Rawatan DAAs

Dr Haniza Omar

Pakar Perunding Gastroenterologi & Hepatologi

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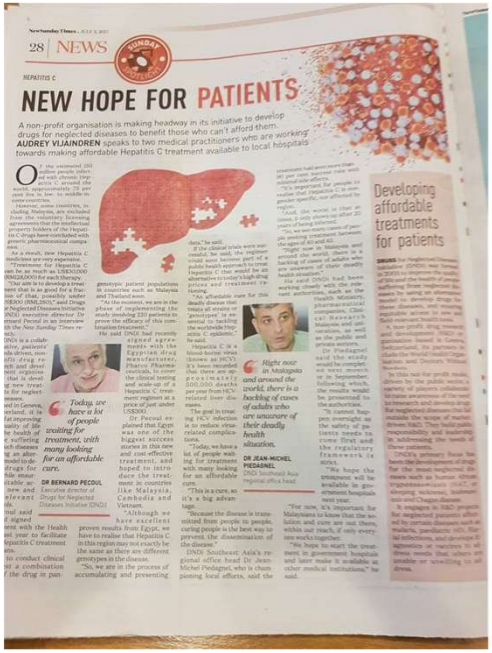
MTAAG

Hotel Tanjung Vista , KualaTerengganu

24.8.2018

Newspaper…



28 | NEWS

HEPATITIS C

NEW HOPE FOR PATIENTS

A non-profit organisation is making headway in its initiative to develop drugs for neglected diseases to benefit those who can't afford them. **AUDREY VIJAINDREN** speaks to two medical practitioners who are working towards making affordable Hepatitis C treatment available to local hospitals

Developing affordable treatments for patients

Today, we have a lot of people waiting for treatment, with many looking for an affordable cure.

DR BERNARD PECOUL
Executive director of Drugs for Neglected Diseases Initiative (DNDi)

Right now in Malaysia and around the world, there is a backlog of cases of adults who are unaware of their deadly health situation.

DR JEAN-MICHEL PEDAGNEL
DNDi Southeast Asia regional office head

FRIDAY 2 MARCH 2018

THE Star
the people's paper

Nation
'A historic moment'
SJK (C) Union is the first Chinese primary school to open in Cyberjaya.
>10

Nation
It's right on track, says Liow
MRT Sungai Buloh-Serdang-Putrajaya Line all set to roll out and will meet the 2021 deadline. >10

WOW
Women do Wonders

Nation
Have g... make... life, wo...
>21

A dose of good news

There's encouraging news for some 400,000 Hepatitis C patients. A new generic drug combination is ready to be rolled out in 18 state hospitals in the country under a government initiative – the first of its kind in the world. The move will see the cost of the treatment fall from RM300,000 to a mere RM1,000.
> See Page 3 for reports by LOH FOON FONG

And, for The Donald, it's bad news

Free Hepatitis C treatment for all

MAJLIS INISIASI UBATAN DIRECT ACTING ANTIVIRAL (DAA) UNTUK RAWATAN HEPATITIS C DI FASILITI KKM

Well taken care of: Patients consulting healthcare personnel on Hepatitis C treatment at the Hepatology Department in Hospital Selayang.

2,000 patients need not pay at government hospitals this year

Reports by LOH FOON FONG and CLARISSA CHUNG
newsdesk@thestar.com.my

SELAYANG: Government hospitals nationwide will be providing free Hepatitis C treatment to patients, says Datuk Seri Dr S. Subramaniam.

The Health Minister said 1,000 hepatitis C patients would be treated this year after the drug sofosbuvir was made available to patients through compulsory licensing.

Twenty patients have been undergoing the anti-viral treatment since it was rolled out more than two weeks ago.

"This is a long-awaited moment for patients," he said during his visit to Hospital Selayang yesterday.

"We did not have an effective hepatitis C treatment before and the ones available were expensive.

"Now, we are able to use a generic drug which can provide a cure and kill the virus," he said, adding that the treatment had a cure rate of ...

The generic version of sofosbuvir is currently imported from Egypt, said ...

Subramaniam said the 23,000 patients in the country's Hepatitis C registry would be treated in stages.

It has been estimated that 400,000 Malaysians are infected with Hepatitis C.

"We are starting treatment with a small number and will increase it," he said.

Subramaniam said the ministry was also looking at more cost-effective testing so that it could carry out mass screening and provide treatment to more patients.

The access to the affordable medicine comes after the Government issued a compulsory licence (CL) to import or produce the generic version of sofosbuvir, one of the drug combinations used for Hepatitis C treatment.

The combination of sofosbuvir and daclatasvir is now being made available in stages at all 18 government hospitals nationwide.

(While sofosbuvir requires a CL, daclatasvir does not because the manufacturer did not apply for patent rights in Malaysia and the Government did not grant data exclusivity to it on public health grounds. Without the patent barrier, the Government is able to buy generic daclatasvir.)

> This is a long-awaited moment for patients. Now, we are able to use a generic drug which can provide a cure and kill the virus.
> Datuk Seri Dr S. Subramaniam

Last July, *The Star* carried a front-page report highlighting the plight of about 400,000 Malaysians who have Hepatitis C.

However, only a fraction could afford the medication, which may cost up to RM300,000 for the full course of treatment.

Malaysia is not given special pricing for the drugs by pharmaceutical companies because it is considered a middle-income country.

NGOs lobbied the Government to issue a CL so patients could gain access to the medication.

In September, the Domestic Trade, Co-operatives and Consumerism Ministry confirmed that the Cabinet had issued a government-use CL to enable the import of generic versions of sofosbuvir.

Dr Subramaniam said that in negotiations with the drug company offering sofosbuvir, the lowest price put forward was RM50,000.

After the failed negotiations, the Government initiated the CL and managed to get the cost down to RM1,000 a patient, which it will now bear.

Malaysia is the first country in the world to invoke the CL for importing or producing the generic version of sofosbuvir.

A CL is an authorisation that does not require the permission of the patent holder.

Under the World Trade Organisation's Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement, countries have the right to issue such licences.

Asked why the Government decided to invoke the CL, Dr Subramaniam said the law allowed it for the greater good of public health.

"It is done purely for the interest of public health.

"We respect the need for patents but we are also holding to the principle that affordable medicines should be made available to those who need them," he said.

He added that Hepatitis C was a big public health issue and if it was left untreated, patients would suffer scarring and even cancer of the liver; and it was an infectious disease that could spread to others.

Watch the video thestartv.com

Other

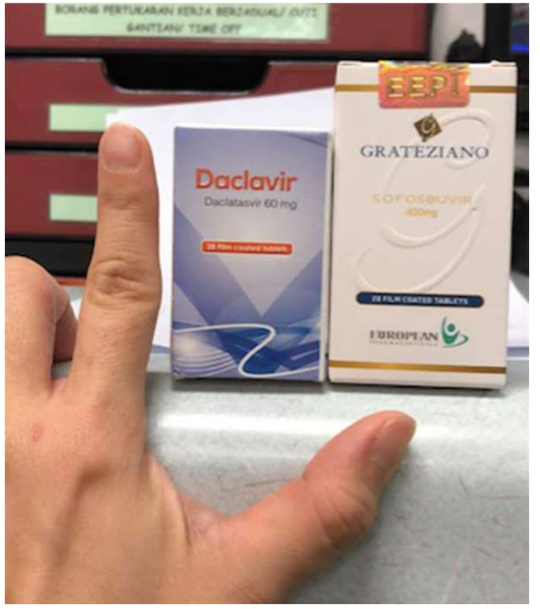
GEORGE TOWN | K. LUMPUR | JOHOR BARU | KOTA BARU | K. KINABALU | KUCHING

Prayer times

ALOR SETAR | PENANG | K. LUMPUR

PENAMBAHAN PEMBEKALAN DI 18 HOSPITAL 2018

- Hospital Selayang
- Hospital Ampang
- Hospital Kuala Lumpur
- Hospital Tengku Ampuan Rahimah
- Hospital Sultanah Bahiyah Alor Setar
- Hospital Tengku Ampuan Afzan, Kuantan
- Hospital Raja Perempuan Zainab II, Kota Bahru
- Hospital Pulau Pinang
- Hospital Queen Elizabeth, Kota Kinabalu
- Hospital Sultanah Aminah, Johor Bahru
- Hospital Umum Sarawak , Kuching
- Hospital Tuanku Fauziah
- Hospital Raja Perempuan Bainun
- Hospital Serdang
- Hospital Sungai Buloh
- Hospital Sulatanah Nur Zahirah
- Hospital Tuanku Jaafar
- Hospital Melaka



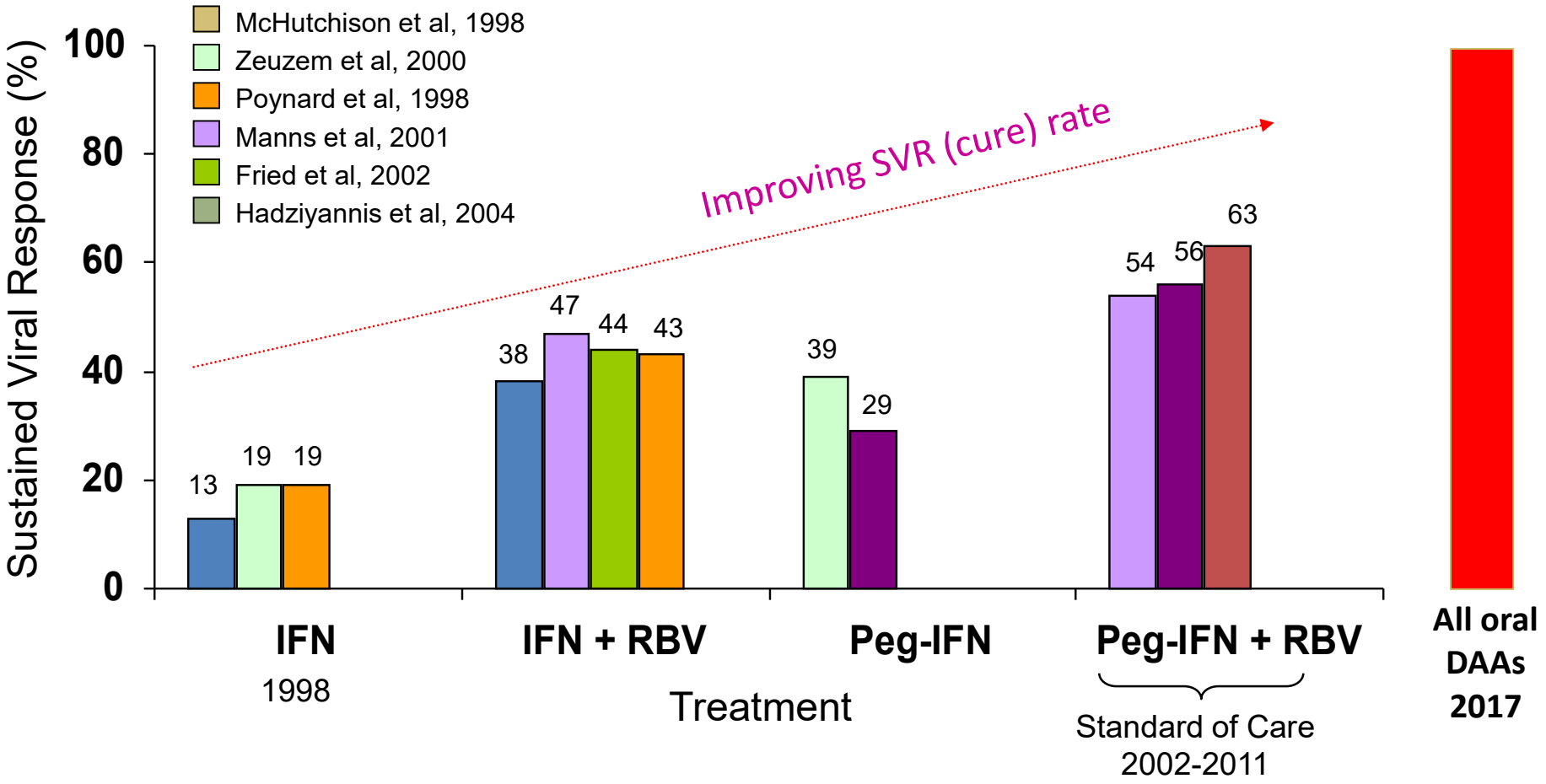
Multidiscipline

- Physicians – Hepatologists/Gastroenterologist / Family Medicine Specialists/ ID Specialist
- Public Health
- Epidemiologists
- Pharmacists
- Laboratory Support – Pathologist / Virologist/ Microbiologist / MLT
- Supporting Staff – Nurses

