Update Guidelines in Management of HCV infection

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MMA

1. Introduction

- Hepatitis C (HCV)-- mainly a blood borne viral infection

- approximately **71 million** people chronically infected worldwide and **399000 --COL** or **HCC**

  (WHO. 2018, July)

- 2007 -- prevalence of anti-HCV among PWIDs--- **66% to 93%**
- 2016-- the prevalence of anti-HCV among the blood donors --- **0.37%**
- 2015, prevalence of anti-HCV in the general population is **2.65%**
- highest occurrence --Mawlamyine (**10.34%**), Mandalay (**7.17%**) and Lashio (**5.03%**)

- Newly developed Direct Acting Antiviral (DAA) therapies

  -- **cure rates of over 90%,**

  -- shorter treatment periods (of 8 - 24 weeks)

- DAA regimens -- protease inhibitors, NS5B polymerase inhibitors, NS5A inhibitors and others

- not contraindicated in persons with advanced chronic liver disease

- In Myanmar, the dominant genotypes are**,** genotype **3 (37.9%)** and genotype **6 (32.1%),** genotype **1 (24.3%)**

- oral pangenotypic DAAs in combination which will be effective ----

  --genotype testing can also be omitted for the therapy

2.Transmission of HCV

- HCV is mostly transmitted through exposure to infectious blood
- The parenteral transmission
- through healthcare-associated practices, HCV-infected blood and blood products and contaminated medical procedures
- Mother-to-child transmission or sexual transmission
- Other -- intranasal drug use and other modes of blood borne transmission, such as cosmetic procedures

Prioritized populations

- In principle, those who come to health facilities should be screened for viral hepatitis C infection due to the high epidemic of Myanmar, emphasis on sub-populations as below.

1. Patients who received blood products or organ transplants prior to the introduction of **anti-HCV screening since 2000**
2. PWID
3. Children born to **mothers infected** with HCV, especially if HIV co-infected
4. People with **HIV** infection
5. People who have used **intranasal drugs**
6. **Prisoners** and previously incarcerated people
7. **MSM**
8. Persons who were ever on **chronic hemodialysis**
9. **Healthcare or public safety workers** after accidental needle sticks, sharps, or other mucosal exposures to HCV-positive blood (or unknown)

3. Prevention

- In the absence of a vaccine for hepatitis C infection
- reduce the risk of exposure to the virus
- reduce transmission by blood transfusion and other unsafe medical procedures
- high-risk groups such as healthcare workers and PWID
- Treatment can prevent development of complications of infection, including cirrhosis and hepatocellular carcinoma

Prevention of HCV in community settings

- Avoid unsafe practices around non-medical or traditional practice (cosmetic, scarification, tattoos, circumcision procedures, traditional medical practice among others)
- Safe household practice – avoid sharing toothbrushes, razors, nail clippers, avoid sharing contaminated needles and syringes
- Promotion of correct and consistent condom use
- It should be emphasized that HCV is not transmitted through household contact such as sharing food, utensils, kissing, hugging, or other casual contact.

Prevention of sexual transmission of HCV infection

- Avoid multiple partners, seek regular screening and treatment for STIs
- Routine screening of sex workers in high-prevalence settings

Prevention of HCV Infection in Health-care Settings ,

- Follow universal precautions
- Hand hygiene: including surgical hand-washing and use of gloves

- Safe handling and disposal of sharps and waste
- Single-use needles, syringes and medical devices when possible

- Safe cleaning of equipment
- Testing of donated blood

- Improved access to safe blood
- Training of health personnel

Injection safety

- The three elements of WHO strategy for the safe and appropriate use of injections are:

(1) **Behavior change among patients and health-care workers** to decrease injection overuse and achieve injection safety

