



Management of persons with hepatitis B or hepatitis C virus infection

REPORT OF RECOMMENDATIONS 2014

Coordinated by Pr Daniel Dhumeaux
for the ANRS and AFEF

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Introduction

After three consecutive plans for the fight against hepatitis B and C this “Report of recommendations on the management of patients with hepatitis B or hepatitis C virus infection” is the result of a collective effort initiated by the French Minister of Health, Marisol Touraine. The National Agency for Research on AIDS and Viral Hepatitis (l’Agence nationale de recherches sur le sida et les hépatites virales, ANRS) and the French Association for the Study of the Liver (l’Association française pour l’étude du foie, AFEF), supported this effort and made it possible.

Nearly 200 clinicians, researchers, other professionals, patients and patient associations worked on this report for more than a year. It was organized into expert groups on 22 themes. An independent committee from the scientific community and from patient associations validated and summarized the experts’ texts.

The purpose of this report was to cover all of the questions facing patients with HBV and HCV; health, social, ethical and organizational. The recommendations of this report are based on the belief that the approach to HBV and HCV, which until now have been considered chronic diseases whose outcome is potentially serious, can be replaced by that of infections that are easy to control or cure. To take this approach, there were several underlying goals:

- Improve the prevention of hepatitis B and C which is considered to be behind in several domains in France (vaccination of hepatitis B in particular),
- Describe the steps of management of patients with HBV and HCV in relation to the specific treatment processes and therapeutic strategies, and
- Defend the values of equality of care and other responses to patients with concrete measures to fight against social inequalities.

By publishing these recommendations, the group responsible for the report took into account the economic burden that was involved in making new treatment widely accessible, in particular for hepatitis C, requiring responsible choices and indications. With treatments that are nearly 100% effective, more or less long-term control of infection is now a real possibility. In the absence of a vaccine, this requires identifying and managing all infected individuals and reducing the cost of treatment.

This report was primarily meant for public authorities but also for everyone involved in the fight against hepatitis B and C (healthcare professionals and other involved professions, patient associations and the pharmaceutical industry) as well as the media. At the end of 2014, a follow-up committee was organized by the Minister of Health whose mission is to support and directly follow-up implementation of the recommendations. This report should help stimulate collective actions so that hepatitis will finally be controlled in our society, in particular in the most disadvantaged groups.

Preface

In a letter addressed to the Director of the ANRS (France Recherche Nord & Sud Sida-HIV Hépatites) dated January 25, 2013, the Minister of Social Affairs and Public Health requested that this agency draft an expert report on hepatitis B and C virus. It stated that the purpose of this report was to provide medical, social, ethical and organizational recommendations, which took into account the epidemiological context, scientific and therapeutic advances and progress in prevention and screening. This request for a report on the management of HBV and HCV in France was received with great interest, especially since this was something that all of the actors in this field had been asking for several years.

The ANRS gave the French Association for the Study of the Liver (AFEF, Association Française pour l'Étude du Foie) the role of creating a group to draft these recommendations, "that would respect the principles of impartiality, transparency, diversity and open debate" in accordance with the Minister's wishes. Professor Daniel Dhumeaux coordinated the different expert groups and the summary statement. In the early stages of its design and execution the report was based on one key idea: a shared belief that the management of patients was not limited to the prescription of antiviral drugs. Based on this approach the report was structured around three main ideas: prevention, the treatment process, and reducing inequalities.

Our country has significant potential for high-level research in the field of hepatitis, placing France in second place worldwide for its scientific publications in this domain. New tools for screening and follow-up of patients are in the pipeline or available. This report is therefore an opportunity to take a look at the future and make useful public health proposals. Nevertheless this report reveals that viral hepatitis is associated with inequalities in certain populations, who too frequently escape testing, vaccination (for hepatitis B) and the healthcare system. Hepatitis, like HIV reveals weaknesses and dysfunctions in the system as well as social, economic and regional inequalities.

This report is a collective effort, which was sponsored by the ANRS and AFEF. The fruitful cooperation between the ANRS and AFEF is based on a single goal: a combined effort to improve patient management. It has resulted in high-level scientific results, which are essential in today's competitive international environment, including the recent CUPIC cohort (ANRS CO 20) that will be further developed in HEPATHER (ANRS CO 22).

This first report, which we are proud to provide to the public health authorities and all of those who are active in the fight against these diseases (healthcare professionals, patient associations, industrials) as well as to the media, provides a global update on the epidemic in our country and strong recommendations for a more effective response from all echelons involved in the fight. We hope that it will create mass mobilization so that HBV and HCV can finally be controlled in all levels of society, including in the most disadvantaged groups and the most highly endemic regions.

This report would not have been possible without the dedication of Professor Daniel Dhumeaux, who coordinated this task with passion and tenacity. We do not doubt that he will make sure that the recommendations in this report become the foundation for a coherent, global healthcare policy for hepatitis B and C in France.

Jean-François Delfraissy (Director ANRS)
Georges-Philippe Pageaux (former Secretary of AFEF)
Victor de Lédighen (Secretary of AFEF)

Foreword

Like its well-known predecessors for HIV this “Report of recommendations for the management of persons with hepatitis B or hepatitis C infection” (“*Rapport de recommandations sur la prise en charge des personnes infectées par les virus de l’hépatite B ou de l’hépatite C*”) is the result of a collective effort in response to a request from our Minister and which was sponsored by the National Agency for Research on AIDS and Viral hepatitis (Agence nationale de recherches sur le sida et les hépatites virales, ANRS) and the French Association for the Study of the Liver (Association française pour l’étude du foie, AFEF).

Everyone agrees that this report is timely. It is a logical continuation of the third plan for the fight against HBV and HCV, which ended in December 2012, and whose goal was to define and set up essential new measures. It comes at a turning point in the history of HBV and HCV, marked by the development of new diagnostic and screening tools for these infections and spectacular therapeutic progress which now makes it possible to control HBV infection and cure HCV in most treated patients. It also plays a role in making progress towards the development of a new national healthcare strategy in France.

Our country, which became rapidly aware of the public health problem created by viral hepatitis, began the fight early on, with joint actions and support from healthcare authorities, professionals in the field, patients and patient associations. These efforts have helped make France the country with the highest existing rates of treatment and diagnosis today. At a moment when, in the presence of therapeutic progress, insufficient screening and limited access to treatment result in an unacceptable loss of opportunity for infected patients, efforts must be continued and even greater efforts must be made.

In the last plan for the fight against HBV and HCV, the report published by the participants¹ as well as an independent evaluation by the Public Health Council (Haut conseil de la santé publique, HCSP)² identified remaining gaps in certain areas: continued deficiencies in prevention, including HBV vaccination, limited access to diagnostic testing (more than 250,000 people are still unaware of their HBV or HCV infection today), delays in making new tools available, inequalities in access to treatment in certain populations and incomplete regional epidemiological data (including in the overseas territories). Because of these observations and others, more than 200 clinicians, research scientists, patients and association representatives worked for more than a year to draft the recommendations that follow. I would like to warmly thank all of them for their untiring dedication.

The report was organized around twenty-two groups of experts, coordinated by one (or two) coordinators, who were in charge of a specific theme. The goal was to cover all areas of HBV and HCV, including health, social, ethics and organizational aspects, as defined in the mission letter from the Minister of Health. To draft the final report an independent committee of representatives from the scientific community and patient associations had the task of validating and summarizing the expert texts to obtain a harmonious and coherent report. The recommendations of each of the chapters are presented in a summary statement at the end of the report.

The measures proposed by the report focus on three main areas: (a) increasing diagnostic screening and strengthening prevention, which is considered to be behind in

1. <http://www.sante.gouv.fr/programmes-et-plans-nationaux-de-lutte-contre-l-hepatite-b-et-c.html>;
http://www.sante.gouv.fr/IMG/pdf/Hepatitis_Rapport_final_comite_de_suiivi_2012.pdf

2. <http://www.sante.gouv.fr/programmes-et-plans-nationaux-de-lutte-contre-l-hepatite-b-et-c.html>;
http://www.sante.gouv.fr/IMG/pdf/Hepatitis_Rapport_final_comite_de_suiivi_2012.pdf

several ways (in particular HBV vaccination) (b) defining the steps of patient management for HBV and HCV in relation to the treatment process and specific therapeutic strategies, and (c) supporting the values of equality of care at all levels by creating concrete measures to correct social and territorial inequalities. By drafting these recommendations, the group responsible for this report is keenly aware of the economic counterpart associated with new treatments, in particular for HCV, which implies making reasonable choices and indications. With treatments that are now nearly 100% effective, eradication of HCV can become a realistic goal. In the absence of a vaccine, this eradication can only happen if all infected patients are identified and treated, and if the cost of drugs is reduced, which is a major challenge for our partners in the pharmaceutical industry.

These recommendations are from professionals who work in a country which, it is true, has economic problems (which extend beyond its borders) but whose conditions of care for its population are often envied. This should not obscure the terrible difficulties of infected individuals or that three quarters of them live in countries with limited resources. This report, which was drafted for our public health authorities, did not discuss this element, but it is so important that the results of this study should be followed by actions that, like the ANRS with its experience in HIV, could achieve significant results that could serve as a model, by providing financial aid, obtaining major reductions in the cost of treatment and developing generic drugs.

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This English (short) version of the Report does not include the full texts of the 22 chapters. The full texts can be found in the French (long) version.

1

Epidemiology of hepatitis B and hepatitis C virus infections in France*

Key points

1. Epidemiological data on hepatitis B and C infections are obtained from structures that have been managing these infections in France for more than 15 years (surveillance by the French institute for public health surveillance ["InVS"] from reference centers and hepatitis networks, 2001-2012).
2. The prevalence of chronic hepatitis B and C: (a) was low (< 1%) in the general population in metropolitan France in 2004; more recent data in blood donors and models suggest that the prevalence has decreased since then; (b) is high in certain high-risk populations such as drug users, prisoners and individuals born in highly endemic countries; (c) has not been clearly determined in the French overseas regions ("DROM-COM").
3. The incidence of acute hepatitis B has markedly decreased in the general population since the early nineties and is low at present. Infection from sexual contact is now the main source of contamination.
4. The incidence of acute hepatitis C remains high among drug users; it is probably low in the general population.
5. In 2001 the estimated number of deaths due to HBV was 1,300, or a mortality rate of 2.2/100,000 inhabitants and the estimated number of deaths due to HCV was 2,600 cases or a mortality rate of 4.5/100,000 inhabitants. These figures have not been updated.
6. The creation of the Hepather cohort will generate transversal epidemiological data on these patients enrolled between 2012 and 2014 and followed up for 8 years.

Recommendations

1. **Update certain epidemiological data** to identify the progression of HBV and HCV infections, to adapt screening strategies as well as treatment and develop models to assist decision-making for policy makers.
2. **Obtain regional and not merely national epidemiological estimations** for HBV, HCV and HDV so that programs can be adapted to the differences/inequalities observed in the regions.

* Full text is only available in the French version.

