug development are: (i) for human immunodeficiency virus (HIV), the use of fixed-dose combinations (FDCs), the most recent example being StribildTM; (ii) for hepatitis C virus (HCV), the pleiade of direct-acting antivirals (DAAs) that should be formulated in the most appropriate
combinations so as to obtain a cure of the infection; (iii)-(v) new strategies (i.e., AIC316, AIC246, and FV-100) for the treatment of herpesvirus infections: herpes simplex virus (HSV), cytomegalovirus (CMV), and varicella-zoster virus (VZV), respectively; (vi) the role of a new tenofovir prodrug, tenofovir alafenamide (TAF) (GS-7340) for the treatment of HIV infections; (vii) the potential use of poxvirus inhibitors (CMX001 and ST-246); (viii) the usefulness of new influenza virus inhibitors (peramivir and laninamivir octanoate); (ix) the position of the hepatitis B virus (HBV) inhibitors [lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir disoproxil fumarate (TDF)]; and (x) the potential of new compounds such as FGI-103, FGI-104, FGI-106, dUY11, and LJ-001 for the treatment of filoviruses (i.e., Ebola). Whereas for HIV and HCV therapy is aimed at multiple-drug combinations, for all other viruses, HSV, CMV, VZV, pox, influenza, HBV, and filoviruses, current strategies are based on the use of single compounds.


Recent data have clearly shown that a sustained virologic response can be achieved in different HCV infected patient populations with various interferon-free treatment regimens. Despite the successful implementation of telaprevir- and boceprevir-based triple therapies, all-oral regimens will certainly become a first choice for a number of HCV-infected patients in the very near future, as triple therapy approaches are burdened with significant side-effects and limited success in patients with advanced liver fibrosis and prior null-response to pegylated interferon-alpha (pegIFN-alpha)/ribavirin therapy. However, available data from phase I and II clinical trials evaluating interferon-free regimens have not yet revealed a clearly outstanding all-oral combination, and numerous challenges remain to be addressed by intensive ongoing and future research. In particular, thus far evaluated all-oral regimens did not cure a satisfactory percentage of patients with unfavorable baseline characteristics, namely patients infected with HCV genotype 1a, previous null-response to pegIFN-alpha/ribavirin, or liver cirrhosis. In this review, we summarize available data of interferon-free regimens for the treatment of chronic hepatitis C and assess implications for perspectives and challenges in the further development of all-oral therapies.


BACKGROUND: To increase cure rates for Hepatitis C, barriers to treatment adherence and completion must be identified and overcome. AIMS: This study systematically reviewed evidence on the psychological, lifestyle and social determinants of achieving viral eradication with antiviral therapy. METHODS: An electronic search strategy was used to identify relevant studies that examined psychological, lifestyle and social factors related to achieving a sustained virological response (SVR). RESULTS: Thirty-four studies that matched our criteria were identified. Of the factors that predict response to treatment, Asian ethnicity was an independent predictor of SVR. We found an indirect relationship between diet and SVR, with non-responders to treatment consuming more polyunsaturated fatty acids, fats and carbohydrates than those who attained SVR. The effect of alcohol consumption relied on the amount consumed; fewer than 30 grams daily had no effect on SVR, whereas >70 grams daily had an adverse impact on a patient's ability to achieve SVR, with termination rates up to 44% in those who drank >2 drinks a day. Patients with psychiatric illnesses had comparable SVR rates to controls if they
continued psychological therapy (average 42%), although discontinuation rates were high with 11 studies reporting rates from 14 to 48%. CONCLUSIONS: There are major gaps in current knowledge of the impact of variables such as diet, exercise, attitudes and coping skills on cure rates in chronic Hepatitis C. Those who drink limited amounts of alcohol or have psychiatric disorders should be offered treatment for their disease, with adjunctive education and support to improve treatment completion.


BACKGROUND: Multiple treatments are available for chronic hepatitis C virus (HCV) infection. PURPOSE: To compare benefits and harms of antiviral regimens for chronic HCV infection in treatment-naive adults. DATA SOURCES: English-language literature from MEDLINE (1947 to August 2012), the Cochrane Library Database, Embase, Scopus, PsychINFO, and clinical trial registries. STUDY SELECTION: Randomized trials of antiviral treatments and cohort studies examining associations between sustained virologic response (SVR) after therapy and clinical outcomes. DATA EXTRACTION: Several investigators abstracted study details and quality by using predefined criteria. DATA SYNTHESIS: No trial evaluated effectiveness of treatment on long-term clinical outcomes. Dual therapy with pegylated interferon alfa-2b plus ribavirin was associated with a lower likelihood of SVR than was pegylated interferon alfa-2a plus ribavirin (absolute difference, 8 percentage points [95% CI, 3 to 14 percentage points]) on the basis of 7 poor- to fair-quality trials. For genotype 2 or 3 infection, dual therapy for 12 to 16 weeks was associated with a lower likelihood of SVR than was therapy for 24 weeks, and lower doses of pegylated interferon alfa-2b were less effective than standard doses (2 to 4 fair-quality trials). For genotype 1 infection, fair-quality trials found that triple therapy with pegylated interferon, ribavirin, and either boceprevir (2 trials) or telaprevir (4 trials) was associated with a higher likelihood of SVR than was dual therapy (absolute difference, 22 to 31 percentage points). Compared with dual therapy, boceprevir triple therapy increased risk for hematologic adverse events and telaprevir triple therapy increased risk for anemia and rash. A large well-designed cohort study and 18 smaller cohort studies found that an SVR after antiviral therapy was associated with lower risk for all-cause mortality than was no SVR.

LIMITATIONS: Trials involved highly selected populations. Observational studies did not always adequately control for confounders. CONCLUSION: SVR rates for genotype 1 infection are higher with triple therapy that includes a protease inhibitor than with standard dual therapy. An SVR after antiviral therapy appears associated with improved clinical outcomes. PRIMARY FUNDING SOURCE: Agency for Healthcare Research and Quality.


The approval of the first protease inhibitors as treatment for hepatitis C virus (HCV) infection is rapidly transforming the way patients with chronic hepatitis C are managed. Treatment regimens are moving to combinations given for shortened periods, excluding poorly tolerated subcutaneous interferon, and providing rates of cure exceeding 75%. The recognition of HCV infection as a systemic disease, not limited to producing liver damage, in which extrahepatic complications play a major role as the cause of morbidity and mortality, is prompting the treatment of a growing
number of HCV-infected individuals. However, new challenges are emerging, including the need to diagnose a substantial proportion of asymptomatic carriers, the risk of potentially harmful drug-drug interactions and the high cost of medications. The future will probably see a progressive marginalization of residual HCV populations, with increasing over-representation of illegal immigrants, alcohol abusers, intravenous drug users and the mentally disabled.


The results from clinical trials testing new direct-acting antivirals (DAAs) for chronic hepatitis C were the major focus of interest at the 2012 annual meeting of the European Association for the Study of the Liver. Besides triple combinations, in which any one of the new DAAs is given along with peginterferon-alpha/ribavirin, clinical trials exploring interferon-free oral regimens combining several DAAs attracted major attention. The good tolerance, broad hepatitis C virus (HCV) genotype activity, and high resistance barrier of sofosbuvir make this nucleotide analogue one of the most promising DAAs. Among HCV protease inhibitors, the safety, potency, and convenient dosing of simeprevir, asunaprevir, faldaprevir, and ABT-450/r were particularly highlighted. Among NS5A inhibitors, the good performance of daclatasvir encourages further clinical development. Finally, intriguing results were released about the role of interleukin 28B (IL-28B) polymorphisms using interferon-free regimens, indirectly supporting the role of innate immunity for clearing HCV definitively.


Telaprevir and boceprevir are the first direct-acting antiviral agents approved for use in HCV treatment and represent a significant advance in HCV therapy. However, these first-generation drugs also have significant limitations related to thrice-daily dosing, clinically challenging side-effect profiles, low barriers to resistance and a lack of pan-genotype activity. A second wave of protease inhibitors are in phase II and III trials and promise to provide a drug regimen with a better dosing schedule and improved tolerance. These second-wave protease inhibitors will probably be approved in combination with PEG-IFN and Ribavirin (RBV), as well as future all-oral regimens. The true second-generation protease inhibitors are in earlier stages of development and efficacy data are anxiously awaited as they may provide pan-genotypic antiviral activity and a high genetic barrier to resistance.


The characterization of the viral life cycle facilitated the development of directly acting antiviral drugs. Among those, several inhibitors of the viral RNA-dependent RNA polymerase have proven effectiveness in clinical trials. The characteristics of different nucleos(t)ide and non-nucleoside polymerase inhibitors, as well as their clinical applications and combinations with other classes of directly acting antiviral drugs are reviewed herein.


Hepatitis C virus (HCV) RNA level monitoring is currently used to guide the duration of interferon-containing treatment regimens. Nowadays, HCV RNA level
quantification is based on real-time polymerase chain reaction assays that are both sensitive and accurate. Assessing the virological response to therapy is used to shorten treatment duration in early responders, in order to reduce the cost and burden of adverse events of therapy without impacting the chance of success. Whether response-guided therapy will still be useful in the era of all-oral, interferon-free regimens remains uncertain.


While patients with chronic hepatitis C virus (HCV) infection are treated in order to prevent liver-related morbidity and mortality, we rely on sustained virological response (SVR) as a virological biomarker to evaluate treatment efficacy in both clinical practice as well as in drug development. However, conclusive evidence for the clinical benefit of antiviral therapy or validity of SVR as surrogate marker, as derived from trials randomizing patients to a treatment or control arm, is lacking. In fact, the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) trial recently showed an increased mortality rate among interferon-treated patients compared to untreated controls. Consequently, the recommendation to treat patients with chronic HCV infection was challenged. Here, we argue that the possible harmful effect of long-term low-dose pegylated interferon mono therapy, as was observed in the HALT-C trial cohort, cannot be extrapolated to potentially curative short-term treatment regimens. Furthermore, we discuss SVR as a surrogate biomarker, based on numerous studies which indicated an association between SVR and improvements in health-related quality of life, hepatic inflammation and fibrosis, and portal pressure as well as a reduced risk for hepatocellular carcinoma (HCC), liver failure and mortality.


Hepatitis C virus infection is a major health problem worldwide and no vaccine has yet been developed against this virus. In addition, currently approved pharmacotherapies achieve suboptimal cure rates and have side effects that result in non-compliance and premature treatment discontinuation. Significant research has been devoted to developing direct-acting antiviral agents that inhibit key viral functions. In particular, several novel drug candidates that inhibit the viral non-structural protein 5A (NS5A) have been demonstrated to possess high potency, pan-genotypic activity, and a high barrier to resistance. Clinical trials using combination therapies containing NS5A inhibitors have reported results that promise high cure rates and raise the possibility of developing interferon-free, all-oral regimens.


Hepatitis C virus (HCV) infection is curable by therapy. The antiviral treatment of chronic hepatitis C has been based for decades on the use of interferon (IFN)-alpha, combined with ribavirin. More recently, new therapeutic approaches that target essential components of the HCV life cycle have been developed, including direct-acting antiviral (DAA) and host-targeted agents (HTA). A new standard-of-care
Treatment has been approved in 2011 for patients infected with HCV genotype 1, based on a triple combination of pegylated IFN-alpha, ribavirin, and either telaprevir or boceprevir, two inhibitors of the HCV protease. New triple and quadruple combination therapies including pegylated IFN-alpha, ribavirin, and one or two DAAs/HTAs, respectively, are currently being evaluated in Phase II and III clinical trials. In addition, various options for all-oral, IFN-free regimens are currently being evaluated. This chapter describes the characteristics of the different drugs used in the treatment of chronic hepatitis C and those currently in development and provides an overview of the current and future standard-of-care treatments of chronic hepatitis C.


Resolution of the three-dimensional structures of several Hepatitis C virus (HCV) proteins, together with the development of replicative cell culture systems, has led to the identification of a number of potential targets for direct-acting antiviral agents (DAA). Numerous families of drugs that potently inhibit the HCV life cycle in vitro have been identified, and some of these molecules have reached early to late clinical development. Two NS3-4A protease inhibitors, telaprevir and boceprevir, were approved in Europe and the United States in 2011 in combination with pegylated interferon (IFN)-alpha and ribavirin for the treatment of chronic hepatitis C related to HCV genotype 1. A number of other DAAs are at the clinical developmental stage in combination with pegylated IFN-alpha and ribavirin or with other DAAs in IFN-free regimens, with or without ribavirin. They include second-wave, first-generation, and second-generation NS3-4A protease inhibitors, nucleoside/nucleotide analogue inhibitors, and non-nucleoside inhibitors of HCV RNA-dependent RNA polymerase, inhibitors of nonstructural protein 5A and host-targeted agents, such as cyclophilin A inhibitors and microRNA-122 antagonists. The proof of concept that IFN-free regimens can lead to HCV eradication has recently been brought. This chapter provides an overview of the current treatment of HCV infection and discusses the future of HCV therapy with new anti-HCV drugs.


Chronic hepatitis C infection remains a major global public health burden associated with substantial morbidity and mortality. Recent advances in antiviral therapy with the US Food and Drug Administration (FDA) approval of the oral protease inhibitors boceprevir and telaprevir introduce a new era of treatment for hepatitis C based on directly acting antiviral agents, which are associated with significant improvements in viral eradication rates in combination with pegylated interferon plus ribavirin. Newer classes targeting the hepatitis C virus (HCV) protease, polymerase, NS5A, and other components of the viral genome demonstrate great promise to further enhance viral eradication with superior efficacy, improved tolerability, shorter duration of therapy, and diminished requirement for interferon. Current and future strategies for HCV pharmacotherapy are reviewed.


The addition of the hepatitis C virus (HCV) protease inhibitors telaprevir and boceprevir to peginterferon alfa with ribavirin therapy has increased cure rates in HCV infection. Numerous other direct-acting antivirals (DAAs) are in advanced stages of development, including next-generation protease inhibitors, nonstructural protein (NS) 5A inhibitors, and nonnucleoside and nucleos(t)ide NS5B polymerase
inhibitors. The classes have different potencies, different resistance mutation profiles, and different barriers to the emergence of resistance. A comprehensive table of resistance mutations for classes of DAAs is presented. Numerous combinations of DAAs with or without ribavirin have been evaluated in early studies of interferon alfa-free regimens, with results indicating that cure is indeed possible with such therapy and suggesting that identification of regimens that could produce cure in the majority of patients may occur within the foreseeable future. This article summarizes a presentation by David L. Wyles, MD, at the IAS-USA live continuing medical education activity held in New York in June 2012.


For the treatment of human immunodeficiency virus (HIV) infections for which there are ample drugs available, the immediate future lies in a once-daily combination pill containing three or four active ingredients. This strategy may also be envisaged for the treatment of hepatitis C virus (HCV) infections as soon as we have at hand the appropriate direct-acting antiviral agents (DAAs) to be combined. A combination drug therapy is generally not entertained for other viruses. Yet, new drugs are at the horizon for the treatment of herpes simplex virus (HSV), varicella-zoster virus (VZV), poxvirus, hepatitis B virus (HBV), influenza and enveloped viruses-at-large.


BACKGROUND & AIMS: The dynamics of hepatitis C virus (HCV) infection, as well as screening practices and access to therapy, vary among European countries. It is important to determine the magnitude of the effects of such differences on incidence and mortality of infection. We compared the dynamics of infection and screening and treatment practices among Belgium, France, Germany, Italy, Spain, and the United Kingdom. We also assessed the effects of treatment with pegylated interferon and additional effects of triple therapy with protease inhibitors.

METHODS: We created a country-specific Markov model of HCV progression based on published epidemiologic data (on HCV prevalence, screening, genotype, alcohol consumption among patients, and treatments) and reports of competitive and hepatocellular carcinoma mortality for the 6 countries. The model was used to predict the incidence of HCV-related cirrhosis and its mortality until 2021 for each country.

RESULTS: From 2002 to 2011, antiviral therapy reduced the cumulative incidence of cirrhosis by 7.1% and deaths by 3.4% overall. Reductions in incidence and mortality values ranged from 4.0% and 1.9%, respectively, in Italy to 16.3% and 9.0%, respectively, in France. From 2012 to 2021, antiviral treatment of patients with HCV genotype 1 infection that includes protease inhibitor-based triple therapy will reduce the cumulative incidence of cirrhosis by 17.7% and mortality by 9.7% overall. The smallest reduction is predicted for Italy (incidence reduced by 10.1% and mortality by 5.4%) and the highest is for France (reductions of 34.3% and 20.7%, respectively).

CONCLUSIONS: Although HCV infection is treated with the same therapies in different countries, the effects of the therapies on morbidity and mortality vary significantly. In addition to common guidelines that are based on virologic response-guided therapy, there is a need for public health policies based on population-guided therapy.

The approval of direct-acting antiviral agents (DAAs) against the hepatitis C virus (HCV) NS3 protease revolutionized antiviral therapy in chronic hepatitis C. They mark the beginning of an era with drugs designed to inhibit specific viral proteins involved in the virus life cycle rather than the nonspecific antiviral activity of interferon. Upcoming generations of antivirals are expected that lead to viral eradication in most patients who undergo treatment with hope held for years that HCV can be cured without interferon. Antiviral drug resistance plays a key role in DAA-treatment failure. Knowledge on molecular escape mechanisms of resistant variants, their time to wild-type reversal and potential persistence is of upmost importance to design treatment strategies for patients with previous DAA-treatment failure.

De Clercq, E. "The race for interferon-free HCV therapies: a snapshot by the spring of 2012." Rev Med Virol 2012 22(6): 392-411. After a decade of having been the standard of care (SOC) for the treatment of chronic HCV infection, PEGylated IFN (combined with ribavirin) is now at the verge of being complemented and then replaced by a combination of new DAAs and even some compounds interacting with host cell factors. Principal targets for the direct-acting antivirals (DAAs) are the protease NS3/4A, the protein NS5A, and the RNA-dependent RNA polymerase NS5B, which offers at least two target sites, the catalytic domain for nucleos(t)ides and several non-catalytic (allosteric) domains for the non-nucleoside type of NS5B inhibitors. Two PIs have already been approved, but many more NS3/4A, NS5A, and NS5B (up to 40!) inhibitors are in (pre)clinical development. The abundance of candidate anti-HCV drugs will, on the one hand, speed up their development but, on the other hand, complicate the choice of the most appropriate drug combination(s).

Chevaliez, S., C. Rodriguez and J. M. Pawlotsky. "New virologic tools for management of chronic hepatitis B and C." Gastroenterology 2012 142(6): 1303-1313 e1301. Molecular biology techniques are routinely used to diagnose and monitor treatment of patients with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. These tools can detect and quantify viral genomes and analyze their sequence to determine their genotype or subtype and to identify nucleotide or amino acid substitutions associated with resistance to antiviral drugs. They include real-time target amplification methods, which have been standardized and are widely used in clinical practice to diagnose and monitor HBV and HCV infections, and next-generation sequencing techniques, which are still restricted to research laboratories. In addition, new enzyme immunoassays can quantify hepatitis B surface and hepatitis C core antigens, and point-of-care tests and alternatives to biologic tests that require whole-blood samples obtained by venipuncture have been developed. We review these new virologic methods and their clinical and research applications to HBV and HCV infections.

Ford, N., K. Singh, G. S. Cooke, E. J. Mills, T. von Schoen-Angerer, A. Kamarulzaman and P. du Cros. "Expanding access to treatment for hepatitis C in resource-limited settings: lessons from HIV/AIDS." Clin Infect Dis 2012 54(10): 1465-1472. The need to improve access to care and treatment for chronic hepatitis C virus (HCV) infection in resource-limited settings is receiving increasing attention. Key priorities for scaling up HCV treatment and care include reducing the cost of current and future treatment; simplifying the package of care; identifying opportunities to shift specific tasks to nonspecialists to overcome human resource constraints; service integration with human immunodeficiency virus (HIV) clinics, prison health services, and needle
syringe and oral substitution therapy programs; improving surveillance, monitoring, and research; encouraging patient and community engagement; focusing specifically on the needs of vulnerable groups; and increasing financial and political commitment. Many of these obstacles have been addressed in rolling out treatment for human immunodeficiency virus during the last decade, and a number of lessons can be drawn to help improve access to HCV care.


BACKGROUND: In Germany, 400 000 to 500 000 people are chronically infected with the hepatitis C virus (HCV), 70% to 80% of them with HCV genotype 1. Combined treatment with peginterferon-alfa and ribavirin leads to a sustained virologic response (SVR) in 40% to 50% of patients with genotype 1 and 70% to 80% of patients with genotypes 2 and 3. The HCV protease inhibitors boceprevir and telaprevir were approved for clinical use in Germany in 2011.

METHODS: Selective literature review.

RESULTS: Treatment with peginterferon and ribavirin is recommended for a variable length of time depending on the HCV genotype (24 to 72 weeks for genotype 1, 16 to 48 weeks for genotypes 2 and 3), the baseline HCV-RNA concentration (greater or less than 600 000 to 800 000 IU/mL), and the decline in HCV-RNA concentration after 4 and 12 weeks of treatment. Either boceprevir or telaprevir is given in addition to peginterferon and ribavirin. In the approval studies, these triple combinations were shown to yield higher SVR rates than dual treatment for genotype 1 (66% to 75% versus 37% to 44%). If there is a favorable early decline in HCV-RNA, the treatment can be shortened to 24 to 28 weeks in 44% to 65% of patients with genotype 1. The SVR rates in genotype 1 patients who failed previous dual therapy were 69% to 88% for prior relapsers, 52% to 59% for partial responders, and 33% for null responders. Triple combination therapy is associated with new adverse events.

