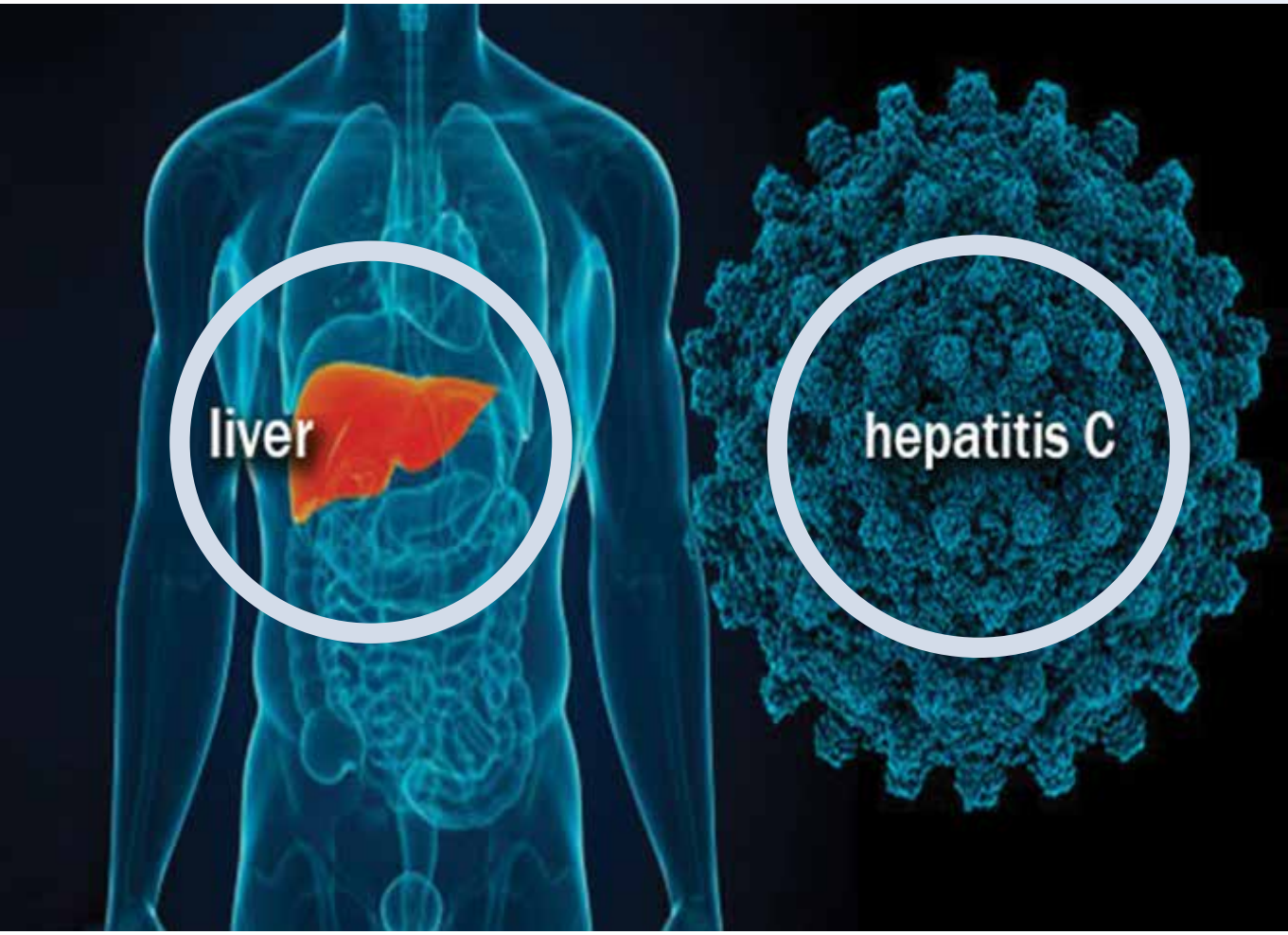
2020

NATIONAL GUIDELINES FOR

SCREENING, CARE AND TREATMENT OF HEPATITIS C INFECTION IN NEPAL



Government of Nepal
Ministry of Health and Population
National Center for AIDS and STD Control
Teku, Kathmandu

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FOREWORD

The rapid growth and development of medical science has saved the lives of many people in the world. One of the greatest achievements so far is a cure for hepatitis C infection with highly effective and safe direct- acting antivirals (DAAs). Globally, several hundred or thousand lives are lost due to the complications of hepatitis C infection. Early diagnosis and treatment of hepatitis C can prevent the development of complications of the infection and its transmission.

In May 2016, the World Health Assembly endorsed the WHO Global Health Sector Strategy (GHSS) on viral hepatitis, 2016–2021, which proposes to eliminate viral hepatitis as a public health threat by 2030. Elimination of viral hepatitis as a public health threat requires 90% of those infected to be diagnosed and 80% of those diagnosed to be treated.

Timely testing and treatment are not only critical to prevent the sequel of HCV infection (cirrhosis and hepatocellular carcinoma) but to prevent Hepatitis C transmission and achieve the global target to eliminate viral hepatitis as a public health threat. Since the available DAA are highly effective and requires minimum laboratory investigations to initiate and monitor for cure of HCV infection. Already developed guidelines was reviewed, discussed and endorsed by the National Hepatitis Steering Committee to move forward to prevent any morbidity and morality from HCV infection and cure the clients with HCV infection.

I would like to acknowledge the technical assistance of the core working team members of the National Hepatitis Steering Committee led by NCASC Director and World Health Organization for their work on this comprehensive guideline.

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MESSAGE FROM DIRECTOR

The estimated number of people living with chronic hepatitis C virus (HCV) infection worldwide is 71million (WHO, 2015) and among them 399, 000 died due to cirrhosis or hepatocellular carcinoma (HCC). In Nepal, the estimated number of people living with chronic HCV infection is around 130 000. Though prevalence of HCV in general population is low; its burden is high among Key populations (KP) like people who inject drugs (PWID) and people living with HIV (PLHIV)

The current HIV program is reaching KPs and PLHIV for prevention and treatment of HIV. The integrated intervention to KPs and providing HCV related activities like prevention, early diagnosis and providing treatment to cure HCV infection would be the cost-effective approach to decrease the burden of HCV among them. The availability of effective treatment – Direct - Acting Antiviral (DAA) has prevented HCV related consequences and cured from HCV infections. The pangenotypic DAA do not require genotyping of the virus and current WHO guidelines recommends that all HCV infected people are treated with minimal lab investigations and follow up. This recommendation helps us to combat Hep C related complications and prevent morbidities and mortalities and provide opportunity to treat clients at all kind of health facilities.

The National Guidelines for Screening, Care and Treatment of Hepatitis C Infection in Nepal was developed and finalized in September 2019, but due to various reasons the guidelines was not finalized and endorsed yet. The National HIV Strategic Plan 2016-2021 commits to provide treatment and manage HCV infection among HIV/HCV co-infected clients. One of the major roles of NCASC is to minimize the mortality and improve the quality of life by decreasing other comorbidities such as HCV infection and its complications like Cirrhosis and Hepatocellular carcinoma

So to facilitate this, the core team member of National Hepatitis Steering Committee reviewed all the documents including the Guidelines and operational plan to implement the HCV testing and treatment from the service delivery points and finalized, and these documents will be the reference materials for the health care providers in all the health facilities.

I would like to acknowledge good work of all the National Hepatitis Steering Committee members and writing team of the National Guidelines for Screening, Care and Treatment of Hepatitis C Infection in Nepal and specially would like to extend my sincere gratitude towards previous Directors of NCASC: Dr Tara Nath Pokhrel and Dr Anuj Bhattachan for taking lead to develop and finalize this guidelines.

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ABBREVIATIONS AND ACRONYMS

AASLD/IDSA	American Association for the Study of Liver Diseases/Infectious Diseases Society of America
AD/RUP/SIP	auto-disable/reuse prevention/sharp injury prevention
AFP	alpha-fetoprotein
anti-HBc	antibody to hepatitis core antigen
anti-HBs	hepatitis B surface antibody
ALT	alanine aminotransferase
APRI	aspartate aminotransferase (AST)-to-platelet ratio index
ART	antiretroviral therapy
ARV	antiretroviral (drug)
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
AST	aspartate aminotransferase
ATV	atazanavir
BCRP	breast cancer resistance protein
CBP	complete blood picture
CKD	chronic kidney disease
Cr-Cl	creatinine clearance
CYP2B6	cytochrome 2B6
CYP2C8	cytochrome 2C8
CYP3A4	cytochrome 3A4
DAA	direct-acting antiviral
DBS	dried blood spot
DDI	drug–drug interaction
DCV	daclatasvir
DRV	darunavir
DSV	dasabuvir
DTG	dolutegravir
EACS	European AIDS Clinical Society
EASL	European Association for the Study of Liver

EBR	elbasvir
EBV	elbasvir
EFV	efavirenz
EGD	oeso-gastro-duodenoscopy
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunoassay
ESRD	end-stage renal disease
ETR	etravirine
FBC	full blood count
FDA	(US) Food and Drug Administration
FDC	fixed-dose combination
GLE	glecaprevir
GZR	grazoprevir
INR	International Normalized Ratio
INSTI	Integrase Strand Transfer Inhibitor
IU/mL	international unit per millilitre
HAV	hepatitis A virus
Hb	haemoglobin
HBcAg	hepatitis B virus core antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
LDV	ledipasvir
LoD	limit of detection
LPV/r	lopinavir/ritonavir
MELD	model for end-stage liver disease
MSM	men who have sex with men
MTCT	mother-to-child transmission
NASH	non-alcoholic steatohepatitis
NAT	nucleic acid test
NNRTI	non-nucleoside reverse transcriptase inhibitor

NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
OATP	organic anion transporting polypeptide
OBV	ombitasvir
od	once daily
OST	opioid substitution therapy
PEP	post-exposure prophylaxis
P-gp	permeability-glycoprotein
PI	protease inhibitor
PIB	pibrentasvir
PLHIV	people living with HIV
Plt	platelet count
PPI	proton pump inhibitor
PTV	paritaprevir
PWID	people who inject drugs
RAL	raltegravir
RAS	resistance-associated substitution
RBV	ribavirin
RDT	rapid diagnostic test
RNA	ribonucleic acid
RTV	ritonavir
SIM	simeprevir
SOF	sofosbuvir
STI	sexually transmitted infection
SVR	sustained virological response
TB	tuberculosis
TDF	tenofovir disoproxyl fumarate
ULN	upper limit of normal
USG	ultrasonography
VEL	velpatasvir
VOX	voxilaprevir
WHO	World Health Organization
ZDV	zidovudine

GLOSSARY OF TERMS

Acute HCV infection	A new infection with HCV that leads to acute symptoms
Anti-HCV antibody	Presence of antibodies to hepatitis C virus (HCV), which is a biomarker of past or present infection
Chronic HCV infection	Continued infection six months or more after acquiring HCV infection
Cirrhosis	Extensive liver scarring secondary to prolonged inflammation of the liver (APRI>=2)
Compensated cirrhosis	Cirrhosis usually without liver-related symptoms
Decompensated cirrhosis	Cirrhosis with the development of symptomatic complications, including ascites or variceal bleeding
Hepatitis B core antibody (anti-HBc)	Antibody to HBV core protein. Anti-HBc antibodies are non-neutralizing antibodies and are detected in both recent and chronic infection
HCV infection	Active replication of HCV in the body. The biomarker of HCV infection is the presence of HCV RNA in the blood
Pangenotypic	Activity and effectiveness of antiviral medicine against all major HCV genotypes
Relapse	Undetectable HCV RNA in the blood at the end of treatment but detectable HCV RNA within 24 weeks of completing treatment
Spontaneous viral clearance	Clearance of HCV infection without treatment
Sustained virological response (12)	Undetectable HCV RNA in the blood 12 weeks
New HCV infection	A new infection with HCV that may or may not be symptomatic
Viral breakthrough	Undetectable HCV RNA in the blood during treatment followed by detectable HCV RNA during treatment, which is not caused by a new HCV infection
HBsAg	Surface antigen of the hepatitis B virus (HBV)

EXECUTIVE SUMMARY

Globally, the morbidity and mortality attributable to hepatitis C virus (HCV) infection continues to increase. Approximately 700 000 persons die each year from HCV-related complications, which include cirrhosis, hepatocellular carcinoma (HCC) and liver failure. HCV infection can be cured by antiviral treatment; however, due to the asymptomatic nature of the disease, many infected persons are unaware of their infection and, for those who are diagnosed, access to treatment remains poor in many settings as in Nepal.

As a result of evolving therapeutics in HCV treatment, several new medicines have been approved by at least one stringent regulatory authority. These medicines, called direct-acting antivirals (DAAs), are transforming the treatment of HCV, enabling regimens that can be administered orally, are of shorter duration (as short as eight weeks), result in cure rates higher than 90%, and are associated with fewer serious adverse events than the older interferon-containing regimens.

In May 2016, the World Health Assembly endorsed the Global Health Sector Strategy (GHSS) on viral hepatitis, 2016–2021, which proposes to eliminate viral hepatitis as a public health threat by 2030 (90% reduction in incidence and 65% reduction in mortality). Elimination of viral hepatitis as a public health threat requires 90% of those infected to be diagnosed and 80% of those diagnosed to be treated. In line with this Global Strategy, the Nepal Government was keen to initiate screening, provide care and treatment of hepatitis C-infected individuals in the country. Hence, this national guideline for screening, care and treatment of hepatitis C infection in Nepal was developed. This guideline was developed using the latest WHO evidence-based recommendations and best practices in other countries, and contextualized to the country needs and situation.

The guidelines is developed by a core working team appointed by National Hepatitis Steering Committee for developing the National Guidelines for Screening, Care and Treatment of Hepatitis C Infection in Nepal with technical support from WHO. This is a dynamic document and will be updated periodically as new evidences and recommendations become available. The audience of this guidelines are programme managers and health-care providers (both in the public and private sectors) who are responsible for planning and implementing hepatitis care and treatment programmes. This guideline is intended to provide clear guidance on screening, diagnosis, management and referral of hepatitis-infected individuals. Nationwide implementation of this national guideline is intended to ensure people-centred care for all Nepalese infected with hepatitis C and enable the country to reach the 2030 target of elimination of viral hepatitis a public health threat in Nepal.

1. INTRODUCTION

The World Health Organization (WHO) estimates that in 2015, 71 million persons were living with chronic hepatitis C virus (HCV) infection worldwide and that 399 000 died from cirrhosis or hepatocellular carcinoma (HCC) caused by HCV infection. In May 2016, the World Health Assembly endorsed the WHO Global Health Sector Strategy on viral hepatitis, which proposes to eliminate viral hepatitis as a public health threat by 2030 (90% reduction in incidence and 65% reduction in mortality). Elimination of viral hepatitis as a public health threat requires 90% of those infected to be diagnosed and 80% of those diagnosed to be treated.

In Nepal, an estimated 130 000 persons are estimated to be living with chronic hepatitis C but robust data regarding the epidemiology of hepatitis C are still lacking. Seroprevalence in the general population is around 0.4%; and is much higher among key populations such as people who inject drugs (PWID) in different regions (20.9–47.5%) and people living with HIV (PLHIV; 2.5–7.3%).[1] The principal serotypes involved are genotype 3 (55–59%) and genotype 1 (40–44%).[2]

There is no universal access to regular diagnosis and treatment of hepatitis in the public sector yet. However, in the private sector, testing is available where indicated and patients receive treatment according to need but not free of cost. The availability of new, safe and highly effective direct-acting antivirals (DAAs) for all persons improves the balance of benefits and harms of treating all persons with chronic HCV infection rather than reserving treatment for persons with advanced disease. Several pangenotypic DAAs have been approved, reducing the need for genotyping to guide treatment decisions. Continued and substantial reduction in the price of DAAs has enabled treatment to be rolled out rapidly in low- and middle-income countries.

It is envisioned that the development of this comprehensive guideline will provide clear guidance on screening, diagnosis, care and treatment of all persons with HCV infection and on prevention.

1. A. Shrestha, Epidemiology of Viral hepatitis and Liver Disease in Nepal, 10.5005/jp-journals-10018-1128.National Centre for AIDS and STD Control, Teku, Kathmandu, IBBS,2017
2. Kinkel et. Al, Prevalence of HIV, hepatitis B and C Infections and an assessment of HCV-genotypes and two IL28B SNPs among people who inject drugs in three regions of Nepal

2. TRANSMISSION OF HCV

- Globally, 8% of current HCV infection is among PWID through needle-sharing.
- In countries where infection control measures are insufficient, HCV infection is associated with unsafe injection practices and procedures such as renal dialysis, surgery, dental care and unscreened blood transfusion. This needs to be addressed through safer health-care practices such as introduction of reuse-prevention devices and a reduction in unnecessary health-care injections.
- Another mode of transmission is mother-to-child transmission (MTCT). If the mother is mono-infected (HCV), the risk of transmission to the child is 4–8% and if co-infected (HIV/HCV), the risk is 11–25%. Other causes of transmission include tattooing and body piercing, and needle-stick injuries in health-care workers (normal body piercing for women does not account to high risk).
- Sexual transmission of HCV occurs infrequently in heterosexual couples. However, it is more frequent in HIV-positive persons, particularly in men who have sex with men (MSM).
- HCV is NOT transmitted through breast milk, sharing food or drinks or hugging and kissing.

