

# الإستراتيجية الوطنية لالتهاب الكبد الفيروسي B و C للمملكة الأردنية الهاشمية

## Jordanian National Consensus on Hepatitis B & C

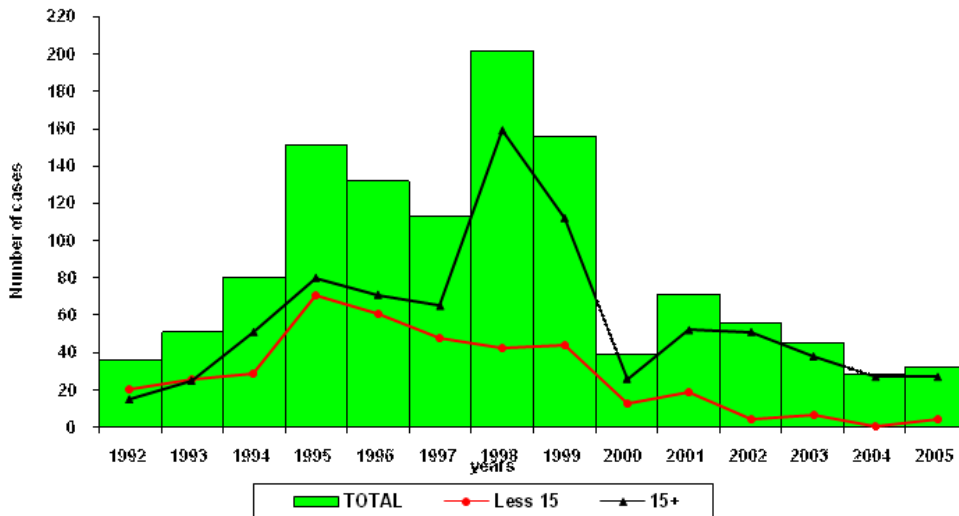
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## **1. Jordanian National Consensus on Hepatitis B & C** **(Epidemiology & Prevention)**

### **1. Epidemiology of hepatitis B & C:**

- Worldwide there is more than 2 billion HBV past/current infection.
- 350-400 million with chronic hepatitis B ( carriers or diseased)
- Jordan has endemicity of hepatitis B of 9%
- Statistical data of the Ministry of health shows that endemicity for those less than 14 years had decreased between the years 1992-2006, this is due to the application of the nation wide vaccination program anti Hepatitis B since 1995.



- WHO estimate that there are more than 170 million infected persons with Hepatitis C virus worldwide.
- In Jordan, there is no organized system for collecting data regarding infection with HCV.

### **Recommendations:**

- **Monitoring the efficacy of vaccination program.**
- **Applying the national strategy for detecting, prevention and treating viral hepatitis.**
- **Initiating workshops in hospitals regarding Bio safety and Universal precaution.**
- **Extending and monitoring sterilization/single use instrumentation countrywide.**
- **Epidemiological studies regarding incidence of HBV/HCV in Jordan.**
- **Initiating surveillance system for HCV in Jordan.**

## 2. Transmission of HBV/HCV:

- HBV/HCV are transmitted through blood contamination (IV injection, IV drug use, accidental needle stick, blood transfusion, Hemodialysis, percutaneous contact with blood or bloody fluids, sexual activity and mother-to-infant transmission through childbirth).
- Vertical transmission between the same family members is the main mod of transmission in Jordan.
- 15% of infected people have no identifiable means of transmission.
- Jordan had applied blood and blood products control since the 80<sup>th</sup> of the last century, with strict monitoring of blood donors (blood bank).
- Generally, all hospitals adhere to universal standard precautions and the use of safe techniques and single use instrumentations to avoid transmission of HBV/HCV.

