Viral Hepatitis Cases

23/02/2018

Greenlane Summer Symposium

Greenlane Medical Specialists

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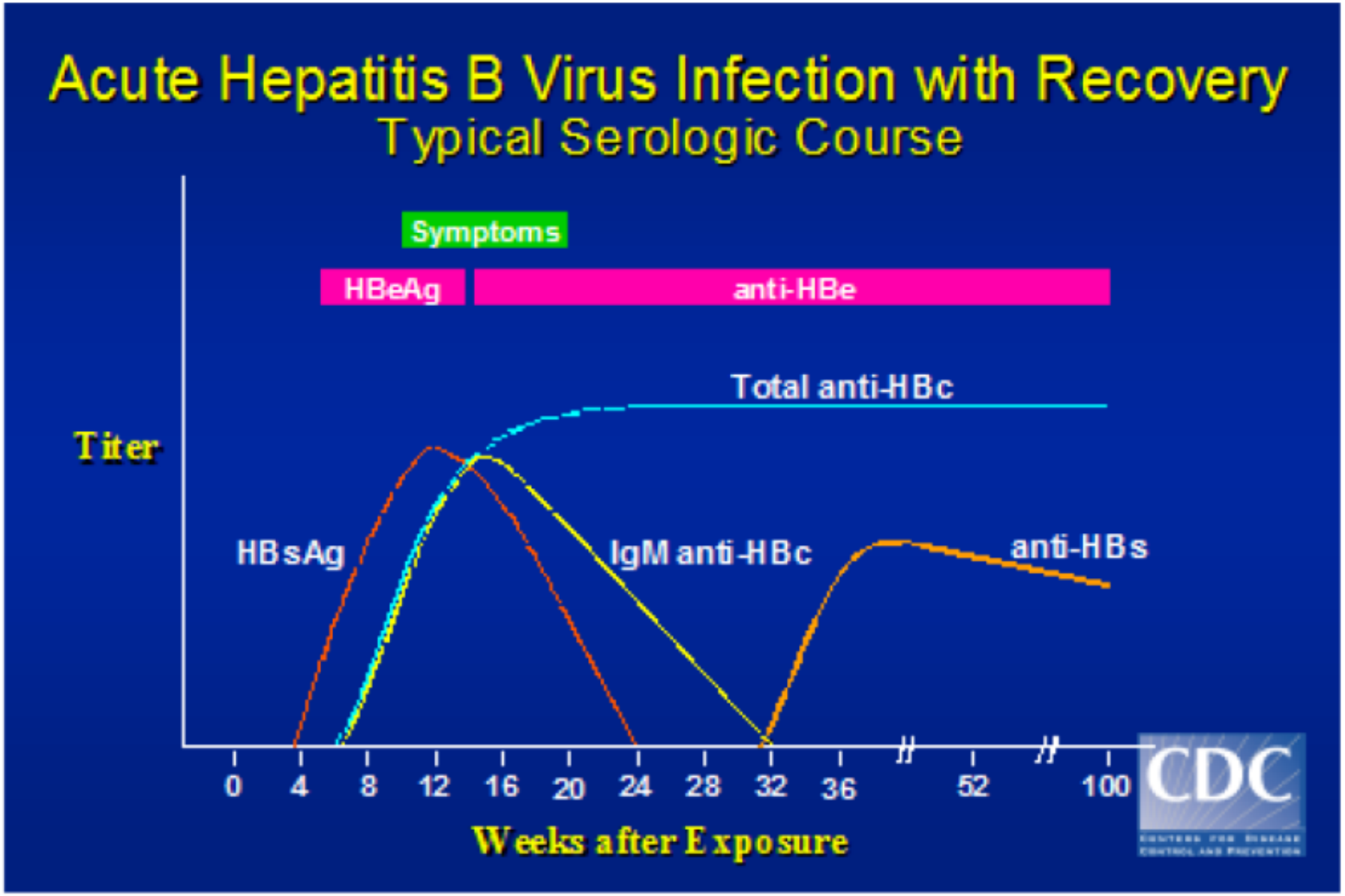
Greenlane
Medical Specialists