OBJECTIVES

- All Hepatitis C needs to be treated
- Eradicate and Eliminate Hepatitis C by 2030
- To reduce all-cause mortality and liver related health adverse consequences, including ESLD and HCC by the achievement of virological cure as evidenced by a sustained virological response (SVR)

Evolution of Antiviral Therapy for HCV



Fung et al. Hepatitis C Virus Disease. Springer;2008: 130-147

Guidelines

GUIDELINES

APASL consensus statements and recommendation on treatment of hepatitis C

Masao Omata[1,2] · Taisen Kanda[3] · Lai Wei[4] · Ming-Lung Yu[5] · Wang-Long Chuang[6] · Alaaddin Ibrahim[7] · Cosmas Rinaldi Adithya Leemarta[8] · Jun Sollano[9] · Manoj Kumar[10] · Ankur Jindal[11] · Barjesh Chander Sharma[12] · Saeed A. Hamid[13] · A. Kadir Dokmeci[14] · Mamun-Al-Mahtab[15] · Geoffrey W. McCaughan[16] · Jafri Wasim[17] · Darrell H. G. Crawford[18] · Jin-Ihorng Kao[19] · Osamu Yokosuka[3] · George K. K. Lau[20] · Shiv Kumar Sarin[10]

Received: 12 December 2015 / Accepted: 18 February 2016 / Published online: 29 April 2016

Abstract The Asian-Pacific Association for the Study of the Liver (APASL) convened an international working party on the "APASL consensus statements and recommendation on management of hepatitis C" in March, 2015, in order to revise "APASL consensus statements and management algorithms for hepatitis C virus infection (Hepatol Int 6:409–435, 2012)". The working party consisted of expert hepatologists from the Asian-Pacific region gathered at Istanbul Congress Center, Istanbul, Turkey on 13 March 2015. New data were presented, discussed and debated to draft a revision. Participants of the consensus meeting assessed the quality of cited studies. Finalized recommendations on treatment of hepatitis C are presented in this review.

Keywords APASL · DAAs · HCV · Interferon-free · Turkey

Introduction

The major aims of antiviral treatment for chronic hepatitis C is to prevent liver-related complications, including HCC, by achievement of sustained virologic response (SVR) [1, 2].

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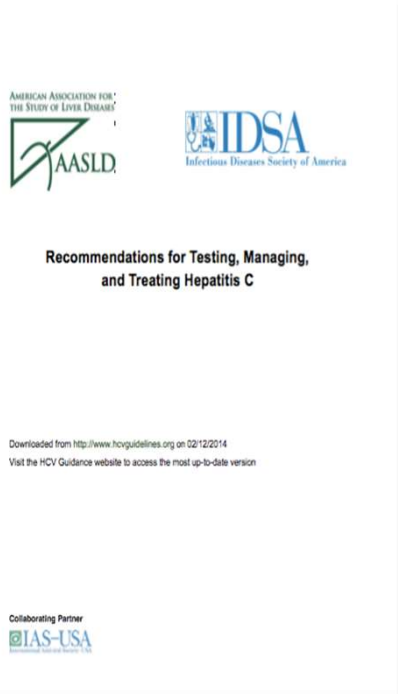


AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES
AASLD
IDSA
Infectious Diseases Society of America

Recommendations for Testing, Managing, and Treating Hepatitis C

Collaborating Partner
IAS–USA

ARTICLE IN PRESS

Guidelines

EASL JOURNAL OF HEPATOLOGY

EASL Recommendations on Treatment of Hepatitis C 2016

European Association for the Study of the Liver*

World Health Organization

GUIDELINES FOR THE SCREENING, CARE AND TREATMENT OF PERSONS WITH CHRONIC HEPATITIS C INFECTION

UPDATED VERSION
APRIL 2016

GUIDELINES

HEPATITIS C

SCREENING, TESTING AND TREATMENT GUIDELINES

Ministry of Health Malaysia
Putrajaya

1st Edition
October 2017

Drugs Available for Hepatitis C in Malaysia

Drug Acting Antivirals

Medication	Brand Name	Dosage form & Strength	Dosage
Sofosbuvir	Sovaldi®	400 mg/ tab	One tablet once daily (morning)
Sofosbuvir/ledipasvir	Harvoni®	400 mg of sofosbuvir and 90 mg of Ledipasvir/ tab	One tablet once daily (morning)
Paritaprevir/ ombitasvir/ ritonavir	Viekirax®	75 mg of paritaprevir, 12.5 mg of ombitasvir and 50 mg of ritonavir/ tab	Two tablets once daily (morning)
Dasabuvir	Exviera®	250 mg of dasabuvir/ tab	One tablet twice daily (morning and evening)
Daclatasvir	Daklinza®	30 or 60 mg/ tab	One tablet once daily (morning)
Elbasvir/ Grazoprevir	Zepatier®	50mg of Elbasvir and 100mg of Grazoprevir/ tab	One tablet once daily (morning)

Treatment duration depends on genotypes, treatment naïve or experience, cirrhosis or without cirrhosis & etc.

Hepatitis C : Screening, testing & treatment guidelines; MOH October 2017

Interferons

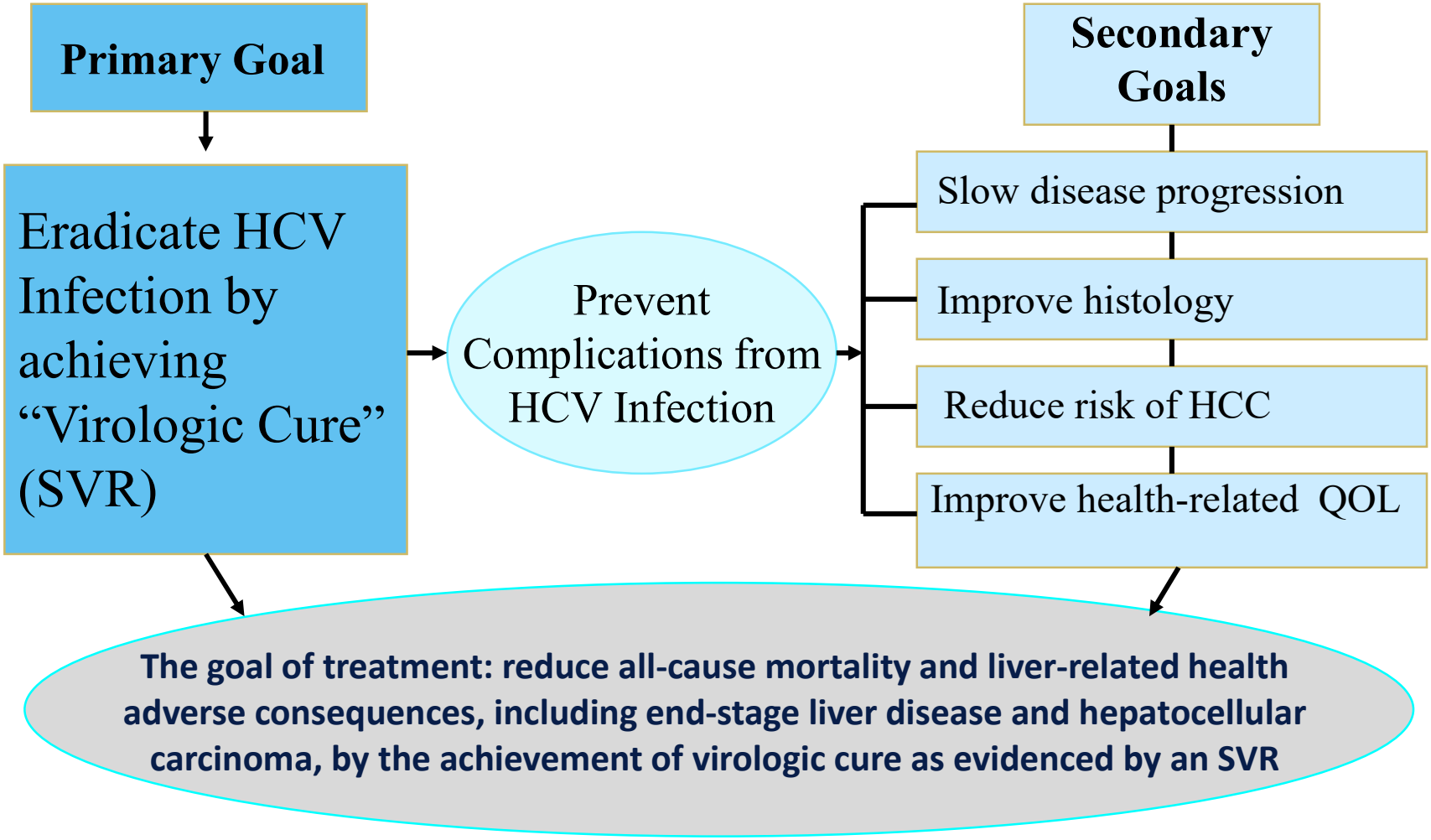
Medication	Brand Name	Dosage form & Strength	Dosage
Pegylated Interferon alpha-2a	Pegasys®	180 mcg prefilled syringe 135mcg prefilled syringe	Once weekly
Pegylated Interferon alpha-2b	Peg-intron®	150 mcg prefilled syringe 120mcg prefilled syringe 100 mcg prefilled syringe 80mcg prefilled syringe	Once weekly

Other

Medication	Brand Name	Dosage form & Strength	Dosage
Ribavirin	Copegus® Rebetol®	200mg/ tab	15mg/kg/day (in 2 divided doses)

Hepatitis C : Screening, testing & treatment guidelines; MOH October 2017

Goals of HCV Treatment



Ghany MG et al. AASLD Practice Guidelines. Diagnosis, Management, and Treatment of Hepatitis C: An Update. Hepatol 2009;49 (4):1335-74.
Lindsay K et al. Introduction to therapy of Hepatitis C. Hepatol 2002;36 (5, Suppl 1):S114-20.