### Recommendations:

- **Maintenance of blood bank policies regarding examination of blood donors, blood and blood products with the most sensitive tools and tests.**
- **Insurance of adherence to fundamental infection control principles, including safe injection practices and appropriate aseptic techniques, using single use instrumentations and health worker/ patient follow up (public and private hospitals).**
- **Examination of all pregnant women for HBV, and administrating immunoglobulin anti HBV and vaccination of newborn from infected mothers with HBV.**

## 3. Individuals at increased risk of acquiring HBV infection that should be routinely vaccinated :

- Newborns of carrier mothers.
- Children under 10 years in high (>2%) prevalence communities.
- Household contacts of acute and chronic hepatitis B carriers.
- Injection drug users.
- Hemodialysis patients (often-poor vaccine responders)
- Blood concentrate recipients.
- Persons with chronic liver disease/hepatitis C.
- Residents and staff of facilities for the intellectually disabled.
- Close contact of de-institutionalized people with intellectual disabilities.
- Long term prison inmates and staff of correctional facilities.
- Health cares workers.
- Travelers to endemic countries.

### Recommendations:

- **Vaccination anti HBV for such exposed workers, three doses (0-1-6 or 0-1-2), to obtain HBsAb titer > 10 IU/ml.**

#### **4. Individuals at risk of acquiring HCV infection:**

- Intravenous drug abusers.
- History of imprisonment.
- Hemodialysis patients.
- Healthcare workers exposed to needle-stick and sharp injuries.
- Recipients to blood transfusion prior to screening of donors.
- Current recipients of multiple blood transfusions.
- Hemophiliacs given clotting factors prior to screening and decontamination.

#### **Recommendations:**

- Screening the abovementioned categories for HCV, and treating those with hepatitis C.

#### **5. Health care workers and HBV/HCV:**

- **Recommendations for prevention health care workers to patient and patients to health care workers transmission:**
  - Screen HCW early in their career.
  - Immunize HCW against HBV.
  - Screen for HBV carriers early, they will have the opportunity to make career choice and seek treatment.
  - Adherence to fundamental infection control principles.
  - Safe injection practices.
  - Appropriate aseptic techniques.
  - Dialysis setting: universal precautions, screening of blood for transfusion, vaccination, dialysis using the same machine as a hepatitis positive patients.
  - All HCW should apply standard precautions to every patient
  - HBsAg-positive HCW (HBeAg-positive or HBeAg-negative) who wish to practice EPP must be referred to an expert panel (formed from gastroenterologist /hepatologist) to assist and treat his condition .
  - All HCW performing EPP should know their HBV and HCV status.
  - All HCW shown to be a source of viral hepatitis transmission to patients should not perform EPP.
  - All efforts must be made to respect the privacy of infected HCW.
- **Recommendations for HCW exposed to needle stick injury (Hepatitis B):**
  - All HCW should be vaccinated against HBV and checked for HBV Ab.
  - For HBV positive patient and not vaccinated HCW: administration of HBV Immunoglobulin within 72 hours and begin vaccination program.
  - For HBV positive patient and vaccinated HCW with HBsAb > 10: nothing.
  - For HBV positive patient and HCW with incomplete vaccination: administration of HBV immunoglobulin within 72 hours and begin vaccination.
  - For not known patient and HCW not vaccinated: administration of HBV immunoglobulin and begin vaccination program.

- **Recommendations for HCW exposed to needle stick injury (Hepatitis C):**
- For HCV known patient and HCW not infected : follow up the HCW at 2 weeks, one month and three months with HCV Ab and HCV RNA by PCR for , if proved to be infected treat as for acute hepatitis C
- For unknown patient for HCV and HCW not infected: same as above.

**6. Tests used for diagnosis of HBV/HCV:**

- *Serological tests for HBV* for HBsAg and markers are done by Enzyme-linked Immunosorbent Assay (ELISA).
- *Molecular tests for HBV* (quantitative and qualitative) are done by HBV DNA by Poly Chain Reaction (PCR), Real time assay may detect copies less than 200.
- *Serological tests for HCVAb* are done by ELISA.
- *Molecular tests for HCV RNA* (quantitative) is done by PCR, and it is indicted by WHO to report in terms of international units (IU) with the most sensitive method called *transcription mediated amplification* (TMA), this technique is sensitive to approximately 5 IU/ml – Real time PCR.
- Genotyping of HCV is important in terms of duration of treatment for HCV infected patients.