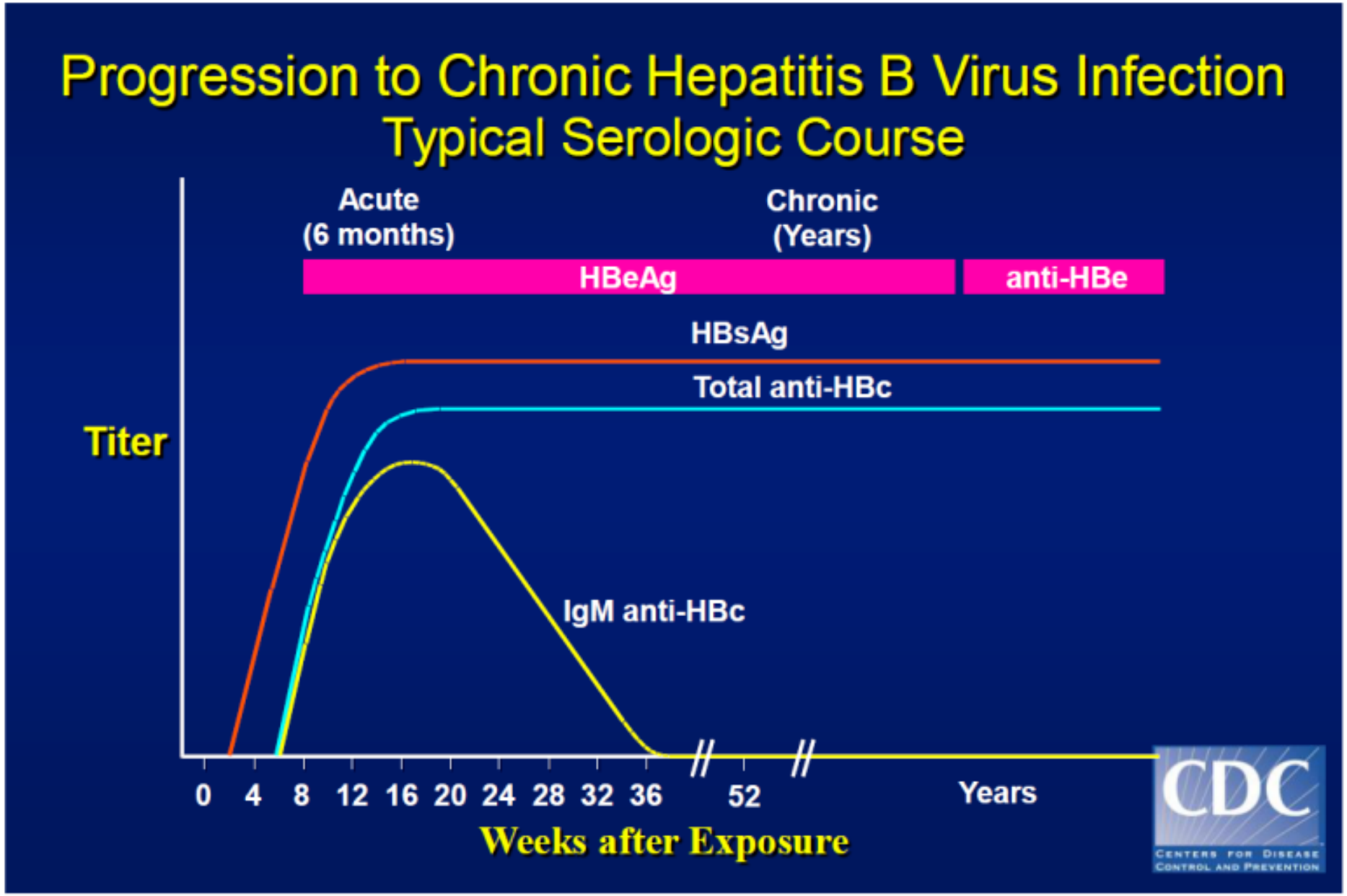
Case 1 HBV

- 34M Presents with symptoms suggestive of an STD
- Blood tests show:
  - Normal LFTs
  - HBsAg positive

  Q: What is the next step?


Acute Hepatitis B Virus Infection with Recovery
Typical Serologic Course
Symptoms
HBeAg
anti-HBe
Total anti-HBc
Titer
HBsAg
IgM anti-HBc
anti-HBs
0
4
8
12
16
20
24
28
32
36
52
100
Weeks after Exposure
CDC

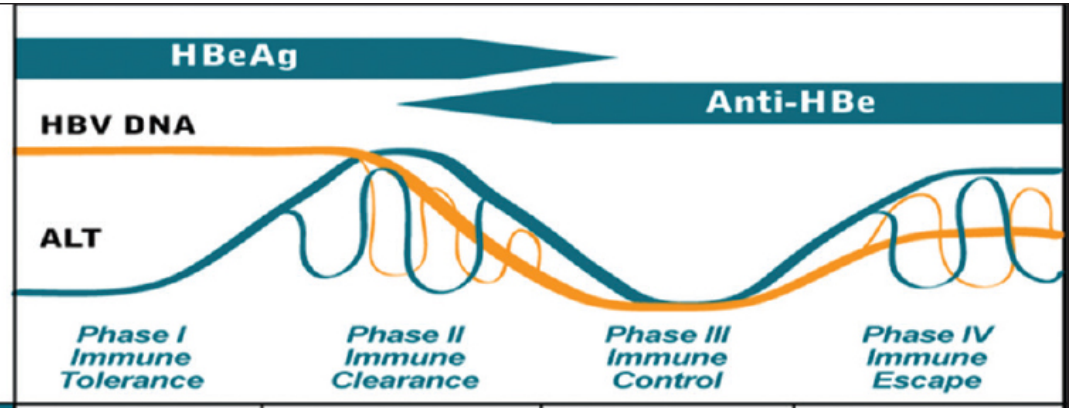
Progression to Chronic Hepatitis B Virus Infection
Typical Serologic Course



Hepatitis B Serology

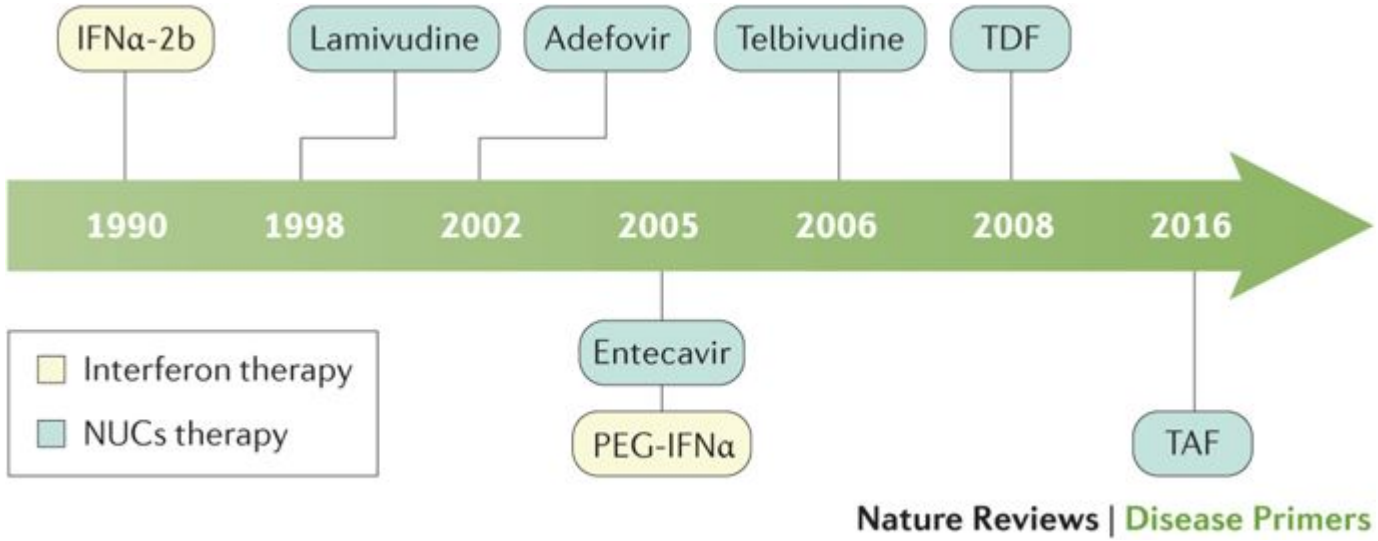
Tests	Results	Interpretation
HBsAg **anti-HBc** **anti-HBs**	negative negative negative	Susceptible
HBsAg **anti-HBc** **anti-HBs**	negative positive positive	Immune due to natural infection
HBsAg **anti-HBc** **anti-HBs**	negative negative positive	Immune due to hepatitis B vaccination
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive positive negative	Acutely infected
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive negative negative	Chronically infected
HBsAg **anti-HBc** **anti-HBs**	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. “Low level” chronic infection 4. Resolving acute infection