3. PREVENTION

In the absence of a vaccine for HCV, the approach to the prevention of HCV transmission is to reduce the risk of exposure to the virus. This is challenging because of the various routes of transmission and the various populations affected. Specific strategies need to be adopted for specific modes of transmission. Treatment can prevent the development of complications of infection, including cirrhosis and HCC, and can also reduce the risk of transmission.

3.1. PREVENTION OF HCV INFECTION IN HEALTH-CARE SETTINGS

- Follow universal precautions, including the use of gloves and other protective measures.
- Ensure safe handling and disposal of sharps and medical devices.
- Use single-use needles, syringes and medical devices when possible.
- Test all donated blood and blood to be used.
- Improve access to safe blood.
- Train health personnel.

3.1.1. Injection safety

A safe injection is not only good for the recipient but also protects the provider from avoidable risks and does not result in waste that is dangerous for other people. Among unsafe practices, the reuse of syringes and/or needles without sterilization is of particular concern. Injection-associated transmission of bloodborne pathogens can be prevented through the development of a strategy to reduce injection overuse and achieve injection safety. The three elements of the WHO strategy for the safe and appropriate use of injections are:

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

(ii) The availability of necessary equipment and supplies; namely, a transition to the exclusive use of WHO-prequalified auto-disable/reuse prevention/sharps (AD/RUP/SIP) syringes for therapeutic injections and

(iii) The management of sharps waste.

3.2. PREVENTION OF HEPATITIS INFECTION (HCV AND HBV) AMONG PEOPLE WHO INJECT DRUGS

- Offer screening for hepatitis B virus (HBV) infection to PWID by the rapid hepatitis B vaccination regimen if found negative.
- Encourage PWID to opt for and complete the hepatitis B vaccination schedule.
- Implement a programme for provision of sterile injection equipment, including needles and syringes, and provide low dead-space syringes for distribution to PWID.
- Offer peer interventions to PWID to reduce the incidence of viral hepatitis.
- Offer opioid substitution therapy (OST) to treat opioid dependence, reduce HCV risk behaviour and transmission through injecting drug use, and increase adherence to HCV treatment.
- Integrate OST and other drug-dependence treatment with medical services for hepatitis.
- Provide targeted information, education and communication on HCV prevention for PWID and their sexual partners.

3.3. PREVENTION OF SEXUAL TRANSMISSION OF HCV INFECTION

- Avoid multiple partners, seek regular screening and treatment for sexually transmitted infections (STIs).
- Routinely screen sex workers in high-prevalence settings.
- Integrate action to eliminate discrimination and gender violence and increase access to medical and social services for vulnerable persons.

3.4. PREVENTION OF HCV IN COMMUNITY SETTINGS

- Avoid unsafe practices around non-medical or traditional practices (cosmetic, scarification, tattoos, circumcision procedures, traditional medical practices among others).
- Follow safe household practices (no sharing of toothbrushes, safe blood contact using gloves in case of having to handle accidental blood contact, etc.)
- Promote correct and consistent condom use.

**** IT SHOULD BE EMPHASIZED THAT HCV IS NOT TRANSMITTED THROUGH HOUSEHOLD CONTACT SUCH AS SHARING OF FOOD, UTENSILS, KISSING, HUGGING, OR OTHER CASUAL CONTACT.***

3.5. POST-EXPOSURE PROPHYLAXIS FOR HCV

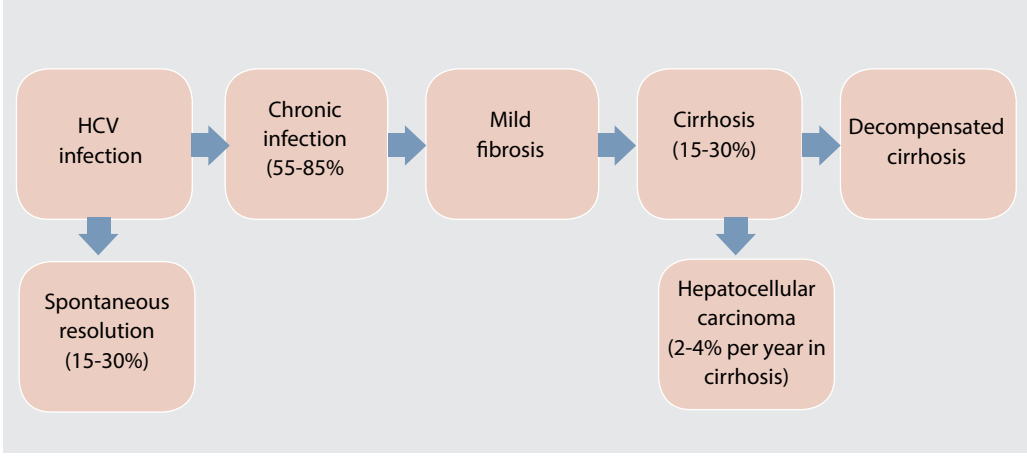
After exposure to blood or other body substances, the following is recommended as soon as possible:

- Wash the wound site with soap and water.
- If the eyes are contaminated, 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 several times.
- If clothing is contaminated, remove the clothing and shower with soap and water.
- Where water is not available, use a non-water cleanser or antiseptic to replace the use of soap and water for washing cuts or punctures of the skin or intact skin.
- Test every exposed person at baseline for HCV, hepatitis B surface antigen (HBsAg), and HIV. Immediately initiate hepatitis B vaccination to HBsAg-negative exposed persons.
- Conduct follow-up testing according to the serological status of the source person.
- No drugs have been approved for post-exposure prophylaxis (PEP) of HCV infection unlike for HIV. However, the person must be followed up for early treatment initiation if found positive.

4. NATURAL HISTORY OF THE DISEASE

The majority of people infected with HCV are unaware of their chronic infection. They are at high risk of developing severe chronic liver disease and associated complications of cirrhosis and HCC and can unknowingly transmit the infection to other people.

Fig. 1. Natural history of HCV Infection



Source: WHO Guidelines for the screening care and treatment of persons with chronic hepatitis C infection, Updated version April 2016.

HCV causes both acute and chronic hepatitis. Acute HCV infection is defined as the presence of HCV within six months of exposure to and infection with HCV. In 15–30% of infected individuals, spontaneous clearance of acute HCV infection occurs within six months of infection in the absence of treatment. Almost all the remaining 55–85% will harbour HCV for the rest of their lives (if not treated) and are considered to have chronic HCV infection. HCV antibodies (anti-HCV) develop as part of acute infection and persist throughout life. For this reason, a nucleic acid test (NAT) for HCV RNA is needed to detect the presence of the virus and confirm chronic infection.

If left untreated, chronic HCV infection can cause liver cirrhosis, liver failure and HCC. The risk of liver cirrhosis is 15–30% within 20 years. The risk of HCC in persons with cirrhosis is approximately 2–4% per year. The risk of cirrhosis and HCC varies, depending upon certain patient characteristics or behaviours.

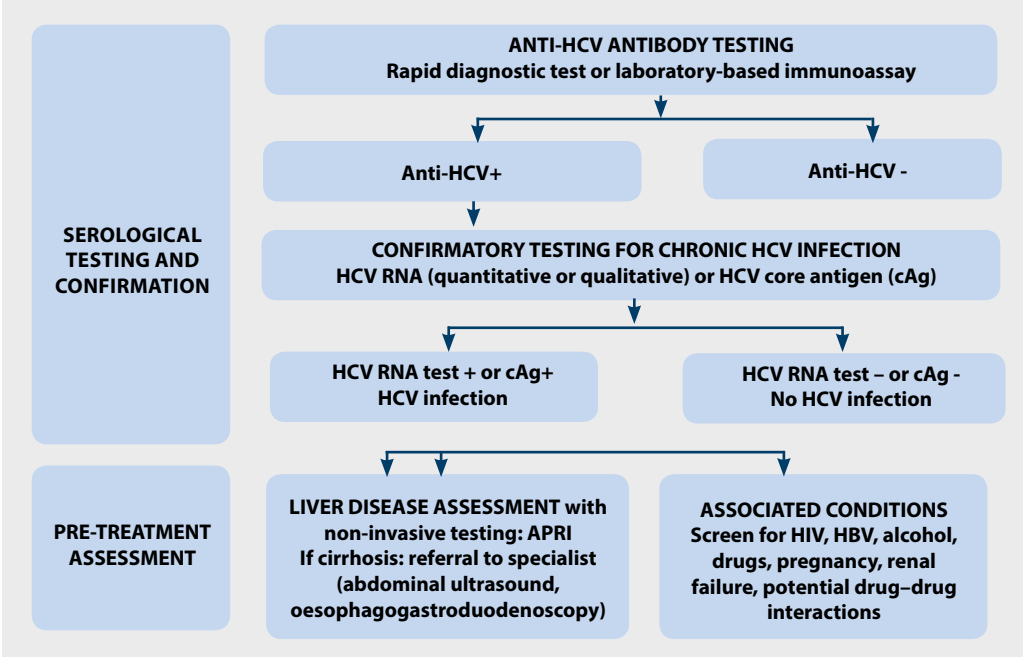
For example, persons who consume excess alcohol, persons with HBV or HIV and immunosuppressed individuals are at a higher risk of developing cirrhosis and HCC.

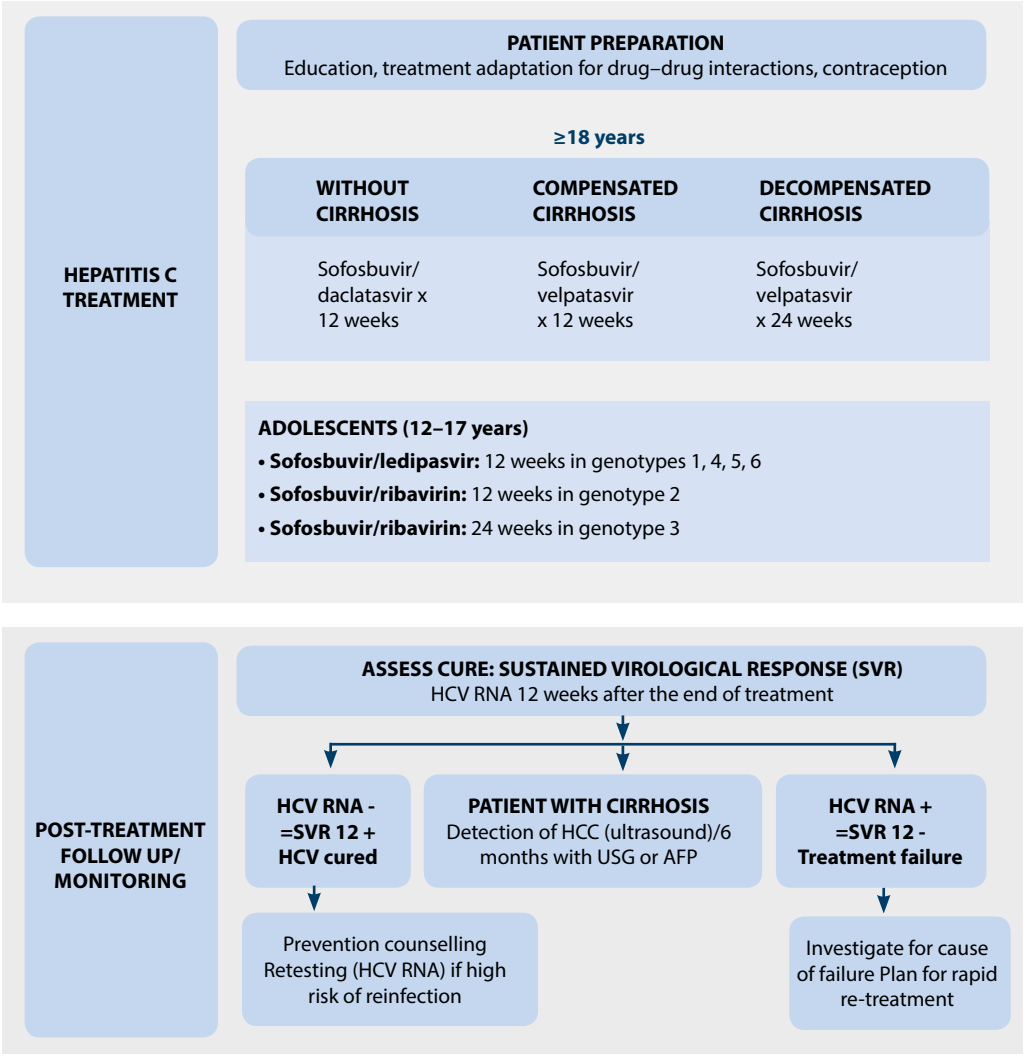
The manifestations of HCV disease are not confined to the liver, and extrahepatic manifestations can include glomerulonephritis, cryoglobulinaemia, thyroiditis and Sjögren syndrome, insulin-resistant type 2 diabetes mellitus, and some skin disorders.

5. SUMMARY ALGORITHM FOR THE DIAGNOSIS, TREATMENT AND MONITORING OF CHRONIC HCV INFECTION

The adoption of DAAs allows for a simplified diagnostic algorithm that was not possible with prior treatment options. With pegylated interferon-based therapy, extensive pretreatment and on-treatment haematological and other investigations and viral load monitoring are required to ensure patient safety and treatment response. The currently available DAAs have far fewer side-effects than the older interferon-based treatment, and therefore eliminate the need for on-treatment monitoring in non-complex patients who do not require specialist care. Pangenotypic DAA options, such as sofosbuvir/daclatasvir and sofosbuvir/velpatasvir, eliminate the need for genotyping as well.

Fig. 2. Summary algorithm for the diagnosis, treatment and monitoring of chronic HCV infection in adults and adolescents





USG: ultrasonography AFP: alpha fetoprotein

6. SCREENING FOR HEPATITIS C

6.1 WHO SHOULD BE SCREENED FOR HEPATITIS C IN NEPAL?

The WHO 2018 guidelines recommend screening for the entire population if the prevalence is more than 2%. However, in resource-limited settings, a prioritization strategy can be followed. Screening for hepatitis C should be done in all settings as per feasibility and should always be linked to a comprehensive package of care and treatment.

The following individuals should be prioritized for testing (focused screening):

- **Adults and adolescents with a clinical suspicion of chronic viral hepatitis/ chronic liver disease**
- **Populations at risk**
  - recipients of blood transfusion prior to the introduction of anti-HCV screening of blood and blood products (before 2000)
  - persons who have received medical or dental interventions in health-care settings where infection control practices are not up to the mark
  - current or former PWID
  - persons who use/have used intranasal drugs
  - persons who have had tattoos, body piercing or scarification procedures done (routine body piercing for women does not account to high risk)
  - children born to mothers with chronic HCV infection at the age of 18 months or more
  - sexual partner of a person living with chronic hepatitis C
  - PLHIV
  - prisoners and previously incarcerated persons
  - female sex workers and MSM
  - health-care workers after accidental needle-stick or sharps injury
  - patients on haemodialysis

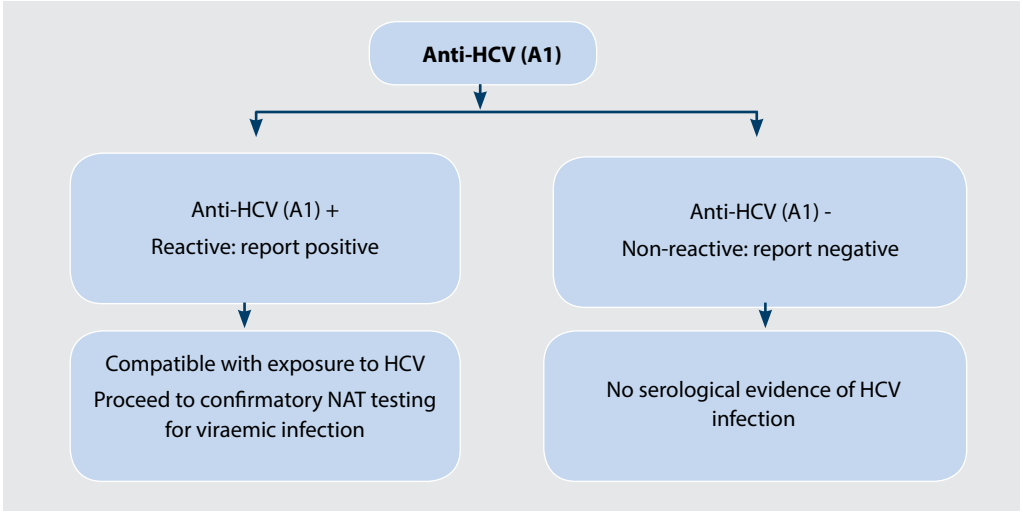
All populations at risk should be tested once and retested at least annually if exposure persists (HCV serology if negative previously, NAT if HCV serology positive previously) and after particular episodes that imply a high risk of reinfection.