3. **Obtain long-term epidemiological estimations for specific high-risk populations** (immigrants, drug users, prisoners, populations from highly endemic areas...).
4. Because of the specific modes of transmission of HBV, **obtain epidemiological data that takes into account the multicultural changes in French society.**
5. **Increase efforts to understand the epidemiology of HBV and HCV infections in the French overseas regions (DROM-COM).**

2

Diagnostic testing of individuals with hepatitis B and C infection*

Key points

1. Unlike HIV infection, reporting of new cases of chronic HBV and HCV infections is not mandatory in France. Available epidemiological data are obtained from occasional surveys or (sometimes outdated) systems of surveillance.
2. Forty-three percent of patients with chronic HCV infection were unaware of their status in 2004, which represents 100,000 undiagnosed individuals (55% were women). In the same study fifty-five percent of chronic HBsAg carriers were unaware of their HBV status in 2004, representing nearly 150,000 undiagnosed individuals with chronic hepatitis (81% were men).
3. HBV testing identifies infected patients and provides both individual benefit (reduction in morbidity and mortality thanks to management of diagnosed patients, reduced risk of viral transmission and vaccination of non-immunized patients) and a collective benefit (reduced risk of viral transmission).
4. Guidelines for HCV testing were defined more than ten years ago (2001), and recommend targeted screening based on risk factors.
5. There is no clearly defined screening strategy for HBV infection. Guidelines generally suggest testing individuals who are at risk of exposure to HBV, so that infected individuals can be treated and non-immunized individuals at risk of exposure can be vaccinated.
6. The acceptance and application of strategic guidelines by healthcare professionals, especially general practitioners, which must be taken into consideration when deciding upon HBV and HCV diagnostic testing methods.
7. Screening strategies for the diagnosis of chronic HBV and HCV infections must evolve and take into consideration the high proportion of patients who are unaware of their serological status and the significant progress made in treatment once the diagnosis has been made, as well as the advances in diagnostic tools with the availability of rapid screening tests which allow testing outside of healthcare facilities (community testing).

* Full text is only available in the French version.

Recommendations

1. **Continue the strategy of targeted testing for HBV and HCV based on risk of contamination** as set out in existing guidelines, but associate this with general information campaigns to the general population and physicians. These activities could be part of the contract on goals and means between the French national health insurance (“Union nationale des caisses d’assurance maladie”) and the government and could become a public health goal for each physician.
2. **Extend targeted testing by increasing screening in the following populations:**
 - men between 18-60 years old,
 - **pregnant women during their first prenatal consultation** and regularly evaluate these strategies.
3. **Perform research associating the three viruses: HBV, HCV and HIV, considering the epidemiological similarities and the interest of combined tests.**
4. **Add « HBV testing » that includes the three markers (HBsAg, anti-HBs antibodies and anti-HBc antibodies) as recommended by the French national health authority (“HAS”) to the list of acts of medical biology and provide 100% reimbursement.**
5. **Organize rapid diagnostic tests developed for HBV and HCV to promote testing in populations that do not consult traditional healthcare facilities.** Individuals who participate in administering tests who are not healthcare professionals must be trained to increase acceptance and ensure appropriate follow-up management.
6. **Provide counseling to subjects with negative test results to inform them of the risk of contamination due to at-risk behaviors and offer HBV vaccination.**

3

Vaccination against hepatitis B*

Key points

1. The vaccination against hepatitis B has been shown to be effective and safe. In particular, 15 years after a scare suggesting a relationship between the HBV vaccine and the development of demyelinating diseases, studies have not confirmed this suspected link.
2. The French HBV vaccination strategy in effect since the 1990's (vaccination of newborns, a catch-up campaign in children and adolescents and vaccination of high risk populations) is well adapted to the existing epidemiological situation.
3. Vaccination coverage in newborns has increased significantly since 2008. Catch-up of children and adolescents is insufficient.
4. The very limited data on vaccination coverage in populations at high risk of HBV suggests that coverage is largely insufficient.
5. The mandatory vaccination of healthcare workers since 1991 has nearly completely eradicated worksite HBV. Nevertheless: (a) persistent circulation of the virus and the risk of healthcare worker-patient transmission and (b) insufficient coverage justifies continued vaccination and mandatory proof of immunization.
6. Specific vaccination protocols are needed because certain comorbidities can reduce the probability and strength of the response to the vaccine. The physician should evaluate this risk on a case-by-case basis and adapt the vaccination protocol accordingly.
7. Between 2007 and 2012, more than 200 patients have undergone liver transplantation associated with HBV (cirrhosis, hepatocellular carcinoma, fulminant hepatitis). Many of these transplantations could have been avoided thanks to vaccination, and these grafts could have been proposed to other patients.

Recommendations

In accordance with WHO guidelines for universal vaccination coverage, whatever the endemicity in the country:

1. **Promote the application of all HBV vaccination strategies recommended in France** and confirmed by the "Haut conseil de la santé publique" opinion dated December 14, 2007.
2. **Continue ongoing efforts to increase HBV vaccination coverage in newborns** by reducing regional differences.

* Full text is only available in the French version.

3. **Make sure that the vaccination status is checked in children and adolescents during medical visits or other situations in which they come in contact with healthcare personnel** and that catch-up shots are offered and if necessary propose an HBV vaccination. This activity could be included in the contract on goals and means between the French national health insurance (“Union nationale des caisses d’assurance maladie”) and the government and could become a public health goal for each physician.
4. **Make sure that HBV status is checked in high-risk patients whatever their age during medical visits, other situations in which they come in contact with healthcare personnel, or in other specific facilities** and propose vaccinations once HBV immunization status has been tested.
5. **Promote HBV vaccinations in adolescents** with the support of their guardians by targeted community programs.
6. **Increase activities to improve HBV vaccination coverage in high-risk patients** in particular by offering free vaccinations at testing sites or treatment centers frequented by these groups.
7. **Provide 100% reimbursement of HBV vaccination** by French national health insurance when it is performed in private medical consultations, rather than the present 65%.
8. **Improve circulation of vaccination guidelines to general practitioners and specialists** (through initial and continuing medical training).

4

Prevention of hepatitis B and C in drug users*

Key points

1. Intravenous drug use is the source of most new cases of HCV infection in France.
2. The harm reduction programs are less effective for HCV than for HIV. This means that harm reduction tools must be diversified for HCV.
3. Certain specific populations of drug users (DU) have a higher risk of contamination (vulnerable or young individuals, women, migrants, prisoners).
4. Drug users who are unaware of their HBV or HCV status have a high risk of contaminating other intravenous DU by sharing material.
5. HCV contamination usually occurs during the first period of time of injection.
6. Increasing diagnostic testing and access to treatment in DU and HBV vaccination are key elements to prevention.
7. Certain new harm reduction approaches have been shown to be effective in reducing the incidence of HBV and HCV infection (new tools, alternatives to injection, making injections safe, providing “testing/access to treatment” in the same place...).
8. Existing treatment of viral hepatitis infections is as effective in DU as in the general population and significantly reduces the risk of transmission.

Recommendations

Global and coordinated disease management, focused on prevention, should be offered to drug users. Harm reduction has been an integral part of healthcare policies for addictions since 2004, however funding is insufficient resulting in poor acceptance, inadequate implementation and efficacy.

1. **Refocus the general policy of the fight against drugs based on the law of 1970 by favoring public health activities** (harm reduction and care) rather than legal control and repression of drug use and by focusing on the direction taken in the 2004 law on public health.
2. **Increase the scope of the harm reduction approach to maximize effectiveness against hepatitis viruses** by improving the quality, availability and access to needles and diversifying and developing approaches to make injections safe: support and education on the risks associated with injection (“AERLI”) and supervised injecting centers (“SCMR”).

* Full text is only available in the French version.

3. **Support approaches that offer global and coordinated care to DU in the same location** (sociomedical treatment of addiction, harm reduction, diagnostic testing, non-invasive testing of liver fibrosis, antiviral treatment and monitoring of liver disease).
4. **Promote earlier treatment of DU** by taking a multidisciplinary medical and socio-medical approach to reduce the risk of transmission.
5. **Improve training of actors in contact with DU** on the risks of HBV and HCV infections as well as on the reality of injection practices so that they can better advise DU about effective harm reduction techniques.
6. **Support and evaluate innovative approaches:** (a) by combining different opioid substitution maintenance therapy and harm reduction approaches and methods; (b) by promoting measures to prevent injection drug use, and alternatives to injection, especially in young DU.
7. **Develop harm reduction activities in prisons.** Existing harm reduction approaches should be updated to adapt to the characteristics of the prison population and to respect the principle of equivalent care and prevention in relation to non-prison populations, and new harm reduction approaches should be evaluated: (a) increased participation of associations and professionals working in the field of addiction, (b) peer interventions, experimentation with syringe exchange programs (which are not allowed at present in prisons), and more generally, (c) actually implementing all the measures set out in the harm reduction reference guidelines concerning the prison environment.

5

Prevention of hepatitis B and C infections in populations except drug users*

Key points

1. Since the development of the diagnostic testing for HBV and HCV in blood donors, the risk of transmission of these virus by blood transfusion is extremely low. It is estimated 1/10,000,000 blood donations for HCV and 1/2,500,000 for HBV.
2. The risk of transmission of HBV and HCV in healthcare workers is difficult to evaluate either because studies do not include a control group or because the study population is not representative of the general population.
3. A history of an invasive medical act before 2001 was found to be an independent risk factor of contamination of HBV or HCV in most published studies.
4. Thanks to the application of standard precautions and respect for rules of disinfection and good professional practices, the number of reported HBV and HCV infections in healthcare workers has decreased, but there is still a risk.
5. National monitoring of healthcare worker infections has been developed by the “InVS” since 1997 for HCV and 2005 for HBV. Since then the number of HCV contaminations has been between 0 and 5 per year and there have been no reported cases of HBV infection.
6. Since 1991 the risk of healthcare workers to patient HBV infection has decreased thanks to mandatory vaccination of healthcare professionals. The rate of HBV vaccination coverage in healthcare workers varies from 64.6% to 93.3%.
7. Invasive medical acts (in particular surgical acts or interventional radiology) are associated with the highest risk of healthcare workers to patient transmission.
8. The risk of tattoo or piercing-induced viral transmission is probably low in France. A 2008 decree set out the conditions for hygiene and cleanliness for tattooing and piercing and requires registration of these activities at the prefecture, and specific training in hygiene for tattoo artists and piercers.

* Full text is only available in the French version.

9. The risk of sexual transmission of HCV is low, but it exists: in the past decade it has mainly been reported in men who have sex with men (MSM) and are HIV positive.
10. The prevalence of anti-HCV antibodies in prisoners is 5%.
11. Treatment coverage of prisoners with HCV infection is insufficient.

Recommendations

1. **Improve the program for mandatory reporting of acute HBV infection** to develop a system that is more sensitive to the modes of transmission and adapt preventive measures of HBV.
2. **Establish a catch-up policy for HBV vaccinations in healthcare workers.**
3. **In case of suspected HBV or HCV contamination following an invasive medical act, systematically perform an investigation which includes an audit of practices.**
4. **Exploit serological results obtained from accidental exposure to blood** to more precisely determine the prevalence of HCV and HBV infections in different types of healthcare workers and better evaluate the risk of healthcare workers-patient transmission. Regularly and individually report this information to healthcare workers.
5. **Perform controls to make sure that the practices set out in the decree describing the conditions for hygiene and cleanliness in relation to tattooing and piercing are respected** in the different tattoo and piercing parlors.
6. **Continue and expand campaigns to screen and educate prison inmates on the risks of contamination.** Systematically offer testing to prison inmates for HBV, HCV and HIV infection during initial medical visits, including by rapid diagnostic tests. **Vaccinate this population against HBV**, and if necessary use accelerated vaccination schedules. **Systematically offer treatment** in case of chronic hepatitis B or C infection to reduce the risk of contamination.
7. **Continue and expand campaigns to educate MSM on the risks of contamination and re-contamination and preventive measures** (especially HBV vaccination). Propose systematic testing for HBV (with the three serological markers), HCV and HIV. Offer HBV vaccination if the individual is not immunized.

