

Kingdom of Cambodia
Nation Religion King



Ministry of Health

**National Guidelines for
Management of Persons with HIV
and Hepatitis C co-infection**

1st Edition in 2017



National Centre for HIV/AIDS, Dermatology and STD

Table of Contents

Preface.....	v
Acknowledgments.....	vi
Technical Working Group for National Guidelines for management of persons with HIV and Hepatitis C co-infection.....	vii
Abbreviations	vii
Chapter 1. Introduction.....	1
1.1 Epidemiology of HIV-HCV Co-infection.....	1
1.1.1 Global epidemiology of Hepatitis C.....	1
1.1.2 Cambodian Epidemiology of Hepatitis C.....	2
1.2 Modes of HCV transmission	3
1.3. Natural evolution of HIV and HCV co-infection.....	5
1.4. HCV Medications Currently and Soon to Be Available.....	5
Chapter 2 Screening for HCV infection among HIV-infected patients and diagnosis of HCV chronic infection.....	7
2.1 Criteria for HCV screening.....	7
2.2 Frequency of screening: When to repeat HCV-Ab testing for PLHIV who had initially tested negative.....	7
2.3 Screening tests.....	7
2.4 HCV Viral Load confirmation test (HCV-RNA PCR)	8
2.5 HCV Genotyping testing.....	9
2.6 Counseling and education about HCV infection and treatment.....	11
2.6.1 People Testing Anti-HCV Negative.....	11
2.6.2 People Testing Anti-HCV Positive	11
2.6.3 People Confirmed with Chronic Hepatitis C (CHC).....	11
2.6.4 People Testing RNA Negative.....	12
Chapter 3 Clinical evaluation of HCV/HIV co-infected	13
3.1 Clinical evaluation of HCV/HIV co- infected patients.....	13
3.2. Screening for alcohol use and counselling to reduce moderate and high levels of alcohol intake	15
Chapter 4. Assessing the degree of liver fibrosis and cirrhosis.....	16
4.1 Invasive Methods of Evaluating Liver Fibrosis.....	16
4.2 Non-Invasive Methods of Evaluating Liver Fibrosis	16
4.2.1 Serum biomarkers of liver fibrosis	17
4.2.2 Liver stiffness measurement	19

Chapter 5. HCV Prevention	21
5.1 Primary prevention.....	21
5.1.1 Prevention of HCV transmission in health-care settings:	21
5.1.2 Prevention of HCV Transmission among people who inject drugs:	22
5.1.3 Prevention of sexual transmission of HCV:.....	23
5.1.4 Prevention of mother-to-child transmission of HCV:	24
5.2 Secondary prevention.....	24
Chapter 6. When to start and select treatment for HCV/HIV co-infected patients ... 25	
6.1 When to start HCV treatment among HIV-HCV co-infected patients.....	25
6.1.1 Criteria to prioritize HIV-HCV patients with confirmed chronic HCV infection	25
6.1.2 Criteria to delay treatment for HIV-HCV patients with confirmed chronic HCV	
infection and seek for expert advice:.....	27
6.2 Treatment selection for HCV among HCV HIV co-infected patients.....	28
6.2.1 Recommended DAA Regimen	29
6.2.2 Antiretroviral therapy in persons with HIV/HCV co-infection:.....	31
6.2.3 Dosing of DAAs and Ribavirin	31
Chapter 7. Monitoring the effectiveness of treatment	33
7.1 Clinical, virological and laboratory at baseline and during follow up of treatment	.33
7.2 Side effects.....	34
7.3 Adherence.....	36
Chapter 8 Drug-Drug Interactions	37
8.1 Summary of DDI Interactions for Available Drugs.....	37
8.2 Drug Interactions in Special Populations	41
Chapter 9. Comorbidities	43
9.1 HIV/HCV/HBV infection	43
9.2 HIV/HCV/TB infection.....	45
9.3 HIV/HCV and Alcohol uses	46
9.4 HIV/HCV/NASH	46
9.5 HIV/HCV/Mental Health Disorders	46
9.6 HIV/HCV/Chronic Kidney Disease	47
9.7. Persons with cirrhosis.....	48
9.8 Children and Adolescents	49
9.9 Pregnant Women.....	51
9.10 People who Inject Drugs	52
Chapter 10. Outcomes of treatment and post-treatment follow up	54

10.1 Post-Treatment Monitoring of Patients Achieving SVR12	54
10.2 Managing Failures on DAAs	54
10.3 Hepatocellular Carcinoma Screening	55
10.4 Follow-up for assessment of liver disease	55
10.4.1 For untreated patients or for treated non-cirrhotic patients who do not achieve SVR:.....	55
10.4.2 For treated patients with SVR:.....	55
10.4.3 For cirrhotic patients, whether or not they have achieved SVR:.....	56
Annexes	57
Annex 3.1. A- WHO-ASSIT V3.0 for patient’s Alcohol, Smoking and Substance.....	57
Annex 3.1. B- WHO ASSIST V3.0 RESPONSE CARD FOR PATIENTS.....	62
Annex 3.1.C-FEEDBACK REPORT CARD FOR PATIENTS.....	63
Annex 3.1 D- RISKS OF INJECTING CARD – INFORMATION FOR PATIENTS.....	67
Annex 6. 1.1. Drug information – Sofosbuvir.....	68
Annex 6-1-2. Drug information Daclatasvir.....	70
Annex 6.1.3 Drug information- Harvoni (Sofosbuvir/Ledipasvir)	71
Annex 6.1.4 Drug information- Ribavirin (COPEGUS).....	72
Annex 7.1 Figure 7.1. Anaemia management of Ribavirin containing regiment	75
Annex 7.2: Adherence Plan	77
References	80

Tables

Table 1.1. Summary of HCV infection route.....	4
Table 1.2. FDA and European Medicines Agency European Medicines Agency (EMA) Approved Drugs, Combinations and Their Drug Classes.....	6
Table 3.1: Summary of Clinical and Biological Examinations to Perform Following Confirmation of CHC and at Subsequent Care Visits Pre-Treatment Initiation.....	14
Table 4.1 METAVIR Liver Biopsy Scoring System	16
Table 4.2. Selected non-invasive tests to assess liver fibrosis.....	16
Table 4.3 Summary of sensitivity and specificity of APRI, FIB-4 and FibroScan for the detection of advanced fibrosis and cirrhosis (all values are percentage.....	18
Table 4.4 Low and high cut-off values for the detection of significant fibrosis and cirrhosis.....	19
Table 5.1 WHO guidance on prevention of HCV infection in health-care settings.....	22

Table 5.2	WHO recommendations for prevention of HCV infection among people who inject drugs	23
Table 5.3.	WHO guidance on prevention of sexual transmission of HCV infection:.....	23
Table 6.1:	Prioritization criteria of HIV/HCV patients with chronic HCV infection for initiating HCV treatment.....	25
Table 6.2:	Criteria for delaying HCV treatment for HIV/HCV co-infected patients with chronic HCV infection.....	27
Table 6.3	Classes of second-generation DAAs available in Cambodia for the treatment of HCV (as of June 2016).....	28
Table 6.4:	Recommended Direct Acting Antiviral (DAA) Regimens When Genotyping is Unavailable	29
Table 6.5:	Recommended DAA regimens when genotyping is available for HCV or HIV HIV co-infected patients without cirrhosis.....	30
Table 6.6:	Recommended anti-HCV DAA treatment when genotyping is available for HIV patients or HIV & HCV co-infected patients with compensated cirrhosis (Child Pugh A)	30
Table 7.1	Clinical & laboratory baseline and follow up	33
Table 7.2	Side effect and management	35
Table 8.1:	Potentially significant drug interactions of sofosbuvir-	37
Table 8.2:	Potentially significant drug interactions of Daclatasvir.....	37
Table 8.3:	Potentially significant drug interactions of Ledipasvir	38
Table 8.4	Potentially significant drug interactions of ribavirin.....	40
TABLE 8.5	Drug–drug interactions between co-administered HCV and HIV treatment.....	41

Figures

Figure 1.1:	Number of HIV/HCV co-infection patients by country.....	2
Figure 2.1	HCV Screening and Confirmatory Testing.....	10
Figure 4.1	APRI and FIB-4 Formulas.....	17
Figure 9.1 :	Diagnostic Algorithm for Perinatal Transmission	51

Preface

It is estimated the sero-prevalence HCV in the general population is 1% to 2% accounting for roughly 98,000 people, however much higher prevalence of 5% to 10% is estimated for HIV-HCV co-infection. Using 2016 second quarter ART reports the estimated number of HIV-HCV co-infected adults who are currently on ART is estimated to range between 2,501 to 4,001 patients.

To achieve the ambitious 90-90-90 goals by 2020 with sustained reduction of HIV/AIDS-related mortality and virtual elimination of new HIV infections by 2025, the *National Guidelines for Management of Persons with HIV and Hepatitis C co-infection* was developed.

These Guidelines are essential to direct ART clinicians at all ART sites:

- 1) to screen for HCV in all PLHIV and all key populations;
- 2) to perform clinical evaluation of HIV-HCV co-infected persons;
- 3) to provide effective treatment and patient monitoring.

These guidelines represent another major success for the HIV/AIDS and STD program. Acknowledgement is given for the valued inputs and good practices from all members of technical working group for their time, efforts, and resources to finalize the first national guidelines for the treatment HIV-HCV co-infection.

The Ministry of Health has officially approved the use of these national guidelines, and hopes that all health care workers involved in care and treatment for PLHIV will strictly follow the guidelines in order to reduce HIV/AIDS related mortality in Cambodia. *OK/12*

Phnom Penh, 28 July 2017



Prof. ENG HUOT
SECRETARY OF STATE

Acknowledgments

The National Center for HIV/AIDS Dermatology and STD (NCHADS) and its development partners invested a significant amount of time, energy, and resources to develop the first National Guidelines for management of persons with HIV and Hepatitis C co-infection. The guidelines were not only aligned with the latest WHO guidelines in 2016, but also build on the extensive experiences among local and internal experts in care and treatment of HIV and HCV.

We would like to appreciate to all partners who have contributed to all process of development of this document. We wish to record our thanks to the following groups and individuals for their efforts, enthusiasm, and hard works to provide inputs to make the guidelines available, including NCHADS' officers (Dr. Ouk Vichea, Dr. Samreth Sovanarith, Dr. Ngov Bora), for overall coordination and technical inputs. At this spacious occasion, special thanks to all member of technical working group, including WHO (Dr. Laurent Ferradini and Dr. Deng Serongkea), MSF (Dr. San Kim Chamroeun, Dr. Shahidul Islam), SHCH (Dr. Phe Thong and Dr. An Sokkab), CHAI (Mr. Andrew McCracken, Dr. Stephen Ko and Jessica Tebor), FHI 360 (Dr. Jean Phillipe, Dr. Chel Sarim), ANRS (Dr. Olivier Segeral), US-CDC (Dr. Ahmed Saadani Hassani and Dr. Chan Sodara), AHF (Dr. Men Pagnaroot), Calmette Hospital (Dr. Lim Sreng SETHA), and Khmer-Soviet Friendship Hospital (Dr. Prak Narom) for their contributions in many ways especially providing financial supports, and technical inputs towards the finalization of this first national guidelines. *h*

Phnom Penh, 21 July 2017

Director of NCHADS



Technical Working Group for National Guidelines for management of persons with HIV and Hepatitis C co-infection

1. Dr. Ly Penh Sun	Director of NCHADS	Chairman
2. Dr. Ouk Vichea	Deputy Director/ NCHADS	Vice-Chair
3. Dr. Samreth Sovannarith	Chief of Technical Bureau/NCHADS	Member
4. Dr. Ngov Bora	Vice-Chief of TB/NCHADS	Member
5. Dr. Kaeun Chetra	Technical Bureau officer/NCHADS	Member
6. Mr. Keo Vannak	NCHADS	Member
7. Dr. Ung Vibol	Vice-Dean of University of Health Science	Member
8. Dr. Chel Sarim	FHI360's Representative	Member
9. Jean Phillipe	FHI360's Representative	Member
10. Dr. Ahmed Saadani Hassani	US-CDC's Representative	Member
11. Dr. Chan Sodara	US-CDC's Representative	Member
12. Mr. Andrew McCracken	CHAI's Representative	Member
13. Ms. Yayne Fekadu	CHAI's Representative	Member
14. Dr. Stephen Ko	CHAI's Representative	Technical Assistant
15. Jessica Tebor	CHAI's Representative	Technical Assistant
16. Dr. Prak Narom	Khmer-Soviet Friendship Hospital	Member
17. Dr. Lim Sreng Setha	Calmettre Hospital	Member
18. Dr. Laurent Ferradini	WHO's Representative	Member
19. Dr. Deng Serongkea	WHO's Representative	Member
20. Dr. Men Pagnaroot	AHF's Representative	Member
21. Dr. Shahidul Islam	MSF-France, Cambodia	Member
22. Dr. San Kim Chamreun	MSF-France, Cambodia	Member
23. Dr. Olivier Segeral	ANRS's Representative	Member
24. Dr. Phe Thong	SHCH's Representative	Member
25. Dr. An Sokkab	SHCH's Representative	Member
26. Dr. Ky Sovathana	NCHADS	Secretariat

Abbreviations

AASLD	American Association for the Study of Liver Disease
ALT	Alanine Aminotransferase
APRI	AST-to-platelet ratio index
ART	Antiretroviral Therapy
ARV	antiretroviral
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
AST	aspartate aminotransferase
BMI	Body Mass Index
CDC	Center for Disease Control
CHC	Chronic Hepatitis C
DAA	direct-acting antiviral (drug)
DDI	drug–drug interaction
EASL	European Association for the Study of the Liver
eGFR	estimated glomerular filtration rate
EIA	Enzyme Immunoassay
EMA	European Medicines Agency
CBC	Complete Blood Count
FDA	United States Food and Drug Administration
FIB-4	Fibrosis 4
gp	glycoprotein
Hb	haemoglobin
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C virus
LMIC	Lower and middle income countries
MSM	Men who have sex with men
NAT	nucleic acid testing
NCHADS	National Center for HIV/AIDS Dermatology and STD
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NS3/4A	Non-structural protein 3/non-structural protein 4A
NS5B	Non-structural protein 5B (of HCV)
OST	Opioid Substitution Therapy
PWID	People who inject drugs
RNA	Ribonucleic Acid
SAE	severe adverse event
SVR	Sustained Virological Response (Undetectable HCV RNA in the blood after the end of HCV treatment, either at 12 weeks (SVR12) or at 24 weeks (SVR24))
TB	Tuberculosis
TE	Transient Elastography
WHO	World Health Organization

Chapter 1. Introduction

1.1 Epidemiology of HIV-HCV Co-infection

Hepatitis C is a liver infection caused by the Hepatitis C virus (HCV). It is currently widely under-diagnosed and untreated, especially in low- and middle-income countries (LMIC)¹.

Today, most people become infected with the Hepatitis C virus by sharing needles or other equipment to inject drugs. In 15-30% of people, spontaneous viral clearance occurs within 6 months following HCV exposure, referred to as 'Acute Hepatitis C Infection', leading to a short-term illness. Hepatitis C infection becomes chronic in 70%–85% of people who are exposed to the Hepatitis C virus, and can result in death due to advanced liver disease or hepatocellular carcinoma².

1.1.1 Global epidemiology of Hepatitis C

Epidemiological data is limited. However, findings from studies have shown a wide variance of HCV prevalence rates and burden of the infection. Africa, Central Asia and East Asia are the most affected regions. Gower estimates that 64–103 million people globally live with chronic hepatitis C infection and that hepatitis C-related liver diseases accounts for approximately 700 000 deaths annually.^{3,4}

Plattl estimates that globally, 2.3 million people are co-infected with HIV/HCV, and that people who inject drugs (PWID) account for half, or 1.3 million of these.⁵ It has also been shown according to the WHO that HIV-infected people are on average 6 times more likely than HIV-uninfected people to have HCV infection, emphasizing the need to improve integrated HIV/HCV services⁶.

In South East Asia, WHO estimated about 30 million hepatitis C carriers, more than 1.6% of total populations. More than 120 000 People in the Region are estimated to die each year due cirrhosis and liver cancer associated with hepatitis C⁷. The Global Burden of Disease regions estimated in South East Asia 1% (0.8%-1.8%) prevalence of HCV infection presenting HCV anti-bodies and 0.7% (0.5%-1.1%) viraemic HCV prevalence with presence of HCV Ribonucleic Acid (RNA) indicating chronic infection.⁸

Maps below shows the number of HCV/HIV co-infected patients by country.

¹ WHO. (n.d.). *WHO/HEPATITIS C*. Retrieved JULY 02, 2016, from WHO: who.int/mediacentre/factsheets/fs164/en/

² CDC. (2015, May 31). *Viral Hepatitis - Hepatitis C Information*. Retrieved from www.cdc.gov/hepatitis/hcv/

³ Gower E, Estes C, Blach S, Shearer K, Razavi H. *Global epidemiology and genotype distribution of the hepatitis C virus infection*. *J Hepatol* 2014; 61(1):S45-57

⁴ Stanaway J.D, Flaxman A.D, Naghavi M, Fitzmaurice C, Vos T, et al, (2016). The Global Burden of Viral Hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. *The Lancet*. Published online July 6, 2016.

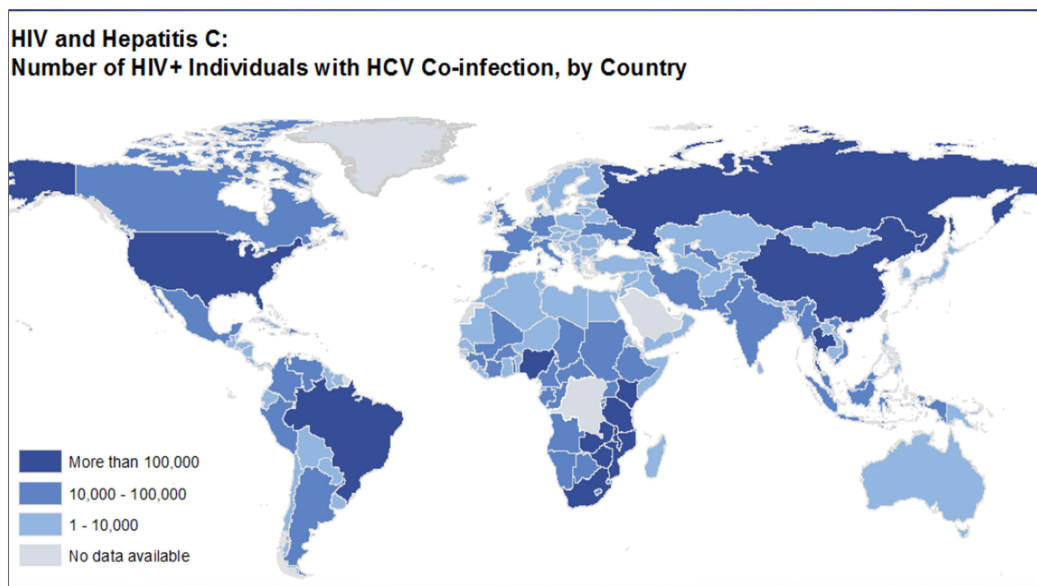
⁵ Platt L, Easterbrook P, Gower E, McDonald B, Sabin K, et al. (2016). Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. *Lancet Infect Dis*. doi:DOI: [http://dx.doi.org/10.1016/S1473-3099\(15\)00485-5](http://dx.doi.org/10.1016/S1473-3099(15)00485-5).

⁶ WHO. (2016, MARCH 7). *More than 2 million people coinfecting with HIV and hepatitis C*. Retrieved from WHO: who.int/hiv/mediacentre/news/hep-hiv-coinfecting/en/

⁷ WHO (2011) *Viral Hepatitis in the WHO south-East Asia Region. Know it Confront it. Hepatitis affects everyone, everywhere.*

⁸ Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. *Global epidemiology and genotype distribution of the hepatitis C virus infection*. *J Hepatol*. 2014;61(1 Suppl):S45–57.

Figure 1.1: Number of HIV/HCV co-infection patients by country⁹



1.1.2 Cambodian Epidemiology of Hepatitis C

Cambodia's epidemiological profile remains uncertain and the general population's prevalence data is still lacking. The Cambodia Pasteur Institute (IPC) estimates the antibody seroprevalence HCV in the general population at 1 to 2 %, roughly 98,000 people, with a wide variance by age groups mainly (> 40 years old), but also geographic location (6% in west provinces), by at-risk-populations (IDUs, men who have sex with men (MSM) and Sex Workers) where concentration may be high, and by HIV co-infection status (5% to 10%). The most affected age groups are those ranging between 18-89 years (> 40 years old are main age group) which makes up 64% of the 15.4 million total Cambodia's population. Genotype 1 is the most common (68%) followed by Genotype 6 (25%) with the other genotypes making up the remaining 7%.

Published literature addressing sero-prevalence is scarce. Two studies conducted in the general adult population in Siem Reap and in potential blood donors in rural Western Cambodia found anti-HCV prevalence rates estimated at 2.3% and 14.7%¹⁰, respectively. Data from the national blood bank in Phnom Penh shows a decreasing prevalence of HCV among blood donors over time, down from 2.5% in 2001 to 1% in 2010. Sihanouk Hospital Center of HOPE and Institute of Tropical Medicine, Antwerp, Belgium identified 231 HCV antibody positive of those there were 107 HCV -RNA positive among 3046 screened HIV patients (7.6% sero-prevalence, 3.5% active co-infection) in cross sectional study in 2014. Genotype results were available for 71 patients. The predominant genotypes were genotype 1 (54.9%) and 6 (40.8%). For genotype 1, subtype 1a was assigned in four samples (10.3%), subtype 1b in 32 samples (82.1%), and the subtype was indeterminate in

⁹ Center for Disease Analysis, Polaris Institute, 2013.

¹⁰ OI HS et al, (2009). Prevalence of hepatitis Band Hepatitis C virus infections in potential blood donors in rural Cambodia 40(5). Retrieved from <http://www.tm.mahidol.ac.th/seameo/2009-40-5/14-4568.pdf>

three samples. For genotype 6, the majority (n=25, 86.2%) were subtyped as 'non 6a or 6b'. Genotypes 2 and 3 were found to be rare, accounting together for less than 5%.¹¹

Among Tuberculosis (TB) patients systematically screened for hepatitis C at Kampong Cham Hospital (MSF OCP intervention) between July 2013 and June 2014, HCV seroprevalence was 1.6%.

The estimated number of people living with HIV in Cambodia is 74,000 (67,000 – 82,000)¹², and by the second quarter of 2016 a total of 53,788 active patients including 50,022 adults and 3,766 children were receiving ART (Antiretroviral Therapy) (NCHADS, 2016)¹³. With an estimated anti-HCV prevalence rate among the HIV population of 5-8%, the estimated number of co-infections is 3,700 – 5,920 among all HIV patients, and the estimated number of HIV-HCV co-infected adults currently on ART is 2,501- 4,001 .