Chronic Hepatitis B

				
HBsAg	> 6 months	> 6 months	> 6 months	> 6 months
HBeAg	+	+	–	–
Anti-HBe	–	Spontaneous seroconversion to anti-HBe may occur	+	+
ALT	Persistently normal	Persistently or intermittently elevated	Persistently normal	Persistently or intermittently elevated
HBV DNA	≥ 20,000 IU / mL	Persistently or intermittently ≥ 20,000 IU / mL	< 2000 IU / mL	Persistently or intermittently ≥ 2,000 IU / mL
Liver Histology	Minimal or mild hepatitis Usually no fibrosis	Inflamation score ≥ 4 Fibrosis: + / -	Inflammation score < 4 Fibrosis: + / -	Inflammation score ≥ 4 Fibrosis: +

Chronic Hepatitis B Treatment

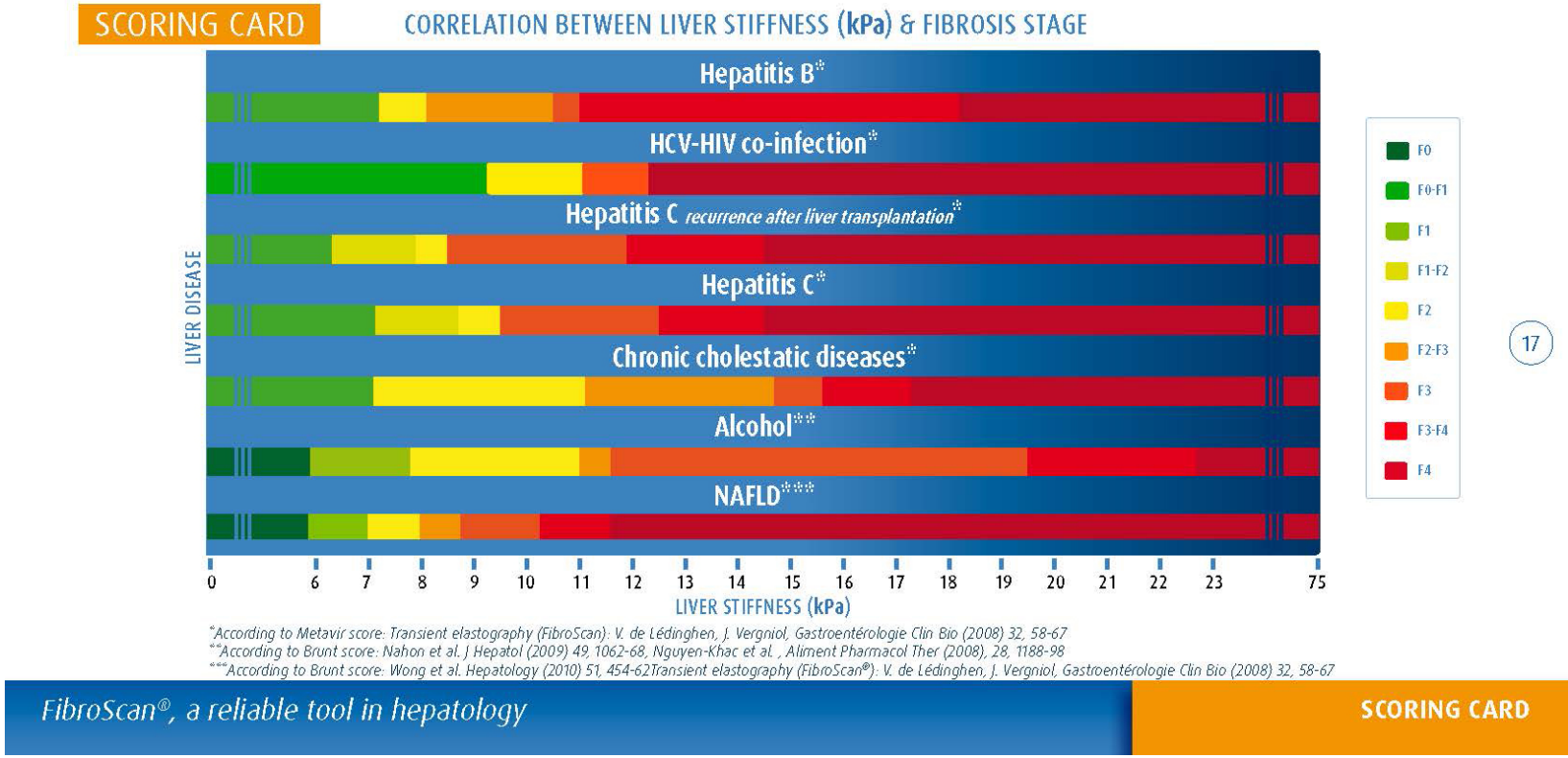
- Entecavir first line – now $50 per month
- Tenofovir – women of child bearing age $38 per month



Hepatitis B

- Adults – Mainly acute infection 95% cure rate
- Children – Mainly Chronic 95% chronic infection
- Chronic – S Ag positive > 6 months
- Treat if ALT abnormal especially if Fibroscan abnormal

Fibroscan



- $350
- Covered by all insurance companies except Southern Cross

Case 2 HCV

- 45M Truck Driver
- No fixed abode
- Previous IVDU last used 12 months ago
- Admitted with abdominal pain and deranged LFTs
- CT shows nodular liver and pancreatic cystic lesion
- INR normal, Albumin normal, Platelets normal
- How should we manage him?

