MINISTRY OF HEALTH **-------**	**THE SOCIALIST REPUBLIC OF VIETNAM** **Independence – Freedom – Happiness** **----------**
Ref.: 4817/QĐ-BYT	*Ha Noi, November 28th 2013*

DECISION

Issuance of technical guideline on "HCV Diagnosis and Treatment"

Minister of Ministry of Health

Pursuant to the Law on Medical Examination and Treatment in 2009;

Pursuant to Decree no. 63/2012/NĐ-CP dated 31/8/2012 by the Government of Vietnam defining the functions, tasks, powers and organizational structure of the Ministry of Health;

Responding to the Request of the Director General of Vietnam Administration for Medical Services

Decides:

Article 1. Promulgating with this Decision is the technical guideline on "Instruction of Diagnosis and Treatment of Hepatitis C Virus".

Article 2. The technical guideline on "Instruction of Diagnosis and Treatment of Hepatitis C Virus" will be applied in state-owned and private health examination and treatment facilities.

Article 3. This Decision becomes effective since the date of signing.

Article 4. The Office Manager of the Ministry, Chief of Inspector of the Ministry, General Director of the Vietnam Administration for Medical Services, General Directors and Directors of the relevant Departments under the Ministry of Health, Directors of the Hospitals, Institutes having patient beds under the control of Ministry of Health, Directors of Department of Health in provinces and cities, Directors in charge of Health of the ministries and Directors of any related bodies are responsible to executing this Decision./.

Delivered to: - As defined in Article 4; - Minister of MOH (reporting); - Vice Ministers of MOH; - Vietnam Social Insurance (for coordination); - MOH Website; - Website of VAMS; - Archive: VT, KCB, PC.	**For MINISTER** **VICE MINISTER** **Nguyễn Thị Xuyên**

GUIDELINE ON HCV DIAGNOSIS AND TREATMENT

(Promulgated by Decision no. 4817/QĐ-BYT dated 28/11/2013 by Minister of Ministry of Health)

I. General

Hepatitis C infection is a disease that is caused by Hepatitis C virus, a sphere-shape virus that belongs to Flaviviridae family. According to the World of Health Organization (WHO), presently, about 170 million people are infected with HCV globally, counting for 3% of total world population. In Vietnam, number of patients infected with HCV infection is to increasing. HCV is blood-born and can cause acute or chronic infection, resulting in cirrhosis and liver cancer.

II. HCV diagnosis

1. Symptom

a) Clinical symptom:

- Most of cases have no clinical symptom (asymptomatic). Th symptoms (if exist) are usually not specific and easy to confuse with other diseases such as: fatigue, malaise, dyspepsia, a bit pain in lower part of right rib side, digestive disorder, and myalgia;

- May appear with icterus but lightly, secretive, periodical, high-fever and losing weight;

- May have symptoms from organs outside of the liver in muscle-bone-joint, skin and mucosa, endocrine system, kidney, cardiovascular.

b) Subclinical symptom:

- It is necessary to test for screening in high-risk people: historically use dugs, operation, blood transmission, unprotected sex, hemodialysis, and newborn from an infected mother during the delivery process.

- Anti-HCV positive

- HCV RNA positive

- Hepatitis C genotyping: it is necessary to test for genotyping that helps prognosis the treatment response and estimate the duration of treatment.

2. Confirmative diagnosis

a) Diagnosis confirming acute HCV:

- HCV RNA positive, anti-HCV may be negative or positive: HCV RNA usually becomes positive 2 weeks after the exposure meanwhile anti - HCV appears after 8-12 weeks.

- AST, ALT is normal or increases

- Duration of infection < 6 months: Patient is monitored if serum is transferring from anti - HCV negative to positive, if clinical symptom appears or not.

b) Confirmative diagnosis for chronic HCV:

- Anti HCV positive, HCV RNA positive;

- Duration of infection > 6 months, or fibrosis phenomenon (identified by APRI indicator or liver biopsy shows imagine of chronic hepatitis and meaningful tendinitis stenosans or FibroScan, Fibrotest shows fibrosis > F2) other than any other origin (Appendix 1)

c) HVC diagnosis in children:

- Testing anti-HCV if children are 18 months and older.

- Identifying HCV RNA 1-2 months after the delivery in order to have an earlier diagnosis.

3. Differential diagnosis:

There are liver diseases due to other causes that can be confused with hepatitis C chronic infection.

III. HCV treatment

1. Acute HCV treatment: Spontaneous viral clearance occurs but many acutely infected persons later develop chronic infection.