1.2 Modes of HCV transmission

The hepatitis C virus (HCV) is a blood-borne virus. HCV is approximately 10 times more infectious than HIV through percutaneous blood exposures and has been shown to survive for weeks in syringes (Sulkowski MS, 2002)¹⁴ (Ciesek S, 2010)¹⁵ (Paintsil E, 2010)¹⁶.

Globally, injecting drug use through the sharing of injection equipment is the most common route of HCV transmission in Europe and US¹⁷. It is estimated that injecting drug users (IDUs) account for a disproportionately large burden of hepatitis C infection worldwide (ninety percent of new infections)¹⁸. Another important route of transmission include reuse or inadequate sterilization of medical equipment, especially syringes and needles in health care settings, and the transfusion of unscreened blood and blood products. This route seems to be predominant in Cambodia (Goyet S, AIDS behav 2013, Apr 24)

Much less commonly established, vertical transmission can occur from mother to baby during childbirth and horizontal transmission by contact with bodily fluids including saliva or semen of an infected person. The estimated rate of vertical transmission is estimated 4-8% among mothers without HIV infection and this rate increased to 10.8-25% among infants born to mothers who are co-infected with HIV and HCV (see table 1.1

¹¹ De Weggheleire A1, An S2, De Baetselier I1 et al, (2014): Hepatitis C prevalence, viral diversity and severity of liver disease in HIV patients in Phnom Penh, Cambodia: preliminary data communicated at AIDS 2016 Durban via poster: <http://programme.aids2016.org/Abstract/Abstract/2644>

¹² UNAIDS. (n.d.). Cambodia | UNAIDS. Retrieved from <http://www.unaids.org/en/regionscountries/countries/cambodia>

¹³ NCHADS. (2016). *NCHADS ART REPORT*.

¹⁴ Sulkowski M.S, Moore R.D, Mahta S.H, Chaisson R.E, Thomas D.L (2002). Hepatitis C and progression of HIV disease. *JAMA*, 199-206. Retrieved from www.ncbi.nlm.nih.gov/pubmed/12095384

¹⁵ Ciesek S, Friesland M, Steinmann J, Becker B, Wedemeyer H, et al. (2010). How stable is the hepatitis C virus (HCV)? Environmental stability of HCV and its susceptibility to chemical biocides, 1859-1866. Retrieved from www.ncbi.nlm.nih.gov/pubmed/20441517

¹⁶ Paintsil E, He H, Peters C, Lindenbach B.D, Heimer R. (2010). Survival of hepatitis C virus in syringes: implication for transmission among injection drug users. *J Infect Dis*, 984-990. Retrieved from www.ncbi.nlm.nih.gov/pubmed/20726768

¹⁷ CDC. (2015, May 31). Viral Hepatitis - Hepatitis C Information. Retrieved from [www.cdc.gov/hepatitis/hc](http://www.cdc.gov/www.cdc.gov/hepatitis/hc)

¹⁸ Margaret Hellard, Sacks-Davis R, Gold. (2009). Hepatitis C Treatment for Injection Drug Users: A Review of the Available Evidence. *Clinical Infectious Diseases*, 561-73.

below). Hepatitis C is not spread through breast milk, food, water or by casual contact such as hugging, kissing and sharing food or drinks with an infected person.¹⁹

Table 1.1. Summary of HCV infection route

(Adapted from Chapter 2.1.3 Routes of transmission and prevention, WHO guidelines for the screening, care and treatment of persons with chronic hepatitis C infection, updated version April 2016²⁰)

Routes of HCV infection	Remarks
Unsafe injection practice and unsafe procedure in health care settings	-In LMIC, infection with HCV is most commonly associated with unsafe injection practices and procedures such as renal dialysis and unscreened blood transfusions ^{21,22} -40% of injections administered are unsafe around the world (mainly in sub-Saharan Africa and Asia) ²³
Use unsterile equipment to injecting drug and contaminated drug solutions	-In middle and high income countries, most HCV occurs among people who use unsterile equipment to inject drugs and contaminated drug solutions -Prevalence of anti-HCV antibody is 67% among PWID globally ²⁴ .
Mother to child transmission ^{25,26,27}	-The risk of transmission of HCV from a mother to her child occurs in 4–8% of births to women with HCV infection, and -10.8–25% of births to women with HIV and HCV coinfection. -There are no proven interventions to reduce this risk of transmission

¹⁹ Guidelines for the screen, care and treatment of persons with chronic hepatitis C infection, Geneva: WHO 2016 (<http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/> accessed 2 Augusty 2016).

²⁰ Guidelines for the screen, care and treatment of persons with chronic hepatitis C infection, Geneva: WHO 2016 (<http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/> accessed August 2 2016).

²¹ Candotti D, Sarkodie F, Allain JP. Residual risk of transfusion in Ghana. *Br J Haematol.* 2001;113(1):37–9.

²² de Oliveira T, Pybus OG, Rambaut A, Salemi M, Ciccozzi M, et al. Molecular epidemiology – HIV-1 and HCV sequences from Libyan outbreak. *Nature.* 2006;444(7121):836–7.

²³ Kane A, Lloyd J, Zaffran M, Simonsen L, Kane M. Transmission of hepatitis B, hepatitis C and human immunodeficiency viruses through unsafe injections in the developing world: model-based regional estimates. *Bull World Health Organ.* 1999;77(10):801–7.

²⁴ Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horyniak D, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet.* 2011;378(9791):571–83.

²⁵ Thomas DL, Villano SA, Riester KA, Hershov R, Mofenson LM, Landesman SH, et al. Perinatal transmission of hepatitis C virus from human immunodeficiency virus type 1-infected mothers. *Women and Infants Transmission Study. J Infect Dis.* 1998;177(6):1480–8.

²⁶ Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. *Clin Infect Dis.* 2014;59(6):765–73.

²⁷ Floreani A. Hepatitis C and pregnancy. *World J Gastroenterol.* 2013;19(40):6714–20.

Sexual transmission	- Occurs infrequently in heterosexual couples (low or no risk HCV infection among non-HIV couples) ^{28,29} - More common in HIV-positive persons, particularly in MSM ³⁰
Other	- Intranasal drug use (sharing inhalation equipment for cocaine) -Other modes of blood borne transmission, such as acquisition by health-care workers, cosmetic procedures (such as tattooing and body piercing), scarification and circumcision procedures ^{31,32}

1.3. Natural evolution of HIV and HCV co-infection

Co-infection with HIV adversely affects the course of HCV infection. It remains unclear whether HCV infection accelerates HIV disease progression, as determined by AIDS-related events or death³³.

HCV/HIV co-infected people display an increased risk of developing liver disease and, due to liver damage and toxicity, co-infected individuals are also at higher risk of mortality and treatment complication³⁴. The risk of kidney diseases, including acute renal failure, and of cardiovascular illnesses is similarly increased among HCV/HIV co-infected people³⁵.

1.4. HCV Medications Currently and Soon to Be Available

Several classes of drugs are now available globally.

Pegylated Interferon. Historically, treatment has involved the use of a medication called **pegylated interferon**.

Ribavirin. **Ribavirin** is an antiviral prodrug whose mechanism of action is not widely understood. However, the addition of ribavirin to pegylated interferon or to direct-acting

²⁸ Terrault NA, Dodge JL, Murphy EL, Tavis JE, Kiss A, Levin TR, et al. Sexual transmission of hepatitis C virus among monogamous heterosexual couples: The HCV partners study. *Hepatology*. 2013;57(3):881–9.

²⁹ Tohme RA, Holmberg S. Is sexual contact a major mode of hepatitis C virus transmission? *Hepatology*. 2010;52(4):1497–505.

³⁰ Danta M, Brown D, Bhagani S, Pybus OG, Sabin CA, Nelson M, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. *AIDS*. 2007;21(8):983–91.

³¹ Jafari S, Copes R, Baharlou S, Etminan M, Buxton J. Tattooing and the risk of transmission of hepatitis C: a systematic review and meta-analysis. *Int J Infect Dis*. 2010;14(11):E928–E940.

³² Karmochkine M, Carrat F, Dos Santos O, Cacoub P, Raguin G. A case–control study of risk factors for hepatitis C infection in patients with unexplained routes of infection. *J Viral Hepat*. 2006;13(11):775–82.

³³ Greub G, Ledergerber B, Battegay M, Grob P, Perrin L, Furrer H, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet*. 2000;356(9244):1800–5.

³⁴ Wandeler G, S. M. (2015). Incident hepatitis C virus infections in the Swiss HIV Cohort Study: changes in treatment uptake and outcomes between 1991 and 2013. *Open Forum Infect Dis*. doi:10.1093/ofid/ofv02

³⁵ Mohd Hanafiah K, Groeger J, Flaxman A.D, Wiersma S.T. (2013). Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology*, 1333–42.

antiviral drugs (DAAs) combinations has been demonstrated to increase rates of sustained virologic response, particularly in cases of cirrhosis.

The new classes of drugs are called Directly Acting Antivirals, and they target several of the non-structural proteins involved in viral replication and assembly. Some combinations can now achieve greater than 90% sustained virologic response rates across genotypes, in the presence or absence of cirrhosis. The formulations currently or Soon to be available in Cambodia include **sofosbuvir/ledipasvir**, **Sofosbuvir+daclatasvir**, and **sofosbuvir/velpatasvir**.

non-structural protein 3/ non-structural protein 4A (*NS3/4A*). NS3/4A protease inhibitors target the protein region NS3/4A and include products like **simeprevir** and **grazoprevir**. The first generation of NS3/4A inhibitors have had low barriers to resistance, high levels of drug-drug interactions and high degrees of side effects, limiting their applicability in settings with limited monitoring capacity and in special populations. Newer generation NS3/4A inhibitors such as grazoprevir have higher barriers to resistance and fewer side effects.

NS5A Inhibitors, NS5A inhibitors target the NS5A protein, which plays a critical role in virus replication and assembly. Currently approved United States Food and Drug Administration (FDA) or European Medicines Agency (EMA) NS5A inhibitors include **daclatasvir**, **ledipasvir** and **velpatasvir**. NS5A inhibitors have increasingly strong pan-genotypic activity and low side effects. Some have low barriers to resistance.

Non-structural protein 5B (*NS5B*) *Inhibitors*. NS5B inhibitors target the RNA polymerase NS5B which regulates replication and viral assembly. The most available version of these is **sofosbuvir**. NS5B inhibitors have high barriers to resistance, are highly efficacious, and most have pan-genotypic activity.

Table 1.2. FDA and European Medicines Agency European Medicines Agency (EMA) Approved Drugs, Combinations and Their Drug Classes

Drug	Drug Class
Sofosbuvir	NS5B
Sofosbuvir/ledipasvir	NS5B/NS5A
Sofosbuvir/daclatasvir	NS5B/NS5A
Sofosbuvir/velpatasvir	NS5B/NS5A
Grazoprevir/elbasvir	NS3/4/NS5A
Paritaprevir/ombitasvir/ritonavir	NS3/4/NS5A/r
Dasabuvir	NS5B
Simeprevir	NS3/4
Ribavirin	Prodrug

Chapter 2 Screening for HCV infection among HIV-infected patients and diagnosis of HCV chronic infection

HCV testing should be voluntary, the results of the test should be confidential and referral for treatment should be considered in all persons with detectable HCV RNA.

2.1 Criteria for HCV screening

Screening for HCV antibodies (HCV-Ab) tests for exposure to hepatitis C infection in adults and children and is performed using a single serological assay, either a rapid diagnostic test (RDT) or an enzyme immunoassay (EIA). The screening should be done for individuals as following:

- *All persons with HIV infection should be screened for HCV antibodies at the time of enrolment into HIV care. People already in HIV care who were not screened at enrolment should receive catch-up screening.*
- Those who are not infected with HCV but practise behaviours that place them at risk for HCV infection (see below) should be retested annually.
- In case of limited availability of capacity for HCV testing , HIV patient groups which should be prioritized for HCV testing include:
 - High risk populations: PWID, MSM, prisoners
 - People with a history of HCV risk exposure/behaviours: frequent or unsafe medical injections, blood transfusions, renal dialysis, tattoos, body piercings, invasive medical, dental or surgical procedures
 - Partners of HCV-positive patients
 - Infants and children born to chronic HCV-infected mothers;
 - Those with symptomatic liver disease including elevated transaminases

2.2 Frequency of screening: When to repeat HCV-Ab testing for PLHIV who had initially tested negative

- Repeat HCV screening at ART initiation, if the last test was done more than 6 months.
- Repeat HCV testing annually for those who are at risk for HCV infection as described above.

2.3 Screening tests

- At the national hospital in Phnom Penh, the recommended serology screening test RDT or EIA for HCV due to the availability of this platform at the hospital and its high throughput.(see figure 2.1 HCV Screening and Confirmatory Testing)
- At the ART sites at sub-national levels, where EIA tests are not available, it is recommended to use a rapid diagnostic test (RDT) which has received FDA approval or WHO pre-qualification and meets the WHO recommended levels of

sensitivity (99%) and specificity (99%). Performing RDTs on whole blood is recommended; follow the instructions in the package insert.

- Patients with a positive serologic test should receive a confirmatory test to diagnose current infection using a nucleic acid test.³⁶

False-negative HCV serological test results among HIV patients:

- People who are infected with both HIV and HCV can have false-negative HCV serological test results.
- This may occur in up to 6% of persons with HIV who undergo testing using a second-generation anti-HCV enzyme immunoassay (EIA),^{37,38} but may occur more often among persons with advanced immunosuppression due to HIV and during early HCV infection.^{39,40}
- Evidence is still missing to suggest a specific CD4 cut-off level below which all those with a negative anti-HCV antibody test should have HCV RNA testing performed.
- Thus, for patients with advanced HIV infection and/or unexplained active liver disease (high transaminases) with initial anti-HCV negative test, HCV viral load should be considered to exclude an HCV infection.

2.4 HCV Viral Load confirmation test (HCV-RNA PCR)

- A positive anti-HCV Ab result (HCV screening test positive) indicates either a past infection that has been resolved, an active HCV infection (acute or chronic), or a false positive result.
- Therefore, all HIV patients who have anti-HCV Ab should be confirmed with quantitative or qualitative HCV-RNA PCR (HCV Viral Load).
- The presence of the virus by quantitative or qualitative HCV-RNA PCR test indicates ongoing HCV infection.
- Dried blood spot sample collection can be considered when following a manufacturer-approved protocol.
- If the HCV viral load is undetectable, there is no current HCV infection. The patient had HCV infection in the past which has spontaneously resolved (or that the serological test was falsely positive).

³⁶ Guidelines for the screen, care and treatment of persons with chronic hepatitis C infection, Geneva: WHO 2016(
<http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/> accessed August 2, 2016).

³⁷ Bonacini M, Lin HJ, Hollinger FB. Effect of coexisting HIV-1 infection on the diagnosis and evaluation of hepatitis C virus. *J Acquir Immune Defic Syndr.* 2001;26(4):340-4.

³⁸ George SL, Gebhardt J, Klinzman D, Foster MB, Patrick KD, Schmidt WN, et al. Hepatitis C virus viremia in HIV-infected individuals with negative HCV antibody tests. *J Acquir Immune Defic Syndr.* 2002;31(2):154-62.

³⁹ Thio CL, Nolt KR, Astemborski J, Vlahov D, Nelson KE, Thomas DL. Screening for hepatitis C virus in human immunodeficiency virus-infected individuals. *J Clin Microbiol.* 2000;38(2):575-7.

⁴⁰ Thomson EC, Nastouli E, Main J, Karayiannis P, Eliahoo J, Muir D, et al. Delayed anti-HCV antibody response in HIV-positive men acutely infected with HCV. *AIDS.* 2009;23(1):89-93.

- The level of the HCV viral load is not a marker of the severity of liver impairment. Only liver evaluation will inform about the severity of liver involvement (see Chapter 4).
- The possibility of reinfection with HCV after spontaneous clearance or successful treatment should be considered, and persons who are still at active risk (e.g. current PWID) should be advised to get retested for HCV annually.
- All patients, whether they receive a positive or a negative result for chronic HCV infection (Continued presence of HCV RNA in the blood six months or more after acquiring infection), should receive post-test counseling upon receipt of results as described in Chapter 2.

- *A positive result for HCV antibodies with an undetectable HCV Viral Load result means past resolved HCV infection with no ongoing disease.*
- *A detectable HCV Viral Load means active HCV infection (acute or chronic).*
- *A negative result for anti-HCV antibodies in an HIV patient with advanced immunosuppression does not exclude the possibility of active HCV infection. The cutoff CD4 level of providing the possibility of false negative HCV antibody has not had a consensus yet. HCV Viral load could detect active HCV infection in these cases and the decision to perform this test should be taken on a case per case basis depending on potential risk of being HCV infected and on clinical or biological evaluation.*

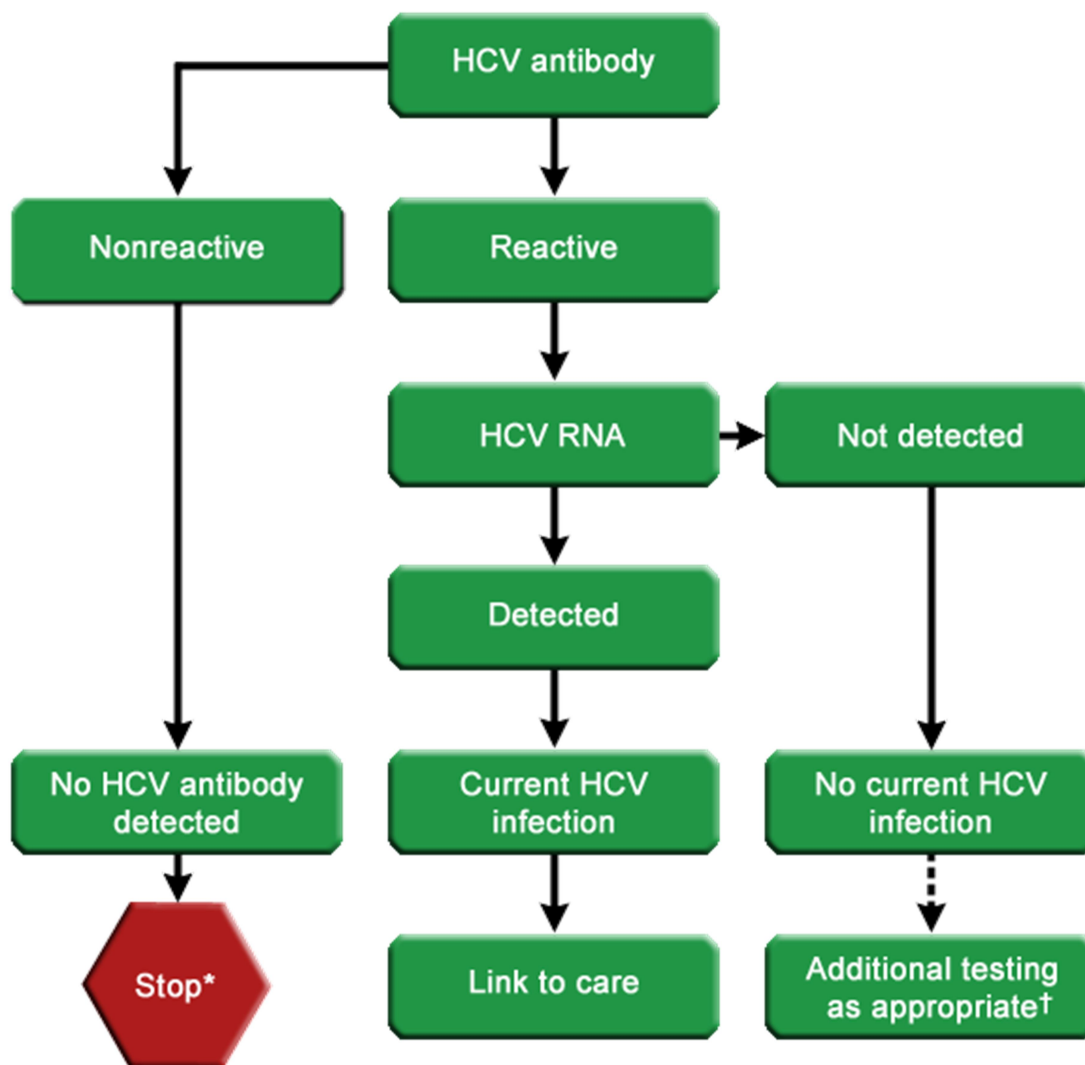
2.5 HCV Genotyping testing

- HCV comprises 7 genotypes numbered from 1-7 with multiple sub-types. A mix of HCV genotypes among chronically infected persons is reported in many countries, although certain genotypes are more prevalent in certain geographies and among certain vectors of transmission.
- In Cambodia, available evidence suggests that the HCV genotypes 1 and 6 predominate at 93% of all infections.
- DAAs have varying rates of efficacy for different HCV genotypes, although treatments are increasingly pan-genotypic (>90% efficacy). If genotype information is available, the choice of DAAs regimen to treat HCV infection can be adapted to the HCV genotype.
- If there is no available DAAs combination that is pan-genotypic for the population in question, a genotyping test is recommended to be performed before starting treatment of HCV infection, if available. However, genotype testing is expensive and may not be widely available in Cambodia.
- Due to its cost, genotype testing should only be performed when chronic infection has been confirmed and the patient has access to HCV treatment.
- When genotype tests are not available in Cambodia, DAAs regimens with high efficacy rates in genotypes 1 and 6 should be selected, such as sofosbuvir/ledipasvir or sofosbuvir/daclatasvir.

In Cambodia, the HCV genotypes 1 & 6 are predominant. DAAs regimens that are pan-genotypic for the Cambodian population should be prioritized to limit the need for expensive and minimally available HCV genotyping.

Figure 2.1 HCV Screening and Confirmatory Testing

(Summarizes the screening algorithm for confirming chronic hepatitis C infection)



* HCV RNA PCR testing should be performed without a first antibody screening test in severely immunocompromised HIV patients on a case per case basis depending on the potential risk of being HCV infected and clinical and/or biological evaluation.

2.6 Counseling and education about HCV infection and treatment⁴¹

2.6.1 People Testing Anti-HCV Negative

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

- Explanation of the results and implications: if the antibody test is nonreactive, no antibodies were found in the blood, and this usually means the patient doesn't have HCV, but should not be confused for future immunity.
- If the patient has recent or ongoing risk, an explanation of the "window" or "lag" period, along with the recommendation of retesting in 6 months.
- General disease education, with emphasis on prevention and modes of transmission.
- Discussion of benefits of retesting in the future.