Looking at hepatitis C in New Zealand
(estimated numbers)

An estimated
50,000 PEOPLE
have hepatitis C
in New Zealand

20,000 APPROX
have been diagnosed with
hepatitis C

11,000 APPROX
could have a diagnosis of
hepatitis C - genotype 1, and can
access funded treatment with
Viekira Pak through their GP in
the community right now

Just over
2,000 PEOPLE
with genotype 1 have had
funded treatment

Which means
9,000
people haven't accessed
funded treatment yet

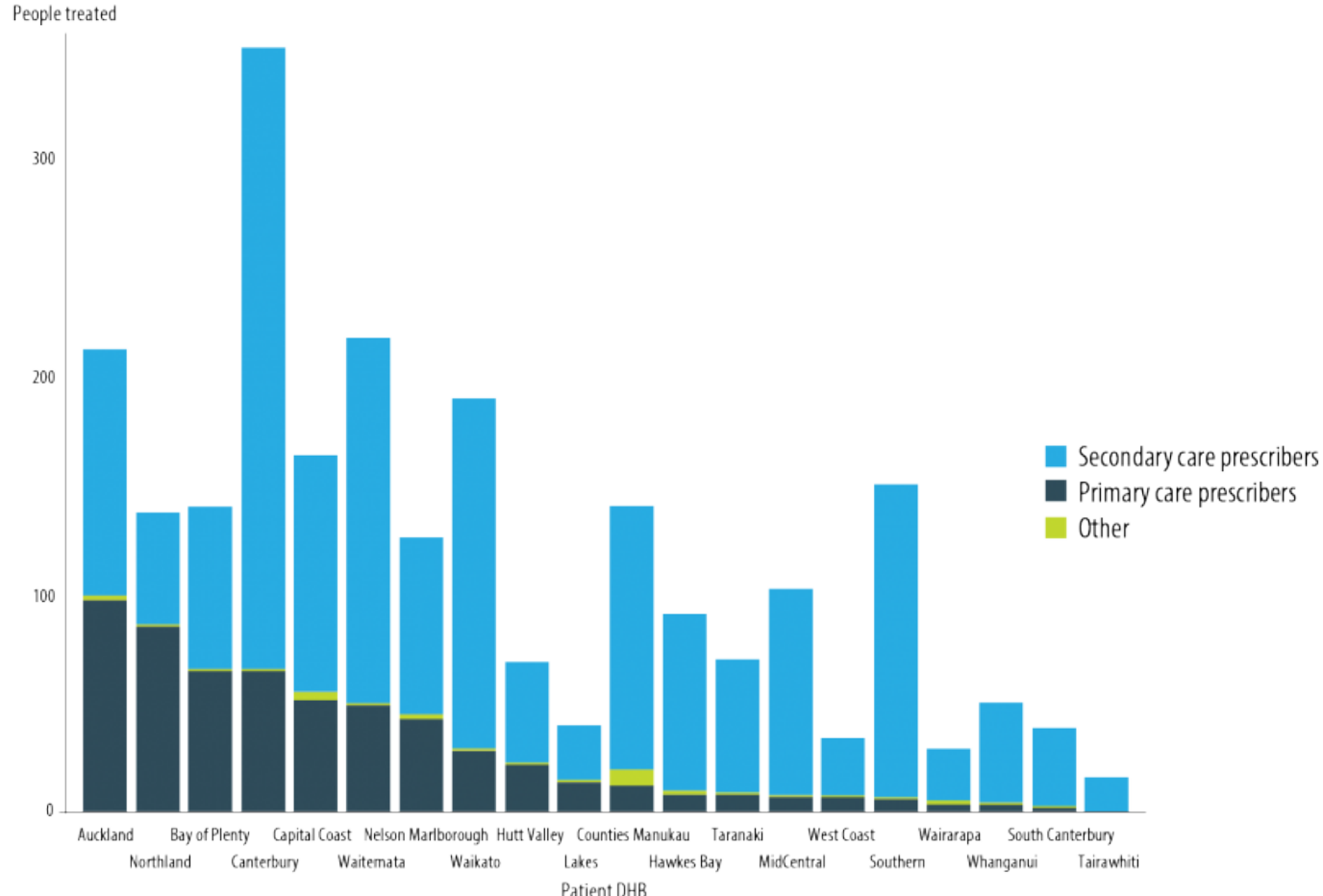
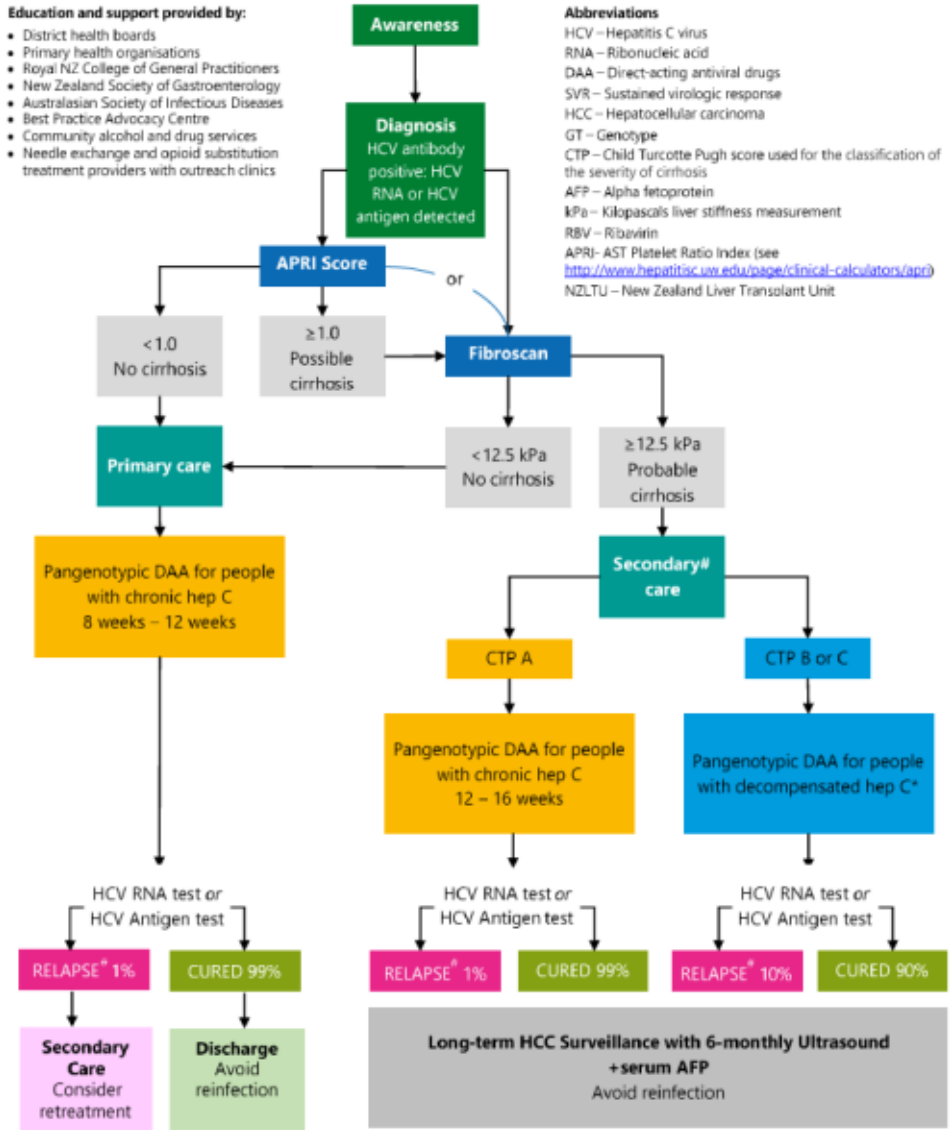