- **Recommendations for HBV:**

1. **Serology by ELISA:** HBsAg, HBsAb, HBeAg, HBeAb and HBcAb.
  2. **Molecular by PCR:** HBV DNA Qualitative & Quantitative.
- HBsAg by ELISA should be available at all hospital & public Health laboratories.
  - HBV Markers (HBsAb HBeAg, HBeAb and HBcAb) should be available at all central hospital laboratories and Central Public Health Laboratory (CPHL)
    - HBV by PCR: Should be available at all teaching hospital laboratories & CPHL

- **Recommendations for HCV:**

1. **Serology by ELISA:** Screening: HCV-Ab  
Confirmatory: by Western blot technique
  2. **Molecular by PCR:** HCV RNA Quantitative and genotyping.
- HCV Ab: by ELISA should be available at all central hospital laboratories and CPHL
  - HCV Quantitative by PCR: Should by available at all teaching hospital laboratories and CPHL.
  - HCV Genotyping: should by available at CPHL.

**7. Epidemiological studies regarding close contact of recently diagnosed patients infected with HBV/HCV:**

- **Recommendations:**
- **Epidemiological study for the mode of infection and transmission.**
- **Vaccination (anti HBV) for close contact of family members for those infected with HBV.**

**8. Transferring infected individuals from blood bank:**

**Recommendations:**

- **Providing monthly follow up chart regarding HBV and HCV discoveries in blood bank to the infectious diseases center in the MOH.**
- **Transferring all discovered cases of HBV/HCV to the gastroenterologist/hepatologist for complete diagnosis and eventual treatment.**

**9. Follow up of the new cases from the General Medicine physicians and transferring them to the specialist:**

**Recommendations:**

- **Conduct an epidemiological study for the detected cases.**
- **Verifying close contacts and providing them with vaccination.**
- **Transferring the infected patient and positive contact to the specialist (gastroenterologist/hepatologist) for further diagnosis and treatment.**

**10. Notifying the Communicable diseases Directorate in the Ministry Of Health of the new detected cases diagnosed as acute or chronic hepatitis B or C :**

- **The committee observed that newly discovered cases of HBV/HCV infection are not registered and informed to the health authorities in the infectious center of the MOH, this include acute and chronic cases of HCV/HBV infection.**

**Recommendations:**

- **Implementation of the public health law by all physicians who detect such cases (acute, chronic or carrier cases), and notify the Communicable Diseases Directorate in the MOH.**
- **Physicians involved in this information are from all sectors, public sector including MOH hospitals, RMS+++, universities, and private sector including private hospitals, private clinics and private universities.**
- **Recommendation of establishing a national data base including all diagnosed patients with HCV/HBV infection (acute or chronic cases) in Jordan, including place of diagnosis and treatment, to avoid overlapping data, especially treatment overlap/redundancy (multiple centers treatment for the same patient).**

## 2. Treatment of chronic hepatitis B

### I. Natural History of HBV Infection

Phase	ALT	Liver histology	HBV DNA	HBeAg	HBsAg
Immune tolerance phase	Normal or minimally elevated	Minimal activity; absent or scant fibrosis	High levels: serum HBV DNA >20,000 IU/mL	Positive; anti-HBe–negative	Positive >6 mo
Immune clearance phase (HBeAg-positive CHB)	Elevated, usually persistently or with intermittent elevations	Active; liver biopsy showing chronic hepatitis (necroinflammatory score $\geq 4$ ) <sup>a</sup>	High levels: serum HBV DNA >20,000 IU/mL	Positive; anti-HBe–negative	Positive >6 mo
Inactive HBsAg carrier state	Persistently normal	Inactive; liver biopsy showing variable, usually minimal fibrosis (necroinflammatory score <4) <sup>a</sup>	Low or undetectable levels: serum HBV DNA negative or <2000 IU/mL	Negative; anti-HBe–positive	Positive >6 mo
Resolution	Normal	Inactive; scant fibrosis	No detectable serum HBV DNA (low levels might be detectable in the liver)	Negative; anti-HBe–positive	Negative
Reactivation phase (HBeAg-negative CHB <sup>b</sup> )	Elevated, often fluctuating levels	Active; liver biopsy showing variable amounts of fibrosis (necroinflammatory score $\geq 4$ ) <sup>a</sup>	Moderate, often fluctuating levels: serum HBV DNA >2000 IU/mL	Negative; anti-HBe–positive	Positive >6 mo