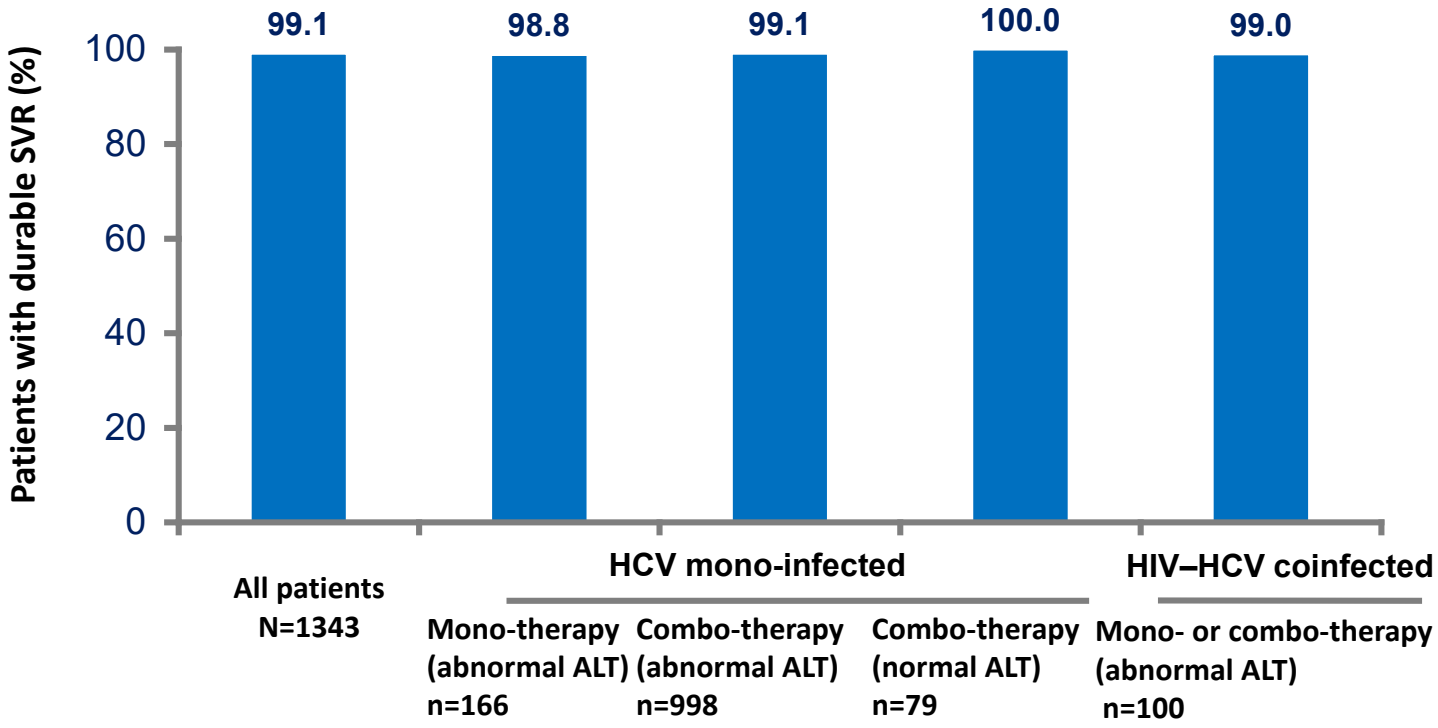
How Do We Measure Response to Treatment?

Response	Definition
RVR Rapid Virologic Response	HCV RNA negative at (<50 IU/mL) at treatment week 4
eRVR Extended Rapid Virologic Response	Undetectable HCV RNA levels at 4 and 12 weeks of treatment
EVR Early Virologic Response	AASLD 2009: HCV RNA negative or ≥2 $\log_{10}$ drop at week 12 of treatment EASL 2011: HCV RNA detectable at week 4, but undetectable at week 12 of treatment
ETR End of Treatment Response	HCV RNA negative at last dose of treatment regimen
SVR Sustained Virologic Response	HCV RNA negative 24 weeks after end of treatment

Ghany MG et al. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. 2009 Apr;49(4):1335-1374.
Sherman KE. *N Eng J Med*. 2011;365;11:1014-1024.
EASL 2011 Guidelines

SVR is Durable for Almost All Patients Treated with PegIFN/RBV

Patients negative for HCV RNA at last follow-up visit



Mean follow-up of 3.9 years (range: 0.8–7.1 years)

ALT = alanine aminotransferase.

Swain M, et al. Gastroenterol. 2010;139:1593–601.

What are the Benefits of Curing HCV Infection?

Liver Disease

- Reduced risk of progression to cirrhosis/HCC/hepatic decompensation
- Potential reversion of fibrosis in some cases
- Disappearance of oesophageal varices
- Reduced risk of recurrence after liver transplantation

Survival/other

- Reduced risk of death from liver disease in the setting of cirrhosis, HCC, HIV/HCV coinfection and transplantation
- Cure and improvement of associated conditions (e.g. cryoglobulinemia, CNS vasculitis, polyneuropathy)

Transmission

- No risk of sexual or perinatal transmission
- No transmission to others (IVDU), benefit to public health

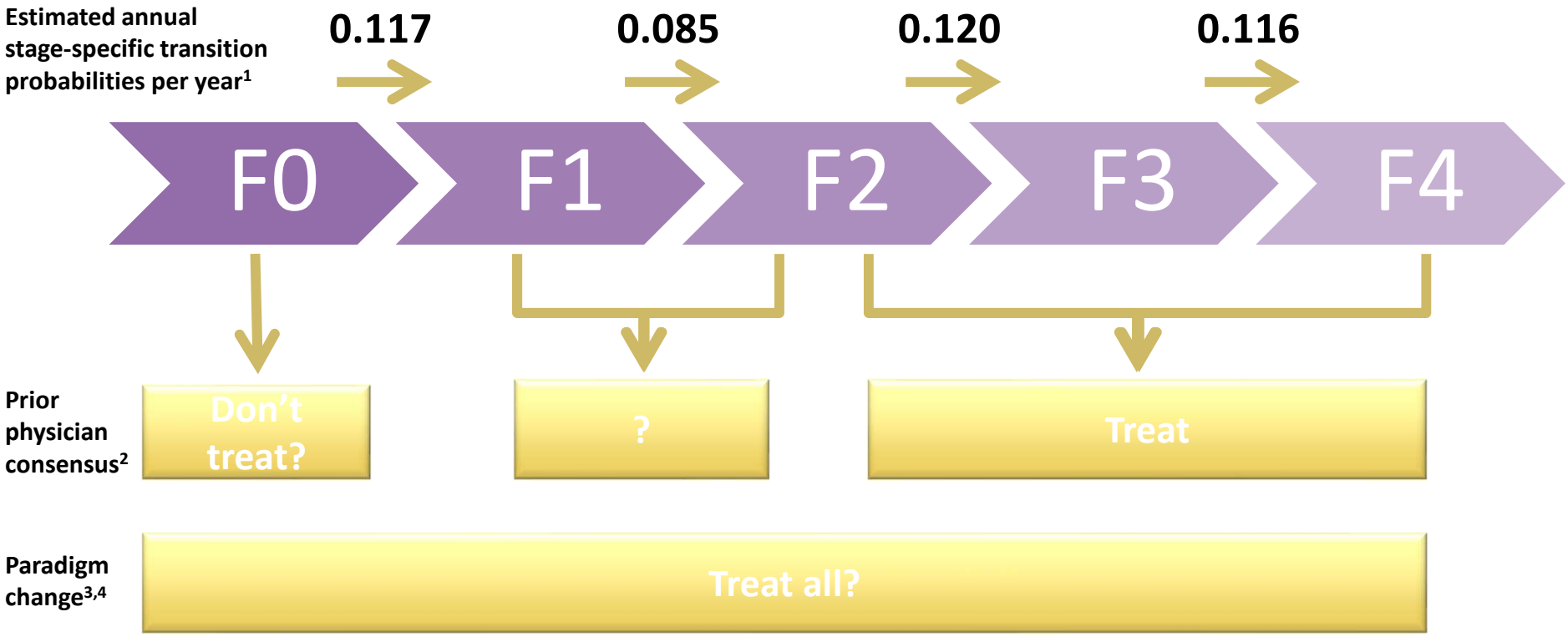
Well-being

- Improved quality of life
- Reduced psychological impact
- Reduced personal, family and social stigma

Marinho RT, et al. J Gastrointestin Liver Dis. 2014;23:85–90.

Liver Fibrosis Progression Is Unpredictable

Fibrosis progression is not linear and some patients may progress rapidly from one stage to the next[1]



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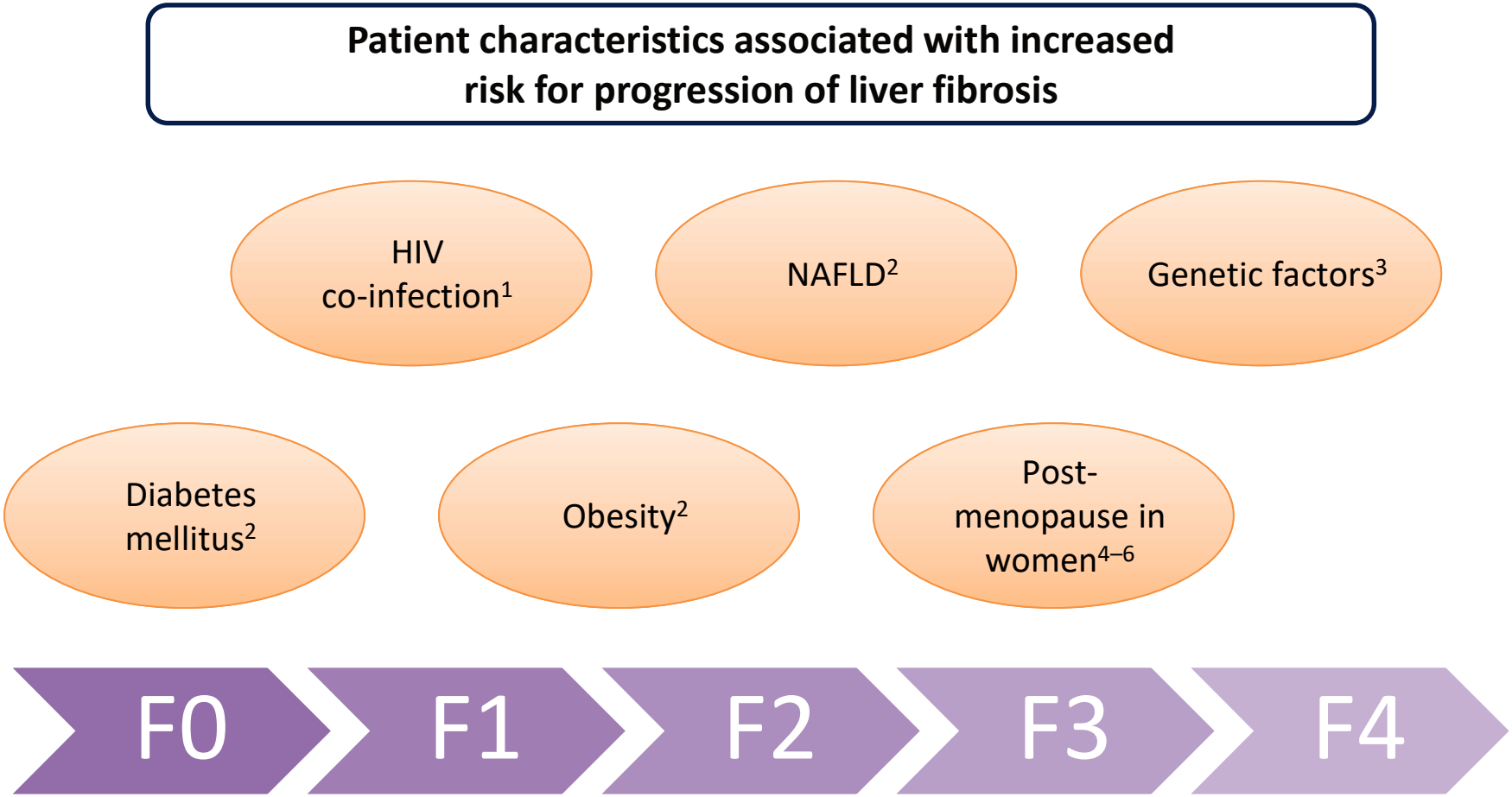
3. Younossi ZM, *et al. J Hepatol* 2014; **60:**530–537; 4. Chahal HS, *et al. JAMA Intern Med* 2016; **176:**65–73.

