This issue of Viral Hepatitis reports the topics covered at the VHPB’s Country Meeting, held on November 18–19th, 2010 in Lisbon, Portugal.

The main objective of this report is to provide an overview of the current situation regarding prevention and control of viral hepatitis in Portugal. An overview is presented of the Portuguese health care system and of the revised national surveillance and notification system of infectious diseases, which includes notifications for viral and other types of hepatitis. The epidemiological situation of viral hepatitis is reviewed. The treatment and follow-up strategies for patients with chronic hepatitis B (HBV) and chronic hepatitis C (HCV), including liver transplant patients, is also discussed. An evaluation of the economic aspects of viral hepatitis and liver disease is presented. Data are also presented for specific populations at risk, such as drug users, haemodialysis patients and pregnant women. An overview of current prevention and control measures is provided, including an assessment of the progress achieved in HBV prevention ten years after the introduction of universal HBV vaccination, targeting newborns, adolescents and risk groups. The possible implementation of new prevention strategies, control measures and monitoring systems is discussed. The report also covers the discussions held during the meeting among participants, including national health authorities, addressing successes, challenges, and barriers that need to be overcome in order to clarify the way forward for an effective prevention and control strategy in Portugal.

Although Portugal has 40 national health programmes, not one is specifically focussed on viral hepatitis. When the number of deaths due to hepatocellular carcinoma (HCC) and liver diseases in HIV patients are included, liver disease is the 8th cause of death in Portugal. In light of this, the need for a comprehensive, coordinated strategy and a specific national public health programme for viral hepatitis is discussed in this report. In the prevention and control of viral hepatitis, there are many pockets of excellence in Portugal. However, Public Health authorities should involve all specialist groups, including liver disease specialists. There is a need for a coordinating body that can liaise between the specialist groups and Health authorities. Public opinion also has an important part to play in this debate.

A new, improved electronic web-based health information system combining clinical and laboratory data, with automated bidirectional data transfer (anonymizing and un-linking of data at higher level), has been developed and will be implemented in 2011.

Epidemiology of hepatitis A (HAV) has changed. As socioeconomic conditions have improved, Portugal has become a country of intermediate HAV endemia, with two thirds of the younger population becoming susceptible to HAV infection. This makes implementation of an adapted HAV vaccination policy an important challenge.

Progress has been achieved in HBV prevention ten years after the successful introduction of universal HBV vaccination. The vaccination coverage in newborns, infants and adolescents is high (> 94%). The successful prevention and control strategies for HBV mean that Portugal is no longer a country of intermediate HBV prevalence, and needs to be re-categorized as a country of low HBV prevalence, with the percentage of HBsAg carriers around 1%.

HCV has an important role in mortality from liver disease, and HCC has been increasing. Efforts should be made to amplify the screening and improve the diagnosis of HCV. There is an increasing burden of HCV, mostly in intravenous drug users (HCV prevalence 60 – 70%), who are often coinfected with HIV (14%, data from The National Institute for Drugs and Drug Addiction, IDT). Therefore, public health strategies, such as needle exchange programmes, could be focussed towards viral hepatitis, in addition to HIV.

A successful liver transplantation programme, with high survival rates (at least 73% after 10 years), is conducted at the Transplantation Center in Lisbon (Hospital Curry Cabral), where about 25% of patients transplanted are infected with HCV or HBV.

Alcoholism is an increasing public health problem in Portugal with a significant role in development of cirrhosis in patients with viral hepatitis. Therefore, public campaigns to raise awareness about harmful consumption of alcohol amongst the general population should be initiated. These campaigns and other awareness activities would be supported by the very active Portuguese liver patients association SOS Hepatites, which also supports patients by providing information and enabling links between patients.

Finally, this meeting report reviews the impact of the viral hepatitis resolution adopted by the World Health Assembly (WHA 63.18) in 2010 and the progress made in developing a comprehensive strategy in follow-up of the resolution. The need to start implementing comprehensive national prevention and control programmes for liver diseases is emphasized.

Rui Tato Marinho and Daniel Lavanchy, on behalf of the Viral Hepatitis Prevention Board
Burden and Prevention of Viral Hepatitis in Portugal, Lisbon, November 18-19, 2010

Health care system and viral hepatitis surveillance in Portugal

Portugal is undergoing a Health Transformation Programme to improve quality in the health care system. The new system takes into account novel developments in epidemiological surveillance for protecting and promoting health in the Portuguese population.

The objectives of the reform include:

- Improvement of knowledge and action in order to protect, promote, and preserve the entire population’s health;
- Standardization of activities and outputs in the new public health units based on knowledge and evidence.

In the age of evidence-based medicine, the need for continuous improvement and a changing relationship with citizens, a reform of public health systems was required. In Portugal, the new legal framework of 2009 shows a continued commitment to change and improvement, including reform of the Health Information System.

Surveillance should allow a systematic and continuous retrieval of data, rapid processing, validation and analysis that will lead to prompt dissemination of information and timely actions. The goals of surveillance include:

- early warning of outbreaks and events;
- detection of important trends;
- epidemic intelligence;
- assessment of results of the interventions;
- definition of more exposed groups to certain risks;
- generation of hypotheses; and
- supporting the definition of priorities.

The new legal framework in Portugal, with the support of central government, has reorganized the public health system. Under the direction of the General Directorate of Health (DG) office there are two autonomous regions (Azores and Madeira), 5 public health regional departments and 74 public health units.

A new electronic death certification system should make the process paperless and provide timely, accessible information where it is required. The form will be accessible to:

- the Ministry of Health (DG office, Central Administration of Health System, National Institute of Medical Emergency);
- the Home Office (National Guard and Police Department);
- the Ministry of Justice;
- the General Attorney; and
- the National Institute of Statistics.

Databases will have automatic updating, facilitating coding and statistical analyses and they will be able to record cases where there are multiple causes of death. Review of the submitted death certificates can identify institutions that require additional training in form completion, in order to improve the quality of mortality statistics.

Portuguese law 81/2009 states that the National Information System for Epidemiological Surveillance is a “Nationwide network operating service involving public health, laboratories,
health authorities and other entities of public, private and social sectors, in which participants contribute to a national information system for epidemiological surveillance”.

The National Information System for Epidemiological Surveillance covers, in a first phase:

- surveillance of communicable diseases (clinical, laboratory; mandatory);
- surveillance of antimicrobial resistance (laboratory); and
- surveillance of agent alerts (laboratory).

Implementation will require reengineering and automating the process with notification through the web and automatic alerts, immediate feedback, automatic production of statistics, and sharing information with international databases (TESSy - the European Surveillance System, WHO, other European countries).

Before the reform, compulsory reporting included only clinical information (not laboratory) filled in by doctors in a paper-based system with hierarchical transmission of data to the DG’s office in Lisbon. In terms of viral hepatitis, this included reporting of HAV, HBV, HCV, other specified hepatitis and non-specified hepatitis.

In the new surveillance system, both clinical and laboratory information will be recorded in a paperless, web-based system. A total of 69 diseases will be notifiable (65 from the European list of Communicable Diseases and 4 from Portuguese rules). Data from laboratories will be automatically transmitted to the central database. Importantly, the new Portuguese surveillance system will be linked to the ECDC European Surveillance System, TESSy, whose objectives are to collect, analyze and disseminate surveillance data in Europe. The automated Portuguese system generates reports at local, regional and national level. Public health doctors have access to the data at a county level and can access data for surrounding counties. Two types of reports will be available (pre-prepared and ad hoc) and filters will determine which report is accessed.

Clear case definitions for HAV, HBV and HCV are provided including clinical and laboratory criteria, see below.

**Case definitions used in Portugal for HAV, HBV and HCV**

<table>
<thead>
<tr>
<th>Health</th>
<th>Clinical Criteria</th>
<th>Laboratory Criteria</th>
<th>Epidemiological Criteria</th>
<th>Case Classification</th>
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| HAV    | • Any person with discrete onset of symptoms (e.g. fatigue, abdominal pain, loss of appetite, intermittent nausea and vomiting) AND at least one of the following: • fever • jaundice • elevated serum aminotransferases | At least one of the following: • detection of HAV nucleic acid in serum or stool • HAV specific antibody response • detection of HAV antigen in stool | At least one of the following: • human to human transmission • exposure to a common source • exposure to contaminated food or drinking water • environmental exposure | Probable case
|        |                   |                     |                         | Confirmed case |
|        |                   |                     |                         | As for HAV     |
| HBV    | As for HAV        | • HBV core antigen specific IgM antibody response • laboratory results interpreted according to vaccination status | An epidemiological link by human to human transmission (e.g. sexual contact, vertical transmission or blood transmission) | As for HAV     |
| HCV    | n/a*              | At least one of the following: • detection of HCV nucleic acid in serum • HCV specific antibody response, confirmed by a different antibody test | n/a*          | Confirmed case |

*other health care providers, not applicable*

The new electronic reporting system is not expected to cause privacy issues, because it has been approved by the National Committee for Protection of Citizen Information. Whilst at local level doctors can access the whole system (relying on ethical conduct of doctors), at a national level the system is anonymous and unlinked. The new health system will be launched in 2011 and its use will be compulsory.

Other web-based and electronic initiatives to be implemented include:

- e-Vaccines (a national immunization registry to be implemented in 2011 that will keep track of the number of vaccines administered and immunization coverage, and that will send automatic recalls),
- e-Health Records
- e-Prescriptions

Based on presentations by

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Epidemiology of viral hepatitis in Portugal

Introduction

Whilst the general picture for viral hepatitis in Portugal shows declining prevalence rates of HBV, the burden of disease due to HCV is increasing. HCV has an important role in mortality from liver disease, but it remains difficult to attribute mortality to viral hepatitis. According to official WHO data, cirrhosis of the liver is among the top ten causes of death in Portugal [1, 2]. In 2008, there were 1351 cases of liver cirrhosis according to the Portuguese National Institute of Statistics [3]. Hepatocellular carcinoma (HCC) has become an increasingly important cause of death over the last few years: the number of HCC cases in Portugal increased from 280 in 2004 to 423 cases in 2008 (compared to 717 HIV cases in 2008) [3].

Migration plays a significant role in the epidemiology of viral hepatitis (in particular HBV and HCV) and liver disease in Portugal. The number of migrants in Portugal is estimated to be close to 0.5 million, and includes migrants from eastern Europe (Ukraine, Moldova) and Asia (China) but also specific migrant groups originating from former colonies (including Brazil, Cape Verde, Angola, Guinea-Bissau).

Epidemiology of hepatitis A in Portugal

A report published by ECDC in 2008, entitled “Intervening to reduce inequalities in infections in Europe”, showed examples of diseases with inequitable distribution [1]. In this report, HAV in Portugal is given as an example of a disease related with poverty and educational level, based on data from a survey of HAV in Portuguese children and adolescents living in Porto [2]. The study showed that HAV seroprevalence increases with increasing age (between 6 and 19 years) and also with increasing crowding index (number of inhabitants/ room), which is an indirect measure of poverty.

Portugal is a country in transition from high to intermediate HAV endemicity. Most of the older population is immune due to earlier contact with the disease during childhood, i.e. when the disease was still highly endemic in the country. The majority of the young population is still susceptible and once exposed to HAV this could result in considerable outbreaks. No fulminant HAV cases among children have been identified so far. The shift in endemicity explains the dramatic decrease in HAV prevalence in the age group 6-19 years when studies from the 1980s and late 1990s are compared (from 75% in 1980 to 20% in 1998 in Porto).

Coinfection of HAV with HIV increases the severity and the duration of the HAV disease. Since drugs to treat HIV are processed in the liver, the risk of liver-related side-effects is higher in HIV/ HAV coinfected patients.

References


*Immunization of adolescents started in 1993 and was fully implemented in 1994. Limited risk group immunization started in 1990, this was substantially expanded to include other groups in 1995.