CONCLUSION: Individualized treatment durations are recommended for the treatment of chronic hepatitis C with peginterferon and ribavirin. Triple therapy in combination with either boceprevir or telaprevir leads to a higher rate of SVR both in previously untreated genotype 1 patients and in those who have failed prior antiviral treatment.


Development of robust cell culture models for hepatitis C viral infection has greatly increased our understanding of this virus and its life cycle. This knowledge has led to the development of many drugs that target specific elements of viral replication, including viral proteins and host factors required for replication. The NS3/4A serine protease inhibitors were the first of these to be used in the clinic, and reagents that target other elements of the viral lifecycle are in advanced stages of clinical development. These include new NS3/4A protease inhibitors, NS5B RNA-dependent RNA polymerase inhibitors, NS5A inhibitors, and host-directed antivirals, such as cyclophilin inhibitors. Alternative interferons with possibly improved tolerability, specifically interferon-lambda1 (interleukin-29), are also under development. These new reagents against hepatitis C virus should lead to highly effective, well-tolerated, and likely interferon-sparing therapies in the next several years.


Until recently, the standard of care (SOC) for patients with chronic hepatitis C virus (HCV) infection has consisted of a combination of pegylated interferon-alpha [corrected] plus ribavirin, administered for 24- to 48-weeks depending on the HCV genotype. The sustained virologic response rate for this SOC has been only about 50% in patients infected with genotype 1 HCV, the most prevalent genotype in Europe and North America. HCV therapy has been revolutionised recently by the approval of two direct-acting antiviral agents (DAA) against the NS3/4A serine protease for use in genotype 1 HCV, the ketoamide inhibitors boceprevir and telaprevir. The novel SOC marks the beginning of an extraordinary new era in HCV therapy. We review this new SOC with an emphasis on practical issues related to protease inhibitors, e.g. prescribing guidelines, futility rules and management of adverse events. We also give a perspective on what to expect in the coming years. Newer DAA with simplified dosing regimens and/or minimal toxicity which, when used in combination, will lead to viral eradication in most if not all CHC patients who undergo treatment. The novel agents in clinical development are paving the way for future interferon-sparing regimens.


The next decade will be a crucial period in the public health response to hepatitis C virus (HCV) infection. The rapid development of direct-acting antiviral therapy for HCV infection has brought considerable optimism to the HCV sector, with the realistic hope that therapeutic intervention will soon be more effective and offer shorter treatment duration. The initial phase of combination pegylated interferon, ribavirin and a protease inhibitor will be associated with increased toxicity and complexity of therapeutic management but, over the course of the decade, strategies including interferon-free combination direct-acting antiviral regimens with enhanced tolerability and simplified dosing schedules and monitoring protocols will emerge.


Twenty years after its original discovery, tenofovir has acquired a crucial position in the fight against human immunodeficiency virus (HIV). First, tenofovir disoproxil fumarate (TDF) is not only efficacious against, and has been licensed for the treatment of HIV (AIDS), but also HBV (hepatitis B). Second, for the treatment of HIV infections, TDF can be used in combination with other anti-HIV drugs, such as emtricitabine (combination termed Truvada(R)) and Truvada can be further combined with efavirenz, rilpivirine, elvitegravir, atazanavir, or darunavir, as a single once-daily oral pill. Third, Truvada can be used prophylactically to prevent transmission of HIV infection. And fourth, to prevent sexual HIV transmission, tenofovir could also be used topically (i.e., as a vaginal gel).


About half of the patients with chronic hepatitis C are still not cured by treatment with the current standard of care, peginterferon alpha/ribavirin. Direct antiviral drugs may overcome the limitations of standard antiviral therapy. The most promising new agents are inhibitors of the NS3/4A protease, the NS5B polymerase and the NS5A protein. Several compounds against these targets have entered clinical evaluation. Early clinical trials have emphasized the high potential for selecting resistant
Hepatitis C virus variants. Furthermore, development of several new direct antivirals was stopped because of concerns over tolerability and safety. Then, in 2010, two phase III trials with the NS3/4A protease inhibitors boceprevir (SPRINT-2) and telaprevir (ADVANCE) showed that the combination of these compounds with standard care increases sustained virologic response rates in treatment-naive genotype 1 patients from 38-44% to 66-75%. Future goals of therapy with direct antiviral agents are to improve tolerability, shorten the duration of therapy and overcome the issue of resistance. Several studies have been initiated that combine different novel therapies, with and without interferon alpha/ribavirin.


Despite years of clinical use and extensive research efforts, the mechanism of action of ribavirin (RBV) is not well understood. Although it has only a mild, transient antiviral effect on HCV replication when administered as monotherapy, when combined with interferon, RBV improves sustained virological response (SVR) rates by approximately 25-30%. Proposed mechanisms of action for RBV against HCV include (1) a direct effect against the HCV RNA dependent RNA polymerase; (2) induction of misincorporation of nucleotides leading to lethal mutagenesis; (3) depletion of intracellular pools via inhibition of inosine monophosphate dehydrogenase; (4) alteration in the cytokine balance between a Th2 profile (anti-inflammatory) to a Th1 profile (pro-inflammatory); and (5) potentiating the effect of interferon via up-regulation of genes involved in interferon signalling. Given the lack of a clear understanding of RBV mechanism of action, it has been challenging to confidently position this drug with new direct antiviral agents (DAA). However, early clinical studies provide strong evidence for a benefit of RBV in combination with DAAs for both IFN containing and sparing regimens. The addition of RBV reduces viral breakthroughs and/or relapses, at least when drugs with low to moderate genetic barriers to resistance are paired together. This is particularly true in patients harbouring HCV subtype 1a. Ongoing studies are now addressing the utility of RBV in nucleoside containing DAA regimens, which offer both potent antiviral activity as well as a high genetic barrier to resistance. It is remarkable that the age-old question of the role of RBV in the future of HCV therapy remains as real today as it was two decades ago.


Development of more effective hepatitis C (HCV) antivirals has been rapid. The addition of orally administered medications that target the virus (direct acting antivirals [DAA]) to pegylated interferon and ribavirin have dramatically increased sustained virologic response rates in genotype 1-infected patients. However, the side effect profile remains challenging and the dosing schedule complicated. The DAAs currently in development possess the promise of once- or twice-daily dosing schedules, improved tolerance profiles, higher resistance barriers, and pan-genotypic antiviral activity. Emerging interferon-sparing, combination DAA data demonstrates that an interferon is not essential to achieve sustained virological response. This will expand the proportion of HCV-infected patients who can be considered for therapy and will allow for better-tolerated regimens. Expertise in HCV antiviral resistance, drug metabolism, and drug-drug interactions and optimization of drug adherence are now key requirements in the DAA era.

Pan, Q. and L. J. van der Laan. "New targets for treatment against HCV infection." Best
Owing to the tremendous effort from both academia and industry, drug development for hepatitis C virus (HCV) infection has been flourishing, with a range of pipeline compounds at various stages of development. Although combination of the recently launched serine protease inhibitors will further improve the response rate of current interferon-based therapy, some intrinsic limitations of these compounds and the tendency of resistance development by the virus, urge the development of alternative or additional therapeutic strategies. In this article we provide an overview of different host and viral factors which have emerged as new potential targets for therapeutic intervention using state-of-the-art technologies.

Since 2007, the annual age-adjusted mortality rate in hepatitis C virus (HCV) infection in the United States has been greater than that in HIV disease, reflecting the continuing decline in HIV-related mortality and the continuing increase in HCV-related mortality. The approval of 2 new direct-acting antivirals within the past year, as well as the promise offered by numerous other direct-acting agents in development, provides hope that we will be able to markedly improve our ability to cure HCV disease. The addition of a protease inhibitor (PI) to what has been the standard HCV therapy of peginterferon alfa and ribavirin dramatically improves sustained virologic response rates in treatment-naive patients with genotype 1 infection. Similar results have been observed in some treatment-experienced patients in whom prior peginterferon alfa/ribavirin therapy has failed. The use of these new agents has also permitted response-guided therapy, wherein early sustained virologic response to treatment allows for a shortened treatment duration. However, these new PIs add cost and adverse effects to HCV therapy. Boceprevir is associated with increased risk of anemia and dysgeusia, and telaprevir is associated with increased risk of anemia and skin and gastrointestinal adverse effects. Early studies indicate that the addition of PIs results in high response rates in patients with HCV/HIV coinfection. Other studies suggest that combinations of PIs and other direct-acting antivirals may ultimately permit cure when used in interferon sparing regimens. This article summarizes a presentation by David L. Thomas, MD, MPH, at the IAS-USA live continuing medical education course held in New York City in October 2011.

The standard of care for the treatment of HCV infected patients was until 2011 the association peginterferon-ribavirin with a sustained virologic response of 50%. In 2011 another class of antivirals was approved by the FDA and EMEA--the HCV-NS3 protease inhibitors. Two molecules are now available: boceprevir and telaprevir. The protease inhibitors are used in association with peginterferon and ribavirin, which remain vital therapy components. Protease inhibitor regimens substantially increased the SVR rate in naive patients and also in previously relapse patients. Because of the high risk of emerging resistance to protease inhibitors, prior null responders are not yet suitable candidates for triple therapy, the SVR rate in these patients is still very low.

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INTRODUCTION: Hepatitis C virus (HCV) affects approximately 3% of the world population. The current standard of care for treatment of HCV is a combination of pegylated interferon and ribavirin. Approximately 10% of patients will stop treatment and 30% of patients require dose reduction because of side effects. For genotype 1 HCV-infected patients, only 40% of patients will achieve undetectable viral load 26 weeks posttreatment. AIMS: The objectives of this review were to identify new treatments that are in clinical trials. These include boceprevir and telaprevir which are in routine clinical use and form part of the American Association for the Study of Liver Diseases (AASLD) 2011 guidelines as well as drugs based on observational studies, improving/modifying ribavirin or interferon-based therapies, modifying the host response and finally the use of direct-acting antiviral agents (DAA). Materials and methods: MEDLINE and EMBASE databases were searched from 2008 to 2011 for treatments for hepatitis C. Furthermore, abstracts and poster presentations for the annual European Association Study of the Liver, AASLD, Digestive Disease Week and Asian Pacific Association for the study of the Liver were searched for relevant material. RESULTS: All four classes of DAA; NS3/NS4a serine protease inhibitors, cyclophilin inhibitors, NS5b polymerase inhibitors and NS5a inhibitors, show good success rates. Trials have been performed without ribavirin or interferon and demonstrate good antiviral activity with a decreased side effect profile. Combinations of DAA are a promising area of research with a high success rate. CONCLUSIONS: Clinical trials show that future HCV therapy could be personalised, achieve higher success rates with decreased adverse incidents.


Improved knowledge of the HCV life cycle and of structural features of HCV proteins have led to the discovery of numerous potential targets for antiviral therapy. Viral replication and polyprotein processing have been tagged as promising viral targets. Clathrin-mediated endocytosis, fusion of HCV with cellular membranes, translation of viral RNA, virus production and release as well as several host cell factors may provide alternative targets for future anti-HCV therapies. Several compounds are currently under investigation in clinical trials and showed high antiviral activity in patients with chronic hepatitis C. Recently, Phase III studies for two protease inhibitors, telaprevir and boceprevir, each given in combination with pegylated interferon (standard of care [SOC]), were completed. In HCV-genotype-1-infected patients, the addition of telaprevir or boceprevir to SOC increased sustained virological response rates from <50% to >70%. Nucleoside/nucleotide inhibitors of the HCV NS5B polymerase have shown antiviral activity against different HCV genotypes, and have a higher barrier to resistance than protease inhibitors. In addition, several allosteric binding sites have been identified for non-nucleoside inhibitors of the NS5B polymerase. Inhibitors of NS5A are potentially active against all HCV genotypes. Among the different host cell-targeting compounds, cyclophilin inhibitors have shown promising results. Future hope lies in the combination of direct-acting antiviral agents with the possibility of interferon-free treatment regimens.


Resolution of the three-dimensional structures of several hepatitis C virus (HCV) proteins, together with the development of replicative cell culture systems, has led to the identification of a number of potential targets for direct-acting antiviral (DAA) agents. Numerous families of drugs that potently inhibit the HCV lifecycle in vitro
have been identified, and some of these molecules have reached early to late clinical development. Two NS3/4A protease inhibitors, telaprevir and boceprevir, were approved in Europe and the United States in 2011 in combination with pegylated interferon (IFN)-alpha and ribavirin for the treatment of chronic hepatitis C related to HCV genotype 1, in both treatment-naïve and treatment-experienced patients. Sustained virological response rates in the range of 66-75% and 59-66% (29-88% if the response to the first course of therapy is taken into account) have been achieved in these two patient populations, respectively, with treatment durations of 24 to 48 weeks. A number of other DAAs are at the clinical developmental stage in combination with pegylated IFN-alpha and ribavirin or with other DAAs in IFN-free regimens, with or without ribavirin. They include second-wave, first-generation, and second-generation NS3/4A protease inhibitors, nucleoside/nucleotide analogue inhibitors and non-nucleoside inhibitorsof HCV RNA-dependent RNA polymerase, inhibitors of nonstructural protein 5A (NS5A) and host-targeted compounds, such as cyclophilin inhibitors and silibinin. The proof of concept that IFN-free regimens may lead to HCV eradication has recently been brought. However, new drugs may be associated with troublesome side effects and drugdrug interactions, and the ideal IFN-free DAA combination remains to be found.


Ribavirin has been used as an antiviral agent for several decades. Although it has activity against numerous viruses, its major use clinically has been in the treatment of respiratory syncytial virus in paediatric patients and chronic HCV infection in both children and adults. This review highlights the clinical application and mechanism of action of ribavirin and discusses the future role of ribavirin in treatment of HCV where there are intense research efforts to improve therapy.


While viral hepatitis is a global problem its prevalence in the UK is often underestimated. Chronic infection with the hepatitis B and/or C virus causes significant morbidity and mortality. New treatments that attenuate viral replication or induce immunity against infection have transformed the management of these conditions, but their effectiveness comes at some cost - both in financial terms and in the side-effect profile associated with treatment. Viral resistance promises to be an ongoing problem, particularly in patients who have an inadequate response to antiviral therapy or are non-adherent with treatment protocols. This article explores new developments in the treatment of chronic hepatitis B and C infection, and describes current protocols for managing patients with these conditions.


Approximately 180 million individuals are chronically infected with hepatitis C, which is strongly associated with the development of cirrhosis, end-stage liver disease and hepatocellular carcinoma. Several virological tools (anti-HCV antibody assays, measurement of HCV-RNA, HCV-genotyping) are useful in management of hepatitis C infected patients. The primary goal of antiviral therapy in chronic hepatitis C is a sustained virological response (SVR). The HCV genotype should be determined in every patient considered for antiviral therapy because the currently recommended treatment duration and ribavirin doses differ among HCV genotypes. Exact subtyping might gain increased importance for future therapies with direct-acting antiviral
agents (DAA) because of differences of antiviral activities and barriers to resistance among HCV subtypes. Monitoring HCV RNA by a highly sensitive assay (LOD <= 15 IU/ml) is the basis for management of response guided therapy of chronic hepatitis C with pegylated IFN plus ribavirin. Rules for early discontinuation of antiviral therapy in non-responders and determination of optimal treatment durations in virologic responders have been developed for application of individualized treatment strategies.


Hepatitis C infection is a global health problem. Spontaneous viral clearance was observed in approximately 30% of individuals with acute infection. In the therapy using a combination of pegylated interferon-alpha and ribavirin, approximately 50% of chronic hepatitis C patients infected with high viremia of hepatitis C virus infection (HCV) genotype 1 reached a sustained viral response. These findings were strongly expected to reflect variations of the host genome. To reveal genetic effects against viral clearance or treatment response, four independent groups applied a genome-wide association study (GWAS) to HCV infection. These groups almost simultaneously reported a strong association of interleukin (IL)-28B polymorphisms with viral clearance or final decision of HCV therapy. The discovered single nucleotide polymorphisms (SNPs) also revealed the enigma that the viral clearance rate was dependent on ethnic type. The significant SNPs are useful for prediction prior to treatment because of the strong association with clinical outcome. In addition, the unexpected results revealed by GWAS could promote the development of a novel drug related to IL-28B. Herein, we present current understanding in regard to the relationship between host variations and clinical outcome of hepatitis C.


Numerous direct-acting drugs to treat hepatitis C virus (HCV) infection are in development, offering the potential for substantial improvement over current interferon alfa-based therapy and the possibility of effective interferon alfa-sparing regimens in achieving cure of HCV infection. Drugs furthest along in clinical development include HCV nonstructural protein 3 (NS3) protease inhibitors (eg, telaprevir, boceprevir), which have potent anti-HCV activity but low barriers to resistance and considerable likelihood of cross-resistance. Nucleoside analogue nonstructural protein 5B (NS5B) polymerase inhibitors exhibit a high barrier to resistance and cross-HCV genotype and subtype activity. Nonnucleoside analogue polymerase inhibitors have a low barrier to resistance and are characterized by a substantial frequency of preexisting resistance mutations. The initial use of direct-acting drugs will be as add-on treatment to interferon alfa and ribavirin regimens. The success of interferon alfa-sparing regimens will depend on presenting a sufficiently high barrier to resistance with direct-acting drugs and whether the immunomodulatory effects of interferon alfa are needed for cure of HCV infection.


Chronic hepatitis C virus (HCV) infection is a major cause of liver cirrhosis and hepatocellular carcinoma. HCV is endemic in most parts of the world, with an estimated 170 million people infected worldwide and 3-4 million new cases each
year. HCV-related end-stage liver disease is now the main indication for liver transplantation in the USA and Western Europe. Unfortunately, no vaccine or immunoglobulin is available to prevent HCV infection. Currently, HCV treatment consists of the combined administration of pegylated interferon and ribavirin for a period of 24-48 weeks, resulting in complete viral eradication in 40-80% of patients, depending on genotype, viral load and patient characteristics. This therapy is often accompanied with side-effects that affect compliance and reduce treatment outcomes. Recently, reliable in vitro culture systems have been developed which accelerated antiviral therapy research. Many new specifically targeted antiviral therapies for hepatitis C (STAT-C) and treatment strategies are evaluated in clinical trials. These new antiviral agents are expected to improve treatment significantly with potentially shorter treatment duration. The most promising antiviral agents will be reviewed.


Hepatitis C virus (HCV) infection is a major and growing global health problem, affecting about 170 million people worldwide, and is a leading cause of liver cirrhosis and hepatocellular carcinoma. Currently, treatment is restricted to interferon alfa and ribavirin, which leads to a successful outcome in only about 50% of individuals. New effective treatments with tolerable side-effect profiles are needed urgently, but development has been hindered by an inability to culture HCV and a scarcity of animal models. Herein, we review progress in HCV biology, including cell culture and new animal models, and the contribution of this work to our understanding of the virus' life-cycle and pathogenesis and development of specifically targeted antiviral treatment. We also discuss changes in our understanding of HCV epidemiology, clinical manifestations, and diagnostics.

Session 4: Overview of Current hepatitis C therapy guidelines

Overview of current treatment policies and recommendations in EASL

Presentation Markus Peck-Radosavljevic, EASL Clinical Practice Guidelines: management of hepatitis C virus infection and the adaptations needed

Issue 5 (released March 2011) - updated June 2011

Revised version is in progress

Presentation Stefan Wiktor WHO Hepatitis C Therapeutic guidelines (they will be released before the end of 2013)

Prevention and Control of Viral Hepatitis Infection: Framework for Global Action


*WHO will provide guidance for screening, care and treatment of HBV and HCV infections, including provision of appropriate pre- and post-test counselling, as part of a framework for care and treatment and support to countries to make treatments more accessible and affordable.*

BACKGROUND & AIMS: The World Health Organisation (WHO) Prevention & Control of Viral Hepatitis Infection: Framework for Global Action offers a global vision for the prevention and control of viral hepatitis. In October 2012, the Coalition to Eradicate Viral Hepatitis in Asia Pacific (CEVHAP) organised the North Asia Workshop on Viral Hepatitis in Taipei to discuss how to implement the WHO Framework in the North Asia region. This paper presents outcomes from this workshop. 

METHODS: Twenty-eight representatives from local liver associations, patient organisations, and centres of excellence in Hong Kong, Japan, Korea, and Taiwan participated in the workshop. 

FINDINGS: Priority areas for action were described along the four axes of the WHO Framework: (1) awareness, advocacy and resources; (2) evidence and data; (3) prevention of transmission; and (4) screening and treatment. Priorities included: axis 1: greater public and professional awareness, particularly among primary care physicians and local advocacy networks. Axis 2: better economic data and identifying barriers to screening and treatment uptake. Axis 3: monitoring of vaccination outcomes and targeted harm reduction strategies. Axis 4: strengthening links between hospitals and primary care providers, and secure funding of screening and treatment, including for hepatocellular carcinoma. 

CONCLUSIONS: The WHO Framework provides an opportunity to develop comprehensive and cohesive policies in North Asia and the broader region. A partnership between clinical specialists, primary care physicians, policy makers, and people with or at risk of viral hepatitis is essential in shaping future policies.