Progression of Fibrosis Is Influenced by Patient-Specific Characteristics

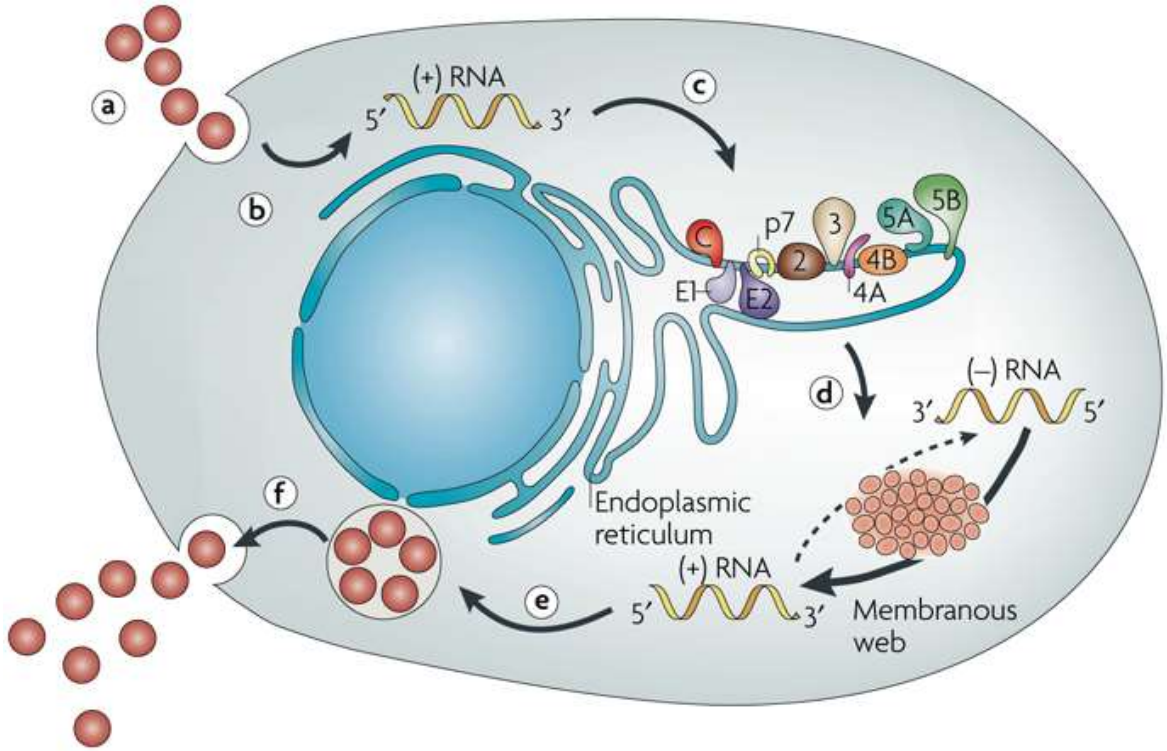


NAFLD, non-alcoholic fatty liver disease.

1. Sulkowski MS, *et al. Liver Int* 2013; **33:**63–67; 2. Dyal HK, *et al. Dig Dis Sci* 2015; **60:**2813–2824; 3. Calvaruso V, *et al. Liver Int* 2016; **36:**7–12; 4. Di Martino V, *et al. Hepatology* 2004; **40:**1426–1433; 5. Villa E, *et al. PLoS One* 2012; **7:**e44624; 6; Villa E, *et al. Gastroenterology* 2011; **140:**818–829.

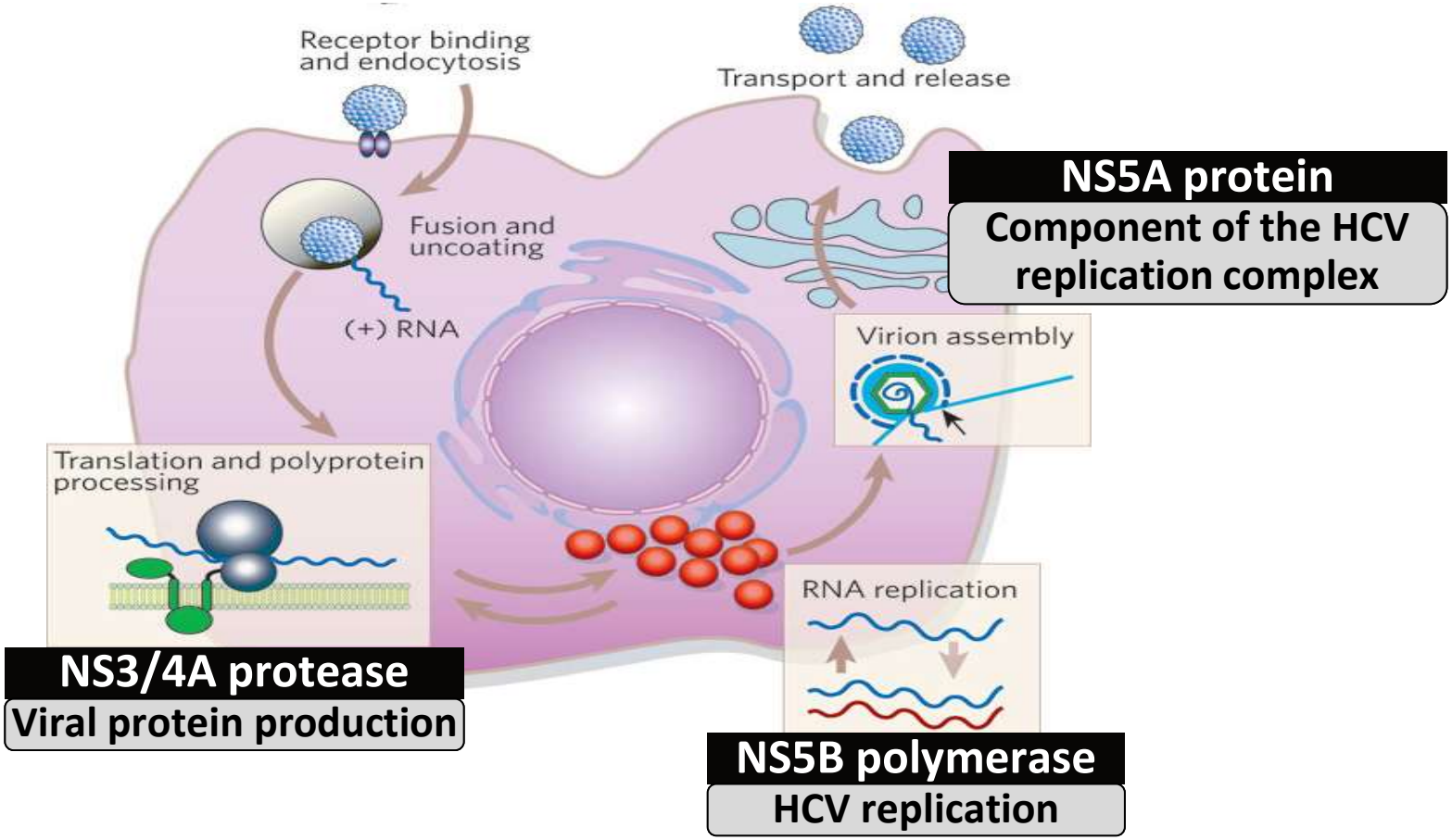
Viral Replication and Life Cycle

A. Receptor-virus binding and endocytosis
B. Fusion and uncoating
C. Translation and polyprotein processing
D. Formation of replication complex (membranous web); RNA replication
E. Assembly/packaging and virion transport and glycoprotein maturation
F. Vesicle fusion/release of infectious mature virion



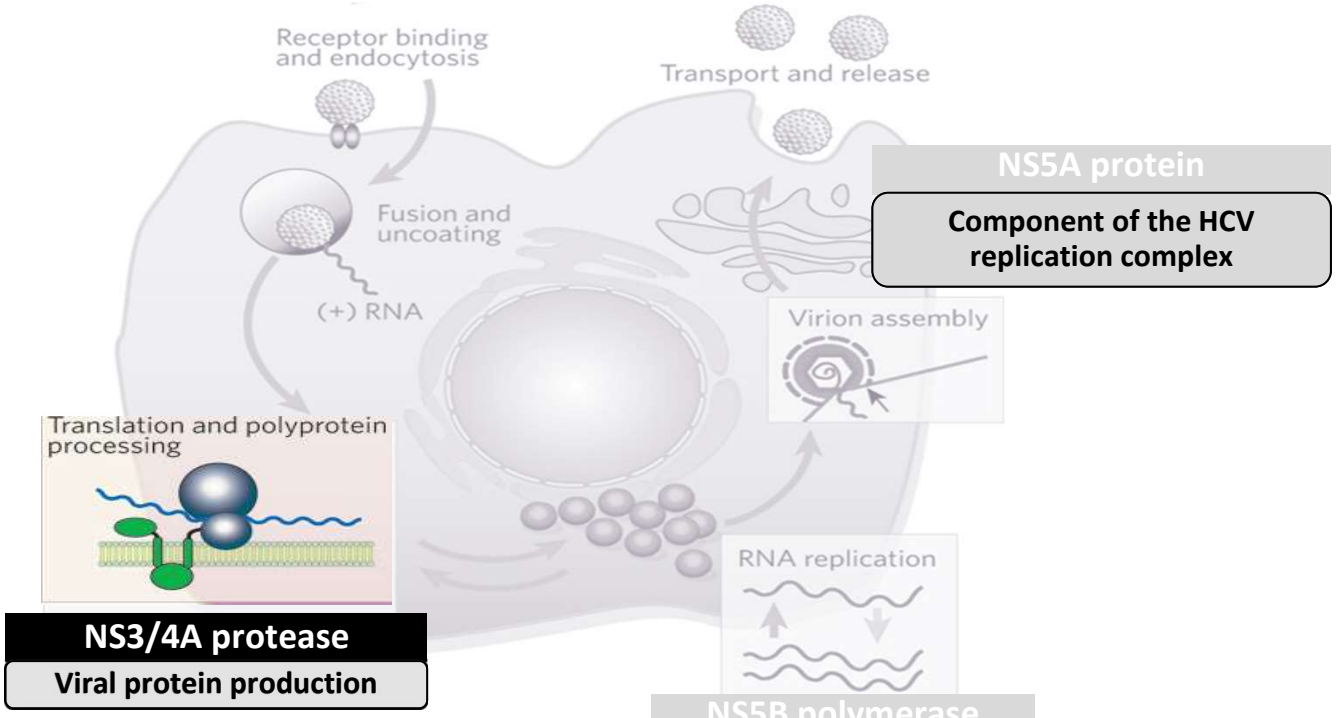
O'Leary JG, Davis GL. Hepatitis C. Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management. 9th ed. 2010:1313–1335.