6

Virological tests for the diagnosis and follow-up of patients infected with HBV and HCV*

Key points

1. Serological and molecular tools are available to the clinician for the diagnosis and treatment of hepatitis B, C and D virus infections.
2. Sensitive molecular biology techniques based on real time PCR are now available for the detection and quantification of the viral hepatitis genomes.
3. New serological tools such as HBsAg, HBeAg and HCAg quantification could play a role in the diagnosis and follow-up of viral hepatitis.
4. Alternative biological matrices to venous blood samples such as gingival crevicular fluid (taken from the lip and gum) and total capillary blood (taken from the finger) allow biological testing of the patient in his/her own environment (point of care testing).
5. Rapid diagnostic tests using non-traditional biological matrices are rapidly evolving and could become an option for diagnostic testing in the field of viral hepatitis.
6. The French national health authority (“HAS”) will publish its opinion on the role of rapid diagnostic tests for the diagnostic screening of HBV and HCV to describe the conditions for performing these tests.
7. The dried blood spot technique could be an alternative option for the diagnosis of viral hepatitis, especially in populations in the developing countries that do not have access to healthcare facilities.

Recommendations

1. **Finalize evaluation of alternative blood testing methods**, including rapid diagnostic tests on gingival crevicular fluid, or the dried blood spot test, for the diagnosis of viral hepatitis including the detection of molecular markers.
2. **Finalize development of “multiplex” rapid diagnostic tests** for the detection of anti-HIV and anti-HCV antibodies, HBsAg, and even syphilis.

* Full text is only available in the French version.

3. **Respect technical conditions when performing alternative testing methods to ensure specificity and sensitivity**, by supporting implementation of these techniques and providing specific training to non-medical personnel.
4. **Confirm rapid diagnostic tests with a reference ELISA test from a venous blood sample.**
5. **Mobilize diagnostic testing facilities for exposed individuals** (“CDAG” and “CARUD”) **and patient associations** to provide appropriate information on alternative testing methods to populations that would not normally consult for testing.
6. **Determine the indication for tests for HCV resistance-mutations** in relation to new direct acting antivirals and future therapeutic protocols without interferon.
7. **Determine HBV antiviral drug resistance** in compliant patients receiving treatment who have a partial or suboptimal virological response or with confirmed virological escape.
8. **Develop WHO norms to standardize HDV RNA detection kits and quantification kits.**

7

Evaluation of liver fibrosis in hepatitis B and C virus infections*

Key points

1. Liver fibrosis must be assessed in patients with HBV and HCV infections because it is an important prognostic factor for the natural history of the disease that must be taken into account when determining the treatment strategy.
2. The METAVIR score is the histological score used in clinical practice to evaluate fibrosis. It is graded as absent or minimal fibrosis (F0 and F1), moderate fibrosis (F2), severe fibrosis (F3) and cirrhosis (F4). Fibrosis is considered to be significant when the score is \geq F2.
3. Liver biopsy is the reference method for the quantitative and qualitative assessment of liver fibrosis. Nevertheless it has certain limitations and cannot be considered a gold standard.
4. Several non-invasive blood tests (FibroTest[®], FibroMeter[®] and Hepascore) as well as liver stiffness by FibroScan[®] were validated in 2008 by the French national authority for health (“HAS”) for the assessment of the extent liver fibrosis and the presence of cirrhosis due to HCV.
5. These non-invasive tests have been reimbursed by French national health insurance since 2012, but only once a year in untreated chronic hepatitis C without comorbidities.
6. The diagnostic accuracy of these different tests is basically similar for the diagnosis of moderate and severe fibrosis as well as cirrhosis.
7. When tests results show that there is no significant fibrosis, the risk of a false negative is approximately 20%.
8. Non-invasive tests, in particular FibroScan[®], reliably exclude a diagnosis of cirrhosis (the risk of false negatives is less than 10%). On the other hand the positive predictive value is approximately 50%.
9. The combination of a blood test and liver stiffness measurement increases the diagnostic accuracy of the results for significant fibrosis, but not cirrhosis. A biopsy is indicated in case of disagreement between the two methods.

* Full text is only available in the French version.

10. The predictive value of non-invasive tests for the risk of hepatic events and survival is high and seems to be better especially for compensated cirrhosis. Although changes in test results over time may be have an even stronger predictive value for the risk of complications, this approach is being validated.
11. Although it has not been validated by the French national authority for health (“HAS”) and it is not reimbursed by French national health insurance, non-invasive tests are used in clinical practice for the evaluation of fibrosis in patients with chronic HBV. The “Direction générale de la santé” (DGS) requested that the use of these non-invasive tests in clinical practice for the diagnosis of HBV be evaluated by the French national authority for health (“HAS”) to measure liver fibrosis in patients with chronic hepatitis B.
12. Certain specificities of chronic HBV make interpretation of non-invasive tests more difficult: (a) a greater frequency of exacerbation of chronic HBV (increased transaminases that can interfere with results) and (b) an underestimation of fibrosis if the HCV thresholds are used.
13. After viral suppression of HBV or viral eradication of HCV, the results of non-invasive tests improve in most patients.

Recommendations

1. **Make sure that non-invasive tests are interpreted by specialists in liver disease**, taking into consideration the quality of the test, the patients’ clinical characteristics, and the results of other tests (biochemical, radiological and endoscopic).
2. **Obtain French national authority for health (“HAS”) guidelines on the use of non-invasive tests in the diagnosis of fibrosis in HCV and HBV infection:**
 - a. in chronic HCV infection:
 - continue evaluating the combination of different tests, to improve diagnostic accuracy,
 - evaluate the role of non-invasive tests in post-treatment monitoring,
 - extend the criteria for reimbursement of these tests,
 - define the indications for liver biopsy.
 - b. in chronic HBV infection:
 - rapidly define the role of non-invasive tests in the diagnosis of fibrosis,
 - propose a non-invasive diagnostic strategy reimbursed by French national health insurance,
 - evaluate the role of non-invasive tests in the monitoring of patients after suppression of viral replication.
3. **Evaluate the interest of using non-invasive tests in the prognosis** of chronic HBV and HCV infections in both treated and untreated patients, by integrating them into multiparametric models.
4. Considering their ability to predict the risk of liver complications, **express the results of non-invasive tests in quantitative values**, and not simply by the “F” value of the METAVIR score.
5. **Support the development of new radiological techniques and new biological markers** that take into account the dynamics of fibrogenesis, fibrolysis and comorbidities.

8

Clinical consequences and treatment of hepatitis B infection*

Key points

1. In 2001, the estimated number of deaths directly due HBV was 1,300 cases, for a mortality rate of 2.2 per 100,000 inhabitants. This figure has not been updated since then.
2. The natural history of chronic HBV is characterized by different phases that are not necessarily sequential and that require constant monitoring of patients. HDV or HCV or HIV coinfections accelerate the progression of liver disease.
3. HBeAg-negative patients represent 90% of the patients in France with chronic HBV infection today.
4. Chronic active HBV infection requires antiviral treatment to prevent progression to cirrhosis or hepatocellular carcinoma.
5. Although the inactive HBV carrier state is assimilated with remission, it requires monitoring because of the risk of viral reactivation.
6. HBV reactivation may occur in patients with HBsAg loss in case of immunosuppressive treatment.
7. Antiviral treatment with interferon for one year results in a sustained virological response in approximately 25% of patients.
8. Antiviral treatment with nucleos(t)ide analogues results in HBV-DNA negativity in most patients but requires long-term, even permanent treatment.
9. Interferon is the only effective treatment against HBV-HDV infection.
10. Viral reactivation in case of immunosuppressive treatment can be prevented by prophylactic antiviral treatment.
11. Children who were infected at birth or in early childhood can be treated. These patients should be treated by pediatric hepatologists.

* Full text is only available in the French version.

Recommendations

1. **Perform HBV serological testing in all direct family members and sexual partners of patients with HBV infection** and vaccinate them against HBV if they are HBV negative.
2. **Evaluate the severity of liver disease before making any therapeutic decision** because of the adverse affects and/or the duration of existing treatments. The choice of available techniques depends on the patient's profile and the treatment strategy being considered:
 - non-invasive tests may be indicated to identity asymptomatic chronic carriers who should not be treated but should be monitored, and patients with cirrhosis who need to be treated, whatever the viral load,
 - liver biopsy which should be offered to patients with chronic hepatitis to evaluate necroinflammatory activity, the degree of fibrosis and to make therapeutic choices.
3. **Inform general practitioners and all doctors that prescribe immunosuppressants about the risk of reactivation in patients with HBV markers** (HBsAg or anti-HBc antibodies alone, by national (scientific societies) and regional (regional networks) circulation of information.
4. **Define the role of HBsAg quantification** in the evaluation of disease and treatment follow-up.
5. **Promote clinical research to limit the duration of treatment by nucleos(t)ide analogues**, in particular be a sequential combination of these analogues with interferon.
6. **Define the types of management and follow-up of immune tolerant HBV patients.**
7. **Perform basic and clinical research to develop new strategies** because of the very low rate of HBsAg loss and the absence of eradication of the viral genome (cccDNA) with existing treatments.

9

Clinical consequences and treatment of hepatitis C virus infection*

Key points

1. Hepatitis C virus is generally asymptomatic and in most cases progresses to chronic infection.
2. The severity of HCV infection varies from chronic inactive carriers with normal transaminases to active chronic hepatitis associated with severe necroinflammatory lesions and fibrosis which can rapidly progress to cirrhosis.
3. The main factors favoring fibrosis are associated with the host and/or the environment: male gender, advanced age, excess alcohol consumption, the presence of the metabolic syndrome and at a lesser degree today HIV or HBV coinfection. Viral factors such as genotype and viral load do not influence the progression of chronic hepatitis C.
4. Chronic hepatitis C progresses to cirrhosis in 10 to 20% of the cases, depending the presence of negative cofactors. In France chronic hepatitis C is the second cause of cirrhosis and hepatocellular carcinoma, after excess alcohol consumption. It is the second cause of liver transplantation (cirrhosis and hepatocellular carcinoma combined). HCV infection is the cause of 2,600 deaths per year.
5. The goal of treatment is to obtain complete inhibition of viral replication (undetectable viral load in the blood) for a long enough time to obtain viral eradication. If HCV RNA is undetectable 12 and 24 weeks after the end of treatment (sustained virological response), the risk of relapse is nearly null and viral eradication can be considered to be successful.
6. Eradication of HCV is associated with a decrease, or even disappearance of necroinflammatory lesions, and often regression of fibrosis, even if cirrhosis has developed.
7. Viral eradication in patients with chronic HCV results in an improved quality of life, prevents progression to cirrhosis and its complications, reduces the indications for liver transplantation for cirrhosis and reduces the mortality associated with HCV. In patients with cirrhosis, although viral eradication is associated with a significant reduction in the risk of hepatocellular carcinoma, there is still a risk. Screening for hepatocellular carcinoma should be continued in patients with cirrhosis, even if viral eradication is obtained.

* Full text is only available in the French version.