**** Donors of blood and blood product and organs (mandatory screening).***

6.2 SCREENING FOR ANTI-HCV ANTIBODY

Screening for the initial detection of HCV exposure (anti-HCV) should be done with a single serological test. Screening can either be done with a rapid diagnostic test (RDT) or an immunoassay that is WHO prequalified or approved by a stringent regulatory authority. A single initial screening test is recommended before confirmatory testing, regardless of the prevalence level within the population. RDTs should be prioritized over immunoassays in settings where they are likely to increase access to testing. All antibody-positive individuals must receive supplementary testing for viraemic active infection with a NAT prior to initiation of HCV treatment. Only patients diagnosed with viraemic current infection will benefit from treatment. Patients who have spontaneously cleared HCV infection (and who are thus anti-HCV positive but test negative on confirmatory testing) should not be treated. Patients with ongoing risk should be retested.

Fig. 3. WHO-recommended single-assay testing strategy for detection of HCV antibody, irrespective of prevalence



6.3 CONFIRMATORY TESTING FOR CHRONIC HCV INFECTION

It is recommended that NAT[3] for HCV RNA (qualitative) be performed directly following a positive HCV serological test to confirm current (active) chronic infection, as 15–30% of patients will clear the virus naturally and will thus not need HCV treatment. Only patients who test positive on confirmatory testing (either NAT or core antigen test) should be assessed for treatment eligibility and placed on treatment.

3. GenXpert can be used for conducting NAT testing at the point of care, using a DBS card and/or sample transfer for confirming chronic HCV infection. Coordination for treatment availability at the center should be done in consultation with specialists.

Patients who are anti-HCV negative or have an undetectable viral load do not require further testing, and the patient can be counselled on preventive measures.

Pending decentralization of NAT testing, dried blood spot (DBS) cards can be used to collect and send whole blood samples to a centralized NAT testing facility.

Interpretation of test results

Antibody test result	HCV RNA test result	Interpretation
Negative		No HCV exposure/infection
Positive	Negative	HCV exposed. Resolved or treated infection *also includes false positive results on antibody testing
Positive	Positive	HCV exposed and current infection

6.4 COUNSELLING FOR PERSONS WITH CHRONIC HEPATITIS

6.4.1 People testing anti-HCV negative

All patients who are confirmed anti-HCV negative should receive post-test counselling with the aim of reducing or eliminating risky behaviours that could lead to future transmission. Certain high-risk groups such as PWID need to be counselled and tested periodically even when they are negative.

The counselling session should include the following:

- Explanation of the results and implications: if the antibody test is non-reactive, no antibodies were found in the blood, and this usually means the patient does not have HCV but this should not be mistaken for future immunity
- If the patient has recent or ongoing risk, an explanation of the "window" or "lag" period should be provided, along with the recommendation of retesting in 6 months
- General education on the disease, with emphasis on prevention and modes of transmission should be provided
- Certain high-risk groups such as PWID need to be in focus for periodic testing even when they are negative
- The benefits of retesting in the future should be discussed.

6.4.2 People testing anti-HCV positive

All people who receive a positive anti-HCV test result should receive education and counselling about their HCV infection, care and treatment. The aim of the counselling should be to encourage confirmatory testing and to prevent transmission before confirmatory testing.

The counselling session should include the following:

- Explanation of the results and implications. Although the patient has been infected with HCV, they may or may not currently have hepatitis C as some people are able to clear the virus, although most do not. The patient will need to have another blood test to find out if they are currently infected
- Emphasis on the need for confirmatory testing and assistance with determining the next steps
- Acknowledgement of concerns about HCV transmission, barriers to returning for additional testing, and addressing questions regarding potential illness
- General education on the disease, with emphasis on prevention and modes of transmission
- Until confirmatory testing, provision of adherence counselling on standard prevention practices to avoid transmission in case there is chronic infection.

6.4.3 People confirmed to have chronic HCV

All people who test positive with NAT are confirmed positive for chronic hepatitis C and should receive education and counselling about their HCV infection, care and treatment. The aim of the counselling should be to help the person reduce progression of liver disease and prevent them from transmitting HCV to others.

The counselling session should include:

- Explanation of the results and implications. The patient has been infected with HCV, and the confirmatory test is positive, which means the patient has hepatitis C. Emphasize that many people with hepatitis C remain healthy throughout their lives highly efficacious treatment options exist, and they can be cured in more than 95% of cases with newer drugs
- Acknowledgement of concerns about stigma, transmission and disease progression
- Education on how to prevent transmission to others, especially in the case of PWID. Counselling should also include an explanation of how HCV is not transmitted (sneezing, coughing, sharing drinking glasses, utensils)
- Counselling all patients that alcohol can worsen the condition and that it is important to abstain from alcohol. Provision of support, if necessary, in identifying resources to support the cessation of alcohol consumption
- Vaccinations/testing. Screen for HBV and provide vaccination if negative, and initiate HBV treatment before HCV if available
- Consider testing for HIV
- Avoid new medicines, including over-the-counter and herbal agents without first checking with a health-care provider
- Helping patients to understand the need to seek additional care and potential treatment and connecting them with the necessary services if not available on-site.

6.4.4 People testing RNA negative

All patients who are confirmed to be RNA negative should receive post-test counselling with the aim of assessing and then reducing or eliminating risky behaviours that could lead to future transmission.

The counselling session should include the following:

- Explanation/interpretation of results. The patient was anti-HCV positive but RNA negative, so the patient was exposed to HCV, but then cleared the virus naturally or has been treated and cured. They do not have chronic hepatitis C
- Education on the disease if patient has not received this education earlier. Highlight the fact that not being currently infected should not be confused with immunity to infection upon subsequent exposure
- If there is an ongoing risk to the patient, emphasize on disease transmission and prevention awareness
- Emphasize the benefits of retesting in the future if engaging in risky behaviours.

6.5 SPECTRUM OF DISEASE IN HCV INFECTION

The spectrum of disease in those infected with HCV extends from mild fibrosis to compensated followed by decompensated cirrhosis and HCC. As part of the care of persons with HCV-related cirrhosis, it is essential to assess and follow up the patient for progression of the disease and for evidence of HCC. Compensated cirrhosis may also progress over time to decompensated cirrhosis associated with ascites, oesophageal and gastric varices, and eventually to life-threatening liver failure, renal failure and sepsis. The diagnosis of decompensated liver disease is made on both laboratory and clinical assessment, and therefore, before starting treatment, a careful medical examination of patients must be done.

6.6 IDENTIFICATION OF HCV GENOTYPE (GENOTYPING)

Genotyping of HCV can be used to select different combinations of DAAs and decide on the duration of therapy. However, genotyping is not required by the National Programme, as it is costly and unavailable in most low-resource settings. Pangenotypic regimens are effective for all genotypes and therefore eliminate the need for this step. In Nepal, the combination of sofosbuvir and daclatasvir and sofosbuvir/velpatasvir are recommended as pangenotypic regimens. Additionally, in instances where patients fail their first-line treatment, genotyping, if accessible, can be considered to guide the selection of appropriate second-line treatment in consultation with a hepatologist.

6.7 PRE-TREATMENT ASSESSMENT

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

1. Alcohol consumption (see Annex 1: Alcohol consumption assessment: Audit interview questions)
2. HIV status, current antiretroviral therapy (ART) regimen
3. Pregnancy status – contraception during treatment and 6 months after end of treatment
4. Baseline biochemistry tests
    a. Liver function tests (LFT) – alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphate, serum bilirubin
    b. Renal function assessment – blood urea and creatinine
    c. Complete blood picture (CBP) to determine the platelet count (Plt)
5. APRI
6. Exclusion of HCC by ultrasonography (USG) if the patient has signs of end-stage liver disease (ESLD)
    a. Alpha-fetoprotein (optional)
7. Screen for symptoms of tuberculosis (TB) such as cough for more than 2 weeks, fever, night sweats, chest pain, etc. and if present, refer for TB tests
8. Other laboratory tests as advised by the physician.

All patients with HCV should be screened for evidence of current or prior HBV infection by testing for HBsAg before initiating HCV therapy as cases of HBV flare-up, including fulminant hepatitis and death, have been reported in HBsAg-positive patients. If found to be HBsAg positive, the patient should be started on HBV treatment first and then treated for HCV. If negative for HBsAg, then vaccinate against HBV (zero, one and six months).

Rapid vaccination of 0, 7, 21 days followed by a fourth dose 12 moths after the first dose can be done for someone who wants to get married or for those scheduled for deployment.

Of these tests, the minimum tests to be performed prior to initiating patients on all-oral DAA therapy are:

AST, Platelet and serum creatinine.

The AST and Plt are used to calculate the AST-to-platelet ratio index (APRI) score to stage the degree of cirrhosis. Serum creatinine level is used to determine renal function. An APRI calculator can be found at 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: shrunken liver with a hard lower edge, spider naevi, palmar erythema, white nails, gynaecomastia and wasting syndrome.

Clinical signs of decompensation: jaundice, ascites, hepatic encephalopathy, variceal bleed (haematemesis and melaena).

6.8 STAGING AND SCORING

Non-invasive tests such as the APRI, abdominal USG and/or liver elastography are the preferred methods for staging. Liver biopsy is no longer recommended as a routine investigation for staging. Staging is important to identify patients with impaired liver function and advanced stages of the disease. Such patients should be prioritized for treatment or may need longer treatment durations or require referral to specialists for clinical management in certain instances.

Table 1. Aminotransferase-to-platelet ratio index (APRI)

Non-invasive test	Components assessed	Non Cirrhosis	Cirrhosis
APRI	AST and platelet count	< 2.0	>= 2.0
APRI= [(AST (IU/L)/AST_ULN (IU/L)) x 100]/ platelet count (10^9/L)			

APRI: aminotransferase/platelet ratio index; AST: aspartate aminotransferase; IU: international unit; ULN: upper limit of normal (often 40 IU/mL)

Example of APRI calculation
AST level (IU/L) = 60
AST upper limit of normal (IU/L) = 40
Platelet count (109/L) = 133 000/cmm (ref: 150 000–400 000/cmm) = 133
APRI = [{60/40} x 100]/133
APRI = [1.5 x 100]/133
APRI = 150/133
APRI = 1.128

6.8.1 If significant fibrosis/cirrhosis (>=2): screen for hepatocellular carcinoma and portal hypertension; refer to a liver specialist

- **abdominal ultrasound every 6 months** to rule out HCC and portal hypertension;
- **if cirrhosis:** baseline oesophagogastroduodenoscopy (EGD) to screen for varices and refer to higher center for standard of care

- Cirrhosis without varices, EGD 2-3 years
- Cirrhosis with small varices, EGD every 2-3 years
- Cirrhosis with large varices, No repeat EGD for diagnosis

6.8.2 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).

Prioritization of patients for HCV treatment

When resources are limited, the following patients should be prioritized for treatment as they are at higher risk for disease progression and developing complications.

- Patients with cirrhosis (with or without decompensation)
- HIV/HCV and HBV/HCV-coinfected patients
- PWID, persons on haemodialysis (PWID should also be referred for needle/ syringe exchange programmes and OST).

6.9 REFERRAL TO A SPECIALIST

Patients with decompensated cirrhosis, irrespective of the APRI score, should be referred to a specialist for clinical management. The referral pathways in Nepal are listed below.

CONDITION	REFER TO
CLINICAL FEATURE OF DECOMPENSATION (ASCITIS, BLEED, HAEMATEMESIS, JAUNDICE)	HIGHER CENTER (SPECIALIST)
FEATURE OF CIRRHOSIS WITH OR WITHOUT DECOMPENSATION	
APRI > = 2.0	

7. TREATMENT OF PERSONS WITH CHRONIC HEPATITIS C

7.1 GOAL OF THERAPY

The goal of therapy is to cure HCV infection to prevent the complications of HCV-related liver and extrahepatic diseases (hepatic fibrosis, cirrhosis, HCC, cryoglobulinaemia, lymphoma, death); improve quality of life; remove stigma and prevent onward transmission of HCV (treatment as prevention).

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

7.2 WHO SHOULD BE TREATED FOR CHRONIC HEPATITIS C INFECTION?

The latest WHO recommendations on hepatitis C infection (2018) advocate for treatment with pangenotypic regimens of all patients living with chronic hepatitis C (regardless of fibrosis status).

Hence, in Nepal, the policy of **TREAT ALL** with confirmed chronic HCV infection will be followed. All patients with chronic HCV infection who are willing to be treated and who have no contraindication to treatment should be treated, irrespective of fibrosis status or prior treatment history, i.e. both treatment-naive and treatment-experienced patients with interferon-based regimens/treatment failure to achieve a sustained virological response (SVR).

Treatment must be considered without delay in the following groups. As these are difficult to diagnose, such cases should be referred to higher centres.

- **Patients with cirrhosis, with or without** decompensation;
- **Patients with clinically significant extrahepatic manifestations** (depression, vasculitis with HCV-related mixed cryoglobulinaemia, HCV immune-complex nephropathy, non-Hodgkin B-cell lymphoma;)
- **Patients with HCV recurrence after liver transplantation;**
- **Patients at risk of a rapid evolution of liver disease because of concurrent comorbidities** (non-liver solid organ or stem cell transplant recipient, HBV coinfection, HIV coinfection, diabetes);

- **Individuals at high risk of transmitting HCV:** PWID, MSM with high-risk sexual practices (involving mucosal trauma, group sex, chemsex, which is the use of any combination of drugs that includes crystal methamphetamine, mephedrone and other cathenones – specifically for the purposes of gay sex.), women of childbearing age who wish to get pregnant (risk of MTCT in mono-infected women is 4–8%, and 10.8–25% in case of those with HIV co-infection), patients on haemodialysis and incarcerated individuals.

7.3 TREATMENT OPTIONS

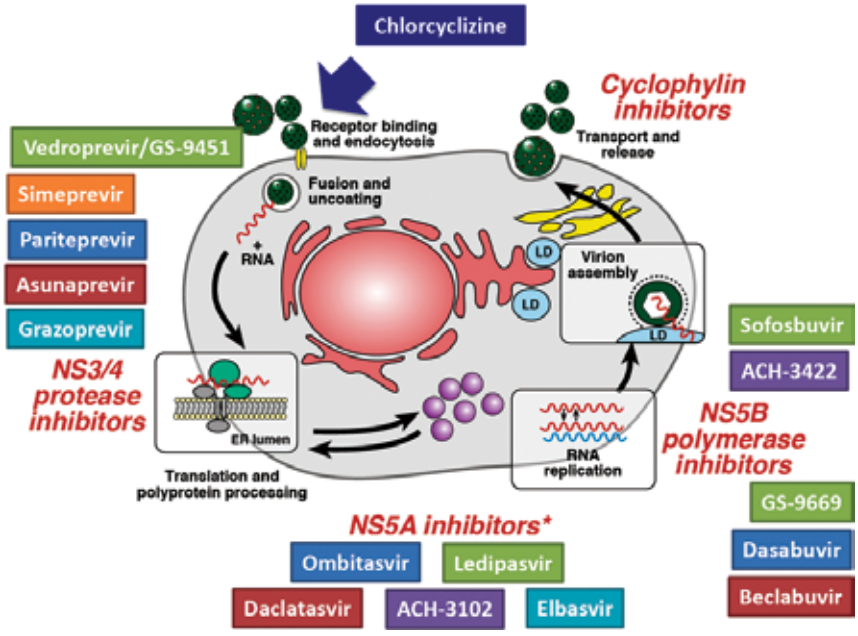
7.3.1 Direct-acting antivirals (DAAs)

The treatment of chronic HCV infection has been transformed by the advent of oral DAAs. These medicines require a shorter treatment duration, are associated with fewer side-effects, and result in significantly higher SVR rates than pegylated interferon-based treatment regimens. Given these benefits, it is recommended that DAAs be used for the treatment of HCV rather than pegylated interferon regimens.

THERE ARE VARIOUS CLASSES OF DAAS:

- protease inhibitors (PIs)
- nucleotide and non-nucleotide NS5B inhibitors
- NS5A inhibitors.