(2) Availability of necessary equipment and supplies

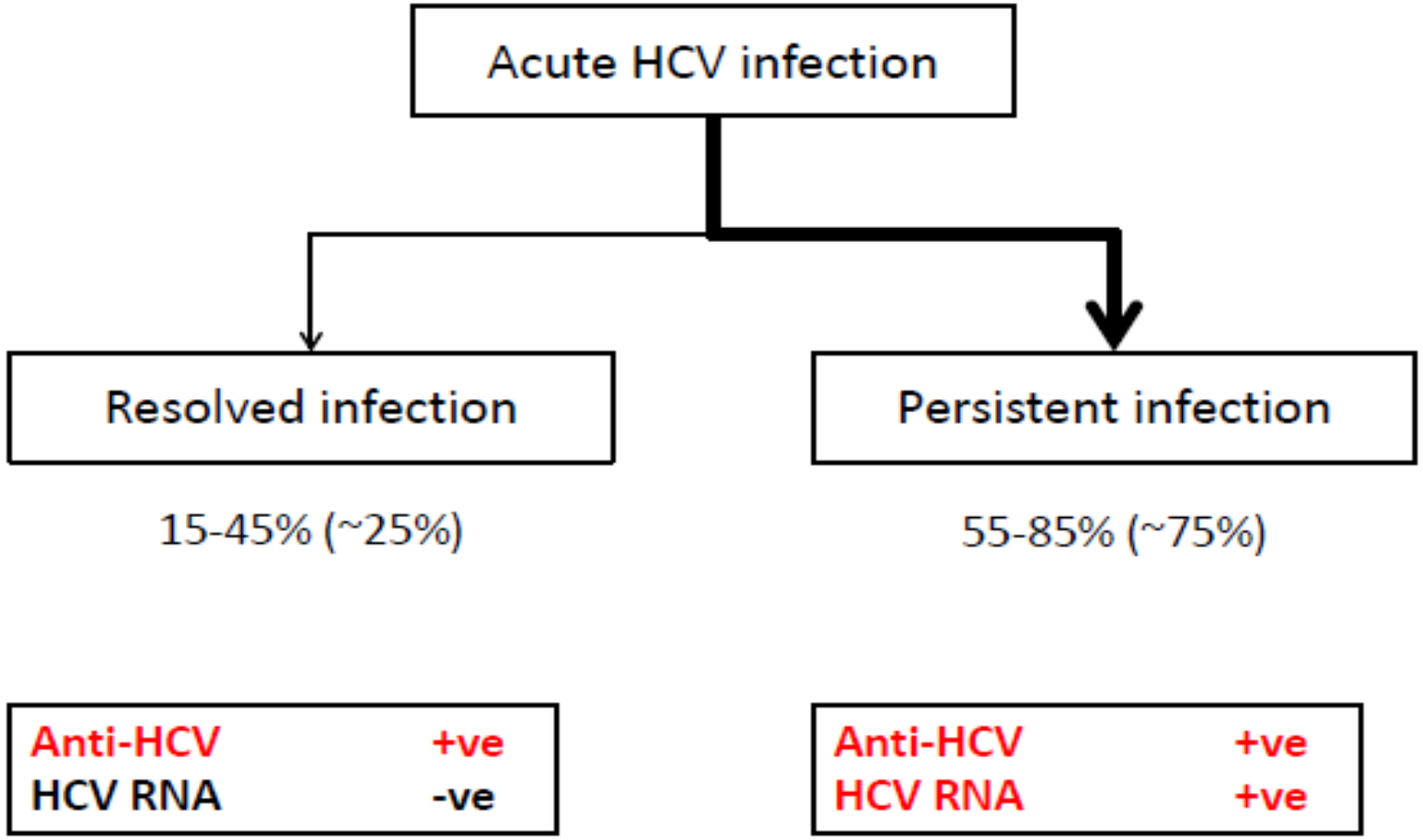
(3) Management of sharps waste

HCV Post Exposure Prophylaxis

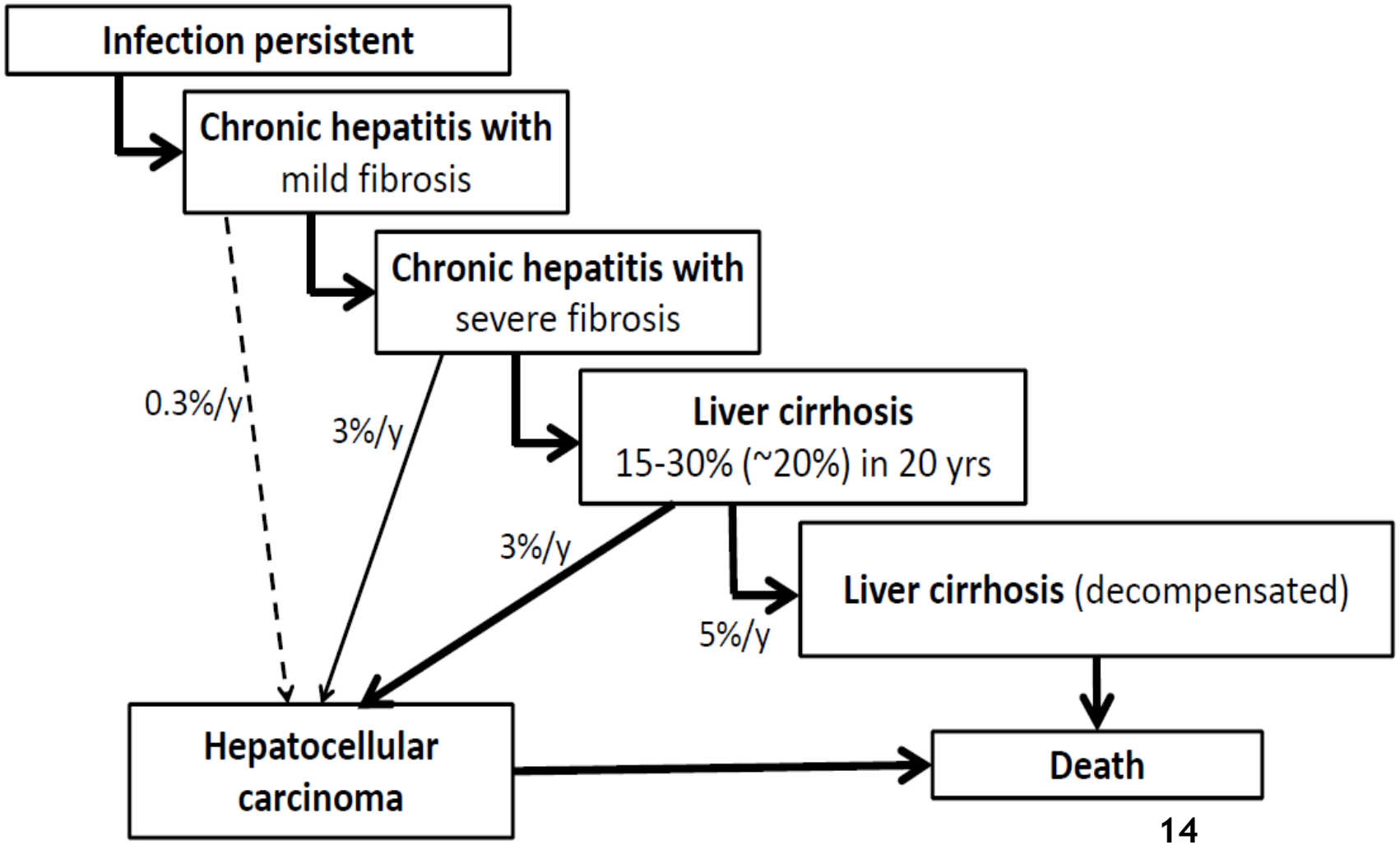
After exposure to blood or other body substances, the following is recommended as soon as possible:

- **Wash** the wound site with soap and water
- If eyes are contaminated then rinse them, while they are open, gently but thoroughly with water or normal saline
- If blood or other body substances get in the mouth, spit them out and then rinse the mouth with water
- If **clothing** is contaminated, **remove** clothing and shower with soap
- Where water is not available use of non-water cleanser or antiseptic should replace the use of soap and water for washing cuts or punctures of the skin or intact skin
- Even after exposure to HCV, every exposed person shall be tested, at the baseline, for HBsAg, anti-HCV an HIV but not alone for HCV; hepatitis B vaccination of the HBsAg negative exposed person shall be initiated immediately
- Follow up testing shall be directed according to the serological status of the source person
- HBV vaccination

4. Natural history of hepatitis C infection



Natural History of Chronic Hepatitis C Infection



- HCV disease association is not confined to the liver, and extrahepatic manifestations can include glomerulonephritis, cryoglobulinaemia, thyroiditis and Sjögren syndrome, insulin resistance type 2 diabetes mellitus, and some skin disorders.

5. Simplified Diagnostic and treatment algorithm

- For detailed diagnosis of viral hepatitis infections, kindly refer to the national hepatitis testing guidelines was published by the NHL.

- The currently available DAAs have far fewer side effects, and therefore eliminate the need for on-treatment monitoring in non-complex patients who do not require specialist care

- Pan-genotypic DAA options, such as sofosbuvir/daclatasvir and sofosbuvir/velpatasvir, eliminate the need for genotyping as well in shown in figure 3

HCV Simplified Diagnostic and Treatment Algorithm

- Referral to specialist for all those with prior treatment experience and/or decompensated cirrhosis and/or HCC.