Most DAAs Currently in Development Target One of Three Viral Proteins: NS3/4A, NS5A and NS5B



NS3/4A Protease Inhibitors Block the Viral Protease and Prevent Cleavage of the Viral Polypeptide

NS3/4A protease inhibitors
ABT-493
ACH-2684
Asunaprevir
Boceprevir
Faldaprevir
Grazoprevir
GS-9857
Paritaprevir
Simeprevir
Sovaprevir
Telaprevir
Vedroprevir



NS5A protein

Component of the HCV replication complex

NS3/4A protease

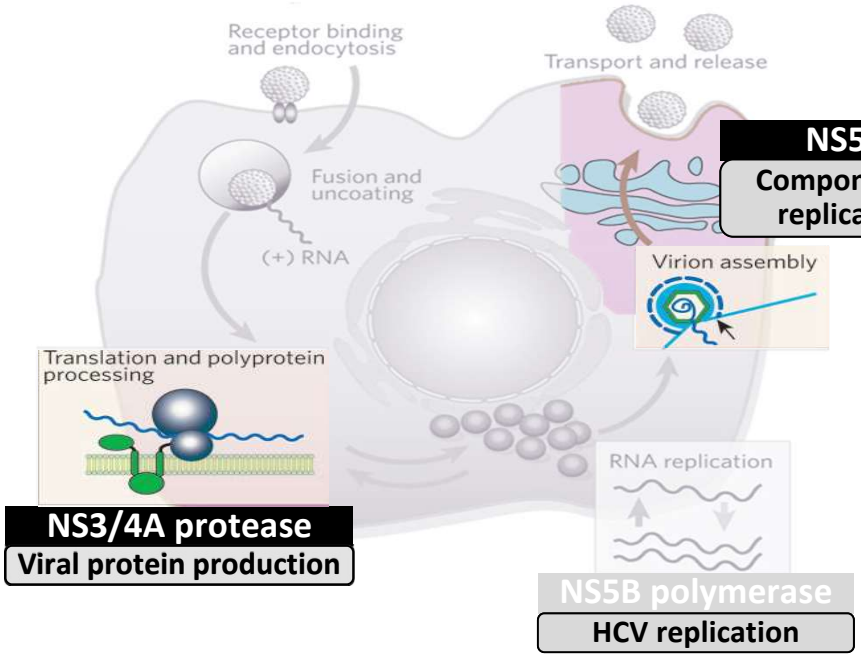
Viral protein production

NS5B polymerase

HCV replication

NS5A Inhibitors Block NS5A Protein, Resulting in the Inhibition of Multiple Steps in HCV Replication

NS3/4A protease inhibitors
ABT-493
ACH-2684
Asunaprevir
Boceprevir
Faldaprevir
Grazoprevir
GS-9857
Paritaprevir
Simeprevir
Sovaprevir
Telaprevir
Vedroprevir



NS5A protein
Component of the HCV replication complex

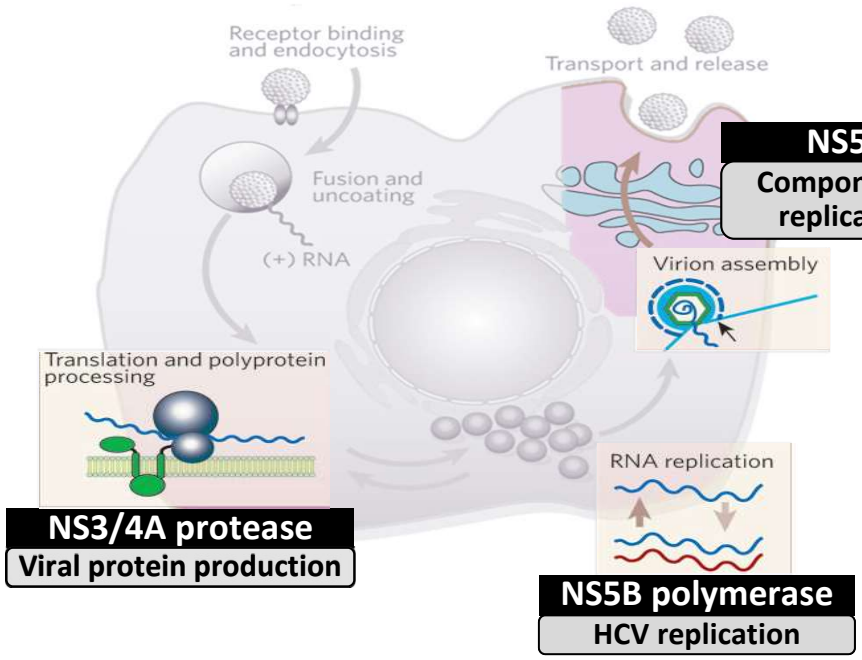
NS3/4A protease
Viral protein production

NS5B polymerase
HCV replication

NS5A inhibitors
ABT-530
ACH-3102
BMS-824393
Daclatasvir
Elbasvir
GS-5816
GSK2336805
Ledipasvir
Ombitasvir
PPI-668
Samatasvir

NS5B Polymerase Inhibitors Suppress Viral RNA Replication Through Binding to Active or Allosteric Sites on the NS5B Polymerase

NS3/4A protease inhibitors
ABT-493
ACH-2684
Asunaprevir
Boceprevir
Faldaprevir
Grazoprevir
GS-9857
Paritaprevir
Simeprevir
Sovaprevir
Telaprevir
Vedroprevir



NS5A protein
Component of the HCV replication complex

NS3/4A protease
Viral protein production

NS5B polymerase
HCV replication

NS5A inhibitors
ABT-530
ACH-3102
BMS-824393
Daclatasvir
Elbasvir
GS-5816
GSK2336805
Ledipasvir
Ombitasvir
PPI-668
Samatasvir

NS5B polymerase inhibitors

Nucleoside	Non-nucleoside	
ACH-3422	ABT-072	GS-9669
IDX20963	Beclabuvir	PPI-383
Sofosbuvir	Dasabuvir	TMC647055
VX-135		

INDICATIONS FOR TREATMENT: WHO SHOULD BE TREATED?

1. All treatment naïve and treatment experienced patients with compensated or decompensated chronic liver disease due to HCV must be considered for therapy.

FACTORS TO BE CONSIDERED IN PRIORITISING TREATMENT

- Patient's willingness to start and adhere strictly to treatment and follow up
- Increased risk of death (e.g. advanced fibrosis and cirrhosis, post-liver transplantation)
- Risk of accelerated fibrosis (e.g. HIV or HBV co-infection, metabolic syndrome)
- Extrahepatic manifestations and evidence of end-organ damage (e.g. debilitating fatigue, vasculitis and lymphoproliferative disorders)
- DAA options that are available
- Patient with no drug-drug interaction with current treatment (eg HAART, amiodarone)

RECOMMENDATION FOR WHEN AND IN WHOM TO INITIATE TREATMENT

- PWID and men who have sex with men with high-risk sexual practices should be made aware of the risk of reinfection and should take preventive measures after successful treatment. .

- Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert.
- Person with cirrhosis (including those who achieved SVR) should be screened for HCC with 6 monthly USG examination and AFP estimation, and should have endoscopy every one or two years to exclude varices.

- HCV/HIV co-infected individuals should be offered treatment or re-treatment like any other individual without HIV infection, regardless of their stage of fibrosis at diagnosis.
- Second generation DAA-based therapies have demonstrated high efficacy and safety in treatment-naıve, treatment experienced and cirrhotic HCV patients co-infected with HIV.
- However, caution should be exercised when using such agents due to known drug–drug interactions with antiretroviral agents.
- A close collaboration with HIV specialist is recommended when treating HCV/HIV co-infected individuals.

- Main issue between DAA and ART
  (eg need dose a adjusted dose of Daclatasvir with :

CYP3A enzyme inducer eg NNTI such as Efavirenz, Etravirine requires Daclatasvir 90 mg and

CYP3A enzyme inhibitor eg Ritonavir or Cobicistat –boosted atrazanavir requires Daclatasvir 30 mg

(Awaiting Daclatasvir 30 mg in next batch

- Also possibilities of HIV/HCV/HBV triple infection – HBV reactivation but usually already on TFV

Sofosbuvir and Daclatasvir

- ALLY 1 - Multicenter, prospective, open-label, phase 3 study of Daclatasvir plus Sofosbuvir plus Ribavirin in treatment-naïve and treatment-experienced patients with advanced cirrhosis or post-liver transplant HCV recurrence. N= 60 C , 53 T. 76 % G1. 20 % CPS A , 53 % B and 27 % C . SVR 12. 93% (CPS A and B) , 56 % (CPS C) . SVR 95% in transplant.

- ALLY 2 –Phase 3 open label Daclatasvir (DCV) plus Sofosbuvir (SOF) in treatment-naïve or experienced, chronic HCV GT 1-4 and HIV coinfection , n = 151 TN, (12 or 8 wks) 52 TE (12 wks). (G1-G4) 83% G1, 14% Comp Cirrhosis, 83 % on HAART . SVR 97 % (12 wks), 76 % (8 wk)

Sofosbuvir and Daclatasvir

- ALLY 3 –All-Oral 12-Week Treatment With Daclatasvir Plus Sofosbuvir in Patients With Hepatitis C Virus Genotype 3 Infection . N= 152(TN 101, TE 51). SVR 12- 90% in TN, 86% in TE, 96% (NC) 63% cirrhosis.

- ALLY 3+ - Daclatasvir, Sofosbuvir, and Ribavirin for Hepatitis C Virus Genotype 3 and Advanced Liver Disease: A Randomized Phase III Study . 12 or 16 weeks with weight based Ribavirin N=50- (37TE 13 TN) , (14 Fibrosis 36 C). SVR 86% overall (12 weeks - 83% (12 wks) , 89% (16-wks), 87% TE- 88 (12 wks) , 86 (16wks)

SOFOSBUVIR

- HCV nucleotide polymerase NS5B inhibitor.
- 400mg (one tablet) once daily
- Approximately 80% of sofosbuvir is renally excreted, whereas 15% is excreted in faeces.
- Used in patients with eGFR of > 30ml/min/1.73m2. Latest EASL 2018 states that can be used with cautious in eGFR of less than 30ml/min/1.73m2 and even haemodialysis patients.
- Not metabolized by cytochrome P450, but is transported by P-gp.
- Sofosbuvir should not be administered with known P450 inducers , such as rifampin, carbamazepine, phenytoin or St. John's wort. Other potential interactions may occur with rifabutin, rifapentine and modafinil.
- Contraindicated in patients who are being treated with the anti-arrhythmic amiodarone due to the risk of life-threatening arrhythmias.