8. The indications for antiviral treatment are based on the severity of chronic hepatitis, in particular evaluated by the degree of fibrosis (using non-invasive tests and/or liver biopsy), the risk of short and intermediate term complications, the presence of extra-hepatic manifestations, as well as the motivation of the patient and his/her acceptance of treatment.
9. The types of antiviral treatment depend on the patient characteristics, viral genotype and will significantly change in 2014, from treatment based on pegylated interferon and ribavirin, associated or not with a first generation antiprotease for 24 to 48 weeks, to a treatment that combines one or several oral direct acting antivirals associated or not with pegylated interferon and ribavirin for 12 to 24 weeks.
10. These new treatments are often less effective in patients with cirrhosis, in patients with HCV genotype 3, and in patients who have not responded (null response) to previous treatment.
11. Initial results of first generation “second wave” treatments or second generation treatments with oral direct acting antivirals without pegylated interferon or ribavirin suggest that these strategies are well tolerated, of short duration (often 12 weeks) and associated with a rate of viral eradication greater than 90%. These treatments will be available in the months or years to come. They are authorized in France for temporary use in patients with severe disease who have not responded to prior treatment.
12. The possibility of curing nearly all patients with HCV justifies an active strategy for screening and access to treatment, as well as expanding and reinforcing the medical structures that manage patients with chronic HCV.

Recommendations

1. **Provide multidisciplinary patient management at diagnosis**, which takes into account the patient’s liver disease, comorbidities, family situation and socio-economic conditions.
2. **Facilitate access to treatment by providing training to all the participants in the management of HCV infection**: general practitioners, public and private hepatogastroenterologists, actors in medical and non-medical facilities.
3. **Promote the creation of multidisciplinary meetings** to optimize management of complex situations.
4. **Treat first, not only based on liver disease, but also the clinical context**:
 - patients with a fibrosis score of \geq F2;
 - whatever the stage of fibrosis: patients with extra-hepatic manifestations, patients on a list for organ transplant, women who would like to get pregnant, drug users and prisoners.
5. **Promote therapeutic trials on the association of second and third generation direct acting antivirals in difficult to treat patients**: patients with cirrhosis, including decompensated cirrhosis, organ transplant patients, patients with HIV coinfection, chronic renal failure, elderly patients.
6. **Define the role of new antivirals in the treatment of acute hepatitis HCV**.
7. **Continue obtaining authorizations for temporary use** for second generation antivirals and associate these authorizations with a scientific evaluation of the efficacy and tolerance to these agents.

8. **Update the guidelines on the medical and sociomedical management of HBV and HCV infection**, at intervals that depend on scientific advances. Regular opinion papers from scientific societies (in particular the Association Française pour l'Etude du Foie) are necessary to redefine the therapeutic strategies as new antivirals become available.
9. **Maintain and effective partnership** between medical professionals, patient associations, pharmaceutical laboratories and health authorities, to optimize patient management and take into account the cost of treatment and budget restrictions.
10. **Perform cost-effective studies** to evaluate the efficacy in our healthcare system of a strategy that provides treatment to all infected patients.

10

Hepatocellular carcinoma in HBV and HCV infections: prevention, screening and management*

Key points

1. Hepatocellular carcinoma (HCC) is a serious complication of chronic liver disease, especially in patients with cirrhosis.
2. In France approximately one third of the cases of HCC are associated with HBV and/or HCV infection. A viral etiology does not strongly influence the features or management of liver cancer.
3. Significant progress has been made in the curative treatment of HCC in particular with the development of percutaneous ablation method, surgical resection, and liver transplantation.
4. In France the epidemiology of HCC has not been well defined, mainly due to a system of data collection that is not well adapted to this entity and is incomplete. Overall survival in patients with HCC is low: around 20% at 2 years and 5% at 5 years.
5. When patients with cirrhosis undergo ultrasound screening every 6 months, HCC is diagnosed at a curable stage in 75% of patients. Nevertheless in France only 20% of patients with HCC were screened and 25% received curative treatment. This is probably because the diagnosis of patients with cirrhosis is insufficient, and because non-specialists are not aware of testing guidelines in these patients.
6. Percutaneous ablation method of HCC, which is the only possible curative treatment option in numerous patients who cannot undergo resection or liver transplantation, is probably underutilized and unevenly distributed throughout the country.
7. Optimal management of HCC requires several types of specialists who are not usually part of the multidisciplinary team for first line treatment (hepatologist, interventional radiologist, liver surgeon) as well as a specific organization to obtain a rapid diagnosis and appropriate treatment.

* Full text is only available in the French version.

Recommendations

1. **Teach non-specialized physicians to identify patients with cirrhosis and promote regular 6-month ultrasound screening** according to French national health authority (“HAS”) guidelines.
2. **Develop training programs for ultrasound screening of patients with cirrhosis**, in particular by creating a specific course in the national inter-university diploma on ultrasound and ultrasound techniques.
3. **Create and organize specialized centers for the management of primary liver cancer**, with all the necessary specialists, diagnostic equipment and treatment, as well as an appropriate organization, especially with a “one-day” diagnosis.
4. **Promote rapid patient access to specialized units** by including primary liver cancer in the organization of existing regional cancer networks.
5. **Structure and generalize access to specialized multidisciplinary teams** and systematically include a hepatologist, a transplant surgeon and an interventional radiologist with adequate coordination and secretarial support.
6. **Promote training in and the development of percutaneous ablation methods**. Make this treatment option available throughout France and include it in the list of medical acts in the French national health insurance system.
7. **Promote the collection of high quality biological data** (within the framework of the biological resource center) ideally, by organizing a thematic network associated with specific, regularly updated, clinical data collection adapted to primary liver cancer.
8. **Harmonize data collection on primary liver cancer** in the existing network of regional registers.
9. **Promote translational research** by supporting interactions between basic and clinical research groups.

11

Liver transplantation and HBV and HCV infections*

Key points

1. HBV and HCV infections complicated by cirrhosis and/or hepatocellular carcinoma represent one third of all indications for liver transplantation in France.
2. Access to liver transplantation is dependent upon the MELD score in patients with cirrhosis and the alpha-foetoprotein (AFP) score in patients with hepatocellular carcinoma. The most severely ill patients are given the priority, those with a short-term risk of death.
3. In the absence of effective prophylaxis in transplanted patients (possible for HBV and being evaluated with new antiviral agents for HCV), viral recurrence occurs in all cases and reduces survival in transplant patients.
4. To prevent recurrence in patients who are transplanted for HBV related liver disease: (a) a negative viral load must be obtained before transplantation using the most recent nucleos(t)ide analogues (entecavir or tenofovir), and (b) after transplantation, a combination of anti-HBs immunoglobulins and a nucleos(t)ide analogue should be proposed.
5. In patients transplanted for HCV-related liver diseases, if possible the virus should be eradicated before transplantation. Results on a combination of new direct acting antivirals are promising.
6. After transplantation for HCV-related liver disease, treatment to prevent recurrence should benefit from new direct acting antivirals. Their use must be defined in this setting.
7. After transplantation for HCV-related liver disease, curative treatment should be proposed six months after transplantation, in patients with fibrosing cholestatic hepatitis or chronic hepatitis associated with a fibrosis score of \geq F2 as the progression of fibrosis is more rapid in immunodeficient patients. The results of association pegylated interferon-ribavirin were disappointing. Although results with triple therapy with boceprevir or telaprevir seem to be better in patients with HCV genotype 1 the adverse effects and interactions with immune suppressant drugs limit the use of this combination. The results of combinations of new direct acting antivirals are very promising.

* Full text is only available in the French version.

8. Liver transplantation can be proposed to patients with HIV-HBV or HIV-HCV coinfection. Transplantation cannot be performed unless the HIV infection is controlled. Interactions between antivirals and immunosuppressants should be expected. The results of liver transplantation for HIV-HBV coinfection are identical to that for HBV infection alone. The results of liver transplantation in HIV-HCV coinfection are not as good as in HCV infection alone because the former patients are in more severe condition when they undergo transplantation and because of the increased severity of recurrent HCV.

Recommendations

1. **Reevaluate the prevention of recurrent HBV infection.** Studies are needed to identify patients who can stop anti-HBs immunoglobulins, while maintaining nucleos(t)ide analogues and patients who can stop all prophylaxis treatments.
2. **Propose a yearly evaluation of fibrosis after liver transplantation for HCV-related liver disease.** Non-invasive tests to evaluate fibrosis after transplantation should be further studied.
3. **Define the influence of comorbidities**, in particular the metabolic syndrome, on the severity of recurrent HCV infection.
4. **Evaluate the efficacy of new direct acting antivirals** in patients infected with HCV before and after transplantation. These patients should have priority in therapeutic studies because of the severity of liver disease. Inclusion of these patients in multicenter cohorts should be encouraged.
5. **Re-evaluate the distribution of liver grafts in patients with HIV-HCV coinfection** taking into account the specific progression of HCV in these patients, which is both rapid and severe.

12

Hepatitis B and C and comorbidities: excess alcohol consumption and the metabolic syndrome*

Key points

1. Cirrhosis is multifactorial and a result of the synergy of a combination of risk factors. The most frequent risk factors are excess alcohol consumption, the presence of the metabolic syndrome and HBV and/or HCV infections.
2. The risk of the combination of excess alcohol consumption and HBV or HCV infection is an important public health issue. Excess alcohol consumption is generally defined according to WHO criteria: more than 21 glasses a week for men, 14 glasses for women and more than 6 glasses on one occasion. There is no threshold for a consumption of alcohol under which the effects of alcohol on health are null.
3. There is a strong epidemiological correlation between HCV infection and diabetes and insulin resistance. This relationship is not found with HBV.
4. In patients with HBV or HCV infection, the excess consumption of alcohol results in: (a) more rapid progression of fibrosis, (b) an increase in the risk of developing hepatocellular carcinoma, (c) an increase in the risk of decompensated cirrhosis, and (d) an increase in the risk of death.
5. In patients with HCV infection, the influence of excess alcohol consumption on the efficacy of antiviral treatment is controversial. In patients with HBV infection, the efficacy of antiviral treatment is not influenced by alcohol consumption.
6. In patients with HBV or HCV the presence of the metabolic syndrome results in: (a) more rapid progression of cirrhosis, (b) an increase in the risk of developing hepatocellular carcinoma, (c) an increase in the risk of decompensated cirrhosis, and (c) an increase in the risk of death.
7. In HCV infection, the effectiveness of pegylated interferon-ribavirin dual therapy is decreased by the metabolic syndrome. This was not observed with first generation triple therapies and new direct acting antivirals.
8. Management of alcohol consumption and the metabolic syndrome should be included in the specific treatment of HBV and HCV infection.

* Full text is only available in the French version.

Recommendations

1. **Systematically screen for excess alcohol consumption and the metabolic syndrome** in HBV and HCV patients.
2. **Refer alcohol-dependent patients to an addiction specialist** and perform a brief intervention in patients with excess alcohol consumption.
3. **Provide optimal management of diabetes** in HBV and HCV patients.
4. **Suggest lifestyle changes and physical activity in overweight or obese patients.**
5. **Continue monitoring liver disease even after eradication of HCV or control of HBV infection** in patients who continue to drink alcohol or in the presence of the metabolic syndrome because of the persistent risk of progression of liver disease.

