The epidemiological changes of HCV and HBV infections in the era of new antiviral therapies and the anti-HBV vaccine

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Summary The World Health Organization (WHO) resolution adopted in 2010 recognized viral hepatitis as a global health problem. In April 2014, for the first time, the WHO produced guidelines for the screening, care and treatment of persons with hepatitis C infections. In May 2014, a follow-up resolution urged WHO Member States to develop and implement a national strategy for the prevention, diagnosis and treatment of viral hepatitis based on the local epidemiological context. Although blood donor screening, which began in the early 1990s, has reduced the spread of the virus in the population, the WHO estimates that 150 million people are chronically infected with hepatitis C virus (HCV) and are at an increased risk of developing liver cirrhosis and hepatocellular carcinoma. In addition, 3–4 million people are infected each year. HCV treatment is currently evolving rapidly, and several drugs are in various stages of development.

With regard to the hepatitis B virus (HBV), in March 2015, the WHO published the first guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection, which were designed to complement the recent guidelines on HCV. Although the introduction of an effective vaccine against the hepatitis B virus has reduced the prevalence and health and economic impact of hepatitis B in industrialized countries, the WHO estimates that more than 2 billion people are HBV-infected and 350 million people are chronic carriers.

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The state of the art

In 2010, the World Health Organization (WHO) resolution recognized viral hepatitis as a global health problem and stressed the need to implement measures for its prevention, diagnosis and treatment [1]. On May 24th, 2014, a follow-up resolution urged WHO Member States to develop and implement a national strategy based on epidemiological data. These measures have not yet been implemented in many countries. The spectrum of viral hepatitis changes in relation to the etiological agents in different geographical areas of the world [2].

Although the screening of blood donors, which started in the early 1990s, has reduced the spread of hepatitis C virus (HCV) in the population, the WHO estimates that 150 million people, i.e., approximately 3% of the world’s population, are chronically infected with HCV and are at an increased risk of developing liver cirrhosis and hepatocellular carcinoma [3]. The incidence of hepatocellular carcinoma increases in both sexes with age. In HCV-positive patients, the cumulative risk of developing hepatocellular carcinoma in the 40–74 age group is 21.6% among males and 8.7% among females. A gradual increase in risk was observed with increased serum levels of alanine aminotransferase or with decreased basal levels of serum cholesterol [4]. In addition to this, 3–4 million people are infected each year. The WHO estimates that 15 million people are currently HCV-infected in European countries [5].

For the first time, the WHO has produced evidence-based recommendations regarding the screening, care and treatment of patients with HCV infection. These recommendations are intended primarily for decision-makers in the ministries of health who work in low and middle-income countries. These guidelines provide country-specific treatment plans and treatment programs for infectious diseases. The guidelines are also intended to be of use to non-governmental agencies and healthcare professionals for defining the elements and services required for the treatment of HCV patients. The guidelines are also helpful for clinicians who manage HCV patients. Recommendations on screening for HCV infection outlined that serological testing for HCV should be offered to people who are part of a population with high HCV prevalence or who have a history of exposure/risk behavior (strong recommendation, moderate quality of evidence). Tests with genomic amplification techniques for the detection of ribonucleic acid are performed immediately after a positive HCV serological test for the diagnosis of chronic HCV infection, and an assessment is required before initiating antiviral therapy (conditional recommendation, very low quality of evidence) [2]. With regard to the hepatitis B virus (HBV), in March 2015, the WHO published the first guidelines for the prevention, care and treatment of people living with chronic HBV infection. These guidelines are based on a public health approach to using antiviral drugs to treat chronic HBV, which considers feasibility and effectiveness with limited resources, for example, in places that do not have the option of performing specialized tests, such as HBV DNA testing and liver biopsy [6]. Although the introduction of an effective vaccine against the hepatitis B virus (HBV) has reduced the prevalence and the health and economic impact of hepatitis in industrialized countries [7], the WHO estimates that more than 2 billion people are infected with the virus and 350 million people are chronic carriers. There are more than 4 million clinical cases of acute HBV infection every year. In low-endemic countries, such as North America and Northern Europe, the estimated prevalence of HBsAg-positive subjects is less than 2%, while in high-endemic countries, such as sub-Saharan Africa and China, the prevalence is ≥ 8%. Italy is among the countries with intermediate endemicity (positivity for HBsAg between 2% and 7%) [7]. The WHO estimates that 13.3 million people are currently HBV-infected in the countries of the European Region [5].