Epidemiology of hepatitis B in Portugal

Acute HBV is a notifiable disease in Portugal, with 53 cases reported in 2008. This represents an incidence of 0.5/100,000 population. This figure is 5 times less than in neighbouring Spain (2.3/100,000) and less than the European average of 3.3 per 100,000 [1], but acute HBV is probably under-reported in Portugal. There has been a sharp decline in the number of notified HBV cases since the introduction of HBV vaccination (see Figure below).

Notification of HBV in Portugal

Source: Direcção-Geral da Saúde

* Immunization of adolescents started in 1993 and was fully implemented in 1994. Limited risk group immunization started in 1990, this was substantially expanded to include other groups in 1995.

Two thirds of patients admitted to hospital with HBV are male and the majority are between the ages of 25-44 years. According to a national serological survey (2001-2002) only 20% of those aged 30-44 years have anti-HBs antibodies and in older individuals the percentage is even lower (less than 5%). The prevalence of antibodies against HBV core antigen (anti-HBc), a better marker for past infection, is 15.2% in over 65 year olds (17.2% in men, 13.4% in women) [2].

In Portugal, the average annual number of acute hepatitis related hospital admissions in 2004-2008 was 216, with a male/female ratio of 2.1/1. Male patients were aged 25-44 years, female patients were aged 15-54 years, and the mortality rate was 2.7%. This represented an average annual cost of 828.232€.
The number of nationally reported deaths in 2005 in Portugal was 14 due to acute HBV, 8 due to chronic HBV and 40 related to the sequelae of viral hepatitis (information from the Ministry of Health) [3]. However, it is important to also consider deaths categorized as HCC, cirrhosis and HIV. Taking into account the contribution of HBV (2008 or 2009 estimates) in deaths due to liver cirrhosis (~5% of 1373 cases), HCC (~50% of 423 cases) and HIV coinfection (~5% of 664 cases) [4, 5, 6] there are an estimated 313 HBV related deaths per year. This indicates that under-reporting may be significant in Portugal.

According to a national study reported in 1984, the general HBsAg prevalence in Portugal was 1.25% based on data of 1440 persons older than 15 years [7]. Regional studies indicate that almost 10 years ago, HBsAg prevalences were 1.4% (0.3% in adolescents) in the north (2000) and 0.9% in the central region (1993) [8, 9]. Local studies conducted in the 1990s found prevalences between 1%-1.8%. HBsAg prevalence decreased sharply after 1990 when vaccination was introduced. According to a national serological survey [2] among private laboratories (2001-2002, N=1096), HBsAg prevalence was 0.36%, indicating that Portugal is a country with low HBsAg prevalence (<2%) although this is not in line with a recent ECDC report or with the WHO report in 2001, where Portugal was presented as having intermediate HBV prevalence (HBsAg 2-8%) [10]. Most recent estimates of HBsAg prevalence rates are between 0.5 and 1% and seem to confirm the low prevalence classification, even taking into account the limitations of available information. A new national population study would be required to provide robust data.

The low national prevalence data, however, hide high rates in specific risk groups. Immigration plays a significant role in the prevalence of HBV in Portugal. Among migrants in Portugal, approximately 5% are estimated to be HBV carriers. This is in line with the estimated 30,000 HBsAg+ migrants in Portugal (corresponding to 0.28% of the population) according to a 2010 ECDC technical report [11]. Screening of HBsAg among migrants should be strongly encouraged.

Among intravenous drug users (IDUs) in Portugal, the younger ones have been vaccinated against HBV. However adult IDUs over the age of 30, who are not protected and who are susceptible, would benefit from vaccination.

Hepatitis D (HDV) can cause severe clinical complications in HBV infected patients. A multicentre study conducted in 2003-2004 in Portugal, found an anti-HDV prevalence of 3.5% in chronic HBsAg carriers, indicating that currently HDV is not a major problem in Portugal.

Prevalence of HBV in first time blood donors
Over 400,000 blood donations are carried out in Portugal each year. Of them, around 250,000 are collected by the Portuguese Blood Institute and 150,000 by hospitals. There are over 44,000 first time donors annually.

Screening blood donors provides data on the prevalence of HBV in this group. Eligibility criteria to become a blood donor in Portugal include age (18-65), weight (>50kg), a screening questionnaire, and a medical examination. In the last 5 years, one in four potential donors presenting to a blood collection centre was not eligible to donate. Less than 10% of blood donations in Portugal are from immigrants.

Screening blood donors for HBV includes testing HBsAg (ELISA) and nucleic acid testing (NAT). In 2009, the prevalence of HBV among 44,052 first time donors was 0.24% based on HBsAg and/or NAT. In this group there were 5 cases that were ELISA-/NAT+, as a consequence of the window period of infection. Most recent data for 2010 (January-September) show that HBV prevalence in first time blood donors is 0.14% (0.15% in males and 0.06% in females) compared with 0.02% in all donors.

Epidemiology of HBV in paediatric patients
There has been a substantial decrease in the number of children infected with HBV since the introduction of the vaccine in 1993-1995 for adolescents and a range of risk groups, screening of pregnant women for HBsAg since 1992, and a vaccination programme of newborns since 2000. Newborns from HBsAg+ mothers are given Hepatitis B immunoglobulin (HBIG) and HBV vaccination within 48 hours of birth.

A review of data collected between 1993 and 2010 in 6 paediatric gastroenterology units identified 114 children with chronic HBV. Gender distribution seems to be similar for males and females, perhaps with a slight predominance of males. There was a very high representation of immigrants from former colonies and children of black ethnic origin. The commonest form of transmission appeared to be perinatal (mother to child transmission), followed by intrafamilial transmission. Eight children were infected through blood products, all of them of African origin. Among the 114 paediatric patients presenting with chronic HBV, 17 were HBV vaccine failures. These were most likely not failures due to viral escape mutants, but probably were failures due to incomplete vaccination course. The role of HBV genotype remains to be investigated.

Molecular epidemiology of HBV
An epidemiological study in the north of Portugal including 400 chronically infected HBsAg+ patients, showed a predominance of genotype D (60.3%) and genotype A (31.5%), with a minor proportion of genotypes E, C and F. In females, intrafamilial transmission was the commonest route of infection, while in males there was an equal proportion of perinatal, sexual, and intrafamilial transmission. The presence of HBV “e” antigen (HBeAg) was associated with genotype D, high viral load and increased ALT/AST, and HBeAg+ cases had more severe liver damage [12]. In HBV infected patients, high alcohol intake (~20g a day) was associated with more severe liver disease that increased with age and was more common in males [13]. This study also confirmed the epidemiological observation of a higher frequency of HBV markers in chronic alcoholics, compared with the general population. The impact of HBV genotype on liver damage remains to be investigated.

References
Epidemiology of hepatitis C in Portugal

There is no mandatory notification of HCV cases in Portugal, however, there is evidence that the number of cases being reported is increasing [1]. HCV is the most reported of the viral hepatitis diseases and this implies that HCV is a serious health problem in the country. In 1998, 676 cases were reported, mainly among males aged 25-34 years. In 2006, based on notified cases, the Department of Health (DGS) estimated an HCV incidence of 0.83/100,000 population.

The prevalence of acute and chronic cases is not known with certainty. It is estimated that the anti-HCV prevalence is in the range of 1%-1.5%. A population based study reported in 1993 (N=657, mostly female, therefore not representative of the typical HCV infected population in which there are more males) showed that the anti-HCV prevalence in Coimbra in the Central region of Portugal was 0.46% [2]. About a third of those tested positive had a history of IDU.

Among 205 patients undergoing gastrointestinal endoscopy at the Hospital de Gaia in Porto in 2009, 1.5% were anti-HCV+. Based on a review published in 2008, the estimated prevalence for Portugal was 0.5-1% [3], which may indicate that the prevalence of HCV is decreasing.

Two national surveys studied HCV epidemiology: one in 2001 (618 participants, 75% male, mean age 38 years [4]), and the second one published in 2009 (1907 participants, mainly from the south, 68% male, mean age 41 years [5]). In both studies most people were Caucasian.

In the 2001 national survey, risk factors could be identified for 86% of patients. History of IDU was the most important risk factor (>60% of patients), followed by previous surgery, transfusion, risky sexual behaviour, household history, parental therapy, visiting high risk countries and being a health care professional. The probable route of infection was identified for 81% of patients and, for more than half of the patients, the route was IDU. Recent reports indicate that the estimated HCV prevalence among IDUs is 50% [1], whereas it was higher in the 1990s (between 70-92%). HCV infection among IDUs is further discussed in the Chapter on viral hepatitis in populations at risk in this report. The incidence of HCC due to HCV is increasing [6].

There have been no initiatives to identify undiagnosed HCV patients in Portugal. A national health survey is planned for 2011. General practitioners (GPs) should be encouraged to check for HCV+ patients. This would prevent patients from being diagnosed too late and would reduce the inherent burden on the health service, that this late presentation causes. At the meeting, a view was expressed that the only way to make people consider that they may be infected is through public awareness campaigns. One such initiative to spread the message about liver health was the Liver on Tour team (organized by the Portuguese Association for the Study of the Liver). In addition, there is a need for an organized HCV screening plan, including low cost diagnostic tests and a follow-up programme.

Prevalence of HCV in first time blood donors

There have been several studies investigating HCV prevalence in blood donors. In a review of 13 studies, the HCV prevalence among blood donors in the early 1990s ranged between 0.47% at Portimão and 2.87% in the oncology hospital in Lisbon. The average prevalence was 0.9% with a gradient from the north (lower prevalence) of Portugal to the south (higher prevalence) [1]. Since then, the prevalence of HCV in blood donors has been decreasing.

Screening for HCV in first time blood donors now includes anti-HCV testing using ELISA and nucleic acid testing (NAT). Recent data from the Portuguese Blood Institute show a difference in HCV prevalence between males (0.19%) and females (0.06%). Most hospitals rely on replacement blood donations (blood donated to the blood bank to replace blood received by a transfused relative/friend), whilst in regional units collection of blood is based on voluntary donations. The prevalence of HCV was three times higher in those donating in hospitals (0.49%), compared to those presenting to the Blood Institute services (0.14%). Overall, the prevalence of HCV amongst 44,057 first time blood donors was 0.28% in 2009 and remained constant in the period 2008-2010.
Haemophiliac patients who had a blood transfusion before the 1990s have much higher HCV prevalence than those that were transfused after the 1990s, but accurate figures on HCV prevalence in haemophiliac patients are not available for Portugal.

**Epidemiology of HCV in paediatric patients**

The current reported prevalence rates of HCV in children, have led to HCV being regarded as a rare disease in children. However, population-based epidemiological data on HCV prevalence in children (including in Portugal) are limited, and thus its true frequency may be underestimated. In the USA, assuming an anti-HCV seroprevalence rate of around 1.8% in the general population, the prevalence in the under 12 year old population is estimated to be 0.2%, and 0.4% in the 12-19 year old age group [7]. If the same proportion were to be applied to Portugal, where the estimated seroprevalence in the general population is 1.5%, the national seroprevalence in the paediatric population (children and adolescents up to the age of 19 years) would be an estimated 0.25%.

The natural history, prognosis and clinical significance of HCV infection acquired early in life are poorly defined. Although the natural course of HCV infection in children is not yet well elucidated, it seems that about 7.5% of cases may become spontaneously seronegative (mostly HCV genotype 3). Moreover, it should be recognized that although long-term follow-up studies are still scarce for paediatric patients, a very small subset of untreated patients may develop decompensated cirrhosis and ultimately terminal liver disease, requiring liver transplantation at a relatively young age. The most relevant risk factors for the latter seem to be maternal drug use and genotype 1a [8].

In a large retrospective study (12,958 births) conducted in a Portuguese district (secondary level) hospital, the perinatal HCV transmission rate was 2.9% in children born to HCV+ mothers (59; 0.45%) between 2002 and 2006. In this study, there was a high rate of inadequate pregnancy surveillance, prematurity and low birth rate, mainly in children born to IDU mothers. Half of the children who were anti-HCV+ at the age of 9 months became seronegative by 18 months [9].