RELATED Abstracts session 4

Pubmed MEDLINE search on {((Hepatitis C OR Hep C OR HCV) AND (treatment OR therapy) AND (guidelines OR recommendations))} in all fields and filters used on this search ‘last 5 year’ and ‘Review’ was performed. Relevant article were manually selected. The reference were sorted by publication year and first author

In total 18 were selected:


Hepatitis C is a frequent cause of liver cirrhosis and, hepatocellular carcinoma worldwide. However, predicting clinical outcomes in patients with chronic hepatitis C is challenging. The risk of disease progression is not linear and can be associated with several factors. With the currently available therapies, around 70% of naive patients, independently of hepatitis C virus genotype can achieve a sustained virologic response. Consequently, all hepatitis C virus patients are candidates for antiviral therapy. The decision to treat a patient with chronic hepatitis C virus infection is based on several factors, including the natural history of the disease, the stage of fibrosis, and the efficacy and adverse effects related to therapy. The decision to treat immediately or wait for a new drug is more difficult and should be tailored to each patient, taking into account the patient's characteristics, the risk of disease
progression, the patient's wishes, and the experience of the attending physician.


The American Association for the Study of Liver Diseases (AASLD) practice guidelines provide recommendations in diagnosing and managing patients with liver disease from available scientific evidence in combination with expert consensus opinions. The aim was to systematically review the evolution of recommendations from AASLD guidelines and identify gaps limiting the evidence-based foundations of these guidelines. Initial and current AASLD guidelines published from January 1998 to August 2012 were reviewed. The AGREE II instrument was used to evaluate rigor and transparency of guideline development. The number of recommendations, distribution of grades (strength or certainty), classes (benefit versus risk), and types of recommendations were evaluated. Whenever possible, multiple versions were evaluated for evolving scientific evidence. A total of 991 recommendations from 28 guidelines on 17 topics were evaluated. From initial to current guidelines, the total number of recommendations increased by 36% (512 to 699). The largest increases were from chronic hepatitis B virus (HBV) (+71), liver transplantation (+53), and autoimmune hepatitis (AIH) (+27). Most current recommendations are grade II (44%) and less than 20% are grade I. The AGREE II evaluation showed global improvement in guideline quality. Both HBV and chronic hepatitis C guidelines had greatest increases in grade I recommendations (+383% and +67%, respectively). The greatest increases in treatment recommendations were from HBV (grade I, +1,150%), liver transplantation (grade II, +112%), and AIH (grade III, +105%). Conclusion: Despite significant increases in the numbers of recommendations within AASLD practice guidelines over time, only a minority are supported by grade I evidence, highlighting the need for developing well-designed investigations to provide evidence for areas of uncertainty and improving the quality of future guidelines in hepatobiliary diseases. (Hepatology 2013).


BACKGROUND: Early treatment of acute hepatitis C virus (HCV) infection with interferon alfa monotherapy is very effective, with cure rates of greater than 85%. However, spontaneous clearance of HCV occurs in 10-50% of cases. We aimed to assess an alternative treatment strategy of delayed antiviral therapy in patients who do not eliminate the virus spontaneously compared with immediate treatment.

METHODS: In our open-label phase 3 non-inferiority trial, we enrolled adults (> =18 years) with acute hepatitis C but no HIV or hepatitis B co-infection at 72 centres in Germany. We randomly allocated patients with symptomatic acute hepatitis C (1:1) to receive immediate pegylated interferon alfa-2b treatment for 24 weeks or delayed treatment with pegylated interferon alfa-2b plus ribavirin (for 24 weeks) starting 12 weeks after randomisation if HCV RNA remained positive. We used a computer-generated randomisation sequence and block sizes of eight, stratified by bilirubin concentration. We assigned all asymptomatic patients to immediate treatment with pegylated interferon alfa-2b for 24 weeks. The primary endpoint was sustained HCV RNA negativity in all randomly allocated participants who completed screening (intention-to-treat analysis), with a non-inferiority margin of 10%. For the primary

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analysis, we calculated the virological response of patients in the immediate and delayed treatment groups and an absolute risk difference stratified by bilirubin status. The trial was stopped early on advice from the study advisory committee because of slow recruitment of participants. This study is registered, number ISRCTN88729946.

FINDINGS: Between April, 2004, and February, 2010, we recruited 107 symptomatic and 25 asymptomatic patients. 37 (67%) of 55 symptomatic patients randomly allocated to receive immediate treatment and 28 (54%) of 52 symptomatic patients randomly allocated to receive delayed treatment had a sustained virological response (difference 13.7%, 95% CI -4.6 to 32.0; p=0.071). 18 (72%) of 25 asymptomatic patients had a sustained virological response. 22 (42%) of 52 symptomatic patients allocated to receive delayed treatment did not complete follow-up compared with 20 (25%) of 80 symptomatic or asymptomatic patients assigned immediate treatment (p=0.037). 11 symptomatic patients (21%) assigned delayed treatment had spontaneous HCV clearance. 14 patients who received delayed pegylated interferon alfa-2b plus ribavirin treatment and completed follow-up achieved sustained virological response. INTERPRETATION: Delayed treatment is effective although not of equal efficacy to immediate treatment; coupled with the rate of spontaneous clearance it can reduce unnecessary treatment in closely monitored populations. Immediate treatment seems preferable in populations where loss to follow-up is great.

FUNDING: German Network of Competence on Viral Hepatitis (HepNet, funded by the German Federal Ministry of Education and Research, grants 01KI0102, 01KI0401, and 01KI0601), MSD, Schering-Plough.


People who inject drugs (PWID) are the group most affected by HCV; however, treatment uptake has been low. Engagement between PWID and healthcare workers has been characterized by mistrust and discrimination. Peer support for HCV is one way to overcome these barriers. Peer support models for chronic disease management have been successfully applied for other diseases. HCV peer support models have been implemented in various settings, but those that include opioid substitution treatment have been more common. Most models have been either service generated (provider led) or community controlled (peer led). Peer support models have been implemented successfully, with a range of outcomes including increased treatment knowledge and uptake and improved service provision. Genuine partnerships between peers and services were common across models and led to positive transformations for both clients and services. Further investigation of peer support for HCV treatment and its impact on both individuals and services is recommended.


In the developed world, the majority of new and existing hepatitis C virus (HCV) infections occur among people who inject drugs (PWID). The burden of HCV-related liver disease in this group is increasing, but treatment uptake among PWID remains low. Among PWID, there are a number of barriers to care that should be considered and systematically addressed, but these barriers should not exclude PWID from HCV treatment. Furthermore, it has been clearly demonstrated that HCV treatment is safe and effective across a broad range of multidisciplinary healthcare settings. Given the burden of HCV-related disease among PWID, strategies to enhance HCV assessment
and treatment in this group are urgently needed. These recommendations demonstrate that treatment among PWID is feasible and provides a framework for HCV assessment, management, and treatment. Further research is needed to evaluate strategies to enhance assessment, adherence, and SVR among PWID, particularly as new treatments for HCV infection become available.


Hepatitis C virus (HCV) infected patients often take multiple co-medications to treat adverse events related to HCV therapy, or to manage other co-morbidities. Drug-drug interactions associated with this polypharmacy are relatively new to the field of HCV pharmacotherapy. With the advent of the direct-acting antivirals telaprevir and boceprevir, which are both substrates and inhibitors of the cytochrome P450 (CYP) 3A iso-enzyme, knowledge and awareness of drug-drug interactions have become a cornerstone in the evaluation of patients starting and continuing HCV combination therapy. In our opinion, an overview of conducted drug-drug interaction studies and a list of contraindicated medications is not enough for the clinical management of these drug-drug interactions. Knowledge of pharmacokinetic profiles and concentration-effect relationships is key for the interpretation of these data, and insight into how to manage these interactions (e.g., dose adjustments, safe alternatives and therapeutic drug monitoring) is of equal importance. This review provides a practical overview of the safe and effective management of these clinical challenges.


Hepatitis C virus (HCV) infection is the most common etiology of chronic liver disease in Western countries. Morbidity and mortality due to HCV-related end-stage liver disease are increasing, just as novel therapeutics arrive with the promise of better cure rates that prevent these complications. However, substantial barriers to successful application of these novel treatments remain, including the lack of providers with sufficient knowledge to address this epidemic. To address these deficits, this article aims to provide a general framework with algorithms to guide initial management decisions for HCV genotype 1 infection, the most commonly found genotype, based on therapies approved as of 2013.


Hepatitis C virus (HCV) is the most common infectious cause of chronic liver disease in Europe. With the introduction of interferon based therapy in combination with ribavirin treatment of chronic HCV has become feasible. This therapy has become the standard of care for patients with HCV and depending on the HCV genotype treatment is successful in 40-70% of patients. In the recent years a new class of drugs have emerged that changed the landscape of HCV treatment. These direct antiviral agents inhibit the NS3/N4A serine protease of HCV. Prototypes are telaprevir and boceprevir and they specifically exert antiviral activity against genotype 1 HCV. A series of landmark trials has paved the way for introduction of these agents, and they have documented a great improvement in the care of genotype 1 HCV patients. Telaprevir and boceprevir are given in combination with pegylated interferon and ribavirin and are useful for treatment naive as well as treatment experienced patients. The clinician should be aware of these developments as they have implications for
side effect management, and drug-drug interactions. Finally, strategic use of these agents comes with stopping rules and require close monitoring of the HCV viral load.


CONTEXT: New trial data and drug regimens that have become available in the last 2 years warrant an update to guidelines for antiretroviral therapy (ART) in human immunodeficiency virus (HIV)-infected adults in resource-rich settings.

OBJECTIVE: To provide current recommendations for the treatment of adult HIV infection with ART and use of laboratory-monitoring tools. Guidelines include when to start therapy and with what drugs, monitoring for response and toxic effects, special considerations in therapy, and managing antiretroviral failure. DATA SOURCES, STUDY SELECTION, AND DATA EXTRACTION: Data that had been published or presented in abstract form at scientific conferences in the past 2 years were systematically searched and reviewed by an International Antiviral Society-USA panel. The panel reviewed available evidence and formed recommendations by full panel consensus. DATA SYNTHESIS: Treatment is recommended for all adults with HIV infection; the strength of the recommendation and the quality of the evidence increase with decreasing CD4 cell count and the presence of certain concurrent conditions. Recommended initial regimens include 2 nucleoside reverse transcriptase inhibitors (tenofovir/emtricitabine or abacavir/lamivudine) plus a nonnucleoside reverse transcriptase inhibitor (efavirenz), a ritonavir-boosted protease inhibitor (atazanavir or darunavir), or an integrase strand transfer inhibitor (raltegravir). Alternatives in each class are recommended for patients with or at risk of certain concurrent conditions. CD4 cell count and HIV-1 RNA level should be monitored, as should engagement in care, ART adherence, HIV drug resistance, and quality-of-care indicators. Reasons for regimen switching include virologic, immunologic, or clinical failure and drug toxicity or intolerance. Confirmed treatment failure should be addressed promptly and multiple factors considered.

CONCLUSION: New recommendations for HIV patient care include offering ART to all patients regardless of CD4 cell count, changes in therapeutic options, and modifications in the timing and choice of ART in the setting of opportunistic illnesses such as cryptoccocal disease and tuberculosis.


The prevention of hepatitis C virus (HCV) infection and associated health conditions (eg, cirrhosis and hepatocellular carcinoma) is a public health priority in the United States. Hepatitis C virus-related morbidity and mortality is increasing at a time when the advent of highly effective therapies greatly increases opportunities to prevent HCV transmission and disease. In 2010, the Institute of Medicine recommended that national action be taken to address this "underappreciated health concern for the nation." In response, in 2011, the US Department of Health and Human Services (HHS) published a viral hepatitis action plan that guides response to the viral hepatitis epidemic by providing explicit steps to be undertaken by specific HHS agencies to improve provider training and community education; expand access to testing, care, and treatment; strengthen public health surveillance; improve HCV preventive services for injection drug users; develop a hepatitis C vaccine; and prevent HCV transmission in healthcare settings. For all aspects of the action plan, infectious disease specialists and other clinicians assume a key role in efforts to reduce HCV-
related morbidity and mortality. With successful collaboration of the public and private sectors, the hepatitis C epidemic can be forever silenced.


PURPOSE OF REVIEW: Chronic hepatitis C infection remains a global public health burden and has important clinical implications due to progressive liver fibrosis and development of cirrhosis and its complications. The role of antiviral therapy in infected children is an area of controversy due to an indolent clinical course in the majority of children, and a low likelihood of viral eradication in response to an intensive interferon-based treatment course that is associated with a wide spectrum of adverse effects. This review summarizes new concepts in the epidemiology, natural history, and management of chronic hepatitis C infection in children. RECENT FINDINGS: In the past 18 months, two large prospective studies demonstrated high rates of sustained virologic response in children with chronic hepatitis C infection, estimated at 53% in genotype 1 with peginterferon alpha-2b-ribavirin, and 47% in genotype 1 with peginterferon alpha-2a-ribavirin. On this basis, both combination regimens have been recently approved by the Food and Drug Administration (FDA) for use in children. SUMMARY: Children with hepatitis C infection may benefit from early treatment, and the decision to pursue antiviral therapy should be based on individual assessment of host and viral characteristics, and stage of liver fibrosis.


In May 2011, hepatitis C virus (HCV) protease inhibitors (PIs) were approved by the US Food and Drug Administration to treat persons with genotype 1 chronic hepatitis C virus (HCV) infection, but not those dually infected with human immunodeficiency virus (HIV). Although critical safety and efficacy data are lacking, the availability of the drugs and substantial medical need justify the off-label use of HCV PIs in select HIV/HCV-coinfected persons. Pending results of ongoing investigations, this article represents provisional guidance on the use of HCV PIs in HIV-infected persons.


The advent of triple therapy (TT) with first-generation protease inhibitors boceprevir (BOC) and telaprevir (TVR) in addition to pegylated interferon and ribavirin resulted in a significant gain in terms of sustained virological response (SVR) when treating naive or previous treated patients with genotype 1 (G1) chronic hepatitis C (CHC). This gain is partly balanced by the increased complexity of treatment and by the raised costs and risks of therapy, making necessary to optimize the indication to TT. Specifically, the identification of patient needing to TT over DT, the choice of the more correct therapeutic approach according to baseline and on treatment SVR predictors, and the timing of antiviral treatment, appear key issues to evaluate when considering TVR or BOC-based therapies. Along this line, further efforts aimed to optimize the current TT regimens are still needed, especially in under-represented groups of patients in phase 3 studies such as those with cirrhosis, where post-marketing data are giving interesting evidences.

Resolution of the three-dimensional structures of several hepatitis C virus (HCV) proteins, together with the development of replicative cell culture systems, has led to the identification of a number of potential targets for direct-acting antiviral (DAA) agents. Numerous families of drugs that potently inhibit the HCV lifecycle in vitro have been identified, and some of these molecules have reached early to late clinical development. Two NS3/4A protease inhibitors, telaprevir and boceprevir, were approved in Europe and the United States in 2011 in combination with pegylated interferon (IFN)-alpha and ribavirin for the treatment of chronic hepatitis C related to HCV genotype 1, in both treatment-naive and treatment-experienced patients. Sustained virological response rates in the range of 66-75% and 59-66% (29-88% if the response to the first course of therapy is taken into account) have been achieved in these two patient populations, respectively, with treatment durations of 24 to 48 weeks. A number of other DAAs are at the clinical developmental stage in combination with pegylated IFN-alpha and ribavirin or with other DAAs in IFN-free regimens, with or without ribavirin. They include second-wave, first-generation, and second-generation NS3/4A protease inhibitors, nucleoside/nucleotide analogue inhibitors and non-nucleoside inhibitors of HCV RNA-dependent RNA polymerase, inhibitors of nonstructural protein 5A (NS5A) and host-targeted compounds, such as cyclophilin inhibitors and silibinin. The proof of concept that IFN-free regimens may lead to HCV eradication has recently been brought. However, new drugs may be associated with troublesome side effects and drug-drug interactions, and the ideal IFN-free DAA combination remains to be found.


PURPOSE OF REVIEW: Despite a high burden of hepatitis C virus (HCV) and HIV infection among IDUs and the advent of effective therapies, assessment and treatment remain limited. The current review focuses on the management of HCV and HIV among IDUs, focusing particularly on recent strategies to enhance assessment, uptake and response to HCV and HIV treatment. RECENT FINDINGS: There are compelling data demonstrating that with the appropriate programs, treatment for HIV and HCV among IDUs is successful. However, assessment and treatment for HCV and HIV lags far behind the numbers of IDUs who could benefit from therapy, related to systems, provider and patient-related barriers to care. Strategies for enhancing assessment and treatment for HCV and HIV have been developed, including novel models integrating HCV/HIV care within existing community-based and drug and alcohol clinics, innovative methods for education delivery (including peer-support models) and directly observed therapy. SUMMARY: As we move forward, research must move beyond demonstrating that HCV and HIV infections can be successfully treated among IDUs. There is clear evidence that this is both feasible and effective. Novel strategies to enhance assessment, uptake and response to treatment should be evaluated among IDUs to elucidate mechanisms to enhance care for this underserved population.


PURPOSE OF REVIEW: To provide an update on the epidemiology and management of HIV and hepatitis C virus (HCV) in resource-limited settings (RLSs).

RECENT FINDINGS: The global prevalence of HIV is 33.3 million people of whom 22.5 million live in sub-Saharan Africa. Hepatitis C affects 170 million people globally with majority of the infected persons living in sub-Saharan Africa and other RLSs. Transmission of these viruses varies greatly even within the RLSs. In the RLSs
Hepatitis C virus (HCV) infection is one of the most important causes of cirrhosis in Europe, Asia and Central/South America, most transmissions occur through injection drug use, whereas in Africa use of needles for medical treatment and blood transfusion may be the main modes of transmission. However, generally there is a rise in injection drug use even in RLSs. SUMMARY: Hepatitis C and HIV are common infections and are more prevalent in RLSs, but there are regional differences in transmission even in RLSs. Treatment is difficult in some of the RLSs and prevention by screening donor blood as well and use of sterile instruments in treatment of patients will be important in curbing transmission in some of these settings.


HCV has been classified into no fewer than six major genotypes and a series of subtypes. Each HCV genotype is unique with respect to its nucleotide sequence, geographic distribution, and response to therapy. Genotypes 1, 2, and 3 are common throughout North America and Europe. HCV genotype 4 (HCV-4) is common in the Middle East and in Africa, where it is responsible for more than 80% of HCV infections. It has recently spread to several European countries. HCV-4 is considered a major cause of chronic hepatitis, cirrhosis, hepatocellular carcinoma, and liver transplantation in these regions. Although HCV-4 is the cause of approximately 20% of the 170 million cases of chronic hepatitis C in the world, it has not been the subject of widespread research. Therefore, this document, drafted by a panel of international experts, aimed to review current knowledge on the epidemiology, natural history, clinical, histological features, and treatment of HCV-4 infections.


The issue of best treatment for chronic hepatitis C virus (HCV) infection is in constant flux, not only in Western countries but also in Asia. Currently, pegylated-interferon plus ribavirin is the standard of care. Studies from Asia provide evidence to support the same broad treatment strategies for Asian patients as recommended in Western countries. Nevertheless, there is increasing evidence that Asians have a higher likelihood of achieving a sustained virological response (SVR) than their Caucasians counterparts when treated with the corresponding regimen. With the recommended 'standard dose and duration treatment regimens', SVR is achieved in Asia for around 70% of HCV genotype 1 (HCV-1) infected cases, approximately 90% of HCV-2/3, approximately 65% of HCV-4, and approximately 80% of HCV-6 patients. Difference of body weight in race might contribute the superior response in Asian patients. HCV genotype distribution in Asia also differs from North-America/Europe. HCV-6 and its variants, previously mistyped as HCV-1, needs accurate genotyping. Increasing data support the proposal that HCV genotype, baseline viral load and on-treatment virological response provide information for decision-making so that treatment can be individualized. Beyond the older recommendations, an abbreviated 24-week regimen could be suggested for HCV-1/4 patients with baseline viral loads < 400 000 IU/mL and a rapid virological response (RVR, HCV RNA undetectable at week 4), and an abbreviated 12-16 weeks of pegylated-interferon with weight-based doses of ribavirin could be suggested for HCV-2/3 patients with a RVR. Such tailored treatment regimens can reduce the costs of treatment and incidence of adverse events without compromising efficacy. Hepatitis C virus (HCV) infection is one of the most important causes of cirrhosis
worldwide, and particularly in some countries of Asia (notably Japan) where it is now more prevalent than chronic hepatitis B virus infection. Hepatitis C virus infection can also lead to hepatocellular carcinoma (HCC). It is estimated that there are more than 170 million people chronically infected with HCV, and 3 to 4 million persons are newly infected each year. The risk for developing cirrhosis 20 years after initial HCV infection among those chronically infected varies between studies, but is estimated at around 10%-15% for men and 1-5% for women. Once cirrhosis is established, the rate of developing HCC is at 1%-4% per year. Approximately 280,000 deaths per year are related to HCV infection. Hepatitis C virus-related end-stage liver disease and HCC have become the leading cause for liver transplantation worldwide. In the Asia-Pacific area, the estimated prevalence of antibodies to HCV (anti-HCV) range from 0.3% in New Zealand to 5.6% in Thailand. In Japan, Middle East, Vietnam and Taiwan, several HCV hyper-endemic areas have been reported with an anti-HCV prevalence rate of 12% to as high as 58%. In addition to the well-known endemic status of HBV infection in most countries of the Asia-Pacific region, HCV infection presents another critical scenario of public health issue in this region, as outlined in Guidelines by the Asia-Pacific Association for Study of the Liver (APASL). Given the lack of an effective vaccine, optimal treatment of chronic HCV infection is now perceived as a 'must' in terms of public health strategies, as well as of the clinical setting for individual patients.
Despite dramatic improvements in antiviral therapy for hepatitis C, there is reason to believe that the uptake of antiviral therapy remains limited. The aims of this study were to determine the number of patients being treated with antiviral therapy in the U.S., to estimate the public health impact of these treatment patterns, and to identify barriers to treatment for patients with hepatitis C. Data on the number of new patient pegylated interferon prescriptions each year, from 2002-2007, was obtained from Wolters Kluwer Inc., which maintains an electronic audit of pharmacies nationwide. A Markov model was created of the population with chronic hepatitis C in the U.S. from 2002 to 2030, and was used to estimate the number of liver-related deaths caused by hepatitis C that will be prevented by current treatment patterns. The National Health and Nutrition Evaluation Survey (NHANES) Hepatitis C Follow-Up Questionnaire was used to investigate reasons for lack of treatment and to identify strategies for improving access. Approximately 663,000 patients received antiviral therapy between 2002 and 2007, and treatment rates appear to be declining. If this trend continues, only 14.5% of liver-related deaths caused by hepatitis C from 2002-2030 will be prevented by antiviral therapy. Results from the NHANES questionnaire suggest that the primary barrier to treatment is lack of diagnosis, with 69/133 (adjusted proportion 49%) of respondents previously unaware that they had hepatitis C. CONCLUSION: Efforts to improve rates of diagnosis and treatment will be required if the future public health burden of hepatitis C is to be ameliorated.