Emmett B. et al. A Treatment Algorithm for the Management of Chronic Hepatitis B Virus Infection in the United States: 2008 Update

### II. Evaluation of Patients with HBV Infection

Baseline evaluation of patients with HBV infection should include:

1. Complete blood count.
2. Prothrombin time.
3. Liver enzymes and liver function tests.
4. HBV DNA quantification.
5. HBeAg, antibody to HBeAg (anti-HBe).
6. Other types of hepatitis (A, C, and D).
7. HIV antibody testing in at-risk subjects.
8. Alpha-fetoprotein.
9. Ultrasound.
10. Selective liver biopsy.

### III. Initial Treatment Criteria

1. Elevated ALT levels. ALT should be elevated before initiation of therapy unless liver biopsy indicates the presence of significant disease. Treatment is recommended only for patients in the immune-clearance and reactivation phases with chronic hepatitis B.
2. High serum HBV DNA levels (> 2000 IU/ml [or approximately 10<sup>4</sup> copies/ml]).
3. Significant Necro-inflammation and fibrosis on liver biopsy.

#### IV. Goals of Therapy and endpoints

1. Suppression of serum HBV DNA.
2. Normalization of ALT levels.
3. Histologic improvements.
4. HBeAg seroconversion in HBeAg-positive patients.
5. HBsAg seroconversion.

#### V. Definitions of response for Interferon alpha and Nucleoside/Nucleotide analogues therapy

- **Primary non-response** is defined as less than 1 log<sub>10</sub> IU/ml decrease in HBVDNA level from baseline at 3 months of therapy.
- **Virological response** is defined as an HBVDNA concentration of less than 2000 IU/ml at 24 weeks of Interferon therapy and 48 weeks for NUCs therapy.
- **Serological response** is defined by HBe seroconversion in patients with HBeAg-positive CHB..
- **Partial virological response** is defined as a decrease in HBVDNA of more than 1 log<sub>10</sub> IU/ml but detectable HBVDNA by real-time PCR assay).
- **Virological breakthrough** is defined as a confirmed increase in HBVDNA level of more than 1 log<sub>10</sub> IU/ml compared to the nadir (lowest value) HBVDNA level on therapy.
- **HBV resistance to NUCs** is characterized by selection of HBV variants with amino acid substitutions that confer reduced susceptibility to the administered NUC(s).

#### VI. Treatment Algorithm

Drug Type	
<b>Nucleoside analogues</b>	- Lamivudine - Entecavir - Telbivudine - Emtricitabine
<b>Nucleotide analogues</b>	- Adefovir - Tenofovir
<b>Cytokines</b>	- Interferon alfa 2 - Pegylated Interferon alfa 2 a

### A. Treatment of finite duration with pegylated interferon alpha or NUCs:

• **Finite-duration treatment with pegylated interferon alpha:** a 48-week course of pegylated interferon alpha is recommended for HBeAg-positive and negative patients.

**Monitoring:** In patients treated with pegylated interferon alpha, full blood counts and serum ALT levels should be monitored monthly. Serum HBVDNA level should be assessed at weeks 12 and 24 to verify primary response.

- In HBeAg-positive patients, HBeAg and anti-HBe antibodies should be checked at weeks 12, 24, 48, and 24 weeks post-treatment.

HBe seroconversion together with ALT normalization and serum HBVDNA below 2000 IU/ml (approximately 10,000 copies/ml), is the desired outcome.

Undetectable serum HBVDNA by real-time PCR during follow-up is the optimal outcome.

- In HBeAg-negative patients, HBV DNA level should be assessed at week 12, 24, 48, and 24 weeks post treatment. Undetectable HBVDNA in real-time PCR is the ideal desired off-treatment sustained response with a high probability of HBsAg loss in the longer term. HBsAg should be checked at 6-month intervals if HBVDNA is undetectable. HBsAg should be checked at 6-month intervals. In case of a primary non-response, i.e. failure to achieve a 1-log<sub>10</sub> reduction from baseline at 12 weeks, interferon treatment should be stopped and replaced by a NUC.