Figure one: Clinical pathway for hepatitis C based on integrated primary and secondary services



Maviret

- Pangenotypic
- Compensated Cirrhotic and Non cirrhotic

MAVIRET will be funded in the community and DHB hospitals without restrictions for all compensated patients infected with HCV regardless of genotype, including those with compensated cirrhosis and those with HIV infection. It will replace VIEKIRA PAK in GT 1 patients.

1. Treatment naïve non cirrhotic patients infected with HCV GT 1-6 will receive 3 tablets once daily for 8 weeks
2. Treatment naïve cirrhotic patients infected with HCV GT 1-6 will receive 3 tablets once daily for 12 weeks
3. Interferon-experienced non cirrhotic patients infected with HCV GT 1, 2, 4, 5, or 6 will receive 3 tablets once daily for 8 weeks
4. Interferon-experienced cirrhotic patients infected with HCV GT 1, 2, 4, 5, or 6 will receive 3 tablets once daily for 12 weeks
5. Interferon-experienced non cirrhotic patients infected with HCV GT 3 will receive 3 tablets once daily for 16 weeks
6. Interferon-experienced cirrhotic patients infected with HCV GT 3 will receive 3 tablets once daily for 16 weeks.

DOSING GUIDE[1]

Recommended MAVIRET treatment duration for patients without prior treatment for hepatitis C

GENOTYPE	NO CIRRHOSIS	CIRRHOSIS‡
GT 1–6	8 weeks	12 weeks

Recommended MAVIRET treatment duration for patients who have previously failed prior therapy*

*peg-IFN + ribavirin +/- sofosbuvir, or sofosbuvir + ribavirin, or any of these in combination with a protease inhibitor.[1]

GENOTYPE	NO CIRRHOSIS	CIRRHOSIS‡
GT 1, 2, 4–6 NS5A-INHIBITOR NAÏVE	8 weeks	12 weeks
GT 1, 2, 4–6 NS5A-INHIBITOR EXPERIENCED^	16 weeks	16 weeks
GT 3 ANY PREVIOUS EXPERIENCE	16 weeks	16 weeks

Introduction

- MAVIRET approval was based on clinical trial data in over 2,300 patients including placebo and active-controlled studies
- MAVIRET is a fixed-dose combination of glecaprevir, an HCV NS3/4A protease inhibitor, and pibrentasvir, an HCV NS5A inhibitor, and is indicated for the treatment of patients with chronic HCV GT 1, 2, 3, 4, 5 or 6 infection without cirrhosis and with compensated cirrhosis (Child-Pugh A)

Glecaprevir (GLE)
pangenotypic NS3/4A protease inhibitor

Pibrentasvir (PIB)
Pangenotypic NS5A inhibitor

MAVIRET is indicated for the treatment of adult patients with chronic HCV GT 1, 2, 3, 4, 5 or 6 infection without cirrhosis and with compensated cirrhosis (Child-Pugh A)

GT=genotype. HCV=hepatitis C virus. NS=non-structural protein.
MAVIRET Data Sheet. Available at www.medsafe.govt.nz

Formulation & Packaging

- Co-formulated, film-coated tablet of glecaprevir (100mg) and pibrentasvir (40mg)
- **Recommended oral dose is 3 tablets taken once daily with food**
- Tablets should be taken whole and not chewed, crushed or broken

Daily blister sheet

Weekly carton

Monthly carton (28 Days)

MAVIRET Data Sheet. Available at www.medsafe.govt.nz

Registrational trials in >2,300 adults with HCV GT 1-6

		Population	N	Treatment	Prior Treatment*	Cirrhosis Status
Phase 2	MAGELLAN-I	GT1, 4	113	GLE/PIB for 12 or 16 weeks	DAA-exp	NC, CC
	SURVEYOR-I	GT 1, 4, 5, 6	66	GLE/PIB for 8 or 12 weeks	TN, TE	NC
	SURVEYOR-II	GT2–6	590	GLE/PIB for 8, 12, or 16 weeks	TN, TE	NC, CC
Phase 3	ENDURANCE-1	GT1	703	GLE/PIB for 8 or 12 weeks	TN, TE	NC
	ENDURANCE-2	GT2	302	GLE/PIB for 12 weeks vs PBO	TN, TE	NC
	ENDURANCE-3	GT3	505	GLE/PIB for 8 or 12 weeks; DCV+SOF for 12 weeks	TN	NC
	ENDURANCE-4	GT4, 5, 6	121	GLE/PIB for 12 weeks	TN, TE	NC
Special Populations	EXPEDITION-1	GT1, 2, 4–6; CC	146	GLE/PIB for 12 weeks	TN, TE	CC
	EXPEDITION-4	GT1–6; CKD	104	GLE/PIB for 12 weeks	TN, TE	NC, CC