- Supportive treatment: Patient should take rest and take symptom-release medications as appropriate

- Specific treatment: Treatment can reduce the risk that acute infection becomes chronic infection. After 12 weeks of the infection, if HCV RNA is still positive, the specific treatment by IFN or PegINF can be indicated, either combined with ribavirin or not. Duration of treatment should be at least 12 weeks, and last up to 24 weeks, subject to the level of virological response.

2. Chronic HCV treatment

a) Objective of treatment

- Prevent the progress of the disease and reduce risk to develop to interstitial hepatitis and liver cancer.

- Improving the quality of life and prolong the life.

- Virologically, the objective is to achieve the sustainable virological response (HCV RNA negative after 24 weeks of treatment suspended).

b) Preparation for treatment

- The patient should take pre-treatment tests (Appendix 2)

- HCV genotype testing

- Counseling with the patient about: treatment regimen, effectiveness, side-effects and treatment response.

c) Treatment administration: if the patient has all conditions below:

- HCV RNA (+);

- Hepatitis compensated cirrhosis: serum bilirubin < 1.5mg/dL, INR < 1.5, Albumin > 34g/L, no hepatic encephalopathy, no Ascite;

- biochemical and haematological tests give acceptable values: Hb > 13g in male, > 12g in female; Neutrophils > 1500/mm^3; platelet > 75G/L; creatinine serum < 1.5mg/dL;

- No contraindication.

d) Contraindication

- Sompensated cirrhosis;

- Serious acedia;

- Organ transplantation;

- Patient with autoimmune Hepatitis – AIH or other autoimmune diseases;

- Uncontrolled thyroid disease;

- Pregnant;

- Other serious medical pathological diseases: serious hypertension, heart failure, coronary artery disease, uncontrolled diabetes, chronic obstructive pulmonary disease;

- Previously alleged with drugs for treatment.

đ) Drugs for treatment

Table 1. Drugs for HCV treatment

Drug		Dose	Side effects
Interferon (IFN) percantaneous	IFN α-2a IFN α-2b Pegylated IFN α-2a Pegylated IFN α-2b	3 MU x 3 times/week 3 MU x 3 times/week 180 mcg x 1 time/week 1.5 mcg/kg x 1 time/week	False-flu syndrome (high fever, headache, muscle aches, fatigue), anemia, thrombocytopenia, decreased leukocyte, acedia, behavior changed, vomit, diarrhoea, thyroid malfunction,...
Ribavirin	Ribavirin	+ Genotypes 1,4,6: 15mg/kg/day ($\leq$ 75kg: 1000mg/day, > 75kg: 1200mg/day). + Genotypes 2, 3: 800mg/day.	Anemia, inflammatory arthropathy, skin allergy, hacking cough, pain in chest, acedia, diarrhoea, difficult to digest.
Protease	Boceprevir	800 mg x 3 time/day	Anemia, decreased

inhibitors	Telaprevir	750 mg x 3 time/day	leukocyte, rash, digest disorder, disorder of sense of taste, nausea, headache

e) Treatment

- Regimen:

+ Standard regimen: Interferon (IFN) + Ribavirin

+ Combining the standard regimen with boceprevir or telaprevir if the HCV type 1 infected patient has failed in treatment with the standard regimen previously.

- Duration of treatment: depends on the type and the virological response.