2.6.2 People Testing Anti-HCV Positive

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

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

2.6.3 People Confirmed with Chronic Hepatitis c (CHC)

All people who receive a positive nucleic acid testing(NAT) test and are confirmed positive for chronic hepatitis C should receive education and counseling about their HCV infection, care and treatment. The aim of the counseling should be to help the person reduce progression of liver disease and prevent him/her from transmitting HCV to others. The counseling session should include the following:

- Explanation of the results and implications: Patient has been infected with hepatitis C virus, and the confirmatory test is positive, which means the patient

⁴¹ Center for Disease Control. (n.d.). *A Guide to Comprehensive Hepatitis C Counseling and Testing*. Retrieved from www.cdc.gov/hepatitis/resources/professionals/pdfs/counselingandtesting.pdf

has hepatitis C, Emphasizing that many people with hepatitis C remain healthy throughout their lives, and highly efficacious treatment options exist.

- Acknowledgement of concerns about stigma, transmission, and disease progression.
- Education on how to prevent transmission to others, especially in the case of injecting drug users. The counseling should also include an explanation of how HCV is not transmitted (sneezing, coughing, sharing drinking glasses, utensils).
 - Discussion on other measures that can be taken to stay healthy: Alcohol and Liver Wellness: All patients should be counseled on the importance of abstaining from alcohol and if necessary support in identifying resources to support the cessation of alcohol consumption.
 - Weight Management: HCV-infected people with a body mass index (BMI) of greater or equal to 25 kg/m² should be counseled on how to reduce weight via nutrition, exercise or medical intervention.
 - Vaccinations/Testing: Consider hepatitis A and B vaccination if susceptible and if liver disease is present. Consider testing for HIV.
 - Caution with Medications: Avoid new medicines, including over-the-counter and herbal agents without first checking with a healthcare provider. Help patient understand the need to seek additional care and potential treatment, and connect him or her with the necessary services if not available on-site.

2.6.4 People Testing RNA Negative

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

- Explanation/interpretation of results: The patient was anti-HCV positive, but RNA negative, so the patient was infected with hepatitis C, but then cleared the virus naturally. They do not have hepatitis C.
- Education on disease if patient has not received this education prior, highlighting that not having a current infection should not be confused with future immunity
- If there is an ongoing risk to the patient, emphasis on disease transmission and prevention awareness
- Emphasis on the benefits of retesting in the future if engaging in risky behaviors.

Chapter 3. Clinical evaluation of HCV/HIV co-infected

- Liver-related complications are increasingly prevalent in patients with HIV infection.
- According to the latest Data collection on Adverse events of Anti-HIV Drugs (D:A:D) report, liver-related events are the second leading cause of death in PLHIV and account for 9% of deaths⁴².
- Fibrosis progression is faster in HIV/HCV co-infection compared with HCV mono-infection.
- Therefore, assessment of liver disease is essential to prevent complications induced by cirrhosis and portal hypertension.
- Moreover, although treatment with DAAs achieves Sustained Virological Response (SVR) for 90% of patients, financial constraints make patient selection and prioritization necessary.
- A variety of non-invasive fibrosis and cirrhosis markers can be used to assess the severity of liver disease including clinical evaluation, serum markers and liver stiffness measurement.

3.1 Clinical evaluation of HCV/HIV co- infected patients

- As liver disease is asymptomatic for a long time, clinical evaluation is essential to detect cirrhosis early and prevent complications.
- When cirrhosis has been detected, patients should be monitored for complications related to portal hypertension (variceal bleeding, ascites) and liver insufficiency (coagulopathy, hepatic encephalopathy, bacterial infections) and regularly screened for hepatocellular carcinoma (HCC).
- Following confirmation of chronic infection in HIV/HCV co-infected patients, clinical evaluations must be done at each consultation in care to assess prioritization of treatment and to manage related complications. This assessment should include:
 1. **Clinical signs of cirrhosis – compensated or decompensated:** big liver with hard lower side, presence of ascites, clinical signs of hepatic insufficiency: jaundice, telangiectasia, palmar erythema, white nail , signs of portal hypertension, collateral circulation, splenomegaly, history of upper gastrointestinal bleeding (in this case, upper endoscopy should be ordered if possible)
 2. **Clinical signs of hepato-cellular carcinoma (HCC):** asthenia , liver mass, weight loss (important); in this case, consider ultrasound
 3. **Assessment of HIV disease:** presence/absence of signs of tuberculosis, CNS and other opportunistic infections, immune-virological status (CD4 cell-count and HIV viral load), adherence to HIV treatment. Refer the patient to specific department if other comorbidity suspected.

⁴² Smith C, Sabin CA, Lundgren JD, Thiebaut R, Weber R, et al. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D Study. AIDS 2010; 24:1537–1548.

4. **Assessment of HCV disease:** socio-economic status (as proxy/adherence to HCV treatment and reinfection), family history of liver cancer and other extra-hepatic manifestations such as: cryoglobulinaemia and vasculitis (cutaneous purpura, polyarthritis, asthenia, peripheral neuropathy, renal disease), debilitating fatigue, lymphoproliferative disorders, cutaneous protoporphyria, Sjögrens syndrome and diabetes.
5. **Presence of other co-infections and co-morbidities:** alcohol consumption, diabetes, hypertension, chronic kidney disease, and hepatitis B disease assessment. (See chapter 9). If hepatitis B status is unknown, at the first clinical assessment, HBsAg testing is highly recommended and necessary prior to starting treatment for HCV.
6. Substance use issues including alcohol (see below) and other drugs consumption
7. **Biological measurements of liver disease:** platelets, albumin, INR/Quick Test, ALT(Alanine Aminotransferase), AST, bilirubin,
8. **Pregnancy.**

Table 3.1: Summary of Clinical and Biological Examinations to Perform Following Confirmation of CHC and at Subsequent Care Visits Pre-Treatment Initiation

Examination	Baseline	Six-Monthly Care Visit
Clinical Evaluation		
Clinical signs of liver insufficiency	X	X
Clinical signs of HCC	X	X
Clinical signs of extrahepatic manifestations	X	X
Addictions (alcohol, tobacco, drugs)	X	X
Status of co-morbidities (diabetes, cardiovascular, chronic Kidney Disease)	X	X
Status of co-infections (HIV, hepatitis B virus (HBV), TB)	X	X
Biological Evaluation		
AST/ALT/Platelets (Fibroscan if available)	X	X
HBsAg	X	
HIV Viral Load	X	X
Pregnancy Test	X	X
Other Tests as Needed	X	X

3.2. Screening for alcohol use and counselling to reduce moderate and high levels of alcohol intake

- An alcohol intake assessment is recommended for all persons with HCV infection followed by the offer of a behavioral alcohol reduction intervention for persons with moderate-to-high alcohol intake.
- The WHO Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)⁴³ questionnaire can be used to quantify the level of alcohol intake as low, moderate or high, based on the responses to eight screening questions that assess the frequency of use and presence of alcohol-associated problems. (see annex 3.2.A.B.C.D)

⁴³ WHO ASSIST package. Geneva: World Health Organization; 2011
(http://www.who.int/substance_abuse/publications/media_assist/en/, accessed 22 March 2016)

Chapter 4. Assessing the degree of liver fibrosis and cirrhosis

- Assessing the degree of liver fibrosis is an important step in the clinical management of persons with HCV infection.
- Although HCV treatment should be considered for all persons with HCV infection, persons with cirrhosis should be prioritized for treatment because they are at increased risk of HCC and death due to liver failure.
- Furthermore, the selection and/or duration of treatment regimens can depend on the presence or absence of cirrhosis.
- Thus, it is important to identify low-cost, effective methods of assessing the degree of fibrosis, that are widely available in Cambodia.

4.1 Invasive Methods of Evaluating Liver Fibrosis

- **Liver biopsy** has been the gold standard for assessment of liver disease but is not widely used in low-income countries because of its invasiveness, risk of complications and need for expert histological interpretation.
- Several **liver biopsy-scoring systems** have been developed, of which the METAVIR system is most widely used (see Table 4.1).

Table 4.1 METAVIR Liver Biopsy Scoring System⁴⁴

METAVIR stage	F0	F1	F2	F3	F4
Definition	No fibrosis	Portal fibrosis without septa	Portal fibrosis with septa	Numerous septa without cirrhosis	Cirrhosis

4.2 Non-Invasive Methods of Evaluating Liver Fibrosis

A variety of non-invasive tests to assess the extent of fibrosis and cirrhosis may currently be used, including clinical evaluation, serum markers and liver stiffness measurement (see Table 4.2).

Table 4.2. Selected non-invasive tests to assess liver fibrosis

Test	Components	Requirements	Cost
APRI	AST, platelets	Simple serum and haematology tests	+
FIB-4	Age, AST, ALT, platelets	Simple serum and haematology tests	+
FibroTest	gGT, haptoglobin, bilirubin, A1 apolipoprotein, α2-macroglobulin	Specialized tests. Testing at designated laboratories	++
FibroScan®	Transient elastography	Dedicated equipment	+++

⁴⁴ Guidelines for the screening, care and treatment of persons with hepatitis infection, WHO, April, 2014

4.2.1 Serum biomarkers of liver fibrosis

- Serum biomarkers have been proposed for staging liver fibrosis, mainly in patients with chronic hepatitis C. Their practical advantages include their high specificity for detecting advanced cirrhosis, their good inter-laboratory reproducibility, and their potential widespread availability for non-patented tests.
- However, results may be influenced by changes in clearance and excretion of each individual parameter. For that reason, results should always be interpreted according to the clinical context and the results of other tests.
- Serum biomarkers using **direct markers of fibrosis** are available but these tests are patented and must be performed in laboratories with high quality standards. They are more expensive and have limited availability in Cambodia.
- **Indirect serum markers** are the most appropriate in low-income countries as they consist of a combination of routine biochemical or hematological tests. The evaluated and recommended tests are **APRI** (Aspartate Aminotransferase (AST)/platelet ratio index) and Fibrosis-4 (**FIB-4**). Their formulas for calculation are shown in figure 4.1. These tests usually have **dual cutoffs**: a high cutoff with high specificity and a low cutoff with high sensitivity⁴⁵. These cutoffs are generally combined to improve accuracy but some patients will fall in the indeterminate range and will need further testing.

Figure 4.1 APRI and FIB-4 Formulas⁴⁶

$$\text{APRI} = \left[\frac{\text{AST (IU/L)}}{\text{AST_ULN (IU/L)}} \times 100 \right] / \text{platelet count (10}^9\text{/L)}$$

$$\text{FIB4} = \text{age (yr)} \times \text{AST (IU/L)} / \text{platelet count (10}^9\text{/L)} \times [\text{ALT (IU/L)}]^{1/2}$$

APRI (AST/platelet ratio index)

- APRI score correlates with METAVIR score;
 - An APRI score of < 0.5 has 82% sensitivity for diagnosing a person with significant fibrosis METAVIR F2 – F4, i.e. can rule out the presence of fibrosis/cirrhosis
 - An APRI score of > 1.5 has 92% specificity for diagnosing significant fibrosis, i.e. METAVIR F2 – F4
 - An APRI score of > 2.0 has 94% specificity for diagnosing cirrhosis METAVIR F4, i.e. there is a high likelihood the patient has cirrhosis⁴⁷

⁴⁵ Crossan C, Tsochatzis EA, Longworth L, Gurusamy K, Davidson B, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. *Health Technol Assess* 2015; 19:1-409.

⁴⁶ Guidelines for the screening, care and treatment of persons with hepatitis infection, WHO, April 2014

⁴⁷ WHO. Guidelines for the Screening, Care and Treatment of Persons with Chronic Hepatitis C Infection. 2016.

- In a meta-analysis of 10 studies including 1848 patients with HIV/HCV co-infection, the area under Receiver Operating Characteristic (ROC) curve (AUROCs) of APRI for detecting advanced fibrosis and cirrhosis were 0.75 and 0.79, respectively⁴⁸.

FIB-4

- FIB-4 was specifically developed in patients with HIV/HCV co-infection for the diagnosis of advanced fibrosis (METAVIR F3 or more).
- The cutoffs of interest are 1.45 for ruling out and 3.25 for diagnosing at least F2
- As shown in a meta- analysis, FIB4 < 1.45 has 89% sensitivity and FIB-4 > 3.25 has 74% specificity in diagnosing patients with significant fibrosis (METAVIR F2-F4).
- Recently, FIB-4 was found to outperform liver biopsy as predictor of overall deaths and liver-related events⁴⁹ and its evolution over time was found as a risk factor for liver-related events in HIV-infected patients, independently of HCV co-infection.

APRI and FIB-4 tests may be less reliable in HIV/HCV co-infection due to the possibility of thrombocytopenia associated with HIV infection. In a case-control study, APRI performance was suboptimal in co-infected patients with CD4 cell count less than 250/mm³⁵⁰. Similar results were not found for FIB-4 score.

Table 4.3 Summary of sensitivity and specificity of APRI, FIB-4 and FibroScan for the detection of advanced fibrosis and cirrhosis (all values are percentage)

		APRI (low cut-off)	APRI (high cut-off)	FIB-4 (low cut-off)	FIB-4 (high cut-off)	Transient elastography
Significant fibrosis (METAVIR ≥F2)	Sensitivity (95% CI)	82 (77–86)	39 (32–47)	89 (79–95)	59 (43–73)	79 (74–84)
	Specificity (95% CI)	57 (49–65)	92 (89–94)	42 (25–61)	74 (56–87)	83 (77–88)
Cirrhosis (METAVIR F4)	Sensitivity 95% CI)	77 (73–81)	48 (41–56)	–	–	89 (84–92)
	Specificity (95% CI)	78 (74–81)	94 (91–95)	–	–	91 (89–93)

APRI: aminotransferase/platelet ratio index

⁴⁸ Lin ZH, Xin YN, Dong QJ, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. *Hepatology* 2011; 53:726–736

⁴⁹ Berenguer J, Zamora FX, Aldamiz-Echevarria T, Von Wichmann M.A, Crespo M et al. Comparison of the prognostic value of liver biopsy and FIB-4 index in patients coinfecting with HIV and hepatitis C virus. *Clin Infect Dis* 2015; 60:950–958

⁵⁰ Singal AG, Thomassen LV, Gretch DR, Shuhart MC. Use of the AST to platelet ratio index in HCV/HIV co-infected patients. *Aliment Pharmacol Ther.* 2011; 33:566–577.

Table 4.4 Low and high cut-off values for the detection of significant fibrosis and cirrhosis

	APRI (low cut-off)	APRI (high cut-off)	FIB-4 (low cut-off)	FIB-4 (high cut-off)	Transient elastography (FibroScan®)
Significant fibrosis (METAVIR \geq F2)	0.5	1.5	1.45	3.25	7–8.5 kPa
Cirrhosis (METAVIR F4)	1.0	2.0	-	-	11–14 kPa

APRI: aminotransferase/platelet ratio index; kPa: kilopascal

Recommendations

- APRI, FIB-4, or a combination can be used for assessing the stage of liver disease.
- The advantage of APRI is the high specificity for the diagnosis of cirrhosis and is useful for identifying persons at greatest risk of morbidity who, therefore, could be prioritized for treatment.
- FIB-4 was specifically developed in patients with HIV/HCV co-infection for the diagnosis of advanced fibrosis and is able to be predictive of liver-related events.
- Patients with FIB-4 and APRI scores between low and high cutoff values who do not receive treatment must be retested every year.
- In patients suspected of thrombocytopenia due to uncontrolled HIV viral load, APRI or FIB-4 may over-estimate the degree of fibrosis. In this case, consider confirming cirrhosis with transient elastography (TE).

4.2.2 Liver stiffness measurement

- Transient elastography (TE) using FibroScan (Echosens, Paris, France) was the first imaging modality used to assess liver fibrosis.
- Performances of TE in HIV/HCV co-infection are similar to those reported in HCV mono-infection and are better for the detection of severe fibrosis/cirrhosis (with AUROCs > 0.90) than for lesser stages.^{51,52}
- Baseline liver stiffness is also predictive of liver-related events. In a cohort of 1043 co-infected patients assessed with transient elastography, patients with liver stiffness values of less than 9.5KPa were not at increased risk of decompensation or overall

⁵¹ Castera L, Winnock M, Pambrun E, et al. Comparison of transient elasto- && graphy (FibroScan), FibroTest, APRI and two algorithms combining thesenoninvasive tests for liver fibrosis staging in HIV/HCV coinfectd patients: ANRS C013 HEPAVIH and FIBROSTIC collaboration. HIV Med 2014; 15:30 – 39.

⁵² TsochatzisEA,GurusamyKS,NtaoulaS,etal.Elastographyforthediagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. J Hepatol 2011; 54:650–659.

mortality in the short term⁵³. This is important to consider when prioritizing patients for treatment with DAAs.

- As recommended by WHO, TE should be performed by an experienced operator (>100 examinations) following a standardized protocol with the patient, fasting for at least 2 hours, in the supine position, right arm in full abduction, on the mid-axillary line with the probe-tip placed in the 9th to 11th intercostal space with a minimum of 10 shots. Correct interpretation of TE results in clinical practice must consider the following parameters:
 - IQR/ median value (<30%)
 - Serum aminotransferases levels (< 5 ULN)
 - Absence of extra-hepatic cholestasis
 - Absence of right heart failure, or other causes of congestive liver
 - Absence of ongoing excessive alcohol intake
 - Use XL probe if BMI > 30 kg/m²

Recommendations

- TE is recommended in complement to APRI and FIB-4 score for assessing the stage of liver disease when the equipment and trained operators are available.
- A TE value > 14 kPa is highly suggestive of cirrhosis and advanced chronic liver disease and treatment with DAAs must be considered in priority.
- A TE value between 9.5 – 14 kPa is suggestive of severe fibrosis and treatment with DAAs must be considered in the short term.
- In absence of TE available, serum biomarkers can be used alone to assess liver disease.

⁵³ Macias J, Mancebo M, Marquez M, et al. Low risk of liver decompensation among human immunodeficiency virus/hepatitis C virus-coinfected patients with mild fibrosis in the short term. *Hepatology* 2015; 61:1503 – 1511.

Chapter 5. HCV Prevention

- There is no vaccine for hepatitis C, therefore prevention of HCV infection depends upon reducing the risk of exposure to the virus according to the known modes of transmission.
- Prevention should occur in health-care settings to prevent unsafe injection practices; inadequate sterilization of medical equipment; and the transfusion of unscreened blood and blood products,
- Prevention should also occur among high risk populations like people who inject drugs and MSM, and through prevention of unsafe sexual contact.
- Early diagnosis is also part of prevention as it can prevent health problems from HCV infection and prevent transmission of the virus.
- Patient counseling and education to raise awareness about HCV infection, prevention and treatment are parts of HCV prevention.

5.1 Primary prevention

Due to the unavailability of any effective vaccine to date, reduction of the risk of exposure constitutes the major reliable means to prevent HCV infection, in particular through sexual contact and among most-at-risk populations of contracting HCV, including PWIDs⁵⁴.

5.1.1 Prevention of HCV transmission in health-care settings:

- In LMIC, infection with HCV is most commonly associated with unsafe injection practices and procedures such as renal dialysis and unscreened blood transfusions. Over 16 billion injections are administered yearly around the world and 40% of these are considered to be unsafe (mainly in sub-Saharan Africa and Asia) (ref. 21,22)
- Universal access to safe blood transfusion requires the implementation of key strategies to ensure access to a safe and sufficient blood supply, including the implementation of voluntary blood donation and achieving 100% quality-assured testing of donated blood. WHO has developed guidelines on best practices in phlebotomy, and best practices for injections and related procedures.⁵⁵ (see table 5.1)
- Table 5.1 provides some guidance on preventing the transmission of HCV infection in health-care settings.

⁵⁴ Hepatitis C Fact sheet , WHO Updated July 2016: <http://www.who.int/mediacentre/factsheets/fs164/en/>

⁵⁵ Guidelines on drawing blood: best practices in phlebotomy. Geneva:WHO;2010 (http://www.who.int/injection_safety/sign/drawing_blood_best/en/; accessed 21 Oct 2016)

Table 5.1 WHO guidance on prevention of HCV infection in health-care settings⁵⁶

• Hand hygiene: including surgical hand preparation, hand-washing and use of gloves
• Safe handling and disposal of sharps and waste
• Safe cleaning of equipment
• Testing of donated blood
• Improved access to safe blood
• Training of health personnel

5.1.2 Prevention of HCV Transmission among people who inject drugs:

In middle and high-income countries, most HCV infections occur among people who use unsterile equipment to inject drugs and contaminated drug solutions.

- PWID infected with HCV are at increased risk of all-cause mortality, reflecting the combined role of injecting drug use, low socioeconomic status, poor access to health care and environmental factors.
- Table 5.2 provides some guidance on preventing the transmission of HCV infection among people who inject drugs.

⁵⁶ Sources: WHO guidelines on hand hygiene in health care. Geneva: World Health Organization; 2009 (http://apps.who.int/iris/bitstream/10665/44102/1/9789241597906_eng.pdf, accessed 10 March 2016).

Safe abortion: technical and policy guidance for health systems, second edition. Geneva: World Health Organization; 2012. (http://apps.who.int/iris/bitstream/10665/70914/1/9789241548434_eng.pdf, accessed 10 March 2016).

Universal access to safe blood transfusion. Geneva: World Health Organization; 2008 (<http://www.who.int/bloodsafety/publications/UniversalAccessToSafeBT.pdf>, accessed 10 March 2016). Blood donor selection: guidelines on assessing donor suitability for blood donation. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/76724/1/9789241548519_eng.pdf, accessed 10 March 2016). WHO guidelines on drawing blood: best practices in phlebotomy. Geneva: World Health Organization; 2010 (http://www.who.int/injection_safety/sign/drawing_blood_best/en/index.html, accessed 10 March 2016).

Table 5.2 WHO recommendations for prevention of HCV infection among people who inject drugs⁵⁷

<ul style="list-style-type: none"> • Offer people who inject drugs the rapid hepatitis B vaccination regimen.
<ul style="list-style-type: none"> • Offer people who inject drugs incentives to increase uptake and complete the hepatitis B vaccination schedule.
<ul style="list-style-type: none"> • Implement sterile needle and syringe programmes that also provide low dead-space syringes for distribution to people who inject drugs.
<ul style="list-style-type: none"> • Offer peer interventions to people who inject drugs to reduce the incidence of viral hepatitis.
<ul style="list-style-type: none"> • Offer opioid substitution therapy to treat opioid dependence, to reduce HCV risk behaviour and transmission through injecting drug use, and to increase adherence to HCV treatment.
<ul style="list-style-type: none"> • Integrate the treatment of opioid dependence with medical services for hepatitis.