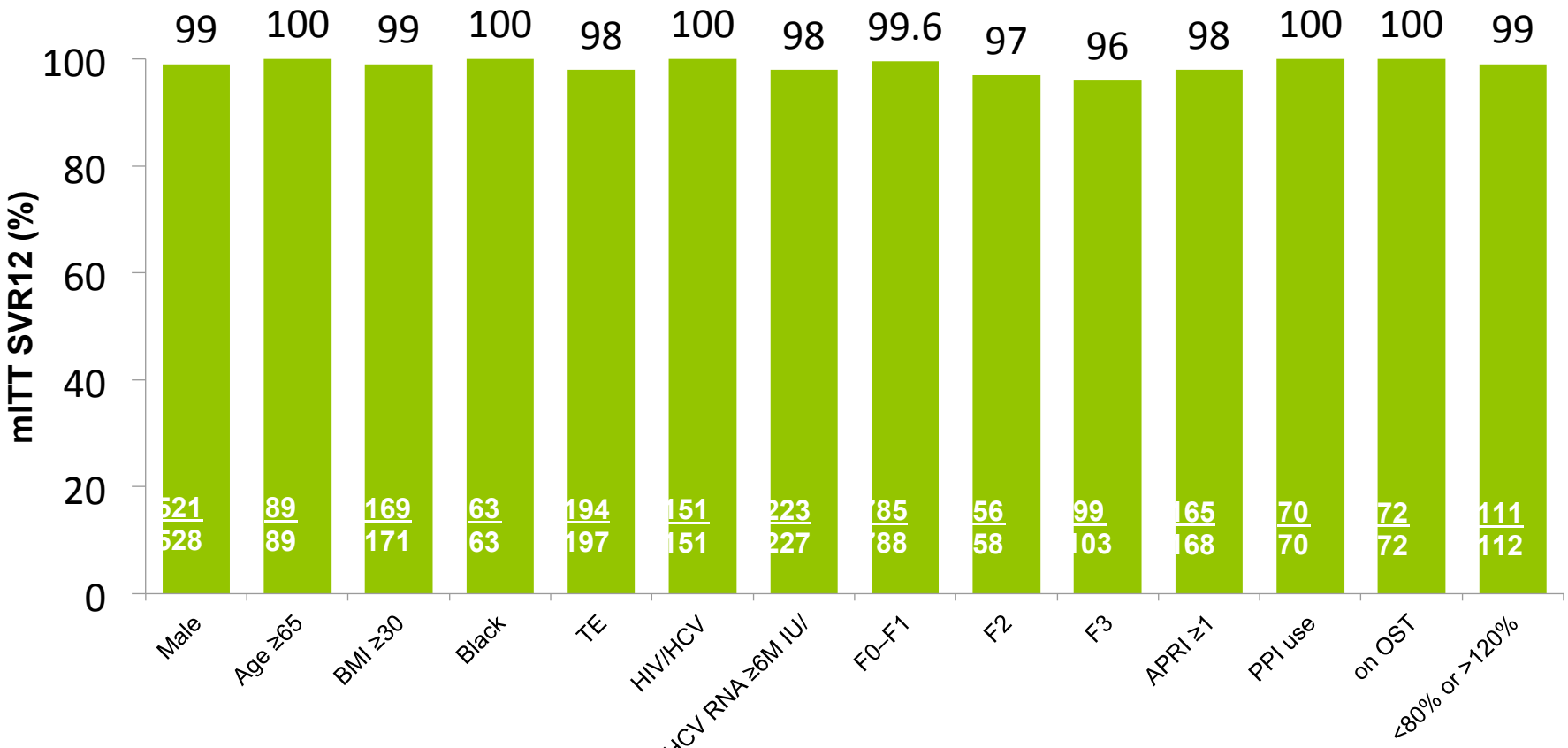
Sustained virologic response (SVR12), defined as HCV RNA below the lower limit of detection at 12 weeks post end-of-treatment, was a primary efficacy endpoint of all studies.

HCV=hepatitis C virus. GT=genotype. GLE/PIB=glecaprevir/pibrentasvir. DAA=direct-acting antiviral. NC=noncirrhotic. CC=compensated cirrhosis. TE=treatment-experienced. TN=treatment-naïve. PBO=placebo. DCV=daclatasvir. SOF=sofosbuvir. CKD=chronic kidney disease. SVR=sustained virologic response. RNA=ribonucleic acid.

MAVIRET Data Sheet. Available at www.medsafe.govt.nz

Integrated Subgroup Analysis of Treatment-naive Non-cirrhotic Patients with HCV GT 1–6

8 weeks of MAVIRET treatment (mITT)



High SVR12 was achieved irrespective of baseline patient and viral characteristics

APRI=aspartate aminotransferase to platelet ratio. BMI=body mass index. GT=genotype. HCV=hepatitis C virus. HIV=human immunodeficiency virus. mITT=modified ITT (excludes patients with non virologic failure). OST=opioid substitution therapy. pegIFN=peginterferon. PPI=proton pump inhibitor. RBV=ribavirin. RNA=ribonucleic acid. SVR=sustained virologic response. SVR12=HCV RNA below the lower limit of detection at 12 weeks post end-of-treatment. TE=treatment experienced. <80% or >120% compliance measured by pill count with adherence defined as taking between ≥80% and ≤120% of the assigned pills at treatment visits at week 4 and week 8.