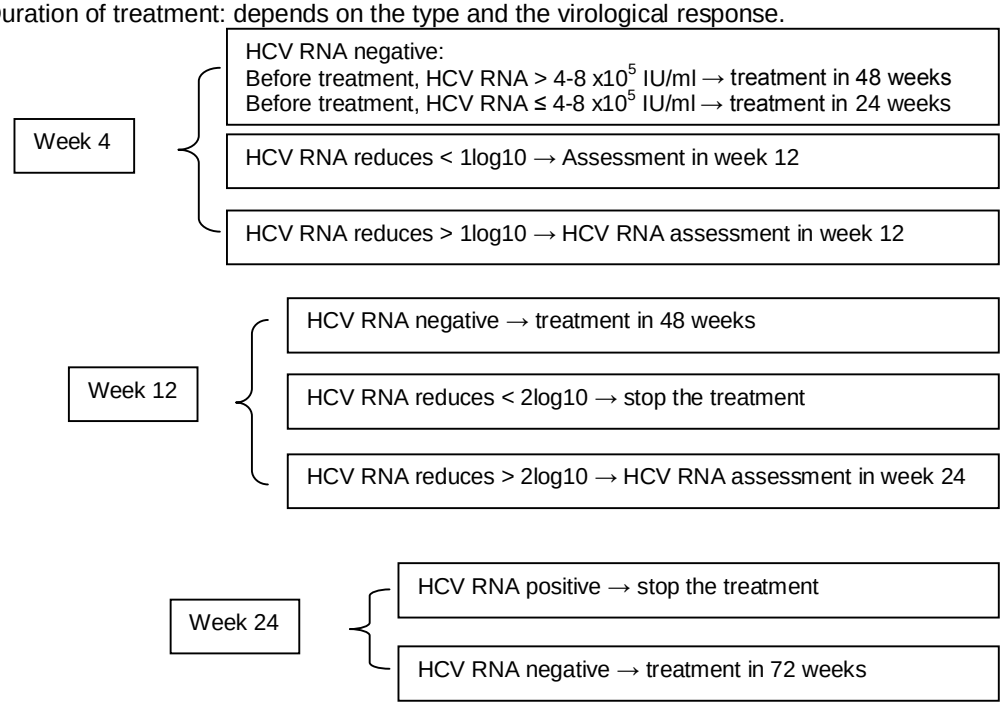

Diagram 1: Treatment regimen in virological response for HCV type 1, 4, 6 infected people

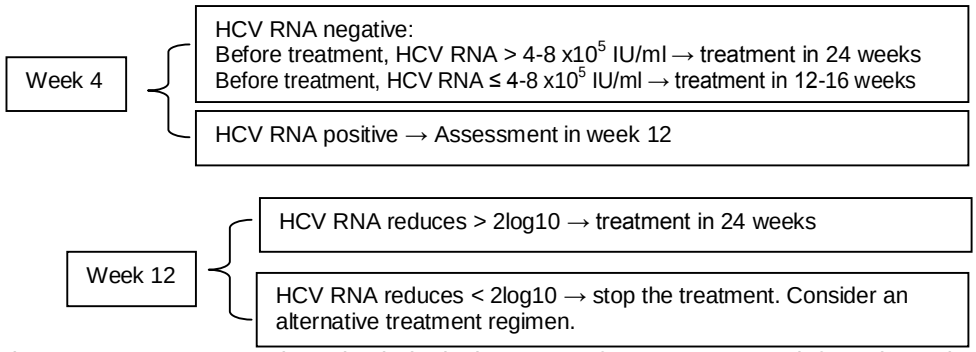

Diagram 2: Treatment regimen in virological response for HCV type 2, 3 infected people

+ Genotypes 1, 4, 6: 48 weeks or complied with Diagram 1.

+ Genotypes 2, 3: 24 weeks or complied with Diagram 2

+ In case, it is failed to identify the genotype of HCV, the treatment regimen should be applied for the genotype 1 or 6 because most of C virus in Vietnam belongs to genotype 1 and 6.

- During treatment monitoring:

+ Clinic: once every 4 weeks, evaluating any clinic symptoms, side-effects caused by the

drug.

+ ALT, peripheral blood cell, creatinine, creatinine clearance: once every 4 weeks.

+ Measuring HCV RNA loads (technically applying with the detective threshold < 50 IU/ml): weeks 4, 12, 24, 48, and suspending the drug taken in 24 weeks

+ Rate of Prothrombin, AFP, thyroid functions (FT4, TSH): once in every 12 weeks.

+ Imagine diagnosis: abdominal ultrasound once in every 12 weeks.

3. Chronic HVC treatment in special cases

a) HVC treatment for children:

- Treatment: Children above 3 years old who are infected with HCV can be considered to treat with a dose of PeglPN α-2b 60 mcg/m^2 of skin area per week + Ribavirin 15mg/kg/day; or PegINF α-2a 180mcg/1,73 m^2 x skin area per week + Ribavirin 15mg/kg/day.

- Duration of treatment: subject to the genotype of virus infected, as similar to the adult.

b) HIV/HCV co-infected patient:

- Applying the standard treatment regimen specified for chronic HCV.

- Duration of treatment: 48 weeks.

Due attention should be given to the drug interaction and undesired side effects that may happen when patients are on antiretroviral drugs.

c) Patients with chronic kidney diseases:

Table 2. HCV treatment for patients with chronic kidney diseases

Status	How to treat
Creatinine clearance > 60 ml/minute	Remain the dose
Creatinine clearance 15-59 ml/minute	• PegINF α-2a 135mcg/week, or PegINF α-2b 1mcg/kg/week. • Ribavirin 200-800mg/day
Haemodialysis	• IFN α-2a, or IFN α-2b: 3 MU x 3 times/week, or • PegINF α-2a 135mcg/week, or PegINF α-2b 1mcg/kg/week. • Ribavirin 200 - 800mg/day
Renal transplantation	• Renal transplanted patient: no indication to treat with interferon. • Patient to have renal transplanted: HCV should be treated before renal transplantation.

d) Cirrhosis infected patient in Child A (Appendix 1): Remain the dosage and monitor side effects.