Volk, M. L. "Antiviral therapy for hepatitis C: why are so few patients being treated?" J Antimicrob Chemother 2010 65(7): 1327-1329.
barriers also exist. Fewer than half of chronic hepatitis C infections are diagnosed, relatively few are referred for treatment, and misperceptions about the disease and its treatment abound amongst patients and physicians alike. This article will discuss patient and physician factors that contribute to the undertreatment of chronic hepatitis C.

Presentation Homie Razavi

Estimating the impact of hepatitis C virus therapy on future liver related morbidity, mortality and costs related to chronic hepatitis in Europe


BACKGROUND/AIMS: Peginterferon plus ribavirin is the state-of-the-art antiviral therapy for prevention of serious complications of hepatitis C. Our aim was to compare market uptake of and access to these drugs across Europe. METHODS: We collected launch and sales data for peginterferons for 21 countries in the WHO European region and compared country-specific sales rates. Additionally, we converted sales figures into patient numbers and related those to country-specific hepatitis C prevalence, taking into account genotype distribution, patient characteristics and practice patterns. RESULTS: Peginterferon sales rates differed considerably across countries. The earliest, most rapid and highest adoption rates were in EU founder states, followed by EU members that joined after foundation, and EU non-member states. Most new member states showed a marked increase in sales. By the end of 2005, approximately 308,000 patients had been treated with peginterferons in the 21 countries evaluated. The number of patients ever treated ranged from 16% of prevalent cases in France to less than 1% of cases in Romania, Poland, Greece and Russia. CONCLUSIONS: Peginterferon market uptake and access differed considerably across Europe, suggesting unequal access to optimised therapy. Besides budget restrictions, national surveillance and treatment policies should be considered as reasons for market access variation.

RELATED Abstracts session 5

Pubmed MEDLINE search on {Hepatitis C OR Hep C OR HCV AND (screening OR impact OR access) AND (public health OR recommendations)} in all fields and filters used on this search ‘last 5 year’ and ‘Review’ was performed. Relevant article were manually selected. The reference were sorted by publication year and first author

In total 26 were selected:


BACKGROUND: The progression of hepatitis C virus (HCV) disease usually occurs over a 10-year period. HCV-related complications as well as the highly debilitating effects on patients represent a significant item of expenditure for the National Health Service. Early detection of HCV infection is an excellent opportunity to improve patients’ quality of life and to rationalize resource allocation. OBJECTIVE: The aim of this study was to provide a cost-effectiveness evaluation of an anti-HCV screening
program in the Italian National Health Service perspective. METHODS: We built a
Markov model made up of two arms. The "Test Strategy" arm involves a screening
program based on the enzyme immunoassay for detection of antibodies as first-level
test and the research of HCV RNA as second-level detection; patients with positive
test results are treated with peg-interferon alfa in combination with ribavirine.
Parameters were derived from the literature and validated through experts' opinion.
Costs and benefits were discounted by 3.5%. Results were expressed as cost/quality-
adjusted life-year (QALY) gained through the screening program compared with the
treatment of symptomatic patients. Deterministic and probabilistic sensitivity analysis
was performed. RESULTS: The incremental cost-effectiveness ratio of the "Test
Strategy" is euro5171/QALY, definitively below the cost/QALY of other approved
treatments in Italy. Model results turned out as sensitive to the age of the target
population, the prevalence of HCV infection, and the time horizon adopted.
CONCLUSIONS: The anti-HCV screening program is a valid health-related
investment improving patients' quality of life and survival with an acceptable
expenditure increase for the National Health Service.

recommendations promote opportunities for care and cure." Ann Intern Med 2013

virus infection in adults: a systematic review for the U.S. Preventive Services Task

BACKGROUND: Identification of hepatitis C virus (HCV)-infected persons through
screening could lead to interventions that improve clinical outcomes. PURPOSE: To
review evidence about potential benefits and harms of HCV screening in
asymptomatic adults without known liver enzyme abnormalities. DATA SOURCES:
English-language publications identified from MEDLINE (1947 to May 2012), the
Cochrane Library Database, clinical trial registries, and reference lists. STUDY
SELECTION: Randomized trials and cohort, case-control, and cross-sectional studies
that assessed yield or clinical outcomes of screening; studies reporting harms from
HCV screening; and large series reporting harms of diagnostic liver biopsies. DATA
EXTRACTION: Multiple investigators abstracted and checked study details and
quality by using predefined criteria. DATA SYNTHESIS: No study evaluated clinical
outcomes associated with screening compared with no screening or of different risk-
or prevalence-based strategies. Three cross-sectional studies in higher prevalence
populations found that screening strategies that targeted multiple risk factors were
associated with sensitivities greater than 90% and numbers needed to screen to
identify 1 case of HCV infection of less than 20. Data on direct harms of screening
were sparse. A large study of percutaneous liver biopsies (n = 2740) in HCV-infected
patients with compensated cirrhosis reported no deaths and a 1.1% rate of serious
adverse events (primarily bleeding and severe pain). LIMITATIONS: Modeling
studies were not examined. High or unreported proportions of potentially eligible
patients in the observational studies were not included in calculations of screening
yield because of unknown HCV status. CONCLUSION: Although screening tests can
accurately identify adults with chronic HCV infection, targeted screening strategies
based on the presence of risk factors misses some patients with HCV infection. Well-
designed prospective studies are needed to better understand the effects of different
HCV screening strategies on diagnostic yield and clinical outcomes. PRIMARY

BACKGROUND & AIMS: The Veterans Health Administration (VHA) is the largest single provider of care for hepatitis C virus (HCV) infection in the United States. We analyzed the cost effectiveness of treatment with the HCV protease inhibitors boceprevir and telaprevir in a defined managed care population of 102,851 patients with untreated chronic genotype 1 infection. METHODS: We used a decision-analytic Markov model to examine 4 strategies: standard dual-therapy with pegylated interferon-alfa and ribavirin (PR), the combination of boceprevir and PR triple therapy, the combination of telaprevir and PR, or no antiviral treatment. A sensitivity analysis was performed. Sources of data included published rates of disease progression, the census bureau, and VHA pharmacy and hospitalization cost databases. RESULTS: The estimated costs for treating each patient were $8000 for PR, $31,300 for boceprevir and PR, and $41,700 for telaprevir and PR. Assuming VHA treatment rates of 22% and optimal rates of sustained virologic response, PR, boceprevir and PR, and telaprevir and PR would reduce relative liver-related deaths by 5.2%, 10.9%, and 11.5%, respectively. Increasing treatment rates to 50% would reduce liver-related deaths by 12%, 24.7%, and 26.1%, respectively. The incremental cost-effectiveness ratios were $29,184/quality-adjusted life-years for boceprevir and PR and $44,247/quality-adjusted life-years for telaprevir and PR vs only PR. With the current 22% treatment rate, total system-wide costs to adopt boceprevir and PR or telaprevir and PR would range from $708 to $943 million. CONCLUSIONS: Despite substantial up-front costs of treating HCV-infected patients in the VHA with PR, or telaprevir and PR, each regimen improves quality of life and extends life expectancy by reducing liver-related morbidity and mortality, and should be cost effective. Further efforts to expand access to direct-acting antiviral therapy are warranted.


The US Centers for Disease Control and Prevention recently issued new recommendations to screen persons born between 1945 and 1965 for hepatitis C virus. Federal facilities in the US Indian Health Service were surveyed on knowledge and support for the hepatitis C virus recommendations, as well as barriers and concerns.


Most individuals infected with the hepatitis C have not received antiviral treatment, with mental health and substance abuse problems being the primary barrier. Interventions have been developed to address these barriers among HCV patients considered "high-risk" for antiviral treatment. We present the design and methods of a prospective, randomized controlled multisite trial being conducted in the Veterans Affairs Healthcare System. The study employed a parallel design and the three study sites randomized a total of 364 VA patients with HCV to either Integrated Care (IC) or Usual Care (UC). The IC intervention consisted of a mental health provider (MHP)
performing a) brief interventions to address risk factors; b) collaborative consultation with the HCV treatment clinicians; and c) case management prior to and during antiviral treatment. Clinical outcomes were abstracted from patient medical records and self-report questionnaires were completed at baseline, 4-months, 16-months, and 22-months after enrollment. The primary outcome of the study was sustained viral response (SVR). Secondary clinical outcomes were HCV treatment initiation and completion rates. Other secondary outcomes included substance use, depression, PTSD symptoms, quality of life, healthcare satisfaction, and healthcare utilization. The Integrated Care intervention has the potential to transform HCV antiviral treatment by increasing the number of HCV-infected individuals that can be successfully treated.


We are entering an important new chapter in the story of hepatitis C virus (HCV) infection. There are clear challenges and opportunities. On the one hand, new HCV infections are still occurring, and an estimated 185 million people are or have previously been infected worldwide. Most HCV-infected persons are unaware of their status yet are at risk for life-threatening diseases such as cirrhosis and hepatocellular carcinoma (HCC), whose incidences are predicted to rise in the coming decade. On the other hand, new HCV infections can be prevented, and those that have already occurred can be detected and treated--viral eradication is even possible. How the story ends will largely be determined by the extent to which these rapidly advancing opportunities overcome the growing challenges and by the vigor of the public health response.


BACKGROUND: Evidence documents successful hepatitis C virus (HCV) treatment outcomes for people who inject drugs (PWID) and interest in HCV treatment among this population. Maximising HCV treatment for PWID can be an effective HCV preventative measure. Yet HCV treatment among PWID remains suboptimal. This review seeks to map social factors mediating HCV treatment access. METHOD: We undertook a review of the social science and public health literature pertaining to HCV treatment for PWID, with a focus on barriers to treatment access, uptake and completion. Medline and Scopus databases were searched, supplemented by manual and grey literature searches. A two step search was taken, with the first step pertaining to literature on HCV treatment for PWID and the second focusing on social structural factors. In total, 596 references were screened, with 165 articles and reports selected to inform the review. RESULTS: Clinical and individual level barriers to HCV treatment among PWID are well evidenced. These include patient and provider concerns regarding co-morbidities, adherence, and side effect management. Social factors affecting treatment access are less well evidenced. In attempting to map these, key barriers fall into the following domains: social stigma, housing, criminalisation, health care systems, and gender. Key facilitating factors to treatment access include: combination intervention approaches encompassing social as well as biomedical interventions, low threshold access to opiate substitution.
therapy, and integrated delivery of multidisciplinary care. **CONCLUSION:**

Combination intervention approaches need to encompass social interventions in relation to housing, stigma reduction and systemic changes in policy and health care delivery. Future research needs to better delineate social factors affecting treatment access.


Recent research has identified high hepatitis C virus (HCV) prevalence among older U.S. residents who contracted HCV decades ago and may no longer be recognized as high risk. We assessed the cost-effectiveness of screening 100% of U.S. residents born 1946-1970 over 5 years (birth-cohort screening), compared with current risk-based screening, by projecting costs and outcomes of screening over the remaining lifetime of this birth cohort. A Markov model of the natural history of HCV was developed using data synthesized from surveillance data, published literature, expert opinion, and other secondary sources. We assumed eligible patients were treated with pegylated interferon plus ribavirin, with genotype 1 patients receiving a direct-acting antiviral in combination. The target population is U.S. residents born 1946-1970 with no previous HCV diagnosis. Among the estimated 102 million (1.6 million chronically HCV infected) eligible for screening, birth-cohort screening leads to 84,000 fewer cases of decompensated cirrhosis, 46,000 fewer cases of hepatocellular carcinoma, 10,000 fewer liver transplants, and 78,000 fewer HCV-related deaths. Birth-cohort screening leads to higher overall costs than risk-based screening ($80.4 billion versus $53.7 billion), but yields lower costs related to advanced liver disease ($31.2 billion versus $39.8 billion); birth-cohort screening produces an incremental cost-effectiveness ratio (ICER) of $37,700 per quality-adjusted life year gained versus risk-based screening. Sensitivity analyses showed that reducing the time horizon during which health and economic consequences are evaluated increases the ICER; similarly, decreasing the treatment rates and efficacy increases the ICER. Model results were relatively insensitive to other inputs. Conclusion: Birth-cohort screening for HCV is likely to provide important health benefits by reducing lifetime cases of advanced liver disease and HCV-related deaths and is cost-effective at conventional willingness-to-pay thresholds.


**BACKGROUND:** Chronic hepatitis C (HCV) infected patients with coexisting mental health and/or substance abuse issues face significant barriers to treatment and are often deferred. This paper sought to highlight critical pre-treatment strategies and provide tangible resources for HCV clinicians to facilitate preparation and successful treatment of these patients. **METHODS:** Guided by the clinical experience of our liver center, a large, tertiary academic medical center, and informed by the extant literature, we summarize pre-treatment strategies and specific resources and recommendations for HCV providers. **RESULTS:** Four key pre-treatment strategies include: 1) screening for mental health/substance abuse issues using brief, reliable and validated instruments; 2) locating and establishing collaborative care with mental health and substance abuse specialists; 3) using a motivational interviewing communication style; and 4) addressing adherence-related issues. **CONCLUSIONS:** HCV clinicians are in a unique position to prepare patients with coexisting mental health and/or substance abuse issues for antiviral therapy.

The 2010 Institute of Medicine report on "Hepatitis and Liver Cancer" indicated that lack of knowledge and awareness about chronic hepatitis B (HBV) and C virus (HCV) infections and insufficient understanding about the extent and seriousness of this public health problem impeded current efforts to prevent and control hepatitis B and C. A single-topic conference was held in June 2011 to discuss strategies to improve the effectiveness of screening, care referral, and clinical management of chronic HBV and HCV infections with the ultimate goal of reducing morbidity and mortality from these infections. Various models that have been shown to improve hepatitis screening and effectiveness of hepatitis treatment in the community, including rural settings and populations that have traditionally been excluded due to comorbidities, were presented. Recent advances in laboratory testing, medical management, and new antiviral therapies will not decrease the burden of viral hepatitis if persons at risk for or who are living with viral hepatitis are not aware of the risks, have not been diagnosed, or have no access to care. Systematic changes in our health care delivery system and enhanced coordination of prevention and care services with partnerships between public health leaders and clinicians through education of the public and health care providers and linkage of infected persons with care and treatment services can increase the success of preventing viral hepatitis and the effectiveness of hepatitis treatment in the real world. Implementation of these changes is feasible and will require policy changes, coordination among government agencies, and collaboration between government agencies, health care providers, community organizations, and advocacy groups.


**BACKGROUND:** In the United States, hepatitis C virus (HCV) infection is most prevalent among adults born from 1945 through 1965, and approximately 50% to 75% of infected adults are unaware of their infection. **OBJECTIVE:** To estimate the cost-effectiveness of birth-cohort screening. **DESIGN:** Cost-effectiveness simulation. **DATA SOURCES:** National Health and Nutrition Examination Survey, U.S. Census, Medicare reimbursement schedule, and published sources. **TARGET POPULATION:** Adults born from 1945 through 1965 with 1 or more visits to a primary care provider annually. **TIME HORIZON:** Lifetime. **PERSPECTIVE:** Societal, health care. **INTERVENTION:** One-time antibody test of 1945-1965 birth cohort. **OUTCOME MEASURES:** Numbers of cases that were identified and treated and that achieved a sustained viral response; liver disease and death from HCV; medical and productivity costs; quality-adjusted life-years (QALYs); incremental cost-effectiveness ratio (ICER). **RESULTS OF BASE-CASE ANALYSIS:** Compared with the status quo, birth-cohort screening identified 808,580 additional cases of chronic HCV infection at a screening cost of $2874 per case identified. Assuming that birth-cohort screening was followed by pegylated interferon and ribavirin (PEG-IFN+R) for treated patients, screening increased QALYs by 348,800 and costs by $5.5 billion, for an ICER of $15,700 per QALY gained. Assuming that birth-cohort screening was followed by direct-acting antiviral plus PEG-IFN+R treatment for treated patients, screening increased QALYs by 532,200 and costs by $19.0 billion, for an ICER of $35,700 per QALY saved. **RESULTS OF SENSITIVITY ANALYSIS:** The ICER of birth-cohort
screening was most sensitive to sustained viral response of antiviral therapy, the cost of therapy, the discount rate, and the QALY losses assigned to disease states. LIMITATION: Empirical data on screening and direct-acting antiviral treatment in real-world clinical settings are scarce. CONCLUSION: Birth-cohort screening for HCV in primary care settings was cost-effective. PRIMARY FUNDING SOURCE: Division of Viral Hepatitis, Centers for Disease Control and Prevention.


DESCRIPTION: The Centers for Disease Control and Prevention (CDC) and a group of governmental and private sector partners developed these evidence-based recommendations to increase the proportion of hepatitis C virus (HCV)-infected persons who know their status and are linked to appropriate care and treatment. The recommendations also address brief alcohol screening, as alcohol accelerates progression of liver disease among HCV-infected individuals. These recommendations augment CDC's 1998 and 1999 recommendations based on risk and medical indications and are not meant to replace those recommendations.

METHODS: These recommendations are based on systematic reviews of evidence published from 1995 through February 2012 in MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Controlled Trials, Sociological Abstracts, and Database of Abstracts of Reviews of Effects. Selected studies included cross-sectional and cohort studies that addressed either prevalence of hepatitis C in the United States or clinical outcomes (for example, hepatocellular carcinoma and serious adverse events) among treated patients and systematic reviews of trials that assessed effectiveness of brief screening interventions for alcohol consumption. The Grading of Recommendations Assessment, Development, and Evaluation framework was used to assess quality of the evidence. RECOMMENDATION 1: Adults born during 1945-1965 should receive 1-time testing for HCV without prior ascertainment of HCV risk. (Grade: strong recommendation; moderate-quality evidence). RECOMMENDATION 2: All persons with identified HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions (Grade: strong recommendation; moderate-quality evidence).


Hepatitis C virus (HCV) is an increasing cause of morbidity and mortality in the United States. Many of the 2.7-3.9 million persons living with HCV infection are unaware they are infected and do not receive care (e.g., education, counseling, and medical monitoring) and treatment. CDC estimates that although persons born during 1945-1965 comprise an estimated 27% of the population, they account for approximately three fourths of all HCV infections in the United States, 73% of HCV-associated mortality, and are at greatest risk for hepatocellular carcinoma and other HCV-related liver disease. With the advent of new therapies that can halt disease progression and provide a virologic cure (i.e., sustained viral clearance following completion of treatment) in most persons, targeted testing and linkage to care for infected persons in this birth cohort is expected to reduce HCV-related morbidity and mortality. CDC is augmenting previous recommendations for HCV testing (CDC. Recommendations for prevention and control of hepatitis C virus (HCV) infection
and HCV-related chronic disease. MMWR 1998;47[No. RR-19]) to recommend one-
time testing without prior ascertainment of HCV risk for persons born during 1945-
1965, a population with a disproportionately high prevalence of HCV infection and
related disease. Persons identified as having HCV infection should receive a brief
screening for alcohol use and intervention as clinically indicated, followed by referral
to appropriate care for HCV infection and related conditions. These recommendations
do not replace previous guidelines for HCV testing that are based on known risk
factors and clinical indications. Rather, they define an additional target population for
testing: persons born during 1945-1965. CDC developed these recommendations with
the assistance of a work group representing diverse expertise and perspectives. The
recommendations are informed by the Grading of Recommendations Assessment,
Development, and Evaluation (GRADE) framework, an approach that provides
guidance and tools to define the research questions, conduct the systematic review,
assess the overall quality of the evidence, and determine strength of the
recommendations. This report is intended to serve as a resource for health-care
professionals, public health officials, and organizations involved in the development,
implementation, and evaluation of prevention and clinical services. These
recommendations will be reviewed every 5 years and updated to include advances in
the published evidence.