Fig. 4. **Site of action of DAAs**



Source: Bhawana Poonia, Shyam Kottili, Newer therapeutics for hepatitis C, http://dx.doi.org/10.3978/j.issn.2305-5839.2015.10.06

7.4 RECOMMENDED HCV TREATMENT REGIMENS IN NEPAL

Table 2. Recommended HCV treatment regimen for adult age 18 years and above

No Cirrhosis	Compensated Cirrhosis	Decompensated Cirrhosis
SOF/DCV x 12 weeks	SOF/VEL x 12 weeks	SOF/VEL x 24 weeks

Table 3. Recommended HCV treatment regimen for children and adolescents (age 12-17 years)

Recommendations for treatment	Regimen type	Treatment duration (weeks)	
		No cirrhosis	Cirrhosis
Regimen	SOF/LEDI	12	12

* in less than 12 years, differ treatment until 12 years of age

treatment with interferon based regimen should no longer be used

7.4.1 HCV Treatment regimens and duration

Table 4. Treatment regimen and duration

Regimen	Drugs	Duration	Special considerations	Comments
Option	**Sofosbuvir + velpatasvir**	**12 weeks** (all genotypes) for compensated cirrhotic and **24 weeks** for decompensated cirrhotic patient (APRI >=2.0)	Velpatasvir is safe for use with most HIV medications but should be avoided in those taking ritonavir-boosted tipranavir, efavirenz, atravirine, and nevirapine. SOF/VEL is not recommended in patients with severe renal impairment (estimated glomerular filtration rate [GFR] <30 mL/min/1.73m^2) or end-stage renal disease.	*See* Annex 2, Table 2.1 for patients on ART
	Sofosbuvir + daclatasvir	12 weeks (all genotypes) for non-cirrhotic patients (APRI <2.0)	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 dosage to 30 mg per day with the antibacterials clarithromycin, telithromycin, erythromycin and the antifungals ketoconazole, itraconazole, posaconazole and voriconazole.	*See* Annex 2, Table 2.1 for patients on ART

7.4.2 Dosing for HCV treatment regimens

Table 5. HCV treatment dosing and frequency

Regimen	Dosage per tablet	Dosing frequency and timing
Velpatasvir/ Sofosbuvir	100 mg/400 mg fixed-dose combination (FDC) (special considerations for ART patients in Annex 2, Table 2.1)	Once daily
Daclatasvir*/ Sofosbuvir	30 mg and/or 60 mg/400 mg tablet (special considerations for ART patients	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
Sofosbuvir	400 mg tablet	Once daily – morning
Sofosbuvir/ledipasvir	400 mg/90gm	Once daily
Sofosbuvir/ribavirin (for children 12-17 years)	Sofosbuvir is same as for adults, 400 mg daily, Ribavirin has to be weight based (<47 kg @ 15 mg/Kg in 2-3 divided doses; 47-49 Kg, 600 mg daily; 50-65 Kg, 800 mg daily; 66-80 Kg, 1000 mg daily)	

*****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 ketoconazole, itraconazole, posaconazole and voriconazole.*

7.4.3 Dose adjustment in renal impairment

In patients with renal impairment on sofosbuvir-containing regimen with GFR >30ml/min are treated as any other patients but if GFR <30ml/min, refer to higher center.

7.5 APPROACH TO TREATMENT

Fig. 5. Approach to treatment

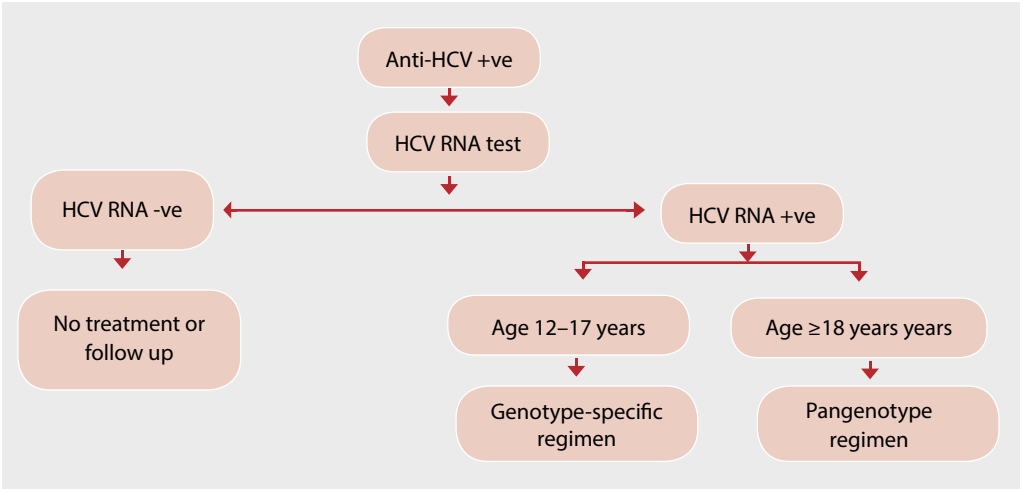


Fig. 6. Treatment of people >18 years with hepatitis C

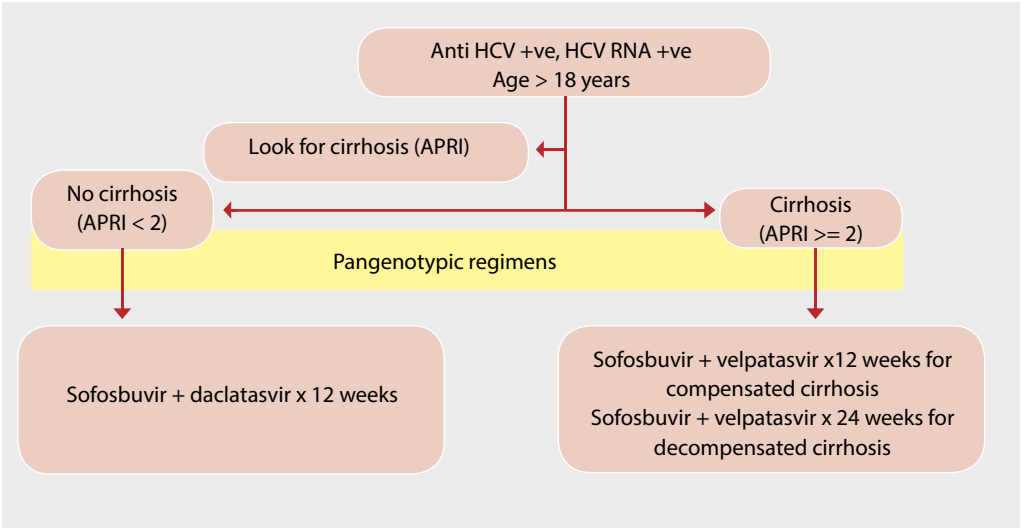
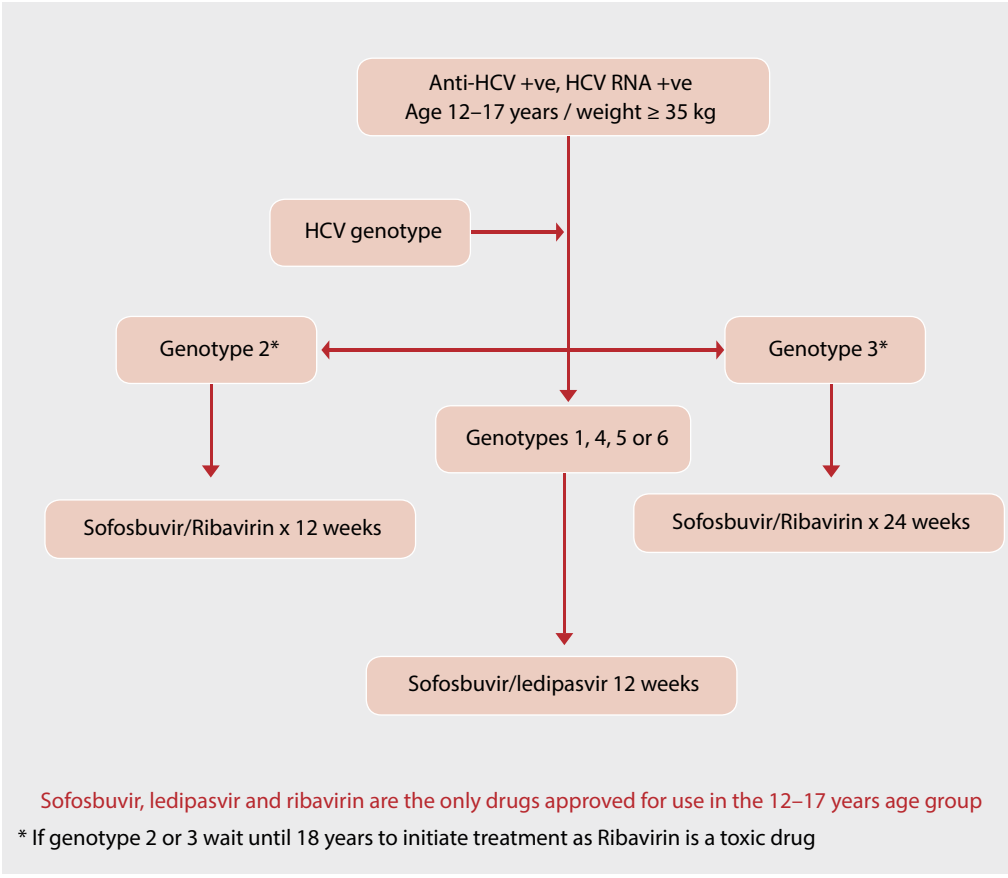


Fig. 7. Treatment of children and adolescents with hepatitis C



Sofosbuvir, ledipasvir and ribavirin are the only drugs approved for use in the 12–17 years age group

* If genotype 2 or 3 wait until 18 years to initiate treatment as Ribavirin is a toxic drug

7.6 TREATMENT MONITORING

7.6.1 Treatment monitoring

Treatment monitoring is not generally required when using all-oral DAA regimens, 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 [CrCl]) as both exhibit renal clearance.
- Treatment with ribavirin-based regimens: severe haemolytic anaemia with significant initial fall in haemoglobin may occur; therefore, careful monitoring should be initiated. CBP and renal function should be monitored at baseline before the initiation of treatment, at week 4 during the treatment and at week 12 after the completion of treatment.[4]

4. WHO Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection Geneva: World Health Organization; 2018.

- CBP should be monitored if on ribavirin.
- Direct monitoring of viral replication through NAT or core antigen testing during treatment is NOT recommended.
- Complex patients in specialist care may require more advanced biochemistry and haematology monitoring and prothrombin time.

** Attending physicians should stop treatment at their own discretion at any time for reasons such as clinical deterioration and life-threatening conditions.

7.6.2 Assessment of response to therapy (post-treatment)

- An HCV RNA viral load test should be conducted at 12 weeks after the completion of treatment to confirm SVR (SVR12). Patients who do not achieve SVR should be referred to a specialist for more advanced testing and retreatment. Core antigen testing is currently not recommended as a test to determine cure.
- Patients with cirrhosis who achieve SVR12 still need to be followed up regularly for the assessment of complications of cirrhosis and HCC with USG with/without alphafetoprotein (AFP). Patients with cirrhosis should be followed up with ultrasound within 6 months.
- Patients who do not achieve SVR should be referred to a specialist.
- Patients without cirrhosis do not need any follow up after achieving SVR12.

7.7 CONTRAINDICATIONS TO HCV THERAPY

There are a few contraindications to treatment with DAAs:

- Use of certain cytochrome p450-inducing agents such as carbamazepine and phenytoin is contraindicated with all DAA regimens due to the risk of significantly reduced concentrations of DAAs
- PI DAAs are contraindicated in patients with current or previous decompensated cirrhosis (risk of increased concentration of the PI and of increased adverse reactions)
- In patients with an estimated glomerular filtration rate (eGFR) <30 mL/min, sofosbuvir should be used only if alternative treatment approved for use in patients with severe renal impairment is not available.
- Due to lack of safety data, DAAs are contraindicated during pregnancy.

8. PATIENT PREPARATION/EDUCATION

8.1 PATIENT PREPARATION EDUCATION

The key element of effective HCV clinical management is proper counselling and ensuring patient adherence. Pre-treatment assessment and preparation are very important. Treatment education needs to take place before and during treatment.

Before treatment: Explain; On-treatment: Assess at each visit

- **Drug regimen prescribed/taken** (number of tablets, number of times per day, with food if ribavirin)
- **Possible adverse reactions**, when and whom to contact/consult in case of adverse reactions
- **Importance of adherence to therapy** (main criterion for treatment success)
  - follow the dosing recommendation.
  - do not miss any dose.
  - in case a dose is missed: if less than 18 hours after usual time, take the dose right away, and the following dose at the usual time; if more than 18 hours after usual time, do not take the missed dose and take the following dose at the usual time.
  - in case of vomiting: if vomiting occurs less than 3 hours after taking the DAA, take another dose; if more than 3 hours, do not take an extra dose.
- **Risk of drug–drug interactions** (DDIs) that may expose the patient to decreased efficacy or increased toxicity of DAAs and/or co-medications prescribed, over-the-counter drugs, herbal therapy, recreational drugs. The patient **needs to report the use of other medications at each visit and consult the team before starting any new medication while on HCV treatment. Specifically check that no contraindicated drug is currently being taken**.
- Inform women of childbearing potential of the **necessity to practise active contraception** during anti-HCV treatment and until 6 months after treatment with DAAs and ribavirin has been discontinued.

8.2 TREATMENT MONITORING

During treatment: monitor adherence and tolerance monthly.

Re-treatment patient or genotype 2 or 3 patient on DAAs + ribavirin: close clinical and biological monitoring is required as such patients have an increased risk of adverse events while on ribavirin.

Table 8 summarizes the recommended systematic biological follow up at baseline (DAA initiation), on treatment and after treatment completion. If the patient has been tested for HCV RNA in the past 6 months before treatment, those results can be used as the baseline HCV RNA (to confirm chronic HCV infection).

Table 6. Monitoring framework before and during DAA treatment

Time	DAAs alone			DAA + ribavirin*		
	CBP, renal, liver function	Adherence, side-effects	HCV RNA	CBP, renal, liver function	Adherence, side-effects	HCV RNA
Baseline	X#		X	X		X
Week 4	X	X		X	X	
Week 12 after end of treatment	X		X	X		X

DAA: direct-acting antiviral; CBP: complete blood picture
*recommended treatment for adolescents with genotypes 2 and 3 HCV infection
If Hb > 10g/dl then no need to check again at week 4

Source: Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. Geneva: WHO; July 2018.

8.2.1 Treatment adaptation/discontinuation

Treatment must be stopped in case of severe (grade 3–4) adverse events or in case of a hepatitis flare (ALT levels more than 10 times the upper limit of normal [ULN], if not already present at the time of starting treatment).

In patients receiving ribavirin, if severe anaemia occurs (haemoglobin <10 g/dL), the dose of ribavirin should be adjusted downward by 200 mg in decrements; a more rapid reduction in dose may be required for patients with rapidly declining haemoglobin levels, particularly if the baseline haemoglobin was low. Ribavirin administration should be stopped if the haemoglobin level falls below 8.5 g/dL.

8.3 ASSESSMENT OF TREATMENT RESPONSE

The end-point of hepatitis C treatment is undetectable HCV RNA in the serum or plasma by a sensitive assay (limit of detection [LoD] <15 IU/mL) 12 weeks (SVR12) after the completion of treatment.

8.4 POST-TREATMENT FOLLOW UP OF PATIENTS WHO ACHIEVE AN SVR

8.4.1 Patient without cirrhosis

- The patient can be considered to be definitively cured of hepatitis C.
- Patients with pre-existing cofactors of liver disease (excessive alcohol drinking, obesity, alcohol, type 2 diabetes) should be periodically assessed clinically, as needed.

8.4.2 Patients with cirrhosis

Continue follow up for the following:

- Cirrhosis without varices, EGD 2-3 years
- Cirrhosis with small varices, EGD every 2-3 years

8.4.3 Patients at risk of re-infection

- Patients such as PWID and MSM should benefit from clear explanations on the risk of reinfection. Behavioural modifications should be positively reinforced, and access to harm reduction strategies made available.
- In case of ongoing risk behaviour, monitoring for reinfection ideally through biannual (or at least annual) HCV RNA testing is recommended, in addition to testing after episodes that are likely to carry a high risk of re-infection.

8.5 DRUG–DRUG INTERACTIONS

The main expected DDIs are listed in Annex 2. **Apart from ART, the main DDIs to consider with DAAs are fibrates/statins, amiodarone, digoxin, carvedilol (beta-blocker), amlodipine, diltiazem, rifampicin.**

For a complete DDI assessment, use www.hep-druginteractions.org.

In case of expected DDIs between the current medication and DAA regimen to be started, ask the following questions:

I. Are all the co-administered drugs necessary during the period of HCV treatment (it might be possible to stop a drug such as a statin for 12 weeks)?
II. If not, is there an alternative in the same therapeutic class without a drug interaction?
III. Can a drug interaction be managed by a change of dose or a clear monitoring plan?

8.6 PHARMACOVIGILANCE

Despite being effective and characterized by a very low rate of adverse effects in clinical trials, few data are available on adverse events in real-life studies of DDAs. New antiviral drugs require careful follow up of any significant adverse event that may occur and can affect adherence. Special populations, such as the elderly and those with comorbidities, should always be managed with caution to avoid the development of serious side-effects. Any side-effect observed should be promptly identified, managed and reported to the Department of Drug Administration (DDA), Nepal.

9. MANAGEMENT OF SPECIAL SITUATIONS AT SPECIALIZED CENTRES

9.1 DAA TREATMENT FAILURE

Most of the situations identified as "DAA failure" are new HCV infections after the completion of DAA treatment rather than lack of viral suppression on treatment.

The following factors increase the risk of DAA failure:

- Baseline resistance-associated substitutions (RASs);
- Cirrhosis/inadequate classification of the fibrosis state at baseline leading to inadequate treatment or duration of treatment;
- Premature discontinuation of treatment due to side-effects;
- DDIs;
- Poor adherence.

Sofosbuvir has a high barrier to resistance (exceptional clinically meaningful RASs that disappear very rapidly after SOF cessation).

On the contrary, most patients with failure of PIs, NS5A inhibitors (LDV, VEL, DCV) and non-nucleotide NS5B inhibitors (dasabuvir) have RASs. In particular, NS5A inhibitor-associated RASs (LDV, VEL, DCV) remain detectable long after DAA cessation, and HCV strains resistant to NS5A I are fit and remain dormant for years.

For any treatment failure change the duration of treatment to 24 weeks, Add Ribavirin and change the drugs from previous treatment regimen. Treatment failure to pegylated interferon (IFN) patients are treated as treatment naive patients.