- Regular follow up for assessment of cirrhosis status and HCC Patients with cirrhosis: 3-6 months

Who should be tested

- Anti-HCV antibody tests should be administered to any patient seeking health services
- Screening for the population at higher risk:
- HIV infected persons, people who inject drugs (PWID),
- men who have sex with men (MSM),
- repeated transfusion recipients,
- health care workers,
- prisoners
- hemodialysis patients
- One time screening (when feasible) is done for
  - Pregnant woman
  - Household contacts
  - Institutionalized populations
- Screening of blood, blood products and organ donors is mandatory

Interpretation of Test Results

Antibody Test Result	HCV RNA Test Result	Interpretation
Negative	Negative	No HCV exposure / infection
Positive	Negative	HCV exposed or resolved or treated infection *also includes antibody false positives
Positive	Positive	HCV exposed & current infection

6.Pre-treatment assessments

- HCV-infected patients should be properly and thoroughly assessed before initiation of treatment

1. **Alcohol consumption** (ANNEX E: Alcohol Consumption Assessment: Audit interview questions)
2. **HIV status**, current ART treatment regimen

3. **Pregnancy status** - contraception during treatment and 6 months after the treatment
4. **Baseline biochemical tests**

   a. Liver Function Test (LFT) -ALT, Aspartate transferase (AST), Alkaline Phosphate, Bilirubin

   b. Renal Function Assessment - Creatinine

5. Complete Blood Count (CBC) to determine platelet count

6.**Exclusion of HCC** by ultrasonography (USG) if patient demonstrates signs of end stage liver disease

- Alpha-feto protein (Optional)

7.Other laboratory tests

a. All HCV patients should be screened for evidence of **current HBV** infection before initiating HCV therapy

b. The minimum tests to be performed prior to initiating patients on all-oral DAA therapy are: AST, Platelets and Creatinine

- The AST and Platelets will be used to calculate the AST to Platelet Ratio Index **(APRI) score** to stage cirrhosis of the patient and creatinine will be used to determine renal function. An APRI calculator can be found here: https://www.hepatitisc.uw.edu/page/clinical-calculators/apri.

- In addition to the tests above, a physical examination by a trained medical professional is necessary to determine whether the patient is suspected of having advanced liver disease (decompensated cirrhosis or HCC), in which case, they should be referred to a specialist

- **Clinical signs of cirrhosis:** firm liver on abdomen palpation, spider nevi, palmar erythema, white nail, gynecomastia, and wasting syndrome

- **Clinical signs of decompensation:** jaundice, ascites, distended abdominal veins and caput medusa, hepatic encephalopathy, haematemesis and malena, and coagulopathy

7. Staging and scoring

- It is important to assess whether the patients have cirrhosis or not before starting DAAs therapy because cirrhosis will influence the possible addition of ribavirin or duration of therapy

- Therefore, for the practical purposes the following methods are recommended to assess the cirrhosis

1. Clinical examination
2. APRI
3. Metavir (fibroscan/elastography)
4. Ultrasound or CT

Table 2. Aspartate Aminotransferase (AST)/Platelets Ratio Index (APRI)

Formula: APRI = [{AST (IU/L)/ AST_ULN (IU/L)} ×100]/platelet count (10^9/L)

AST - Aspartate aminotransferase

IU- International Unit

ULN- Upper Limit of Normal of the Lab (often 40 IU/ml)

Non-invasive test	Components assessed	Lower cut off	Upper cut off
APRI	AST and platelet count	0.5	1.5

APRI Calculation Example

AST Level (IU/L) = 60

AST Upper Limit of Normal (IU/L) = 40

Platelet Count (10^9/L) = 133,000/mm^3 (Ref: 150,000-400,000/mm^3) = 133

APRI = [{60/40} x 100] / 133

APRI = [1.5 x 100] / 133

APRI = 150/133

APRI = 1.128

Table 3. APRI Score Interpretation

APRI score	Interpretation
> 1.5	Cirrhosis
0.5 - 1.5	Fibrosis, risk of cirrhosis
< 0.5	No Fibrosis

8. Treatment of patients with chronic HCV infection

- **All patients** with chronic HCV infection should be considered for treatment, regardless of fibrosis stage or presence of co-infection (except pregnant women).
- **Prioritized populations**

The National Hepatitis Control Program prioritizes the following patients for treatment:

1.Patients who are at fibrosis stage F3 and F4

2.Patients with decompensated cirrhosis

3.HIV/HCV co-infected patients

9. Referral to Specialist

- Patients with decompensated cirrhosis, irrespective of APRI score, should be referred to specialists for clinical management.
- The referral pathways for Myanmar are listed below.