Current evidence suggests that the post-natal transmission rate is low. No association has been shown between transmission of HCV and the type of delivery or IDU status in HIV mothers. Breastfeeding transmission is assumed to be rare in HCV+/HIV mothers (although HCV virus is identifiable in colostrum and breast milk), and thus breastfeeding is not contra-indicated.

A retrospective review of chronic HCV cases seen in paediatric gastroenterology units and paediatric departments (tertiary level centres) in Portuguese public hospitals, included 48 cases reported (mean age: 9.2 years, age range >2y, < 16y) within a 16 year period (1993-2008). The route of infection was perinatal (mother to child transmission) in 47 cases and sexual in one case. There was HIV/HCV co-infection in 2 cases. Assuming an estimated seroprevalence in pregnant women of 0.2% and a vertical transmission rate of 2%, it might be expected that in Portugal 4 HCV+ cases would be born annually from 200 infected mothers. Both clinical and epidemiological data, collected prospectively, are needed to assess the true HCV incidence in the paediatric population in Portugal and to confirm these estimations.

As in other countries, there is no formal recommendation for systematic screening of pregnant women, since there is no effective intervention and Ribavirin treatment is contraindicated in pregnancy. Thus, HCV prevalence in pregnant women and in newborns remains largely undetermined in Portugal.

Screening of pregnant women is recommended in high risk settings, including IDU, recipients of transfusions or transplants, haemodialysis patients, HIV+ patients, women with risky sexual behaviour, and women with persistently high AST/ALT [10, 11, 12]. In light of the low national HCV incidence among pregnant women that is reported in some European countries, cost-effectiveness analyses would be required at country level, before the implementation of systematic HCV screening during pregnancy. When considering public health policies, an important argument in favour of HCV screening of pregnant women would be the putative identification of infected children after birth, who remain silently infected and later may develop severe disease [13].

It is generally accepted that the screening of infants born to HCV+ mothers is not advisable before 18 months of age, due to a significant false positivity rate, as antibodies will mostly be passively transmitted from the mother [10, 11, 12]. If performed after the age of 2 years, RNA PCR determination is advisable on 2 separate occasions, at least 3 months apart. Diagnosis using ELISA and Western blot is an alternative possibility, recommended from the age of 18 months onwards. If the result is positive, then confirmation by RNA PCR is advisable and should be repeated 6 months apart, due to the recognized possibility of viraemia fluctuation.

**Molecular epidemiology of HCV**

In 2001, the predominant genotype was 1 (53%), followed by genotypes 3 (34%) and 4 (7%). In 2009, genotype 1 was still the most prevalent genotype (60%, predominant in the north and south), followed by genotype 3 (24.7%, mainly in the centre) and genotype 4 (9.4% with a gradient from the north to the south of the country). The genotype distribution in Portugal is similar to other countries in the South of Europe [13].

A review of 9 papers found subtype 1b to be the most frequent (34-59%), followed by 1a (24-38%) and 3a (12-30%). In one hospital the distribution differed from other studies, because a significant proportion of genotype 2 was found (38% of patients, mainly those undergoing dialysis).

There has been a shift in predominance from genotype 1b before 1990s to 3a after the 1990s, perhaps due to IDU. The HCV genotype pattern in Portugal is also changing due to immigration (former Portuguese colonies). Genotype 4 is emerging in Portugal possibly due to a migration effect, but additional investigation is required to confirm this. In a hospital in Lisbon, genotype 4b has been identified, but its epidemiology is unknown [14]. Viraemia according to genotype showed that half of patients infected with genotype 1 had high viral load, those with genotype 2 or 3 in the south and centre of Portugal had high viral load, but low viral load was detected in patients from the north. Most patients with genotype 4 had low viral load. Liver biopsy results indicated that most patients had F1/F2 degree of liver fibrosis (Metavir classification) and no association with a particular HCV genotype could be identified.
Studying the HCV genome variability may open new therapeutic options. In an ongoing project, mutations possibly affecting HCV replication and translation were studied, however, no significant differences were found between responders and non-responders. Several other host and viral factors that could influence the sustained virologic response were identified and are under investigation. For instance, one such study demonstrated a correlation between sustained virologic response to treatment and increased frequency of HCV specific CD8 T-lymphocytes.

**Epidemiology of HIV/HCV coinfection**

Although exact HCV figures are not available, the prevalence is estimated to be between 1%-1.5%, which means that the estimated number of HCV+ cases in Portugal is between 100,000 and 140,000. The number of reported cases of HIV is 38,000. According to a European multi-centre study (EuroSIDA), the prevalence of HCV infections among HIV+ individuals in Europe is 33%, and more specifically in the South of Europe it is 41.4% [15], which means that the number of coinfected patients in Portugal would be approximately 16,000.

A retrospective study (by the Portuguese Study Group on Coinfection, GEPCOI) comparing monoinfected HCV patients with HIV/ HCV coinfected patients found that the gender distribution (male: female) in coinfected patients was 4:1 and not different from monoinfected patients. The mean age of coinfected patients at the time of diagnosis was 38-39 years. IDU is the most important mode of transmission of both HCV and HIV viruses in coinfected patients (84%), compared to 68.9% in the monoinfected group. Sexual transmission (13.6% vs 9.9%) and transmission via blood transfusion (5.7% vs 0.4%) were more relevant in the monoinfected group than in the coinfected group. There was no difference in the overall distribution of genotypes between the monoinfected and coinfected groups (see Figure below).

**HCV genotype distribution in monoinfected and HIV coinfected HCV patients**

Immunosuppressed HIV/HCV coinfected patients had lower ALT levels compared to the HCV monoinfected group, and this correlated with CD4 levels. ALT levels were significantly higher when infected with HCV genotype 3 than with other genotypes.

HCV viral load was higher in coinfected patients, regardless of genotype. In coinfected patients, HCV viral load and CD4 cell count were inversely correlated, which will influence the treatment policy for chronic HCV in HIV+ patients (see Chapter on Treatment of patients infected with HBV or HCV).

**References**


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Epidemiology of hepatitis E in Portugal

Hepatitis E (HEV) can be transmitted via contaminated water and food and there is also evidence of zoonotic transmission. In HEV endemic countries, it can occur as sporadic cases or as outbreaks. Epidemics are cyclical, occurring a few years apart; where outbreaks frequently follow heavy rainfall and floods which create conditions that favour the mixing of human excreta with water. In non endemic countries it occurs as sporadic cases, usually related to travelling. It is generally thought that the incidence is highest among young adults in endemic countries, whilst in non endemic countries it is thought that the virus occurs most often in older adults.

To date, 4 human genotypes have been identified. Genotypes 1 and 2, which are considered more pathogenic, are most common in endemic countries while genotypes 3 and 4 are more common in non endemic countries.

The majority of countries in Europe are non endemic for HEV and most HEV infected cases are travellers to endemic countries; however this scenario is changing and reports of autochthonous HEV are increasing. Although there are many migrants from Africa, an HEV endemic region, many HEV infected persons in Portugal never travelled to endemic areas.

Six local HEV prevalence studies have shown significant variation (2.1% -29%) (see Table below), depending on the region and the populations studied [1-6].

Grouping the several HEV studies conducted in Portugal between 1994 and 2010, a total of 3027 samples were tested and this cohort included travellers to endemic countries as well as HCV and HBV patients. In total there were 233 HEV+ cases (7.7%). Among the 2691 non travellers, 101 cases were HEV+ (3.8%), which is similar to the prevalence of HEV in countries like UK or Italy. This pooled analysis was an attempt to provide an idea of national HEV epidemiology in Portugal, but a more systematic investigation is required.

There are no available data on HEV genotypes in Portugal, since there are only few cases of acute HEV.

The number of HEV+ cases reported to the DG is low (25 acute hospitalized cases over the period 1995-2008), because HEV is not listed as a specific disease in the notification system and is not a notifiable disease (even in the new system). Understanding the prevalence of HEV is hampered by the fact that HEV is not regularly tested (only when other tests yield negative results), because access to the serological HEV tests is limited in Portugal and, generally, physicians do not consider the possibility of HEV infection until they have exhausted all other diagnoses. For these reasons, HEV can be considered under-diagnosed in Portugal.

Testing for HEV should be considered in cases of acute hepatitis of unidentified cause, immunosuppressed patients with increased liver enzymes, and high risk groups with increased liver enzymes. Since the incidence of HEV infection is increasing in European countries, even in non-travellers, it was recommended that, in addition to other serologic tests for viral hepatitis, anti-HEV IgG and IgM antibodies should also be tested to study acute hepatitis cases. The focus of HEV studies conducted so far has been on clinical samples collected from urban areas and distinguishes between patients who travelled to endemic regions and non-travellers. More attention should be given to rural areas and possible zoonotic HEV infection.

References

Based on a presentation by
S. Folgado Alberto, Serviço de Gastrenterologia,
Hospital Prof Dr Fernando Fonseca, Amadora, Portugal.

HEV Epidemiology in Portugal

<table>
<thead>
<tr>
<th>Region studied</th>
<th>Year reported</th>
<th>Population studied (sample size)</th>
<th>Prevalence (%)</th>
<th>Test used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisbon [1]</td>
<td>1994</td>
<td>Heterogeneous (360)</td>
<td>29</td>
<td>ELISA</td>
</tr>
<tr>
<td>North [2]</td>
<td>1997</td>
<td>HBD (1473)</td>
<td>2.5</td>
<td>ELISA</td>
</tr>
<tr>
<td>Porto [3]</td>
<td>1998</td>
<td>HBD (50)</td>
<td>4</td>
<td>ELISA +ve confirmed with Western blot</td>
</tr>
<tr>
<td>North [4]</td>
<td>1998</td>
<td>HBD (681)</td>
<td>2.1</td>
<td>ELISA</td>
</tr>
<tr>
<td>Lisbon [5]</td>
<td>2007</td>
<td>CLD (152) HBD (85)</td>
<td>3.3 3.5</td>
<td>ELISA +ve results re-tested</td>
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<tr>
<td>Lisbon [6]</td>
<td>2011</td>
<td>GE (95)</td>
<td>3.2</td>
<td>ELISA +ve results re-tested</td>
</tr>
</tbody>
</table>

HBD - healthy blood donors; CLD - chronic liver disease; GE- gastroenterology patients
Viral hepatitis follow-up strategies in Portugal

Treatment of patients infected with HBV or HCV

Treatment of HBV infected paediatric patients

Treatment of paediatric patients raises a lot of complex questions, since no therapeutic policies exist, but currently most HBV infected children are treated before they have symptoms. Treatment is started based on transaminase elevation and viraemia.

Of 114 paediatric patients with chronic HBV presenting to 6 paediatric gastroenterology units in Portugal, 38 (33%) received treatment; the most frequent therapies were Lamivudine (18); IFNa (9) or a combination of IFN + Lamivudine (7). A complete response, characterized by a sustained disappearance of viraemia, was achieved for 15 patients (39%); 21 patients (55%) achieved a partial response, characterized by decreased viraemia and/or liver enzyme normalisation, and only one did not respond on the used therapy. As Lamivudine YMDD resistant mutants do emerge, long-term follow-up of Lamivudine treatment is recommended but data are currently unavailable since the drug was only recently (<5 year) introduced for paediatric patients.

Treatment of HCV infected adult and paediatric patients

Factors that affect sustained viral response to HCV treatment can be related to the host or to the virus. Host factors predicting a worse response to HCV infection include: age >40 years; male gender; the degree of liver fibrosis; and high body mass index. Viral factors predicting poor response include genotype 1, lack of diversity in core and NS5a regions of the genome and a high pre-treatment viral load. In a cohort of 6243 HCV patients, the overall rate of sustained viral response was 61%, 50% in patients with HCV genotype 1 and 80% in patients with HCV genotype 3.

Treatment of pregnant women infected with HCV remains an issue, with no approved drugs (see Chapter on viral hepatitis in populations at risk).