High levels of viremia or an infection contracted at a young age, which mostly affects males, are associated with an increased risk of death or of developing hepatocellular carcinoma [8,9].

The impact of screening programs for viral hepatitis and HBV vaccination, which have significantly reduced viral hepatitis, have been appreciated
since the 1990s. Epidemiological studies conducted on mortality showed that increased life expectancy is attributable to healthcare interventions and, specifically, the introduction of new drugs as well as general sanitary improvements. The evolution of epidemiology in hepatology is most certainly the overall result of the introduction of new treatments (especially in recent years) and the development of a clinical hepatology-oriented approach to shared guidelines.

Based on these premises, this review uses national surveys to examine the changes in HCV and HBV epidemiology that are due to the introduction of screening measures and the anti-HBV vaccine, with a view toward strengthening and promoting liver disease stage assessment and eligibility for treatment throughout the world, particularly in low- and middle-income countries, based on the World Health Organization guidelines.

### Acute HCV and HBV infection

The data available on acute viral hepatitis needs to be interpreted with caution because patients are often asymptomatic. Approximately 80% of people developing an acute HCV infection have symptomatic disease [9]. Similarly, less than 10% of children and 30—50% of adults with acute HBV infection have icteric disease [10,11].

There are two monitoring systems for acute viral hepatitis in Italy: the Integrated Epidemiological System for Acute Viral Hepatitis (SEIEVA) and data from the Italian Association of Infectious and Tropical Diseases (SIMIT). These two systems also estimate the risk factors associated with the infections. Notification shall be made by the spokespersons of hospitals taking part in the monitoring of infected people.

The most effective preventive measures for HCV currently include blood and organ donor screening and testing (Table 1), the implementation of practices in healthcare settings and a strong education program. As the virus has frequent genetic variations, no vaccine has been developed against HCV.

In 1992, only 31 countries vaccinated infants for HBV. This year, the World Health Assembly passed a resolution to recommend global vaccination for HBV. Vaccinations increased significantly in 2012, when 183 Member States (members of the WHO are grouped according to regional distribution, with a total of 194 regions) vaccinated infants for HBV, and 79% of children received the vaccination for HBV.

Universal immunization from birth and other successful HBV vaccination strategies have resulted in a dramatic reduction in HBV transmission in many high-endemic countries. This has led to a reduction in chronic HBV, liver cirrhosis and hepatocellular carcinoma, which have caused major concerns for public health and the economy in those areas [13]. Table 2 shows the percentage of HBV immunization coverage among 1 year olds in the WHO region [14].

Data from Italy shows a significant reduction in HBV notifications since 1991, when vaccination became mandatory for all newborns and 12-year-old adolescents [15].

### Chronic HCV and HBV infection

Surveillance for HCV and HBV chronic liver disease could provide information about the prevalence and burden of the disease, associated risk factors and prevention and treatment strategies. Recently, in the United States [16] and some regions of Italy, such as Tuscany (Italy), specifically the Health Agency of Tuscany, pilot programs were proposed for chronic liver disease, providing information about the burden of the disease, prevention programs and newly developed therapies.

Several drugs are currently available to treat HCV-infected patients, and the cure rates are continuously improving because of the introduction of new drugs. In Europe, currently available treatments for HCV infection include standard pegylated interferon (PegINF) and ribavirin (RBV), protease inhibitors (boceprevir, telaprevir — first generation — and simprevir — second generation -), the RNA polymerase inhibitor of HCV NS5B RNA-dependent (sofosbuvir) and NS5A replication complex inhibitors (daclatasvir).