13

Comorbidities of hepatitis B and hepatitis C: drug use, psychiatric disorders*

Key points

1. Psychiatric comorbidities and/or addictions are frequent in patients with HBV and HCV infections and their presence or development is frequently an important cause of discontinuation, or non-initiation of interferon.
2. Comorbidities should be identified and stabilized to facilitate the implementation of antiviral treatment and increase the chances of disease control or cure.
3. Patients with psychiatric problems (mainly depression) seem to be more frequent in those with HCV than HBV infections. The increased prevalence of drug users in patients with HCV only partially explains this difference.
4. A multidisciplinary approach should be taken for patients who abuse psychoactive drugs.
5. The vaccination against hepatitis B is recommended for all patients who frequent psychiatric facilities.
6. Psychiatric symptoms are more frequent in patients receiving interferon treatment for HCV than in those for HBV infection.
7. Patients should receive information, education, and psychological or psychiatric monitoring if they receive interferon treatment, especially for HCV infection.
8. Prophylactic antidepressants are not recommended in HCV patients receiving interferon.
9. Direct acting antivirals developed for the treatment of HCV and nucleos(t)ide analogues used for the treatment of HBV infection are not associated with psychiatric disorders.

* Full text is only available in the French version.

Recommendations

1. **Train general practitioners and psychiatrists in HBV and HCV management** and make them aware of the frequent psychiatric symptoms during these diseases.
2. **Promote and develop diagnostic testing for HBV and HCV** in patients in psychiatric facilities and in drug users.
3. **Encourage and promote vaccination against hepatitis B** in patients in psychiatric facilities and drug users.
4. **Systematize and standardize the evaluation of psychiatric disorders, addiction and risk of suicide** before, during and after antiviral treatment including interferon, in particular in patients with HCV infection.
5. **Update therapeutic guidelines** by including risk factors of thymic disorders (sleeping disorders, stressful events, lack of support).
6. **Improve coordination of treatment** by developing and supporting coherent communication between general practitioners, hepatologists, psychiatrists and addiction specialists.
7. **Support patient associations** by developing listening platforms managed by mental health specialists.
8. **Support research** in the mechanisms of psychiatric disorders and cognitive disorders in patients with HCV infection.

14

HIV/HCV/HBV coinfections*

Key points

1. Chronic hepatitis C concerns 14 to 19% of patients infected with HIV in France.
2. HIV infection worsens the natural history and prognosis of chronic HCV infection.
3. Individuals with HIV-HCV coinfection have two potentially different profiles:
 - in most patients, HIV-HCV coinfection is usually old and therefore a large proportion of these patients have severe fibrosis or cirrhosis;
 - the remaining patients have more recent HIV-HCV coinfection, with earlier management of HIV, more effective, less hepatotoxic antiretroviral treatment, and a natural history of chronic HCV infection that is similar to that of patients with HCV infection alone.
4. Death from liver disease is the primary cause of mortality in patients with HIV-HCV coinfection (43% for all causes).
5. The incidence of acute hepatitis C is increasing, in particular in men who have sex with men (MSM), and acute hepatitis C is often associated with HIV coinfection. If there is no early spontaneous decrease in hepatitis C viral load, HCV antiviral treatment should be begun. The association of pegylated interferon-ribavirin results in a sustained viral response in nearly 80% of the cases.
6. Chronic hepatitis B concerns 7% in patients infected with HIV in France.
7. HIV coinfection worsens the natural history and prognosis of chronic HBV infection.
8. Twelve percent of the patients with HIV-HBV coinfection have HDV hepatitis, which is associated with more severe lesions, as in patients without HIV infection.
9. In patients with HIV infection, hepatocellular carcinoma is an important cause of death due to liver disease. This can occur in patients with cirrhosis, even if viral replication has stopped.

Recommendations

In all patients

1. **Expand HCV prevention campaigns** especially in drug users and men who have sex with men (MSM).
2. **Systematically test for HCV and HBV infection when HIV infection is diagnosed** and perform regular serological testing, at least once a year in non-infected individuals with a high risk of exposure.

* Full text is only available in the French version.

3. **Vaccinate non-immunized patients against hepatitis B** in an accelerated vaccination schedule.

In patients with HCV coinfection

4. **Assess liver fibrosis with a blood test and transient elastography.** If there is disagreement between non-invasive test results and in case of comorbidities consider performing liver biopsy.
5. **Choose compatible antiretroviral treatment** especially in relation to drug-drug interactions with any later antiviral HCV treatments that may be used.
6. **Determine the indications and treatment modalities for chronic hepatitis C** with a multidisciplinary team.
7. **Make new anti-HCV treatments available to HIV-HCV coinfecting patients,** in particular by obtaining specific temporary authorizations for use and by favoring inclusion of these patients into observational cohorts.
8. **In the absence of spontaneous and early eradication of HCV RNA treat acute hepatitis C with a combination of pegylated interferon and ribavirin,** whatever the HCV genotype, for between 24 and 48 weeks depending on the viral response after 4 weeks of treatment.
9. **Perform regular tests to confirm that HCV viral load is negative** (whether it is spontaneous or treatment induced) and renew prevention campaigns because of the high frequency of HCV recontamination.

In patients with HBV coinfection

10. **Search for anti-HDV antibodies in all HBsAg carriers** and repeat in case of a continued risk of exposure to HBV and HDV.
11. **Prescribe antiretroviral treatment,** which preferably includes two antiretrovirals that are active against HBV. Tenofovir is the treatment of choice, in association with lamivudine or emtricitabine. In case of prior and prolonged exposure to lamivudine, investigate the presence of the YMDD mutation.
12. **Do not use lamivudine or emtricitabine alone for the treatment of HBV infection.**
13. **Never interrupt antiretroviral treatment for HBV suddenly,** except in rare cases.

15

Social representation of HBV and HCV infection in the general population and in infected individuals: patients' experiences and expectations*

Key points

1. The general population has a poor understanding of HBV and HCV, which is why it is difficult for high-risk patients to imagine that they may be infected. Women have a better understanding of hepatitis B and C than men.
2. The general population is willing to receive information on the disease and is not really resistant to screening or vaccinations, unlike physicians who are not comfortable with their level of understanding, and therefore do not inform their patients about the modes of transmission and testing.
3. Migrant populations from highly endemic areas also lack understanding of the modes of transmission of viral hepatitis. Ideas on viral hepatitis in migrant populations are paradoxical. Because they associate the disease with sexual excess, drug use or poverty, these populations hesitate to seek testing for fear of being stigmatized.
4. Drug users feel somewhat excluded from access to treatment because they feel that physicians consider them to be non-adherent. These populations are in need of models of integrated disease management favoring coordination between hepatologists and addiction specialists.
5. The patient's ideas on HBV and HCV are not always taken into account by healthcare workers: thus inactive carriers, who may worry about their status, may not be reassured by the physician's attempted explanations. Patients feel that the impact of the disease on their social and personal lives is not adequately taken into account by the healthcare workers.
6. All published studies show that the quality of life of individuals with viral hepatitis is altered compared to the general population.

* Full text is only available in the French version.

7. The treatment of HCV infection affects the patient's professional, family, social and marital life. Fear of stigmatization associated with the disease favors silence, withdrawal and hiding by infected individuals.
8. Although the role of those close to the patient is pivotal for successful treatment, this role is not sufficiently taken into account.
9. Patient management in healthcare facilities is mainly biomedical and does not take into account the effect of the disease on other aspects of life.

Recommendations

1. **Increase understanding of HBV and HCV in the general population.** Its impact, prevention, modes of transmission and treatment so that high-risk individuals can be aware of their potential status and seek testing.
2. **Fight against stigmatization by information campaigns and targeted prevention.**
3. **Make physicians aware of the importance of proposing HBV and HCV testing,** especially to immigrants from highly endemic areas, whatever their social status.
4. **Take a global approach to the disease and promote global patient management.** Improve continuing medical education for healthcare professionals, create consultations on adherence or patient therapeutic education and involve social workers or psychologists to provide support to patients living with hepatitis.
5. **Closely involve family and/or friends,** in particular the patient's spouse when the diagnosis is announced and throughout the entire process of treatment, by considering them partners in particular for the psychological aspects.
6. **Promote access to associations for all patients.**
7. **Continue epidemiological and social science research** on the viral hepatitis treatment process in vulnerable populations with HBV and HCV infections.
8. **Develop social science research on the representation of chronic viral hepatitis and adherence to treatment** to adapt prevention campaigns and promote testing and treatment.
9. **Make more extensive use of quality of life measurements** during follow-up of patients with hepatitis B or C to better evaluate the effects of disease severity, psychiatric complications, cognitive troubles, sexual dysfunction, discrimination, the impact, management and observance to treatment, drug addiction and its management, HIV coinfection and resiliency and emotional instability.

16

Hepatitis B and C: the role of therapeutic patient education*

Key points

1. Treatment of HCV infection, in particular with interferon, has severe adverse effects resulting in poor patient observance to treatment.
2. Therapeutic patient education (TPE) is a way to improve treatment adherence and success. That patient plays an active role and his/her experience and autonomy are recognized.
3. Therapeutic patient education should not be limited to adherence to treatment. It must take into account all the elements that may worsen hepatitis C, from treatment failures, to a reduction in the patient's quality of life: comorbidities, addiction and a reduced quality of social and personal life.
4. Therapeutic patient education is now legally organized according to the law on Hospital, patients, health and territories (HPST). The TPE program is developed by a group of healthcare professionals, patients and patient associations based on well-defined rules. The patient is an active participant in the management of his/her disease with the goal of increasing autonomy and improving quality of life.
5. There are different phases to the TPE program: a pre-educational evaluation before treatment, therapeutic support when treatment is indicated and post-therapeutic follow-up even after viral eradication to confirm that the patient is healthy and that there are no long term complications.
6. Therapeutic patient education methods vary considerably. There are many different tools, and the types of interaction with the TPE team also vary (individual or group).
7. Therapeutic patient education programs are evaluated at different levels: individual patient assessments and evaluations of the program itself. The TPE program is auto-evaluated yearly and every 4 years by health authorities.
8. A protocol for cooperation among healthcare professionals is being tested for HCV.

* Full text is only available in the French version.

9. Therapeutic patient education programs are also important for HBV infection but they are slightly different because the clinical features, progression, treatment and social aspects are different from those in HCV: in HBV infection, treatment results in viral suppression, rather than a cure and is often very long.

Recommendations

1. **Develop TEP programs for HCV** to include future interferon and ribavirin-free treatment strategies.
2. **Extend the goals of TEP programs** to the diagnosis and follow-up of the patient as well as management of comorbidities.
3. **Include patient associations** in the development and implementation of TEP programs.
4. **Make sure that TPE programs are accessible to vulnerable patients and in all regions**, including the overseas departments.
5. **Extend criteria for results in TPE programs to include quality of life, restore their overall health** and not only eradication of the virus, in particular when there are potential complications to liver disease (hepatocellular carcinoma).
6. **Extend the role of non-medical caretakers**: diagnostic education, certain diagnostic acts, short interventions in addiction and information on the risks of transmission.
7. Because HBV treatment can last several years, **create specific HBV TEP programs** that focus on observance.

17

Organization of the hepatitis B and C management process*

Key points

1. Diagnosis of HBV and HCV infections concerns both populations who consult their general practitioner as well as vulnerable social groups who are excluded from traditional healthcare.
2. In France, vaccinations are usually performed by pediatricians and general practitioners, who may be ambivalent about vaccination against hepatitis B.
3. Management of patients with HBV or HCV infection is complicated by: (a) treatment which must be prescribed by specialists, (b) the frequent presence of comorbidities which requires global patient management, and (c) the frequent existence of social difficulties requiring specific expertise.
4. Treatment of patients with HBV or HCV infections is generally managed by specialists associated with general practitioners; however access to treatment is difficult for many patients (drug users, immigrants, prisoners).
5. Although numerous structures and healthcare or sociomedical professionals are involved in the treatment of patients with HBV or HCV infections, there is a lack of coordination.
6. Any coordination of healthcare structures and professionals requires a common, recognized standard. The only existing references are the protocols from the French national health authority (“HAS”) which are limited to hepatological and virological aspects. Social and sociomedical aspects, which are not financed by French national health insurance, are not mentioned.
7. In the 2004 study on prevalence by the French institute for public health surveillance (“InVs”), a poor social condition, identified by those receiving “CMUc” (universal welfare) was a risk factor for HBV and HCV infection. Nevertheless, these results were not used in the fight against HBV and HCV, although these diseases are marked by significant social inequalities.