The dose of ribavirin is weight-based: <75 kg = 1000 mg/day; ≥75 kg = 1200 mg/day. In patients with decompensated cirrhosis, ribavirin can be started at 600 mg/day and the dose subsequently adjusted depending on tolerance. If there is a contraindication to the use of ribavirin or poor tolerance to ribavirin resulting in discontinuation, the treatment duration with DAAs will be 24 weeks.

The lower SVR rate in patients with decompensated cirrhosis compared to patients with compensated cirrhosis is attributed to treatment discontinuation rather than virological failure.

Patients with decompensated cirrhosis should be treated in experienced centres (with access to liver transplantation). Close monitoring is required during therapy, with the possibility of stopping HCV therapy if there is evidence of worsening decompensation during treatment.

A patient with decompensated cirrhosis and no HCC waiting for a liver transplantation with a MELD score <18–20 should be treated before liver transplantation and started on HCV therapy as soon as possible to complete a full course of treatment before transplantation.

A patient with decompensated cirrhosis and no HCC waiting for a liver transplantation with a MELD-score ≥18–20 should be transplanted first, without HCV therapy, and HCV infection treated after the transplant. If the waiting time on the transplant list exceeds 6 months, HCV therapy can be initiated before transplantation.

10. TREATMENT RECOMMENDATIONS FOR SPECIFIC POPULATIONS

10.1 HIV COINFECTION

The WHO 2018 guidelines for the treatment of HCV recommend that all persons with HIV/HCV coinfection be considered for HCV treatment as there is generally more rapid progression of liver fibrosis in HIV/HCV-coinfected persons, especially in patients with a CD4 count of <200 cells/mm^3. In addition, the risk of hepatic decompensation remains higher in coinfected patients even if HIV infection has been successfully controlled.

The choice of ART for persons with HIV/HCV coinfection should follow the same guidelines as for those with HIV alone, although the choice of HCV treatment must consider DDIs between ARVs and DAAs and dose adjustments of DAA therapy, depending on the DDI in question. If there is a need to alter the HIV regimen in order to avoid a DDI between the ART and DAA regimen, this should be done only in consultation with the patient's HIV treatment provider. While treatment of this population was traditionally difficult with interferon- and ribavirin-containing regimens, DAA therapy has simplified treatment, and the treatment of monoinfected and coinfected patients with DAAs is now largely the same.

10.1.1 Treatment initiation

In most cases, it is advisable to first initiate treatment for HIV and achieve HIV suppression before staring HCV treatment, although in specific circumstances, it may be advisable to treat the HCV infection first.

This could include persons at risk of rapid progression of liver disease but not experiencing significant immunosuppression.

It is recommended that DAA treatment to be initiated once the HIV viral load is suppressed, regardless of the CD4 count.

In the era of the test-and-treat strategy and rapid initiation of ART, ART will in most cases be started first, and it is recommended to delay HCV treatment initiation by one month after ART initiation to assess tolerance to ART. Similarly, if the ART regimen needs to be modified due to DDIs with DAAs, it is recommended to wait for 4 weeks after ART modification before starting DAAs (reduce HIV viral load after 4 weeks on the new ART regimen, but do not wait for the result to start DAA therapy).

ART may be given initially in HIV/HCV-coinfected patients to avoid DDIs, keeping in mind that VEL is contraindicated with efavirenz (EFV): a dolutegravir (DTG)-based regimen would be the recommended first-line ART in case of HIV/HCV coinfection.

If a patient is diagnosed concomitantly with both advanced liver fibrosis/cirrhosis due to confirmed chronic hepatitis C and HIV infection with a CD4 count >500/mm^3, at low risk of transmitting HIV and rapidly available DAA therapy, treating HCV first and delaying ART by 3 months is a reasonable option (less pill burden, less risk of hepatotoxicity and DDIs).

10.1.2 Choice of ART regimen in patients with chronic hepatitis

Non-nucleoside reverse transcriptase inhibitors

EFV is the preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) in patients who have HIV and HCV coinfection. There is no cross-liver toxicity between EFV and nevirapine (NVP). NVP should be avoided if the AST and/or ALT are >5 ULN and is contraindicated in the case of decompensated cirrhosis. Liver function should be monitored at treatment initiation and throughout.

Nucleoside reverse transcriptase inhibitors

Zidovudine (ZDV) has been associated with hepatic steatosis leading to some hepatic dysfunction. However, nucleoside reverse transcriptase inhibitors (NRTIs) are usually well tolerated during HIV treatment in coinfected patients.

Protease inhibitors

PIs might affect the liver either directly or by affecting the metabolism of other drugs to reach hepatotoxic ranges. Ritonavir (RTV), particularly at higher doses, has been associated with increased liver function abnormalities and hepatotoxicity. Atazanavir (ATV) and darunavir (DRV) are not recommended in case of cirrhosis.

Integrase strand transfer inhibitors

The integrase strand transfer inhibitors (INSTIs) raltegravir (RAL) and dolutegravir (DTG) are not hepatotoxic.

10.2 PEOPLE WHO INJECT DRUGS AND PATIENTS RECEIVING OPIOID SUBSTITUTION THERAPY

People with a history of injecting drug use include former injectors who have ceased injecting, some of whom might be on OST (methadone or buprenorphine) and recent/current PWID.

10.2.1 Screening

PWID should be prioritized for screening due to their high rates of HCV prevalence, morbidity and ongoing transmission. Screening should be performed annually as an integral part of the harm reduction package among PWID, which also includes OST, sterile injection equipment and addiction counselling. Screening for HBV and HIV is also recommended.

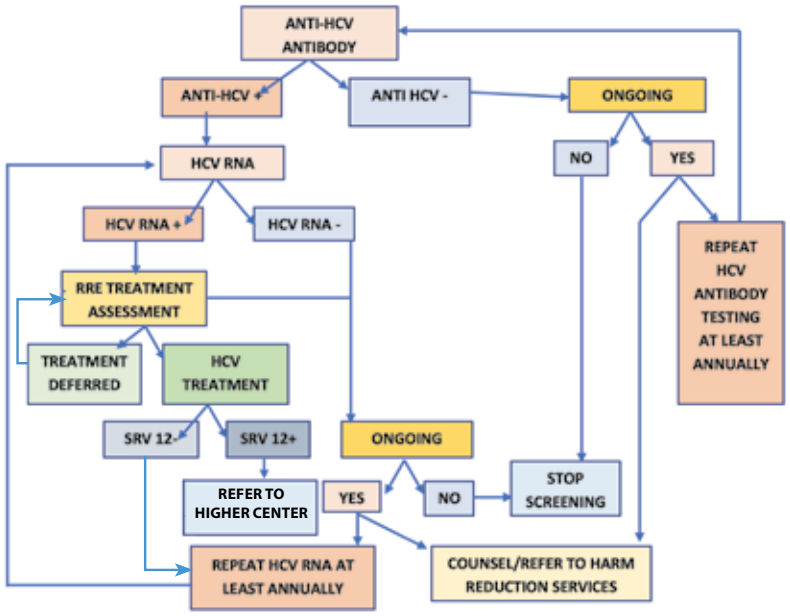
For PWID who have successfully achieved SVR12 and are continuing to inject drugs, reinfection is possible. Therefore, screening with NAT should be continued annually.

PWID are at increased risk of HCV-related disease and transmission, as well as all-cause mortality and morbidity. Therefore, they require specialized care and should be considered as a priority for HCV treatment. When caring for PWID, the central tenets of respect and non-discrimination should be followed.

10.2.2. Care and treatment

HCV treatment has been proven effective in PWID and may have a treatment-as-prevention effect if networks of drug users are treated. Multiple studies have demonstrated that there is no difference between SVR12 rates for PWID and non-PWID, even when the PWID are active users. A recent study of treatment response to SOF/VEL among people receiving OST demonstrated no impact of OST on adherence, treatment completion, SVR or safety. PWID who complete treatment must receive counselling on the possibilities of reinfection due to continuing risk behaviours such as sharing of needles and paraphernalia.

Fig. 8. HCV testing in people who inject drugs



Pre-treatment education should include discussion of HCV transmission, risk factors for progression of fibrosis, treatment, risk of reinfection and harm reduction strategies.

Consideration must be given to DDIs between both prescribed and non-prescribed drugs; no DDI exists between DAAs and methadone or buprenorphine, but the patient should be monitored for signs of over-/under dosing.

Reinfection may occur. Thus, patients who injected drugs during the year preceding treatment should ideally be offered biannual, or at least annual, testing for reinfection after achieving DAA-induced SVR, in addition to testing after episodes that may imply a high risk of reinfection (*see* post-treatment follow up, section 8.4). When reinfection is detected, a new course of HCV treatment should be offered, with a 3-month delay to allow for possible spontaneous clearance, except if urgent treatment is needed.

10.3 WOMEN OF CHILDBEARING POTENTIAL

None of the **DAAs** has been evaluated in pregnant women. Thus, women of childbearing potential should be counselled to use **effective contraception during treatment and for 6 months after completion of therapy.** All contraceptive measures can be safely used during HCV therapy with SOF, LDV, DCV, VEL, RBV.

Ribavirin is associated with fetal abnormalities: it is contraindicated in pregnant women and those with childbearing potential unless effective contraception can be guaranteed during treatment and for 6 months after completing therapy.

A pre-treatment pregnancy test should be conducted prior to treatment initiation.

10.4 CHILDREN (<12 YEARS) AND ADOLESCENTS (12–17 YEARS)

10.4.1 Screening

Targeted screening is indicated for children who have had medical interventions or who have received blood products in countries where screening of blood is not carried out routinely or where medical equipment is inadequately sterilized. Children born to mothers with HCV infection are also at risk; the risk of vertical (mother-to-child) transmission is approximately 4–8% and is substantially higher in children born to HCV/HIV-coinfected mothers (10.8–25%). All children born to an HCV-infected mother should be tested for HCV infection from the age of 18 months.

Adolescents are at risk via injecting drug use.

10.4.2 Care and treatment

Integrated health care is a key aspect of child health-care provision. Linkage is necessary with maternal and child health services, primary care, services for PWID and, if required, referral for HIV care and treatment.

Cirrhosis and HCC are rare in children; however, liver disease may progress during early life. Individuals with thalassaemia and iron overload, as well as those with HIV coinfection and childhood haematological or solid tumours receiving chemotherapy may develop advanced hepatic fibrosis.

10.5 DECOMPENSATED CIRRHOSIS

Decompensated cirrhosis is associated with jaundice, ascites, coagulopathy, encephalopathy, and oesophageal and gastric varices. It can eventually progress to liver failure, renal failure and sepsis, leading to multiorgan failure syndrome (MOFS), all of which are life-threatening. The diagnosis of decompensated liver disease is based on both laboratory and clinical assessment, and therefore a careful medical examination of patients must be made before starting treatment. While certain treatment regimens have been shown to be safe for use in patients with decompensated liver cirrhosis, close monitoring is required in these patients, and it is thus recommended that treatment for these patients be considered only under close supervision of specialist teams with experience in treating and managing complications.

10.6 TREATMENT-EXPERIENCED PATIENTS

It is recommended that all treatment-experienced patients be referred to specialist teams with experience in treating and managing patients with complications to help determine tailored regimens.

10.7 COMORBIDITIES

10.7.1 HCV/HBV coinfection

HCV may suppress HBV replication in acutely or chronically infected patients with reduction of HBsAg serum titre observed in HCV/HBV-coinfected patients. Although some studies demonstrate mutual suppression of HCV and HBV, dual infection with both viruses may lead to increased hepatitis-related morbidity. Additionally, during treatment with DAA medications and after HCV clearance, there is a risk of HBV reactivation and potentially fatal acute flares.[5]

Given the risk of reactivation, all patients with HCV should be screened for evidence of current or prior HBV infection before initiating HCV therapy. The US Federal Drug Administration (FDA) recommends screening of all patients for evidence of current or prior HBV infection by estimating HBsAg and anti-HBc titres, as cases of liver flares during HCV treatment have been reported in HBsAg-positive patients and those with evidence of resolved infection (HBsAg-negative and anti-HBc-positive). Patients with chronic HCV infection with evidence of active or resolved HBV infection should be treated by physicians with expertise in managing and monitoring hepatitis B and consider HBV antiviral treatment in HBV/HCV-coinfected patients. It has been recommended that patients who meet the criteria for treatment of active HBV infection be started on therapy before HCV DAA therapy is started. Monitoring of patients with active or resolved HBV infection should include clinical and laboratory monitoring (i.e. HBsAg, serum aminotransferase levels, bilirubin) for hepatitis flare or HBV reactivation during DAA treatment and post-treatment follow up.

- **Test all patients initiating DAAs** for HBsAg
  - if negative: vaccinate against HBV.
  - if HBsAg positive: treat with nucleoside/nucleotide analogue (tenofovir, entecavir) and monitor ALT until SVR12. HBV treatment may then be discontinued but ALT will need to be monitored regularly (risk of hepatitis B flare).

5. WHO Guidelines for the screening care and treatment of persons with chronic hepatitis C infection, updated version. Geneva: WHO; April 2016.

10.7.2 HCV/TB coinfection

Screening for tuberculosis (TB) should be done before considering HCV treatment, especially among those with advanced immunosuppression. It is reasonable to exclude active TB infection if cough, fever, weight loss or night sweats are absent.

Concurrent treatment of TB and HCV should be avoided secondary to interactions between HCV DAAs and TB medications. Specifically, anti-tuberculosis medicines such as rifampicin, rifapentine and rifabutin modulate the concentration of several DAAs used for treating HCV infection when given concurrently. Active TB should generally be treated first, with close monitoring of liver function tests due to increased risk of antimycobacterial-induced hepatotoxicity in TB/HCV-coinfected patients.

10.7.3 HCV and alcohol use

The consumption of alcohol, even in moderate amounts, in people with chronic HCV infection results in more rapid progression of advanced liver disease and HCC.[6] People diagnosed with chronic HCV should be counselled to limit or abstain from alcohol consumption and offered access to alcohol cessation services, where possible. The WHO Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) project can provide a framework and tools for evaluating alcohol dependence and implementing counselling.

For patients with alcohol disorders who are eligible for treatment, it is recommended that patients stop drinking prior to treatment due to its deleterious effects on adherence.For patients who continue drinking during treatment, clinicians should provide extra support to ensure adherence.

10.7.4 HCV/non-alcoholic steatohepatitis

Non-alcoholic steatohepatitis (NASH) is a liver disease characterized by a build-up of fat in the liver along with inflammation and damage. Like hepatitis C, NASH develops slowly over time and progresses to advanced liver disease.

Patients with chronic HCV with NASH are a recommended target population for treatment to halt the progression of liver disease. Patients should be monitored carefully during treatment for any complications arising from more severe underlying liver disease. There is currently no treatment for NASH other than lifestyle changes to reduce obesity and promote liver health.

6. Vandenbulcke H, Moreno C, Colle I, Knebel JF, Francque S, Serste T et al. Alcohol intake increases the risk of HCC in hepatitis C virus-related compensated cirrhosis: a prospective study. J Hepatol. 2016;65(3):543–51.

10.7.5 HCV/mental health disorders

HCV is associated with higher rates of mental health disorders compared to the general population. The higher rate of mental health disorders can be attributed to multiple causes, including a high rate of transmission in populations with psychiatric disorders due to risk behaviours, the effect of HCV on the central nervous system, and the psychosocial effects of stigma and discrimination from the disease.[7]

Pegylated interferon treatment is also associated with various neurological and psychiatric effects, including debilitating fatigue, depression, anxiety and cognitive disturbances, with rare instances of suicidal thoughts. DAAs have not been associated with a significant impact on mental health and are not believed to have neuropsychiatric effects.

Mental health disorders have a high likelihood of affecting treatment access and adherence rates and a robust assessment of the patient's psychiatric condition prior to treatment is essential for mitigating any negative effects on treatment success. It is important to involve appropriate mental health personnel in the care and treatment plan of the patient. Depending on the degree, treatment of the mental health disorder may be warranted before initiating HCV treatment.

During treatment, patients with mental health disorders should be assessed for mood changes every four weeks. There is a high risk of DDIs between psychiatric medications and DAAs. Pharmacists must pay attention to potential DDIs between mental health medications and HCV medications. St John's Wort, commonly prescribed for depression, and carbamazepine, are contraindicated with SOF.

10.7.6 HCV/chronic kidney disease

(*SEE* ANNEX 4 FOR ADAPTATION OF DAA/RBV DOSE IN CASE OF RENAL FAILURE.)

Comorbidity of HCV and renal impairment is common. Renal impairment includes patients with:

- Stage 4 disease, where the eGFR is between 15 and 29 mL/min
- Stage 5 disease, where the eGFR is less than 15 mL/min and patients are on dialysis
- Post-renal transplant
- Mixed essential cryoglobulinaemia and related liver damage.

7. Schaefer M, Capuron L, Friebe A, Diez-Quievedo C, Robaeys G, Neri S et al. Hepatitis C infection, antiviral treatment and mental health: a European expert consensus statement. J Hepatol. 2012;57(6): 1379–90. http://dx.doi.org/10.1016/j.hep.2012.07.037.

Patients with renal impairment have a high risk of morbidity, disease progression and mortality, and are a priority group for treatment, in cases where it is clinically safe to do so. However, treatment options for patients with advanced renal disease are currently limited.