• **Finite-duration treatment with NUCs** for HBeAg-positive patients who develop HBe seroconversion on treatment. Once HBe seroconversion occurs on NUC, treatment should be prolonged for an additional 6 to (preferentially) 12 months; a durable response (persistence of anti- HBe antibodies off-treatment).

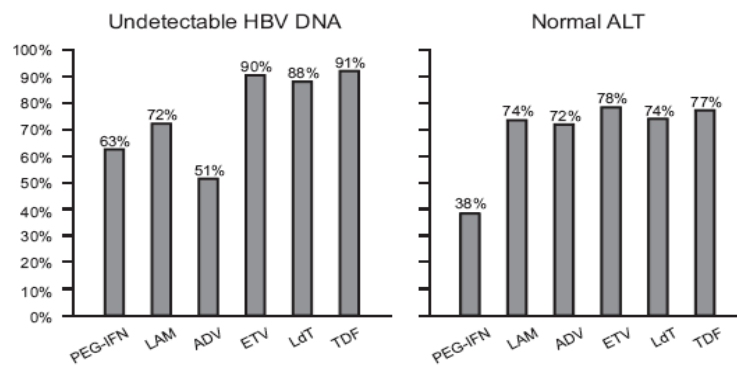
#### Monitoring:

HBVDNA should be measured every 12 weeks. NUC therapy can be stopped 24 to 48 weeks after HBe seroconversion. HBsAg should be checked at 6-month intervals after HBe seroconversion.

### B. Long-term treatment with NUCs:

- This strategy is necessary for patients who cannot achieve a sustained virological response off-treatment and require extended therapy (1. HBeAg-positive patients who do not develop HBe seroconversion. 2. HBeAg-negative patients. 3. patients with cirrhosis irrespective of HBeAg status or HBe seroconversion on treatment).

- Comparisons of the drugs used in treating HBV infection, regarding their potency in reducing ALT and suppressing HBV DNA (at one year of treatment).



- The panel advises the use of Lamivudine as initial therapy due to its potency and least cost amongst available therapies thus allowing the treatment of greatest number of patients in the allocated budget.

**Monitoring:**

HBVDNA levels should be monitored at week 12 to ascertain virological response and then every 12 to 24 weeks. In HBeAg-positive patients, HBeAg and subsequently anti-HBe antibodies once HBeAg is negative should be measured at intervals of 6 to 12 months. Appropriate dosing adjustments are recommended for patients with reduced creatinine clearance.

**VII. Management of treatment failure**

- 1. Primary non-response.** Check for compliance, identification of possible HBV resistance mutations and change to a more potent drug that is active against the resistant HBV variant.
- 2. Partial virological response.** Check for compliance. Two strategies can be used: change to a more potent drug (entecavir or tenofovir) or addition of a more potent drug that does not share cross-resistance (add tenofovir to lamivudine or telbivudine, or add entecavir to adefovir).
- 3. Virological breakthrough.** Resistance should be identified early before clinical breakthrough (increased ALT) by means of HBVDNA monitoring, and initiating rescue therapy by adding-on a second drug without cross-resistance.
  - **Lamivudine resistance:** add adefovir or tenofovir.
  - **Entecavir resistance:** Add tenofovir.

**VIII. Treatment of patients with compensated cirrhosis:**

- Treat these patients if HBV BNA level > 2000 IU with potent nucleosides/nucleotides
- Long-term therapy is indicated, with strict monitoring of HBV DNA flares.

**IX. Treatment of decompensated cirrhosis:**

- Treatment is indicated even if HBVDNA level is low in order to prevent recurrent reactivation.
- Potent NUCs with good resistance profiles (entecavir or tenofovir) should be used or combination of lamivudine and adefovir.

**X. Prevention of recurrent hepatitis B after liver transplantation:**

- Pre-transplant therapy with a potent NUC with a high barrier to resistance is recommended for all HBsAg-positive patients undergoing liver transplantation for HBV-related end-stage liver disease or HCC, to achieve the lowest possible level of HBVDNA before transplantation.
- Lamivudine and/or Adefovir have for post-transplant in combination with hepatitis B immunoglobulin (HBIG). This regimen has reduced the risk of graft infection to less than 10%.