đ) Cirrhosis infected patient in Child B: precaution is requested because interferon accelerates the liver failure process. Positively use with low dosage, closely monitor side-effects in order prepare for the patient to have liver transplanted.

4. Handling unexpected effects

a) Decreased leukocyte:

- Counts of leukocyte < 1,5G/L: reduce the dose of PeglFN α-2a to 135mcg/week, reduce the dose of PeglFN α-2b to 1 mcg/kg/week, and then reduce to 0.5mcg/kg/week. Possibly use G-CSF (Granulocyte colony-stimulating);

Counts of leukocyte < 1G/dL: stop the treatment;

- Neutrophils < 0,75g/dL: reduce the dose of PeglFN α-2a to 135mcg/week, PeglFN α-2b

1mcg/kg/week then reduce to 0.5mcg/kg/week. Possibly use G-CSF;

Neutrophils < 0,5g/dL: stop the treatment.

b) Anemia:

- Hb < 10g/dL: reduce the dose of ribavirin and can be taken erythropoietin, darbepoietin;

- Hb 8.5-10g/dL: reduce the dose of PeglFN and ribavirin 50% to the dose of 200mg/day;

- Hb < 8.5g/dL: stop ribavirin.

c) Thrombocytopenia:

- Counts of platelet< 50g/dL: reduce the dose of PeglFN α-2a to 90mcg/week, PeglFN α-2b: reduce the dose to 1mcg/kg/week, then, continuously reduce to 0.5mcg/kg/week;

Counts of platelet< 25g/dL: stop the treatment.

d) Acedia: Selective serotonin reuptake inhibitors, consulting with doctors specialized in the mental background.

đ) Damaging liver cells seriously, with sepsis: stop the treatment

e) Patient with thyroid malfunction: consulting with the endocrinologist.

APPENDIX 1

INTERPRETATION OF TESTS

Promulgated by Decision no. 4817/QĐ-BYT dated 28/11/2013 by Minister of Ministry of Health)

1. FibroScan

F0: 1-5kPa

F1: 5-7kPa

F2: 7.1-8.6kPa

F3: 8.7-14.5kPa

F4: > 14.6kPa

2. APRI:

$$APRI = \frac{AST \text{ x } 100/ASTGHTBT}{\text{Platelets } \mathbf{(10^9/1)}}$$

F0-F2: APRI < 1.45

F4: APRI > 2

3. Table on Child Pugh 1991 Point

Criteria to be assessed	1 point	2 points	3 points
Mental - nervous disorder (Encephalopathy symptom)	nil	marginal	coma
Ascite	nil	marginal, easy to control	significant, difficult to control
Bilirubin serum (mg/ml)	< 35	35-50	> 50
Albumin serum (g/l)	> 35	28-35	< 28
Rate of Prothrombin (%)	> 64	44-64	< 44

Points of each patient obtained are equal to total points of the criteria. The status of patient is grouped into 3 levels in line with the total points s/he gains.

Child A: 5-6 points; Child B: 7-9 points; Child C: 10 points

APPENDIX 2

PRIOR-TREATMENT EVALUATION TEST
Promulgated by Decision no. 4817/QĐ-BYT dated 28/11/2013 by Minister of Ministry of Health)

1. Blood formula, urine, creatinine, electroencephalograph

2. Assessment of liver functions (AST, ALT, GGT, bilirubin, albumin, AFP, rate of Prothrombin, INR)

3. Straight (vertical) heart lung Radiography

4. Endocrine: FT4, TSH

5. Coronary artery: Electrocardiogram

6. Abdominal untrasound

7. Assessment of Cirrhosis status (liver biopsy, or Fibrotest, or Fibroscan, or APRI)

8. HBsAg, anti-HIV

9. Pregnant test for female patient.

APPENDIX 3

SOME TERMS ON VIROLOGICAL RESPONSE
(Promulgated by Decision no. 4817/QĐ-BYT dated November 28th 2013 by Minister of Ministry of Health)

Term	Definition
RVR *(Rapid Virological response)*	HCV RNA negative after 4 weeks of treatment
EVR *(Early Virological Response)*	Fully early virological response: HCV RNA negative after 12 weeks of treatment Partially early virological response: HCV RNA reduced > 2 log10 after 12 weeks of treatment
ETR (End Treatment Response)	HCV RNA negative at the end of the treatment period
SVR *(Sustained Virological Response)*	HCV RNA negative after 24 weeks in suspension of treatment
Flare-out	HCV RNA increases high during treatment
Relapse	HCV RNA re-increase after the treatment is suspended
No response	HCV RNA still positive after 24 weeks of treatment