- Patients with eGFR rates above 30 mL/min can be treated with normal doses of DAAs, including SOF/DCV and SOF/VEL.
- Studies are ongoing to further investigate the safety of SOF in patients with eGFR rates below 30 mL/min.
- However, treatment with SOF is currently contraindicated in patients with eGFR rates below 30 mL/min as it is eliminated through the renal system. Clinical studies in this population are limited, and studies such as the TARGET 2.0 real-world cohort study showed progressive deterioration of renal function among patients with advanced renal disease taking SOF-containing regimens.
- Another newer pangenotypic DAA combination: GLE/PIB can be used in patients with severe renal failure (eGFR <30 mL/min). However, this combination is not available in Nepal.
- In patients with low eGFR rates, referral to a specialist is recommended.
- RBV is also associated with treatment difficulties in patients with ESRD. Patients with an eGFR <30 mL/min require dose adjustment of RBV and those on dialysis must have the dose lowered to 200 mg per day or take it three times per week. Increased monitoring is required in this group.

ANNEXURES

Annex 1. The Alcohol, Smoking And Substance Involvement Screening Test (Assist V3.1)

Clinician's name | Clinic

Client's ID or name | Date

Introduction (please read to client or adapt to local circumstances) *

The following questions ask about your experience of using alcohol, tobacco products and other drugs across your lif time and in the past three months. These substances can be smoked, swallowed, snorted, inhaled or injected (show response card).

Some of the substances listed may be prescribed by a doctor (like amphetamines, sedatives, pain medications). For this interview, we will ***not*** *record medications that are used* ***as prescribed*** *by your doctor. However, if you have taken such medications for reasons* ***other*** *than prescription or taken them more frequently or at higher doses than prescribed, please let me know.*

While we are also interested in knowing about your use of various illicit drugs, please be assured that information on such use will be treated as strictly confidential.

Before asking questions, give the ASSIST response card to client

	QUESTION 1 | In your life, which of the following substances have you *ever used* (non-medical use only)?		
a	Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	No	Yes
b	Alcoholic beverages (beer, wine, spirits, etc.)	No	Yes
c	Cannabis (marijuana, pot, grass, hash, etc.)	No	Yes
d	Cocaine (coke, crack, etc.)	No	Yes
e	Amphetamine-type stimulants (speed, meth, Ecstasy, etc.)	No	Yes
f	Inhalants (nitrous, glue, petrol, paint, thinner, etc.)	No	Yes
g	Sedatives or sleeping pills (diazepam, alprazolam, flunitrazepam, midazolam, etc.)	No	Yes
h	Hallucinogens (LSD, acid, mushrooms, trips, ketamine, etc.)	No	Yes
i	Opioids (heroin, morphine, methadone, buprenorphine, codeine, etc.)	No	Yes
j	Other – specify: _____	No	Yes

Probe if all answers are negative:
"Not even when you were in school?"

If "No" to all items, stop interview.
If "Yes" to any of these items, ask Q2 for each substance ever used

*ASSIST V3.1 Is to be utilized by for screening in clinical settings. For research purposes, please use the previous version ASSIST V3.0.

	QUESTION 2 | In the *past three months,* how often have you used the substances you mentioned (first drug, second drug, etc.)?	Never	Once or twice	Monthly	weekly	Daily or almost daily
a	Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	2	3	4	6
b	Alcoholic beverages (beer, wine, spirits, etc.)	0	2	3	4	6
c	Cannabis (marijuana, pot, grass, hash, etc.)	0	2	3	4	6
d	Cocaine (coke, crack, etc.)	0	2	3	4	6
e	Amphetamine-type stimulants (speed, meth, Ecstasy, etc.)	0	2	3	4	6
f	Inhalants (nitrous, glue, petrol, paint, thinner, etc.)	0	2	3	4	6
g	Sedatives or sleeping pills (diazepam, alprazolam, flunitrazepam, midazolam, etc.)	0	2	3	4	6
h	Hallucinogens (LSD, acid, mushrooms, trips, ketamine, etc.)	0	2	3	4	6
i	Opioids (heroin, morphine, methadone, buprenorphine, codeine, etc.)	0	2	3	4	6
j	Other – specify: _____	0	2	3	4	6

If "never" to all items in Q2, skip to Q6.
If any substances in Q2 were used in the previous three months, continue with Questions 3, 4 and 5 for each substance used.

	QUESTION 3 | In the *past three months,* how often have you had a strong desire or urge to use (first drug, second drug, etc.)?	Never	Once or twice	Monthly	weekly	Daily or almost daily
a	Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	3	4	5	6
b	Alcoholic beverages (beer, wine, spirits, etc.)	0	3	4	5	6
c	Cannabis (marijuana, pot, grass, hash, etc.)	0	3	4	5	6
d	Cocaine (coke, crack, etc.)	0	3	4	5	6
e	Amphetamine-type stimulants (speed, meth, Ecstasy, etc.)	0	3	4	5	6
f	Inhalants (nitrous, glue, petrol, paint, thinner, etc.)	0	3	4	5	6
g	Sedatives or sleeping pills (diazepam, alprazolam, flunitrazepam, midazolam, etc.)	0	3	4	5	6

h	Hallucinogens (LSD, acid, mushrooms, trips, ketamine, etc.)	0	3	4	5	6
i	Opioids (heroin, morphine, methadone, buprenorphine, codeine, etc.)	0	3	4	5	6
j	Other – specify: _____	0	3	4	5	6
QUESTION 4 | In the *past three months,* how often has your use of (first drug, second drug, etc.) led to health, social, legal or financial problems?		Never	Once or twice	Monthly	weekly	Daily or almost daily
a	Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	4	5	6	7
b	Alcoholic beverages (beer, wine, spirits, etc.)	0	4	5	6	7
c	Cannabis (marijuana, pot, grass, hash, etc.)	0	4	5	6	7
d	Cocaine (coke, crack, etc.)	0	4	5	6	7
e	Amphetamine-type stimulants (speed, meth, Ecstasy, etc.)	0	4	5	6	7
f	Inhalants (nitrous, glue, petrol, paint, thinner, etc.)	0	4	5	6	7
g	Sedatives or sleeping pills (diazepam, alprazolam, flunitrazepam, midazolam, etc.)	0	4	5	6	7
h	Hallucinogens (LSD, acid, mushrooms, trips, ketamine, etc.)	0	4	5	6	7
i	Opioids (heroin, morphine, methadone, buprenorphine, codeine, etc.)	0	4	5	6	7
j	Other – specify: _____	0	4	5	6	7
QUESTION 5 | In the *past three months,* how often have you failed to do what was normally expected of you because of your use of (first drug, second drug, etc.)?		Never	Once or twice	Monthly	weekly	Daily or almost daily
a	Tobacco products (cigarettes, chewing tobacco, cigars, etc.)					
b	Alcoholic beverages (beer, wine, spirits, etc.)	0	5	6	7	8
c	Cannabis (marijuana, pot, grass, hash, etc.)	0	5	6	7	8
d	Cocaine (coke, crack, etc.)	0	5	6	7	8
e	Amphetamine-type stimulants (speed, meth, Ecstasy, etc.)	0	5	6	7	8
f	Inhalants (nitrous, glue, petrol, paint, thinner, etc.)	0	5	6	7	8

g	Sedatives or sleeping pills (diazepam, alprazolam, flunitrazepam, midazolam, etc.)	0	5	6	7	8
h	Hallucinogens (LSD, acid, mushrooms, trips, ketamine, etc.)	0	5	6	7	8
i	Opioids (heroin, morphine, methadone, buprenorphine, codeine, etc.)	0	5	6	7	8
j	Other – specify: _____	0	5	6	7	8

Ask questions 6 and 7 for all substances ever used (i.e. those endorsed in Q1).

QUESTION 6 | Has a friend or relative or anyone else *ever* expressed concern about your use of (first drug, second drug etc.)?		No, Never	Yes, in the past 3 months	Yes, but not in the past 3 months
a	Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	6	3
b	Alcoholic beverages (beer, wine, spirits, etc.)	0	6	3
c	Cannabis (marijuana, pot, grass, hash, etc.)	0	6	3
d	Cocaine (coke, crack, etc.)	0	6	3
e	Amphetamine-type stimulants (speed, meth, Ecstasy, etc.)	0	6	3
f	Inhalants (nitrous, glue, petrol, paint, thinner, etc.)	0	6	3
g	Sedatives or sleeping pills (diazepam, alprazolam, flunitrazepam, midazolam, etc.)	0	6	3
h	Hallucinogens (LSD, acid, mushrooms, trips, ketamine, etc.)	0	6	3
i	Opioids (heroin, morphine, methadone, buprenorphine, codeine, etc.)	0	6	3
j	Other – specify: _____	0	6	3

Ask questions 6 and 7 for all substances ever used (i.e. those endorsed in Q1).

QUESTION 7 | Have you *ever* tried to cut down on using (first drug, second drug etc.) but failed?		No, Never	Yes, in the past 3 months	Yes, but not in the past 3 months
a	Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	6	3
b	Alcoholic beverages (beer, wine, spirits, etc.)	0	6	3

c	Cannabis (marijuana, pot, grass, hash, etc.)	0	6	3
d	Cocaine (coke, crack, etc.)	0	6	3
e	Amphetamine-type stimulants (speed, meth, Ecstasy, etc.)	0	6	3
f	Inhalants (nitrous, glue, petrol, paint, thinner, etc.)	0	6	3
g	Sedatives or sleeping pills (diazepam, alprazolam, flunitrazepam, midazolam, etc.)	0	6	3
h	Hallucinogens (LSD, acid, mushrooms, trips, ketamine, etc.)	0	6	3
i	Opioids (heroin, morphine, methadone, buprenorphine, codeine, etc.)	0	6	3
j	Other – specify: _____	0	6	3

Ask questions 6 and 7 for all substances ever used (i.e. those endorsed in Q1).

QUESTION 8 | Have you *ever* used any drug by injection (non-medical use only)?	No, Never	Yes, in the past 3 months	Yes, but not in the past 3 months
(Please tick the appropriate box)			

IMPORTANT NOTE

Clients who have injected drugs in the past 3 months should be asked about their pattern of injecting during this period to determine their risk levels and the best course of intervention.

Pattern of injecting	Intervention guidelines
4 days per month, on average, over the past 3 months or less	Brief intervention, including the risks of injecting drugs
More than 4 days per month, on average, over the past 3 months	Further assessment and more intensive treatment

How to calculate a specific substance involvement score

For each substance (labelled 'a' to 'j') add up the scores received for questions 2 through 7 inclusive. Do not include the results from either Q1 or Q8 in this score. For example, a score for cannabis would be calculated as: **Q2c + Q3c + Q4c + Q5c + Q6c + Q7c.**

Note that Q5 for tobacco is not coded and is calculated as**: Q2a + Q3a + Q4a + Q6a + Q7a.**

The type of intervention is determined by the patient's specific substance involvement score					
		Record specific substance score	**No intervention**	**Receive brief Intervention**	**More intensive treatment**
a	Tobacco		0–3	4–26	27 +
b	Alcohol		0–10	11–26	27 +
c	Cannabis		0–3	4–26	27 +
d	Cocaine		0–3	4–26	27 +
e	ATS		0–3	4–26	27 +
f	Inhalants		0–3	4–26	27 +
g	Sedatives		0–3	4–26	27 +
h	Hallucinogens		0–3	4–26	27 +
i	Opioids		0–3	4–26	27 +
j	Other drugs		0–3	4–26	27 +
Now use the ASSIST feedback report card to give the client a brief intervention.					

ANNEX 2. TABLES OF COMMON DDIs WITH DAAs

Table 2.1. Drug-drug interactions between antiretrovirals and direct-acting antivirals

DAAs	ABC	ATZ/r	DRV/r	DTG	EFV	LPV/r	NVP	RAL	TDF	TAF	ZDV	XTC
Daclatasvir		Adjust dose			Adjust dose							
Sofosbuvir												
Sofosbuvir/ ledipasvir		Monitor for renal toxicity when used with TDF	Monitor for renal toxicity when used with TDF		Monitor for renal toxicity when used with TDF	Monitor for renal toxicity when used with TDF			Monitor for renal toxicity when used with EFV or boosted protease inhibitor			
Sofosbuvir/ velpatasvir		Monitor for renal toxicity when used with TDF	Monitor for renal toxicity when used with TDF			Monitor for renal toxicity when used with TDF			Monitor for renal toxicity			

Red = do not co-administer

Yellow = possible toxicity/interaction/dose adjustment, as specified

Green = no interaction; can be co-administered

ABC: abacavir; ATZ/r: atazanavir/ritonavir; DRV/r: darunavir/ritonavir; DTG: dolutegravir; EFV: efavirenz; LPV/r: lopinavir/r; NVP: nevirapine; RAL: raltegravir; ZDV: zidovudine; TDF: tenofovir disproxil fumarate; XTC: emtricitabine/lamivudine; TAF: tenofovir alafenamide

Table 2.2. DDIs between HCV DAAs and illicit/recreational drugs or drugs of abuse

	SOF	SOF/LDV	SOF/VEL	DCV
Amphetamine				
Buprenorphine				
Cannabis				
Cocaine				
Diamorphine				
Diazepam				
Fentanyl				
Gamma-hydroxybutyrate				
Ketamine				
MDMA (Ecstasy)				
Mephedrone				
Methadone				
Methamphetamine				
Oxycodone				
Phencyclidine (PCP)				
Temazepam				

Red = do not co-administer
Yellow = possible toxicity/interaction/dose adjustment, as specified
Green = no interaction; can be co-administered
DCV: daclatasvir; LDV: ledipasvir; SOF: sofosbuvir; VEL: velpatasvir

Table 2.3. DDIs between HCV DAAs and lipid-lowering drugs

	SOF	SOF/LDV	SOF/VEL	DCV
Atorvastatin				
Bezafibrate				
Ezetimibe				
Fenofibrate				
Fluvastatin				
Gemfibrozil				
Lovastatin				
Pitavastatin				
Pravastatin				
Rosuvastatin				
Simvastatin				

Red = do not co-administer
Yellow = possible toxicity/interaction/dose adjustment, as specified
Green = no interaction; can be co-administered
DCV: daclatasvir; LDV: ledipasvir; SOF: sofosbuvir; VEL: velpatasvir

Table 2.4. DDIs between HCV DAAs and central nervous system drugs

	SOF	SOF/LDV	SOF/VEL	DCV
Antidepressants				
Amitriptyline				
Citalopram				
Duloxetine				
Escitalopram				
Fluoxetine				
Paroxetine				
Sertraline				
Trazodone				
Venlafaxine				
Antipsychotics				
Amisulpiride				
Aripiprazole				
Chlorpromazine				
Clozapine				
Flupentixol				
Haloperidol				
Olanzapine				
Paliperidone				
Quetiapine				
Risperidone				
Zuclopentixol				

Red = do not co-administer
Yellow = possible toxicity/interaction/dose adjustment, as specified
Green = no interaction; can be co-administered
DCV: daclatasvir; LDV: ledipasvir; SOF: sofosbuvir; VEL: velpatasvir

Table 2.5. DDIs between HCV DAAs and antiplatelet and anticoagulant drugs

	SOF	SOF/LDV	SOF/VEL	DCV
Clopidogrel				
Dabigatran				
Ticagrelor				
Rivaroxaban				
Apixaban				
Edoxaban				
Warfarin				

Red = do not co-administer
Yellow = possible toxicity/interaction/dose adjustment, as specified
Green = no interaction; can be co-administered
DCV: daclatasvir; LDV: ledipasvir; SOF: sofosbuvir; VEL: velpatasvir

Table 2.6. DDIs between HCV DAAs and cardiovascular drugs

	SOF	SOF/LDV	SOF/VEL	DCV
Antiarrhythmics				
Amiodarone				
Digoxine				
Flecainide				
Vernakalant				
Beta-blockers				
Atenolol				
Bisoprolol				
Carvedilol				
Propanolol				
Calcium-channel blockers				
Amlodipine				
Diltiazem				
Nifedipine				
Hypertension and heart failure agents				
Aliskiren				
Losartan				
Doxazocin				
Enalapril				

Red = do not co-administer
Yellow = possible toxicity/interaction/dose adjustment, as specified
Green = no interaction; can be co-administered
DCV: daclatasvir; LDV: ledipasvir; SOF: sofosbuvir; VEL: velpatasvir

Table 2.7. DDIs between HCV DAAs and immunosuppressants

	SOF	SOF/LDV	SOF/VEL	DCV
Azathioprine				
Cyclosporine				
Etanercept				
Mycophenolate				
Sirolimus				
Tacrolimus				

Red = do not co-administer
Yellow = possible toxicity/interaction/dose adjustment, as specified
Green = no interaction; can be co-administered
DCV: daclatasvir; LDV: ledipasvir; SOF: sofosbuvir; VEL: velpatasvir

Table 2.8. Potentially significant drug interactions of sofosbuvir[8,9]

Concomitant drug class: drug name	Effect on concentration	Clinical comment
Antiarrhythmics: amiodarone	Effect on amiodarone and sofosbuvir concentrations unknown	Co-administration of amiodarone with sofosbuvir in combination with another DAA may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Co-administration of amiodarone with sofosbuvir in combination with another DAA is not recommended; if co-administration is required, cardiac monitoring is recommended.
Anticonvulsants: carbamazepine, phenytoin, phenobarbital, oxcarbazepine	↓ sofosbuvir	Co-administration of sofosbuvir with carbamazepine, phenytoin, phenobarbital or oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Co-administration is not recommended.
Antimycobacterials: rifabutin, rifampin rifapentine	↓ sofosbuvir	Co-administration of ledipasvir + sofosbuvir with rifabutin or rifapentine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of ledispasvir + sofosbuvir. Co-administration is not recommended. Co-administration of ledispasvir + sofosbuvir with rifampin, a permeability glycoprotein (P-gp) inducer, is not recommended.
Herbal supplements: St John's wort (*Hypericum perforatum*)	↓ sofosbuvir	Co-administration of sofosbuvir with St John's wort, an intestinal P-gp inducer, is not recommended.
HIV PIs: tipranavir/ ritonavir	↓ sofosbuvir	Co-administration of sofosbuvir with tipranavir/ritonavir is expected to decrease the concentration of sofosbuvir, leading to a reduced therapeutic effect of sofosbuvir. Co-administration is not recommended.

8. AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. (http://www.hcvguidelines.org, accessed 5 June 2019).
9. EASL Recommendations on treatment of hepatitis C 2015. European Association of the Study of the Liver. J Hepatol. 2015;63(1):199–236.

Table 2.9. Potentially significant drug interactions of daclatasvir

Concomitant drug class: drug name	Effect on concentration	Clinical comment
HIV antiviral agents		
Protease inhibitors: atazanavir with ritonavir, indinavir, nelfinavir or saquinavir	↑ Daclatasvir	Decrease daclatasvir dose to 30 mg once daily.
Other antiretrovirals: Cobicistat-containing antiretroviral regimens Examples: atazanavir/ cobicistat, elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate	↑ Daclatasvir	Decrease daclatasvir dose to 30 mg once daily except with darunavir combined with cobicistat.
Strong CYP3A inhibitors		
Examples: clarithromycin, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, voriconazole	↑ Daclatasvir	Decrease daclatasvir dose to 30 mg once daily when co-administered with strong inhibitors of CYP3A.
Moderate CYP3A inducers		
Examples: bosentan, dexamethasone, modafinil, nafcillin, rifapentine	↓ Daclatasvir	Increase daclatasvir dose to 90 mg once daily when co-administered with moderate inducers of CYP3A.
Anticoagulants		
Dabigatran etexilate mesylate	↑ Dabigatran	Use of daclatasvir with dabigatran etexilate is not recommended in groups with specific renal impairment, depending on the indication. Please see the dabigatran prescribing information for specific recommendations.
Cardiovascular agents		
Antiarrhythmic: amiodarone	Amiodarone: effects unknown	Co-administration of amiodarone with daclatasvir in combination with sofosbuvir is not recommended because it may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. If co-administration is required, cardiac monitoring is recommended.
Antiarrhythmic: digoxin	↑ Digoxin	**Patients already receiving daclatasvir and initiating digoxin**: initiate treatment using the lowest appropriate dose of digoxin. Monitor digoxin concentrations; adjust digoxin doses if necessary and continue monitoring. **Patients already receiving digoxin prior to initiating daclatasvir**: Measure serum digoxin concentrations before initiating daclatasvir. Reduce digoxin concentration by decreasing digoxin dosage by approximately 15–30% or by modifying the dosing frequency and continue monitoring.

Lipid-lowering agents		
HMG-CoA reductase inhibitors: atorvastatin fluvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin	↑ Atorvastatin ↑ Fluvastatin ↑ Pitavastatin ↑ Pravastatin ↑ Rosuvastatin ↑ Simvastatin	Monitor for HMG-CoA reductase inhibitor-associated adverse events such as myopathy.
Narcotic analgesics/treatment of opioid dependence		
Buprenorphine Buprenorphine/naloxone	↑ Buprenorphine ↑ Norbuprenorphine	For buprenorphine or buprenorphine/naloxone, no adjustment is needed, but clinical monitoring for buprenorphine-associated adverse events is recommended.

Antiretrovirals for HIV		
Regimens containing tenofovir DF without an HIV protease inhibitor/ritonavir or cobicistat	↑ Tenofovir	Monitor for tenofovir-associated adverse reactions in patients receiving sofosbuvir/ledipasvir concomitantly with a regimen containing tenofovir DF without an HIV protease inhibitor/ritonavir or cobicistat.
Regimens containing tenofovir DF and an HIV protease inhibitor/ritonavir or cobicistat •atazanavir/ritonavir or cobicistat + emtricitabine/tenofovir DF •darunavir/ritonavir or cobicistat + emtricitabine/tenofovir DF •lopinavir/ritonavir + emtricitabine/tenofovir DF	↑ Tenofovir	The safety of increased tenofovir concentrations in the setting of sofosbuvir/ledipasvir and an HIV protease inhibitor/ritonavir or cobicistat has not been established. Consider alternative HCV treatment or ART to avoid increase in tenofovir exposure. If co-administration is necessary, monitor for tenofovir-associated adverse reactions.
Elvitegravir, cobicistat, emtricitabine, tenofovir DF	↑ Tenofovir	The safety of increased tenofovir concentrations in the setting of sofosbuvir/ledipasvir and the combination of elvitegravir, cobicistat, emtricitabine and tenofovir DF has not been established. Co-administration is not recommended.
Tipranavir/ritonavir	↓ Ledipasvir ↓Sofosbuvir	Co-administration of sofosbuvir/ledipasvir with tipranavir/ritonavir is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of ledipasvir + sofosbuvir co-administration is not recommended.
Herbal supplements: St John's wort (*Hypericum perforatum*)	↓Ledipasvir ↓ Sofosbuvir	Co-administration of sofosbuvir/ledipasvir with St John's wort, a P-gp inducer, is not recommended.
HMG-CoA reductase inhibitors: rosuvastatin	↑ Rosuvastatin	Co-administration of sofosbuvir/ledipasvir with rosuvastatin may significantly increase the concentration of rosuvastatin, which is associated with an increased risk of myopathy, including rhabdomyolysis. Co-administration of sofosbuvir/ledipasvir with rosuvastatin is not recommended.

Table 2.10. Potentially significant drug interactions of ribavirin[10]

Drug name	Effect on concentration	Clinical comment
Atazanavir (ATV)	Increased risk of jaundice when used with ribavirin, although this is unlikely to be clinically significant	Patient should be warned of possible increased jaundice and reassured that this is unlikely to be dangerous.
Abacavir (ABC)	Possible antagonism with ribavirin	Use weight-based ribavirin dosing to ensure adequate levels
Zidovudine (AZT)		Risk of anaemia
Didanosine (ddI)	Ribavirin may increase the toxicity of didanosine and may also increase the serum concentration	Should not be used together. *ddI is no longer recommended for the treatment of HIV infection due to mitochondrial toxicity.
Azathioprine	Ribavirin may increase the concentration	Consider using alternative agents OR monitor very closely for signs of bone marrow suppression.
Influenza virus vaccine	Ribavirin may decrease the therapeutic effect of the vaccine	Repeat vaccine if received ribavirin within 2 weeks of the vaccination.

Table 2.11. Potentially significant drug interactions of sofosbuvir/velpatasvir

Concomitant drug class: drug name	Effect on concentration	Clinical effect/recommendation
Acid-reducing agents	↓ velpatasvir	Velpatasvir solubility decreases as pH increases. Drugs that increase the gastric pH are expected to decrease the concentration of velpatasvir.
Antacids (e.g. aluminum and magnesium hydroxide)		Separate antacid and (sofosbuvir 400 mg/velpatasvir 100 mg) administration by 4 hours.
H2-receptor antagonists (e.g. famotidine)		H2-receptor antagonists may be administered simultaneously with or 12 hours apart from sofosbuvir 400 mg/velpatasvir 100 mg at a dose that does not exceed or are comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors (e.g. omeprazole)		C-oadministration of omeprazole or other proton-pump inhibitors is not recommended. If it is considered medically necessary to co-administer, sofosbuvir 400 mg/velpatasvir 100 mg should be administered with food and taken 4 hours before omeprazole 20 mg. Use with other proton-pump inhibitors has not been studied.
Antiarrhythmics: amiodarone	Effect of amiodarone on sofosbuvir and velpatasvir concentrations unknown	Co-administration of amiodarone with sofosbuvir 400 mg/velpatasvir 100 mg may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Co-administration of amiodarone with sofosbuvir 400 mg/velpatasvir 100 mg is not recommended; if co-administration is required, cardiac monitoring is recommended

10. EASL Recommendations on treatment of hepatitis C 2016. European Association of the Study of the Liver. J Hepatol. 2015;63(1):199–236.

digoxin	↑ digoxin	Therapeutic concentration monitoring of digoxin is recommended when co-administered with sofosbuvir 400 mg/velpatasvir 100 mg. Refer to digoxin-prescribing information for monitoring and dose modification recommendations for concentration increases of less than 50%.
Anticancer drugs: topotecan	↑ topotecan	Co-administration is not recommended.
Anticonvulsants: carbamazepine, phenytoin, phenobarbital, oxcarbazepine	↓ sofosbuvir ↓ velpatasvir	Co-administration is not recommended.
Antimycobacterials: rifabutin, rifampin,rifapentine	↓ sofosbuvir ↓ velpatasvir	Co-administration is not recommended.
Antiretrovirals for HIV:		
efavirenz	↓ velpatasvir	Co-administration of sofosbuvir 400 mg/velpatasvir 100 mg with efavirenz-containing regimens is not recommended.
Regimens containing tenofovir DF	↑ tenofovir	Monitor for tenofovir-associated adverse reactions in patients receiving sofosbuvir 400 mg/velpatasvir 100 mg concomitantly with a regimen containing tenofovir DF. Refer to the prescribing information of the tenofovir DF-containing product for recommendations on renal monitoring.
Tipranavir/ritonavir	↓ sofosbuvir ↓ velpatasvir	Co-administration is not recommended.
Herbal supplements: St John's wort *(Hypericum perforatum)*	↓ sofosbuvir ↓ velpatasvir	Co-administration is not recommended.
HMG-CoA reductase inhibitors: rosuvastatin	↑ rosuvastatin	Co-administration of sofosbuvir 400 mg/velpatasvir 100 mg with rosuvastatin may significantly increase the concentration of rosuvastatin, which is associated with an increased risk of myopathy, including rhabdomyolysis. Rosuvastatin may be administered with sofosbuvir 400 mg/ velpatasvir 100 mg at a dose that does not exceed 10 mg.
atorvastatin	↑ atorvastatin	Co-administration of sofosbuvir 400 mg/velpatasvir 100 mg with atorvastatin is expected to increase the concentration of atorvastatin, which is associated with an increased risk of myopathy, including rhabdomyolysis. Monitor closely for HMG-CoA reductase inhibitor-associated adverse effects.

ANNEX 3. SAFETY PROFILES OF DAAs AND RIBAVIRIN

Table 3.1. SOFOSBUVIR (SOF)

SOFOSBUVIR (SOF)	
Inhibitor class	NS5B polymerase inhibitor (NS5BI); pangenotypic
Posology	400 mg (one tablet) once daily, with or without food
Side-effects	Usually well tolerated Most common adverse events in association with ribavirin (>20% of patients): headache, fatigue
Elimination Metabolism	80% eliminated through renal excretion (renal clearance of active metabolite) Patients with eGFR <30 mL/min/1.73m2: currently no dose recommendation but accumulating evidence on safe use of SOF-based regimens (despite SOF exposure increased up to 20-fold in end-stage renal disease) Moderate liver impairment: SOF exposure increased 2–3-fold Transport by P-gp Median half-life of SOF metabolite = 27 h
Main DDIs	• Reduction in SOF exposure • Rifampicin, carbamazepine, phenytoin, St John's wort = contraindicated • Increase in drug exposure/other mechanism • Amiodarone (risk of life-threatening arrhythmia): wait 3 months after discontinuation of amiodarone before starting SOF.
Contraindications	Co-medication with the above drugs

Table 3.2. LEDIPASVIR (LDV)

LEDIPASVIR (LDV)	
Inhibitor class	NS5A inhibitor (NS5AI); genotype 1 (a,b), 4, 5, 6
Posology	9 0mg once daily with or without food Co-formulated with SOF: 1 tablet = SOF 400 mg+LDV 90 mg
Side-effects	Headache, fatigue
Elimination Metabolism	Biliary excretion of unchanged ledipasvir Transport by P-gp and breast cancer resistance protein (BCRP)
Main DDIs	<u>Reduction in LDV exposure</u> • Rifampicin, carbamazepine, phenytoin, St John's wort: contraindicated • H2 blocker (famotidine): give simultaneously or 12 h apart, maximum dose equivalent to famotidine 40 mg. • Proton-pump inhibitors: give simultaneously, maximum dose equivalent to omeprazole 20 mg. <u>Increase in drug exposure</u> • Rosuvastatin, amiodarone: contraindicated • Other statins, digoxin, dabigatran, amlodipine, buprenorphine, carvedilol: use with caution • Tenofovir disoproxil fumarate (TDF) if associated with ritonavir or cobicistat, or EFV: monitor renal function closely
Contraindications	Co-medication with rifampicin, carbamazepine, phenytoin, St John's wort rosuvastatin, amiodarone

Table 3.3. VELPATASVIR (VEL)

VELPATASVIR (VEL)	
Inhibitor class	NS5A inhibitor; pangenotypic
Posology	100 mg once daily with or without food Co-formulated with SOF: 1 tablet = SOF 400 mg + VEL 100 mg
Side-effects	Headache, fatigue, nausea (same frequency as in placebo group)
Elimination Metabolism	Biliary excretion Metabolism by CYP2B6, CYP2C8, CYP3A4 Transport by P-gp, BCRP and organic anion transporting polypeptide (OATP) Median half-life 15 h
Main DDIs	Reduction in VEL exposure • Rifampicin, rifabutin, carbamazepine, phenobarbital, phenytoin, St John's wort, modafinil: contraindicated • Proton-pump inhibitors (PPIs): take SOF/VEL with food 4 hours before PPI, maximum dose of PPI equivalent to omeprazole 20 mg Increase in drug exposure • Digoxin, dabigatran, ticagrelor, carvedilol, amlodipine, diltiazem, aliskiren, statins: use with caution • Amiodarone: contraindicated • Efavirenz, nevirapine, etravirine: contraindicated • Tenofovir disoproxil fumarate (TDF) if associated with ritonavir or cobicistat, or EFV: monitor renal function closely
Contraindications	Amiodarone, EFV, NVP, etravirine, rifampicin, rifabutin, carbamazepine, phenobarbital, phenytoin, St John's wort, modafinil

Table 3.4. DACLATASVIR (VEL)

DACLATASVIR (DCV)	
Inhibitor class	NS5A inhibitor; pangenotypic
Posology	60 mg once daily with or without food Reduce to 30 mg once daily with atazanavir Increase to 90 mg once daily with efavirenz
Side-effects	Headache, fatigue, nausea
Elimination Metabolism	90% in faeces (half as unchanged drug) 10% in urine (half as unchanged drug) P-gp (substrate and inhibitor), CYP34A (substrate), OATP1B1 and BCRP (inhibitor)
Main DDIs	Reduction in DCV exposure • Carbamazepine, phenytoin, oxcarbazepine, phenobarbital, rifampicin, rifabutin, St John's wort, dexamethasone: contraindicated • Efavirenz, nevirapine, etravirine: increase DCV daily dosage to 90 mg Increase in DVC exposure: reduce DCV daily dosage to 30 mg • Atazanavir/ritonavir, cobicistat • Clarithromycin, telithromycin, erythromycin, ketoconazole, itraconazole, voriconazole, posaconazole Increase in drug exposure • Dabigatran, digoxin: use with caution
Contraindications	Carbamazepine, phenytoin, oxcarbazepine, phenobarbital, rifampicin, rifabutin, St John's wort, dexamethasone

Table 3.5. RIBAVIRIN (RBV)

RIBAVIRIN (RBV)	
Posology	Take with food Weight <75 kg: 1000 mg per day (600–0–400mg) Weight ≥75kg: 1200 mg per day (600 mg twice daily) Dose adjustment if eGFR <30 mL/min/1.73m^2
Side-effects	Rash, cough Haemolytic anaemia: management with step-wise reduction of ribavirin dose
Main DDIs	Low potential for DDIs Risk of cumulative toxicity (e.g. anaemia with AZT: contraindication)
Contraindications	**Absolute** • Pregnancy • Unwillingness to use contraceptives (during treatment and until 6 months after ribavirin discontinuation, for men and women) • Breastfeeding women • Poorly controlled cardiac failure • Chronic obstructive pulmonary disease • Comedication with AZT • Haemoglobin level <8.5 g/dL at baseline check **Relative:** need close monitoring+++ because of risk of anaemia • Cardiovascular disease • Pulmonary disease • Haemoglobinopathies (sickle cell, thalassaemia) • Renal impairment (adapt ribavirin dose to eGFR)

ANNEX 4. ADAPTATION OF DOSE IN SPECIAL SITUATIONS

Table 4.1. Adaptation of DAA/ ribavirin dose in case of renal failure

Drug	Standard dose (no dose adjustment required if eGFR ≥30 mL/min)	eGFR 15–30 mL/min	eGFR <15 mL/min or haemodialysis
SOF 400 mg	1 tablet od	Should be used (without dose adaptation) only if no alternative treatment approved for use in patients with severe renal impairment is available. * (EASL, 2018) Monitor renal function, discontinue DAA if renal function deteriorates. Take after dialysis on the day of dialysis.	
SOF 400 mg/ LDV 90 mg	1 tablet od		
SOF 400 mg/ VEL 100 mg	1 tablet od		
SOF 400 mg/ VEL 100 mg	1 tablet od		
DCV 60 mg DCV 30 mg DCV 60+ DCV 30 mg	1 tablet od (morning) 1 tablet od with ATZ 1 tablet of each od with EFV	No dose adjustment Take after dialysis on the day of dialysis.	
Ribavirin 200 mg	Weight <75 kg: 3 in the morning + 2 in the evening Weight >75 kg: 3 bd	200 mg od or 200 mg thrice weekly (eGFR <15 mL/min) Monitor Hb; discontinue if Hb <8.5 g/dL Take before or after dialysis on the day of dialysis.	