* Full text is only available in the French version.

8. Clinical evaluation of patients with HBV and HCV infections in specialized centers makes it impossible to determine whether the social inequalities associated with these infections and their management have been corrected.
9. In regional health policies, the organization of the treatment of HBV and HCV infections is broken down into three approaches: prevention (vaccination, testing, therapeutic patient education), treatment (healthcare facilities and consultations) and sociomedical (drug users, immigrants).
10. There are significant regional inequalities in the organization of treatment of patients with HBV and HCV infections (including French overseas regions).
11. The involvement of patients with HBV or HCV infections in the treatment process is both a prognostic factor and a social necessity.

Recommendations

To create an organized, effective treatment process that includes patients and takes into account their quality of life, it is necessary to:

1. **Encourage general practitioners to participate in the prevention of HBV and HCV infections** (HBV vaccination, testing for HBV and HCV) within the framework of public health goal based-payments.
2. **Systematically include testing for hepatitis B and C and offer the HBV vaccination when caring for vulnerable population** (individuals in a state of poverty or precarity, drug users and individuals in legal custody).
3. **Update French national health authority (“HAS”) protocols** by specifying the sociomedical assistance that HBV and HCV patients may need.
4. **Create multidisciplinary meetings in each region for the management of complex cases of HBV and HCV infections**, including in particular the general practitioner, specialist (hepatologist, hepatogastroenterologist, internist or infectious disease specialist), addiction specialist, and social worker to draft a written proposition for patients.
5. **Markedly improve therapeutic patient education for patients with HBV and HCV** by developing the HBV programs and systematically involving general practitioners and seeking equality among the regions and access to patients with social problems.
6. **Evaluate the use of the “CMUc”** to direct and evaluate response to prevention and management of HBV and HCV infection.
7. **Experiment with flat fee funding of treatment in patients with HBV and HCV infections** based on an extended “ALD6” protocol and by focusing on medicoeconomic evaluation.
8. **Experiment with systems to coordinate treatment in patients with HBV and HCV infections** based on extended “ALD6” protocols and by performing a medicoeconomic evaluation.
9. **Draft a method of monitoring of prevention activities** in association with the French institute for public health surveillance (“InVs”) (HBV vaccination, HBV and HCV testing) and the management (in particular inclusion in the appropriate therapeutic patient education programs) on a regional level.

10. **Draft and circulate yearly in each region** (including in the French overseas regions) in association with Regional health authorities (“ARS”) **a spreadsheet including all available data on prevention (vaccination, testing), treatment and sociomedical management of HBV and HCV infections found throughout the region.**
11. **Perform a yearly follow-up of prevention and treatment of HBV and HCV infections in regions that are considered to be epidemiologically disadvantaged** (high prevalence, specific populations) **and/or for the organization of access to treatment.**

18

Care and support of vulnerable population*

Key points

1. The unequal distribution of HBV and HCV infections in the French population can be explained in part by underprivileged social conditions, which means that the medical treatment of these diseases must be associated with general measures of social support.
2. While vulnerable populations are particularly affected by HCV and HBV infections, validated tools to evaluate this phenomenon are not sufficiently put to use.
3. Certain programs and measures that are effective to diagnose, treat and accompany underprivileged populations with HBV and HCV infections have not been supported even though they would facilitate individual follow-up of these populations and help reduce the social inequalities of healthcare.
4. The sociomedical and social assistance necessary for underprivileged and vulnerable populations with HBV and HCV infections, including housing, should be developed and more effectively exploited.
5. The social inequalities of healthcare must be taken into account in the fight against HBV and HCV.

Recommendations

The treatment process and the social and medical information system

- 1. **Evaluate the social vulnerability of patients with hepatitis B and C** and propose appropriate multidisciplinary support.
- 2. **Develop a medical and social information system that takes into account HBV and HCV** to improve the evaluation of factors affecting vulnerability and to act upon the social determinants of health, in particular by improving healthcare and support services in relation to results.

Situations of vulnerability “here and there”, and immigration

- 3. **Increase awareness and provide training to healthcare professionals and social workers in HBV and HCV testing for immigrants from highly or moderately endemic areas.** Adapt interventions and information campaigns on the modes of transmission to the level of risk present in the country of origin and during the immigration process.

* Full text is only available in the French version.

- 4. **Provide professional interpreters in healthcare settings** and make them available to non-French speaking, vulnerable individuals (800 number, free for patients, including during testing).
- 5. **Facilitate the residence permit for medical reasons for individuals with chronic HBV and HCV infections** based on the recommendations and instructions from the “Direction générale de la santé” on November 10, 2011.
- 6. **Develop international cooperation and support changes in the healthcare systems** to provide prevention and care to patients with hepatitis B and C in countries with limited resources.

Insurance coverage, access to treatment, and clinical trials

- 7. **Guarantee the same level of care to all patients** through medical insurance coverage and access to care for the most underprivileged, whatever their level of coverage in accordance with the guidelines of the National political counsel in the fight against poverty and exclusion.
- 8. **Revise complementary “CMU” and “ACS” thresholds** so that all individuals below the poverty line can benefit from national health insurance coverage and improve coverage by the supplemental “CMU” in particular for dental work, as recommended by the “CMU” funds.
- 9. **Fight effectively against treatment refusal** : emphasize the importance of testing, change the burden of proof to benefit the presumed victim, allow registered associations to plea for others, allow national health insurance to investigate and impose sanctions on healthcare professionals as set out in the Hospital, patients, health and territories (“HPST”) law decree.
- 10. **Include individuals with health insurance of any sort in research programs**, whatever their status, whether they are covered by French national health insurance (which exists at present) or State medical aid (“AME”) (partially excluded for the moment) and modify the article L1121-8-1 of the public health code accordingly.

Handicaps

- 11. **Develop prevention campaigns for the personnel in social and sociomedical facilities** by providing support to managers of these facilities, representatives of users and their families and Departmental homes for the handicapped (“MDPH”), by make sure that the information being circulated is appropriate for each type of handicap.
- 12. **Remove the criteria “long term restriction to access to employment”** which prevents most people with HBV and HCV infection from receiving Allocation to handicapped adults (“AAH”) benefits.
- 13. **Revise minimum social benefits** so that they are above the poverty line without preventing eligible parties from obtaining supplementary “CMU”. No longer make length of residency a pre-requisite for access to minimum social benefits for foreigners with a residence permit.

Prostitution and drug use

- 14. **Improve the health, safety and respect the rights of prostitutes support a public health and reduction of risk approach to sexually transmitted diseases in general and viral hepatitis in particular**, rather than a policy of punishment and repression.

- 15. **Guarantee continued coverage of healthcare costs and social benefits** especially in case of geographic mobility.
- 16. **Privilege a global approach to the reduction of risk** that includes individual characteristics and changes in the types of drug consumption by improving the coherence of different public health, social and criminal policies.

Prison inmates

- 17. **Propose better conditions** (respect of confidentiality, medical secrecy) **during testing in prison and strengthen the reduction of risk policy.**
- 18. **Facilitate the process for obtaining medical and social coverage when released from prison and increase social support after release**

Innovative approaches to be supported: mediation, appropriate housing, advanced strategies

- 19. **Coordinate prevention, treatment, social support and accommodations and use mediators** to facilitate coordination in a community based healthcare system, seeking support from, and establishing alliances with associations.
- 20. **Facilitate access to treatment and medical coverage, and encourage testing of HBV and HCV as well as the HBV vaccination in vulnerable populations** (free and vaccination for the family) based on other successful experiences: mediation, appropriate housing, advanced strategies, and this, in coherence with continuity, of residency and long term care.
- 21. **Support mobile services** that offer a range of tools including vaccination against HBV, rapid diagnostic tests for hepatitis and FibroScan® and develop training courses in counseling, in particular for rapid diagnostic tests.
- 22. **Increase the capacity to welcome and accommodate individuals with chronic infections**, in particular from vulnerable groups, with psychological problems, based on an approach that is centered on the individual empowerment of these patients whatever their administrative status.

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Mother-to-child transmission of HBV and HCV: consequences and prevention*

Key points

1. In the absence of liver insufficiency there are no contraindications to hormonal or mechanical contraception in women with HBV or HCV infections.
2. HBV or HCV infection alone is not a contraindication for pregnancy. Cirrhosis is a relative contraindication and should be discussed on a case-by-case basis in relation to the severity of liver insufficiency.
3. The decision to prescribe anti-HBV treatment in women of childbearing age should take into account the risk-benefit for a future pregnancy. In case of a treatment with a nucleo(s)tide analogue, tenofovir is the treatment of choice.
4. Effective contraception must be used if a patient is receiving anti-HCV treatment. A woman should wait 4 months after the end of a treatment with ribavirin before becoming pregnant. A man should use contraception for 7 months after the end of a treatment with ribavirin. Men receiving treatment with ribavirin should use a condom during sexual relations with a pregnant woman.
5. Systematic screening for HBV by HBsAg testing must presently be performed in the 6th month of pregnancy, and HCV must presently be tested by anti-HCV antibodies in serum during pregnancy if the patient has risk factors.
6. Specialized care should be provided if HBsAg or anti-HCV antibodies with positive HCV RNA is found in serum of a pregnant woman.
7. HBV and HCV infections in pregnant women do not affect the way the baby is delivered.
8. Maternal breast-feeding is not contraindicated in the presence of HBV or HCV infection. Treatment with an anti-HBV nucleo(s)tide analogue is a relative contraindication, especially tenofovir.
9. A serovaccination should be rapidly performed in all children born to HBsAg-positive mothers, ideally in the delivery room, using an intramuscular injection of anti-HBs immunoglobulins (100 IU) + infant vaccine 10 µg (repeated at M1 and M6). The efficacy of the serovaccination as well as the absence of contamination of the newborn should be systematically controlled by obtaining HBV serology 1 to 3 months after the last vaccine injection.

* Full text is only available in the French version.

10. Treatment with an anti-HBV nucleos(t)ide analogue in the third trimester associated with a serovaccination at birth may decrease the rate of serovaccination failure in HBsAg-positive pregnant women with elevated HBV DNA ($> 7 \log \text{ IU/ml}$). The three possible analogues are lamivudine, telbivudine and tenofovir.
11. The rate of mother-to-child transmission of HCV is approximately 3 to 5% and only observed in HCV RNA-positive patients. There is no known way to reduce this risk. Children born from mothers with HCV infection should be tested at 18 months.
12. Medically assisted procreation in women with hepatitis B or C infection should be performed for problems of infertility and not due to the risk of sexual transmission of the virus. Medically assisted procreation should be performed in an at “viral risk” unit.