**XI. HIV co-infected patients:**

- The indications for therapy are the same as in HIV-negative patients, based on HBVDNA levels, serum ALT levels and histological lesions.
- Most coinfecting patients have to be simultaneously treated for both HIV and HBV (Tenofovir and emtricitabine (FTC) together), plus a third agent active against HIV, are indicated.
- Lamivudine, entecavir and tenofovir have activity against both HIV and HBV and are contraindicated as single agents for hepatitis B in coinfecting patients.

**XII. HDV co-infected patients:**

- Active co-infection with HDV is confirmed by the presence of detectable HDVRNA, immuno-histochemical staining for HDV antigen, or IgM anti-HDV.
- Interferon alpha (conventional or pegylated) is the only drug effective on HDV replication. The efficacy of interferon alpha therapy should be assessed at 24 weeks by measuring HDVRNA levels.
- Nucleotides/nucleosides are not indicated.

**XIII. HCV co-infected patients:**

- HBVDNA level is often low or is undetectable and HCV is responsible for the activity of chronic hepatitis in most patients.
- Thus, patients should receive pegylated interferon alpha with ribavirin as for HCV.
- There is a potential risk of HBV reactivation during or after clearance of HCV that must then be treated with NUCs.

**XIV. Acute severe hepatitis:**

- Some patients with fulminant hepatitis or severe protracted subacute hepatic necrosis may benefit from NUC treatment ( Lamivudine)
- Continuation of antiviral therapy for at least 3 months after seroconversion to anti-HBs or at least 6 months after HBe seroconversion without HBsAg loss is recommended.

**XV. Children:**

- Chronic hepatitis B causes benign disease in most children.
- Only conventional interferon alpha, lamivudine and Adefovir have been evaluated for safety and efficacy comparable to adults.

**XVI. Pregnant women:**

- Treat after delivery.

**XVII. Pre-emptive therapy before immunosuppressive therapy or chemotherapy:**

- All candidates for chemotherapy and immunosuppressive therapy should be screened for HBsAg and anti-HBc antibodies prior to initiation of treatment.
- Vaccination against HBV in seronegative patients is highly recommended.
- HBsAg-positive candidates for chemo- and immunosuppressive therapy should be tested for HBVDNA levels and receive pre-emptive NUC administration during therapy (regardless of HBVDNA levels) and for 12 months after cessation of therapy.

- HBsAg-negative patients with positive anti-HBc antibodies and undetectable HBVDNA in the serum who receive chemotherapy and/or immunosuppression should be followed carefully by means of ALT and HBVDNA testing and treated with NUC therapy upon confirmation of HBV reactivation before ALT elevation.
- NUC prophylaxis is also recommended in patients receiving bone marrow transplantation from a non-immune donor.
- Recipients of anti-HBc-positive liver grafts should receive NUC prophylaxis combined with HBIg.

**XVIII. Dialysis and renal transplant patients:**

- Most data in this group are available for lamivudine; the dose of lamivudine should be adapted for renal failure.
- There are reports of worsening of renal graft function in patients treated with adefovir.
- Entecavir may be the optimal choice of drug for patients undergoing renal transplantation.
- Tenofovir should be used with caution in renal impairment.

### 3. Hepatitis C treatment

#### **I. Evaluation/Diagnosis**

- Testing for hepatitis C virus (HCV Ab)
- Testing for HCV RNA by PCR (Quantity)
- HCV genotyping.
- Liver biopsy (should be in selective cases)
- Liver ultrasonography (considered but not recommended)
- Ages less than 65 and more than 12.