Although treatment of children infected with HCV has been controversial, recent evidence supports its benefit and, according to current guidelines, Portuguese tertiary centres have adopted a consensus approach favouring treatment. The current FDA approved treatment regimen for children is pegIFNα-2b combined with Ribavirin. Liver biopsy is not required in order to start treatment, however, co-morbidities or other etiologies of liver disease must be excluded as a pre-requisite. Treatment should ideally be initiated before adolescence, although usually after 3 years of age, as spontaneous clearance of the virus can occur at a young age. The duration of treatment is based on the viral genotype: 6 months for genotypes 2 and 3, and 12 months for the remaining genotypes (including genotype 1). Sustained virological response in children is comparable to the response achieved in adults and similarly, it is higher in children with genotypes 2 and 3, than in those with genotype 1. The overall tolerance and side-effect profile of the current HCV treatment regimen for children has been reported to be favourable.

Based on presentations by

A.I. Lopes, Departamento da Criança e da Família, Unidade de Gastroenterologia Pediátrica, Centro Hospitalar Lisboa Norte, Lisboa, Portugal; A. Martinho, University Hospital Coimbra, Coimbra, Portugal; G. Cordeiro Ferreira, Dept of Pediatrics, Hospital Dona Estefânia, Lisbon, Portugal.

Treatment of HCV/HIV coinfected patients

Nowadays, HIV infected patients are living longer. HIV coinfection increases HCV viral load and coinfected patients progress much quicker to liver cirrhosis with increased mortality due to ESLD (End Stage Liver Disease) than those with HCV monoinfection [1]. The risk of hepatotoxicity following antiretroviral therapy (ART) is also higher in HCV/HIV coinfected patients [2]. It is therefore important to treat HCV patients that are coinfected with HIV, in order to address the increasing mortality in this group of patients.

IDUs coinfected with HCV and HIV are generally reluctant to start HCV treatment because they do not feel ill; are concerned about the side-effects and the length of treatment; have other health problems; do not want a liver biopsy; or are inadequately informed.

A study in Portugal has reported that only 10-15% of HCV/HIV coinfected patients received treatment [3]. The main reasons for exclusion from treatment included patients having a CD4 cell count below 200/mm³ (27%), chronic alcohol abuse (17%), psychiatric conditions (18%) and being active IDU (14%). Other studies that have looked at reasons for non-treatment have shown that 39.5% of coinfected patients did not want treatment, 20% had concomitant disease, 18.3% were active IDU, and 5.2% had decompenated liver disease [4].

A significant barrier to start treating coinfected IDU is the clinician’s decision not to treat IDUs because they are less likely to adhere to a treatment regime and to complete the treatment course. However, research in Portugal has shown that a group of HIV/HCV coinfected IDUs taking methadone responded to treatment in a comparable way to other, non-IDU, treatment groups.

The sustained virological response to HCV treatment is significantly better in patients with HCV monoinfection (N=296, 69%), than in HCV/HIV coinfected patients (N=290, 47%). For patients monoinfected with HCV genotype 1, 62% had good sustained virological response, whilst this was only achieved in 25.9% of the coinfected group. In patients with genotype 3, the proportion who achieved sustained response was 84% among monoinfected and 78% among coinfected patients.

Mortality from liver disease is increasing in HIV patients. In 2000, in the Department of Infectious Diseases at the Hospital Joaquim Urbano in Porto, none of the 52 deaths of HIV patients were due to liver disease. However, in 2006, the second cause of mortality among HIV patients on ART (N=23,441) was liver disease related to HBV, HCV, HDV or drug related liver toxicity [5]. In 2009, 43 HIV patients died and liver disease was the third cause of mortality, after opportunistic and respiratory infections. All efforts must be made to treat coinfected patients to prevent mortality due to liver disease.

References

Liver transplantation and viral hepatitis

The number of liver transplants performed annually in Portugal is expected to increase in the coming years. To date, 1191 liver transplants have been carried out at the Hepato-Bilio-Pancreatic and Transplantation Center in Lisbon. About 25% of all liver transplants in the Center are performed on patients with viral etiology (HBV, HCV). About 40% of all cirrhotic patients that received a transplant at the Center had a viral etiology.

HBV

In HBV patients, the main challenge is to suppress viral replication before transplantation. In the Hepato-Bilio-Pancreatic and Transplantation Center in Lisbon, patients with HBV replication are not eligible for transplantation, because it is cost prohibitive and outcomes are poor. The Center also considers fulminant HBV to be a contraindication to transplantation. The Figure below shows that survival rates for HBV patients following liver transplantation in the Unit are high.

Survival rates in HBV+ liver transplant patients

HCV

Graft and patient survival rates in HCV patients with cirrhosis are worse than those for other indications, because infection occurs during reperfusion of the graft. By day 4, HCV viral load can be as high as before the transplantation with hepatic lesion observed by 3 weeks after surgery. After 1 year, the viral load is 10 to 100 times higher than before the transplantation.

HCV virus graft recurrence is a dynamic process, within a highly variable disease progression pattern. Fibrosis develops faster after liver transplantation (0.3 to 0.8 stages/year), compared to HCV patients that are not transplanted (0.1 to 0.2 stages/year). While cirrhosis tends to develop in HCV patients in a period of 20-40 years, after liver transplantation cirrhosis occurs within 10 years.

The risk of hepatic dysfunction is also much higher after liver transplantation (42% in 1st year, 62% within 5 years), compared to those that are not transplanted (< 5% in 1st year, < 20% within 5 years). In the early post-transplantation period, histological alterations are difficult to interpret, because they can be due to rejection or preservation and reperfusion lesions. In HCV+ transplanted patients, by the third post-operative month all are HCV RNA+ and 90% of liver biopsies are HCV Ag+.

Risk factors associated with the severity of graft recurrence include those related to the donor, the host, the genotype of the virus (increased risk with types 1 and 4) and the post-operative clinical course (e.g. episodes of rejection).

Familial Amyloid Polyneuropathy (FAP) is a prevalent disease in Portugal and standard treatment is liver transplantation. The liver from a FAP patient can in turn be transplanted to a patient with cirrhosis, in a so called “domino transplant”. Although this carries a theoretical risk of transmission of FAP to the recipient, in practice, the results are very good because these livers come from relatively young patients and have a very short ischaemic time.

Therapeutic strategies to decrease the risk of post transplantation HCV recurrence aim to achieve viral clearance and sustained viral load at different times: pre-liver transplantation, peri-operative period and post-transplantation. Re-transplantation of these patients is very controversial, because the outcomes are poor.

The survival rates for HCV patients following transplantation in the Transplantation Center in Lisbon are shown in the graph below. Results are compared to the European Liver Transplant Registry (ELTR).
Economic aspects of viral hepatitis and liver disease

Whilst the mortality rate due to viral hepatitis is lower than the 4% national average, the mortality rate due to HCC is above 20%. Chronic hepatic disease and cirrhosis are amongst the 10 most common causes of death in Portugal, as shown in the Table below.

Disease categories ranked by mortality rate (2006) in Portugal

<table>
<thead>
<tr>
<th>Disease categories</th>
<th>No. of deaths</th>
<th>Death Rate/100,000</th>
<th>No. of deaths</th>
<th>Death Rate/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular disease</td>
<td>14495</td>
<td>159.9</td>
<td>7727</td>
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<td>Ischemic heart disease</td>
<td>5045</td>
<td>47.7</td>
<td>3732</td>
<td>35.2</td>
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<td>Pneumonia</td>
<td>5215</td>
<td>56.4</td>
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<td>Diabetes mellitus</td>
<td>1642</td>
<td>16.1</td>
<td>1259</td>
<td>12.0</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma, colon/rectal</td>
<td>1362</td>
<td>12.5</td>
<td>1450</td>
<td>13.1</td>
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<td>Malignant neoplasm of trachea, bronchus and lung</td>
<td>2773</td>
<td>21.5</td>
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<td>12.5</td>
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<tr>
<td>Malignant neoplasm of stomach</td>
<td>1642</td>
<td>16.1</td>
<td>1259</td>
<td>12.0</td>
</tr>
<tr>
<td>Malignant neoplasm of prostate</td>
<td>1362</td>
<td>12.5</td>
<td>1450</td>
<td>13.1</td>
</tr>
<tr>
<td>Chronic hepatic disease and cirrhosis</td>
<td>1362</td>
<td>12.5</td>
<td>1450</td>
<td>13.1</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>691</td>
<td>6.5</td>
<td></td>
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</tr>
</tbody>
</table>

In the ranking of disease categories with high rates of lost life years (LLY), chronic hepatic disease combined with cirrhosis was at the 5th place in 2006, due to the large impact of premature death. Despite the fact that liver disease is an important cause of death in Portugal, there is no specific health programme for viral hepatitis amongst the country’s 40 health programmes.

Data obtained in 97 public hospitals of the National Health System of Portugal and from the national mortality database were analysed to determine the social and economic burden of disease. It is evident that the social and economic impact of liver disease, although not quantified exactly, is substantial. Between 2000 – 2008, liver patients leaving hospital with a diagnosis of viral hepatitis remained reasonably stable (10% decrease), whereas those with HCC has increased by 65% (see Figure on this page). In 2008, cirrhosis represented 56% of total discharged liver patients and HCC represented 10%. Viral hepatitis (HBV or HCV) was responsible for 6% of hospital discharges.

There are four times more discharges for men with liver disease than women. For liver disease, 61% of hospital discharges are within the age group of 20 to 64 years. The impact of such a high proportion of discharges in this age group is significant, because these are considered to be the years of active life. Hospital stays and absenteeism from work within this age group represent a high cost and loss of economic productivity.

In 2008, the total direct cost of inpatient stays due to liver disease in Portugal was close to €63 million, or 599.530€ per 100,000 population. This included €32 million for cirrhosis and over €9 million for HCC. The total cost of hospital admissions related to liver transplantation in 2008 was approximately €15 million (28.4% related to HCC, 12.2% related to non-alcoholic cirrhosis and 38.5% related to alcoholic cirrhosis) [1]. Consequently, liver disease is the third most costly condition to treat after ischaemic heart disease and cerebrovascular disease. The average length of inpatient stay due to liver disease is 10 days, which is above the national average of 6 days.

The direct inpatient cost for cirrhosis represents 51% of the expenditure on liver disease (42.6% is spent on alcoholic cirrhosis and 8.5 % is spent on non-alcoholic cirrhosis). The contribution of HBV and/or HCV to cirrhosis should be investigated. It is surprising that HCC represents only 15% of direct inpatient costs of hospital admission, since costs related to transplantation (surgery, blood transfusion and post operative care) are much higher for HCC than for cirrhosis. Alcohol abuse appears to be a growing health problem in Portugal in the last years. The impact of the combination of alcoholism and HBV or HCV infection on liver damage is unknown and requires further investigation.

References


Based on a presentation by J. Giria, Epidemiology and Statistics Department, General Directorate of Health, Lisbon, Portugal.

Viral hepatitis in specific populations

Viral hepatitis and pregnancy

Prevalence of HBV and HCV infection among pregnant women

From 2004-2009, the Alfredo da Costa Maternity hospital in Lisbon (which specializes in high risk pregnancies) had 33,862 deliveries and of them, 1.32% mothers were HBsAg+ and 0.75% were HCV+.

According to a retrospective study (1998-2000) in the same hospital, 113 pregnancies of HCV infected women were analysed, of whom 73% were IDUs and 33% were co-infected with HIV or were HBsAg+. In this cohort most women did well during pregnancy, but there was a higher incidence of pre-term delivery and
low birthweight in newborns of HCV+ pregnant women compared to newborns of HCV- mothers. In the cohort of 47 newborns born to these HCV+ mothers with follow-up results available, two cases of HCV mother to child transmission (4.3%) occurred. The 2 mothers who transmitted the HCV virus were both coinfected with HIV. Amongst IDU pregnant women in an outpatient clinic from July 1996 to September 1998, 60% were HCV+ (versus 50.3% in 2001-2003), 41% had evidence of HBV past infection and 3.8% were HBsAg+.

The prevalence in 132 HIV+ pregnant women on AVT, seen in an outpatient clinic, was 2.4% for HBsAg+ and 17% for HCV+ (2006-2009), but no cases of mother to child transmission of HCV nor HIV were reported.