5.1.3 Prevention of sexual transmission of HCV

- Sexual transmission of HCV occurs infrequently in heterosexual couples. It is more common in HIV-positive persons, particularly in MSM.
- HIV-infected heterosexual partners of HCV-infected people are also more likely to acquire HCV.
- Table 5.3 provides some guidance on preventing the sexual transmission of HCV infection:

Table 5.3. WHO guidance on prevention of sexual transmission of HCV infection⁵⁸

<ul style="list-style-type: none"> • Promotion of correct and consistent condom use
<ul style="list-style-type: none"> • Routine testing of sex workers in high-prevalence settings
<ul style="list-style-type: none"> • Integrated action to eliminate discrimination and gender violence, and increased access to medical and social services for vulnerable persons

⁵⁷ Sources: Guidance on prevention of viral hepatitis B and C among people who inject drugs. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/75357/1/9789241504041_eng.pdf, accessed 10 March 2016). WHO guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. Geneva: World Health Organization; 2009 (http://www.who.int/substance_abuse/publications/opioid_dependence_guidelines.pdf, accessed 10 March 2016).

⁵⁸ Prevention and treatment of HIV and other sexually transmitted infections for sex workers in low- and middle-income countries: recommendations for a public health approach. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/77745/1/9789241504744_eng.pdf, accessed 11 March 2016). Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with men and transgender people. Geneva: World Health Organization, Department of HIV/AIDS; 2011 (http://www.who.int/hiv/pub/guidelines/msm_guidelines2011/en/, accessed 11 March 2016).

5.1.4 Prevention of mother-to-child transmission of HCV

- The risk of transmission of HCV from a mother to her child occurs in 4–8% of births to women with HCV infection, and in 10.8–25% of births to women with HIV and HCV co-infection ^(ref 25,26,27)
- There are no proven interventions to reduce this risk of transmission.

5.2 Secondary prevention

For people infected with the hepatitis C virus, WHO recommends:

- Education and counselling on options for care and treatment; including maintaining good adherence to treatment
- Immunization with the hepatitis A and B vaccines to prevent coinfection;
- Early and appropriate medical management including antiviral therapy if appropriate;
- Early diagnosis of those with chronic infection to allow people to take precautions to protect the liver from additional harm, specifically by abstaining from alcohol and tobacco consumption and avoiding certain drugs that are known to be toxic to the liver; *(see detail in chapter 3. 3.2. Screening for alcohol use and counselling to reduce moderate and high levels of alcohol intake.)*
- Regular monitoring for early diagnosis of chronic liver disease.

Chapter 6. When to start and select treatment for HCV/HIV co-infected patients

6.1 When to start HCV treatment among HIV-HCV co-infected patients

- Treatment for HCV infection is both efficacious and cost-effective in all patient groups including PWID and therefore *WHO recommends that all adults and children with chronic HCV infection, including PWID, should be assessed for antiviral treatment.*
- Treatment is also an effective prevention measure, as persons cured of HCV infection do not transmit the virus.

According to the current HIV treatment guidelines⁵⁹, ALL adult and children HIV patients co-infected with HCV should be considered for HCV treatment

6.1.1 Criteria to prioritize HIV-HCV patients with confirmed chronic HCV infection

In case there are limitations in HCV treatment availability, patients should be prioritized according to the following criteria:

- The priority should be given to patients who need HCV treatment rapidly because of their clinical condition which requires urgent HCV treatment.

Table 6.1: Prioritization criteria of HIV/HCV patients with chronic HCV infection for initiating HCV treatment

- **Prerequisite: Controlled HIV infection on ART for more than 6 months with:**
 - CD4 count > 50/ μ L, and
 - HIV viral load < 1000 copies/mL) *and*
 - Controlled opportunistic infections
- **Degree of liver disease** (in descending order of priority and following assessment methods described in Chapter 4):
 - Compensated cirrhosis (F4: Child Pugh A): APRI > 2, TE > 14 kPa
 - Advanced fibrosis: F3: TE :10-14 kPa
 - Liver fibrosis \geq F2 if enough treatments are available: APRI > 1.5; FIB-4 >3.25; 7-10 kPa

⁵⁹ Cambodian National HIV clinical management guidelines for Adults and Adolescents, NCHADS, 2016

- Patients with mild liver disease (F1) with or without extra-hepatic manifestations: APRI < 0.5; TE < 7 kPa
- **Presence of extra-hepatic manifestations such as:**
 - Cryoglobulinaemia and vasculitis (cutaneous purpura, polyarthritis, peripheral neuropathy, renal disease),
 - Debilitating fatigue,
 - Lymphoproliferative disorders,
 - Protoporphyrria
- **Presence of comorbidities such as:**
 - Alcohol consumption
 - Diabetes
 - Obesity (BMI > 25 kg/m²)
 - Co-infection with HBV
 - Chronic kidney disease
- **Significant psychosocial morbidity due to stigma, discrimination or fear of transmitting to others**
- **Key HIV-positive populations at risk of transmitting HCV:**
 - Active injection drug users (Controlled drug use^{**})
 - Men who have sex with men, transgender women
 - Prisoners
- **Other specific populations:**
 - PLHIV women of child-bearing potential

^{**} Drug use including IDU is not a contra-indication to treatment. However, treatment eligibility will be decided on a case by case basis (at a minimum but not limited to being on opioid substitution therapy (OST) if present, adhering to regular HIV consultations and receiving mental health support, not sharing needles and materials).

Decompensated cirrhosis and renal failure are not included as a priority criteria because the benefits from treatment may be limited because of short life expectancy (e.g. unavailability of liver transplant, liver or renal failure), and the complications of both ART treatment and HCV infection are more likely (liver failure, possible renal impairment, etc.).

- Criteria of cirrhosis decompensation:
 - At least one episode of cirrhosis complication including: ascites, hepatic encephalopathy, variceal bleeding
- Criteria for renal failure:
 - A glomerular filtration rate of less than 30 mL/min/1.73m²
- The decision of HCV treatment in case of decompensated cirrhosis will be evaluated on a case by case basis:
 - Following multidisciplinary expert consultation including a hepatologist who will decide the orientation and additional investigation and consultancy for each cases. Decompensated cirrhosis patient with some signs of gravity should not be considered for treatment includes:
 - Indication to palliative care
 - HCC diffuse with infiltration
 - Hepatorenal syndrome type 1
 - Multiple variceal bleeding recurrences
 - Untreatable patients for cirrhosis complications (bleeding and refractory ascites).

Evaluation of adherence is important

- The best adherence predictor in a co-infected patient being considered for HCV treatment is an undetectable HIV VL which suggests good adherence.
- No HCV treatment should be initiated without an HIV VL evaluation within the last year
- If the HIV VL is detectable, the priority is to assess the reasons (poor adherence, ART failure) and adapt HIV treatment accordingly before initiating HCV treatment.

6.1.2 Criteria to delay treatment for HIV-HCV patients with confirmed chronic HCV infection and seek for expert advice:

In some situations, HCV treatment should not be initiated in HIV/HCV co-infected patients with confirmed chronic HCV infection:

Table 6.2: Criteria for delaying HCV treatment for HIV/HCV co-infected patients with chronic HCV infection

Severe clinical conditions:

- Evidence of hepato-cellular carcinoma (HCC) or any other neoplasia
- Advanced/terminal liver, renal or other organ disease

Advanced or uncontrolled HIV disease:

- Repeated ART failures and impossibility of designing an effective ART regimen
- Last HIV viral load > 1000 copies/mL (within the last year)
- Active uncontrolled OI or tuberculosis
- During the first 6 months of a new ART regimen (unless minor **antiretroviral**

(ARV) change for toxicity)

For women in child-bearing age:

- Current pregnancy or breast feeding.

Special situation of HIV-HCV co-infected children and adolescents (age below 18 years):

- None of the DAAs have been approved for use among children less than eighteen years of age (See Chapter 9 for more details).

6.2 Treatment selection for HCV among HCV HIV co-infected patients

WHO recommends that DAA regimens be used for the treatment of persons with hepatitis C infection rather than regimens with pegylated interferon/ribavirin⁶⁰.

- DAAs have higher sustained virologic responses (SVRs) than interferon-based regimens, need shorter treatment duration, are orally administered and have fewer side-effects.
- Individual DAAs vary in therapeutic efficacy, genotypic efficacy, adverse events and drug-drug interactions (DDIs), and must be used in combination with at least one other DAAs.
- They are well tolerated among patients with advanced liver disease and can be prescribed to patients without cirrhosis as well as those with compensated and decompensated cirrhosis.
- Sofosbuvir+Daclatasvir and Sofosbuvir/Ledipasvir as well as Ribavirin are now available in Cambodia under partnership procurement and project pilot process.

Table 6.3 Classes of second-generation DAAs available in Cambodia for the treatment of HCV (as of June 2016)

Protease (NS3/4A)* inhibitors	NS5A Inhibitors	Polymerase (NS5B) inhibitor, nucleos(t)ide analogue	Polymerase (NS5B) inhibitor, non-nucleoside analogue
	Daclatasvir	Sofosbuvir	
	Ledipasvir		

* non-structural protein 3/non-structural protein 4A

⁶⁰ Guidelines for the screen, care and treatment of persons with chronic hepatitis C infection, Geneva: WHO 2016(<http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/> accessed August 2, 2016).

6.2.1 Recommended DAAs Regimen

- DAAs have been shown to have distinct therapeutic efficacy depending on HCV genotypes
- In Cambodia, genotypes 1 and 6 have been shown to be predominant.⁶¹
- Where genotyping is not available or affordable, the recommended treatment regimens are:
 - Non-cirrhotic patient: sofosbuvir/daclatasvir for 12 weeks or sofosbuvir/ledipasvir for 12 weeks
 - Compensated cirrhotic patient: sofosbuvir/ledipasvir +ribavirin for 12 weeks, sofosbuvir/daclatasvir for 24 weeks or sofosbuvir/daclatasvir+ ribavirin for 12 weeks if adequate laboratory monitoring capabilities are available
 - Decompensated cirrhotic patient: specialist evaluation and genotyping critical.
- When sofosbuvir/velpatasvir is available in Cambodia, it is recommended for 12 weeks in non-cirrhotic and cirrhotic populations.

Table 6.4: Recommended Direct Acting Antiviral (DAAs) Regimens When Genotyping is Unavailable

Degree of Cirrhosis	DAAs Regimen
No Cirrhosis (F0-F3)	Sofosbuvir+ Daclatasvir 12 weeks OR Sofosbuvir/Ledipasvir 12 weeks OR Sofosbuvir/Velpatasvir 12 weeks when available
Compensated Cirrhosis (F4)	Sofosbuvir+Daclatasvir 24 weeks OR Sofosbuvir+Daclatsvir+Ribavirin 12 weeks OR Sofosbuvir/Ledipasvir /Ritonavir 12 weeks OR Sofosbuvir/Velpatasvir 12 weeks when available
Decompensated Cirrhosis (CPC-B/A)	Refer to specialist for genotyping and evaluation. Toleration of RBV should be evaluated to reduce treatment duration.

Thus, a genotype test is optional to adapt the anti-HCV treatment to the genotype before initiation.

⁶¹ Lerolle N, Limsreng S, Fournier-Nicolle I, Ly S, Nouhin J, et al. (2012) High Frequency of Advanced Hepatic Disease among HIV/HCV Co-Infected Patients in Cambodia: The HEPACAM Study (ANRS 12267). J AIDS Clinic Res 3:161. doi:10.4172/2155-6113.1000161

Table 6.5: Recommended DAAs regimens when genotyping is available for HCV or HIV HIV co-infected patients *without cirrhosis**

Genotype	Sofosbuvir and Ledipasvir	Sofosbuvir and Daclastavir	Sofosbuvir and Ribavirin**
Genotype 1	8 ^a -12 weeks	12 weeks	No
Genotype 2	No	12 weeks	12 weeks
Genotype 3	No	12 weeks	24 weeks
Genotype 4	12 weeks	12 weeks	No
Genotype 5	12 weeks	12 weeks	No
Genotype 6	12 weeks	12 weeks	No

* Treatment durations are adapted from the 2015 guidelines of the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL).

** If adequate clinical and laboratory monitoring resources are available, adding ribavirin can be considered.

^a Treatment may be shortened to 8 weeks in treatment-naïve persons without cirrhosis if their baseline HCV RNA level is below 6 million (6.8 log) IU/mL. The duration of treatment should be shortened with caution.

Table 6.6: Recommended anti-HCV DAAs treatment when genotyping is available for HIV patients or HIV & HCV co-infected patients with compensated cirrhosis (Child Pugh A)***

Genotype	Sofosbuvir and Ledipasvir	Sofosbuvir and Daclastavir	Sofosbuvir and Ribavirin
Genotype 1	12 weeks ^b with Ribavirin or 24 weeks without Ribavirin	12 weeks with Ribavirin or 24 weeks without Ribavirin	No
Genotype 2	No	12 weeks with Ribavirin or 24 weeks without Ribavirin	16-20 weeks
Genotype 3	No	24 weeks with Ribavirin	No
Genotype 4	12 weeks ^b with Ribavirin or 24 weeks without Ribavirin	12 weeks with Ribavirin or 24 weeks without Ribavirin	No
Genotype 5	12 weeks ^b with Ribavirin or 24 weeks without Ribavirin	12 weeks with Ribavirin or 24 weeks without Ribavirin	No
Genotype 6	12 weeks ^b with Ribavirin or 24 weeks without Ribavirin	12 weeks with Ribavirin or 24 weeks without Ribavirin	No

*** Treatment durations are adapted from the 2015 guidelines of the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL).

^b with Ledipasvir, if platelet count <75 x 10³/microl, then 24 weeks' treatment should be given

6.2.2 Antiretroviral therapy in persons with HIV/HCV co-infection:

- In 2016, WHO updated its HIV treatment recommendations to recommend treatment for **all** persons living with HIV regardless of WHO clinical stage or CD4 cell count.⁶²

All HIV-HCV co-infection patients should be on ART, regardless of CD4 count.

- The choice of ART for persons with HCV co-infection is the same as for those with HIV alone. The choice of HCV treatment must take into account drug-drug interactions between ARVs and DAAs.
- **HIV VL suppression should be achieved before HCV treatment initiation:**
 - ART should be initiated first and HCV treatment deferred until CD4 > 50/μL, and HIV viral load undetectable within the last year.
 - If the patient is already on ART, check HIV VL if not done in the last year: If HIV VL is detectable, assess for HIV treatment failure, adapt ART treatment if necessary, and get the patient suppressed before starting HCV treatment.
- Persons with HIV/HCV co-infection on ART are at higher risk of developing side-effects of HCV therapy because of drug–drug interaction (DDI) and should be monitored closely.
- Before starting HCV therapy, careful consideration of drug-drug interactions (DDIs) is essential. Where DDIs are likely, ARV drug substitutions should be made before commencement of HCV therapy or dose adjustments of DAA therapy, depending on the DDI in question. See Chapter 8 on drug-drug interactions.

6.2.3 Dosing of DAAs and Ribavirin

(For detail DAA information, see Annex 6.1.1 .Sofosbuvir, Annex 6.1.2- Harvoni (Sofosbuvir/Ledipasvir) and Annex 6.1.3. Ribavirin (COPEGUS))

1. *Administration of Sofosbuvir + Daclastavir*
 - Sofosbuvir 400 mg (1 tab 400mg) + Daclastavir 60mg (1 tab 60mg) once a day
 - Dose adjustment of Daclastavir :
 - If used with non-nucleoside reverse transcriptase inhibitor (NNRTI) such as EFV or NVP:

⁶² Consolidated ARV guidelines , 2nd Edition. France : WHO; 2016 (<http://www.who.int/hiv/pub/arv/arv-2016/en/> accessed 29 June 2016).

- Increase the dose of Daclastavir : 90 mg /day (1 tab 60mg + 1 Tab 30mg)
 - If use with ATV/r:
 - Decrease the dose of Daclastavir: Daclastavir 30mg once a day
2. *Administration of the FDC Sofosbuvir (400mg) + Ledipasvir (90 mg):*
- FDC 1 tab once a day
 - Cautious if TDF is used as well
 - Monitor the creatinine clearance once a month
3. *Administration of Ribavirin:*
- If weight < 75 kg : Ribavirin 1000mg per day in two administrations (tab 200mg : 3-0-2)
 - If weight > 75 kg : Ribavirin 1200mg /day in two administrations (tab 200mg : 3-0-3)
 - Anemia is a common side effect of treatment with ribavirin and requires monitoring of hemoglobin levels.
 - If hemoglobin levels fall below 10 g/dL, ribavirin dosing should be decreased from 1000-1200 mg per day to 600 mg per day.
 - If hemoglobin levels fall below 8 g/dL, discontinue ribavirin treatment.
 - Patients with a history of cardiovascular disease may require dosing adjustments.
 - If hemoglobin levels decrease by more than or equal to 2 g/dL in a 4-week period, reduce dose to 600 mg per day.
 - If hemoglobin levels remain below 12 g/dL, discontinue ribavirin treatment.
 - Patients with renal disease require dose adjustment of ribavirin.
 - **Mild:** estimated glomerular filtration rate eGFR/Creatinine clearance: 50-80 ml/min
 - Dose :1000 mg or 1200 mg
 - **Moderate:** estimated glomerular filtration rate eGFR: 30-50 ml/min
 - Dose: Alternating 200mg and 400 mg every other day.
 - **Severe:** estimated glomerular filtration rate eGFR < 30ml/min
 - **Dose :** 200 mg daily
 - Hemodialysis / (End-stage kidney disease) ESRD : 200 mg daily
 - 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.

Chapter 7. Monitoring the effectiveness of treatment

7.1 Clinical, virological and laboratory at baseline and during follow up of treatment ⁶³

Table 7.1 Clinical & laboratory baseline and follow up

Examination	Baseline ¹	Ongoing Monitoring (weeks of Treatment)									12 weeks after end treatment
		1	2	3	4	8	12	16	20	24	
Clinical Evaluation	X		X		X	X	X	X	X	X	X
HBsAg ²	X										
CBC (Complete blood count)	X	X*	X*		X	X*	X*				X*
CD4 count ³	X										
HIV Viral Load ^{**}	X										
INR/Quick Test ⁴	X										
ALT	X	X*	X*		X	X*	X*				X
AST ⁴	X	X*	X*		X	X*	X*				X
Creatinine, Creatinine clearance	X	X*	X*		X	X*	X*			X	X
Bilirubin total ⁴	X				X		X			X	
Albumin ⁴	X				X		X			X	
Glucose ⁵	X				X						
HCV Viral Load	X										X
HCV Genotype ⁶	X										
Pregnancy Test	X				X	X	X	X ⁷	X ⁷	X ⁷	
Fibroscan	X										
ECG ⁸	X	X				X	X				
Ultrasound ⁹	X										

Note:

- ¹ All biochemical test results should be repeated if date of the result is longer than three months from baseline examinations;
- ² If previously not done in last one year from baseline.
- ³ If CD4 was not checked > 1 year
- ⁴ for cirrhosis case and affordable only
- ⁵ Optional;
- ⁶ Optional; if test are available and accessible.

⁶³ AASLD 2015 guidelines, available at <http://hcvguidelines.org>; MSF expert recommendations

⁷ pregnancy tests for women of child bearing age and female partner of men who receive RBV treatment should be performed up to six months after the end of ribavirin containing therapy; HCV follow up visits will be integrated into the HIV clinic visit schedule as to minimize the number of visits to the clinic. Patients will be educated about side effects & should return to the clinic at any time if problems arise

⁸ applies to SOF containing regimen if clinically found bradycardia

⁹ baseline for all and repeated every 6 months for cirrhosis

* For Ribavarin containing regimen only

Hepatic function and management (AASLD recommendation):

-ALT 10 fold increase more than the upper limit of normal at W4,

→ Discontinue therapy

-ALT < 10 fold increase at W4 and accompanied by any weakness, nausea, vomiting, jaundice, or significantly increased bilirubin, alkaline phosphatase or INR

→ Discontinue therapy

-ALT < 10 fold increase at W4 but asymptomatic

→ Should be closely monitored and repeated at week 6 and week 8. If levels remain persistently elevated, consideration should be given to discontinuation of therapy.

** If HIV viral load was not checked > 1 year.

HCV follow up visits will be integrated into the HIV clinic visit schedule as to minimize the number of visits to the clinic. Patients will be educated about side effects & should return to the clinic at any time if problems arise.

7.2 Side effects⁶⁴

New DAAs regimens appear to be well tolerated by patients in both clinical studies and “real-world” observational studies. Certain regimens have been shown to be safe for use in patients with decompensated liver cirrhosis and those who have undergone liver transplantation. However, close monitoring is required in these patients and it is recommended that such regimens be undertaken only in units with the expertise to manage these patients and treat complications if they arise. Cases of cardiac arrhythmia have been reported with sofosbuvir. Association with amiodarone is a risk factor but some cases have been described without this drug-drug interaction for patients with preexisting anomalies.

⁶⁴ Guidelines for the screening, care and treatment of persons with Chronic Hepatitis C infection Updated Version April 2016 Guidelines. AASLD 2015 guidelines, available at <http://hcvguidelines.org>

Table 7.2 Side effect and management

Side effect	Connected with drugs	Suggested Management Strategies
Fatigue, headache ,Insomnia, and nausea	<ul style="list-style-type: none"> • Daclatavir either used in combination with or without Sofosbuvir/Ribavirin • Sofosbuvir with or without Ledispavir 	<ul style="list-style-type: none"> • Check haemoglobin if suspect anaemia • Screen for depression • Review for contributing factors including anaemia, Sleep disturbance • Suggest behavioural strategies to conserve energy e.g. rest periods, Adequate fluid intake <p>✓ <i>General caution for prescribing any side effects drugs with liver impairment.</i></p>
Anaemia	<p>Regimen containing Ribavirin (Ribavirin causes haemolytic anaemia and bone marrow suppression Usually occurs within 1-2 weeks of starting treatment in about 10% patients.)</p>	<ul style="list-style-type: none"> • Ribavirin is not recommended for patient with anemia or blood disorder. • Precautious, closely monitoring and dose adjustment should be made for patients with cirrhosis, cardiovascular, pulmonary and renal disease; and patient older than 60 years old • Dose reductions maybe required. Careful clinical evaluation of patients before and during treatment is important to identify those in need of closer monitoring. <p><i>(please refer to Annex 7.1 Figure 7.2: Algorithm Anaemia management of Ribavirin containing regiment)</i></p>
Bradycardia	Ledipasvir/Sofosbuvir	<ul style="list-style-type: none"> • Co-administration with ledipasvir/Sofosbuvir and amiodarone may result in serious symptomatic bradycardia. Ledipasvir is safe for use with many HIV medications but should be avoided in those taking tipranavir/ritonavir. • Significant bradyarrhythmias associated with Sofosbuvir in patients also taking amiodarone and therefore it is contraindicated in these patients. Sofosbuvir is renally excreted and is also not recommended in those with eGFR <30 mL/min/1.73 m² or those with end-stage renal failure.
<p>Ribavirin is teratogenic and thus cannot be used during pregnancy and breast feeding. 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 to ensure that the patients and male partners can access and use reliable contraception.</p>		

7.3 Adherence

Adherence to treatment is very important and crucial for treatment success. The treatment will not be under directly observed therapy, so medical team will have specific role to ensure the treatment adherence throughout the duration of treatment.