- Patients with prior treatment failure with DAAs
- Patients with hepatic decompensation +/- APRI >1.5
- Patients with HCC -→Specialist

10.Counseling and education about HCV infection and treatment

People Testing Anti-HCV Negative

- All patients who are confirmed anti-HCV negative should receive post-test counseling with the aim of reducing or eliminating risky behaviors which could lead to future transmission. The counseling session should include the following:

- Explanation of the results and implications: if the antibody test is nonreactive, no antibodies were found in the blood, and this usually means the patient doesn’t have HCV, but should not be confused for future immunity

11. Treatment

11. 1. Goals of Therapy

- To reduce mortality related to HCV infection, prevent complications of HCV infected person and reduce transmission of HCV.

- **Note: The aim of HCV treatment is viral cure having undetectable HCV RNA, but it should be noted that anti-HCV will be detectable for life. Additionally, cure does not prevent re-infection so it is important to ensure robust infection prevention and control procedures, especially among those at high ongoing risk such as PWIDs.**

11.2 Anti-viral agents

11.2.1 Direct-acting Antivirals (DAAs)

- There are various classes of DAAs including:
  - Protease Inhibitors (PI)
  - Nucleotide and Non-nucleotide NS5B Inhibitors
  - NS5A inhibitors

11.2.2 Indications for antiviral therapy

11.2.3 Recommended Regimens

DAA regimens can be used for the treatmen t of persons with hepatitis C infection rather than regimens with ribavirin.

Recommendations for treatment	Regimen type	Treatment duration (weeks)	
		Cirrhosis	Non-cirrhosis
Preferred regimen	SOF/VEL	12	12
Alternative regimen 1	SOF/DCV	24	12
Alternative regimen 2	SOF/DCV+ Ribavirin	12	12

11.2.4 Dosing for HCV Treatment Regimens

Table 4. Dosing for Recommended HCV Treatment Regimens

Regimen	Dosage per tablet	Dosing Frequency and Timing
Velpatasvir/ Sofosbuvir	100mg/400mg FDC (special considerations for ART patients in table 10)	Once daily
Daclatasvir*/ Sofosbuvir	30 mg and/or 60 mg/400 mg tablet (special considerations for ART patients in table 10)	once daily - morning
Oral Ribavirin	200 mg capsule or tablet	body weight < 75 kg - 2 in the morning and 3 in the evening body weight ≥ 75 kg - 3 in the morning and 3 in the evening

*Increase daclatasvir dosage to 90 mg per day when co-administered with Efavirenz. Decrease daclatasvir dosage to 30 mg per day when co-administered with Atazanavir/Ritonavir. Decrease daclatasvir dosage to 30 mg per day with the antibacterials clarithromycin, telithromycin, erythromycin and the antifungals keto-conazole, itraconazole, posaconazole and voriconazole

11.2.5 Dose adjustment in renal impairment

- In patients with renal impairment on ribavirin or sofosbuvir containing regimen, dose adjustments should be made based on the severity of the renal impairment as follows:
  - **Ribavirin:**
    - **Moderate (30-50 ml/min) = Alternating doses of 200 mg and 400 mg every other day**
    - **Severe (< 30 ml/min) = 200 mg/day**
    - **ESRD = 200 mg/day**
  - **Sofosbuvir:**
    - **Mild-Moderate (30 - 80 ml/min) = No dose adjustment**
- Severe and ESRD = Not recommended

12. Treatment Monitoring

12.1 On Treatment Monitoring

- On-treatment monitoring is not generally required when using all-oral DAA regimen, except in the following situations:

- **Renal impairment**: If Sofosbuvir or Ribavirin based regimens are utilized in patients with chronic kidney disease, renal function should be monitored (Creatinine clearance) as both exhibit renal clearance.

12.2 Assessment of Response to Therapy (Post-treatment)

- Sustained Viral Response (SVR12).
- Patients that do not achieve SVR should be referred to a specialist.
- Cirrhotic Patients who achieve SVR12 still need to be followed-up regularly for the assessment of complications of cirrhosis and hepatocellular carcinoma (HCC) with ultrasound with/without AFP.
- Patients with cirrhosis - Follow up with ultrasound within 3-6 months

THANK YOU VERY MUCH