Daclatasvir

- First -ever approved HCV NS5A replication complex inhibitor with pangenotypic activity.
- The dose of 60 mg (one tablet) or 30 mg (one tablet) when a reduced dose is needed, once daily dose
- With or without food
- May interact with other drugs e.g. Anti TB, antibiotics, herbals containing St John Worts
- Generally well tolerated, not known side effects (SE) of its own.
- The most common SEs combination Sofosbuvir and Daclatasvir = fatigue , nausea and headache (10%)

Ribavirin

- Used for combination with Sofosbuvir and Daclatasvir
- The dose = 1000 mg/ day for body weight of < 75 kg or or 1200 mg/day, for ≥ 75 kg,split in two administrations.
- Dose adjustment is needed in patients with severe renal insufficiency or ESRD
- In decompensated cirrhosis, ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance.
- Black box FDA warning : SEs may be severe and serious
- SEs : Flu like symptoms, headcahe, fatigue, mood changes
- Serious SEs : anaemia , birth defect, Suicidal thoughts.

Sofosbuvir /Ledispasvir (Harvoni)

- Two drug fixed dose combination containing 400 mg and 90 mg combination
- One tablet daily with or without food.
- Ledisprevir – Biliary excretion

Sofosbuvir and Velpatasvir (Epclusa)

- Pangenotypic
- Two fixed dose combination 400 mg Sofosbuvir and 100 mg Velpatasvir
- Velpatasvir plasma exposure (AUC) is similar in subjects with moderate or severe hepatic impairment
- Cirrhosis (including decompensated cirrhosis) has no clinical relevant effect on Velpatasvir

Viekirax/Exvira: High SVR Across a Broad Range of Patients in the Phase III Program HCV GT1 infected patients

Study	Population	Regimen	SVR12	Relapse	On-treatment virologic failure
SAPPHIRE-I[1,2] (n=631)	GT1, non-cirrhotic, treatment-naïve	3DAA + RBV for 12 wks (n=473) Placebo for 12 wks (n=158)	96%	1.5%	0.2%
SAPPHIRE-II[1,2] (n=394)	GT1, non-cirrhotic, P/R treatment-experienced	3DAA + RBV for 12 wks (n=297) Placebo for 12 wks (n=97)	96%	2.4%	0%
TURQUOISE-II[1,2] (n=380)	GT1, treatment-naïve and -P/R experienced, with compensated cirrhosis (C-P A)	3DAA + RBV for 12 wks (n=208) 3DAA + RBV for 24 wks (n=172)	92% 97%	5.9% 0.6%	0.5% 1.7%
PEARL-II[1,2] (n=179)	GT1b, non-cirrhotic, P/R treatment-experienced	3DAA + RBV for 12 wks (n=88) 3DAA - RBV for 12 wks (n=91)	98% 100%	0%	0%
PEARL-III[1,2] (n=419)	GT1b, non-cirrhotic, treatment-naïve	3DAA + RBV for 12 wks (n=210) 3DAA - RBV for 12 wks (n=209)	99.5% 100%	0%	0.5% 0%
PEARL-IV[1,2] (n=305)	GT1a, non-cirrhotic, treatment-naïve	3DAA + RBV for 12 wks (n=100) 3DAA - RBV for 12 wks (n=205)	97% 90%	1% 5%	1% 2.9%

1. Viekirax™ tablets (ombitasvir/paritaprevir/ritonavir) Summary of product characteristics.
Maidenhead, UK. AbbVie, Ltd.
2. Exviera™ tablets (dasabuvir) Summary of product characteristics.
Maidenhead, UK. AbbVie, Ltd.

3DAA: three direct-acting antivirals, ombitasvir/paritaprevir/ritonavir and dasabuvir
P/R: peginterferon+ribavirin; C-P A, Child-Pugh A

Grazoprevir and Elbasvir (Zepatier)

- Fixed dose combination 100 mg Grazoprevir and 50 mg Elbasvir
- No dose adjustment with mild , moderate , severe (including patients with haemodialysis or peritoneal dialysis)

EBR/GZR Core Phase 3 Program[1-3]

Study	Genotype	Fibrosis Staging	Treatment History	Comorbidity	Regimen (wk)
C-EDGE TN	1, 4, 6	± Cirrhosis	TN	—	12, no RBV
C-EDGE COINFECTION	1, 4, 6	± Cirrhosis	TN	HIV	12, no RBV
C-EDGE TE	1, 4, 6	± Cirrhosis	PR-PTF	± HIV	12 or 16, ± RBV
C-SURFER	1	± Cirrhosis	TN/PR-PTF	CKD	12, no RBV
C-EDGE CO-STAR	1, 4, 6	± Cirrhosis	TN	OAT, ± HIV	12, no RBV
C-EDGE IBLD	1, 4, 6	± Cirrhosis	TN/PR-PTF	IBLD, ± HIV	12, no RBV
H-2-H TRIAL	1, 4, 6	± Cirrhosis	TN/PR-PTF	—	12, no RBV vs SOF/PR

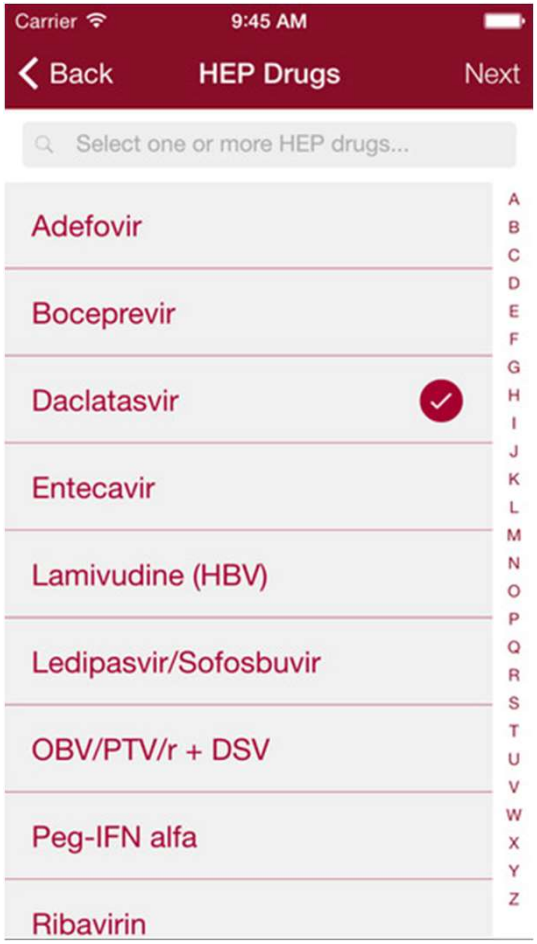
IBLD = inherited blood disorders; CKD = chronic kidney disease, including hemodialysis; OAT = opiate agonist therapy; TN = treatment-naive; PR = peginterferon + ribavirin; PTF = prior-treatment failure; RBV = ribavirin; HIV = human immunodeficiency virus; SOF = sofosbuvir; EBR/GZR = elbasvir/grazoprevir.

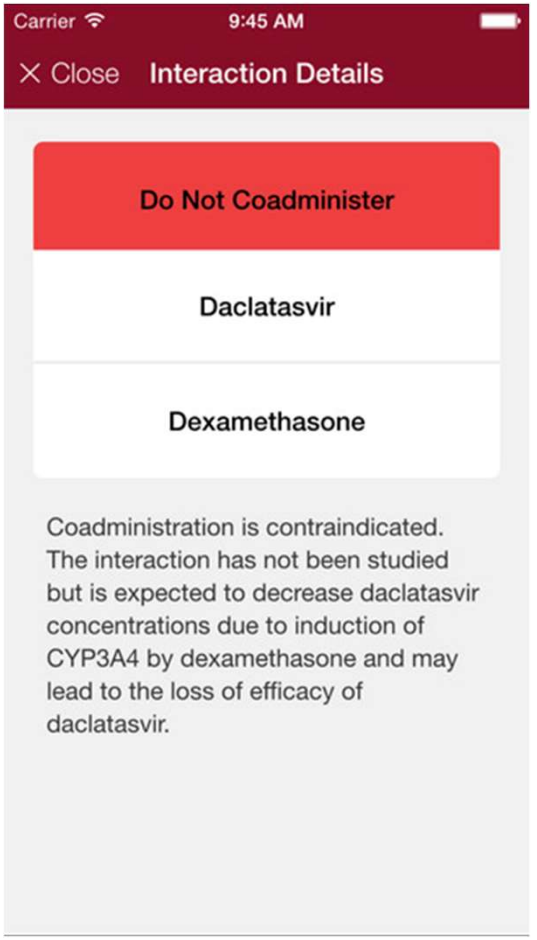
1. Zepatier EU SmPC. **2.** Hezode C et al. EASL 2016, SAT-128. **3.** Sperl J et al. EASL 2016, PS002.

Look out for Drug-Drug Interactions

- Review all medications : herbals/supplements, prescription , OTC meds , including contraception and PPI
- Ask about PRN usage of other drugs
- Work with clinical Pharmacist when possible
- Streamline patients prescription
- Actions : change medication / dose / timing
- www.hep-druginteractions.org

- Please refer to www.hep-druginteractions.org for drug-drug interaction and EASL HCV Advisor (application can be downloaded for Apple and Android user) for further reference





http://www.hep-druginteractions.org/

Close **Interaction Details**

Potential Interaction
Ledipasvir/Sofosbuvir
Esomeprazole

Coadministration has not been studied, but data with omeprazole show only a small decrease in ledipasvir exposure. Proton pump inhibitor doses comparable to omeprazole 20 mg can be administered simultaneously with ledipasvir/sofosbuvir. Proton pump inhibitors should not be taken before ledipasvir/sofosbuvir.

Close **Interaction Details**

Potential Interaction
OBV/PTV/r + DSV
Pantoprazole

Coadministration has not been studied. Pantoprazole exposure may decrease when administered with by ombitasvir/paritaprevir/ritonavir + dasabuvir. Pantoprazole is a substrate of CYP2C19, CYP3A4 and CYP2C9, and is also metabolised by sulfotranseferases. Exposure of omeprazole, a model CYP2C19 substrate, decreased by 40-50% when administered with ombitasvir/paritaprevir/ritonavir + dasabuvir, but exposure of the DAA was not affected. An interaction of similar magnitude is expected with other CYP2C19 substrates. Use higher doses of pantoprazole, if clinically indicated.