In 2004, 7.7% of all deliveries at the Alfredo da Costa Maternity hospital in Lisbon were migrant women, mainly (60%) of African origin. Among these pregnant migrant women, 6.3% were HIV+ and 6.5% were HBsAg+ and there was a correlation between education level and the level of prenatal care. Also, African pregnant women had higher coinfection rates and more pregnancy complications. The contribution of HBsAg carrier status in immigrant women to the proportion of perinatal transmission in Portugal as a whole has not been studied. It is, however, important to be aware that the HBsAg carrier rate in pregnant immigrant women can be quite high, even if the national prevalence is low.

Management of HBV infected pregnant women and their newborns

A substantial proportion of infected neonates that have contracted HBV perinatally will develop chronic HBV at some point in their lives. Most pregnant HBV infected women are in an inactive carrier phase or immune active phase. In general, chronically infected pregnant women do well and treatment can be deferred till after delivery [1]. However, some women have hepatitis flares after delivery [2], such as exacerbation of hepatitis [3], and even fulminant hepatic failure [4].

Routine HBV screening of all pregnant women is recommended to prevent perinatal transmission. Benefits of screening are:

- identification of infants who require prophylaxis;
- identification of women that may benefit from treatment; and
- identification of their sexual and household contacts who may benefit from testing, counselling, vaccination or treatment.

If pregnancy occurs after HBV treatment has started, then a decision has to be made about the treatment course. There is limited experience of using nucleos(t)ides in pregnancy. The use of Tenofovir, Adefovir, Entecavir, Telbivudine and Lamivudine has been reported [5]. More information exists for Lamivudine and Tenofovir, because they are used to treat pregnant HIV infected women. A low rate of birth defects, similar to that of the general population, has been reported when these nucleos(t)ide analogues are used in the 1st trimester of pregnancy. Pregnant women are usually not treated with antivirals for HBV in the 3rd trimester, unless the viral load is very high. In this case, some recommend the use of antiviral therapy when HBV DNA is more than 8 log copies/ml, from the 32nd week until 4 weeks after birth.

In Portugal, all pregnant women are tested for HBV at their first obstetric appointment and at 32 weeks.

Without immunoprophylaxis in newborns, the perinatal HBV transmission rate is high (80–90%) if mothers are HBsAg+ and 10–20% if mothers are HBsAg-. Perinatal transmission also appears to vary with viral load. According to one study, no transmission occurred with low viral load, but the transmission rate could be up to 8.5% with high viral load [6].

Immunoprophylaxis (passive and active) to prevent HBV infection in neonates of HBsAg+ mothers is safe and effective and consists of a birth dose of HBV vaccine within 24 hours and administration of hepatitis B immune globulin (HBIG). In Portugal, these children are vaccinated according to the same schedule (0-2-6 months) as non-exposed children. Their vaccination coverage and rate of completion of the course is not known with certainty, but is probably more than 95%. Children born to HBV+ women should be referred to specialist paediatric departments of central hospitals. It is also recommended that supervision of the quality control of HBsAg screening among pregnant women is ensured.

There are some cases of HBV transmission even when prophylaxis is provided, probably via intra-uterine transmission in highly viraemic women. According to 2009 EASL guidelines, recent reports suggest that Lamivudine therapy during the last trimester of pregnancy in HBsAg+ women with high levels of viraemia reduces the risk of intra-uterine and perinatal transmission if given in addition to passive and active immunoprophylaxis using HBIG and HBV vaccination [7]. Treatment with Tenofovir or Telbivudine could be considered; although apparently safe, these protocols require further testing.

Breastfeeding does not pose an additional risk for HBV transmission in neonates who received passive/active immunoprophylaxis [8, 9], however women on AVT should not breastfeed.

Some of the remaining questions in the prevention of mother to child transmission of HBV include:

- In which scenarios should antiviral drugs be used for prophylaxis?
- What viral level increases the risk of mother to child transmission despite HBIG and vaccination?
- How early in pregnancy should treatment be initiated?
- Are all nucleos(t)ides safe in pregnancy?
- Which drug is most appropriate?
- What are the risks and benefits for the mother?
- When should therapy be stopped?
- What are the risks of resistance?
- What are the risks of flares?
Management of HCV infected pregnant women

There is no approved therapy for treatment of HCV in pregnancy. Ribavirin and IFNα treatment must not be used in pregnancy. The risk of mother to child transmission of HCV is low (~5-6%). There is a 2-3 fold increase in the risk of mother to child transmission of HCV if the mother is coinfected with HIV, although the risk is less if the mother is taking AVT. There is no evidence that the mode of delivery has an effect on mother to child transmission, or that there is an increased risk of mother to child transmission due to breastfeeding.

References

Based on a presentation by
C. Guerreiro, Maternidade Dr Alfredo da Costa, Lisbon, Portugal

Viral hepatitis in haemodialysis

Liver disease, mainly caused by chronic HBV and HCV, has great impact on morbidity and mortality in haemodialysis and kidney transplant patients and it is associated with reduced graft and patient survival. Therefore, prevention of viral hepatitis in this setting is important. HBV vaccination, erythropoietin use, screening and universal prophylactic measures have had a positive impact on the incidence and prevalence of HBV and HCV infection in haemodialysis patients. Antiviral therapy should be considered for acute or chronic hepatitis patients on haemodialysis, but with caution.

A major issue is the impact of chronic HBV and HCV infection in kidney transplant recipients. In a retrospective study (n=1432) from the University Hospital of Coimbra, 8% of kidney transplant recipients had chronic hepatitis: 42 patients had HBV, 64 patients had HCV, and 9 patients were coinfected [1]. Transplanted patients infected with HBV and/or HCV, especially those with chronic HBV infection, have a worse prognosis in terms of patient and graft survival. However, the quality of life and survival for transplanted chronic hepatitis patients is still better than those that continue haemodialysis treatment. Selection for transplantation of infected haemodialysis patients should be done with care. The stage of liver disease is the most relevant factor for prognosis and liver biopsy should form part of pre-transplant evaluation. Patients with liver cirrhosis or severe fibrosis should be excluded, unless HCV can be eradicated or HBV replication can be suppressed.

HBV

In a study of 22 haemodialysis patients with acute HBV (14 patients coinfected with HCV), 3 patients died and among those who survived, 14 (74%) developed chronic HBV infection (including 3 patients coinfected with HCV). The high risk of development of chronic HBV emphasises the importance of preventing HBV infection in these patients.

However, immunological response to HBV vaccination in haemodialysis patients is poor (about 50%). There is no significant relationship between post-vaccine immunisation and age, gender, duration of haemodialysis or anti-HCV positivity; indicating that compromised immune response is probably the reason for reduced efficacy of HBV vaccination in these patients. Nevertheless, vaccination in haemodialysis patients is recommended. Prophylactic measures to control the spread of HBV, including vaccination, have led to a reduced HBV prevalence among haemodialysis patients (from 19.6% in 1991 to 2.4% in 2007). In 2009, the prevalence of HBsAg in haemodialysis patients was 1%, which is the same as in the general population [2].

It is possible to effectively treat HBV infected haemodialysis and kidney transplant patients with nucleos(t)ide analogues with high antiviral efficacy and good resistance profile. During haemodialysis, Tenofovir or Entecavir can be used. Following kidney transplantation Entecavir is preferred, because it has less renal toxicity.

HCV

In the first studies investigating the incidence and prevalence of HCV infection in Portuguese haemodialysis patients in the 1990s, almost one third of the patients had anti-HCV antibodies. In 1995, a study of 300 patients from 7 haemodialysis units in the central region of Portugal showed an anti-HCV prevalence of 70%, 25% were coinfected with HBV. Most patients had normal liver enzymes, and only 22% reported a history of acute hepatitis. A positive correlation was found with the number of blood transfusions (64.3% HCV+ if <5 blood units transfused versus 80.0% if >5 units, p <0.01) and with haemodialysis duration (84.9% HCV+ if >2 years on haemodialysis versus 35.2% if dialysed for <2 years, p <0.001). This suggests that nosocomial transmission is a principal cause of HCV spread to these patients and emphasises the need for strict prophylactic measures.

Important developments that have contributed to the prevention of HCV have included erythropoietin use, screening of new donors for anti-HCV, and the recommendations of the Portuguese Society of Nephrology for strict prophylactic measures in all haemodialysis units. By 2009, adoption of prophylactic measures in haemodialysis units resulted in a further significant decline in HCV prevalence to 5%.

Strict adherence to prophylactic measures remains a priority and any failure can result in transmission of infection. Following one such failure in 2007, 5 patients developed acute HCV due to
contamination of a heparin vial. All patients had contracted HCV genotype 5a, which is rare in Portugal, but consistent with the index case. Four male Caucasian haemodialysis patients were treated with pegIFN monotherapy. Only one patient had achieved a sustained viral response after 24 weeks and, after 48 weeks, a further 2 patients had achieved a response. Therefore, treatment beyond 24 weeks should be considered for haemodialysis patients.

Presently, a reduced dose of IFN or pegIFN monotherapy is the only treatment option for haemodialysis patients, since Ribavirin cannot be used. IFN is not recommended in kidney transplant patients, since it can cause acute rejection. One possible alternative therapy is the use of ursodeoxycholic acid. However, in a study of 25 transplanted HCV+ patients on ursodeoxycholic acid treatment, the virus persisted although ALT normalised in 68% of them.

No significant difference in the severity of liver disease was found between a group of Portuguese haemodialysis patients and a control group of chronic HCV patients, unless they were coinfected with HBV. Amongst the haemodialysis patients, 44% of HBV/HCV coinfected patients had severe cirrhosis or fibrosis, compared to 15% of HCV+ patients on haemodialysis, and 18% of a control group.

Concerns remain about the risk of HBV or HCV reactivation after renal transplantation due to immune suppression, with high viral load resulting in liver disease. This can have a negative impact on graft and patient survival.

References
*Portuguese reference

Based on a presentation by A. Carvalho, Serviço de Medicina Interna, Hospitais da Universidade de Coimbra, Coimbra, Portugal

Viral hepatitis and drug addiction in Portugal
Portugal is a leading country in the world in terms of decriminalization of drug use. Individuals arrested following drug use are assessed, and those that are dependent on drugs are referred for therapy.

The National Institute for Drugs and Drug Addiction (IDT), focuses on prevention, harm reduction, treatment and re-integration for individuals addicted to drugs or alcohol. The Institute also has a role of national coordination, defining national strategies for control of alcohol consumption and illicit drugs and evaluation of such strategies.

The IDT collaborates with several international organisations, including the European Centre for Drugs and Drug Addiction (EMCDDA), which is working to harmonise indicators and practices within Europe. The EMCDDA has recently produced guidelines for testing HIV and viral hepatitis in IDU [1].

At the outpatient treatment centres of the IDT, an integrated approach is provided by a team composed of a psychiatrist and/or GP, nurses, social workers and psychologists. They provide medical, psychiatric, psychological and social care. They also vaccinate against HBV and aim to screen everyone for TB, HIV and HCV. Anyone found to be infected, is referred for treatment.

The number of patients visiting the different settings has increased over the last ten years. In 2008, 38,532 patients visited the different IDT centres, resulting in 634,759 consultations.

Although HCV prevalence amongst drug users is decreasing over time, the rate among IDT outpatients remains high: 53.5% over the period 2000-2010. In 2006, 61.8% of all patients attending an IDT detoxification unit were anti-HCV+. Among those who had ever been IDU, the HCV prevalence was 84.8% and among patients who reported that they had never injected it was 17.6%, although it seems likely that they had injected in the past. Amongst IDU (ever used in life) presenting to IDT facilities over the last ten years. In 2000 and 2010, 4.4% outpatients were HBsAg+ and 43.1% were anti-HBc+.

The table below shows the results of screening 38,313 outpatients presenting at IDT facilities over the last ten years. Between 2000 and 2010, 4.4% outpatients were HBsAg+ and 43.1% were anti-HBc+. Of these patients, 19.2% had been vaccinated for HBV; some of them were vaccinated in the treatment centres if screening showed that they had no previous exposure to HBV.