Hepatitis C virus (HCV) is a leading cause of liver disease worldwide, as 130-170
million individuals are chronically infected and 350,000 patients die every year from
HCV infection. The HCV prevalence varies widely among countries being highest in
several African and Eastern Mediterranean countries. The incidence of new HCV
infections may be declining in developed countries, but there is still a large reservoir
of chronic infections. The most important mode of HCV transmission has been
injecting drug use in developed countries with low prevalence and unsafe therapeutic
injections in developing countries with moderate-high prevalence. Since there are no
systematic screening policies, most patients remain undiagnosed. Even among
diagnosed patients, a minority receives treatment due to several barriers to therapy.
Given the high efficacy of treatment, public health authorities should recognise the
importance of HCV and make resources available for the implementation of effective
primary prevention, screening and management policies.


BACKGROUND: Many countries have developed, or are developing, national
strategies aimed at reducing the harms associated with hepatitis C infection. Making
these strategies relevant to the vast majority of those affected by hepatitis C requires a
more complete understanding of the short and longer term impacts of infection. We
used a systematic approach to scope the literature to determine what is currently
known about the health and psychosocial impacts of hepatitis C along the trajectory
from exposure to ongoing chronic infection, and to identify what knowledge gaps
remain. METHODS: PubMed, Current Contents and PsychINFO databases were
searched for primary studies published in the ten years from 2000-2009 inclusive.
Two searches were conducted for studies on hepatitis C in adult persons focusing on:
outcomes over time (primarily cohort and other prospective designs); and the
personal and psychosocial impacts of chronic infection. All retrieved studies were
assessed for eligibility according to specific inclusion/exclusion criteria, data
completeness and methodological coherence. Outcomes reported in 264 included studies were summarized, tabulated and synthesized. RESULTS: Injecting drug use (IDU) was a major risk for transmission with seroconversion occurring relatively early in injecting careers. Persistent hepatitis C viraemia, increasing age and excessive alcohol consumption independently predicted disease progression. While interferon based therapies reduced quality of life during treatment, improvements on baseline quality of life was achieved post treatment--particularly when sustained viral response was achieved. Much of the negative social impact of chronic infection was due to the association of infection with IDU and inflated assessments of transmission risks. Perceived discrimination was commonly reported in health care settings, potentially impeding health care access. Perceptions of stigma and experiences of discrimination also had direct negative impacts on wellbeing and social functioning. CONCLUSIONS: Hepatitis C and its management continue to have profound and ongoing impacts on health and social well being. Biomedical studies provided prospective information on clinical aspects of infection, while the broader social and psychological studies presented comprehensive information on seminal experiences (such as diagnosis and disclosure). Increasing the focus on combined methodological approaches could enhance understanding about the health and social impacts of hepatitis C along the life course.


In the US, application of antibody-based and nucleic acid testing for HCV has dramatically reduced HCV transmissions over the past two decades. In addition to testing donors of blood, tissue and organs to reduce the risk of transfusion/transplantation-associated HCV, testing can also motivate individuals to adopt safer behaviours. HCV testing, when accompanied by appropriate care and treatment, can reduce the extent of morbidity and mortality that often accompanies chronic HCV infection. Options for HCV treatment have recently been expanded and improved with the availability of more effective, anti-HCV drugs; furthermore, the remarkable results of clinical trials of these drugs suggest that safe, all-oral therapies requiring relatively short duration are on the immediate horizon. These advances have prompted new US initiatives to recommend HCV testing to the wider community (including those populations with a high prevalence of hepatitis C) and promote linkage to treatment for those found to be HCV-infected. Crucial to the success of these initiatives are the development of tests capable of identifying active infection, recent infection, or both, and the implementation of testing strategies that facilitate broad access to HCV testing linked to care and treatment.


The Extension for Community Healthcare Outcomes (ECHO) Model was developed by the University of New Mexico Health Sciences Center as a platform to deliver complex specialty medical care to underserved populations through an innovative educational model of team-based interdisciplinary development. Using state-of-the-art telehealth technology, best practice protocols, and case-based learning, ECHO
trains and supports primary care providers to develop knowledge and self-efficacy on a variety of diseases. As a result, they can deliver best practice care for complex health conditions in communities where specialty care is unavailable. ECHO was first developed for the management of hepatitis C virus (HCV), optimal management of which requires consultation with multidisciplinary experts in medical specialties, mental health, and substance abuse. Few practitioners, particularly in rural and underserved areas, have the knowledge to manage its emerging treatment options, side effects, drug toxicities, and treatment-induced depression. In addition, data were obtained from observation of ECHO weekly clinics and database of ECHO clinic participation and patient presentations by clinical provider. Evaluation of the ECHO program incorporates an annual survey integrated into the ECHO annual meeting and routine surveys of community providers about workplace learning, personal and professional experiences, systems and environmental factors associated with professional practice, self-efficacy, facilitators, and barriers to ECHO. The initial survey data show a significant improvement in provider knowledge, self-efficacy, and professional satisfaction through participation in ECHO HCV clinics. Clinicians reported a moderate to major benefit from participation. We conclude that ECHO expands access to best practice care for underserved populations, builds communities of practice to enhance professional development and satisfaction of primary care clinicians, and expands sustainable capacity for care by building local centers of excellence.


BACKGROUND: An overall prevalence rate of HCV infection in Romanian adult population was recently estimated to be 3.23%. The proportion of treated patients with chronic hepatitis C in our country has never been assessed. AIMS: 1) to analyze the quality and quantity of antiviral therapy delivery; 2) to determine the proportion of patients being annually and ever treated with antiviral therapy in Romania and 3) to identify barriers against treatment of HCV infected-population in Romania. RESULTS: The number of annually treated patients remained relatively stable between 2002 and 2007 (1,813 patients treated with pegylated interferon and ribavirin in 2002 and 2,446 in 2007). There was a doubled increase in reimbursed treatment in 2008 and 2009 (4,503 and respectively 4,701 treated patients) due to a special campaign organized to increase awareness and prevention of HCV transmission. The median time to therapy approval varies from county to county; overall it is 10.23 months. A total number of 25,318 patients with chronic C hepatitis were treated between 2002-2009, corresponding to a cumulative proportion of 4.1% of the prevalent cases of HCV infection treated in Romania until 1st January 2010. The main limiting factor of access to antiviral therapy for hepatitis C in Romania remains the lack of funds. CONCLUSIONS: This is the first analysis of the nationwide practice for treatment of hepatitis C in Romania. Increased public health efforts are required to improve access to antiviral therapy for hepatitis C in Romania.


Language barrier, race, immigration status, mental health illness, substance abuse and socioeconomic status are often not considered when evaluating hepatitis C virus (HCV) sustained virological response (SVR) in human immunodeficiency virus (HIV) infection. The influence of these factors on HCV work-up, treatment initiation
and SVR were assessed in an HIV-HCV coinfected population and compared to patients with HCV mono-infection. The setting was a publicly funded, urban-based, multidisciplinary viral hepatitis clinic. A clinical database was utilized to identify HIV and HCV consults between June 2000 and June 2007. Measures of access to HCV care (ie, liver biopsy and HCV antiviral initiation) and SVR as a function of the above variables were evaluated and compared between patients with HIV-HCV and HCV. HIV-HCV co-infected (n = 106) and HCV mono-infected (n = 802) patients were evaluated. HIV-HCV patients were more often white (94% versus 84%) and male (87% versus 69%). Bridging fibrosis or cirrhosis on biopsy was more frequent in HIV-HCV (37% versus 22%; P = 0.03). HIV infection itself did not influence access to biopsy (50% versus 52%) or treatment initiation (39% versus 38%). Race, language barrier, immigration status, injection drug history and socioeconomic status did not influence access to biopsy or treatment. SVR was 54% in HCV and 30% in HIV-HCV (P = 0.003). Genotype and HIV were the only evaluated variables to predict SVR. Within the context of a socialized, multidisciplinary clinic, HIV-HCV co-infected patients received similar access to HCV work-up and care as HCV mono-infected patients. SVR is diminished in HIV-HCV co-infection independent of language barrier, race, immigration status, or socioeconomic status.


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.


Hepatitis C is a common cause of liver disease and many infected individuals remain undiagnosed. Patients may be asymptomatic or have non-specific symptoms, and community nurses can help to identify those at risk and arrange testing. Community nurses can also encourage and support infected individuals to attend specialist
hospital clinics for assessment and treatment by giving clear and accurate information about infection and therapy, including common side-effects. Treatment lasts for 6-12 months and patients require regular monitoring with good support. This paper provides an overview of the diagnosis and management of hepatitis C and aims to educate community nurses about this viral infection.


ISSUE ADDRESSED: Increasing the uptake of hepatitis C treatment by injecting drug users (IDUs) is a key strategy in addressing the escalating disease burden of chronic hepatitis C virus (HCV) infection in Australia. Little is known about barriers to treatment uptake among culturally diverse groups of IDUs. Indo-Chinese IDUs represent a marginalised group with high rates of incident and prevalent HCV infection. METHODS: An ethnographic study was conducted to explore barriers to HCV treatment uptake experienced by Indo-Chinese IDUs and inform the development of policies and practices that promote access to treatment. Following a baseline interview, participants (n=23) received a brief intervention about HCV treatment and an offer of facilitated referral to a tertiary liver clinic. Follow-up interviews were conducted three and six months post intervention, to explore decision-making about treatment-seeking and experiences accessing the clinic. RESULTS: While 'getting rid of' HCV was regarded as highly desirable, only three participants were assessed for treatment. For most participants, seeking treatment was not seen as feasible given social and structural barriers related to their drug use, lack of resources and support. Institutional barriers included the clinic's administrative procedures, limited flexibility and apparent reluctance to consider current IDUs suitable candidates for treatment. CONCLUSIONS: Resources and support, flexible, low threshold approaches to assessment and a willingness to provide treatment to current IDUs, would promote equitable access to treatment among these groups.
Session 6:  Country examples of national Hepatitis C controlling programmes

Presentation Tatjana Reic/ Prof Raiko Ostojic Croatia

Presentation Floor Berden  The Netherlands:  Hepatitis C treatment guidelines

In this new Dutch guideline for hepatitis C virus infection we provide recommendations for the management of hepatitis C infection. Until 2012 the standard for treatment consisted of pegylated interferon alpha (peg-IFNa) and ribavirin. The advent of first-generation direct antiviral agents such as boceprevir and telaprevir has changed the concept of treatment of adult chronic hepatitis C genotype 1 infected patients. There are three benefits of boceprevir and telaprevir. They increase the likelihood of cure in 1) naive genotype 1 patients and 2) in patients who did not respond to earlier treatment with peg-IFNa and ribavirin, while 3) allowing shortening of treatment duration from 48 weeks to 24 or 28 weeks, which is possible in 40-60% of non-cirrhotic naïve (boceprevir and telaprevir) and relapsing patients (telaprevir). The use of boceprevir and telaprevir is associated with multiple side effects and awareness of these side effects is needed to guide the patient through the treatment process. This guideline, formulated on behalf of The Netherlands Association of Hepato-gastroenterologists, The Netherlands Association of Internal Medicine, and The Dutch Association for the Study of Liver Disease, serves as a manual for physicians for the management and treatment of acute and chronic hepatitis C virus monoinfection in adults.


Swedish recommendations for the treatment of hepatitis C virus (HCV) infection were updated at a recent expert meeting. Therapy for acute HCV infection should be initiated if spontaneous resolution does not occur within 12 weeks. The recommended standard-of-care therapy for chronic HCV genotype 1 infection is an HCV protease inhibitor in combination with peginterferon (peg-IFN) and ribavirin. Treatment is strongly recommended in patients with bridging fibrosis and cirrhosis, whereas in patients with less advanced fibrosis, deferring therapy may be preferential in light of likely therapeutic improvements in the near future. Patients with chronic genotype 2/3 infection should generally be treated with peg-IFN and ribavirin for 24 weeks. In patients with a very rapid viral response (i.e. HCV RNA below 1000 IU/ml on day 7), or favourable baseline characteristics and undetectable HCV RNA week 4, treatment can be shortened to 12-16 weeks, provided that no dose reductions are needed.
The burden of disease due to chronic viral hepatitis constitutes a global threat. In many Balkan and Mediterranean countries, the disease burden due to viral hepatitis remains largely unrecognized, including in high-risk groups and migrants, because of a lack of reliable epidemiological data, suggesting the need for better and targeted surveillance for public health gains. In many countries, the burden of chronic liver disease due to hepatitis B and C is increasing due to ageing of unvaccinated populations and migration, and a probable increase in drug injecting. Targeted vaccination strategies for hepatitis B virus (HBV) among risk groups and harm reduction interventions at adequate scale and coverage for injecting drug users are needed. Transmission of HBV and hepatitis C virus (HCV) in healthcare settings and a higher prevalence of HBV and HCV among recipients of blood and blood products in the Balkan and North African countries highlight the need to implement and monitor universal precautions in these settings and use voluntary, nonremunerated, repeat donors. Progress in drug discovery has improved outcomes of treatment for both HBV and HCV, although access is limited by the high costs of these drugs and resources available for health care. Egypt, with the highest burden of hepatitis C in the world, provides treatment through its National Control Strategy. Addressing the burden of viral hepatitis in the Balkan and Mediterranean regions will require national commitments in the form of strategic plans, financial and human resources, normative guidance and technical support from regional agencies and research.

RELATED Abstracts session 6

Pubmed MEDLINE search on {(Hepatitis C OR Hep C OR HCV) AND (national plan) } in all fields and filters used on this search ‘last 5 year’ was performed. Relevant article were manually selected. The reference were sorted by publication year and first author

In total 8 were selected:


In the present update of the guidelines, a starting combination antiretroviral treatment (cART) is recommended in symptomatic patients, in pregnant women, in serodiscordant couples with a high risk of transmission, in patients co-infected with hepatitis B virus requiring treatment, and in patients with HIV-related nephropathy. Guidelines on cART are included in the event of a concurrent diagnosis of HIV infection with an AIDS-defining event. In asymptomatic naïve patients, cART is
recommended if the CD4+ lymphocyte count is <500 cells/μL, if the CD4+ lymphocyte count is >500 cells/μL, cART can be delayed, although it may be considered in patients with liver cirrhosis, chronic infection due to hepatitis C virus, high cardiovascular risk, plasma viral load (PVL) >10^5 copies/mL, CD4+ lymphocyte percentage <14%, cognitive impairment, and age >55 years. cART in naive patients requires a combination of 3 drugs, and its aim is to achieve undetectable PVL. Treatment adherence plays a key role in sustaining a favorable response. cART can, and should be, changed if virological failure occurs, in order to return to undetectable PVL. Approaches to cART in acute HIV infection, in women, in pregnancy, in tuberculosis, and post-exposure prophylaxis are also examined.


INTRODUCTION: Nationwide studies comparing patients with hepatitis B and C virus (HBV and HCV) infections are mandatory for assessing changes in epidemiology. AIM: The aim of this study was to compare epidemiological data and initial management of newly diagnosed patients with persistent HBV (HBsAg positive) or HCV (detectable HCV RNA) infection in Belgium. PATIENTS AND METHODS: Data were extracted from two Belgian observational databases. RESULTS: A total of 655 patients (387 HBV and 268 HCV) were included. Compared with HCV patients, HBV patients were younger, more frequently men, more often of Asian or African origin (43 vs. 10%, P<0.0001), and less frequently contaminated by transfusion or intravenous drug use (9 and 6% vs. 34 and 44%, P<0.0001). Viral replication was assessed in 89% of HBV patients. Compared with HCV patients, HBV patients more frequently had normal alanine aminotransferase (ALT) levels (65 vs. 29%, P<0.0001), less frequently underwent liver biopsy (29 vs. 67%, P<0.0001), and were less often considered for antiviral therapy (25 vs. 54%, P<0.0001). When taking only HBV patients with detectable viral replication into consideration, results remained unchanged. During the multivariate analysis, ALT was a major factor for performing liver biopsy or considering antiviral therapy in both groups. CONCLUSION: HBV and HCV screening policies should be targeted toward immigrants and intravenous drug users, respectively. Guidelines recommending systematic search for viral replication should be reinforced in HBV patients. HBV patients less frequently underwent liver biopsy and were less often considered for antiviral therapy compared with HCV patients. Despite the lack of sensitivity and specificity, ALT remains a pivotal decision-making tool for liver biopsy and antiviral therapy in both infections.


The recent marketing authorizations and hence availability of the new protease inhibitors, telaprevir and boceprevir, have profoundly changed the management of chronic hepatitis C patients. Guidelines for the use of these new drugs as part of a triple therapy, in combination with the standard therapy of peginterferon plus ribavirin, are proposed. The guidelines have been drawn up and evaluated by a meeting of the French Association for the Study of the Liver, posted online for comments, and extensively reviewed by international experts. The current published
data on the various treatment strategies are reviewed. The guidelines address the majority of patient profiles including treatment-naive patients and patients with failure of previous treatment. They recommend which patients should be treated with triple therapy and consider the results of triple therapy including the factors that are predictive of response. They consider the circumstances in which the length of triple therapy can be shortened and the advantages of a peginterferon plus ribavirin lead-in phase. Virological monitoring, stopping criteria, the evaluation of resistance to protease inhibitors, practical treatment management, treatment adherence and the management of side effects are discussed and simple guidelines proposed.


Worldwide, 130-170 million persons are living with chronic hepatitis C virus (HCV) infection, which, if left untreated, can result in cirrhosis and liver cancer. Egypt has the largest burden of HCV infection in the world, with a 10% prevalence of chronic HCV infection among persons aged 15-59 years. HCV transmission in Egypt is associated primarily with inadequate infection control during medical and dental care procedures. In response, the Egyptian Ministry of Health and Population (MOHP) in 2001 implemented a program to reduce health-care-associated HCV transmission and in 2008 launched a program to provide care and treatment. This report describes the progress of these programs, identifies deficiencies, and recommends enhancements, including the establishment of a comprehensive national viral hepatitis control program. Infection control programs implemented in 2001 at MOHP facilities resulted in improvements in infection control practices and a decrease in the annual incidence of HCV infection among dialysis patients from 28% to 6%. Through June 2012, a total of 23 hepatitis treatment facilities had been established in Egypt, providing care and treatment to nearly 190,000 persons with chronic HCV infection. Despite these programs, Egypt continues to face an ongoing hepatitis C epidemic. A comprehensive plan is needed to prevent and control hepatitis C in Egypt. This plan should address increasing community awareness and education, preventing of HCV infection in health-care settings, ensuring a safe blood supply, establishing surveillance and monitoring to track the effectiveness of control programs, and providing care and treatment..


Around 80% of hepatitis C virus (HCV) infections in England are among injecting drug users (IDUs). The HCV Action Plan launched in 2004 includes targets to reduce HCV prevalence in recent initiates (those starting injecting in the preceding 3 years), and to increase HCV voluntary confidential testing (VCT). The Action Plan's impact is examined using surveillance data from recent initiates participating in an annual survey of IDUs in contact with specialist services across England, 2000-2008. Participants provided an oral fluid sample (tested for anti-HCV) and completed a short questionnaire (including HCV VCT and result of last test). Overall, anti-HCV prevalence among the recent initiates was 18% (619/3463); in 2004, it was 20% (59/291), other than being lower in 2000 [11%, 73/672, adjusted odds ratio (AOR) = 0.63 95%CI 0.42-0.93] there was no change over time. Prevalence increased with age; was higher among those ever imprisoned, using a needle exchange, and having a HCV VCT; and varied by region. Overall, 42% (1460) had ever had a HCV VCT; in 2004 uptake was 45% (130/291) having increased from 26% (175/672, AOR = 0.57 95%CI 0.42-0.77) in 2000, and it rose to 62% (197/320, AOR = 2.12 95%CI 1.50-
The proportion of anti-HCV-positive IDUs aware of their infection was higher in 2006-2008 than in earlier years. The HCV Action Plan has probably helped increase recent initiates’ uptake of HCV VCT and the proportion of those diagnosed with HCV infection. However, its impact on HCV transmission is unclear. There is a need to reinvigorate, and improve coverage of, interventions to prevent HCV transmission.


The 2010 Institute of Medicine report on "Hepatitis and Liver Cancer" indicated that lack of knowledge and awareness about chronic hepatitis B (HBV) and C virus (HCV) infections and insufficient understanding about the extent and seriousness of this public health problem impeded current efforts to prevent and control hepatitis B and C. A single-topic conference was held in June 2011 to discuss strategies to improve the effectiveness of screening, care referral, and clinical management of chronic HBV and HCV infections with the ultimate goal of reducing morbidity and mortality from these infections. Various models that have been shown to improve hepatitis screening and effectiveness of hepatitis treatment in the community, including rural settings and populations that have traditionally been excluded due to comorbidities, were presented. Recent advances in laboratory testing, medical management, and new antiviral therapies will not decrease the burden of viral hepatitis if persons at risk for or who are living with viral hepatitis are not aware of the risks, have not been diagnosed, or have no access to care. Systematic changes in our health care delivery system and enhanced coordination of prevention and care services with partnerships between public health leaders and clinicians through education of the public and health care providers and linkage of infected persons with care and treatment services can increase the success of preventing viral hepatitis and the effectiveness of hepatitis treatment in the real world. Implementation of these changes is feasible and will require policy changes, coordination among government agencies, and collaboration between government agencies, health care providers, community organizations, and advocacy groups.