As noted by the WHO, HCV treatments are rapidly evolving, and several drugs are in various stages of development. These new molecules are able to treat more than 90% of HCV-infected patients and are effective against genotypes that were previously difficult to treat. The use of these agents reduces the necessity of close follow-up monitoring, the hospitalization rate for adverse effects, the need for specialist care

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<th>Seroprevalence (%) of HCV</th>
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and the amount of resources required for disease progression, including end-stage liver disease, liver cancer and liver transplantation. However, the cost of a 3-month treatment course of all-oral, direct-acting antivirals (DAAs) is roughly estimated at between $100 and $270 [17].

Current guidelines contain recommendations for all drugs that were approved by December 2013, but these will be updated periodically with recommendations for newly approved drugs [2].

The recommendations for treating HCV infection outlined that persons with chronic HCV infection, including those who inject drugs, should be assessed for antiviral treatment (strong recommendation, moderate quality of evidence); treatment with PegIFN in combination with RBV is recommended for antiviral treatment of chronic HCV infection rather than standard non-PegIFN with RBV (strong recommendation, moderate quality of evidence); treatment with the direct-acting antivirals telaprevir or boceprevir, administered with PegIFN and RBV, is suggested for a genotype 1 chronic HCV infection rather than PegIFN and RBV alone (conditional recommendation, moderate quality of evidence); treatment with sofosbuvir, administered with RBV with or without PegIFN (depending on the HCV genotype), is recommended in genotypes 1, 2, 3 and 4 HCV infection rather than PegIFN and RBV alone (or no treatment for persons who cannot tolerate interferon) (strong recommendation, high quality of evidence); pimepivir, in combination with PegIFN and RBV, is recommended for persons with genotype 1b HCV infection and for persons with genotype 1a without the Q80K polymorphism rather than PegIFN and RBV (strong recommendation, high quality of evidence) [2].

Several longitudinal studies have shown that a sustained virological response is associated with fibrosis regression [18,19].

The WHO guidelines on HCV have not yet been updated with currently available drugs, such as daclatasvir and ledipasvir.

Interferon-free therapies are well tolerated and effective, but their high cost forces clinicians down more cost-effective paths.

Regarding HBV, several lines of evidence suggest that long-term complete suppression of HBV replication by nucleosides/nucleotides results in an improved outcome in the long-term that significantly reduces the risk of developing liver cirrhosis, hepatocellular insufficiency and, potentially, the risk of hepatocellular carcinoma [20]. Moreover, a longitudinal assessment of liver fibrosis has demonstrated a histologically proven regression of liver fibrosis during entecavir/tenofovir therapy [21]. Recent studies have shown that HBsAg

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quantification predicts the treatment response to PegINF in chronic patients [22–24].

The recent guidelines for HBV prevention, care and treatment [6] provide a framework for the development or strengthening of these HBV programs in low- and middle-income countries, but they are also of relevance to some high-income countries.

In the non-invasive assessment of the liver disease stage at baseline and during follow-up, the aspartate aminotransferase (AST)-to-platelet ratio index (APRI) is recommended to assess the presence of cirrhosis (APRI score > 2 in adults) in settings with limited resources. Transient elastography (e.g., FibroScan) or the FibroTest may be the preferred method where available and if cost is not a major constraint. (Conditional recommendation, low quality of evidence.) All adults, adolescents and children with chronic HBV infection and compensated or decompensated cirrhosis (or cirrhosis based on APRI score > 2 in adults) should be treated regardless of their ALT levels, HBeAg status or HBV DNA levels (strong recommendation, moderate quality of evidence). Treatment is recommended for adults with chronic HBV infection who do not have clinical evidence of cirrhosis (or based on an APRI score < 2 in adults) but who are over the age of 30 and have persistently abnormal ALT levels and high levels of HBV replication (HBV DNA > 20,000 IU/mL), regardless of HBeAg status (strong recommendation, moderate quality of evidence). Where HBV DNA testing is not available, the treatment may be considered based on persistently abnormal ALT levels alone, regardless of HBeAg status (conditional recommendation, low quality of evidence).

These guidelines, based on a public health approach, seek to ensure the widest possible access to high-quality services at the population level based on what is feasible on a large scale in settings with limited resources.

Where are we now?

Currently, interferon- and ribavirin-free treatment regimens are available and require shorter treatment periods (3 months). These regimens do not have the substantial associated side effects, and preliminary results suggest that these treatments are also effective in patients with decompensated cirrhosis [25].