MAVIRET Data Sheet. Available at www.medsafe.govt.nz
Puoti M et al. J Hepatol 2018; doi: 10.1016/j.hep.2018.03.007

Safety & Tolerability

Adverse events observed in ≥5% of approximately 2,300 patients who received 8, 12 or 16 weeks of MAVIRET in Phase 2 and 3 clinical studies

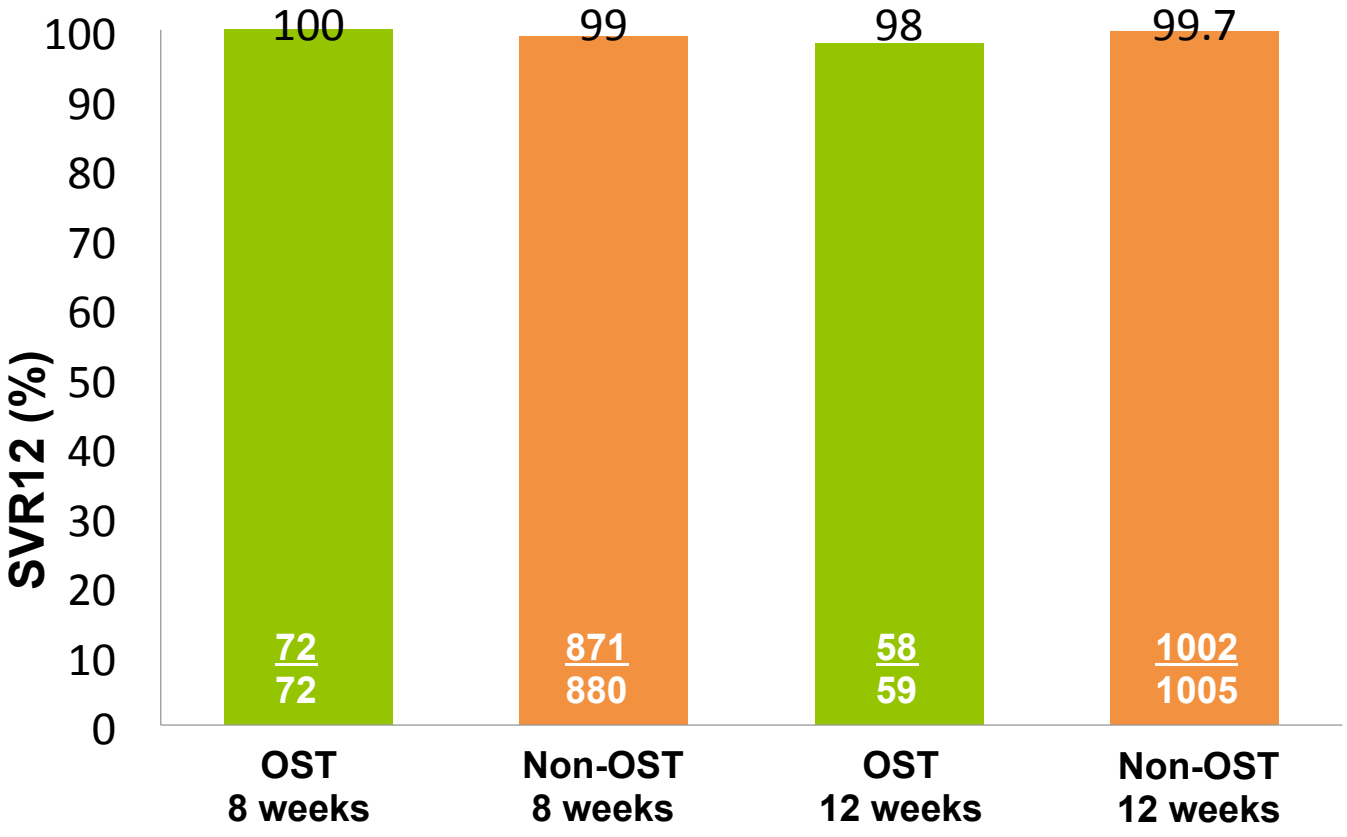
Adverse Event	MAVIRET (8, 12 or 16 weeks) N=2265	Placebo (12 weeks) N=100
Headache	13.2%	6%
Fatigue	11.4%	8%
Nausea	7.6%	2%

- The rate of adverse events in patients receiving MAVIRET (8, 12 or 16 weeks) was similar to those who received placebo
- The proportion of patients treated with MAVIRET who permanently discontinued treatment due to adverse events was 0.1%
- The type and severity of adverse events in patients with cirrhosis were overall comparable to those seen in patients without cirrhosis

MAVIRET Data Sheet. Available at www.medsafe.govt.nz

Patients on Opioid Substitution Therapy

Integrated sub-group analysis of nine clinical trials, including non-cirrhotic and cirrhotic patients treated for 8 or 12 weeks of MAVIRET



Concomitant treatment with opioid substitution therapy had no effect on SVR

OST=opioid substitution therapy, SVR=sustained virologic response.

Puoti M et al. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.007

SPECIAL POPULATIONS

Paediatric population

- The safety and efficacy of MAVIRET in children and adolescents aged less than 18 years have not yet been established. No data are available.

Elderly patients

- No dose adjustment of MAVIRET is required in elderly patients.

Patients with renal impairment

- No dose adjustment of MAVIRET is required in patients with any degree of renal impairment, including patients on dialysis

Patients with hepatic impairment

- No dose adjustment of MAVIRET is required in patients with mild hepatic impairment (Child-Pugh A) MAVIRET is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and is contraindicated in patients with severe hepatic impairment (Child-Pugh C).

Liver or kidney transplant patients

- MAVIRET may be used for a minimum of 12 weeks in liver or kidney transplant recipient. A 16-week treatment duration should be considered in patients who are NS5A inhibitor-experienced or genotype 3-infected transplant patients who are treatment experienced.

MAVIRET Data Sheet. Available at www.medsafe.govt.nz

Contraindications & warnings & precautions

- **Contraindications**
  - **Severe hepatic impairment (Child Pugh C)**
  - **Concomitant use with atazanavir containing products, rifampicin**
  - **Hypersensitity to the active substance or any of the excipients**

- **Warnings & Precautions**
  - **HBV co-infection** - MAVIRET has not been studied in patients with HCV/HBV coinfection. Screening for current or past HBV infection, including testing for HBV surface antigen (HBsAg) and HBV core antibody (anti-HBc), should be performed in all patients before initiation of treatment. Patients with serologic evidence of current or past HBV infection should be monitored and treated according to current clinical practice guidelines to manage potential HBV reactivation. Consider initiation of HBV antiviral therapy, if indicated
  - **Liver Transplant** – MAVIRET may be used for a minimum of 12 weeks in liver transplant recipients. A longer treatment duration should be considered in patients who are NS5A inhibitor-experienced or GT 3-infected patients who are treatment experienced
  - **Hepatic Impairment** – MAVIRET is not recommended in patients with moderate hepatic impairment (Child Pugh B) and is contraindicated in patients with severe hepatic impairment (Child Pugh C)
  - **Drug-Drug Interactions** – Co-administration of MAVIRET is not recommended with several medicinal products (dabigatran, carbamazepine, St John's Wort, darunavir, efavirenz, lopinavir/ritonavir, atorvastatin, lovastatin, simvastatin, stable ciclosporin >100mg/day, ethinyloestradiol)
  - **Lactose intolerence** – MAVIRET contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

MAVIRET Data Sheet. Available at www.medsafe.govt.nz

Pregnancy and breastfeeding

Pregnancy

- There are no or limited data from the use of glecaprevir or pibrentasvir in pregnant women.
- Animal studies with glecaprevir or pibrentasvir do not indicate direct harmful effects on reproductive toxicity. Maternal toxicity in the rabbit precluded evaluation of glecaprevir at clinical exposures. As a precautionary measure, MAVIRET use is not recommended in pregnancy.