The prevalence of coinfection in 31,000 patients presenting to IDT facilities is illustrated in the Figure on the next page. Over ten years 2000-2010, 1% of patients were positive for all 4 tests (HBsAg, HIV+, anti-HBc+ and HCV+); 4.4% were HIV/ HCV+ and had been exposed to HBV in the past, but were no longer HBsAg+; and 2.3% were HCV+/HBsAg+, but did not have HIV.

**Screening and registered positive tests in IDT outpatients, 2000-2010**

<table>
<thead>
<tr>
<th></th>
<th>HBsAg+</th>
<th>Anti-HBc+</th>
<th>HCV+</th>
<th>HIV+</th>
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<tbody>
<tr>
<td><strong>Total screened</strong></td>
<td>38,331</td>
<td>37,238</td>
<td>39,049</td>
<td>44,667</td>
</tr>
<tr>
<td><strong>% Screened</strong></td>
<td>46.0%</td>
<td>44.6%</td>
<td>46.8%</td>
<td>53.5%</td>
</tr>
<tr>
<td><strong>Total positive cases</strong></td>
<td>1,694</td>
<td>16,052</td>
<td>20,874</td>
<td>6,438</td>
</tr>
<tr>
<td><strong>% Positive</strong></td>
<td>4.4%</td>
<td>43.1%</td>
<td>53.5%</td>
<td>14.4%</td>
</tr>
</tbody>
</table>
The number of new patients presenting to outpatient clinics has been increasing in recent years (up to 7019 in 2008). The proportion of patients that are alcoholic is a growing concern and needs to be a focus of attention during consultations.

The number of drug users receiving treatment from the IDT each year has been increasing since the late 1990s. Heroin remains the main drug of use. The proportion of IDU among users treated by IDT has been clearly decreasing from almost 40% in 2008 to 18% in 2010. Also there has been a decreasing trend in sharing syringes. On average, IDU have regularly used drugs for 10 years before they seek treatment for the first time. In the past, most of the focus on infections in IDUs has been on HIV, but today more patients die from HCV than HIV, therefore it is important that more focus is directed on HCV. Less than 2% of HCV+ drug users seen by IDT are on treatment for HCV. Hospitals in Portugal do not treat HCV infected people as long as they are active IDU. In the last 3–4 years, treatment is starting to be offered to HCV infected people on methadone.

Prevention, control and awareness of viral hepatitis in Portugal

Hepatitis A

Improved environmental conditions to avoid faecal contamination of food and water has been an important way of preventing HAV infection. In addition to improvements in hygiene practices, vaccination against HAV, introduced in the late 1990s, has led to a dramatic decrease in the incidence of the disease, for example, in Catalonia (Spain) [1].

An advisory committee of paediatricians and epidemiologists provides guidance to the Ministry of Health about immunization implementation. The HAV vaccination policy is under discussion, but is currently not considered a priority due to financial constraints. Universal HAV immunization is considered to have an unacceptably high financial cost. A cost-effectiveness study on HAV immunization in Portugal is ongoing, but no data are available yet. To date, HAV vaccination, which also exists as part of a combined HAV/HBV vaccine, is only recommended for travellers to areas with a high prevalence of HAV and for use during outbreaks, which has been successful in the past.

Immunization targeted to specific risk groups on a regional basis, based on knowledge of the local epidemiology of HAV is currently considered by Portuguese Health Authorities to be the best approach. However, because Portugal is a country in transition from high to intermediate HAV endemicity, the majority of the young population remain susceptible and this could result in significant outbreaks. Therefore, vaccination at a young age should be recommended.

For HAV antibody testing, it was recommended not only to test for IgG, but also IgM, to distinguish between new and previous infections and to allow earlier detection of outbreaks. HCV+ patients, particularly in areas with high anti-HAV prevalence, are at higher risk of HAV infection. Testing HCV+ patients for anti-HAV before vaccination is considered cost-effective and was therefore recommended. However, testing is currently not reimbursed by the government.

HAV is one of the most common vaccine-preventable diseases in travellers to developing countries [2], therefore health care professionals should encourage travellers to endemic regions to be vaccinated.

Vaccination against HAV is recommended for HIV+ patients, especially those with a low CD4 cell count, and a booster dose is often required. HAV vaccination should also be recommended for HBV carriers.

References


Based on presentations by
S. Guedes, Departamento de Higiene e Epidemiologia, Faculdade de Medicina, Porto, Portugal
Hepatitis B immunization policies and lessons learnt after 10 years

A successful immunization programme requires:

- a correct strategy, based on the knowledge of the targeted population;
- good acceptance by the population;
- good vaccine coverage, and;
- reliable surveillance to assess the effectiveness of the strategy.

In Portugal, vaccines are generally well accepted by the public. The immunization policies for HBV in Portugal have evolved over time and are shown below.

<table>
<thead>
<tr>
<th>Year</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>Haemodialysis patients</td>
</tr>
<tr>
<td>1992</td>
<td>Patients undergoing haemodyalisis and haemophiliac patients</td>
</tr>
<tr>
<td>1993</td>
<td>Screening of pregnant women</td>
</tr>
<tr>
<td>1994</td>
<td>Immunization of newborns of HBsAg+ mothers</td>
</tr>
<tr>
<td>1995</td>
<td>Firemen (who are also paramedics in Portugal)</td>
</tr>
</tbody>
</table>

HBV risk-based immunization policies in Portugal:

- 1990 - Haemodialysis patients
- 1992 - Patients undergoing haemodyalisis and haemophiliac patients
- 1993/94 - Immunization of adolescents
- 1995 - Immunization of other risk groups

Universal Immunization:
- 2000 - Universal immunization of newborns, in addition to adolescents and risk groups

In 2001, the risk groups for HBV were redefined as shown below:

- Healthcare professionals;
- Patients undergoing haemodyalisis;
- Haemophiliac patients;
- Household contacts and sexual partners of HBsAg+ individuals;
- Professors and students of medical, dental, nursing and health technology universities;
- Workers and juveniles in institutional facilities for children with behavioural problems;
- Sex workers;
- Drug addicts; and
- Other risk groups, upon recommendation by their attendant physician.

Vaccines for public safety workers (policemen, firemen, etc) are provided and paid for by their organization.

A national serological survey conducted in 2001-2002 among private laboratories showed that 51% of the population tested were susceptible, 3.5% were immune due to past infection (anti-HBc+, mostly people >20 years, born before 1980), and 43% were immune due to vaccination (anti-HBc/-anti-HBs+). The levels of anti-HBs were around 50% in the age group of 20-29 years and very low (<5%) in those older than 45 years.

In the first part of 2010 in Portugal, vaccine coverage at birth was 95% and coverage by 12 months of age was >97%. In the 10-14 yr age group, coverage was still high (>94%). This has resulted from a period of approximately 15 years of infant HBV immunization, because many babies were already vaccinated before implementation of universal immunization in 2000. These excellent vaccination coverage rates are reflected in a substantial decrease in HBV incidence, as shown in the Chapter on Epidemiology of HBV in this report.

The universal immunization policy has proved to be more reliable and more effective than Portugal’s previous risk-based policy, with better coverage and more rapid results.

Migrants are not among the list of specific risk groups for targeted vaccination (see above), although the HBsAg seroprevalence rate in migrants (>5%) is often higher than in the general population. However, all children, even illegal migrants, are entitled to free immunization from health centres. Although migrant children are not actively identified, specific communities with a reluctance to have their children immunized, are actively approached but it is not known if they are actually reached. Vaccination is also offered to children presenting at hospitals for other reasons.

HBV vaccination of health students and health care workers is not mandatory, but they are entitled to receive free vaccination and the uptake rate is believed to be high. Doctors that have chosen not to be vaccinated, and subsequently become infected with HBV occupationally, are not entitled to compensation. HBV vaccination coverage in other risk groups is currently unknown.

The role of the Syringe Exchange Programme (SEP) in the prevention of viral hepatitis in Portugal

The Syringe Exchange Programme (SEP) is part of a series of harm reduction activities that aim to reduce infectious diseases (including HIV and HCV) among IDUs. In Portugal, knowledge on the prevalence of IDU is scarce. From the data available at the beginning of the century, Portugal had one of the highest prevalence rates in Western Europe. However, it seems that the number of IDUs has decreased in recent years. In 2005, the prevalence of IDU in Portugal ranged between 1.5 and 3.0 per 1000 population aged 15-64 years.

A timeline showing the important steps that have led to the present SEP programme in Portugal is shown below.

A timeline for Syringe Exchange Programme (SEP) in Portugal

The Portuguese SEP began as a partnership established in 1993, between the Ministry of Health, through the National Coordination for HIV/AIDS, and the National Association of Pharmacies, with the collaboration of pharmaceutical wholesalers and local municipalities. This pilot scheme, which was initially due to last for three months (October to December 1993), was run exclusively through
community pharmacies. Their involvement has been voluntary and no fee for this service is provided.

Portugal was the 16th country in the EU to implement a SEP. In late 1993, a mobile SEP unit was established by the Ministry of Health to support community pharmacies in Lisbon in areas with a high prevalence of IDU.

In 1999, non-governmental organizations (NGO) started to be involved in SEP and this resulted in a wider coverage of the programme.

In 2001, Portuguese drug policy was fundamentally changed. A law was approved that decriminalised all drug use, meaning that instead of being sent to prison, drug users are routinely referred to treatment centres. Also in 2001, the establishment of drug consumption rooms was authorized. However this arrangement was unpopular and, to date, no consumption room exists, leading to the continuation of “open” drug use.

In 2007, the Portuguese government authorised the introduction of SEP in prisons and two pilot programmes were launched. However, a number of problems have had a negative effect on the prison SEP, including issues of confidentiality and objections from prison guards. To date, not one syringe has been distributed.

Due to the relatively high infectivity of the virus, HCV can be spread not only via the sharing of needles and syringes, but also through the sharing of other injection equipment and the SEP kit (distributed since 2007) is designed to address this problem. The present kit includes two syringes, two filters, two ampoules of water, two drug preparation cups, two citric acid sachets, two swabs, and a condom. All SEP facilities, regardless their region and mode of service delivery (e.g. community pharmacy-based SEP, NGO) provide the same equipment, free of charge to IDUs. Although the use of one syringe per injection is considered preferable, single use syringes have proved unpopular amongst IDUs in Portugal and are not distributed free of charge by the government.

Since the beginning of the programme, 46.5 million used syringes have been collected by all SEP facilities. Between 2000 and the first half of 2010, the return rate of used syringes to SEP facilities was 95%. However, in some years the number of used syringes collected was higher than those distributed. These figures can only be considered as rough estimates, because it is difficult to obtain accurate data on injecting equipment returns and on distribution (distribution data refers to injection equipment distributed to SEP facilities, rather than directly to IDUs). Even taking into account questions about data quality, this finding suggests a “one-for-one” injecting equipment dispensation policy in Portugal is likely to be effective. SEP providers should consider the least restrictive approach possible. This must include the abolishment of the cap on the number of syringes distributed per visit and strict exchange policies, as numerous studies show these are detrimental for the prevention of HIV and other infectious diseases. Nonetheless, the return of used needles and syringes should not be neglected, but be actively encouraged in order to protect wider public health. It is important that the facilities are “user-friendly” and create a welcoming environment, in order for the programme to be successful.

Despite the fact that Portugal has the second highest rate of pharmacy involvement in SEP (after France), a decreasing trend in participation has been observed, from 67% in 1994 to 42% in the first half of 2010. This trend is particularly noticeable in Lisbon and Porto, where the highest HIV/AIDS infection rate and drug use prevalence is observed. In contrast, the number of NGO involved in SEP has increased. There are 50 NGO involved, mainly concentrated in urban areas. In rural areas, pharmacy-based SEP remains the only option for IDUs to obtain sterile injection equipment.

The SEP received financial support from the National Coordination for HIV/AIDS. This covered the value of the injection material distributed, the collection and destruction of used syringes, the functioning of the mobile post, and the operational management; but does not include the operational costs related to the NGO or pharmacies involved in SEP. The cost of the programme was 1.6 million Euro in 2008.