The doctor will explain the importance of adherence to the treatment by explaining why it is important: probability getting of cure, stop infectiousness, expensive treatment, toxicity, developing resistance, losing chance to be cured if s/he is not taking treatment properly with the provision of additional support needed.

The nurse counselor will have different patient education and counseling sessions at the different stage during diagnosis, treatment and follow up.

The Pharmacist also will provide medicine strictly according to the doctor's prescription and by cross checking consumption of previous supply.

In an ideal case scenario, development and tracking of an adherence and life style plan is recommended such as the example in Annex 7.2. ⁶⁵

⁶⁵ MSF Patient education and counseling guide, For adults infected with Hepatitis C

Chapter 8. Drug-Drug Interactions

8.1 Summary of DDI Interactions for Available Drugs

A summary of DDI interactions for the available treatment options in Cambodia is noted below, and additional details can be found in Annex 6.

Table 8.1: Potentially significant drug interactions of sofosbuvir⁶⁶⁻⁶⁷

Drug class: drug name	Effect on concentration	Clinical comment
Anticonvulsants: Carbamazepine, Phenytoin, Phenobarbital, Oxcarbazepine	↓ Sofosbuvir	Coadministration is not recommended. Change anticonvulsant therapy
Antimycobacterials: Rifabutin, Rifampicin, Rifapentine	↓ Sofosbuvir	Coadministration is not recommended. Finish tuberculosis treatment before starting HCV treatment
HIV Protease Inhibitors: Tipranavir/ritonavir	↓ Sofosbuvir	Coadministration is not recommended. Administration of atazanavir/ritonavir with sofosbuvir

Table 8.2: Potentially significant drug interactions of Daclatasvir⁶⁸

Drug class: drug name	Effect on concentration	Clinical comment
NNRTIs: Efavirenz, Nevirapine	↓ Daclatasvir	The dose of daclatasvir should be <u>increased to 90mg if administered with efavirenz or nevirapine</u>

⁶⁶ Hepatitis C Guidance: AASLD-IDSA Recommendations for Testing, Managing, and Treating Adults Infected With Hepatitis C Virus. AASLD; 2015: (<http://onlinelibrary.wiley.com/doi/10.1002/hep.27950/pdf>; accessed 15 Oct 2016).

⁶⁷ Recommendations on Treatment of Hepatitis C, Guideline EASL; 2015. (<http://www.easl.eu/medias/cpg/HEPC-2015/Full-report.pdf>; accessed 15 Oct 2016)

⁶⁸ Recommendations on Treatment of Hepatitis C, Guideline EASL; 2015. (<http://www.easl.eu/medias/cpg/HEPC-2015/Full-report.pdf>; accessed 15 Oct 2016)

HIV Protease Inhibitors: Atazanavir/ritonavir Saquinavir/ritonavir Tipranavir/ritonavir Ritonavir Indinavir/ritonavir Fosamprenavir/ritonavir	↑ Daclatasvir	The dose of Daclatasvir should be <u>reduced to 30mg</u> for Atazanavir/ritonavir régime.
HIV Protease Inhibitors: Darunavir/ritonavir Lopinavir/ritonavir	(potentially Daclatasvir) ↑	No dose modification
Antifungals: Ketoconazole	↑ daclatasvir	The dose of Daclatasvir should be <u>reduced to 30mg</u>
Anticonvulsants: Carbamazepine, Phenytoin, Phenobarbital, Oxcarbazepine	↓ daclatasvir	Co administration is contraindicated Change anticonvulsant therapy

Table 8.3: Potentially significant drug interactions of Ledipasvir⁶⁹

Drug class: drug name	Effect on concentration	Clinical comment
Antacids: Aluminium, magnesium hydroxide	↓ ledipasvir	It is recommended to separate antacid and SOF/LDV administration by 4 hours
H2-receptor antagonists: Famotidine	↓ ledipasvir	May be administered simultaneously with or 12 hours apart from SOF/LDV at a dose that does not exceed doses comparable to famotidine 40mg twice daily
Proton-pump inhibitors: Omeprazole	↓ ledipasvir	Doses of 20mg or lower can be administered simultaneously with SOF/LDV under fasted conditions

⁶⁹ Recommendations on Treatment of Hepatitis C , Guideline EASL; 2015.(<http://www.easl.eu/medias/cpg/HEPC-2015/Full-report.pdf>, accessed 15 Oct 2016)

Antiarrhythmic: Amiodarone	Effect unknown	Co-administration is not recommended and may result in serious symptomatic bradycardia
Antiarrhythmic: Digoxim	↑ digoxin	Therapeutic concentration monitoring of digoxin is recommended
Anticonvulsants: Carbamazepine, Phenytoin, Phenobarbital, Oxcarbazepine	↓ ledipasvir	Co-administration is not recommended
Antimycobacterials: Rifabutin, Rifampin, Firapentine	↓ ledipasvir	Co-administration is not recommended
HIV Antiretrovirals: Efavirenz, Emtricitabine, Tenofovir Disoproxil, Dumarate	↑ tenofovir	Monitor for tenofovir-associated adverse reactions
HIV Antiretrovirals: Regimens containing tenofovir DV and HIV protease inhibitor/ritonavir/ cobicistat	↑ tenofovir	Consider alternative HCV or antiretroviral therapy to avoid increases in tenofovir exposure
HIV Antiretrovirals: Tipranavir/Ritonovir	↓ ledipasvir	Co-administration not recommended
HCV Products: Simeprevir	↑ ledipasvir, ↑ simeprevir	Co-administration is not recommended
Herbal Supplements: St. John's Wort	↓ ledipasvir	Co-administration is not recommended
HMG-CoA Reductase Inhibitors: Rosuvastatin	↑ rosuvastatin	Co-administration is not recommended

Co administration of Harvoni with Elvitegravir, Cobicistat, Emtricitabine, Tenofovir are not recommended.

Table 8.4. Potentially significant drug interactions of ribavirin⁷⁰

Drug name	Interaction	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 anemia
Didanosine (ddI)	Ribavirin may increase 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 concentrations	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

Note: TDF and Ribavirin has potential interaction: In a pharmacokinetic study in healthy volunteers, coadministration of tenofovir and ribavirin does not result in substantial changes to the pharmacokinetic profile of either drug. However, **hepatic decompensation (some fatal)** has occurred in cirrhotic HIV/HCV co-infected patients receiving NRTI-containing HIV therapy and interferon alpha and ribavirin. Patients receiving interferon with ribavirin and NRTIs should be closely monitored for treatment-associated toxicities, especially hepatic decompensation and anaemia.

(source : <http://www.hep-druginteractions.org/checker>)

⁷⁰ Recommendations on Treatment of Hepatitis C , Guideline EASL; 2015.(<http://www.easl.eu/medias/cpg/HEPC-2015/Full-report.pdf>, accessed 15 Oct 2016)

8.2 Drug Interactions in Special Populations

Drug-Drug Interactions in HIV/HCV Co-Infected Patients

Full details on drug interactions between DAAs and ARVs can be found on the University of Liverpool HIV Drug Interactions website. A summary of key drug-drug interactions for HIV drugs commonly used in Cambodia are below⁷¹:

TABLE 8.5 Drug–drug interactions between co-administered HCV and HIV treatment⁷²

HIV antiviral drugs	Daclatasvir	Ledipasvir/ sofosbuvir	Sofosbuvir	Ribavirin (See table 8.4)	SOF/ VEL
Nucleoside reverse transcriptase inhibitors (NRTIs)					
Abacavir (ABC)					
Emtricitabine (FTC)					
Lamivudine (3TC)					
Tenofovir (TDF)		E			E
Zidovudine (AZT)					
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)					
Efavirenz (EFV)	↓	↓			
Nevirapine (NVP)	↓				
Protease inhibitor					
Lopinavir					
Atazanavir (ATV/r)	↑				
Ritonavir					
HIV entry/integrase inhibitor					
Dolutegravir (DTG)					

Legend:

- These drugs should not be co-administered
- Potential interact
- No clinically significant interaction expected

⁷¹ AFEF - Société Française d'Hépatologie: <http://www.afef.asso.fr/>

⁷² University of Liverpool Hepatitis drug interactions webpage (<http://www.hep-druginteractions.org/>) and HIV drug interactions webpage www.hiv-druginteractions.org/.

- ↓ : Potential decreased exposure of DAA
↑ : Potential elevated exposure of DAA
E : Potential elevated exposure of ARV drug

Ledipasvir

The AASLD 2015 guidelines advise caution with ledipasvir in patients with HIV/HCV co-infection: “Because ledipasvir increases tenofovir levels, when given as Tenofovir Disoproxil Fumarate, concomitant use mandates consideration of creatinine clearance (CrCl) rate and should be avoided in those with CrCl below 60 mL/min. Because potentiation of this effect occurs when Tenofovir is used with Ritonavir-boosted HIV protease inhibitors , Ledipasvir should be avoided with this combination, unless antiretroviral regimen cannot be changed and the urgency of treatment is high” (AASLD 2015 guidelines).

Drug-drug interactions between HCV DAAs and illicit recreational drugs⁷³ (EASL 2015):

There is no interaction between DCV, SOF, SOF/LED and Amphetamine, Cannabis, Cocaine, Diamorphine, Diazepam, Gamma-hydroxybutyrate, Ketamine, Ecstasy(MDMA), Methamphetamine, Phencyclidine (PCP) and Temazepam. DCV, SOF, LED, Simeprevir can be used in people using drugs on Opioid substitution therapy.

⁷³ EASL Recommendations on Treatment of Hepatitis C 2016. European Association of the Study of the Liver. Journal of Hepatology. <http://dx.doi.org/10.1016/j.jhep2016.09.001>

Chapter 9. Comorbidities

9.1 HIV/HCV/HBV infection

- HBV and HCV coinfection may result in an accelerated disease course; HCV is considered to be the main driver of disease. Severe chronic hepatitis or cirrhosis was more frequent in patients with HBV/HCV co infection than single HBV or HCV infection. Although some studies found HCV and HBV could lead mutual suppression of both virus, the dual infection of both virus may enhance the severity of hepatitis. A multicenter case-control study in Italia found that moderate, severe chronic hepatitis or cirrhosis were more frequent in patients with HBV/HCV co infection than single HBV or HCV infection ($P < 0.05$)⁷⁴
- Persons with HIV/HCV coinfection generally have more rapid progression of liver fibrosis, especially those with a CD4 cell count of < 200 cells/mm³ (^{75, 76, 77}). Furthermore, even among patients in whom ART leads to successful control of HIV infection (i.e. undetectable HIV viral load), the risk of hepatic decompensation among coinfecting patients is higher than among patients with HCV mono-infection⁷⁸
- All-cause mortality was higher in participants with triple infection of HIV-HCV-HBV and HIV-HCV co-infection than in those with HIV only, but not in those with HIV-HBV co-infection. People with triple infection were also more likely to have virological failure than were those with HIV only, whereas the difference was not significant for those with HIV-HBV co-infection or HIV-HCV co-infection. No co-infection was significantly associated with a difference in CD4 cell count after 1 year of treatment. Loss to follow-up was more common among participants with triple infection and HIV-HCV co-infection but not HIV-HBV co-infection than among those with HIV only⁷⁹

⁷⁴ Liu Z, Hou J. Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) Dual Infection. *Int J Med Sci* 2006; 3(2):57-62

⁷⁵ Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfecting patients. *The Multivirc Group. Hepatology.* 1999;30(4):1054-8.

⁷⁶ Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis.* 2001;33(4):562-9.

⁷⁷ Gane EJ, Hyland RH, An D, Svarovskaia E, Pang PS, Brainard D, et al. Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks in patients with HCV genotype 3 or 6 infection. *Gastroenterology.* 2015;149(6):1454-61 e1.

⁷⁸ Lo Re V 3rd, Kallan MJ, Tate JP, Localio AR, Lim JK, Goetz MB, et al. hepatic decompensation in antiretroviral-treated patients co-infected with HIV and hepatitis C virus compared with hepatitis C virus-mono-infected patients: a cohort study. *Ann Intern Med.* 2014;160(6):369-79.

⁷⁹ Zhang F, Zhu H, Wu Y, Dou Z, Zhang Y et al, HIV, hepatitis B virus, and hepatitis C virus co-infection in patients in the China National Free Antiretroviral Treatment Program, 2010-12: a retrospective observational cohort study.

For these reasons

- It is important to check for the presence of HBV infection before starting HCV/HIV treatment
- all persons with HIV/HCV coinfection should be considered for HCV treatment

- There are fewer DDIs between DAAs and ARV medicines, and SVR rates with DAA-based therapy among persons with HIV coinfection are higher than 95%, even for those with prior HCV treatment failure or advanced fibrosis.
- However, DDIs must be checked between HIV and HCV drug before initiating treatment. Telbivudine, in particular, may be associated with a higher risk of neuropathy if given with interferon-containing regimens.
- Therefore, there is no longer a need to consider HIV/HCV co-infected patients as a special, difficult-to treat patient population.

It is advisable to first initiate treatment for HIV and achieve HIV suppression before starting HCV treatment, although there are some circumstances where it may make sense to treat HCV infection first and then initiate therapy for HIV.

- *For instance: include persons with moderate-to-severe fibrosis at risk of rapid liver disease progression if the HIV infection is not associated with significant immunosuppression at the time of treatment.*

- Raised liver enzymes may be the result of ART-induced drug toxicity and/or opportunistic infections. ALT and aspartate aminotransferase (AST) should be monitored at 1 month after ART initiation and then every 3–6 months. A significant elevation of AST/ALT may prompt careful evaluation for other causes of liver function impairment (e.g. alcoholic hepatitis, hepatobiliary disease), and may require short-term interruption of the ART regimen or specific drug suspected of causing the elevation.
 - Cambodian HIV Clinical Management guidelines suggested using TDF+ 3TC containing regimen as first line regimen; this will automatically include treatment for HBV. (For detail management of HIV/HBV, please refer to refer to *National HIV Clinical Management guidelines for Adults and Adolescents, NCHADS 2015*)
- **Monitoring of therapy in persons with HIV/HCV co-infection**
- An increase in tenofovir concentrations when a pharmacokinetic enhancer (ritonavir or cobicistat) is present in an ARV regimen, these combinations should be used with frequent renal monitoring. Tenofovir concentration is also increased in efavirenz-containing regimens and caution with regard to renal monitoring is also required.

- A higher risk of haematological suppression is also present in persons with HIV infection; these are important dose-limiting side-effects, especially with co-administration of certain ARV drugs.
- Monitoring during ribavirin treatment with or without protease inhibitor therapy is therefore recommended at multiple time points. Additional time points may be required for persons with evidence of side-effects and in persons at highest risk (for example, persons with cirrhosis and HIV, and those on protease inhibitor therapy). Additional monitoring of liver function is recommended in persons with cirrhosis, including albumin, bilirubin and coagulation tests. Persons with evidence of neutropenia, thrombocytopenia and anaemia require 1–2-weekly monitoring. (refer to the side effect monitoring table for detail)

9.2 HIV/HCV/TB infection

- The TB screening should be done before considering to start HCV treatment, especially among those having advanced immunosuppression. The absence of four symptoms (cough, fever, weight loss or night sweat) should be reasonable to exclude active TB infection, otherwise, the patient should undergo further investigations for TB or other diseases.
- ***TB treatment should be started before starting HCV treatment***, and closely monitor liver function test as TB medicine will increase hepatotoxicity⁸⁰ ***The concurrent treatment TB and HCV should be avoid*** as most of DAAs will be reduced or increased the drug level in blood if co-administration with antituberculosis such as rifampicine , rifapentin and rifabutin.
- Concurrent treatment of HCV infection and multidrug-resistant TB is particularly complicated because of many DDIs between DAAs and secondline antimicrobials. There are limited data on the management of persons coinfectd with HCV, HIV and TB, but such cases need sound clinical judgement in order to reduce the additive side-effects, pill burden and DDIs. Clinicians need to be aware of the risk of reactivation of TB if the person, particularly if HIV coinfectd, receives interferon-based therapy, as interferon-based therapy could increase the incidence of active TB ⁸¹
- Baseline liver function tests for individuals with chronic liver disease are encouraged prior to initiating treatment for latent TB infection. For individuals with abnormal baseline test results, routine periodic laboratory testing should be carried out during the treatment of latent TB infection⁸² .

⁸⁰ Guidelines for the screen, care and treatment of persons with chronic hepatitis C infection, Geneva: WHO 2016 (<http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/> accessed 30 May 2016).

⁸¹ Lin SY, Chen TC, Lu PL, Lin CY, Lin WR, Yang YH, et al. Incidence rates of tuberculosis in chronic hepatitis C infected patients with or without interferon based therapy: a population-based cohort study in Taiwan. BMC Infect Dis. 2014;14:705.

⁸² Guidelines on the management of latent tuberculosis infection. Geneva: World Health Organization; 2015 (http://www.who.int/tb/publications/ltbi_document_page/en/, accessed 22 March 2016).

9.3 HIV/HCV and Alcohol uses

- The consumption of alcohol, even in moderate amounts, in people with chronic HCV infection has been demonstrated to speed progression of advanced liver disease and HCC.⁸³ People diagnosed with chronic HCV should be counseled to limit or abstain from alcohol consumption and offered access to alcohol cessation services, where possible.
- The WHO ASSIST framework can provide a framework and tools for evaluating alcohol dependence and implementing counseling.
- For patients with alcohol disorders who are eligible for treatment, it is ***recommended that patients stop drinking prior to treatment due to its effect on adherence.***⁸⁴

For patients who continue to drink during treatment, clinicians should provide extra support to ensure adherence. Pharmacists must consider any potential drug-drug interactions.

9.4 HIV/HCV/NASH

- Non-alcoholic steatohepatitis 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.
- The interaction between NASH and HCV has not been widely studied, and no studies have examined the effect of triple infection with HIV. Studies completed to date have demonstrated an association between co-infection and higher steatosis and fibrosis scores, higher triglyceride levels, and lower total and high density lipoprotein cholesterol levels.⁸⁵
- Chronic HCV patients with NASH are a recommended target population for treatment in order to halt progression of liver disease. Patients should be monitored carefully during treatment for any complications arising from the more severe underlying liver disease. There are currently no treatments for NASH other than lifestyle changes to reduce obesity and promote liver health.

9.5 HIV/HCV/Mental Health Disorders

- HIV and HCV are both associated with higher rates of mental health disorders compared to the general population. In the case of HCV, the higher rate of disorders can be attributed to multiple causes including a high rate of transmission in populations with psychiatric disorders due to risk behaviours, the

⁸³ Vandenbulcke, H, Moreno C, Colle I, Knebel J.F, Francque S, et al., (2016). *Alcohol Intake Increases the Risk of HCC in hepatitis C virus-related compensated cirrhosis: A prospective study.* J Hep Vol 65 543-551.

⁸⁴ Anand BS, Currie S, Dieperink E, Bini EJ, Shen H, Ho SB, et al. (2006). *Alcohol Use and Treatment of Hepatitis C Virus: Results of a National Multicenter Study.* Gastroenterology. 2006. 130: 1607-1616.

⁸⁵ Bedossa, P., Moucari, R., Chelbi, E., Asselah, T., Paradis, V., Vidaud, M. et al. *Evidence for a role of nonalcoholic steatohepatitis in hepatitis C: a prospective study.* Hepatology. 2007; 46: 380-387

effect of HCV on the central nervous system, and the psychosocial effects of stigma and discrimination from the disease.⁸⁶

- Pegylated interferon treatment is also associated with various neurological and psychiatric effects including debilitating fatigue, depression, anxiety and cognitive disturbances, with rare cases of suicidal thoughts. DAAs have not been associated with significant impact on mental health and are not believed to have neuropsychiatric effects.
- Mental health disorders have a high chance of affecting access to treatment and treatment adherence rates and a robust assessment of a patient's psychiatric history prior to treatment history is essential for mitigating any negative effects on treatment success. Involvement of appropriate mental health personnel in the care and treatment plan of the patient is important. Depending on the degree of mental health disorder, pretreatment of the mental health disorder may be warranted prior to initiating HCV treatment.
- ***During treatment, patients with mental health disorders on treatment should be assessed for mood changes every four weeks. There is a high risk of drug-drug interactions between psychiatric medications and DAAs.*** Pharmacists must pay attention to potential drug-drug interactions between mental health medications and HCV medications. St John's Wort*, commonly prescribed for depression, and carbamazepine, are contra-indicated with sofosbuvir.

** The St. John's wort plant has yellow flowers and is sometimes thought of as a weed in some parts of the United States. It has been used for medical purposes in other parts of the world for thousands of years. Many studies have been conducted to evaluate the effectiveness of St. John's wort. Some studies have suggested benefit, but other studies have not*

9.6 HIV/HCV/Chronic Kidney Disease

- Co-morbidity between HIV, HCV and renal impairment is common. Renal impairment includes patients with:
 - Stage 4 disease where eGFR is between 15 and 29 mL/min/1.73m²
 - Stage 5 disease where eGFR is less than 15mL/min/1.73m² and patients are on dialysis
 - Post-renal transplant patients
 - Mixed essential cryoglobulinemia and related liver damage
- Renal impairment patients have a high risk of morbidity, disease progression and mortality and are a priority group for treatment, where clinically safe to do so. However, limited treatment options for patients with advanced renal disease currently exist.

⁸⁶ Schaefer M, Capuron L, Friebe A, Diez-Quevedo C, Robaey G, et al. (2012). Hepatitis C infection, antiviral treatment and mental health: A European expert consensus statement. J Hepatol. <http://dx.doi.org/10.1016/j.hep.2012.07.037>.

- Patients with eGFR rates above 30 mL/min/1.73m² can be treated with normal doses of DAAs, including sofosbuvir/ledipasvir and sofosbuvir/daclatasvir.
- However, eGFR rates below 30 mL/min/1.73m², are currently contraindicated for treatment with sofosbuvir as it is eliminated through the renal system. Limited clinical studies have been conducted in this population, and studies like the TARGET 2.0 real-world cohort study showed progressive deterioration of renal function among patients with advanced renal disease taking sofosbuvir-containing regimens.⁸⁷
- In patients with low eGFR rates, currently recommended regimens include grazoprevir/elbasvir and ritonavir-boosted paritaprevir, ombitasvir and dasabuvir.
- Ribavirin is also associated with treatment difficulties for patients with end stage renal disease. Patients with an eGFR <50 mL/min/1.73 m² 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.