To assess the impact of the French national hepatitis C prevention programme initiated in 1999, we analysed trends in hepatitis C virus (HCV) prevalence, testing and characteristics of HCV-infected patient at first referral from 1994 to 2006. We used four data sources: Two national population-based sero-prevalence surveys carried out in 1994 and 2004; two surveillance networks, one based on public and private laboratories throughout France and the other on hepatology reference centres, which aim to monitor, respectively, trends of anti-HCV screening and of epidemiological-clinical characteristics of HCV patients at first referral. Between 1994 and 2004, the anti-HCV prevalence for adults aged 20-59 years decreased from 1.05 (95% confidence interval 0.75-1.34) to 0.71 (0.52-0.97). During the same period, those anti-HCV positive with detectable HCV RNA decreased from 81 to 57%, whereas, the proportion of anti-HCV positive persons aware of their status evolved from 24 to 56%. Anti-HCV screening activity increased by 45% from 2000 to 2005, but decreased in 2006 (-10%), while HCV positivity among those tested decreased from 4.3 to 2.9%. The proportion of cirrhosis at first referral remains around 10%
between 2001 and 2006, with many patients with excessive alcohol consumption (34.7% among males) or viral co-infections (HIV seropositivity for 5.2% patients). Our analysis indicates that the national programme had a positive impact at the population level through improved prevention, screening and management. There is still a need to identify timely those at risk for earlier interventions, to assess co-morbidities better and for a multidisciplinary approach to HCV management.


Two national HCV projections have been published in France which assumed that a part of observed hepatocellular carcinoma (HCC) deaths is a consequence of HCV epidemic. They applied the back-calculation method, in combination with a Markov model, to reconstruct the past history of HCV infection and then to predict HCV-related mortality. A preliminary model was first developed in the absence of effective therapy. It allowed testing many assumptions to model HCV natural history that were compatible with observed incidence of HCV-related HCC deaths. This model was then updated to take into account the availability of treatment and more recent epidemiological data. These two models are described in detail and results are discussed with a view to addressing the models’ limitations. The models offered a useful tool to assess public health policy scenarios in planning healthcare responses to the HCV epidemic.
Session 7: Prevention of hepatitis C

**Presentation Jake Liang** Prospects for prophylactic and Therapeutic vaccines against the hepatitis C viruses in the world of improving treatment.


Despite major advances in the understanding and treatment of hepatitis C, a preventive vaccine remains elusive. The marked genetic diversity and multiple mechanisms of persistence of hepatitis C virus, combined with the relatively poor immune response of the infected host against the virus, are major barriers. The lack of robust and convenient model systems further hampers the effort to develop an effective vaccine. Advances in our understanding of virus-host interactions and protective immunity in hepatitis C virus infection provide an important roadmap to develop potent and broadly directed vaccine candidates targeting both humoral and cellular immune responses. Multiple approaches to generating and testing viral immunogens have met with variable success. Several candidates have advanced to clinical trials based on promising results in chimpanzees. The ultimate path to a successful preventive vaccine requires comprehensive evaluations of all aspects of protective immunity, innovative application of state-of-the-art vaccine technology and properly designed vaccine trials that can affirm definitive endpoints of efficacy.

**Presentation Julio Montaner** Lessons learned from the treatment as prevention approach for HIV applicable to HCV.

**Presentation Sharon Hutchinson** Prevention of Hepatitis C Virus transmission Among People Who Inject Drugs

Presentation will be based on the following publications:


BACKGROUND: Injecting drug use is an important risk factor for transmission of viral hepatitis, but detailed, transparent estimates of the scale of the issue do not exist. We estimated national, regional, and global prevalence and population size for hepatitis C virus (HCV) and hepatitis B virus (HBV) in injecting drug users (IDUs).

METHODS: We systematically searched for data for HBV and HCV in IDUs in peer-reviewed databases (Medline, Embase, and PsycINFO), grey literature, conference abstracts, and online resources, and made a widely distributed call for additional data. From 4386 peer-reviewed and 1019 grey literature sources, we reviewed 1125 sources in full. We extracted studies into a customised database and graded them according to their methods. We included serological reports of HCV antibodies (anti-HCV), HBV antibodies (anti-HBc), or HBV surface antigen (HBsAg) in studies of IDUs with more than 40 participants (<100% HIV-positive) and sampling frames that did not exclude participants on the basis of age or sex. With endorsed decision rules,
we calculated prevalence estimates with anti-HCV and anti-HBc as proxies for exposure and HBsAg as proxy for current infection. We combined these estimates with IDU population sizes to calculate the number of IDUs with positive HBV or HCV statuses. FINDINGS: We located eligible reports with data for prevalence of anti-HCV in IDUs for 77 countries; midpoint prevalence estimates suggested 60-80% of IDUs had anti-HCV in 25 countries and more than 80% of IDUs did so in 12 countries. About 10.0 million (range 6.0-15.2) IDUs worldwide might be anti-HCV positive. China (1.6 million), USA (1.5 million), and Russia (1.3 million) had the largest such populations. We identified eligible HBsAg reports for 59 countries, with midpoint prevalence estimates of 5-10% in 21 countries and more than 10% in ten countries. Worldwide, we estimate 6.4 million IDUs are anti-HBe positive (2.3-9.7 million), and 1.2 million (0.3-2.7 million) are HBsAg positive. INTERPRETATION: More IDUs have anti-HCV than HIV infection, and viral hepatitis poses a key challenge to public health. Variation in the coverage and quality of existing research creates uncertainty around estimates. Improved and more complete data and reporting are needed to estimate the scale of the issue, which will inform efforts to prevent and treat HCV and HBV in IDUs. FUNDING: WHO and US National Institutes of Health (NIDA R01 DA018609).


RELATED Abstracts session 7

Pubmed MEDLINE search on {(Hepatitis C OR Hep C OR HCV) AND (vaccine* OR Prevention) in all fields and filters used on this search ‘last 5 year’ and REVIEW was performed. }. Relevant article were manually selected. The reference were sorted by publication year and first author

In total 19 were selected:
VACCIN

Approximately 170 million individuals, representing 3% of the global population, are infected with hepatitis C virus (HCV). Whereas strategies for antiviral therapies have markedly improved resulting in clinical licensing of direct-acting antivirals, the development of vaccines has been hampered by the high genetic variability of the virus as well as by the lack of suitable animal models for proof-of-concept studies. Nevertheless, there are several promising vaccine candidates in preclinical and clinical development. After a brief summary of the molecular virology and immunology relevant to vaccine development, this review explains the model systems used for preclinical vaccine development, and highlights examples for most recently developed HCV vaccine candidates.

Lauer, G. M. "Immune responses to hepatitis C virus (HCV) infection and the prospects for an effective HCV vaccine or immunotherapies." J Infect Dis 2013 207 Suppl 1: S7-S12.

Infection with hepatitis C virus (HCV) typically leads to persistent infection, with >170 million people estimated to be affected worldwide, putting them at risk for chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. Importantly, 20%-30% of individuals are able to control the virus spontaneously, usually within 6 months of exposure. This suggests that HCV vaccines and immunotherapies are a distinct possibility. We discuss here the role of T cells in controlling HCV, the gaps in our understanding of protective HCV immunity, and the recent introduction of a HCV T-cell vaccine into clinical trials.


Although a cure for HCV is on the near horizon, emerging drug cocktails will be expensive, associated with side-effects and resistance making a global vaccine an urgent priority given the estimated high incidence of infection around the world. Due to the highly heterogeneous nature of HCV, an effective HCV vaccine which could elicit broadly cross-neutralizing antibodies has represented a major challenge. In this study, we tested for the presence of cross-neutralizing antibodies in human volunteers who were immunized with recombinant glycoproteins gpE1/gpE2 derived from a single HCV strain (HCV1 of genotype 1a). Cross neutralization was tested in Huh-7.5 human hepatoma cell cultures using infectious recombinant HCV (HCVcc) expressing structural proteins of heterologous HCV strains from all known major genotypes, 1-7. Vaccination induced significant neutralizing antibodies against heterologous HCV genotype 1a virus which represents the most common genotype in North America. Of the 16 vaccinees tested, 3 were selected on the basis of strong 1a virus neutralization for testing of broad cross-neutralizing responses. At least 1 vaccinee was shown to elicit broad cross-neutralization against all HCV genotypes. Although observed in only a minority of vaccinees, our results prove the key concept that a vaccine derived from a single strain of HCV can elicit broad cross-neutralizing antibodies against all known major genotypes of HCV and provide considerable
encouragement for the further development of a human vaccine against this common, global pathogen.


Approximately 170 million people worldwide are chronic carriers of Hepatitis C virus (HCV). To date, there is no prophylactic vaccine available against HCV. The standard-of-care therapy for HCV infection involves a combination of pegylated interferon-alpha and ribavirin. This therapy, which is commonly associated with side effects, has a curative rate varying from 43% (HCV genotype 1) to 80% (HCV genotype 2). In 2011, two direct-acting antiviral agents, telaprevir and boceprevir, were approved by the US Food and drug Administration and are now being used in combination with standard-of-care therapy in selected patients infected with HCV genotype 1. Although both drugs are promising, resulting in a shortening of therapy, these drugs also induce additional side effects and have reduced efficacy in patients who did not respond to standard-of-care previously. An alternative approach would be to treat HCV by stimulating the immune system with a therapeutic vaccine ideally aimed at (i) the eradication of HCV-infected cells and (ii) neutralization of infectious HCV particles. The challenge is to develop therapeutic vaccination strategies that are either at least as effective as antiviral drugs but with lower side effects, or vaccines that, when combined with antiviral drugs, can circumvent long-term use of these drugs thereby reducing their side effects. In this review, we summarize and discuss recent preclinical developments in the area of therapeutic vaccination against chronic HCV infection. Although neutralizing antibodies have been described to exert protective immunity, clinical studies on the induction of neutralizing antibodies in therapeutic settings are limited. Therefore, we will primarily discuss therapeutic vaccines which aim to induce effective cellular immune response against HCV.


INTRODUCTION: Studies have explored whether spontaneous clearance of hepatitis C virus (HCV) infection decreases the likelihood of reinfection or increases the probability of clearance. This analysis investigates whether the conflicting findings from these studies could be due to differences in frequency of HCV RNA testing. METHODS: A model simulated the dynamics of HCV reinfection and clearance among a cohort of injection drug users. For different reinfection incidence and clearance rates, the model evaluated the accuracy of epidemiological studies that used different HCV testing frequencies. RESULTS: Experimental estimates for the reinfection incidence and clearance probability will be accurate (<20% error) if the testing interval is less than the reinfection clearance duration. Otherwise, experimental estimates can greatly underestimate the real values (<66% error if reinfection duration is 1 month and the testing interval is 3 months). Uncertainty in experimental estimates also increases at lower reinfection incidences, whereas for lower clearance probabilities the uncertainty in the estimated clearance probability increases but estimated reinfection incidence decreases. DISCUSSION: Differences in HCV testing interval could account for most between-study variability in the estimated probability of clearing reinfections and is likely to have biased reinfection incidence estimates. Our findings suggest that a high reinfection clearance probability (>75%) is consistent with data.
Hepatitis C virus (HCV) was discovered more than two decades ago, but progress towards a vaccine has been slow. HCV infection will spontaneously clear in about 25% of people. Studies of spontaneous HCV clearance in chimpanzees and human beings have identified host and viral factors that could be important in the control of HCV infection and the design of HCV vaccines. Although data from studies of chimpanzees suggest that protection against reinfection is possible after spontaneous clearance, HCV is a human disease. Results from studies of reinfection risk after spontaneous clearance in injecting drug users are conflicting, but some people seem to have protection against HCV persistence. To guide future vaccine development, we assess data from studies of HCV reinfection after spontaneous clearance, discuss flaws in the methods of previous human studies, and suggest essential components for future investigations of control of HCV infection.


BACKGROUND: A safe and efficacious vaccine may be the most efficient and cost-effective strategy for controlling the hepatitis C virus (HCV) epidemic among people who inject drugs (PWID) and several candidates are in development. However, little is known about the factors that influence willingness to participate (WTP) in candidate HCV vaccine trials among this group. METHODS: HCV seronegative PWID recruited between 2008 and 2010 as part of a prospective observational cohort study in Sydney, Australia were asked whether they would be willing to participate in a future candidate hepatitis C vaccine trial and to provide reasons to explain their decision. RESULTS: Of 113 participants, 74% indicated WTP, 15% were unwilling to participate and 11% reported WTP that was contingent on vaccine characteristics and trial design issues. The most commonly reported motivator for hypothetical trial participation was altruism, followed by potential health benefits, financial remuneration, and knowledge gain. Barriers to hypothetical participation included fears about possible harms to health, such as concerns about vaccine safety, side effects, and acquiring HCV from the vaccine; other barriers included mistrust of biomedical research and time constraints. CONCLUSIONS: These results may be useful in designing strategies to enhance HCV vaccine trial recruitment and retention and have ethical implications for developing informed consent processes and standards of care.


Natural cross-protective immunity is induced after spontaneous clearance of primary hepatitis C virus (HCV) infection. Although this suggests that effective prophylactic vaccines against HCV are possible, there are still several areas that require further study. Current data indicate that, at best, vaccine-induced immunity may not completely prevent HCV infection but rather prevent persistence of the virus. However, this may be an acceptable goal, because chronic persistence of the virus is the main cause of pathogenesis and the development of serious liver conditions. Therapeutic vaccine development is also highly challenging; however, strategies have been pursued in combination with current or new treatments in an effort to reduce the costs and adverse effects associated with antiviral therapy. This review summarizes
the current state of HCV vaccines and the challenges faced for future development and clinical trial design.


In countries where hepatitis A is highly endemic, exposure to hepatitis A virus (HAV) is almost universal before the age of 10 years, and large-scale immunization efforts are not required. In contrast, in areas of intermediate endemicity or in transition from high to intermediate endemicity, where transmission occurs primarily from person to person in the general community (often with periodic outbreaks), control of hepatitis A may be achieved through widespread vaccination programmes. Hepatitis B virus (HBV) is one of the world's most widespread infectious agents and the cause of millions of infections each year. Between 500,000 and 700,000 people die each year from chronic infection-related cirrhosis, hepatocellular carcinoma (HCC) or from acute hepatitis B. Hepatitis B vaccine provides protection against infection and its complications including liver cirrhosis and HCC. It is therefore, the first vaccine against a cancer, the first vaccine protecting from a sexually transmitted infection, and the first vaccine against a chronic disease ever licensed. Control and significant reduction in incidence of new HBV infections as well as hepatocellular carcinoma has repeatedly been reported in countries in East Asia (i.e. Taiwan) and Africa (i.e. The Gambia). Two experimental vaccines against hepatitis E have been developed; one of them has been recently licensed but is not yet widely available. Attempts to develop a hepatitis C vaccine were so far unsuccessful.


Hepatitis C virus (HCV) is a blood borne disease estimated to chronically infect 3% of the world's population causing significant morbidity and mortality. Current medical therapy is curative in approximately 50% of patients. While recent treatment advances of genotype 1 infection using directly acting antiviral agents (DAAs) are encouraging, there is still a need to develop vaccine strategies capable of preventing infection. Moreover, vaccines may also be used in future in combination with DAAs enabling interferon-free treatment regimens. Viral and host specific factors contribute to viral evasion and present important impediments to vaccine development. Both, innate and adaptive immune responses are of major importance for the control of HCV infection. However, HCV has evolved ways of evading the host's immune response in order to establish persistent infection. For example, HCV inhibits intracellular interferon signalling pathways, impairs the activation of dendritic cells, CD8(+) and CD4(+) T cell responses, induces a state of T-cell exhaustion and selects escape variants with mutations CD8(+) T cell epitopes. An effective vaccine will need to produce strong and broadly cross-reactive CD4(+) and CD8(+) T cell and neutralising antibody (NAb) responses to be successful in preventing or clearing HCV. Vaccines in clinical trials now include recombinant proteins, synthetic peptides, virosome based vaccines, tarmogens, modified vaccinia Ankara based vaccines, and DNA based vaccines. Several preclinical vaccine strategies are also under development and include recombinant adenoviral vaccines, virus like particles, and synthetic peptide vaccines. This paper will review the vaccines strategies employed, their success to date and future directions of vaccine design.


Encouraging efficacy data have been obtained in the hepatitis C virus (HCV)
chimpanzee model using prophylactic vaccines comprising adjuvanted recombinant envelope gpE1/gpE2 glycoproteins or prime/boost immunization regimens using defective adenoviruses and plasmid DNA expressing non-structural genes. While usually not resulting in sterilizing immunity after experimental challenge, the progression to chronic, persistent infection (which is responsible for HCV-associated pathogenicity in human) is inhibited. These and other vaccine candidates are in clinical development for both prophylactic as well as possible therapeutic applications. Given that other vaccines tested in the chimpanzee model may be possibly increasing the rate of chronicity, it is very important that this model continues to be available and used prior to initiation of clinical development. Several vaccine monotherapy trials in chronically infected HCV patients are resulting in small declines in viral load, suggesting that in future, combining vaccination with antiviral drug treatment may be beneficial.


INTRODUCTION: Around 3% of the world population is infected with HCV, with 3 - 4 million newly infected subjects added to this reservoir every year. At least 10% of these people will develop liver cirrhosis or cancer over time, while no approved vaccine against HCV infection is available to date. AREAS COVERED: This paper includes a detailed and correlated patent (selected by HCAPLUS search database) and literature (searched by PubMed) review on the HCV genome, proteins and key epitopes (including underestimated HCV proteins, alternate reading frame proteins), HCV immunology, immunosuppressive mechanisms and protective correlations of immunity in acute and chronic states of infection (features for prophylactic and therapeutic HCV vaccine design), recent HCV cell culture systems (HCV/JFH1) and animal models. In part two of this review, advances in HCV vaccine formulations and modalities as well as a detailed list of the current trials for HCV vaccine and discussion of the pros and cons of different strategies will be provided. EXPERT OPINION: By using the advanced basic knowledge and tools obtained about HCV vaccinology in recent years and the application of novel formulations and modalities, at least partially effective vaccines will become available in the near future to prevent (or treat) the chronic (if not the acute) state of HCV infection. A few of such vaccines are already in clinical trials.


There is a logarithmic increase in the cost and complexity of the research and development process when transitioning a promising candidate vaccine from the laboratory into the clinic. Managing complex development programs involving people from diverse technical, cultural and geographical backgrounds is a specialised skill. It is essential that the group is clear on their objectives and how their activities affect others, that communication is open, inclusive and effective, and that the most rigorous, scientific approach based on statistical principles in compliance with regulatory requirements is used. Applying these standards to all vaccine development programs will filter out inappropriate candidates more readily and enhance the efficiency of vaccine development. The challenges of developing a new vaccine are illustrated in human immunodeficiency virus (HIV) vaccinology. Selecting vaccine candidates for HIV requires the ability to evaluate the large number of potential antigens in imperfect and non-standardised animal models. Further, using these models to evaluate questions such as dose scaling to humans, optimal route of
administration, the use of adjuvants and potential formulation improvements adds variable to variable, making the interpretation of results particularly challenging. This may lead to the promotion of a poor candidate or the elimination of a good one. The absence of precise immunological correlates of protection and the prohibitive cost of confirmatory clinical trials are further significant barriers. However, there are practical steps that can be taken to standardise early vaccine evaluation, which would result in more efficient development of new vaccines for HIV and other disease areas with similarly challenging development issues (such as hepatitis C virus, influenza, Mycobacterium tuberculosis and malaria).

PREVENTION


AIM: To measure patient perceptions about preventing hepatocellular carcinoma (HCC) and to predict the factors that influence patient willingness to receive therapy.

METHODS: A cross-sectional descriptive study was conducted at an outpatient clinic of a medical institution in southern Taiwan. Four hundred patients with chronic hepatitis B/C were recruited as participants. Two structured questionnaires based on the health belief model were utilized in this study, including the scales of perceptions about preventing HCC and knowledge of hepatitis B/C.

RESULTS: The statistical results demonstrated that the participants' perceived susceptibility (r = -0.22, P < 0.001), benefits (r = -0.11, P = 0.028) and cues to action (r = -0.12, P = 0.014) about the prevention of HCC was significantly correlated with their age. The participants' perceptions were also associated with their educational levels, household incomes and knowledge of hepatitis. Older patients and those with a lower socioeconomic status tended to have negative perceptions and less knowledge of hepatitis. Multivariate logistic regression further indicated that the participants' age (B = -0.044, SE = 0.017, odds ratio = 0.957, P = 0.008, 95% CI: 0.926-0.989) and perceived barriers (B = -0.111, SE = 0.030, odds ratio = 0.895, P < 0.001, 95% CI: 0.845-0.949) were correlated with their willingness to receive antiviral therapy.

CONCLUSION: Healthcare professionals should provide appropriate and effective guidance to increase their patients' awareness and to decrease the perceived barriers for continuing surveillance and antiviral therapy.