Table 1 : Summary of recommended preferred regimes with treatment durations, person without cirrhosis

Genotype		Interferon/ Ribavirin	Sofosbuvir/ Daclatasvir	Sofosbuvir/ Ledipasvir	Sofosbuvir/R ibavirin	Sofosbuvir/ Velpatasvir	Sofosbuvir/ Semiprevir	Ombitasvir/Paritaprevir/ Ritonavir/ Dasabuvir	Grazoprevir/Elbasvir
Genotype 1a	treatment naive	48 weeks	12 weeks	8-12 weeks	No	12 weeks	No	12 weeks with Ribavirin	12 wk, no Ribavirin ifHCV RNA≤800,000 (5.9log) IU/ml or 16 wk with Ribavirin if HCV RNA>800,000 (5.9log) IU/mlb
	treatment experience		12 wk with Ribavirin Or 24 wk, no Ribavirin	12 wk with Ribavirin or 24 wk, no Ribavirin					
Genotype 1b	treatment naive		12 weeks	8-12 weeks	No	12weeks	No	8-12 weeks	12 weeks
	treatment experience			12 weeks			No	12 weeks	
Genotype 2	treatment naive	24 weeks	12 weeks	No	12 weeks	12 weeks	No	No	No
	treatment experience								
Genotype 3	treatment naive	24 weeks	12 weeks	No	24 weeks	12 weeks	No	No	No
	treatment experience		12 wk with Ribavirin Or 24 wk, no Ribavirin			12 wk with Ribavirin Or 24 wk, no Ribavirin			
Genotype 4	treatment naive	48 weeks	12 weeks	12 weeks	No	12 week	12 weeks	No	12 weeks
	treatment experience		12 wk with Ribavirin or 24 wk, no ribavirin	12 wk with Ribavirin or 24 wk, no ribavirin			12 wk with Ribavirin or 24 wk, no ribavirin		12 wk, no Ribavirin if HCV RNA≤800,000 (5.9log) IU/ml or 16 wk with Ribavirin if HCV RNA>800,000 (5.9log) IU/mlb
Genotype 5	treatment naive		12 weeks	12 weeks	No	12 weeks	No	No	No
	treatment experience		12 wk with Ribavirin or 24 wk, no Ribavirin	12 wk with Ribavirin or 24 wk, no Ribavirin					
Genotype 6	treatment naive	48 weeks	12 weeks	12 weeks	No	12 weeks	No	No	No
	treatment experience		12 wk with Ribavirin or 24 wk, no	12 wk with Ribavirin or 24 wk, no					

Table 2 : Summary of recommended preferred regimes with treatment duration, person compensated cirrhosis CPS A

Genotype		Interferon/ Ribavirin	Sofosbuvir/ Daclatasvir	Sofosbuvir/ Ledipasvir	Sofosbuvir/ Ribavirin	Sofosbuvir/ Velpatasvir	Sofosbuvir/ Semiprevir	Ombitasvir/Paritaprevir / Ritonavir/Dasabuvir	Grazoprevir/Elbasvir
Genotype 1a	treatment naive	48 weeks	12 weeks	8-12 weeks	No	12 weeks	No	12 weeks with Ribavirin	12 wk, no Ribavirin ifHCV RNA≤800,000 (5.9log) IU/mlor16 wk withribavirin if HCV RNA>800,000 (5.9log) IU/mlb
	treatment experience		12 wk with Ribavirin or 24 wk, no Ribavirin	12 wk with Ribavirin Or 24 wk, no Ribavirin					
Genotype 1b	treatment naive		12 weeks	12 weeks	No	12weeks	No	12 weeks	12 weeks
	treatment experience								
Genotype 2	treatment naive	24 weeks	12 weeks	No	12 weeks	12 weeks	No	No	No
	treatment experience								
Genotype 3	treatment naive	24 weeks	24 week with Ribavirin	No	24 weeks	12 wk with Ribavirina or 24 wk, no Ribavirin	No	No	No
	treatment experience								
Genotype 4	treatment naive	48 weeks	12 weeks	12 weeks	No	12 week	12 weeks	No	12 weeks
	treatment experience		12 wk with Ribavirin Or 24 wk, no Ribavirin	12 wk with Ribavirin Or 24 wk, no Ribavirin			12 wk with Ribavirin Or 24 wk, no Ribavirin		12 wk, no Ribavirin if HCV RNA ≤800,000 (5.9log) IU/ml or 16 wk with Ribavirin if HCV RNA>800,000 (5.9log) IU/mlb
Genotype 5	treatment naive		12 weeks	12 weeks	No	12 weeks	No	No	No
	treatment experience		12 wk with Ribavirin Or 24 wk, no Ribavirin	12 wk with Ribavirin or 24 wk, no Ribavirin					
Genotype 6	treatment naive	48 weeks	12 weeks	12 weeks	No	12 weeks	No	No	No
	treatment experience		12 wk with Ribavirin or 24 wk, no	12 wk with Ribavirin or 24 wk, no					

Table 3 : Summary of recommended preferred regimes with treatment durations, person decompensated cirrhosis CPS B&C

	Sofosbuvir / Daclatasvir	Sofosbuvir / Ledipasvir	Sofosbuvir / Velpatasvir
Genotype 1	12 weeks with Ribavirin	12 weeks with Ribavirin	12 weeks with Ribavirin
Genotype 2	12 weeks with Ribavirin	No	12 weeks with Ribavirin
Genotype 3	24 weeks with Ribavirin	No	24 weeks with Ribavirin
Genotype 4	12 weeks with Ribavirin	12 weeks with Ribavirin	12 weeks with Ribavirin
Genotype 5	12 weeks with Ribavirin	12 weeks with Ribavirin	12 weeks with Ribavirin
Genotype 6	12 weeks with Ribavirin	12 weeks with Ribavirin	12 weeks with Ribavirin

I. Not Recommended Regime for Patients with Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment; CPS B or C)
• Simeprevir-based regimes
• Paritaprevir-based regimes
• Elbasvir/Grazoprevir-based regimes

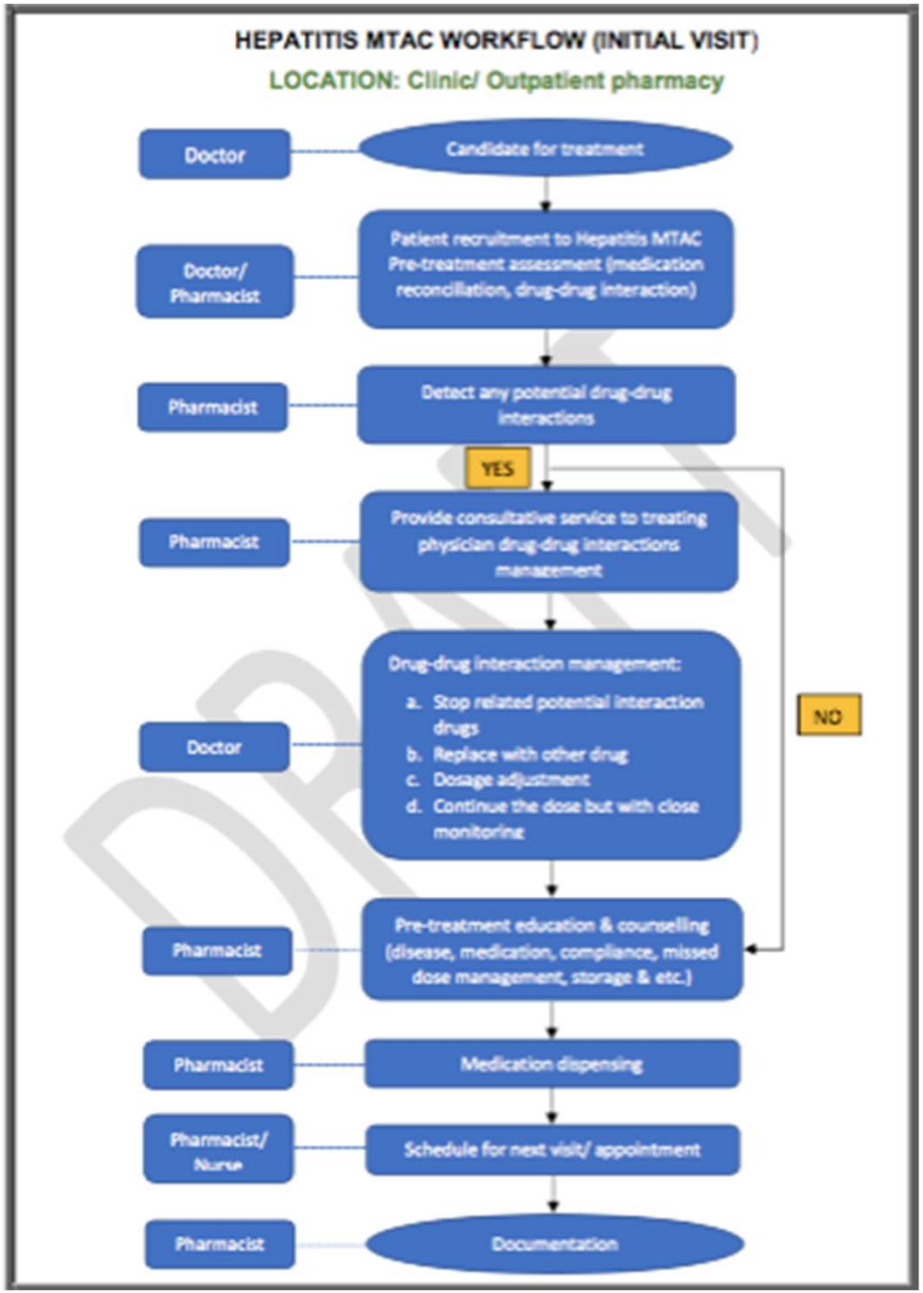
II . Regimes Not Recommended
• Daily Sofosbuvir (400mg) and weight-based ribavirin for 24 weeks
• Peg-IFN/ribavirin with or without sofosbuvir, simeprevir, telaprevir or boceprevir
• Monotherapy with Peg-IFN , ribavirin or direct-acting antiviral

			AASLD 2017	EASL 2016
Genotype 1a	No Cirrhosis	Treatment naïve	12 weeks	12 weeks
		Treatment Exp PR	12 weeks	12 weeks with RBV or 24 without RBV
	Compensated Cirrhosis	Treatment naive	24 weeks ± RBV	12 weeks
		Treatment experience	24 weeks ± RBV	12 weeks with RBV or 24 without RBV
Genotype 1 b	No Cirrhosis	Treatment naïve	12 weeks	12 weeks
		Treatment Exp PR	12 weeks	12 weeks
	Compensated Cirrhosis	Treatment naïve	24 weeks ± RBV	12 weeks
		Treatment Exp PR	24 weeks ± RBV	12 weeks
Genotype 3	No Cirrhosis	Treatment naïve	12 weeks	12 weeks
		Treatment Exp PR	12 weeks	12 weeks with RBV or 24 wks without RBV

Genotype	Treatment naive/ experience	Non cirrhosis	Compensated cirrhosis	Decompensated cirrhosis
Genotype 1a	Treatment naive	12 weeks	12 weeks	12 weeks with RBV
	Treatment experience	12 weeks with RBV or 24 weeks without RBV	12 weeks with RBV or 24 weeks without RBV	12 weeks with RBV
Genotype 1b	Treatment naive	12 weeks	12 weeks	12 weeks with RBV
	Treatment experience	12 weeks	12 weeks	12 weeks with RBV
Genotype 2	Treatment naive	12 weeks	12 weeks	12 weeks with RBV
	Treatment experience	12 weeks	12 weeks	12 weeks with RBV
Genotype 3	**Treatment naive**	12 weeks	24 weeks with RBV	24 weeks with RBV
	Treatment experience	12 weeks with RBV or 24 weeks without RBV	24 weeks with RBV	24 weeks with RBV