9.7. Persons with cirrhosis

- Between 15% and 30% of persons infected with HCV will go on to develop cirrhosis of the liver within 20 years and a proportion of these will progress to HCC.
- The risk is markedly increased in those who consume excess alcohol⁸⁸ and in those coinfecting with HBV and/or HIV, particularly those who do not have access to ART^{89,90}
- Persons with cirrhosis have the least time available for treatment, the most to lose and much to gain from achieving SVR. Treatment of HCV infection should be commenced before the onset of decompensated disease because medical management is more complicated and some HCV medicines can precipitate liver failure and death if administered at this stage.
- Regular clinical examination and monitoring of serum bilirubin, albumin and coagulation profile⁹¹ are necessary in persons with cirrhosis on interferon based treatment in order to detect decompensated disease.

⁸⁷ Saxena V, Korashy FM, Sise ME, Lim JK, Schmidt M, Chung RT, et al. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. *Liver Int* 2016;36:807–816.

⁸⁸ Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA*. 2000;284(4):450–6.

⁸⁹ Tong MJ, Elfarra NS, Reikes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis-C. *N Engl J Med*. 1995;332(22):1463–6.

⁹⁰ Tremolada F, Casarin C, Alberti A, Drago C, Tagger A, Ribero ML, et al. Long-term follow-up of non-A, non-B (type C) post-transfusion hepatitis. *J Hepatol*. 1992;16(3):273–81.

⁹¹ Piasecki BA, Lewis JD, Reddy KR, Bellamy SL, Porter SB, Weinrieb RM, et al. Influence of alcohol use, race, and viral coinfections on spontaneous HCV clearance in a US veteran population. *Hepatology*. 2004;40(4):892–9.

- The treatment of such persons with interferon-containing regimens carries a higher risk of serious side-effects, and the use of haemopoietic factors is recommended in settings where these are available⁹².
- Use of certain DAAs regimens among persons with cirrhosis has been shown to be both safe and efficacious, especially in those with compensated disease.
- The addition of ribavirin to treatment increases the risk of severe adverse events (SAE), most notably those related to anaemia, and requires additional monitoring.
- Simeprevir and ombitasvir/paritaprevir/ritonavir/dasabuvir are not approved for use in patients with decompensated liver disease.
- Daclatasvir, ledipasvir, Velpatasvir and sofosbuvir have been studied in persons with decompensated cirrhosis and their use has been demonstrated to be both feasible and effective. However, a proportion of patients with decompensated liver disease could deteriorate on treatment and currently there are no pretreatment predictors to identify these patients. Therefore, treatment of patients with decompensated liver cirrhosis should be considered only in centres with the expertise to manage complications.
- Assessment and follow up for the progression of disease and for evidence of HCC is an essential part of the care of persons with HCV related cirrhosis. Compensated cirrhosis may also progress over time to decompensated cirrhosis associated with ascites, oesophageal and gastric varices, and eventually to liver failure, renal failure and sepsis, 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.
- Persons with cirrhosis (including those who have achieved SVR should be screened for HCC with six-monthly ultrasound examination, and should have endoscopy every 1–2 years to exclude oesophageal varices⁹³.

9.8 Children and Adolescents

Risk Factors: Most HCV infection among children is due to vertical transmission and iatrogenic transmission in hospitals. Some transmission in adolescents is due to injecting drug use. Seroprevalence rates of 10-20% have been reported among children who have received invasive procedures in hospitals, such as haemodialysis or surgical procedures.^{94,95}

⁹² European Association for Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol.* 2014;60(2):392–420.

⁹³ European Association for Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol.* 2014;60(2):392–420.

⁹⁴ Locasciulli A, Gornati G, Tagger A, Ribero ML, Cavalletto D, Cavalletto L, et al. Hepatitis C virus infection and chronic liver disease in children with leukemia in long-term remission. *Blood.* 1991;78(6):1619–22.

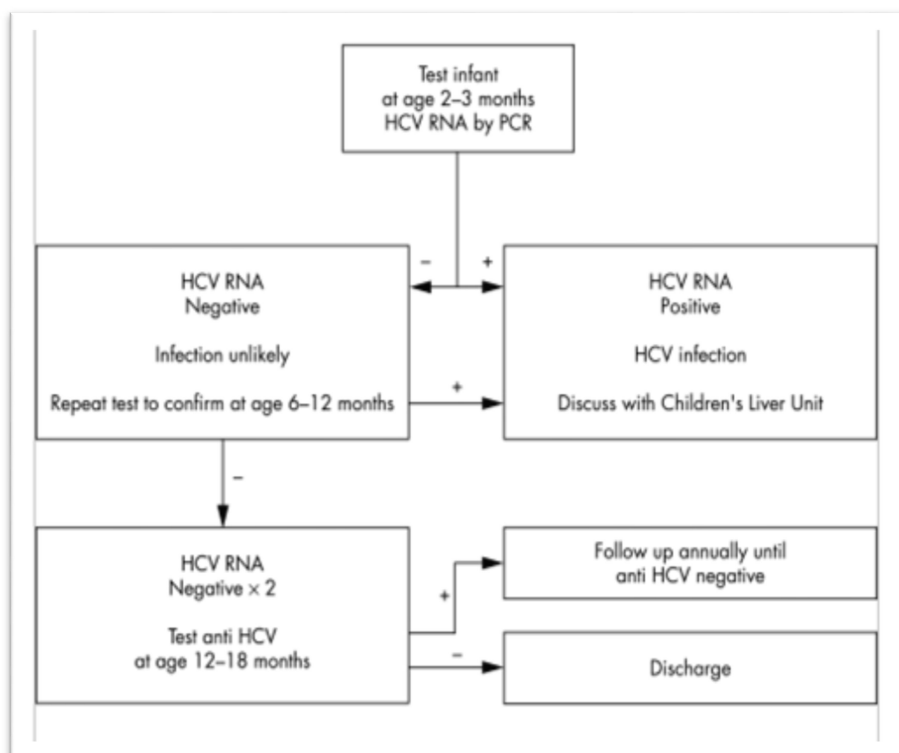
⁹⁵ Rossetti F, Cesaro S, Pizzocchero P, Cadrobbi P, Guido M, Zanescio L. Chronic hepatitis B surface antigen-negative hepatitis after treatment of malignancy. *J Pediatr.* 1992;121(1):39–43.

Screening: Overall likelihood of HCV infection is lower among children and adolescents than adults in most settings. Targeted screening of children at risk is recommended. Infants born to HCV-infected mothers, especially those with HIV co-infection, are a key population to target; as are children who have had had medical interventions, surgical or transfusion.

For infants born to chronically infected mothers (HCV RNA-positive), diagnosis of chronic infection can be difficult due to the presence of maternal antibodies for 13 to 18 months post-birth and spontaneous clearance. An infant is considered chronically infected if they receive two positive HCV RNA tests over six months. Known exposed children should receive an RNA test at 3 months. If the RNA test at 3 months is positive, then the patient should be referred and a confirmatory RNA should be performed at 12 months of age to rule out spontaneous clearance. If the RNA test at 3 months is negative, infection is unlikely, but alanine aminotransferase levels should be monitored every three months. If alanine aminotransferase levels become elevated, the infant should be tested again for viraemia. If alanine aminotransferase levels remain normal, infants should be tested at 18-24 months for antibodies.⁹⁶

⁹⁶ Davison, S.M, Mieli-Vergani G, Sira J, Kelly D.A. (2006). Perinatal Hepatitis C Virus Infection: Diagnosis and Management. Arch Dis Child. 2006 Sep; 91(9): 781-785.

Figure 9.1: Diagnostic Algorithm for Perinatal Transmission



For children who are exposed horizontally after infancy, screening algorithms are the same as for adults.

Care and Treatment: Currently, the only available treatment for children between the ages of 2 years to 18 years is pegylated interferon and ribavirin. No treatments are recommended for children under the age of 2. Pediatric trials and the availability of pediatric formulations of directly acting antivirals are required before their use.

Some patients with rapidly advancing disease may benefit from treatment with pegylated interferon and ribavirin during their childhood. Given the low prevalence of advanced disease among children, clinicians may prefer to wait for new DAA treatments or until adulthood to treat the majority of their pediatric patients. During childhood, HCV-infected children should continue to be monitored for liver function and advancing disease.

9.9 Pregnant Women

Screening: Screening of pregnant women for HCV can identify women whose infants will need to be tracked postpartum. Due to the lack of treatment available for pregnant women, screening and treating women of child-bearing age *prior* to pregnancy is recommended.

Care and Treatment: There are currently no treatments available that have been designated as safe during pregnancy. Trials are still required with DAAs. Women who are

screened antibody-positive should be linked to care and retained to start treatment following delivery and breastfeeding.

- There are no safety data for the use of any DAAs regimen during pregnancy, with all Pharmaceutical Benefit Scheme (PBS)-listed DAA regimens classed as Category B (sofosbuvir, B1; ledipasvir, B1; daclatasvir, B3; PrOD, B3) for their risk in pregnancy. Treatment of pregnant women with DAAs therapy is therefore not recommended. All DAAs regimens are contraindicated in pregnancy when combined with ribavirin (Category X), with or without pegIFN. As noted, ribavirin requires contraceptive precautions.
- People treated with ribavirin should be counselled about the risk of teratogenicity and the importance of not becoming pregnant during treatment or for 6 months after treatment. The safety of the listed DAAs regimens during lactation has not yet been established, and treatment of women who are breastfeeding is therefore not recommended.
- It is recommended to avoid pregnancy (not to have baby for man) during the treatment HCV duration and 6 month after treatment if regimen contain ribavirin.
- Some experts recommend double contraceptive projective (both barrier and Oral Contraceptive Pill) to make they are pregnant for above mentioned duration.
- The pregnancy test before starting HCV treatment and monthly follow up pregnancy test is the routine practice for those who are child bearing age. In case any pregnancy detected, it is better to delay HCV treatment if clinical condition allow.

9.10 People who Inject Drugs

Screening: PWIDs should be prioritized for screening due to their high rates of prevalence, morbidity and ongoing transmission. Screening should be performed as part of the harm reduction package annually among PWID, which also includes opioid substitution therapy, sterile injection equipment and addiction counselling. For PWID who have successfully achieved SVR12 and are continuing to inject drugs, re-infection is possible. Therefore, screening should be continued annually using nucleic acid testing (NAT).

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 no difference between SVR12 rates for PWID and non-PWID, even when PWID are active users. A recent study of treatment response on sofosbuvir/velpatasvir among people receiving opioid substitution therapy (OST)

demonstrated no impact of Opioid Substitution Therapy (OST) on adherence, treatment completion, sustained virologic response or safety.⁹⁷

Harm reduction strategies, including the provision of Opioid Substitution Therapy (OST) and sterile injection equipment, are required in order to prevent acquisition of HCV and other blood borne viruses such as HBV and HIV. At all times, avoidance of discrimination or stigmatization of PWID is essential.

PWID who complete treatment must receive counseling on the possibilities of re-infection due to continuing risk behaviors such as sharing of needles and paraphernalia.

⁹⁷ Grebeley et al. *Efficacy and safety of sofosbuvir/velpatasvir in patients with chronic hepatitis C virus infection receiving opioid substitution therapy: Analysis of Phase 3 Astral Trials*. Clin Inf Dis. 2016. <http://cid.oxfordjournals.org>.

Chapter 10. Outcomes of treatment and post-treatment follow up

10.1 Post-Treatment Monitoring of Patients Achieving SVR12

Patients who achieve SVR12 can be considered cured and have a very low (<1%) rate of relapse on treatment. However, it is that a single HCV viral load estimation be performed at any time point between 12 and 24 weeks post treatment to confirm successful eradication of the virus. If patients have low rates of fibrosis (FIB-4 below 1.45 or TE below 10kPa), no additional follow up is required. If there is persistently abnormal liver function, the patient should be evaluated for other types of liver disease.

If patients have compensated or decompensated cirrhosis, some of the fibrosis, cirrhosis and its complications may reverse over a period of months or years. Patients will still require regular monitoring and management of their liver disease. See section 10.4 for guidance on monitoring cirrhosis and section 10.3 for monitoring HCC.

If patients are believed to remain at high risk of re-infection, patients should be counseled to receive regular (every 1 year) HCV RNA tests.

10.2 Managing Failures on DAAs

Despite high cure rates, some patients may not be cured following their first treatment with DAAs. Failure may be due to poor adherence, the existence of pre-treatment resistance-associated substitutions (RAS), the development of new RAS during treatment, or the progression of the liver disease.

Any patient who has failed treatment (***did not achieve Sustained Virological Response at Week 12 after the end of treatment- SVR 12***) and is being considered for a second therapy should first be evaluated for adherence on their first treatment. If the clinician believes that adherence was not the original cause or that adherence will be improved during the second treatment, the patient can be evaluated by a specialist for future treatment options.

Until treatment is available, liver function should continue to be evaluated annually to monitor disease progression.

If a patient had not received a genotype test prior to initiation on their first treatment, a genotype test is recommended to identify the most likely treatment regimen for achieving success. Resistance testing may be useful, although it is not widely available or affordable in Cambodia.

Managing failure on DAAs is still a new area of scientific research and guidelines are still being developed about which treatment regimens to use. If treatment can be deferred, this is recommended until guidelines are available. If treatment cannot be deferred, the clinician could consider:

- Retreating with the same regimen for 24 weeks and adding ribavirin;
- Retreating with a different regimen approved for the genotype in question for 24 weeks and adding ribavirin.

For patients who failed treatment previously with pegylated interferon and ribavirin, the standard DAA guidelines for non-cirrhotic and cirrhotic patients can be followed.

10.3 Hepatocellular Carcinoma Screening

- Liver ultrasound must be performed at the first assessment of liver disease for all HIV/HCV co-infected patients in order to screen for HCC, analyze surface nodularity, echotexture, segmental hypertrophy/atrophy and identify signs of portal hypertension.
- Liver ultrasound must continue to be performed every 6 months in cirrhotic patients, whether they achieve SVR12 or not, in order to identify HCC as early as possible.

10.4 Follow-up for assessment of liver disease

10.4.1 For untreated patients or for treated non-cirrhotic patients who do not achieve SVR

- Fibrosis progression is faster in HIV/HCV co-infection compared with HCV mono-infection⁹⁸.
- In Konerman's analysis of 435-paired liver biopsies, 34% of patients progressed at least one fibrosis stage according to the METAVIR scoring system within 2.5 years.

Recommendation:

For untreated patients and for treated patients who do not achieve SVR, liver disease should be assessed annually using APRI or FIB-4 score and TE if available.

10.4.2 For treated patients with SVR

- HCV Sustained Virologic Response (SVR) reduces the risk of end-stage liver-related events such as HCC and mortality and is also associated with lower HIV-related mortality.
- Nevertheless, regression of liver fibrosis after SVR remains unclear as well as persistence of HCC risk. In the ANRS CO13 HEPAVIH cohort, the probability of achieving a 30% decrease in TE values was 51% at 1 year and 74% at 2 years⁹⁹. In the same study, SVR was associated with an increased likelihood of achieving a 30% decrease in FIB4 values. Nevertheless, reduction in TE values does not necessarily mean fibrosis regression and is rather related to a decrease of inflammation after SVR.

⁹⁸ Konerman MA, Mehta SH, Sutcliffe CG, et al. Fibrosis progression in human immunodeficiency virus/hepatitis C virus coinfecting adults: prospective analysis of 435 liver biopsy pairs. *Hepatology* 2014; 59:767-775

⁹⁹ The ANRS CO13 HEPAVIH Cohort. Regression of liver stiffness after sustained hepatitis C virus (HCV) virological responses among HIV/HCV-coinfecting patients. *AIDS* 2015, 29:1821-1830

- In a recent multi-analysis among HCV-infected persons, SVR was associated with reduced risk for HCC (relative risk for all persons, 0.24). Nevertheless, HCC may still develop after viral clearance, specifically for HIV/HCV co-infected patients.
- Longer follow-up is needed to see whether this decrease in liver stiffness is correlated with a decrease in fibrosis regression and of the risk of hepatocellular carcinoma.

Recommendations

- For treated patients with SVR and FIB-4 above 1.45 or TE above 10kPa, liver disease should be assessed annually using APRI and FIB-4 score and TE if available until FIB-4 is below 1.45 and/or TE is below 10 kPa.
- Perform six-monthly ultrasound examination for patients with severe fibrosis or cirrhosis (FIB-4 > 3.25 and/or TE > 10 kPa) before treatment initiation. This follow-up must be continued until new recommendations will be available.

10.4.3 For cirrhotic patients, whether or not they have achieved SVR

- Assessment and follow up for the progression of disease and for evidence of HCC is an essential part of the care of persons with HCV-related cirrhosis¹⁰⁰.
- Compensated cirrhosis may progress over time to decompensated cirrhosis associated with ascites, oesophageal and gastric varices, and eventually to liver failure, renal failure and sepsis, all of which are life-threatening.

Recommendations

- Persons with cirrhosis (including those who have achieved a SVR) should be screened by ultrasound for HCC every six months
- Upper gastrointestinal endoscopy must be performed periodically based on physician's discretion.
- These patients must be referred to an hepatologist for specific follow-up and treatment.

¹⁰⁰ Bourcier V, Winrock M, Ait Ahmed M, et al; ANRS C013 Hepaviv study group; ANRS C012 Cirvir study group. Primary liver cancer is more aggressive in HIV-HCV coinfection than in HCV infection. A prospective study. Clin Res Hepatol Gastroenterol. 2012 Jun; 36(3):214-21

Annexes

Annex 3.1. A- WHO-ASSIT V3.0 for patient's Alcohol, Smoking and Substance Involvement Screening Test. There are 8 questionnaires to identify the score of each substances used and their related intervention approaches.

Interviewer Name/ID Hospital

Patient Name/ID Date

INTRODUCTION (Please read to patient)

Thank you for agreeing to take part in this brief interview about alcohol, tobacco products and other drugs. I am going to ask you some questions about your experience of using these substances across your lifetime and in the past three months. These substances can be smoked, swallowed, snorted, inhaled, injected or taken in the form of pills (show drug 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.

NOTE: BEFORE ASKING QUESTIONS, GIVE ASSIST RESPONSE CARD TO PATIENT

Question 1

(if completing follow-up please cross check the patient's answers with the answers given for Q1 at baseline. Any differences on this question should be queried)

In your life, which of the following substances have you <u>ever used</u> ? (NON-MEDICAL USE ONLY)	No	Yes
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	3
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	3
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	3
d. Cocaine (coke, crack, etc.)	0	3
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	3
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	3
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	3
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	3
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	3
j. Other - specify:	0	3

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 Question 2 for each substance ever used.

Question 2

In the <u>past three months</u> , how often have you used the substances you mentioned (<i>FIRST DRUG, SECOND DRUG, ETC</i>)?	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, diet pills, 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 (Valium, Serepax, Rohypnol, etc.)	0	2	3	4	6
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	2	3	4	6
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	2	3	4	6
j. Other - specify:	0	2	3	4	6

If “Never” to all items in Question 2, skip to Question 6.

If any substances in Question 2 were used in the previous three months, continue with Questions 3, 4 & 5 for each substance used.

Question 3

During the <u>past three months</u> , how often have you had a strong desire or urge to use (<i>FIRST DRUG, SECOND DRUG, ETC</i>)?	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, diet pills, 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 (Valium, Serepax, Rohypnol, etc.)	0	3	4	5	6
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	3	4	5	6
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	3	4	5	6
j. Other - specify:	0	3	4	5	6

Question 4

During the <u>past three months</u> , how often has your use of (<i>FIRST DRUG, SECOND DRUG, ETC</i>) 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, diet pills, 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 (Valium, Serepax, Rohypnol, etc.)	0	4	5	6	7
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	4	5	6	7
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	4	5	6	7
j. Other - specify:	0	4	5	6	7

Question 5

During the <u>past three months</u> , how often have you failed to do what was normally expected of you because of your use of (<i>FIRST DRUG, SECOND DRUG, ETC</i>)?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
a. Tobacco products					
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, diet pills, 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 (Valium, Serepax, Rohypnol, etc.)	0	5	6	7	8
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	5	6	7	8
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	5	6	7	8
j. Other - specify:	0	5	6	7	8

Ask Questions 6 & 7 for all substances ever used (i.e. those endorsed in Question 1)

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, diet pills, ecstasy, etc.)	0	6	3
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	6	3
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	6	3
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	6	3
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	6	3
j. Other – specify:	0	6	3

Question 7

Have you <u>ever</u> tried and failed to control, cut down or stop using (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, diet pills, ecstasy, etc.)	0	6	3
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	6	3
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	6	3
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	6	3
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	6	3
j. Other – specify:	0	6	3

Question 8

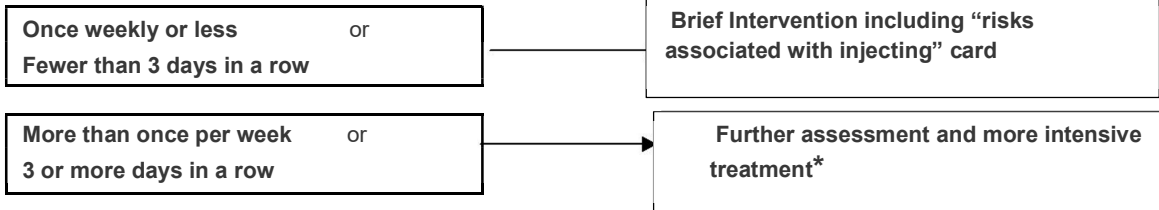
	No, Never	Yes, in the past 3 months	Yes, but not in the past 3 months
Have you <u>ever</u> used any drug by injection? (NON-MEDICAL USE ONLY)	0	2	1

IMPORTANT NOTE:

Patients who have injected drugs in the last 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



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. amphetamine		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+

NOTE: *FURTHER ASSESSMENT AND MORE INTENSIVE TREATMENT may be provided by the health professional(s) within your primary care setting, or, by a specialist drug and alcohol treatment service when available.

Annex 3.1. B- WHO ASSIST V3.0 RESPONSE CARD FOR PATIENTS

(for patient’s guidance to assist them, while being asked, sort out types of substance they used (for instance, tobacco products include cigarettes, chewing tobacco, cigar, etc.) and the frequency of utilization (i.e. once or twice means 1 to 2 times per week, etc.).The response card for patient is given to them before asking the screening test)

Response Card – substances

• Tobacco products (cigarettes, chewing tobacco, cigars, etc.)
• Alcoholic beverages (beer, wine, spirits, etc.)
• Cannabis (marijuana, pot, grass, hash, etc.)
• Cocaine (coke, crack, etc.)
• Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)
• Inhalants (nitrous, glue, petrol, paint thinner, etc.)
• Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)
• Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)
• Opioids (heroin, morphine, methadone, codeine, etc.)
• Other - specify:

Response Card (ASSIST Questions 2 – 5)

Never: not used in the last 3 months

Once or twice: 1 to 2 times in the last 3 months.