A 2009 study looking at the current injection equipment dispensation policies and the availability of other services provided to IDUs by all SEP providers, found that pharmacies offered a very low level of additional harm reduction services to IDUs, when compared to NGO and international pharmacies [1]. The level of additional services provided by NGO in Portugal was also low compared to NGO in other countries.

Unfortunately, the SEP programme mainly focuses on HIV prevention and is not linked to viral hepatitis prevention and control activities. This is considered a missed opportunity, because the SEP has access to an important proportion of the IDUs population and is often the only source of health care accessed by IDUs. SEP are a proven method for delivering other needed health and social services to the IDU population (e.g. counselling and testing, prevention and control of infectious disease including vaccination, primary care, methadone treatment, referral to drug treatment centre, and personal hygiene) [2]. Increasing the availability of harm reduction services should be a priority and the government should provide NGO and pharmacies the tools to provide additional services, e.g., they could take advantage of reaching a large proportion of IDUs for catch up HBV vaccination or HCV screening.

References

Based on a presentation by C. Torre, Centre for Health Evaluation & Research (CEFAR), Lisbon, Portugal

**SOS Hepatites (Liver Patients Association)**

SOS Hepatites is a non-governmental, not-for-profit organization that was established in April 2005; and is run by people infected or affected by viral hepatitis. It is the only patient support group in Portugal for individuals affected by viral hepatitis and their families.
The target audience of SOS Hepatites includes:

- War veterans;
- Patients having surgery or transfusion, blood donors;
- Individuals with elevated ALT, GGT;
- Individuals with piercings, tattoos;
- Haemophiliacs;
- Drug addicts;
- Prisoners; and
- HIV+ patients.

One of the main objectives of the organization is to stop the spread of viral hepatitis through raising the awareness of the public and of health professionals about risk factors, transmission routes, prevention and treatment. This dissemination of information is achieved via the organization’s website (www.soshepatites.org.pt/), publications, television appearances, newspapers, magazines, and attendance at national and international meetings.

Another principal objective is to provide support via patient information and enabling links between patients through meetings and via the website forum. Every year since 2005, the number of supported patients and relatives has increased and reached over 3000 patients to date.

SOS Hepatites collaborates with international organizations with the same objectives, such as The European Liver Patients Association (ELPA). Since 2009, the organization has been participating in the World Hepatitis Day, and recently actively contributed to the awareness campaign ‘Am I Number 12?’. SOS Hepatites collaborates with several professionals and has a Scientific Committee of seven experts to ensure the dissemination of valuable scientific information. SOS Hepatites promotes the training of psychologists with an expertise in chronic liver disease and also the training of nurses specialised in palliative care.

SOS Hepatites hopes that through its work it can create awareness of the disease and raise the profile of viral hepatitis, whilst removing the stigma associated with the disease.

\[\text{Based on a presentation by} \]
\[E. \text{ Rodrigues, SOS Hepatites, Lisbon, Portugal}\]

**International progress towards prevention and control of viral hepatitis**

The resolution designated a World Hepatitis Day (28th July 2010), which was endorsed by all 193 WHO Member States (see textbox below).

The resolution calls for expansion of the activities into African, European and Eastern Mediterranean regions, thereafter followed by the 3 remaining WHO regions (i.e. the Americas, South-East Asia and Western Pacific).

<table>
<thead>
<tr>
<th>The resolution called for Member States to:</th>
<th>The resolution called for WHO Secretariat to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• improve surveillance;</td>
<td>• establish guidelines, strategies, time-bound goals and tools for surveillance, prevention and control of viral hepatitis;</td>
</tr>
<tr>
<td>• strengthen laboratory capacity;</td>
<td>• support research, assess global and regional economic impact and burden;</td>
</tr>
<tr>
<td>• support integration;</td>
<td>• support events to mark World Hepatitis Day;</td>
</tr>
<tr>
<td>• incorporate policies, strategies and tools recommended by WHO;</td>
<td>• strengthen surveillance, prevention and control programmes, diagnostic and laboratory capacity, and management of viral hepatitis;</td>
</tr>
<tr>
<td>• strengthen national health systems;</td>
<td>• enhance access to treatments in developing countries;</td>
</tr>
<tr>
<td>• protect health care workers;</td>
<td>• strengthen Safe Injection Global Network (SIGN); and</td>
</tr>
<tr>
<td>• promote injection safety;</td>
<td>• report to 65th WHA on the implementation.</td>
</tr>
<tr>
<td>• provide access to preventive, diagnostic and treatment technologies against viral hepatitis;</td>
<td></td>
</tr>
<tr>
<td>• implement monitoring and evaluation tools; and</td>
<td></td>
</tr>
<tr>
<td>• observe World Hepatitis Day.</td>
<td></td>
</tr>
</tbody>
</table>

It is predicted that implementation of the resolution would cost $30 million for the next five years. At WHO there is no single unit that deals with viral hepatitis, and activities are spread between units. It was recognised in the resolution that these units may need additional resources (including 3 members of staff at WHO headquarters, 1 additional staff member in each of the 6 regional offices, dedicated national staff in at least the 10 high priority countries).

At present, WHO is trying to establish a global viral hepatitis programme and a comprehensive strategy is being drafted. This strategy has 4 components: prevent, identify and treat, integrate and innovate (see next page).

The WHO is in a process of consultation about the draft strategy. An internal consultation at the WHO Headquarters (November 2010) included an inventory of current activities by functional areas and several gaps were identified:

- coordination of hepatitis-related activities in WHO (activities are spread throughout many units);
- coordination with other stakeholders;
• advocacy activities – there is currently no advocacy hub;
• resource mobilization;
• case definitions, especially for chronic viral hepatitis;
• screening guidelines;
• risk-group prevention (specifically health care workers);
• core indicators (exist for key prevention areas, but need to be developed for surveillance, screening, care & treatment, integration, innovation); and
• treatment strategies.

Consultation has taken place with regional and internal colleagues and with a small group of external experts (Jan 2011).

Prevent
WHO work in the area of prevention is well established, but there is a need to scale-up activities including:
• immunization against HBV
  • birth dose, increase coverage of the third dose
  • increase coverage in older children, most at risk populations (MARPs), health care workers
  • Set and achieve control goals
• safe health care to prevent blood borne pathogen transmission
  • safe blood, safe injection, community awareness
  • immunization, safe food and water to prevent HAV.

Identify and treat
Historically, WHO has worked less in the area of viral hepatitis, but the Member States recognize that this needs to be addressed, since there are millions of people who are chronically infected with viral hepatitis and need to be identified and treated. Focus in this area includes:
• the development of an evidence and a policy basis for screening and treatment of viral hepatitis;
• the formulation of guidelines for treatment of chronic viral hepatitis, especially for priority resource-constrained settings;
• the expansion of care and treatment services for people chronically infected with hepatitis viruses.

Integrate
Services and programmes can provide good entry points for both infected and most at-risk people, and coordination can promote synergies. The resolution called for the integration of services across the health sector, involving:
• integration of interventions for the prevention, treatment and care of HBV/HCV into existing services for those at risk for HIV and sexually transmitted infections (STI), migrants and for IDUs, including access to sterile needles and syringes, HBV vaccination, and antiviral treatment;
• integration of viral hepatitis prevention and control into national cancer control programmes.

Innovate
In terms of research and development, the WHO intends to prioritize new preventive strategies to prevent chronic liver disease and liver cancer, including:
• encouraging the development of vaccines for HCV and HEV;
• technologies for vaccination: use of vaccine out of cold chain, needle free delivery, etc;
• technologies for screening; and
• technologies for safe health care.

The WHA resolution should be seen as a starting point, now countries and regions also need to take responsibility and declare what is required for implementation. The WHO Eastern Mediterranean region has recently adopted a very comprehensive hepatitis prevention goal that includes HBV; implementation is ongoing. In the WHO Africa region, 2 technical advisory group meetings were organized (October and December 2010) and the Regional Committee will meet in 2011. The WHO South-East Asia region has conducted consultation with hepatologists and other experts (June 2010). Although there has been discussion about a comprehensive viral hepatitis strategy in Europe and the Americas, significantly more work needs to be done.

The WHO needs to mobilize resources for the strategy ($30 million) and there has been some interest expressed from potential donors such as US, Germany, Qatar and other Gulf States. After funding has been secured, the work of implementation will begin and will be guided by monitoring and evaluation.

Based on a presentation by
S. Wiersma, Immunization, Vaccines & Biologicals, WHO,
Geneva, Switzerland

The French example of a national hepatitis programme
In France, prevention of viral hepatitis has been a priority since the early 1990s (initially HCV, later also HBV). Several national population-based studies have provided accurate epidemiological data. A conference on HCV treatment in 2002 led to guidelines which allowed the initiation of treatment for patients with HCV genotypes 2 and 3 without prior liver biopsy. This measure has made access to treatment easier. Creation of hepatology reference centres has facilitated the organisation of epidemiological surveillance, which is ongoing. The purpose of the two national programmes implemented in 1999 and 2002, has been to improve prevention, identification and management of HCV, and later, HBV.

Timeline of national viral hepatitis programme activities in France
A significant step has been the establishment of a strategic committee for the control and management of viral hepatitis (2003-2007), which represents all those involved in viral hepatitis prevention.

After analysis of epidemiological and clinical situations, the strategic committee proposed 54 actions according to the following 5 main strategies:
• Reduction of HBV and HCV transmission;
• Stepping up HBV and HCV screening;
Health care system and viral hepatitis surveillance in Portugal

In the ongoing “Health Transformation Programme”, a new integrated national health information system, backed by a legal framework, was developed and will be launched in 2011. The new system aims to create and improve knowledge and action by using evidence, raising quality and applying web-based technology. The compulsory disease notification system will combine clinical and laboratory data and allow automated bidirectional data transfers, data will be anonymized and un-linked at higher levels, and data will be analyzed at General Directorate of Health (DG) level. The first phase will introduce virtual death certificates, a national information system for epidemiological surveillance, and a national immunization registry. Electronic health records and prescriptions are scheduled to follow later in 2011.

Portugal will adopt the European List of Communicable Diseases and the notification system will be linked to the European surveillance system (TESSy), assisting ECDC in their role in regional policy making and the setting of norms and standards.

Follow-up of the programme has shown that 5 (9%) actions have been achieved, 35 (65%) actions are in progress, and 5 (9%) are expected to start in 2011. The costs of the French national programme for viral hepatitis were not presented.

A more restricted committee to focus on new actions and research and 3 working groups have been formed; these groups have the advantage of being more reactive. A delegate from the Health Ministry in charge of the health programme participates in all meetings of the 3 working groups and the restricted committee.

Being able to update a health programme is an important aspect, allowing it to adapt according to new information and developments. Examples of such updates in the French national plan include:

- Modelling data to anticipate the number of patients that will benefit from new treatments (Telaprevir, Boceprevir) and the extra human resources that will be required to cope with such demand;

- Evaluation of safety, efficacy and resistance development of new drugs (e.g. anti-protease) before full market approval;

- Cost-effectiveness analysis of universal HCV testing.

It was concluded that in most European countries there is too little coordination in terms of viral hepatitis prevention and control. The example of France shows that to improve this, it is important to define and involve all stakeholders and to ensure communication between all areas of expertise. The importance of regular evaluation of health programmes with the possibility to update according to needs was underlined. It is also necessary to have a focal point at a country level (preferably at the Ministry of Health), at a WHO regional level, and at the WHO global level.

Based on a presentation by
F. Roudot-Thoraval, Departement de Santé Publique, Hôpital Henri Mondor, Creteil, France.

Stakeholders involved in the follow-up of the French hepatitis programme

Source: E. Delarocque-Astagneau, Summit conference, Brussels October 2010

Conclusions

There are 40 national public health plans in Portugal, but there is no specific plan for the control of viral hepatitis, despite its important contribution to liver disease mortality.