BACKGROUND: A systematic review was conducted to determine whether behavioural interventions are effective in preventing transmission of hepatitis C virus (HCV) amongst people who inject drugs. METHODS: Medline, EMBASE, the Cochrane Clinical Trial Database, PSYCHINFO and hand-searching of bibliographies were used to identify controlled trials of behavioural interventions for reducing HCV transmission amongst people who inject drugs. Behavioural interventions were defined as non-pharmacological interventions that aimed to change individual behaviours without explicitly attempting to change population norms. RESULTS: Six trials evaluating peer-education training and counselling interventions were included in the review. There was considerable variation between trials with respect to intervention duration, control and study population. Trials evaluated the impact of interventions on HCV incidence (three studies, 1041 participants) and frequency of injecting risk behaviours (six studies, 2472 participants). Amongst the three studies which measured the impact of the
intervention on HCV incidence, none found a statistically significant difference between intervention and control groups. Measures of frequency of injecting risk behaviours varied greatly and could not be pooled. Only two studies (n=418, 854) showed significantly greater reductions in injecting risk behaviours in the intervention group compared with the control group. CONCLUSIONS: There was considerable variation in study design, outcome measures and magnitude, direction and statistical significance of findings between studies. Nonetheless, it is unlikely that behavioural interventions can have a considerable effect on HCV transmission. It is likely that multi-component interventions are required.


BACKGROUND: Treatment of hepatitis C (HCV) is very effective, achieving a cure in 50-90% of patients. Besides its own good for individuals, this most likely translates in reduced transmission, but this phenomenon has yet to be fully explored.

METHODS AND FINDINGS: In this mathematical modeling study done in the context of Vietnam, we estimated the public health benefit that HCV therapy for injecting drug users (IDUs) may achieve. Treatment coverage of 25, 50 and 75% of chronically HCV-infected IDUs (4 years into infection) is predicted to reduce the chronic HCV viremia prevalence respectively by 21, 37 and 50%, 11 years after full scale up to the intended coverage. At a constant 50% coverage level, earlier treatment, 3, 2, and 1 year into infection is predicted to reduce the chronic HCV viremia prevalence by 46, 60 and 85%. In these later 3 scenarios, for every 100 treatment courses provided, a total of respectively 50, 61 and 94 new infections could be averted. These benefits were projected in the context of current low coverage of methadone maintenance therapy and needles/syringes exchange programs, and these services expansion showed complementary preventive benefits to HCV therapy. The program treatment commitment associated with the various scenarios is deemed reasonable. Our model projections are robust under adjustment for uncertainty in the model parameter values. CONCLUSIONS: In this case study in Vietnam, we project that treatment of HCV for injecting drug users will have a preventative herd effect in addition to curing patients in need for therapy, achieving a substantial reduction in HCV transmission and prevalence.


The HCV direct-acting antiviral treatment era is underway. Although there are some important differences, it is likely that the experience with HCV will be similar in many respects to what already occurred with HIV. This paper considers seven important lessons learned with HIV and the degree to which they should be anticipated with HCV.

Session 7: Barriers to hepatitis C Treatment

**Presentation Philip Bruggmann** Barriers to hepatitis C treatment

Bruggmann, P. "Accessing Hepatitis C patients who are difficult to reach: it is time to overcome barriers." J Viral Hepat 2012 19(12): 829-835.

With the arrival of simple, efficient and safe interferon-free treatment regimens, hepatitis C virus (HCV) therapy will have the potential to be successfully used for the majority of infected patients and prevent the associated morbidity and mortality. With the current treatment uptake rates, only a very small proportion of HCV-infected patients are reached. Paradoxically, treatment rates are lowest in the most affected at-risk group - people who inject drugs (PWID) - which is the major driving force behind the spread of HCV infection. To conquer the increasing problem of HCV-related liver disease, many existing but modifiable obstacles, which prevent detection, assessment and treatment uptake, have to be overcome in this population. This review article summarizes the existing literature on the most relevant barriers preventing HCV care and describes measures to overcome these obstacles.


Despite the availability of highly effective therapy for hepatitis C virus (HCV) infection, few patients receive treatment. Barriers arising at multiple levels, from diagnosis to specialist referral, may impede the delivery of hepatitis C care. At the patient level, lack of awareness, fear of side effects, poor adherence and comorbid conditions may prevent treatment. For providers, limited knowledge, lack of availability and communication difficulties may be problematic. At the government and payer level, a lack of promotion, surveillance and funding may interfere. Each of these barriers needs to be addressed if wider implementation of antiviral therapy is to be achieved.

**RELATED Abstracts**

Pubmed MEDLINE search on '{(Hepatitis C OR Hep C OR HCV) AND (Barriers AND (Treatment OR Therapy))}' in all fields and filters used on this search 'last 5 year' and REVIEW was performed. Relevant article were manually selected. The reference were sorted by publication year and first author.

In total 34 were selected:

BACKGROUND: Infection with hepatitis C virus (HCV) is associated with high morbidity and increased mortality but many patients avoid initiation of treatment or report challenges with treatment completion. The study objective was to identify motivators and barriers for treatment initiation and completion in a community sample of HCV-infected patients in the United States. METHODS: Survey methods were employed to identify factors reported by patients as important in their decision to start or complete HCV treatment. Study participants included 120 HCV-infected individuals: 30 had previously completed treatment with pegylated interferon/ribavirin (PR), 30 had discontinued PR, 30 were treated with PR at the time of the survey, and 30 were treatment-naive. Telephone interviews occurred between May and August of 2011 and employed a standardized guide. Participants assigned factors a rating from 1 (not at all important) to 5 (extremely important). Trained researchers coded and analyzed interview transcripts. RESULTS: Of 33 factors, expected health problems from not treating HCV infection was reported as most encouraging for treatment initiation and completion, while treatment side effects was most discouraging. Sixty-nine percent of participants reported that the ability to obtain information during treatment on the likelihood of treatment success (i.e., results of viral load testing) would motivate them to initiate therapy. Median preferred timing for learning about test results was 5 weeks (range: 1--23 weeks). CONCLUSION: Understanding challenges and expectations from patients is important in identifying opportunities for education to optimize patient adherence to their HCV treatment regimen.


The majority of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) coinfection occurs among persons who inject drugs. Rapid improvements in responses to HCV therapy have been observed, but liver-related morbidity rates remain high, given notoriously low uptake of HCV treatment. Advances in HCV therapy will have a limited impact on the burden of HCV-related disease at the population-level unless barriers to HCV education, screening, evaluation, and treatment are addressed and treatment uptake increases. This review will outline barriers to HCV care in HCV/HIV coinfection, with a particular emphasis on persons who inject drugs, proposing strategies to enhance HCV treatment uptake and outcomes.


OBJECTIVE: Much of the research to date on barriers to treatment for patients with hepatitis C has approached the problem from either the perspective of the medical provider or the healthcare system. METHODS: To better understand these barriers from the patients' perspectives, nine exploratory focus groups of patients with hepatitis C (N=48) were conducted in 2008 and 2009, using a hybrid qualitative analysis. RESULTS: Eight content categories emerged. Treatment-related issues, including barriers to care, were most emphasized, representing nearly one-half of the entire content. Need for accurate disease-related information was also extensively discussed. Social factors were important, including considerable focus on stigma. Participants described coping abilities including faith and perseverance. CONCLUSION: Areas of concern expressed in these focus groups represent underexplored areas that may warrant additional attention or areas for intervention.
and investigation, such as exploring differences between perceptions of patients and providers regarding the hepatitis C treatment process and addressing barriers to care.


While patients with chronic hepatitis C virus (HCV) infection are treated in order to prevent liver-related morbidity and mortality, we rely on sustained virological response (SVR) as a virological biomarker to evaluate treatment efficacy in both clinical practice as well as in drug development. However, conclusive evidence for the clinical benefit of antiviral therapy or validity of SVR as surrogate marker, as derived from trials randomizing patients to a treatment or control arm, is lacking. In fact, the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) trial recently showed an increased mortality rate among interferon-treated patients compared to untreated controls. Consequently, the recommendation to treat patients with chronic HCV infection was challenged. Here, we argue that the possible harmful effect of long-term low-dose pegylated interferon mono therapy, as was observed in the HALT-C trial cohort, cannot be extrapolated to potentially curative short-term treatment regimens. Furthermore, we discuss SVR as a surrogate biomarker, based on numerous studies which indicated an association between SVR and improvements in health-related quality of life, hepatic inflammation and fibrosis, and portal pressure as well as a reduced risk for hepatocellular carcinoma (HCC), liver failure and mortality.


A large body of literature emphasizes the relationship between stigma and adverse health outcomes and health access measures. For people living with hepatitis C virus (HCV), stigma is a defining feature given the association of HCV with the socially demonized practice of injection drug use. However, there is little literature that specifically examines stigma as a barrier to HCV care and treatment. This review argues that the relationship between the person living with HCV and their health worker can work to ameliorate the effects of stigma. We draw on an emerging literature that examines the positive association between a patient's "trust" in their health worker and outcomes such as increased healthcare utilization and reduced risk behaviors. We investigate a growing body of health services research that acknowledges the importance of stigma and demonstrates ways to build positive, enabling relationships between patient, health worker, and health setting.


Chronic infection with the hepatitis C virus (HCV) is a leading cause of global morbidity and mortality. Although recent advances in antiviral therapy have led to significant improvements in treatment response rates, only a minority of infected patients are treated. Multiple barriers may impede the delivery of HCV therapy. The aim of this study was to identify perceived barriers to care, knowledge, and opinions among a global sample of HCV treatment providers. An international, multidisciplinary survey of HCV treatment providers was conducted. Each physician responded to a series of 214 questions concerning his or her practice characteristics, opinions regarding the state of HCV care, knowledge regarding HCV treatment, and perception of treatment barriers. A total of 697 physicians from 29 countries completed the survey. Overall, physicians viewed patient-level barriers as most
significant, including fear of side effects and concerns regarding treatment duration and cost. There were distinct regional variations, with Central and Eastern European physicians citing government barriers as most important. In Latin America, the Middle East, and Africa, payer-level barriers, including lack of treatment coverage, were prominent. Overall, the perception of barriers was strongly associated with physician knowledge, experience, and region of origin, with the fewest barriers reported by Nordic physicians and the most reported by Middle Eastern and African physicians. Globally, physicians demonstrated deficits in basic treatment principles, including the role of viral kinetics and the management of treatment nonresponders. Two thirds of surveyed physicians believed that patients do not have adequate access to providers in their community. CONCLUSION: Barriers to HCV treatment vary globally, though patient-level factors are viewed as most significant by treating physicians. Efforts to improve awareness, education, and specialist availability are needed.


BACKGROUND: Illicit drug users have a high prevalence of HCV and represent the majority of newly infected persons in the U.S. Despite the availability of effective HCV treatment, few drug users have been evaluated or treated for HCV. Racial and ethnic minorities have a higher incidence and prevalence of HCV and higher HCV-related mortality. Factors contributing to poor engagement in care are incompletely understood. METHODS: Fourteen mixed-gender focus groups of either African American or Latino/a drug users (N = 95) discussed barriers to HCV testing and treatment. Themes were identified through content analysis of focus group discussions. RESULTS: Many drug users were tested for HCV in settings where they were receiving care. Outside of these settings, most were unaware of voluntary test sites. After testing HCV positive, drug users reported not receiving clear messages regarding the meaning of a positive HCV test, the impact of HCV infection, or appropriate next steps including HCV clinical evaluations. Many drug users perceived treatment as unimportant because they lacked symptoms, healthcare providers minimized the severity of the diagnosis, or providers did not recommend treatment. Mistrust of the motivations of healthcare providers was cited as a barrier to pursuing treatment. Social networks or social interactions were a source of HCV-related information and were influential in shaping drug users perceptions of treatment and its utility. CONCLUSION: Drug users perceived a paucity of settings for self-initiated HCV testing and poor provider-patient communication at test sites and during medical encounters. Notably, drug users reported having an unclear understanding about the meaning of a positive HCV test, the health implications of HCV infection, the importance of clinical evaluations and monitoring, and of treatment options for HCV. Efforts to improve the delivery of clinical messages about HCV infection for drug users at test settings and clinical encounters are needed.


OBJECTIVES: To explore attitudes toward hepatitis C antiviral therapy in a real-world setting, we asked patients in opioid agonist treatment who were offered antiviral therapy about perceived barriers to initiating therapy. METHODS: We recruited patients in opioid agonist treatment who had previously been offered cost-

INTRODUCTION AND AIMS: Uptake of treatment for hepatitis C virus (HCV) infection among people who inject drugs is low. Further understanding is required of the relationship between HCV knowledge and treatment willingness, assessment and treatment in this population. DESIGN AND METHODS: A cross-sectional self-administered survey was conducted with clients of four opioid substitution therapy (OST) clinics and the Medically Supervised Injecting Centre in Sydney, Australia. RESULTS: Of 132 participants, 85 (64%) self-reported having HCV infection. HCV knowledge was mixed (mean 6.5, range 0-12) and was relatively lower on items measuring knowledge of factors impacting HCV-related liver disease progression. The likelihood of being in a higher knowledge category was associated with being female [adjusted odds ratio (AOR) = 3.78, 95% confidence interval (CI) (1.79, 7.98)], higher formal education [AOR = 3.28, 95% CI (1.57, 6.88)], being on a current OST program [AOR = 2.61, 95% CI (1.10, 6.19)] and being older [AOR = 1.04, 95% CI (1.01, 1.09)]. Participants receiving OST were more likely to report higher willingness to have HCV treatment [OR = 4.45, 95% CI (2.23, 8.17)]. Having been assessed for HCV treatment was associated with younger age [AOR = 0.93; CI 95% (0.88, 1.00)] and higher formal education [AOR = 7.81; 95% CI (1.62, 37.71)]. DISCUSSION AND CONCLUSIONS: Overall, knowledge scores were mid-range. Knowledge of modifiable factors influencing HCV-related liver disease progression was particularly low indicating the need for ongoing education. Education should also be targeted at older people and those not on OST, and be inclusive of those with lower literacy levels.


The need to improve access to care and treatment for chronic hepatitis C virus (HCV) infection in resource-limited settings is receiving increasing attention. Key priorities for scaling up HCV treatment and care include reducing the cost of current and future treatment; simplifying the package of care; identifying opportunities to shift specific tasks to nonspecialists to overcome human resource constraints; service integration with human immunodeficiency virus (HIV) clinics, prison health services, and needle syringe and oral substitution therapy programs; improving surveillance, monitoring, and research; encouraging patient and community engagement; focusing specifically...
on the needs of vulnerable groups; and increasing financial and political commitment. Many of these obstacles have been addressed in rolling out treatment for human immunodeficiency virus during the last decade, and a number of lessons can be drawn to help improve access to HCV care.


BACKGROUND: The morbidity and mortality of hepatitis B virus- and hepatitis C virus-related complications are disproportionately higher in the culturally and linguistically diverse population (CALD) when compared with Australian-born individuals. AIM: This project aims to elucidate the barriers faced by the CALD population in accessing viral hepatitis management. METHOD: CALD outpatients attending a viral hepatitis clinic in a tertiary teaching hospital were invited to participate in interviews. Questions pertained to: reason for screening for viral hepatitis, barriers to healthcare, perceived community view of viral hepatitis, main source of information of viral hepatitis and suggestions to engage members of CALD to seek healthcare. RESULTS: The total number of participants was 60. The two major countries of birth included China (40%) and Egypt (17%). In 40% of the cohort, viral hepatitis was identified through screening programmes. Importantly, 37% were diagnosed as a result of complications of hepatitis infection, presenting late in the stage of disease. Forty-five per cent of participants perceived language to be a chief barrier. twenty-two per cent reported cultural barriers to accessing healthcare. Of these, 53% reported fear of discrimination/stigma. The lack of knowledge of available treatments/options was stated as a major obstacle in 40%. The two prevailing recommendations were greater education and awareness (85%) and changes in the health system itself (11%). CONCLUSION: Substantial hurdles identified by participants include cultural differences, language difficulties, cultural beliefs, stigma and misinformation. These data demonstrate the need for the greater dissemination of information in culturally and linguistically appropriate mediums to raise awareness about viral hepatitis, pathogenesis and available treatments.


INTRODUCTION: The combination of pegylated interferon-alpha plus ribavirin (pegIFNalpha-RBV) has been the only therapeutic option for patients with chronic hepatitis C virus (HCV) infection during the last decade. Unfortunately, it provides cure to less than a half of individuals infected with HCV genotype 1, which is by far the most prevalent worldwide. The recent introduction of new direct-acting antivirals (DAA) has revolutionized the hepatitis C field. The addition of any of the two recently approved HCV protease inhibitors, boceprevir or telaprevir, to pegIFNalpha-RBV results in the cure for two-thirds of HCV genotype 1, interferon-naive patients. AREAS COVERED: This paper reviews new antivirals for hepatitis C and HCV treatment failures, along with HCV drug resistance and rescue therapies. EXPERT OPINION: The application of early stopping rules may reduce the enrichment of drug-resistant viruses in patients failing first-generation HCV protease inhibitors, potentially allowing more chances of response to rescue interventions with other compounds within the same class in the near future. On the other hand, the advent of DAA belonging to distinct drug families may provide further opportunities for clearing definitively HCV in patients currently failing first-generation HCV protease
inhibitors. Thus, hepatitis C has entered a new era that hopefully will end with its eradication. In the meantime, a wise use of DAA is warranted, including adequate selection of candidates for therapy, close monitoring of drug adherence, proper management of side effects and early application of stopping rules.


OBJECTIVES: Guidelines for hepatitis C (HCV) strongly recommend antiviral treatment for patients with more severe liver disease given their increased risk of developing cirrhosis and other liver-related complications. Despite the proven benefits of therapy, 70%-88% of patients chronically infected with HCV do not undergo treatment. The goal of this paper is to describe patterns of treatment initiation among patients with both mild and severe disease and to assess the factors that are associated with treatment initiation and completion. METHODS: Subjects completed previously validated questionnaires to ascertain sociodemographic characteristics, choice predisposition, and clinical characteristics prior to meeting with the hepatologist to discuss treatment initiation and were followed for 12 months. We examined the association between patient characteristics and treatment patterns controlling for liver disease severity. RESULTS: Of the 148 eligible subjects entered into our study, 55 (37%) initiated treatment during the 12-month follow-up period. Of the 86 subjects with severe liver disease, 43 (50%) initiated treatment. Financial barriers and geographic access to care were the most common reasons for treatment deferral. Of the 55 patients initiating treatment, 24 (44%) discontinued treatment, with intolerance of side effects being the most common reason for discontinuation. After adjusting for liver disease severity, patient choice predisposition (prior to discussion with their provider) was strongly associated with initiation of treatment, while sociodemographic characteristics were not. CONCLUSION: Treatment initiation did align with current recommendations (patients with severe disease were more likely to initiate treatment), however, rates of treatment initiation and completion were low. Patient choice predisposition is the strongest predictor of treatment initiation, independent of disease severity. Improving individualized treatment outcomes for patients with chronic HCV requires efforts at identifying patients’ choice predisposition, and improving access for those wishing to initiate therapy.


Between 1999 and 2003, Asian Americans and Pacific Islanders (APIs) in the US experienced more rapid growth in the number of AIDS cases than any other racial or ethnic group. In addition, the prevalence of HBV and HIV co-infection is estimated to be significantly higher among APIs in the US than in other racial/ethnic groups. High rates of HIV and hepatitis B or C (HBV and/or HCV) co-infection, in concert with language and cultural barriers, create significant challenges to effective coordination of treatment. The purpose of this study is to identify barriers to care and treatment in APIs with HIV with and without hepatitis co-infection. Specifically, we analyze results from semi-structured interviews with health care providers (N=23) and Asian Americans who are HIV and hepatitis (HBV and/or HCV) co-infected (N =17) in order to clarify how stigma in particular may impede/limit access to coordinated health care provision. Providers and clients recognize the need for integrated,
culturally and linguistically appropriate access to care while simultaneously acknowledging that stigma is a severe barrier to access to care. This article sheds light on the complexities of the stigma experienced by HIV and hepatitis co-infected Asian Americans and suggests a need for further research and renewed efforts by caregivers to reduce stigma in these communities.


Hepatitis C (HCV) and HIV coinfection is common and liver disease is a leading cause of morbidity and mortality among coinfected patients. Despite advances in HCV treatment, few HIV coinfected patients actually initiate treatment. We examined patient and provider characteristics associated with a patient's decision to accept or refuse HCV treatment once offered. We conducted patient chart abstraction and surveys with 127 HIV coinfected patients who were offered HCV treatment by their provider and surveys of their HCV care providers at three HIV clinics. Participants were mostly male (87%), minority (66%), and had a history of injection drug use (60%). Most had been diagnosed with HIV for several years (X=13.7 years) and reported HIV transmission through unprotected sex (47%). Of the 127 patients, 79 accepted treatment. In multivariate analysis, patients who had a CD4 greater than 200 cells/mm(3) and a provider with more confidence about HCV treatment were more likely to accept the recommendation to start treatment; younger age was marginally associated with treatment acceptance. In bivariate analysis, added correlates of treatment acceptance included male gender, no recent drug use, and several provider attitudes regarding treatment and philosophy about determination of patient treatment readiness. Patient and provider characteristics are important when understanding a patient's decision to start or defer HCV treatment. Further research is needed to better understand barriers to treatment uptake as new and more effective HCV treatments will soon be available.