Monthly: 1 to 3 times in one month.

Weekly: 1 to 4 times per week.

Daily or almost daily: 5 to 7 days per week.

Response Card (ASSIST Questions 6 to 8)

No, Never

Yes, but not in the past 3 months

Yes, in the past 3 months

Annex 3.1.C-FEEDBACK REPORT CARD FOR PATIENTS

(for identifying specific substance involvement scores, related risk levels and types of risk associated with each substance. The report card is given to patient at the end of the test)

Name _____ Test Date _____

Specific Substance Involvement Scores

Substance	Score	Risk Level
a. Tobacco products		0-3 Low 4-26 Moderate 27+ High
b. Alcoholic Beverages		0-10 Low 11-26 Moderate 27+ High
c. Cannabis		0-3 Low 4-26 Moderate 27+ High
d. Cocaine		0-3 Low 4-26 Moderate 27+ High
e. Amphetamine type stimulants		0-3 Low 4-26 Moderate 27+ High
f. Inhalants		0-3 Low 4-26 Moderate 27+ High
g. Sedatives or Sleeping Pills		0-3 Low 4-26 Moderate 27+ High
h. Hallucinogens		0-3 Low 4-26 Moderate 27+ High
i. Opioids		0-3 Low 4-26 Moderate 27+ High
j. Other – specify		0-3 Low 4-26 Moderate 27+ High

What do your scores mean?	
Low:	You are at low risk of health and other problems from your current pattern of use.
Moderate:	You are at risk of health and other problems from your current pattern of substance use.
High:	You are at high risk of experiencing severe problems (health, social, financial, legal, relationship) as a result of your current pattern of use and are likely to be dependent

Are you concerned about your substance use?

a. tobacco	Your risk of experiencing these harms is:..... Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/> (tick one)
	Regular tobacco smoking is associated with:
	Premature aging, wrinkling of the skin
	Respiratory infections and asthma
	High blood pressure, diabetes
	Respiratory infections, allergies and asthma in children of smokers
	Miscarriage, premature labour and low birth weight babies for pregnant women
	Kidney disease
	Chronic obstructive airways disease
	Heart disease, stroke, vascular disease
	Cancers

b. alcohol	Your risk of experiencing these harms is:..... Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/> (tick one)
	Regular excessive alcohol use is associated with:
	Hangovers, aggressive and violent behaviour, accidents and injury
	Reduced sexual performance, premature ageing
	Digestive problems, ulcers, inflammation of the pancreas, high blood pressure
	Anxiety and depression, relationship difficulties, financial and work problems
	Difficulty remembering things and solving problems
	Deformities and brain damage in babies of pregnant women
	Stroke, permanent brain injury, muscle and nerve damage
	Liver disease, pancreas disease
	Cancers, suicide

c. cannabis	Your risk of experiencing these harms is:..... Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/> (tick one)
	Regular use of cannabis is associated with:
	Problems with attention and motivation
	Anxiety, paranoia, panic, depression
	Decreased memory and problem solving ability
	High blood pressure
	Asthma, bronchitis
	Psychosis in those with a personal or family history of schizophrenia
	Heart disease and chronic obstructive airways disease
	Cancers

d. cocaine	Your risk of experiencing these harms is:....	Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/>
	Regular use of cocaine is associated with:	
	Difficulty sleeping, heart racing, headaches, weight loss	
	Numbness, tingling, clammy skin, skin scratching or picking	
	Accidents and injury, financial problems	
	Irrational thoughts	
	Mood swings - anxiety, depression, mania	
	Aggression and paranoia	
	Intense craving, stress from the lifestyle	
	Psychosis after repeated use of high doses	
	Sudden death from heart problems	

e. amphetamine type stimulants	Your risk of experiencing these harms is:.....	Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/>
	Regular use of amphetamine type stimulants is associated with:	
	Difficulty sleeping, loss of appetite and weight loss, dehydration	
	jaw clenching, headaches, muscle pain	
	Mood swings –anxiety, depression, agitation, mania, panic, paranoia	
	Tremors, irregular heartbeat, shortness of breath	
	Aggressive and violent behavior	
	Psychosis after repeated use of high doses	
	Permanent damage to brain cells	
	Liver damage, brain haemorrhage, sudden death (ecstasy) in rare situations	

f. inhalants	Your risk of experiencing these harms is:.....	Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/>
	Regular use of inhalants is associated with:	
	Dizziness and hallucinations, drowsiness, disorientation, blurred vision	
	Flu like symptoms, sinusitis, nosebleeds	
	Indigestion, stomach ulcers	
	Accidents and injury	
	Memory loss, confusion, depression, aggression	
	Coordination difficulties, slowed reactions, hypoxia	
	Delirium, seizures, coma, organ damage (heart, lungs, liver, kidneys)	
	Death from heart failure	

g. sedatives	Your risk of experiencing these harms is:	Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/> (tick one)
Regular use of sedatives is associated with:		
	Drowsiness, dizziness and confusion Difficulty concentrating and remembering things Nausea, headaches, unsteady gait Sleeping problems Anxiety and depression Tolerance and dependence after a short period of use. Severe withdrawal symptoms Overdose and death if used with alcohol, opioids or other depressant drugs.	
h. hallucinogens	Your risk of experiencing these harms is:.....	Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/> (tick one)
Regular use of hallucinogens is associated with:		
	Hallucinations (pleasant or unpleasant) – visual, auditory, tactile, olfactory Difficulty sleeping Nausea and vomiting Increased heart rate and blood pressure Mood swings Anxiety, panic, paranoia Flash-backs Increase the effects of mental illnesses such as schizophrenia	
i. opioids	Your risk of experiencing these harms is:	Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/> (tick one)
Regular use of opioids is associated with:		
	Itching, nausea and vomiting Drowsiness Constipation, tooth decay Difficulty concentrating and remembering things Reduced sexual desire and sexual performance Relationship difficulties Financial and work problems, violations of law Tolerance and dependence, withdrawal symptoms Overdose and death from respiratory failure	

Annex 3.1 D- RISKS OF INJECTING CARD – INFORMATION FOR PATIENTS

(for patient awareness on harm from injection and tips for risky behavior change)

Using substances by injection increases the risk of harm from substance use.

This harm can come from:

The substance

If you inject any drug you are more likely to become dependent.

If you inject amphetamines or cocaine you are more likely to experience psychosis.

If you inject heroin or other sedatives you are more likely to overdose.

The injecting behavior

If you inject you may damage your skin and veins and get infections.

You may cause scars, bruises, swelling, abscesses and ulcers.

Your veins might collapse.

If you inject into the neck you can cause a stroke.

Sharing of injecting equipment

- If you share injecting equipment (needles & syringes, spoons, filters, etc.) you are more likely to spread blood borne virus infections like Hepatitis B, Hepatitis C and HIV.

❖ It is safer not to inject

❖ If you do inject:

- ✓ always use clean equipment (e.g., needles & syringes, spoons, filters, etc.)
- ✓ always use a new needle and syringe
- ✓ don't share equipment with other people
- ✓ clean the preparation area
- ✓ clean your hands
- ✓ clean the injecting site
- ✓ use a different injecting site each time
- ✓ inject slowly
- ✓ put your used needle and syringe in a hard container and dispose of it safely

❖ If you use stimulant drugs like amphetamines or cocaine the following tips will help you reduce your risk of psychosis.

- ✓ avoid injecting and smoking
- ✓ avoid using on a daily basis

❖ If you use depressant drugs like heroin the following tips will help you reduce your risk of overdose.

- ✓ avoid using other drugs, especially sedatives or alcohol, on the same day
- ✓ use a small amount and always have a trial "taste" of a new batch
- ✓ have someone with you when you are using
- ✓ avoid injecting in places where no-one can get to you if you do overdose
- ✓ Know the telephone numbers of the ambulance service

Annex 6. 1.1 .Drug information –Sofosbuvir

Full information contents are here:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204671s002lbl.pdf

SOVALDI® (sofosbuvir) tablets, for oral use Initial U.S.

Approval: 2013

Indication and uses:

SOVALDI is a hepatitis C virus (HCV) nucleotide analog non-structural protein 5B (NS5B) polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen.

SOVALDI efficacy has been established in subjects with HCV genotype 1, 2, 3 or 4 infections, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection.

DOSAGE AND ADMINISTRATION

- One 400 mg tablet taken once daily with or without food
- Should be used in combination with Daclastavir with or without Ribavirin for the treatment of Chronic hepatitis C
- SOVALDI in combination with ribavirin for 24 weeks can be considered for CHC patients with genotype 1 infection who are interferon ineligible.
- Should be used in combination with ribavirin for treatment of CHC in patients with hepatocellular carcinoma awaiting liver transplantation for up to 48 weeks or until liver transplantation, whichever occurs first
- A dose recommendation cannot be made for patients with severe renal impairment or end stage renal disease

DOSAGE FORMS AND STRENGTHS

Tablets: 400 mg

CONTRAINDICATIONS

- When used in combination with peg interferon alfa/ribavirin or ribavirin alone, all contraindications to peg interferon alfa and/or ribavirin also apply to SOVALDI combination therapy
- Because ribavirin may cause birth defects and fetal death, SOVALDI in combination with peg interferon alfa/ribavirin or ribavirin is contraindicated in pregnant women and in men whose female partners are pregnant

WARNINGS AND PRECAUTIONS

- Bradycardia with amiodarone coadministration: Serious symptomatic bradycardia may occur in patients taking amiodarone and SOVALDI in combination with another direct acting antiviral (DAA), particularly in patients also receiving beta blockers, or

those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with SOVALDI in combination with another DAA is not recommended. In patients without alternative, viable treatment options, cardiac monitoring is recommended. (5.1, 6.2, 7.2)

- Pregnancy: Ribavirin may cause birth defects and fetal death and animal studies have shown interferons have abortifacient effects; avoid pregnancy in female patients and female partners of male patients. Patients must have a negative pregnancy test prior to initiating therapy, use at least 2 effective methods of contraception and have monthly pregnancy tests. (5.2)

ADVERSE REACTIONS

The most common adverse events (incidence greater than or equal to 20%, all grades) observed with SOVALDI in combination with ribavirin were fatigue and headache. The most common adverse events observed with SOVALDI in combination with peg interferon alfa and ribavirin were fatigue, headache, nausea, insomnia and anemia

DRUG INTERACTIONS

- Coadministration of amiodarone with SOVALDI in combination with another DAA may result in serious symptomatic bradycardia
- Drugs that are potent intestinal P- glycoprotein (gp) inducers (e.g., rifampin, St. John's wort) may alter the concentrations of sofosbuvir
- Consult the full prescribing information prior to use for potential drug-drug interactions

USE IN SPECIFIC POPULATIONS

- Patients with HCV/HIV-1 co-infection: Safety and efficacy have been studied

Patients with hepatocellular carcinoma awaiting liver transplantation: Safety and efficacy have been studied

Annex 6-1-2. Drug information Daclatasvir

Full prescription information contents are here;

http://packageinserts.bms.com/pi/pi_daklinza.pdf

DAKLINZA™ (daclatasvir) tablets, for oral use Initial U.S. Approval: 2015

INDICATIONS AND USAGE

DAKLINZA is a hepatitis C virus (HCV) NS5A inhibitor indicated for use with sofosbuvir, with or without ribavirin, for the treatment of chronic HCV genotype 1 or 3 infection

Limitations of Use:

- Sustained virologic response (SVR12) rates are reduced in genotype 3 patients with cirrhosis receiving DAKLINZA in combination with sofosbuvir for 12 weeks

DOSAGE AND ADMINISTRATION

- Testing prior to initiation: HCV genotype 1a with cirrhosis, consider testing for the presence of virus with NS5A resistance-associated polymorphisms
- 60 mg taken orally once daily with or without food in combination with sofosbuvir with or without ribavirin
- Recommended treatment duration: 12 weeks
- Dose modification: Reduce dosage to 30 mg once daily with strong CYP3A inhibitors and increase dosage to 90 mg once daily with moderate CYP3A inducers

DOSAGE FORMS AND STRENGTHS

Tablets: 60 mg, 30 mg, and 90 mg

CONTRAINDICATIONS

Strong inducers of CYP3A, including phenytoin, carbamazepine, rifampin, and St. John's wort

WARNINGS AND PRECAUTIONS

Bradycardia When Coadministered with Sofosbuvir and Amiodarone: Serious symptomatic bradycardia may occur in patients taking amiodarone with sofosbuvir in combination with another HCV direct-acting agent, including DAKLINZA (daclatasvir), particularly in patients also receiving beta blockers or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with DAKLINZA in combination with sofosbuvir is not recommended. In patients with no alternative treatment options, cardiac monitoring is recommended

ADVERSE REACTIONS

Most common adverse reactions ($\geq 10\%$) observed with DAKLINZA in combination with sofosbuvir were headache and fatigue. Most common adverse reactions ($\geq 10\%$) observed with DAKLINZA in combination with sofosbuvir and ribavirin were headache, anemia, fatigue, and nausea

DRUG INTERACTIONS

Drug Interactions: Coadministration of DAKLINZA can alter the concentration of other drugs and other drugs may alter the concentration of daclatasvir. Consult the full prescribing information before use for contraindicated drugs and other potential drug-drug interactions.

Annex 6.1.3 Drug information- Harvoni (Sofosbuvir/Ledipasvir)

Full prescription information contents are here:

www.gilead.com/~ /media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf

HARVONI® (ledipasvir and sofosbuvir) tablets, for oral use Initial U.S.

Approval: 2014

INDICATIONS AND USAGE

HARVONI is a fixed-dose combination of ledipasvir, a hepatitis C virus (HCV) NS5A inhibitor, and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor, and is indicated with or without ribavirin for the treatment of chronic hepatitis C virus (HCV) genotype 1, 4, 5 or 6 infection

DOSAGE AND ADMINISTRATION

- Recommended dosage: One tablet (90 mg of ledipasvir and 400 mg of sofosbuvir) taken orally once daily with or without food
- HCV/HIV-1 co-infection: For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in the table above
- If used in combination with ribavirin, follow the recommendations for ribavirin dosing and dosage modifications
- A dosage recommendation cannot be made for patients with severe renal impairment or end stage renal disease

DOSAGE FORMS AND STRENGTHS

Tablets: 90 mg Ledipasvir and 400 mg sofosbuvir

CONTRAINDICATIONS

If used in combination with ribavirin, all contraindications to ribavirin also apply to HARVONI combination therapy

WARNINGS AND PRECAUTIONS

- Bradycardia with amiodarone coadministration: Serious symptomatic bradycardia may occur in patients taking amiodarone, particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with HARVONI is not recommended. In patients without alternative, viable treatment options, cardiac monitoring is recommended
- Use with other drugs containing sofosbuvir is not recommended.

ADVERSE REACTIONS

The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with HARVONI were fatigue, headache and asthenia

DRUG INTERACTIONS

- Coadministration with amiodarone may result in serious symptomatic bradycardia. Use of HARVONI with amiodarone is not recommended
- P-gp inducers (e.g., rifampin, St. John's wort): May alter concentrations of

Ledipasvir and sofosbuvir. Use of HARVONI with P-gp inducers is not recommended

- Consult the full prescribing information prior to use for potential drug interactions

Annex 6.1.4 Drug information- Ribavirin (COPEGUS)

Full prescription information contents are here

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021511s023lbl.pdf.

COPEGUS[®] (ribavirin) Tablets Initial U.S. Approval: 2002

INDICATIONS AND USAGE

- COPEGUS is a nucleoside analogue indicated for the treatment of chronic hepatitis C (CHC) virus infection in combination with PEGASYS in patients 5 years of age and older with compensated liver disease not previously treated with interferon alpha, and in adult CHC patients coinfecting with HIV.

DOSAGE AND ADMINISTRATION

- CHC: COPEGUS is administered according to body weight and genotype
- CHC with HIV coinfection: 800 mg by mouth daily for a total of 48 weeks, regardless of genotype
- Dose reduction or discontinuation is recommended in patients experiencing certain adverse reactions or renal impairment.

DOSAGE FORMS AND STRENGTHS

- COPEGUS tablets 200 mg

CONTRAINDICATIONS

- Pregnant women and men whose female partners are pregnant
- Hemoglobinopathies
- Coadministration with didanosine
- COPEGUS in combination with PEGASYS is contraindicated in patients with:
 - Autoimmune hepatitis
 - Hepatic decompensation in cirrhotic patients.

WARNINGS AND PRECAUTIONS

- Birth defects and fetal death with ribavirin: Do not use in pregnancy and for 6 months after treatment. Patients must have a negative pregnancy test prior to therapy, use at least 2 forms of contraception and undergo monthly pregnancy tests
- PEGASYS/COPEGUS: Patients exhibiting the following conditions should be closely monitored and may require dose reduction or discontinuation of therapy:

- Hemolytic anemia may occur with a significant initial drop in hemoglobin. This may result in worsening cardiac disease leading to fatal or nonfatal myocardial infarctions
- Risk of hepatic failure and death: Monitor hepatic function during treatment and discontinue treatment for hepatic decompensation
- Severe hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, and anaphylaxis, and serious skin reactions such as Stevens-Johnson Syndrome
- Pulmonary disorders, including pulmonary function impairment and pneumonitis, including fatal cases of pneumonia
- Severe depression and suicidal ideation, autoimmune and infectious disorders, suppression of bone marrow function, pancreatitis, and diabetes
- Bone marrow suppression with azathioprine coadministration
- Growth impairment with combination therapy in pediatric patients

ADVERSE REACTIONS

- The most common adverse reactions (frequency greater than 40%) in adults receiving combination therapy are fatigue/asthenia, pyrexia, myalgia, and headache.
- The most common adverse reactions in pediatric subjects were similar to those seen in adults.

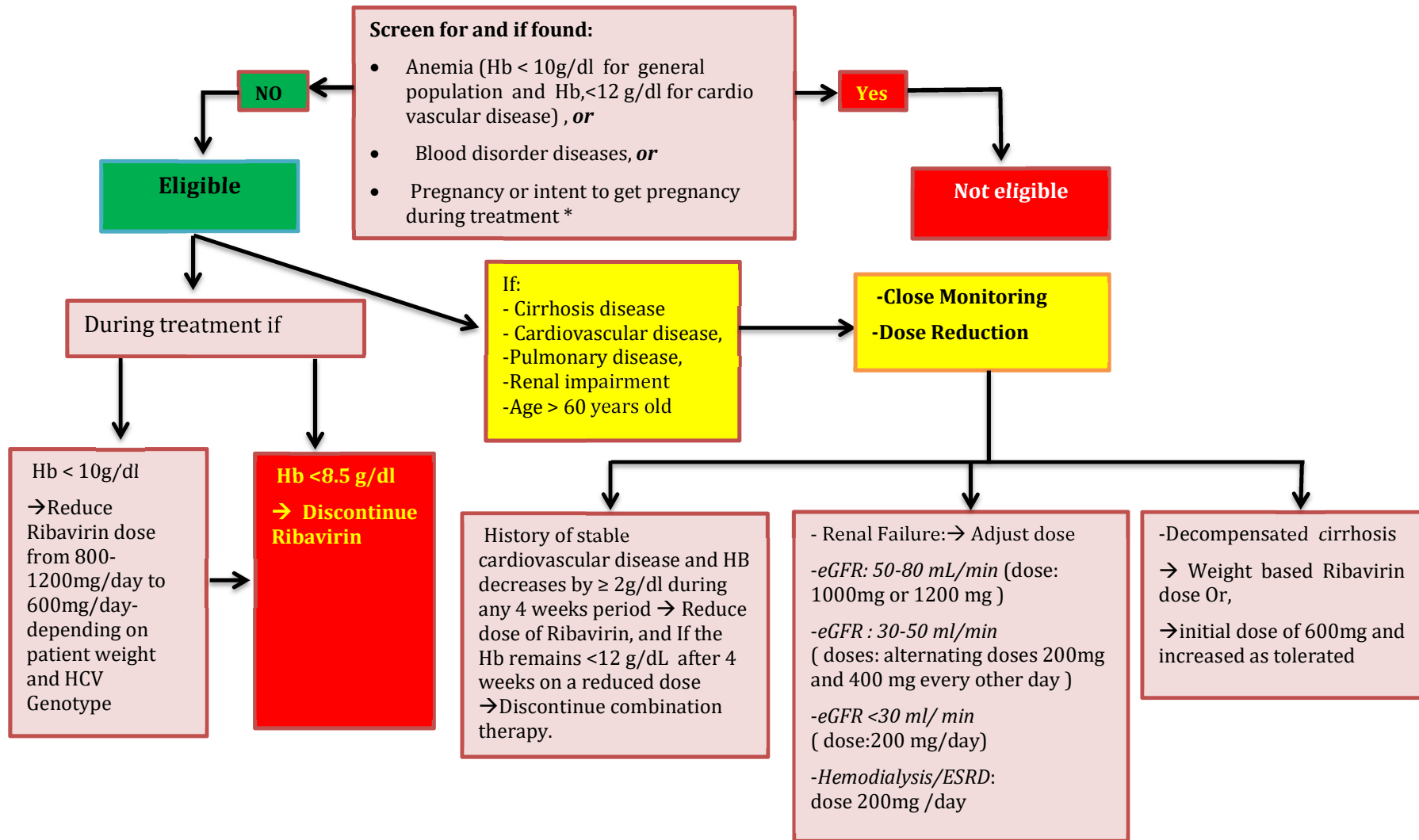
DRUG INTERACTIONS

- Nucleoside analogues: Closely monitor for toxicities. Discontinue nucleoside reverse transcriptase inhibitors or reduce dose or discontinue interferon, ribavirin or both with worsening toxicities
- Azathioprine: Concomitant use of azathioprine with ribavirin has been reported to induce severe pancytopenia and may increase the risk of azathioprine-related myelotoxicity.

USE IN SEPCIFIC POPULATIONS

- Ribavirin Pregnancy Registry
- Pediatrics: Safety and efficacy in pediatric patients less than 5 years old have not been established
- Renal Impairment: Dose should be reduced in patients with creatinine clearance less than equal to 50 mL/min
- Organ Transplant: Safety and efficacy have not been studied.

Annex 7.1 Figure 7.1. Anaemia management of Ribavirin containing regimen



Annex 7.2: Adherence Plan

Name patient:

Date of positive PCR session: Phone number:

Address:

My motivation to stay healthy / start treatment is:

.....