Epidemiology of viral hepatitis in Portugal

Hepatitis A

The epidemiology of HAV is changing as socioeconomic conditions improve. This makes Portugal a country in transition, with most (two thirds) of the young population becoming susceptible to HAV infection. As a consequence, the risk of community-wide outbreaks has increased. Since the age of the susceptible population is increasing, more severe cases can be expected.

Hepatitis B

HBV is a notifiable disease, but is probably under-reported. Several studies indicate that, 10 years after the introduction of universal vaccination, Portugal is now a country with low HBsAg prevalence (about 0.5 - 1.0%), therefore WHO and ECDC categorization needs updating. However, data at a national level
do not identify clearly the high prevalence in specific groups (e.g. migrants, possibly 5%, and IDUs, 4%). In first-time blood donors, the HBsAg prevalence rate is low (0.24% in 2009). Based on genotype analysis, different patterns of transmission for males and females were observed. Females were mainly infected through an intra-familial route, while males were infected via equal proportions of perinatal, sexual and intra-familial transmission. Genotyping of HBV in HBsAg+ subjects showed a predominance of genotype D, A and some E (adult and paediatric cases) and links with migration. Demography of paediatric HBV cases reflects migration (mainly from former colonies); mostly resulting from perinatal transmission, although there is also some familial transmission.

When other complications related to HBV infection are included (HCC, cirrhosis and coinfection with HIV), deaths due to HBV may be 15 times higher than the official statistics.

HDV prevalence among chronic HBsAg carriers is low (3.5% in 2003-2004) and therefore currently not considered a problem.

Hepatitis C
There is also a problem of under-reporting of HCV cases, therefore the prevalence of acute and chronic HCV infections is not known with certainty, but estimated to be 1.0-1.5%. Highest prevalence rates are found for IDUs and young adult men aged 15-34 years; and there is a north-south gradient (higher in the south). First-time blood donors have a low rate of HCV (0.28% in 2009). IDU is the main risk factor for HCV infection, followed by previous surgery, risky sexual behaviour and blood transfusion. The number of HCC cases due to HCV is increasing.

HCV genotyping indicates a pattern similar to other southern European countries with a predominance of genotypes 1 (>50%, mostly 1b) and 3a. Genotype 4 seems to be emerging, probably linked with migration. Genotype is associated with the natural course of HCV and treatment response.

There are limited data on HCV in children, but most cases are transmitted perinatally. Most children progress to persistent viraemia, although viral clearance is possible. A study in one maternity centre showed an overall HCV prevalence of 1% in pregnant women. HCV prevalence in pregnant women and in newborns remains largely undetermined in Portugal. Currently, routine screening for anti-HCV in pregnant women is only recommended for pregnant women with risk factors such as IDU and HIV infection.

Coinfection with HBV, and/or HIV, worsens pathology and the prognosis for HCV patients. HCV (mostly genotypes 1 and 3) is detected in 40% of the HIV-infected population. The proportional distribution of the different HCV genotypes in HIV coinfected patients is the same as in monoinfected patients.

Hepatitis E
HEV is under-detected due to limited testing and because HEV disease is not notifiable (even in the new information system). However, a study (excluding, where possible, people that had travelled to endemic areas), indicated a low HEV prevalence of about 3%. HEV data are generated based on clinical samples from heterogeneous populations, including IDUs, and blood donors. Little is known about zoonotic transmission in Portugal or seroprevalence rates in animals.

Disease burden and management of viral hepatitis in Portugal
Analysis of data from the national database of hospital admissions indicates a substantial social and economic burden of liver disease, with high intapent costs. The length of stay and mortality for patients with liver disease are above the national average. There were more than 210 hospital admissions for acute HBV in 2008, representing a total annual cost of €820,000. The contribution of different aspects of viral hepatitis (role of acute and chronic disease and of HCC) to mortality due to liver disease is not well understood. Cirrhosis of the liver is among the top 10 causes of death in Portugal. Chronic hepatic disease was the 5th cause of Lost Life Years (LLY), due to the impact of premature death. In terms of economic impact, viral hepatitis in the population aged 20-64 years (i.e., those in the active phase of their working life) represents a considerable burden. In Portugal, costs for treating liver disease in patients admitted to hospitals greatly exceed those for treatment of common cancers (colon, lung or breast cancer). The direct and indirect costs for cirrhosis and HCC are much higher than those recorded for HBV and HCV. In terms of hospital admission, HCC was the most costly of all liver diseases (€8,639 for each admission).

HCV genotype is associated with treatment response, for example, in a Portuguese study in HCV paediatric patients, genotype 1 was associated with a poor response to treatment. When looking at predictors of response to HCV treatment, none of the viral factors, other than genotype, appeared to be associated with improved sustained response. Treatment of HCV infected children has been controversial in the past but more recent evidence supports its benefit and, in line with current guidelines, the consensus in Portugal is in favour of treatment. Ideally, treatment should commence before adolescence, but usually after 3 years of age, as spontaneous clearance of the virus can occur at young age. The treatment of HBV in children raises important questions, for example about the timing and duration of treatment, due to the lack of long-term data.

Viral hepatitis in specific populations
Pregnant women
Treatment of HBV infected pregnant women with antiviral therapy (AVT) is generally deferred until after delivery. Screening during pregnancy and immunization of newborns (HBIG and vaccination) are used to prevent perinatal HBV transmission. In women with high level of viraemia, approved AVT may be considered. The establishment of a central body to evaluate implementation of screening policy for pregnant women for HBsAg and their immunization should be considered.

An approved treatment for HCV during pregnancy is not available. Viral hepatitis is more prevalent in pregnant women that are IDU, HIV+, or migrants. In addition, there is a 2-3 fold increased risk of mother to child transmission of HCV in HCV+ women coinfected with HIV.

Blood donors
Among first-time blood donors in hospital and private settings during the first nine months in 2010, seroprevalence rates were low. For HBV, seroprevalence was 0.14% (compared with 0.02% in all donors) and for HCV it was 0.12% (compared to 0.02%).

Haemodialysis and renal transplant recipients
Chronic HBV and HCV infections are the main causes of liver disease in haemodialysis and renal transplant patients, for whom AVT should be considered. Tenofovir or Entecavir can be used to treat haemodialysis patients, and Entecavir for renal transplant recipients. The prevalence of HBsAg in haemodialysis patients has declined since 1990s to around 1% and anti HCV similarly to about 5%.

Chronic HBV and HCV infections reduce survival rates in kidney transplant recipients. In these patients, liver biopsy or hepatic elastography are recommended, because the stage of liver disease affects prognosis of patients following kidney transplant. Despite poor response, vaccination of haemodialysis patients against HBV is recommended; experience shows dramatic reductions in prevalence of HBV infection after prophylaxis including vaccination.
Patients undergoing haemodialysis should be screened for HBV and HCV and vaccinated against HBV. Prophylaxis against HCV infection, and evaluation before renal transplantation, should be mandatory and AVT is recommended.

Impressive results were presented by a major centre of kidney and liver transplantation, where nearly 1200 liver transplants have been performed. Chronic HBV and HCV infection represent about 25% of liver diseases in transplant patients, for whom AVT should be considered.

IDU
In Portugal, there is a nationwide network of clinics and centres, coordinated by the Institute for Drugs and Addiction (IDT), to which IDUs can be referred. Over the past decade there has been a marked decline in the number of IDUs (but an increased attendance at outpatient clinics), and a reduction in HCV infection rate (but it remains high, up to 70%).

Prevention, control and awareness of viral hepatitis in Portugal
To date, HAV vaccination is only recommended in Portugal for travellers to endemic areas and during outbreaks, which has been successful in the past. Anti-HAV testing for HCV+ patients and vaccination of the susceptible individuals is a cost-effective strategy. However, the view of the Portuguese Government is that universal vaccination against HAV is costly and not a priority. A cost-effectiveness study on HAV immunization in Portugal is ongoing, but no data are available yet.

There has been a decline in acute cases of HBV since the introduction of vaccination of risk groups, adolescents and newborns. The universal vaccination policy has proven to be more reliable and effective than the previous risk-based policy, with HBV incidence falling to low levels. Following approximately 15 years of infant immunization, vaccine coverage of children aged 10-14 years is now 95%, with comparably high figures for vaccination at birth and at 12 months.

Valuable experience has been gained from HIV prevention, showing the feasibility of syringe exchange programmes (4-5 million syringes each year in Portugal) and the role that they could play in the prevention of viral hepatitis. Their successes and failures could be used to improve the prevention and control of other infectious diseases in IDUs, but currently only a small number of syringe exchange programmes also provide testing and counselling for hepatitis (only 16% for HCV compared to 44% for HIV).

Nongovernmental organizations and patients associations are active in prevention and control of viral hepatitis. Public awareness campaigns are important, one such initiative is the Liver on Tour project (Portuguese Association for the Study of the Liver) which promotes liver health. “SOS Hepatitis” is a patients organization that disseminates information for the public and health professionals in a variety of media and conferences, promotes training of psychologists and nurses, and gives support to patients and families.

International progress towards prevention and control of viral hepatitis
Following the resolution WHA 63.18 on viral hepatitis, progress is being made by the WHO in developing a comprehensive strategy for prevention and control of viral hepatitis. The resolution should be seen as a starting point; it legitimates regions and governments of Member States to act and declare what is required for implementation.

The need for a coordinating body in Portugal that can liaise between all specialist groups and health authorities was emphasized. The French National Programme for hepatitis was presented as an example of how such a strategy can be effective.

Lessons learnt, challenges and recommendations
• Awareness of viral hepatitis must be raised with a clear consistent message, in both the general population and among health professionals, including policy-makers. The role of HBV and HCV in mortality from liver disease should be highlighted. There is a need for initiatives to diagnose unrecognized infections and to address the lack of patient awareness about their infection status.
• More research is needed to quantify the costs and benefits of screening, disease burden and the economic aspects of prevention and treatment. Also the association of genotypes with pathology and response to treatment, including subtyping and IL28B determination, needs further investigation.
• More information is needed on prevalence of HBV in various groups, including migrants and the impact of these groups on Portuguese public health. Portugal should be reclassified as a country of low endemicity for HBV, since the overall seroprevalence rate is estimated to be around 1.0-1.5%.
• Better epidemiology data are also needed on HCV infection, in particular in war veterans and in groups at risk, including IDUs, haemophiliacs and migrants, especially those of former colonies.
• Further studies are needed on the prevalence of HEV, including genotypes and risk factors such as links with animals and occupations.
• Consideration should be given to making testing available free of charge or reimbursable (anti-HCV and HBsAg). Efforts should be made to increase the diagnosis of HCV (e.g. GPs should have a low threshold to check for HCV). This will lead to an increased rate of treatment, which can be curative.
• Attempts should be made to reduce harmful consumption of alcohol at a population level, in order to reduce its associated burden of disease and the effects it has on HBV and HCV patients.
• The syringe exchange programme provides the opportunity to access an important proportion of the IDU population, and should be linked to viral hepatitis prevention and control activities. The issues surrounding the use of auto-disable syringes in prevention kits should be examined (cost differential with re-usable syringes is marginal). Access to clean injecting equipment and harm-reduction kits should be expanded, especially in rural areas.
• Now that HAV epidemiology has changed, there is a need to reach consensus on the policy for vaccination against HAV, including cost-effectiveness analysis of universal vaccination, evaluation of the effectiveness of immunization for outbreak control, the use of combination vaccines against HAV and HBV, and the role of screening.
• Social workers need to be involved with pregnant women found to be positive for HBsAg. Families and contacts of HBsAg+ mothers should be screened, vaccinated and the follow-up of their newborns should be ensured. Consideration should be given to the establishment of a policy for screening and follow-up of pregnant women.
• Implementation and evaluation of the national health information system is crucial, with quality control and analysis of data. Continued review and, as appropriate, updating of case definitions, disease lists and information systems is necessary.
• As viral hepatitis spans several disciplines, public health experts, vaccinologists, gastroenterologists, liver specialists, other experts and civil society should be closely involved in the decision-making process with a view to the possible creation of a national public health programme for liver disease. There is a need for a strategic committee, ideally with DG representation, to drive this cause.
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