Genotype	Treatment naive/ experience	Non cirrhosis	Compensated cirrhosis	Decompensated cirrhosis
Genotype 4	**Treatment naive** **Treatment experience**	12 weeks 12 weeks with RBV or 24 weeks without RBV	12 weeks 12 weeks with RBV or 24 weeks without RB	12 weeks with RBV 12 weeks with RBV
Genotype 5	**Treatment naive** **Treatment experience**	12 weeks 12 weeks with RBV or 24 weeks without RBV	12 weeks 12 weeks with RBV or 24 weeks without RB	12 weeks with RBV 12 weeks with RBV
Genotype 6	**Treatment naive** **Treatment experience**	12 weeks 12 weeks with RBV or 24 weeks without RBV	12 weeks 12 weeks with RBV or 24 weeks without RB	12 weeks with RBV 12 weeks with RBV

Hepatitis C : Screening, testing & treatment guidelines; MOH October 2017
EASL Recommendations on Hepatitis C Treatment 2016


HEPATITIS MTAC WORKFLOW (INITIAL VISIT)
LOCATION: Clinic/ Outpatient pharmacy
Doctor
Candidate for treatment
Doctor/ Pharmacist
Patient recruitment to Hepatitis MTAC Pre-treatment assessment (medication reconciliation, drug-drug interaction)
Pharmacist
Detect any potential drug-drug interactions
YES
NO
Pharmacist
Provide consultative service to treating physician drug-drug interactions management
Doctor
Drug-drug interaction management:
a. Stop related potential interaction drugs
b. Replace with other drug
c. Dosage adjustment
d. Continue the dose but with close monitoring
Pharmacist
Pre-treatment education & counselling (disease, medication, compliance, missed dose management, storage & etc.)
Pharmacist
Medication dispensing
Pharmacist/ Nurse
Schedule for next visit/ appointment
Pharmacist
Documentation

Pre -treatment screening
-Role of physicians

A : Document patient's medical history:

1.Risk Factors for HCV acquisition

2.Medical Comorbidies/extrahepatic manifestations

3.Review concomitant medications including OTC/ HDS/ OCP

4.Cardiology assessment in patient with cardiac co-morbidity for those patients requiring Ribavirin regimen based on the clinician's discretion (ECG, Echocardiography)

5.Co-infections (CHB / RVD)

6.Complication of Liver Disease if cirrhotic

7.Prior Treatment for hepatitis C, types of treatment received previously and type of response :

- ❖Non responders (HCVRNA detected at the end of treatment)
- ❖Relapsers (HCVRNA not detected at the end but detected at any time within 24weeks post treatment
- ❖Treatment discontinuation due to lack of EVR (HCVRNA <1log drop at week 12 on treatment)
- ❖Premature discontinuation due to intolerance adverse effect

B. Perform the baseline screening

1. Confirmatory test / HCV RNA and Genotype
2. Hepatitis B Surface Antigen and Anti HIV Antibody
3. Ultrasound liver - ? presence of HCC in liver cirrhosis
4. Fibrosis score / APRI Score
5. Full Blood Count/Liver Function Test/ Creatinine
6. Coagulation Marker if liver cirrhosis
7. Other relevant investigation based on clinician's discretion

C. Explain on treatment flow and follow-up schedule

Pre treatment screening
- Role of Nurses/ Medical Assistance

1. Vital signs
2. Perform viral Hepatitis notification
3. Perform Hepatitis Education
4. Family planning (esp: Ribarivin Regime)

Pre treatment screening
- Role of Pharmacist

1. Reconcile a complete medication (including prescribed medications, OTC, traditional/herb medication/drink and health supplement) history must be assessed, including start and stop dates.
2. Counter check patient's potential drug-drug interaction profile and provide consultative service to treating physician on drug-drug interaction management.
3. Document any allergies to any medications and their formulations

Treatment initiation- Role of physician

1. Perform symptom directed assessment and Child Pugh Score for cirrhotic patients
2. Perform the laboratory baseline screening : Full Blood Count , Liver Function Test,creatinine,coagulation Marker (if cirrhotic)
3. Other relevant investigations based on clinician's discretion
4. Inform possible side effects, emphasize compliance to medications and follow up
5. If concurrent medications with possible interactions with DAAs : may advise to stop temporarily , change time of administration, advise stop HDS/ OTC medications.
6. Check Vital Signs (by nurse)

Management of drugs with potential interaction

- Stop the particular related drug for the period of treatment (2 weeks prior to treatment/ half life drug should be considered for longer withhold) eg: statin
- Replace the drug with an alternative product without a drug interaction in the same therapeutic class.
- Adapt the dose with a clear monitoring plan
- Dosage adjustment

Example: Daclatasvir -Decrease dose to 30mg: Coadministration with strong CYP3A inhibitors , Increase dose to 90mg: Coadministration with strong CYP3A inducers

Treatment initiation
- Role of pharmacist

- Drug Dispensing (for 4-8 weeks supply)
- Counsel on:

-Adherence

-Missed dose management

-Administration time

-Drug Storage: room temperature (Below 30’C)

-Suggest patient diary card to record each drug intake

-Bring back all balance medications and empty bottle for each visit

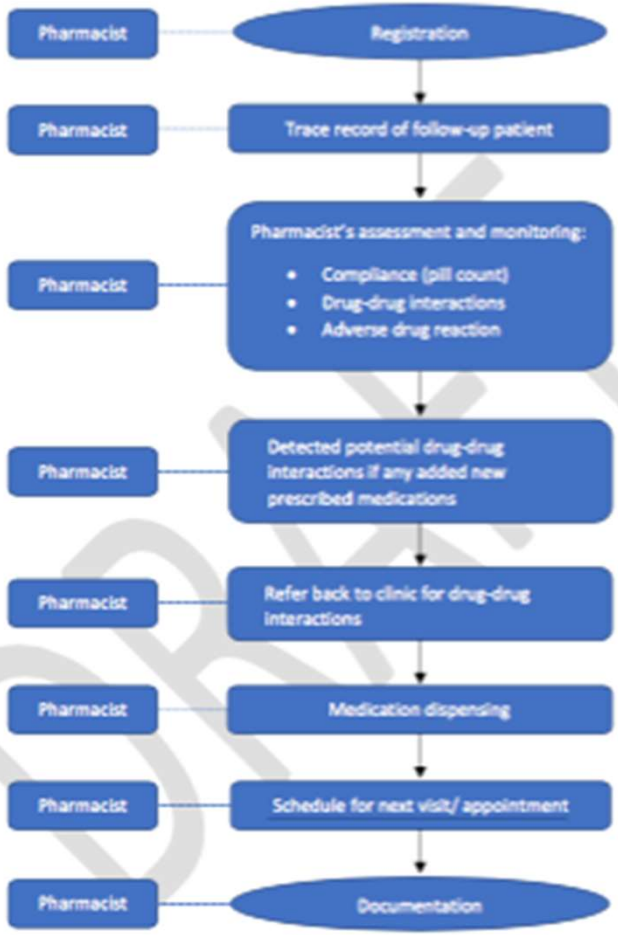
-Use of any medication or herbal/supplement product not prescribed by a licensed physician is prohibited

Follow up visits

	12 Weeks Course	***24 Weeks Course***
Without Ribavirin	*Week 4* *Week 8* *Week 12 (End of treatment)* *Week 24 – (SVR 12 HCV RNA)*	*Week 4* *Week 8* *Week 12* *Week 16* *Week 20* *Week 24 (End of treatment)* *Week 36 (SVR 12 HCV RNA)*
With Ribavirin	*Week 2* *Week 4* *Week 8* *Week 12 (End of treatment)* *Week 24 – (SVR 12 HCV RNA)*	*Week 2* *Week 4* *Week 8* *Week 12* *Week 16* *Week 20* *Week 24 (End of treatment)* *Week 36 (SVR 12 HCV RNA)*

HEPATITIS MTAC WORKFLOW (SUBSEQUENT VISITS)

Location: Clinic/ Outpatient pharmacy



Follow up visits- Role of physician

- Perform symptom directed assessment /look for decompensation if cirrhotic
- Ask and document any side effects / new complaints
- Ask and document any new concurrent medications
- Repeat the laboratory baseline screening
- Full Blood Count / Creatinine / LFT including AST
- INR (if patient cirrhotic)
- Repeat HCV RNA on Week 4 during treatment (optional)
- HCV RNA SVR 12 (12 weeks after completing treatment)

Follow up visits
- Role of pharmacist

- Assess patient's compliance by drug accountability (Form 1)
- Re-ensure patient's compliance on OTC, health supplement/traditional medication
- Screen potential drug-drug interactions if any added new prescribed medications
- Drug Dispensing for 4 weeks supply on week 4 follow up only
- Report all related adverse effects (ADRs) related to Hepatitis C treatment to NPRA
- Reassess patient's knowledge on:

- Adherence
- Missed dose management
- Administration time
- Drug Storage: room temperature (Below 30'C)
- Patient dairy card to record each drug intake
- bring back all balance medications and empty bottle for each visit
- Use of any medication or herbal/ health supplement product not prescribed by a licensed physician is prohibited

Modifications of Ribavirin dose

Haemoglobin level (g/dL)	No cardiac disease	Stable cardiac disease
< 10 .0	Reduce to 600 mg / day	Decrease ≥ 2g/dL during 4 weeks period : reduce to 600 mg/ day (permanent dose reduction)
< 8.5	Discontinue	Hb < 12g/dL despite 4 weeks in reduced dose : discontinue

Post treatment follow up

- Not cirrhotic , achieve SVR12 : Optional to repeat HCV RNA in 1 year ,and may discharge . Patients who achieve SVR but remains abnormal liver function test should be evaluated for other causes of transaminitis.

- Cirrhotic , achieve SVR12: Continue follow up for HCC survellance : 6 monthly US liver and blood for AFP. Endoscopy for OV survellance

- No SVR12 : Should monitor for progression of liver disease and considered for retreatment once alternative treatment is available

SUMMARY

- All treatment-naive and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV must be considered for therapy
- Availability of DAAs options plays a big role in choosing and strategizing treatment options
- However, caution should be exercised when using such agents due to known drug–drug interactions.
- In dealing with special population such as HCV/HIV coinfection / ESRD patients , a close collaboration with HIV specialist/ Hepatologist / Gastroenterologist is recommended when treating these individuals.

References:

1. EASL Recommendation on Treatment of hepatitis C 2018. J Journal (2018)

2. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j. jhep.2016.09.001

3. AASLD 2017 HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis .

4. Hepatitis C - Screening, Testing and Treatment Guidelines, Ministry of Health,1st edition October 2017

QUIZ 1

- Name 3 medication that can be used to treat Hepatitis C

QUIZ 2

- Sofosbuvir can be used for patients with ESRD on dialysis

QUIZ 3

- Namakan 3 hospital yang membekalkan ubat Hepatitis C