#### **II. Management/Treatment**

1. Combination of subcutaneous injection of pegylated interferon (PEG-IFN) alfa weekly and oral Ribavirin daily.
2. 48-week treatment for persons with genotype-1 and 4 HCV infection and 24-week treatment for persons with genotype-2 or 3 HCV infection
3. Monitoring HCV RNA levels at 3,6,12 (response to antiviral therapy). Also HC RNA level at 6 months after completion of treatment.
4. Management of adverse effects of antiviral therapy (acetaminophen, nonsteroidal anti-inflammatory drugs, sleep-promoting agents, antidepressants; in cases of severe neutropenia - granulocyte colony stimulating factor)

#### **III. Predictors of Response to PEG-IFN Plus Ribavirin Therapy in Previously Untreated, Immunocompetent Patients With Compensated Chronic Hepatitis C**

- Non-genotype 1
- Low HCV RNA levels
- Absence of cirrhosis/bridging fibrosis
- Duration of therapy (for genotype 1)
- Age 40 years or younger
- Lighter body weight
- Nonblack ethnicity
- Adherence
- Absence of steatohepatitis

#### **IV. Contraindications to therapy**

- Decompensated cirrhosis
- Pregnancy, and 6 months after birth
- Uncontrolled depression or severe mental illness
- Active substance abuse in the absence of concurrent participation in a drug treatment program.

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- Advanced cardiac or pulmonary disease, severe cytopenias, poorly controlled diabetes, retinopathy, seizure disorders, immunosuppressive treatment, autoimmune diseases, or other inadequately controlled co morbid conditions (active chronic infections, malignancies and post kidney transplant).
- Breast feeding.
- Children less than 3 years.

### **V. Definitions of Response to Antiviral Therapy**

- Baseline and 12-week monitoring of HCV RNA levels should be performed with the same quantitative amplification assay.
- **Early viral response (EVR)** is defined as loss of HCV RNA at week 12 (complete EVR), or decreasing the viral load at least with 2 log (Incomplete EVR).
- **End of treatment (EOT)** are defined as patients with no viral load detection at week 24 (6 months) for genotype 2 and 3 and 48 (one year) for genotype 1 and 4.
- **Sustained viral response (SVR)** is defined as patients with no viral load detection at week 72 (one and half year).
- **Delayed responders:** are those patients with incomplete EVR at 12 weeks, but are negative HCV RNA at 24 weeks
- **None responders** is defined as patients that failed to obtain EVR or failed to clear the virus at week 24 (6 months).
- **Relapse:** is defined as reemergence of HCV RNA after completion of therapy and when HCV RNA was negative during therapy.
- **Rapid viral response (RVR)** is defined as loss of HCV RNA at 4 weeks of initiation of treatment.

### **VI. Determinants of management:**

- **Complete EVR:** continue treatment up to 48 weeks for genotype 1 and 4, or 24 weeks for genotype 2 and 3.
- **Incomplete EVR:** continue therapy for up to 6 months and check HCV RNA, if still positive, stop treatment and consider the patient as non-responder. If HCV RNA is negative at 6 months, consider continuing the treatment for 72 weeks.

### **VII. Monitoring and managing side effects due to Antiviral Therapy**

- Frequent hematologic monitoring is necessary to identify marked anemia, neutropenia, and thrombocytopenia, every two weeks for two months, then monthly; monitoring of thyroid-stimulating hormone level is indicated to identify hypothyroidism or hyperthyroidism, before treatment and every 3 months).
- Flu-like side effects of IFN can be managed with acetaminophen or nonsteroidal anti-inflammatory drugs.
- Sleep-promoting agents can be used for insomnia.
- Antidepressants can be used for depression.
- For management of neutropenia, addition of granulocyte colony-stimulating factor is considered in individual cases of severe neutropenia.
- If anemia occurs, options include ribavirin dose reduction or the addition of erythropoietin.

- Contraceptive must be used if either male or female (or both) partners are infected by HCV and receiving combination therapy during the treatment period and for 6 months after the end of therapy.

## VIII. Special groups

### 1. Decompensated Cirrhosis.

- In patients with decompensated cirrhosis, antiviral therapy is not recommended; instead, referral for liver transplantation is indicated.

### 2. Previous relapsers and nonresponders.

Patients in whom HCV RNA is undetectable during and at the end of therapy but reappears again after completion of therapy (relapsers) are likely to respond and experience a relapse again with a subsequent course of the same therapy. **So the panel recommend not to re-treat with the same therapy.** Waiting for new therapy to appear in the market.