Adherence step 1: Support system **Disclosure: ok / not ok**

I will disclose to:

If necessary, the person who can help me disclose to my family is.....

Household members to be tested:**ok / not ok**

Adherence step 2: prevention of transmission

Possible risk behaviors are

.....

I will limit transmission risk by

.....

Adherence step 3: Future appointments **Agrees to home visit: Yes No**

How will I get to my appointments:

.....

Back-up plan if anything interferes with the appointment:

.....

How will I remember my appointments:

.....

<p>Name & phone n° of contact person:</p> <p>.....</p>
<p>Adherence step 4: Medication schedule</p> <p>Best time to take treatment is: and</p> <p>(if associated with Ribavirin: twice a day)</p> <p>Special attention in weekend or on holidays:</p> <p>.....</p> <p>When I forget a dose and I remember the same day, I will take it immediately.</p> <p>When I forget a dose and I remember only the next day, I will NOT take it but just take my usual dose of that day.</p>
<p>Adherence step 5: Reminders</p> <p>My trick to remember the medication is:</p> <p>.....</p>
<p>Adherence step 6: storage of medication</p> <p>I will store my drugs at home in:</p> <p>.....</p> <p>I will keep extra doses at:.....stored in.....</p> <p>.....</p> <p>Adherence step 7: Side effects</p> <p>When I experience side effects, I will</p> <p>.....</p> <p>To prevent fatigue, I will</p> <p>.....</p> <p>If I feel face malaise with dizziness or palpitation, I will:</p> <p>.....</p> <p>Adherence step 8: Avoiding self-medication</p> <p>When I feel a headache or have other complaints, I will:</p> <p>.....</p> <p>Adherence step 9: Planning for trips</p>

When I suddenly have to travel, I will:

.....

If I find myself without medication, I will:

.....

Lifestyle step 1: Balanced diet

Action plan to ensure enough fruit and vegetables:

.....

..... Food / snacks to cut back on are:

.....

I will replace these by:

.....

I will discuss diet adaptations with

.....

Lifestyle step 2: Avoiding alcohol / drugs

Consumer: YES/NO

I will drink no more than Doses of alcohol per.....

What can help me to drink less alcohol/ use less drugs:

.....

Lifestyle step 3: Avoiding tobacco

Consumer: YES/NO

My motivation to stop smoking:

.....

When I feel the urge to smoke, I will do the following activity:

..... The person who can support me in my efforts to stop smoking is

References

1. WHO. (n.d.). *WHO/HEPATITIS C*. Retrieved JULY 02, 2016, from WHO: who.int/mediacentre/factsheets/fs164/en/
2. CDC. (2015, May 31). *Viral Hepatitis - Hepatitis C Information*. Retrieved from www.cdc.gov/hepatitis/hcv/
3. Gower E, Estes C, Blach S, Shearer K, Razavi H. *Global epidemiology and genotype distribution of the hepatitis C virus infection*. *J Hepatol* 2014; 61(1):S45-57.
4. Stanaway J.D, Flaxman A.D, Naghavi M, Fitzmaurice C, Vos T, et al, (2016). *The Global Burden of Viral Hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013*. *The Lancet*. Published online July 6, 2016.
5. Platt L, Easterbrook P, Gower E, McDonald B, Sabin K, et al. (2016). Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. *Lancet Infect Dis*. doi:DOI: [http://dx.doi.org/10.1016/S1473-3099\(15\)00485-5](http://dx.doi.org/10.1016/S1473-3099(15)00485-5).
6. WHO. (2016, MARCH 7). More than 2 million people coinfecting with HIV and hepatitis C. Retrieved from WHO: who.int/hiv/mediacentre/news/hep-hiv-coinfecting/en/
7. WHO (2011) Viral Hepatitis in the WHO south-East Asia Region. Know it Confront it. Hepatitis affects everyone, everywhere.
8. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol*. 2014;61(1 Suppl):S45-57.
9. Center for Disease Analysis, Polaris Institute, 2013.
10. OI H.S, Bjoerkvoll B, Sothy S, Heng Y.V, Hoel H, et al., (2009). Prevalence of hepatitis Band Hepatitis C virus infections in potential blood donors in rural Cambodia. 40(5). Retrieved from <http://www.tm.mahidol.ac.th/seameo/2009-40-5/14-4568.pdf>
11. De Weggheleire A1, An S2, De Baetselier II et al, (2014): Hepatitis C prevalence, viral diversity and severity of liver disease in HIV patients in Phnom Penh, Cambodia: preliminary data communicated at AIDS 2016 Durban via poster: <http://programme.aids2016.org/Abstract/Abstract/2644>
12. UNAIDS. (n.d.). Cambodia | UNAIDS. Retrieved from <http://www.unaids.org/en/regionscountries/countries/cambodia>
13. NCHADS. (2016). *NCHADS ART REPORT*.
14. Sulkowski M.S, Moore R.D, Mahta S.H, Chaisson R.E, Thomas D.L (2002). Hepatitis C and progression of HIV disease. *JAMA*, 199-206. Retrieved from www.ncbi.nlm.nih.gov/pubmed/12095384
15. Ciesek S, Friesland M, Steinmann J, Becker B, Wedemeyer H, et al. (2010). How stable is the hepatitis C virus (HCV)? *Environmental stability of HCV and its susceptibility to chemical biocides*, 1859-1866. Retrieved from www.ncbi.nlm.nih.gov/pubmed/20441517
16. Paintsil E, He H, Peters C, Lindenbach B.D, Heimer R. (2010). Survival of hepatitis C virus in syringes: implication for transmission among injection drug users. *J Infect Dis*, 984-990. Retrieved from www.ncbi.nlm.nih.gov/pubmed/20726768
17. CDC. (2015, May 31). *Viral Hepatitis - Hepatitis C Information*. Retrieved from www.cdc.gov/hepatitis/hc

18. Margaret Hellard, Sacks-Davis R, Gold J. (2009). Hepatitis C Treatment for Injection Drug Users: A Review of the Available Evidence. *Clinical Infectious Diseases*, 561–73.
19. Guidelines for the screen, care and treatment of persons with chronic hepatitis C infection, Geneva: WHO 2016(<http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/> accessed August 2, 2016).
20. Guidelines for the screen, care and treatment of persons with chronic hepatitis C infection, Geneva: WHO 2016(<http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/> accessed August 2, 2016).
21. Candotti D, Sarkodie F, Allain JP. Residual risk of transfusion in Ghana. *Br J Haematol*. 2001;113(1):37–9.
22. de Oliveira T, Pybus OG, Rambaut A, Salemi M, Cassol S, Ciccozzi M, et al. Molecular epidemiology – HIV-1 and HCV sequences from Libyan outbreak. *Nature*. 2006;444(7121):836–7.
23. Kane A, Lloyd J, Zaffran M, Simonsen L, Kane M. Transmission of hepatitis B, hepatitis C and human immunodeficiency viruses through unsafe injections in the developing world: model-based regional estimates. *Bull World Health Organ*. 1999;77(10):801–7.
24. Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horyniak D, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet*. 2011;378(9791):571–83.
25. Thomas DL, Villano SA, Riester KA, Hershow R, Mofenson LM, Landesman SH, et al. Perinatal transmission of hepatitis C virus from human immunodeficiency virus type 1-infected mothers. *Women and Infants Transmission Study*. *J Infect Dis*. 1998;177(6):1480–8.
26. Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. *Clin Infect Dis*. 2014;59(6):765–73.
27. Floreani A. Hepatitis C and pregnancy. *World J Gastroenterol*. 2013;19(40):6714–20.
28. Terrault NA, Dodge JL, Murphy EL, Tavis JE, Kiss A, Levin TR, et al. Sexual transmission of hepatitis C virus among monogamous heterosexual couples: The HCV partners study. *Hepatology*. 2013;57(3):881–9.
29. Tohme RA, Holmberg S. Is sexual contact a major mode of hepatitis C virus transmission? *Hepatology*. 2010;52(4):1497–505.
30. Danta M, Brown D, Bhagani S, Pybus OG, Sabin CA, Nelson M, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. *AIDS*. 2007;21(8):983–91.
31. Jafari S, Copes R, Baharlou S, Etminan M, Buxton J. Tattooing and the risk of transmission of hepatitis C: a systematic review and meta-analysis. *Int J Infect Dis*. 2010;14(11):E928–E940.
32. Karmochkine M, Carrat F, Dos Santos O, Cacoub P, Raguin G. A case–control study of risk factors for hepatitis C infection in patients with unexplained routes of infection. *J Viral Hepat*. 2006;13(11):775–82.
33. Greub G, Ledergerber B, Battegay M, Grob P, Perrin L, Furrer H, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet*. 2000;356(9244):1800–5.

34. Wandeler G, S. M. (2015). Incident hepatitis C virus infections in the Swiss HIV Cohort Study: changes in treatment uptake and outcomes between 1991 and 2013. *Open Forum Infect Dis*. doi:10.1093/ofid/ofv02
35. Mohd Hanafiah K, Groeger J, Flaxman A.D, Wiersma S.T. (2013). Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology*, 1333–42.
36. Guidelines for the screen, care and treatment of persons with chronic hepatitis C infection, Geneva: WHO 2016(
<http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/> accessed August 2, 2016).
37. Bonacini M, Lin HJ, Hollinger FB. Effect of coexisting HIV-1 infection on the diagnosis and evaluation of hepatitis C virus. *J Acquir Immune Defic Syndr*. 2001;26(4):340–4.
38. George SL, Gebhardt J, Klinzman D, Foster MB, Patrick KD, Schmidt WN, et al. Hepatitis C virus viremia in HIV-infected individuals with negative HCV antibody tests. *J Acquir Immune Defic Syndr*. 2002;31(2):154–62.
39. Thio CL, Nolt KR, Astemborski J, Vlahov D, Nelson KE, Thomas DL. Screening for hepatitis C virus in human immunodeficiency virus-infected individuals. *J Clin Microbiol*. 2000;38(2):575–7.
40. Thomson EC, Nastouli E, Main J, Karayiannis P, Eliahoo J, Muir D, et al. Delayed anti-HCV antibody response in HIV-positive men acutely infected with HCV. *AIDS*. 2009;23(1):89–93.
41. Center for Disease Control. (n.d.). A Guide to Comprehensive Hepatitis C Counseling and Testing. Retrieved from
www.cdc.gov/hepatitis/resources/professionals/pdfs/counselingandtesting.pdf
42. Smith C, Sabin CA, Lundgren JD, Thiebaut R, Weber R, et al. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D Study. *AIDS* 2010; 24:1537–1548.
43. WHO ASSIST package. Geneva: World Health Organization; 2011 (http://www.who.int/substance_abuse/publications/media_assist/en/, accessed 22 March 2016)
44. Guidelines for the screening, care and treatment of persons with hepatitis infection, WHO, April, 2014
45. Crossan C, Tsochatzis EA, Longworth L, Gurusamy K, Davidson B, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. *Health Technol Assess* 2015; 19:1–409.
46. Guidelines for the screening, care and treatment of persons with hepatitis infection, WHO, April 2014
47. WHO. Guidelines for the Screening, Care and Treatment of Persons with Chronic Hepatitis C Infection. 2016.
48. Lin ZH, Xin YN, Dong QJ, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. *Hepatology* 2011; 53:726–736
49. Berenguer J, Zamora FX, Aldamiz-Echevarria T, Von Wichmann M.A, Crespo M et al. Comparison of the prognostic value of liver biopsy and FIB-4 index in patients coinfecting with HIV and hepatitis C virus. *Clin Infect Dis* 2015; 60:950–958

50. Singal AG, Thomassen LV, Gretch DR, Shuhart MC. Use of the AST to platelet ratio index in HCV/HIV co-infected patients. *Aliment Pharmacol Ther.* 2011; 33:566–577.
51. Castera L, Winnock M, Pambrun E, et al. Comparison of transient elastography (FibroScan), FibroTest, APRI and two algorithms combining these noninvasive tests for liver fibrosis staging in HIV/HCV coinfecting patients: ANRS CO13 HEPAVIH and FIBROSTIC collaboration. *HIV Med* 2014; 15:30 – 39.
52. Tsochatzis EA, Gurusamy KS, Ntaoula S, et al. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. *J Hepatol* 2011; 54:650–659.
53. Macias J, Mancebo M, Marquez M, et al. Low risk of liver decompensation among human immunodeficiency virus/hepatitis C virus-coinfecting patients with mild fibrosis in the short term. *Hepatology* 2015; 61:1503 – 1511.
54. Hepatitis C Fact sheet, WHO Updated July 2016:
<http://www.who.int/mediacentre/factsheets/fs164/en/>
55. Guidelines on drawing blood: best practices in phlebotomy. Geneva: WHO; 2010 (http://www.who.int/injection_safety/sign/drawing_blood_best/en/; accessed 21 Oct 2016)
56. Sources: WHO guidelines on hand hygiene in health care. Geneva: World Health Organization; 2009 (http://apps.who.int/iris/bitstream/10665/44102/1/9789241597906_eng.pdf, accessed 10 March 2016).
Safe abortion: technical and policy guidance for health systems, second edition. Geneva: World Health Organization; 2012. (http://apps.who.int/iris/bitstream/10665/70914/1/9789241548434_eng.pdf, accessed 10 March 2016).
Universal access to safe blood transfusion. Geneva: World Health Organization; 2008 (<http://www.who.int/bloodsafety/publications/UniversalAccessToSafeBT.pdf>, accessed 10 March 2016).
Blood donor selection: guidelines on assessing donor suitability for blood donation. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/76724/1/9789241548519_eng.pdf, accessed 10 March 2016).
WHO guidelines on drawing blood: best practices in phlebotomy. Geneva: World Health Organization; 2010 (http://www.who.int/injection_safety/sign/drawing_blood_best/en/index.html, accessed 10 March 2016).
57. Sources: Guidance on prevention of viral hepatitis B and C among people who inject drugs. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/75357/1/9789241504041_eng.pdf, accessed 10 March 2016).
WHO guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. Geneva: World Health Organization; 2009 (http://www.who.int/substance_abuse/publications/opioid_dependence_guidelines.pdf, accessed 10 March 2016).
58. Prevention and treatment of HIV and other sexually transmitted infections for sex workers in low- and middle-income countries: recommendations for a public health approach. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/77745/1/9789241504744_eng.pdf, accessed

- 11 March 2016). Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with men and transgender people. Geneva: World Health Organization, Department of HIV/AIDS; 2011 (http://www.who.int/hiv/pub/guidelines/msm_guidelines2011/en/, accessed 11 March 2016).
59. Cambodian National HIV clinical management guidelines for Adults and Adolescents, NCHADS, 2016
 60. Guidelines for the screen, care and treatment of persons with chronic hepatitis C infection, Geneva: WHO 2016(<http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/> accessed August 2, 2016).
 61. Lerolle N, Limsreng S, Fournier-Nicolle I, Ly S, Nouhin J, et al. (2012) High Frequency of Advanced Hepatic Disease among HIV/HCV Co-Infected Patients in Cambodia: The HEPACAM Study (ANRS 12267). *J AIDS Clinic Res* 3:161. doi:10.4172/2155-6113.1000161
 62. Consolidated ARV guidelines , 2nd Edition. France : WHO; 2016 (<http://www.who.int/hiv/pub/arv/arv-2016/en/> accessed 29 June 2016).
 63. AASLD 2015 guidelines, available at <http://hcvguidelines.org>; MSF expert recommendations
 64. Guidelines for the screening, care and treatment of persons with Chronic Hepatitis C infection Updated Version April 2016 Guidelines. AASLD 2015 guidelines, available at <http://hcvguidelines.org>
 65. MSF Patient education and counseling guide, For adults infected with Hepatitis C
 66. Hepatitis C Guidance: AASLD-IDS Recommendations for Testing, Managing, and Treating Adults Infected With Hepatitis C Virus. AASLD; 2015: (<http://onlinelibrary.wiley.com/doi/10.1002/hep.27950/pdf>; accessed 15 Oct 2016).
 67. Recommendations on Treatment of Hepatitis C , Guideline EASL; 2015. (<http://www.easl.eu/medias/cpg/HEPC-2015/Full-report.pdf>, accessed 15 Oct 2016)
 68. Recommendations on Treatment of Hepatitis C , Guideline EASL; 2015. (<http://www.easl.eu/medias/cpg/HEPC-2015/Full-report.pdf>, accessed 15 Oct 2016)
 69. Recommendations on Treatment of Hepatitis C , Guideline EASL; 2015. (<http://www.easl.eu/medias/cpg/HEPC-2015/Full-report.pdf>, accessed 15 Oct 2016)
 70. Recommendations on Treatment of Hepatitis C , Guideline EASL; 2015. (<http://www.easl.eu/medias/cpg/HEPC-2015/Full-report.pdf>, accessed 15 Oct 2016)
 71. AFEF - Société Française d'Hépatologie: <http://www.afef.asso.fr/>
 72. University of Liverpool Hepatitis drug interactions webpage (<http://www.hep-druginteractions.org/>) and HIV drug interactions webpage www.hiv-druginteractions.org/.
 73. EASL Recommendations on Treatment of Hepatitis C 2016. European Association of the Study of the Liver. *Journal of Hepatology*. <http://dx.doi.org/10.1016/j.jhep.2016.09.001>
 74. Liu Z, Hou J. Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) Dual Infection. *Int J Med Sci* 2006; 3(2):57-62
 75. Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfecting patients. The Multivirc Group. *Hepatology*.1999;30(4):1054–8.
 76. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis*. 2001;33(4):562–9.

77. Gane EJ, Hyland RH, An D, Svarovskaia E, Pang PS, Brainard D, et al. Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks in patients with HCV genotype 3 or 6 infection. *Gastroenterology*. 2015;149(6):1454–61 e1.
78. Lo Re V 3rd, Kallan MJ, Tate JP, Localio AR, Lim JK, Goetz MB, et al. hepatic decompensation in antiretroviral-treated patients co-infected with HIV and hepatitis C virus compared with hepatitis C virus-monoinfected patients: a cohort study. *Ann Intern Med*. 2014;160(6):369–79.
79. Zhang F, Zhu H, Wu Y, Dou Z, Zhang Y et al, HIV, hepatitis B virus, and hepatitis C virus co-infection in patients in the China National Free Antiretroviral Treatment Program, 2010-12: a retrospective observational cohort study.
80. Guidelines for the screen, care and treatment of persons with chronic hepatitis C infection, Geneva: WHO 2016 (<http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/> accessed 30 May 2016).
81. Lin SY, Chen TC, Lu PL, Lin CY, Lin WR, Yang YH, et al. Incidence rates of tuberculosis in chronic hepatitis C infected patients with or without interferon based therapy: a population-based cohort study in Taiwan. *BMC Infect Dis*. 2014;14:705.
82. Guidelines on the management of latent tuberculosis infection. Geneva: World Health Organization; 2015 (http://www.who.int/tb/publications/lbti_document_page/en/, accessed 22 March 2016).
83. Vandenbulcke, H, Moreno C, Colle I, Knebel J.F, Francque S, et al., (2016). Alcohol Intake Increases the Risk of HCC in hepatitis C virus-related compensated cirrhosis: A prospective study. *J Hep Vol 65* 543-551.
84. Anand BS, Currie S, Dieperink E, Bini EJ, Shen H, Ho SB, et al. (2006). Alcohol Use and Treatment of Hepatitis C Virus: Results of a National Multicenter Study. *Gastroenterology*. 2006. 130: 1607-1616.
85. Bedossa, P., Moucari, R., Chelbi, E., Asselah, T., Paradis, V., Vidaud, M. et al. Evidence for a role of nonalcoholic steatohepatitis in hepatitis C: a prospective study. *Hepatology*. 2007; 46: 380–387
86. Schaefer M, Capuron L, Friebe A, Diez-Quevedo C, Robaeys G, et al. (2012). Hepatitis C infection, antiviral treatment and mental health: A European expert consensus statement. *J Hepatol*. <http://dx.doi.org/10.1016/j.hep.2012.07.037>.
87. Saxena V, Korashy FM, Sise ME, Lim JK, Schmidt M, Chung RT, et al. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. *Liver Int* 2016;36:807–816.
88. Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA*. 2000;284(4):450–6.
89. Tong MJ, Elfarra NS, Reikes AR, Co RL. Clinical outcomes after transfusion associated hepatitis-C. *N Engl J Med*. 1995;332(22):1463–6.
90. Tremolada F, Casarin C, Alberti A, Drago C, Tagger A, Ribero ML, et al. Long-term follow-up of non-A, non-B (type C) post-transfusion hepatitis. *J Hepatol*. 1992;16(3):273–81.
91. Piasecki BA, Lewis JD, Reddy KR, Bellamy SL, Porter SB, Weinrieb RM, et al. Influence of alcohol use, race, and viral coinfections on spontaneous HCV clearance in a US veteran population. *Hepatology*. 2004;40(4):892–9.

92. European Association for Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol.* 2014;60(2):392–420
93. European Association for Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol.* 2014;60(2):392–420.
94. Locasciulli A, Gornati G, Tagger A, Ribero ML, Cavalletto D, Cavalletto L, et al. Hepatitis C virus infection and chronic liver disease in children with leukemia in long-term remission. *Blood.* 1991;78(6):1619–22.
95. Rossetti F, Cesaro S, Pizzocchero P, Cadrobbi P, Guido M, Zanesco L. Chronic hepatitis B surface antigen-negative hepatitis after treatment of malignancy. *J Pediatr.* 1992;121(1):39–43.
96. Davison, S.M, Mieli-Vergani G, Sira J, Kelly D.A. (2006). Perinatal Hepatitis C Virus Infection: Diagnosis and Management. *Arch Dis Child.* 2006 Sep; 91(9): 781-785.
97. Grebeley et al. Efficacy and safety of sofosbuvir/velpatasvir in patients with chronic hepatitis C virus infection receiving opioid substitution therapy: Analysis of Phase 3 Astral Trials. *Clin Inf Dis.* 2016. <http://cid.oxfordjournals.org>.
98. Konerman MA, Mehta SH, Sutcliffe CG, et al. Fibrosis progression in human immunodeficiency virus/hepatitis C virus coinfecting adults: prospective analysis of 435 liver biopsy pairs. *Hepatology* 2014; 59:767–775
99. The ANRS CO13 HEPAVIH Cohort. Regression of liver stiffness after sustained hepatitis C virus (HCV) virological responses among HIV/HCV-coinfecting patients. *AIDS* 2015, 29:1821–1830
100. Bourcier V, Winnock M, Ait Ahmed M, et al; ANRS CO13 Hepavir study group; ANRS CO12 Cirvir study group. Primary liver cancer is more aggressive in HIV-HCV coinfection than in HCV infection. A prospective study. *Clin Res Hepatol Gastroenterol.* 2012 Jun; 36(3):214-21