BACKGROUND: In Canada, more than 70% of new cases of hepatitis C virus (HCV) infection per year involve injection drug users (IDUs) and, currently, there is no consensus on how to offer them medical care. OBJECTIVE: To examine the characteristics of Canadian specialist physicians and their likelihood to provide treatment to HCV patients who are IDUs. METHODS: A nationwide, cross-sectional study was conducted in the specialty areas of hepatology, gastroenterology and infectious diseases to examine HCV services. The questionnaire requested information regarding basic demographics, referral pathways and opinions (yes/no), and examined how a physician's treatment regimen is influenced by factors such as treatment eligibility, HCV care management and barriers to providing quality service. RESULTS: Despite the fact that the majority of prevalent and incident cases of HCV are associated with injection drug use, very few specialist physicians actually provide the necessary therapy to this population. Only 19 (19.79%) comprehensive service providers were likely to provide treatment to a current IDU who uses a needle exchange on a regular basis. The majority of comprehensive service providers (n=86 [89.58%]) were likely to provide treatment to a former IDU who was stable on substitution therapy. On bivariate analysis, factors associated with the likelihood to provide treatment to current IDUs included physicians' type, ie, infectious disease specialists compared with noninfectious specialists (OR 3.27 [95% CI 1.11 to 9.63]),
and the size of the community where they practice (OR 4.16 [95% CI 1.36 to 12.71] [population 500,000 or greater versus less than 500,000]). Results of the multivariate logistic regression analysis were largely consistent with the results observed in the bivariate analyses. After controlling for other confounding variables, only community size was significantly associated with providing treatment to current IDUs (OR 3.89 [95% CI 1.06 to 14.26] [population 500,000 or greater versus less than 500,000]).

CONCLUSION: The present study highlighted the reluctance of specialists to provide treatment to current IDUs infected with HCV. Providing treatment services for HCV-infected substance abusers is challenging and there are many treatment barriers. However, effective delivery of treatment to this population will help to limit the spread of HCV. The present study clearly identified a need for improved HCV treatment accessibility for IDUs.


BACKGROUND: The primary care physician (PCP) diagnoses chronic Hepatitis C virus (HCV) infection in most patients. He serves as gatekeeper and plays a key role in counselling and treatment guidance. OBJECTIVES: To calculate the approximate HCV caseload per practice and characterize PCPs management of the disease; in particular, to determine antiviral treatment rates and reasons for PCPs for withholding treatment. The ultimate objective was to identify potentially modifiable barriers to treatment. METHODS: A confidential self-administered questionnaire centred on the above-mentioned questions was distributed to 2371 Swiss primary care physicians. All respondents of the main questionnaire received an additional small questionnaire focussed on the initial disease workup. Descriptive statistics were used to describe questionnaire responses and PCP demographics. RESULTS: The response rate was 53.1%. Of all participating PCPs (n = 1084), 86.2% reported having patients with chronic HCV, with an average number of 4 patients per practice; 18.6% (n = 142) of PCPs did not monitor their chronic HCV patients. Two-thirds (66.8%) of the sample chronic HCV patient population (n = 4626) never received antiviral therapy. The main reasons given by PCPs for withholding treatment were HCV-specialist advice, patient preference, normal liver enzymes and patient related factors like substance abuse or psychiatric co morbidity. CONCLUSIONS: Most PCPs follow patients with chronic hepatitis C, but practice caseloads are low, which may account for insecurity in managing this complex disease.


BACKGROUND: Alcohol consumption, current injecting drug use, and pre-existing mental illness have been identified as 3 of the main reasons for excluding patients from treatment for hepatitis C. OBJECTIVES: We reviewed the literature to obtain an evidence base for these common exclusion criteria. MATERIALS AND METHODS: We reviewed original research and meta-analyses investigating the effects of alcohol consumption, current injecting drug use, and pre-existing mental illness. RESULTS: We identified 66 study reports relevant to the review, but found only limited evidence to support withholding of treatment on the basis of the 3 previously mentioned exclusion criteria. CONCLUSIONS: Currently, there is a lack of evidence for many of the barriers faced by patients in availing treatment for hepatitis C. Adherence to treat routine was found to be a better predictor of sustained virological response than
injecting drug or alcohol consumption during treatment period or the presence of a pre-existing mental disorder. Although several challenges remain, we need to ensure that treatment decisions are based on the best available evidence and the treatment is performed appropriately on a case-by-case basis.


Drug users (DU) are a marginalized group and at risk for viral hepatitis, who seldom access health services. A cross-sectional survey was conducted with 111 DU with chronic HBV/HCV and 15 in-depth interviews with health professionals/policymakers in Rio de Janeiro, Brazil. Most interviewees were male, non-white, with a low educational background, unemployed and/or living on less than $245 a month (minimum wage). In the last 6 months, 61.8% of interviewees snorted cocaine, 64.7% at least once a week. Half of the interviewees had a stable partner and 38.3% of those with occasional partners never/almost never using condoms. Addiction treatment seeking was found to be associated with: being white (OR:5.5), high-school degree (OR:8.7), and employment (OR:5.7). Hepatitis treatment seeking was high (80.9%), and access to low-threshold, user-friendly health services was key for treatment seeking behaviors (OR:3.6). Missed opportunities for hepatitis treatment seem to be associated with structural (uneven political/financial support to hepatitis programs) and patient-related barriers (severe addiction and non-adherence). Those most in need were less likely to access treatment, calling for renewed strategies, in order to curb hepatitis among impoverished drug users and their sexual partners.


We sought to identify barriers to offering services for HIV/AIDS, hepatitis C virus, and sexually transmitted infections in substance abuse treatment programs. We surveyed treatment program administrators and clinicians within the National Drug Abuse Treatment Clinical Trials Network to evaluate the availability of medical and non-medical services for patients with or at risk for acquiring these infections. A substantial proportion of programs do not offer services (particularly medical services) for these infections. The most commonly cited barriers were funding, health insurance benefits, patient acceptance, and staff training. The findings highlight a missed opportunity to positively impact these infectious disease epidemics.


Assessment and treatment for hepatitis C virus (HCV) in the community remains low. We evaluated factors associated with HCV specialist assessment and treatment in a cross-sectional study to evaluate treatment considerations in a sample of 634 participants with self-reported HCV infection in New South Wales, Australia. Participants having received HCV specialist assessment (n = 294, 46%) were more likely to be have been older (vs <35 years; 35-44 OR 1.64, P = 0.117; 45-54 OR 2.00, P = 0.024; >/=55 OR 5.43, P = 0.002), have greater social support (vs low; medium OR 3.07, P = 0.004; high OR 4.31, P < 0.001), HCV-related attributed symptoms (vs none; 1-10 OR 3.89, P = 0.032; 10-21 OR 5.01, P = 0.010), a diagnosis of cirrhosis
(OR 2.40, P = 0.030), have asked for treatment information (OR 1.91, P = 0.020), have greater HCV knowledge (OR 2.49, P = 0.001), have been told by a doctor to go onto treatment (OR 3.00, P < 0.001), and less likely to be receiving opiate substitution therapy (OR 0.10, P < 0.001) and never to have seen a general practitioner (OR 0.24, P < 0.001). Participants having received HCV treatment (n = 154, 24%) were more likely to have greater fibrosis (vs no biopsy; none/minimal OR 3.45, P = 0.001; moderate OR 11.47, P < 0.001; severe, OR 19.51, P < 0.001), greater HCV knowledge (OR 2.57; P = 0.004), know someone who has died from HCV (OR 2.57, P = 0.004), been told by a doctor to go onto treatment (OR 3.49, P < 0.001), were less likely to have been female (OR 0.39, P = 0.002), have recently injected (OR 0.42, P = 0.002) and be receiving opiate substitution therapy (OR 0.22, P < 0.001). These data identify modifiable patient-, provider- and systems-level barriers associated with HCV assessment and treatment in the community that could be addressed by targeted interventions.


The purpose of this study was to determine factors that influence the frequency of hospital clinic visits for hepatitis C patients in Taiwan and identify data related to healthcare-seeking behaviors of patients by using a developed questionnaire based on the Health Belief Model. Consistent clinic visits for follow-up and treatment are required of the hepatitis C patient to be compliant with therapy guidelines. Recent studies targeted only Western communities in which hepatitis C is nonepidemic, unlike hepatitis C virus-endemic regions of Taiwan where patients may exhibit 10-20 times higher seroprevalence. Influences on hospital clinic visit attendance were identified as educational level, income, and aspartate aminotransferase level at diagnosis. Perceived benefits from and barriers to action were similar among the 390 evaluable subjects at various frequencies of hospital clinic visits (both p > .05); however, subjects who visited the hospital clinic between 1 and 6 months exhibited significantly higher scores of perceived susceptibility to disease and severity of disease than those who visited the hospital clinic at 7-9 months or less often (all p </= .001). Findings lay the foundation for future studies to address strategies to increase compliance with treatment regimens for Taiwanese patients with hepatitis C.


BACKGROUND: Patients with hepatitis C viral (HCV) may perceive barriers to accessing speciality care for HCV, and these barriers may be related to depressive symptoms. AIM: To evaluate the relationship between barriers to care, demographics, and depressive symptoms. METHODS: A cross-sectional analysis of 126 patients referred for HCV at two speciality HCV clinics. Barriers to care, depressive symptoms and sociodemographics were measured using standardized instruments. A retrospective chart review was conducted to collect clinical outcome data. RESULTS: Depressive symptoms were reported in 26%. Common barriers included lack of personal financial resources; lack of HCV knowledge in the community; lack of professionals competent in HCV care; stigmatization of HCV; and long distances to clinics offering care. After we controlled for sociodemographics, depression accounted for an additional 7-18% of variability in all barriers (all p values <0.01). Lower depression, marital and employment status were associated with subsequent receipt of HCV treatment in 38% (45/120) of patients; perceived barriers were not. CONCLUSIONS: Depression is independently associated with perceived barriers to
Higher depressive scores, but not perceived barriers, were associated with nontreatment. Healthcare providers who diagnose HCV need to be cognizant of numerous perceived barriers to accessing HCV care, and the impact that depression may have on these perceptions and receipt of treatment.


The objective of this study was to assess the prevalence of barriers to interferon treatment in a population of HIV/HCV coinfected patients. A cross-sectional study was conducted at two AIDS Outpatient Clinics in Brazil. The study included all HIV infected patients followed at these institutions from January 2005 to November 2007. Medical records of 2,024 HIV-infected patients were evaluated. The prevalence of anti-HCV positive patients among them was 16.7%. Medical records of HCV/HIV coinfected patients were analyzed. 189 patients with the following characteristics were included in our study: mean age 43 years; male gender 65%; former IDUs (52%); HCV genotype 1 (66.4%); HCV genotype 3 (30.5%); median CD4+ T cell count was 340 cells/mm(3). Among 189 patients included in the analyses, only 75 (39.6%) were considered eligible for HCV treatment. The most frequent reasons for non-treatment were: non-compliance during clinical follow-up (31.4%), advanced HIV disease (21.9%), excessive alcohol consumption or active drug use (18.7%), and psychiatric disorders (10.1%). CONCLUSIONS: In Brazil, as in elsewhere, more than half of HIV/HCV coinfected patients (60.4%) have been considered not candidates to received anti-HCV treatment. The main reasons may be deemed questionable: non-adherence, drug abuse, and psychiatric disease. Our results highlight the importance of multidisciplinary teams to optimize the access of coinfected patients to HCV treatment.


Volk, M. L. "Antiviral therapy for hepatitis C: why are so few patients being treated?" J Antimicrob Chemother 2010 65(7): 1327-1329.

Despite the long-term morbidity associated with hepatitis C and the availability of effective treatment, fewer than a quarter of infected individuals are treated with antiviral therapy. While this is partly related to inherent limitations of currently available medications and the underlying patient population, numerous health system barriers also exist. Fewer than half of chronic hepatitis C infections are diagnosed, relatively few are referred for treatment, and misperceptions about the disease and its treatment abound amongst patients and physicians alike. This article will discuss patient and physician factors that contribute to the undertreatment of chronic hepatitis C.


BACKGROUND: Nowadays intravenous drug use is the main source of hepatitis C transmission, but only a small proportion of those who acquired infection via intravenous drug use receive antiviral treatment. AIM: to assess the barriers of access to antiviral treatment of infected intravenous drug users. METHODS: A retrospective chart review was carried out in a hepatology outpatient clinic including all hepatitis C infected intravenous drug users in a 3-year period. RESULTS: Only one-third of the
infected former intravenous drug users received antiviral treatment. The main barrier to antiviral treatment was the lack of abstinence. Former intravenous drug users in prison or in long-term drug rehabilitation institutes were more likely to enter antiviral treatment. CONCLUSIONS: The low proportion of patients entering antiviral treatment calls the attention to further improving the pretreatment management of this patient population. Special attention should be paid to the maintenance of abstinence.


Hepatitis C (HCV) infection is common among injecting drug users (IDUs), yet accessing of HCV care, particularly HCV treatment, is suboptimal. There has been little in-depth study of IDUs experiences of what enables or prevents them engaging at every level of HCV care, including testing, follow-up, management and treatment processes. This qualitative study aimed to explore these issues with current and former IDUs in the greater Dublin area, Ireland. From September 2007 to September 2008 in-depth interviews were conducted with 36 service-users across a range of primary and secondary care services, including: two addiction clinics, a general practice, a community drop-in center, two hepatology clinics, and an infectious diseases clinic. Interviews were analyzed using a grounded theory approach. Barriers to HCV care included perceptions of HCV infection as relatively benign, fear of investigations and treatment, and feeling well. Perceptions were shaped by the discourse about HCV and "horror stories" about the liver biopsy and treatment within their peer networks. Difficulties accessing HCV care included limited knowledge of testing sites, not being referred for specialist investigations and ineligibility for treatment. Employment, education, and addiction were priorities that competed with HCV care. Relationships with health care providers influenced engagement with care: Trust in providers, concern for the service-user, and continuity of care fostered engagement. Education on HCV infection, investigations, and treatment altered perceptions. Becoming symptomatic, responsibilities for children, and wanting to move on from drug use motivated HCV treatment. In conclusion, IDUs face multiple barriers to HCV care. A range of facilitators were identified that could inform future interventions.


Uptake of treatment for hepatitis C virus (HCV) infection is very low particularly among people who have injected drugs. Opiate substitution treatment (OST) programs, with a high prevalence of people living with HCV, have been a site of growing interest in the delivery of hepatitis C treatment. There has been no exploration of OST clients' and health professionals' perceptions of the barriers and facilitators to uptake and delivery of HCV treatment in OST clinics from personal and organizational perspectives. This qualitative study involved interviews with 27 OST clients in New South Wales and a focus group and interviews with 22 Australian OST health professionals. Clients and health professionals viewed hepatitis C treatment in OST as a 'one-stop-shop' model which could increase access to and uptake of treatment and build on existing relationships of trust between OST client and health professional. Elements of the organizational culture were also noted as barriers to HCV treatment delivery including concerns about confidentiality, lack of discussion of HCV treatment and that HCV treatment was not perceived by clinicians as a
legitimate activity of OST clinics. OST client participants also reported a number of personal barriers to engaging with HCV treatment including family responsibilities (and concerns about treatment side effects), unstable housing, comorbidities and perceptions of the unsatisfactory level of treatment efficacy. These findings emphasize the need for future research and delivery of services which addresses the complexity of care and treatment for people in marginalized social circumstances.


BACKGROUND: Contraindications to interferon and ribavirin for treatment of chronic hepatitis C (CHC) are well recognized, and previous data indicated the consequent suboptimal treatment uptake. AIM: To evaluate the treatment rate of CHC patients in a tertiary referral center in Hong Kong, and to examine the reasons for non-treatment. METHODS: A retrospective review of all referred CHC patients to the outpatient clinic was conducted. Treatment uptake rate was evaluated and patients' sociodemographic, biochemical, and histological data were examined to identify reasons for treatment decision. RESULTS: CHC patients (303) were assessed for antiviral therapy from 2000 to 2009. Of the patients, 138 (45.5%) did not receive antiviral therapy. Reasons for non-treatment were as follows: 31.9% declined treatment, 18.8% had decompensated cirrhosis, 12.3% were considered too elderly, 17.4% had too mild liver disease, 7.2% had psychiatric history, 7.2% had significant comorbidities, and 2.9% had ongoing alcohol or substance abuse. Independent factors associated with non-treatment were older age (adjusted odds ratio [aOR] 1.05, 95% confidence interval [CI] 1.03-1.08, p < 0.001), significant comorbidities (aOR 2.53, 95% CI 1.34-4.78, p = 0.004), psychiatric history (aOR 6.04, 95% CI 2.14-17.02, p < 0.001), mild liver disease (aOR 7.72, 95% CI 3.86-15.44, p < 0.001) and decompensated cirrhosis (aOR 9.42, 95% CI 2.57-34.50, p < 0.001). CONCLUSIONS: Current treatment uptake for CHC patients was suboptimal, as a large proportion of patients were either reluctant for treatment or not suitable for the current antiviral therapy. Multidisciplinary interventions are needed in the short term while alternative antiviral therapy is desired in the long term to overcome barriers to treatment.


OBJECTIVE: Hepatitis C virus (HCV) prevalence in certain Canadian immigrant populations is higher than that of the overall population. Disparities in care related to immigration status as well as to race and language are well recognized. Identifying and understanding these disparities is vital to the provision of optimal and inclusive HCV care. METHODS AND MATERIALS: HCV RNA-positive patients assessed at The Ottawa Hospital Viral Hepatitis Clinic between June 2000 and June 2007 were identified using a clinical database. As measures of access to care, liver biopsy rates, treatment initiation rates, supportive care provision (i.e. erythropoietin for treatment-related anemia) and sustained virological response (SVR) rates were assessed as a function of immigration status, race and spoken language. RESULTS: Nine hundred and ten patients were evaluated, of which 20% were immigrants. Biopsy rates (54 vs. 51%), HCV treatment initiation (37 vs. 38%), erythropoietin prescription (13 vs. 18%) and SVR rates (52 vs. 51%) did not differ between immigrants and Canadian-born individuals. Spoken language and race did not influence access to treatment. SVR was predicted by genotype, HIV status and race. CONCLUSION: In the context
of a multidisciplinary, multilingual universal health care system, by studying the influence of barriers to HCV investigation and successful therapy can be abrogated.


Liver disease is a leading cause of death among patients with HIV coinfected with hepatitis C (HCV); yet, studies show that less than 10% receive HCV treatment, in part because of limited treatment response, high treatment toxicity, and psychosocial barriers to treatment readiness. Using a process model framework, we sought to explore the factors and processes by which providers make HCV treatment decisions for HIV-coinfected patients. We conducted 22 semistructured interviews with primary care providers and support staff at three HIV clinics in Los Angeles, California, in which rates of HCV treatment uptake varied from 10% to 38%. Providers agreed that stable HIV disease, favorable genotype, and significant signs of liver disease progression are all signs of need for treatment. However, two divergent treatment approaches emerged for genotype 1 and 4 patients with minimal disease, and in definitions of patient readiness. Providers with lower treatment rates preferred to delay treatment in hopes of better future treatment options, and were more conservative in requiring complete mental health screens and treatment and abstinence from substance use. Conversely, providers with higher treatment rates viewed all patients as needing treatment as soon as possible, and defined readiness more leniently, with some willing to treat even in the context of untreated depression and drug use, so long as ability to adhere well was demonstrated. Regardless of whether an aggressive or cautious approach to treatment is used, development of effective programs for promoting patient treatment readiness is critical to ensuring greater treatment uptake.


BACKGROUND: In eastern Europe, the high prevalence rates of HIV and the hepatitis C virus (HCV) are concentrated among injecting drug users (IDUs). Harm reduction programmes such as needle and syringe programmes and opioid substitution therapy (OST) have been shown to be effective in preventing these infections. However, structural barriers can limit their effectiveness by hindering access. METHODS: Through use of a semi-structured online survey sent to 65 professionals in the region, this study explores the prevalences of age restrictions, user fees or a lack of confidentiality for these programmes as well as HIV/HCV testing programmes. RESULTS: Twenty respondents reported that age restrictions were not widespread in the 11 reporting countries, apart from for OST. User fees were found to be very common in HCV testing and varied for other services. It was stated to be common to inform parents of young IDUs who receive HIV services, but not to inform public authorities when IDUs enter harm reduction programmes. CONCLUSION: Where access to services is limited or confidentiality is compromised, as reported in this pilot study, it is crucial that health-care guidelines and national legislation are reformed to ensure access to these evidence-based interventions.
2. Bibliography of the Speakers

List of publications achieved via speakers form when this form was not available a Pubmed MEDLINE search was performed on Name of the speaker in [Author]-field and ‘hepatitis’ in [all fields]. If more than 10 references only the most recent articles are shown.

ERIKA DUFFEL (ECDC)

See ECDC Hepatitis


JOHN WARD (CDC, Centre for Disease Control-Atlanta,USA)

(10 recent articles from Pubmed search [Ward, J. and Hepatitis C])

Viral hepatitis on CDC website http://www.cdc.gov/hepatitis/index.htm


BENJAMIN MAASOUMY (Hannover Medical School, Germany)


MARKUS PECK-RADOSAVLJEVIC (Secretary General, EASL)


**Stefan Wiktor** (WHO- Global Hepatitis Program)


**David Goldberg** (Health Protection Scotland, UK)


**DAVID REIN** *(NORC at University of Chicago, USA)*

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**Tatjana Reig** *(President ELPA)*
FLOOR BERDEN (Radboud University Nijmegen Medical Centre, The Netherlands.)

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JULIO MONTANER (Chair AIDS Research program, University British Colombia, USA)


SHARON HUTCHINSON (Glasgow Caledonian University, Glasgow, Scotland, UK)


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