Table 4.2. Dose adjustment of ARVs for impaired hepatic function (EACS, 2017)

ART	DOSE ADJUSTMENT
NRTI	
3TC/ FTC	No dose adjustment
TDF	No dose adjustment
NNRTI	
EFV	No dose adjustment, use with caution in patients with hepatic impairment
Protease Inhibitors	
LPV/r	No dosage recommendation. Use with caution in persons with hepatic impairment.
INSTI	
RAL	No dose adjustment
DTG	No dose adjustment

ANNEX 5. SIDE-EFFECTS OF DAAs

New DAA regimens appear to be well tolerated by patients in both clinical studies and "real-world" observational studies. Discontinuation rates due to side-effects are very low, in most cases <1%. Nevertheless, adverse events did occur in clinical trials of DAAs, although at a rather low frequency.

Table 5.1. Side-effects of drugs and its management

DRUGS	SIDE-EFFECT	SUGGESTED MANAGEMENT STRATEGIES
Sofosbuvir	**Fatigue, headache, insomnia and nausea**	Check haemoglobin Screen for depression Review for contributing factors such as anaemia, sleep disturbance Suggest behavioural strategies to conserve energy, e.g. rest periods, napping, planning ahead Ensure adequate fluid intake
Sofosbuvir/ daclatasvir	**Fatigue, headache and nausea**	Check haemoglobin Screen for depression Review for contributing factors such as anaemia, Sleep disturbance Suggest behavioural strategies to conserve energy, e.g. rest periods, napping, planning ahead Ensure adequate fluid intake **Note: Paracetamol should not be used in patients with liver impairment.**
Regimen containing ribavirin	**Anaemia** Ribavirin can cause haemolytic anaemia and bone marrow suppression. Usually occurs within 1–2 weeks of starting treatment in about 10% of patients	Administration of ribavirin is complicated because it should be taken with food and causes a predictable, dose-dependent haemolytic anaemia. Therefore, it should not be administered to patients with anaemia or those with blood disorder such as thalassaemia. Moreover, patients with cirrhosis, cardiovascular disease, pulmonary disease, renal impairment and all those older than 60 years of age need close monitoring when treated with ribavirin-containing regimens. Dose reductions may be required (*see* text bow below). Careful clinical evaluation of patients before and during treatment is important to identify those in need of closer monitoring. **Dose adjustment of ribavirin** Anaemia is a common, predictable side-effect of ribavirin therapy and dose adjustment is often required. Patients whose haemoglobin (Hb) level falls below 10 g/dL should have their ribavirin dose reduced from 800–1200 mg/day (depending on the patient's weight and HCV genotype) to 600 mg/day. A patient whose Hb level falls below 8.5 g/dL should discontinue ribavirin therapy. For patients with a history of stable cardiovascular disease, dose reduction of ribavirin is required if the Hb decreases by ≥2 g/dL during any 4-week period. In addition, for these patients, if the Hb remains <12 g/dL after 4 weeks on a reduced dose, the patient should discontinue combination therapy. The dose of ribavirin in patients with renal failure must also be adjusted. • Patients with an eGFR <50 mL/min/1.73 m^2 should not be treated with ribavirin and those on dialysis must have the dose lowered to 200 mg per day or take it three times per week. Increased monitoring is required in this group. **Ribavirin in patients with decompensated cirrhosis** Among patients with decompensated cirrhosis, ribavirin dosing should either be weight-based or started at an initial dose of 600 mg and increased as tolerated. **Ribavirin cannot be used during pregnancy** Ribavirin is teratogenic and thus cannot be used during pregnancy and breastfeeding. Women of childbearing age must avoid pregnancy by using at least two reliable forms of contraception. Ribavirin also has a long half-life; thus, pregnancy must be prevented for at least 6 months after the end of ribavirin therapy. It is recommended that the patient and mal partners access and use reliable contraception.
Sofosbuvir/ velpatasvir	**Bradycardia** SOF/VEL treatment may result in bradycardia, along with other symptoms when taken with amiodarone **Headache and fatigue**	Velpatasvir is a substrate of P-gp and BCRP with slow metabolism noted with CYP2B6, CYP2C8, and CYP3A4. Therefore, P-gp inducers and moderate/strong inducers of the cytochrome P-450 system may decrease plasma concentrations of VEL and should not be used. Acid-reducing agents should be used with caution secondary to VEL solubility decreasing with decreasing acidity. Co-administration of SOF/VEL and amiodarone may result in serious symptomatic bradycardia. Velpatasvir is safe for use with most HIV medications but should be avoided in those taking ritonavir-boosted tipranavir, efavirenz, atravirine and nevirapine. Adequate fluid intake: limit the intake of coffee, tea and soda with caffeine. Suggest behavioural strategies to conserve energy, e.g. rest periods, napping, planning ahead. SOF/VEL is not recommended in patients with severe renal impairment (estimated GFR <30 mL/ min/1.73 $m^{2)}$ or end-stage renal disease. Insufficient data exist for the use of SOF/VEL in pregnant women or postpartum breastfeeding mothers.

ANNEX 6. Adverse Event Reporting Form

A. Patient and Health Facility Information

Patient ID number:			Treatment Centre:
Date of Birth (*or* Age):			Province:
Sex:	☐ Male	☐ Female	☐ Other
Retro status:	☐ Non-reactive	☐ Reactive	
Pregnancy:	☐ No	☐ Yes	Trimester:
Weight (kg):			

B. Adverse events experienced by patient

Adverse event	**Onset date**	**End date**	**Seriousness ***	**Outcome** §

* Please select: ***D*** *died* ***LT*** *life threatening* ***HA*** *caused or prolonged hospital admission* ***PD*** *permanent disability* ***OS*** *other medically serious* ***CA*** *congenital abnormality* ***NS*** *not serious*

§ Please select: ***A*** *recovered* ***B*** *recovering* ***C*** *recovered with residual effects* ***D*** *died* ***E*** *not recovered* ***F*** *unknown*

Detailed description of adverse event(s):

Was treatment of adverse event required? ☐ No ☐ Yes (please specify):

C. Laboratory assessment: Results of tests if any

Test performed	Test date	Result	Unit	Reference range

D. Medicines: List all medicines used for the treatment as well as other commitment medications if any

☑ *Tick if medicine suspected of causing adverse event*

Medicine	Dose	Frequency	Start date	Stop date	Reason for use	Action taken †	Response ‡
☐							
☐							
☐							
☐							
☐							
☐							

† *Action taken in response to AE:* ***DW*** *drug withdrawn* ***DR*** *dose reduced* ***DI*** *dose increased* ***DNC*** *dose not changed* ***UK*** *unknown* ***NA*** *not applicable*

‡ *Response to action taken:* ***RA*** *recovered* ***NE*** *no effect on AE* ***FA*** *fatal AE* ***UN*** *unknown* ***NA*** *not applicable*

E. Other relevant information

Name and Brand name of the Drug used:

Batch number:

Expiration date:

Any other information on the drug:

G. Reporter Information

Name:			Phone number:	
Email:				
Occupation:	☐ Doctor	☐ Nurse	☐ Paramedics	☐ Other (please specify):
Signature:			Date	

Submit form to:

NCASC, Teku AEHCV@gmail.com

NCASC Use Only:

Date received:		
Causality assessment:	☐ Likely	☐ Unlikely
Comment:		

ANNEX 7. SIMPLIFIED DIAGNOSTIC ALGORITHM FOR A PANGENOTYPIC REGIMEN

The following table provides an overview of a simplified diagnostic algorithm and the justification for the inclusion/exclusion of each stage in the simplified diagnostic algorithm made possible by DAAs.

ITEM	PROTOCOL SECTION	STANDARD-OF-CARE LAB DESCRIPTION	INCLUDED (YES/NO)	JUSTIFICATION FOR INCLUSION/EXCLUSION
1	Pretreatment screen	**Hepatitis C antibody** (serum HCV Ab)	**Yes**	The HCV Ab test can be performed using one of the rapid tests or enzyme-linked immunoassay (ELISA). There are a number of rapid tests available and these have been reported to have varying test characteristics. When possible, these tests characteristics should be considered in the selection of choice of screening test. Regardless of the possibility of false-positive results, a confirmatory qualitative RNA will be performed in the pretreatment assessment, which confirms whether the patient has active HCV infection.
2	Pretreatment assessment	**Qualitative HCV RNA**	**Yes**	This is a sensitive test for detecting the presence of HCV and confirming the diagnosis of HCV, even when the amount of circulating HCV is low. Since some people with a positive HCV Ab may have a false-positive result or may have cleared the virus on their own (cured themselves), this test essentially confirms the diagnosis of HCV prior to treatment.
3	Pretreatment assessment	**Physical exam**: blood pressure, heart rate, pulse, cardiac, respiratory, abdominal and neurological exam	**Yes**	This vital step in the protocol will allow for an evaluation to rule out advanced liver disease (decompensated cirrhosis). This will be manifested by evidence of bleeding from varices in the stomach or oesophagus, jaundice, ascites (fluid in the abdomen), oedema of the lower extremities and confusion. Individuals with evidence of decompensated cirrhosis will be referred to a liver disease specialist, as decision-making on the benefit of therapy and additional liver disease management will be required.
4	Pretreatment assessment	**Complete blood count** (CBC): **haemoglobin haematocrit (Hct), white blood cell and platelet counts**	**Yes**	1. The prescribed medication should not cause significant anemia (low Hgb/Hct). 2. The prescribed medication should not cause significant thrombocytopenia (low platelet count [PLT]). 3. PLT will allow us to calculate the AST-to-platelet ratio index (APRI score). This can be used as a non-invasive measure of the degree of liver damage with respect to advanced scarring (fibrosis) or cirrhosis. The APRI score will be used to determine the length of therapy and will determine which patients require ongoing liver disease care after cure when/where available.

5	Pretreatment assessment	**Hepatic function panel:** **Albumin** **Bilirubin** **Alkaline phosphatase (Alk phos)** **Alanine aminotransferase and aspartate aminotransferase (ALT, AST)**	**Yes – AST** **No – Albumin, Bilirubin, Alk phos, ALT**	While the hepatic function panel provides insight into the overall liver function and degree of inflammation from the HCV infection, these parameters will not impact the treatment decision in this protocol. We would treat regardless of these lab values. Furthermore, those individuals with evidence of advanced liver disease (ascites, encephalopathy, gastrointestinal bleeding) will be referred to a tertiary treatment centre to be evaluated by a specialist. The AST and Plt will allow us to calculate the APRI score. This can be used as a non-invasive measure of the degree of liver damage (advanced scarring [fibrosis] or cirrhosis) and, as discussed above, guides decision-making on the length of treatment and need for ongoing liver disease management after cure. Referral to a specialist is not required for commencing treatment in patients with APRI >2 and no signs of decompensation, but when/where available, should result in, at a minimum, liver cancer screening.
6	Pretreatment assessment	**Creatinine/calculated glomerular filtration rate**	**Yes**	One of the medications used in this protocol **(sofosbuvir)** is renally cleared and there is currently limited safety data in patients with poor kidney function. A GFR <30 mL/min would be an indication to consider delay in therapy until more safety data are available or other regimens are available.
7	Post-treatment assessment (end of treatment + 12 weeks)	12 weeks after ending treatment: qualitative HCV RNA	**Yes**	This is when we measure sustained virological response (SVR). If there is no HCV detected in the blood stream 12 weeks after finishing treatment, the patient has achieved "SVR 12" and is considered to have been **cured.**

ANNEX 8. TEMPLATE FOR A MANAGEMENT CARD OF A PATIENT WITH CHRONIC HEPATITIS C

Template for management card of a patient with hepatitis C

IDENTIFICATION:		
Unique identifier |_|_|_|_|_|_|_|_|_|_|		
District:	Health unit:	District clinician/team:
Name:	First name:	Patient clinic number:
Sex: |_| Female |_| Male |_| Other	Date of birth: ___ /___ /___	Nationality:
Address:	District:	Telephone:
INFECTION STATUS ON ENROLMENT:		Enrolment date: ___ /___ /___
Anti-HCV: |_| Positive |_| Negative |_| Not done Date of first diagnosis of HCV infection: ___ /___ /___	HCV RNA (IU/mL): ___Value |_| Negative |_| Not done HCV genotype: |_|	HCV core Ag: |_| Positive |_| Negative |_| Not done
Anti-HIV: |_| Positive |_| Negative |_| Not done Latest HIV viral load (copies/ mL): _____|_| Not done Tuberculosis: |_| Active |_| On treatment |_| No	HIV treatment regimen: CD4 count: _____x10^9/L |_| Not done	Date HIV treatment started: ___ /___ /___
Injection drug use: |_| Active (past 12 months) |_| Past history |_| No	Daily alcohol consumption:	Metabolic syndrome:

STAGING: /___ /___		Staging date: ___
ALT: __IU/L AST: __IU/L PLT: __/mL	Clinical diagnosis of cirrhosis: |_| Yes |_|No	If yes, Child–Pugh score:
APRI score: ___ |_| Not done FIB4: _____ |_| Not done	Transient elastography (kPa): _____ |_| Not done	Liver biopsy stage (F): _____ |_| Not done
Bilirubin: Total ____µmol/L and Direct: ____µmol/L	Ultrasound scan:	Prothrombin time/INR: _____
HEPATITIS C TREATMENT:		
Past experience with treatment: |_| Yes |_| No	Past treatment:	
HCV treatment regimen started:	Date started: ___ /___ /___	Date completed: ___/___/___
Sustained viral response assessment post treatment (usually at SVR 12, i.e. 12 weeks after the completion of treatment)		
Date tested: ___ /___ /___	HBV DNA (IU/mL): |_| Positive |_| Negative |_| Not done	

ANNEX 9. TEMPLATE FOR FOLLOW-UP VISITS

FOLLOW-UP VISITS

Unique identifier |_|_|_|_|_|_|_|_|_|_|_| First name: _____ Last name: _____ Patient clinic number: _____

Date	Clinical assessment	Liver function test and staging					HBV tests			HCV tests	Renal function	Screening for hepatocellular carcinoma		Treatment regimen used	Side-effects/toxicity	Observations
		ALT (IU/L)	AST (IU/L)	Platelets (#/mL)	APRI	Transient elastogra-phy (kPa)	HBsAg (+/-)	HBeAg (+/-)	HBV DNA (IU/mL)	HCV RNA (+/-)	Creatinine (mg/dL)	Ultrasound	AFP (ng/mL)			

AFP: alpha fetoprotein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; APRI: AST-to-platelet ratio index; DNA: deoxyribonucleic acid; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen;
HBV: hepatitis B virus; HCV: hepatitis C virus; INR: International Normalized Ratio; IU: international units; PLT: platelets; RNA: ribonucleic acid

ANNEX 10. REPORTING FORM TO MONITOR THE CASCADE OF CARE FOR HCV INFECTION FROM HEALTH-CARE FACILITIES TO THE NATIONAL LEVEL

Data during the quarterly reporting period													
Quarter	Testing and diagnosis (C.6)				Treatment initiation and continuation (C.7)					Monitoring of treatment effectiveness (C.8)		Mortality from sequelae* (C.10)	
	Number of infected people already identified before the reporting quarter (treated or not)	Number of people tested with serology (anti-HCV) in the reporting quarter	Number of infected people newly diagnosed with infection in the reporting quarter (HCV RNA or HCV core antigen positive, treated or not)	PLHIV among number of infected people newly diagnosed with infection in the reporting quarter (HCV RNA or HCV core antigen positive, treated or not)	Number of people continuing treatment started before the reporting quarter	Number of people newly starting treatment in the selected quarter			Number of people completing treatment	Number of people assessed for treatment effectiveness in the reporting quarter #	Number of people with effective treatment in the reporting quarter	Proportion (%) of people dying from cirrhosis who were positive for viral hepatitis infection	Proportion (%) of people dying from hepatocellular carcinoma who were positive for viral hepatitis infection
						Total	PWID in the reporting quarter (among the total above)	PLHIV in the reporting quarter (among the total above)					
1													
2													
3													
Total													

*Estimates from sentinel sites

Tested for sustained viral response (SVR) using HCV RNA or HCV core antigen

Government of Nepal
Ministry of Health and Population
National Center for AIDS and STD Control
Teku, Kathmandu