Recommendations

1. **Evaluate the overall situation in a pregnant woman with HBV or HCV infection** (socio-economic and administrative conditions, ethnic origin, illicit drug use...) in relation to the possible consequences to adherence to treatment or follow-up.
2. **Develop a more extensive screening program for HBV in pregnant women** similar to that in the general population including the three tests (HBsAg, anti-HBc antibodies and anti-HBs antibodies).
3. **Test for HBV, HCV and HIV during the first prenatal visit.**
4. **Organize a specialized follow-up if the patient is positive for one of these tests**, to accompany the patient when she is informed of the results, and for management during pregnancy and delivery.
5. **Prescribe HBV DNA testing in HBsAg-positive pregnant women.** Treat with an anti-HBV nucleos(t)ide analogue in the last trimester of pregnancy in case of HBV DNA $> 7 \log \text{ IU/ml}$ or contamination of a child in a previous pregnancy, after having a multidisciplinary team discussion and providing information to the parents.
6. **Evaluate the safety of anti-HBV nucleos(t)ide analogues in children *in utero*** exposed to these molecules. Continue ongoing studies, in particular by evaluating genotoxicity at birth and confirming the lack of effect on the child’s development in the first five years of life by comparing children who were exposed to analogues at conception, or only at the third trimester of pregnancy.
7. **Improve adherence to guidelines for mandatory screening of HBsAg during pregnancy, serovaccination of newborns and hepatitis B serology after serovaccination in infants.** This requires: (a) providing targeted information to healthcare professionals (initial training and continuing medical education) and parents, (b) improving the tools of information, in particular the child health card, and c) better use of mandatory child health certificates (8th day of life) (confirm that HBsAg was tested during pregnancy, and serovaccination performed at birth) and at 9 months (confirm that the vaccination and follow-up test have been performed).
8. **Improve follow-up of children born from HCV RNA-positive mothers** with testing for anti-HCV antibodies at 18 months.

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Specific problems of chronic renal insufficiency, hemodialysis and kidney transplantation*

Key points

Hepatitis C

1. HCV infection is more frequent in patients on dialysis and kidney transplant patients than in the general population. The incidence of HCV infection has markedly declined in these patients thanks to preventive measures.
2. HCV infection reduces survival in dialysis patients and patients with kidney transplantation compared to the same category of patients who are not infected by HCV.
3. HCV is associated with extrahepatic manifestations, in particular in the kidneys, which should be searched for and included when deciding upon the treatment strategy. The association of HCV and diabetes should be taken into account.
4. If HCV infection is diagnosed, the extent of fibrosis should be determined by liver biopsy until non-invasive tests have been validated in this population.
5. Anti-viral HCV treatment should be offered to all patients who are candidates for kidney transplantation, whatever the stage of liver fibrosis, to patients with chronic renal insufficiency with a fibrosis score of \geq F2, to patients with chronic renal insufficiency and extrahepatic manifestations and to all patients with acute hepatitis C.
6. The use of interferon-ribavirin for HCV is complicated. Interferon is poorly tolerated in patients with chronic renal insufficiency and contraindicated in kidney transplant patients because of the risk of rejection. Ribavirin can cause severe anemia in patients with chronic renal insufficiency and the posology is difficult to adapt.
7. First generation tritherapies associating boceprevir or telaprevir and interferon-ribavirin have not been extensively evaluated in these patients. They may not play a role in future treatment strategies. Second generation direct acting antivirals developed for interferon- and/or ribavirin-free treatment strategies are being tested patients with chronic renal insufficiency or kidney transplantation.

* Full text is only available in the French version.

Hepatitis B

8. The incidence and prevalence of HBV infection has significantly decreased in dialysis and kidney transplant patients thanks to screening and prevention campaigns. All patients with chronic renal insufficiency should be vaccinated against hepatitis B.
9. HBV infection is associated with extrahepatic manifestations in particular in the kidneys, which should be investigated and included when deciding upon the treatment strategy.
10. If HBV infection is diagnosed, the extent of fibrosis should be determined by liver biopsy until non-invasive tests have been validated in this population.
11. The efficacy of treatment by nucleos(t)ide analogues has changed the prognosis of patients with chronic renal failure and kidney transplant patients with HBV infection, eliminating the increased risk of mortality in this population.
12. Anti-HBV treatment should be offered: (a) to all patients with chronic renal insufficiency who are candidates for transplantation and HBV carriers, whatever their fibrosis score, and (b) to all patients with a kidney disease that is directly related the HBV. Unless the patient is to be transplanted, indications for treatment are the same as international recommendations. Entecavir and tenofovir are the recommended treatment in these patients because of their efficacy and their high genetic barrier to resistance. The dosage should be adapted to the glomerular filtration rate. The risk of proximal tubulopathy associated with tenofovir should be taken into account.

Recommendations

1. **Increase prevention, testing and vaccination against hepatitis B campaigns** in all patients with chronic renal insufficiency.
2. **Evaluate non-invasive tests of fibrosis** in patients with chronic renal insufficiency, under dialysis or not, and in kidney transplant patients and infected with HCV or HBV.
3. **Rapidly evaluate the efficacy of and tolerance to new direct acting antivirals for HCV infection** in difficult to treat populations, privileging interferon- and ribavirin-free strategies. This is urgent because of the increased mortality from HCV in these patients.
4. **Study the long-term toxicity of nucleotide analogues used in the treatment of HBV**. Develop simple tools for the early detection of renal tubular damage.

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HBV and HCV infections in the overseas departments, regions and collectivities (DROM-COM)*

Key points

1. The French overseas territories, characterized by isolation and distance from mainland France, have a high demographic and sociological diversity which affects the management of HBV and HCV infections.
2. Except for La Réunion, the prevalence of HBsAg seems to be higher in the DROM-COM (from 1.4% to 10% depending on the territories) than in mainland France. In an “InVS” study in 2004, the prevalence of anti-HBc antibodies in people living in mainland France and born in the DROM-COM was four times higher than in individuals born in mainland France.
3. The vaccination against hepatitis B and testing campaign in the DROM-COM had a significant impact in pregnant women, resulting in a reduction in the prevalence of HBV infections in all these territories.
4. In the “InVS” survey in 2004, the prevalence of anti-HVC antibodies in persons born in the DROM-COM was not statistically different than that of individuals born in mainland France. However, in 2012, the prevalence of anti-HCV antibodies in new blood donors was higher in Guadeloupe (3.5/10,000), in Martinique (7.9 per 10,000) and in La Réunion (6.8 per 10,000) than on the French mainland (2.6 per 10,000).
5. Treatment and access to treatment in patients with HBV and HCV infections are similar to those offered to patients in metropolitan France, but the demographics, and even the absence (Mayotte) of specialists in hepatogastroenterology limits access in fact.
6. Patient associations have played an important role in the implementation of different campaigns to raise awareness about viral hepatitis, however funding is insufficient.

* Full text is only available in the French version.

Recommendations

1. **Update epidemiological data** for each of the DROM-COM territories.
2. **Improve monitoring of chronic inactive HBV carriers** by a training program for general practitioners that is adapted to each of these territories.
3. **Improve access to specialized private or hospital facilities** to support local patient management.
4. In the specific case of Mayotte, centralize management of patients with chronic hepatitis B in local hospital.
5. **Give patients from the DROM-COM access to new direct acting antivirals for HCV** within the framework of therapeutic trials.
6. **Provide regular funding for patient associations** involved in the field in the fight against HBV and HCV.

Research on hepatitis B and C virus*

Key points

1. French research on HBV and HCV has been particularly productive in the past ten years, and France is now in the second place worldwide, in particular thanks to the financial and organizational support of the “Agence nationale de recherches sur le sida et les hépatites virales” (ANRS) French research teams have made significant contributions to the understanding of viral hepatitis and recent therapeutic advances.
2. Numerous scientific questions concerning the clinical, translational and basic aspects of viral hepatitis remain unanswered.
3. The efficacy of new treatments for HBV and HCV infections do not solve the problem of viral hepatitis on an international scale. This concerns 400 million individuals worldwide and is associated with an annual mortality of more than one million patients.
4. Efforts in French research in viral hepatitis should be increased.
5. The prevention of HBV and HCV infections has to be developed in France because: (a) vaccination against hepatitis B coverage is very incomplete and (b) testing for HBV and HCV is partial, while access to treatment is insufficient in certain populations: drug users, immigrants and other underprivileged individuals.
6. Research in viral hepatitis is part of a long-term effort to eradicate infection on an international scale. Even if this is a difficult goal, the combination of vaccination, treatment and prevention of transmission, makes this a viable goal.

Recommendations

1. **Gradually increase funding of research in viral hepatitis in the next five years.**
2. **Make sure that the ANRS**, in association with scientific and technological public groups “AFEF”, universities, hospitals, “InVS”, “ANGH”, “CREGG”, **remains the structure that funds, manages and coordinates viral hepatitis research.**
3. **Perform research that is independent from the pharmaceutical industry** to respond to major questions in the treatment of chronic viral hepatitis that have not been solved by phase III studies.

* Full text is only available in the French version.

4. **Create an observatory for antiviral resistance** used for HBV and HCV infections in association with “ANRS”, “AFEF” and “InVS”.
5. **Support research to understand the mechanisms of carcinogenesis** and the growth of liver tumors during chronic viral hepatitis and after they have been controlled or cured. Encourage the development of approaches to prevent the development of hepatocellular carcinoma.
6. **Support research to understand and control the mechanisms responsible for the worsening of viral hepatitis from excess alcohol consumption, the metabolic syndrome, insulin resistance and ageing.**
7. **Fund innovative therapeutic research for HBV eradication (*HBV cure*).**
8. **Fund immunological research to develop vaccine approaches against HCV.**
9. **Develop new therapeutic approaches to HDV infection from basic research.**
10. **Continue basic research in HCV and HBV.** These two viruses and the original models developed to study them are also excellent models for basic research on similar viruses.
11. **Perform macroeconomic analyses** to compare the efficacies of the different HCV and HBV testing and therapeutic strategies.
12. **Perform more research on unsolved public health issues** in France in relation the HBV and HCV, in particular in the field of prevention.
13. **Create ambitious research projects in the developing countries in the fields of public health and social sciences.**

Summary

Viral hepatitis B and C are major health issues in France, owing not only to their high prevalence (about 500,000 cases) and potential severity (about 4,000 deaths annually), but also to their impact on patients' mental and social well-being.

This report, organized into 22 themes examined collectively by specialists from various disciplines, makes a number of recommendations aimed at the public authorities, healthcare professionals, healthcare industry, patients and patient associations. It takes into account the prospects raised by new diagnostic and prognostic tools and more effective treatments. Indeed, hepatitis B virus infection can now be effectively controlled by treatment, and also prevented through vaccination. Likewise, it is now possible to permanently cure patients with hepatitis C. Further advances should come from the construction in 2014 of a coherent national health strategy in France.

In this respect, the authors of the report propose:

- to reinforce the prevention of hepatitis B and C, which is suboptimal in several respects,
- to organize specific healthcare pathways for patients with hepatitis B and those with hepatitis C,
- to ensure equitable treatment of patients with hepatitis B and C, based on concrete proposals designed to fight social inequities (of which hepatitis is a striking marker) and geographic disparities (across French regions, including overseas territories).

The authors call for efforts to enhance awareness of patients with hepatitis B and C, whose representatives do not receive the attention they deserve from healthcare professionals. The authors also encourage regional health agencies, which are in charge of adapting healthcare policy to local specificities, to lend their full weight to the fight against hepatitis B and C.

Hepatitis B and C prevention in France

Prevention of these two viral infections is mainly the responsibility of the primary care, as defined in the 21 July 2009 law on "Hospitals, Patients, Health and Territories". The authors of the report make two complementary recommendations:

- to encourage general practitioners to promote preventive measures among their patients, based on vaccination and screening for hepatitis B, and screening for hepatitis C; these activities should be specifically remunerated, based on achievement of public health goals (ROSP, *rémunérations sur objectifs de santé publique*),

- to integrate these preventive measures in all healthcare facilities dealing with people in difficult social situations, including the poor and vulnerable, immigrants, drug users, and prisoners.