However, given the high number of chronically infected patients and the high cost of these drugs, the new regimens will be inaccessible to many patients throughout the world. In the United States, the estimated manufacturing cost of 12 months of treatment per person is US$68–136 with sofosbuvir and US$130–270 with simeprevir [26]. Sofosbuvir and simeprevir were approved by the European Medicines Agency (EMA) for the antiviral treatment of HCV-infected adults in 2013. The price of sofosbuvir is $1000 per 400 mg pill. Accordingly, the cost of the sofosbuvir component in a 12-week treatment course is $84,000 (the total regimen cost depends on the other medications used in combination with sofosbuvir) [27]. The price of simeprevir is $790 per capsule. The cost of simeprevir in a 12-week supply is $66,360. A 12-week course of simeprevir plus sofosbuvir costs approximately $150,000 [28]. Daclatasvir was approved by the EMA in January 2014.

In July 2013, the WHO estimated that over 150 million people are chronically infected worldwide. It is estimated that 12% of the 150 Million HCV-infected people live in low-, 15% in high- and 73% in middle-income countries [29]. The 5 countries with the highest prevalence of people with chronic HCV infection are China (29.7 million), India (18.2 million), Egypt (11.8 million), Indonesia (9.43 million) and Pakistan (9.42 million) [29]. Gilead has finalized an agreement for the introduction of sofosbuvir in Egypt. It has offered to supply the medicine to Egypt at a 99 percent discount of the U.S. price [30]. In general, access to new treatments is extremely difficult in low- and middle-income countries due to the high costs and the complexity of the management of these patients. The currently available data fails to clearly estimate the epidemiology of chronic HCV infection at different stages of the disease, but the preferred strategy is to treat patients in advanced stages of chronic HCV infection with newly accessible drugs.

As in the case of HIV/AIDS, competition among several anti-HCV (including INF-Free) products is likely to bring about a reduction in treatment costs. Several studies have shown a sustained virological response of up to 100% in both cirrhotic and non-cirrhotic patients and also in null responders with interferon-free regimens [31].

Antiviral HBV treatment has improved dramatically, and potent agents, such as tenofovir and entecavir, cause a minimal risk of resistance [32]. Unfortunately, the cost of treatment may be too high for the vast majority of those living in low-income countries, especially because most patients will require long-term therapy [33]. Education and public awareness is very important for reducing the transmission of HBV and its sequelae.

HBV drugs are also currently being trialed, which compared to the current nucleoside/nucleotide analogs, could induce persistent suppression of
HBV-DNA and cause HBsAg negativity and the eradication of cccDNA. The advantage of third generation nucleoside/nucleotide analogs is viral suppression of over 99%, the regression of fibrosis, the probability of HCC reduction (ultrasound is requested every 6 months), and tolerability (only 2% of patients had adverse events after 7 years of treatment). The disadvantages include the unlimited duration of treatment, the low rate of loss of HBsAg and the seroconversion to anti-HBs. With regard to HBV, certain drugs have been available for several years; however, nucleosides/nucleotides are still not able to eradicate cccDNA. Indeed, the target of these drugs is viral polymerase, a multifunctional reverse transcriptase. Interferon induces both the immunomodulation and suppression of cccDNA transcription. New drugs are being tested that target cccDNA, in particular, inhibitors of the formation of cccDNA, transcription inhibitors and drugs that disrupt or degrade the cccDNA. Other drugs still undergoing testing include translocation inhibitors of the virus in the cytoplasm or assembly of the nucleocapsid to DNA or inhibitors of the release of HBsAg. Finally, new immunomodulators are in a more advanced trial stage. Among these is a vaccine treatment that boosts the immune response.

Agonists of toll-like receptors act on adaptive and innate immunity and on antiviral cytokines [34]. Therefore, the treatment goal would be a specific process with which to achieve HBsAg loss and HBV eradication.

In conclusion, the epidemiology of both HCV and HBV is changing constantly and rapidly and requires the support of policy-makers to promote prevention and treatment programs.

References


HBV and HCV epidemiology