### 3. Acute hepatitis C.

The risk of HCV infection after an accidental needle stick is sufficiently low to delay antiviral therapy until HCV infection is documented virologically and biochemically. Case series have focused primarily on IFN or PEG-IFN monotherapy administered for 12 to 24 weeks. Combination therapy was tried successfully also. Based on available data, **the panel recommends to initiate treatment no later than 2 to 3 months after presentation with acute hepatitis and would extend therapy for at least 24 weeks.**

### 4. Injection drug or alcohol use

- Therapy is recommended for recovered drug users, including those on methadone maintenance.
- Abstinence should be recommended before and during antiviral treatment in alcoholic persons, and treatment of alcohol abuse should be linked with efforts to treat hepatitis C in alcoholic patients.

### 5. Hematologic disorders.

in thalassemic patients, primary therapy should be focused on reducing iron overload. Chronic hepatitis C may be treated with PEG-IFN plus ribavirin, at reduced doses (mainly for thalassemia minor and intermedia)  
In patients with a genetic predisposition to anemia, ribavirin-associated hemolysis would be predicted to be more severe, transfusion requirements may increase during antiviral therapy.  
Treatment guidelines for hemophiliac patients are the same as those in the nonhemophiliac population.

**6. Children.** For children, the general principles of management are the same as those for adults, except that treatment is not recommended for children younger than 3 years. The panel recommend to treat children over the age of 12.

**7. End-stage renal disease.**

- Currently, ribavirin is contraindicated in patients with renal failure.
- At present, the role of antiviral therapy in patients with end-stage renal disease remains undefined.
- For individual patients, the potential benefit of therapy should be weighed against the higher risk of toxicity, and treatment should be undertaken in centers with experienced clinicians.
- For PEG-IFN alfa-2a, a dose reduction from 180 to 135 micrograms is recommended by the manufacturer for patients with renal failure;
- for PEG-IFN alfa-2b, the manufacturer makes no specific recommendation about dose reduction for patients with renal failure, but 50% dose reductions are recommended for other clinical indications (e.g., hematologic).
- Also regular interferon can be used as alternative to pegylated interferon, three times weekly.
- Patients with end-stage renal disease and chronic hepatitis C who are candidates for kidney transplantation should be evaluated for advanced hepatic fibrosis, which is associated with reduced graft and patient survival.

**8. Extrahepatic disease.**

- In patients with cutaneous vasculitis and glomerulonephritis resulting from HCV-associated mixed essential cryoglobulinemia, indefinite maintenance therapy may be required.
- Hepatitis C associated B-cell lymphoma may respond to antiviral therapy.

**9. Human immunodeficiency virus and HCV coinfection.**

- All patients with human immunodeficiency virus (HIV) infection should be screened for HCV infection.
- Ideally, the HIV infection should be well controlled with antiretroviral therapy before treatment of the HCV infection is initiated.
- Optimal therapy consists of PEG-IFN alfa at the routine weekly dose plus ribavirin at a daily dose of 600–800 mg (higher if tolerated) for 48 weeks, regardless of genotype.
- Because of potential drug-drug interactions in patients on HIV treatment regimens that include didanosine, HIV regimens should be altered in those starting combination therapy for HCV infection. If didanosine is critical to the HIV regimen, ribavirin should be avoided.

**10. Liver transplantation.**

- Results of antiviral therapy for hepatitis C after liver transplantation have been disappointing.
- Whether begun prophylactically immediately after transplantation to prevent reinfection or initiated to treat established posttransplantation hepatitis C, antiviral therapy, even with combination PEG-IFN alfa and ribavirin, may suppress HCV replication but results in an SVR in <20% of treated patients.
- Moreover, IFN, PEG-IFN, and ribavirin have not been well tolerated after liver transplantation, necessitating dose reductions for adverse events such as anemia and serious infections.
- Therefore, after liver transplantation, the risks and benefits of antiviral therapy should be weighed carefully for each patient, and treatment should be initiated with caution by transplantation teams experienced in the treatment of hepatitis C.
- Because immunosuppression increases HCV replication, which is associated with increased HCV-associated liver injury and may contribute to disease progression, doses of immunosuppressive drugs should be kept to a minimum in patients who undergo liver transplantation for chronic hepatitis C.

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