Hepatitis B vaccination: universal prevention

This report represents a contribution to the goal of long-term hepatitis B virus eradication at the international level, a goal supported by the World Health Organization and one that warrants mass vaccination. The stakes (hundreds of deaths and dozens of liver grafts for cirrhosis or hepatocellular carcinoma avoided each year in France) are such that major efforts have to be made especially to the large number of adolescents who have been unvaccinated. A relevant specific remuneration associated with these achievements of public health target might be proposed to general practitioners.

Vaccinal coverage of healthcare professionals must also be reinforced, not only because of their particular risk of exposure, but also to serve as an example to patients.

Risk reduction: a requirement for drug users and their close contacts

Drug users are both the social group most heavily affected by viral hepatitis and the main source of these viruses, at least in the case of hepatitis C. In order to break this vicious cycle, risk-reduction measures for drug injections must be explained to public opinion, and more resources must be deployed in the field to meet drug users in the places they frequent. New, more effective measures are outlined in this report. These measures will benefit both drug users and their contacts.

Screening and advice

When offered to people at high risk of hepatitis B or C virus infection, screening may paradoxically reinforce risky behaviors if the test result is negative. The authors of this report therefore recommend that individuals concerned should systematically receive preventive advice at the same time as the results. This advice would be best delivered by general practitioners, who are the main prescribers of these tests.

As this screening targets high-risk groups, it also concerns migrants from areas of moderate or high endemicity, who are culturally highly diverse. Some may have negative perceptions of screening and poor knowledge of the disease, and may therefore be reluctant to be screened. Training of those involved in the screening process, as well as specific measures (use of an interpreter, for example) and the use of appropriate media are all essential to increase screening coverage, which is currently highly inadequate.

A coherent care pathway for each patient

The design of a coherent care pathway must take into account anticipated changes in the healthcare system.

- All care pathways must be based on explicit rules. The authors of the report propose to update the ALD6 protocols developed by the French national authority for health recommendations, and to define the needs of patients with hepatitis B or C in terms of welfare and medico-social assistance.
- Coherent, long-term care of patients with hepatitis B or C will require specific funding. The authors of the report recommend experimenting with a fixed sum for each of the HBV and HCV care pathways, based on the extended ALD6 protocols.

This experimental period should include a medico-economic comparison with the current system.

- Coherent care pathway could also benefit from improved coordination, based on the same extended ALD6 protocols and also involving a medico-economic comparison with the current system.

Screening in order to offer more patients an appropriate and effective care pathway

The large proportion of individuals who are unaware they are infected by hepatitis B or C virus calls for a special effort. In view of recent therapeutic advances, this lack of awareness results in a significant loss of opportunity for disease control or even cure. It also represents a continuing risk of viral transmission. The authors of the report recommend efforts focusing on:

- coherence: by systematically screening for HBV, HCV and HIV simultaneously,
- methods: expanding the use of rapid diagnostic tests proposed by persons who do not necessarily belong to a medical profession, targeting people in difficult social situations and those with poor access to standard care,
- targets: extending screening to pregnant women at their first medical visit and to men aged 18 to 60 years, at least once in their lifetime (in addition to situations at risk).

Pretreatment concertation

The report highlights the multiple factors involved in the management of patients with hepatitis B or C, including the indications, prescription and monitoring of antiviral treatment, the complications of liver disease and related disorders (which may involve different specialists), and social difficulties (requiring specific skills). The authors of the report recommend the creation of multidisciplinary teams in each region, modeled on the approach currently used in oncology, especially for the most complex cases. These meetings should involve the patient's physician, medical specialists (hepatologist, gastroenterologist, internist, or infectious diseases specialist), a physician trained in addiction, and a social worker, in order to develop a draft proposal for patient management. This initial step in the care pathway will ensure:

- a response to the viral infection, taking into account the degree of hepatic fibrosis, namely for treatment decision. This latter factor is crucial, and the authors of the report recommend finalizing health authority evaluation of non invasive tests in certain situations (including hepatitis B),
- a response to comorbidities: the report insists on the need to take account of the patient's psychological status, including misuse of alcohol and other drugs, and the possible presence of the metabolic syndrome (overweight, insulin resistance),
- systematic detection and management of social precariousness and property, without which even the best treatment plan will be ineffective.

This collaborative approach should help to optimize patient care in even the most complex of cases. The report further deals with questions posed by patients with chronic renal failure, patients coinfecting with HIV, women of childbearing age, and future mothers.

Getting patients involved: therapeutic patient education

As in other chronic diseases, patients with hepatitis B and C have an active role to play in their own care. Solidarity is growing, particularly in the form of patient associations. The care pathway for these patients should systematically include an invitation to participate in a therapeutic education program. Such programs must be accessible even to the most disadvantaged patients and in every region, including French overseas territories, and must take into account all the different facets of health. They must also ensure that patients are accompanied in the long term. The authors of the report recommend the development of therapeutic education programs for patients with chronic hepatitis B, based on experience gained in hepatitis C.

Specific remuneration based on public health goals would have the advantage of involving physicians in these programs, in turn helping to make them more accessible and holistic.

Treatment: implementation and accompaniment

Although very good outcomes are now possible for many patients, the report underlines the fact that hepatitis B and C are chronic diseases necessitating sustained long-term management.

The report highlights the most important advances in the cure of hepatitis C: shorter, more efficient and better tolerated treatments. It recommends that new therapeutic strategies be adopted for patients with a high risk of developing severe liver disease and for patients with extrahepatic manifestations regardless of the degree of fibrosis.

Long-term patient accompaniment must include monitoring of the treatment response and drug surveillance focusing on new drugs with limited follow-up data. The report highlights the difference between the management of patients with hepatitis C, who are tending to receive shorter treatments, and patients with hepatitis B, whose treatment remains very lengthy.

Monitoring and support are necessary for both patient categories, as the risks are not only related to the infections themselves. In particular, the report highlights the worrying discrepancy between the clear benefits of early detection of hepatocellular carcinoma in patients with cirrhosis and the very low screening rate. Screening for cirrhosis is also inadequate. Improvement of these two points would significantly improve patient outcomes.

In the same vein, the report restates the importance of long-term support for the many patients with comorbidities and social difficulties, above and beyond strictly medical interventions.

What does it mean to “cure” hepatitis B or C?

The report summarizes established criteria used to judge the effectiveness of treatments for viral hepatitis, again underlining the major difference between hepatitis C, in which the virus can be cleared, and hepatitis B, in which the virus can still only be controlled.

Nevertheless, the ever-present risk of hepatocellular carcinoma in patients with cirrhosis, even when the virus is cleared or controlled, means that the term “cure” is not entirely appropriate. An increase in the incidence of hepatocellular carcinomas in coming years should be anticipated, including (although less frequently) in patients in whom viral replication has been controlled. The frequency and significance of comorbidities,

especially the misuse of alcohol and illicit drugs and the presence of the metabolic syndrome or psychiatric disorders, are separate issues that can greatly undermine overall health, even when the virological situation appears satisfactory. Thus, the results of patient management must be judged on the basis of the patient's overall condition, and not just the outcome of viral hepatitis. This implies more extensive use of quality-of-life scales to assess the impact of patient management in its different dimensions.

Reducing health inequities related to hepatitis B and C

The report also examines population inequities, both social and territorial, with respect to hepatitis B and C. The implementation and impact of corrective measures such as those recommended in this report must be monitored through a dedicated information system.

In this respect, the *Institut national de veille sanitaire* (InVS) might develop a system based on multiple sources of information and medico-economic databases that cover prevention (vaccination against hepatitis B, screening for hepatitis B and C), care management, and even participation in therapeutic patient education programs. This would provide a regular nationwide picture of the situation, as well as regional analyses.

Similarly, it may be possible to use data from the universal healthcare assurance system (*couverture médicale universelle*, CMU) to analyze new responses to the prevention and management of hepatitis B and C among patients facing social difficulties.

Social inequities in health

The link identified by the 2004 InVS prevalence survey between viral hepatitis B and C and poverty-precariousness calls for strictly medical approaches to be combined with general welfare measures (accommodation, financial support, socialization, etc.) in order to ensure decent living conditions at least during treatment and monitoring.

These measures have implications far beyond hepatitis B and C virus infection.

Three groups require special attention.

- *Drug users*. This group is at a particularly high risk of infection. The frequent poverty and precariousness of these individuals contributes to their exclusion from normal care pathways. Entry to care for these patients requires easy access, compatibility with their lifestyles, and integration of the various care components (other addictions, mental health, etc.).
- *Migrants from countries with moderate or high endemicity*. The large number of persons in this category, as well as their level of risk and multiple obstacles of a cultural, social or technical nature, perpetuates social inequities with respect to hepatitis B and C in France. Reducing these inequalities represents a challenge for our healthcare system. Viral hepatitis reveals the often precarious health of immigrants and the difficulties they face in obtaining treatment. The authors call for responses at the level of the welfare system (improved complementary health assurance coverage), ethics (right to residence for medical reasons), social measures, access to care, and the fight against refusal of treatment, regardless of the reason.
- *Prisoners*. These individuals are particularly affected by hepatitis B and C because of their behaviors, social status and isolation. Their legal rights, in terms of access to screening and, if necessary, to treatment, are not respected. In addition, their release

from detention can interrupt the care they had been receiving. Fairness requires that these persons receive precisely the same health care as all other citizens.

Territorial inequities in health

Available data reveal significant regional inequities in the prevalence of hepatitis B and C, the number of diagnostic tests and the number of positive results, and also hospital care, particularly in specialized units. Since 2010, regional health agencies have been responsible for regional health policies and, thus, for reducing these inequities. However, they have only incomplete and sometimes outdated data on the regional situation with respect to hepatitis B and C. The authors of this report recommend that all available data, which are currently scattered around different organizations (prevention, treatment, medico-social), be regularly collated for each region. This would help the national authorities to monitor regions with unfavorable epidemiological situations (high prevalence, specific populations) or poorly organized access to care.

The case of French overseas territories is particularly revealing. Although the epidemiological situation appears more worrying than in mainland France, we have only a vague overall picture of the situation in these highly heterogeneous territories. The report calls for urgent epidemiological studies, as a prerequisite for formulating appropriate healthcare responses.

Conclusions

Several preconditions must be met if the recommendations contained in this report are to be successfully implemented.

Reinforced epidemiological surveillance

The fight against hepatitis B and C in France has benefitted from a high-quality information system, in which InVS played a noteworthy role, combining estimates of health indicators, treatment and prevention in both the general population and specific subgroups. This system must be maintained and expanded in order to monitor the implementation and impact of these measures, especially in high risk patient groups and regions. This will be facilitated by the creation of cohorts such as Hepather, and by access to medico-economic databases.

Likely costs and impact

The authors are fully aware of the economic burden of new treatments and improved access to care for patients with hepatitis B or C. In this difficult macroeconomic context, the choice of preventive and therapeutic strategies must be justified by medico-economic arguments, as recommended in this report.

Maintaining research activity

The recent history of hepatitis C illustrates how new treatments can transform the prognosis of a given disease. The authors of this report call for continued strong support for high-level basic and translational research and projects in public health and social sciences, as exemplified ANRS.

Management of persons with hepatitis B or hepatitis C virus infection



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