Breastfeeding

- It is unknown whether glecaprevir or pibrentasvir are excreted in human milk. Available pharmacokinetic data in animals have shown excretion of glecaprevir and pibrentasvir in milk, and a risk to newborns or infants cannot be excluded. Therefore, a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from MAVIRET therapy, taking into account the benefits of breastfeeding for the child and the benefit of therapy for the woman.

MAVIRET Data Sheet. Available at www.medsafe.govt.nz

OVERVIEW DRUG INTERACTIONS

- All direct-acting antivirals interact with drug metabolising enzymes or transporters.
  - Glecaprevir and pibrentasvir are substrates of P-gp and/or BCRP transporters.
  - Glecaprevir is a substrate of OATP1B1/3 transporters.
  - Co-administration of MAVIRET with medicinal products that inhibit hepatic P-gp, BCRP, or OATP1B1/3 may increase the plasma concentrations of glecaprevir and/or pibrentasvir.
  - Co-administration of MAVIRET with medicinal products that induce P-gp/CYP3A may decrease plasma concentrations of glecaprevir and pibrentasvir.
- MAVIRET undergoes hepatic metabolism.
- All patients with hepatitis C should undergo a careful medicines review before treatment
- Many drug interactions are not clinically relevant, or can be managed by monitoring and /or dose adjustment. Others are contraindicated, and should be stopped or switched to alternatives
- There is no dose adjustment for MAVIRET itself
- During each on treatment follow-up, ask the patient to tell you about any other medicines they are taking, including recreational drugs and any remedies they buy without a prescription from the pharmacy, supermarket or health food store

MAVIRET Data Sheet. Available at www.medsafe.govt.nz

Interactions*

Contraindicated
Atazanavir
Rifampicin

***This is not an exhaustive list please refer to the full data sheet on www.medafe.govt.nz & The University of Liverpool Hep Drug Interactions www.hep-druginteractions.org. In some instances, the recommendations in the data sheet may differ to those on the University of Liverpool Hep Drug Interactions website.**

Not Recommended – may lead to increased concentrations of GLE/PIB
Ciclosporin >100mg
Darunavir
Lopinavir/ritonavir
Not Recommended – may lead to reduced therapeutic effect of GLE/PIB
Carbamazepine
Efavirenz
St John's Wort
Not Recommended – may increase concentrations of co-administered drug
Atrovastatin†
Dabigatran
Lovastatin†
Simvastatin†
Not Recommended – due to risk of ALT elevations
Ethinyloestradiol

GLE/PIB=glecaprevir/pibrentasvir. ALT=alanine aminotransferase.
†Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis.

MAVIRET Data Sheet. Available at www.medsafe.govt.nz;
University of Liverpool. HEP drug interactions. Available at: www.hep-druginteractions.org. Accessed: Jan 2019.

No expected interaction with OST (Opioid Substitution Treatment) or the majority of Illicit drugs

OST	Interaction
Methadone	No interaction expected
Buprenorphine	No interaction expected
ILLICIT DRUGS	**Interaction**
Cannabis	No interaction expected
Cocaine	No interaction expected
Lysergic acid diethylamide (LSD)	No interaction expected
MDMA (Ecstasy)	No interaction expected
Mephedrone	No interaction expected
Amphetamine	No interaction expected
Methamphetamine	No interaction expected
Phencyclidine	No interaction expected
Gamma-hydroxybutyrate (GHB)	Potential interaction

This is not an exhaustive list. Please visit www.hep-druginteractions.org to check all drug–drug interactions for HCV treatments.

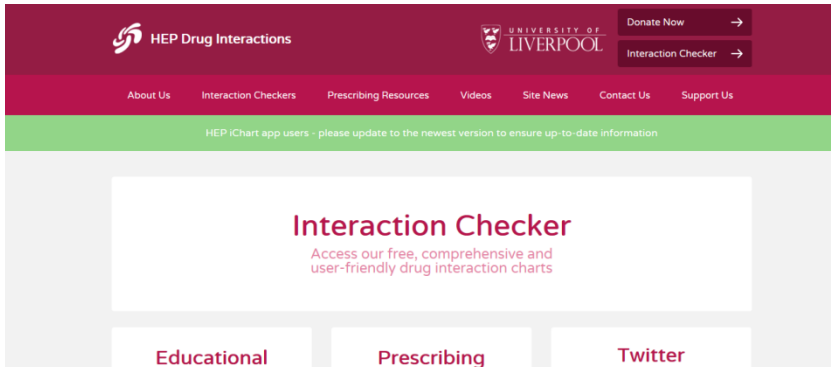
MAVIRET Data Sheet. Available at www.medsafe.govt.nz;
University of Liverpool. HEP drug interactions. Available at: hep-druginteractions.org. Accessed: Jan 2019.

Where to Find Information on Interactions

1. **Medsafe-approved Data Sheet**: www.medsafe.govt.nz
   - Please first refer to the New Zealand label for all contraindicated medications, drug interactions, and precautions

2. **University of Liverpool website**: http://hep-druginteractions.org/
   - Searchable by alphabetical list of drugs (A-Z), by drug class, or by trade name. A mobile app is also available

3. **AbbVie Medical Information:** 0800 900 030, medinfoanz@abbvie.com
   - AbbVie can provide creditable clinical and scientific information regarding MAVIRET



Summary

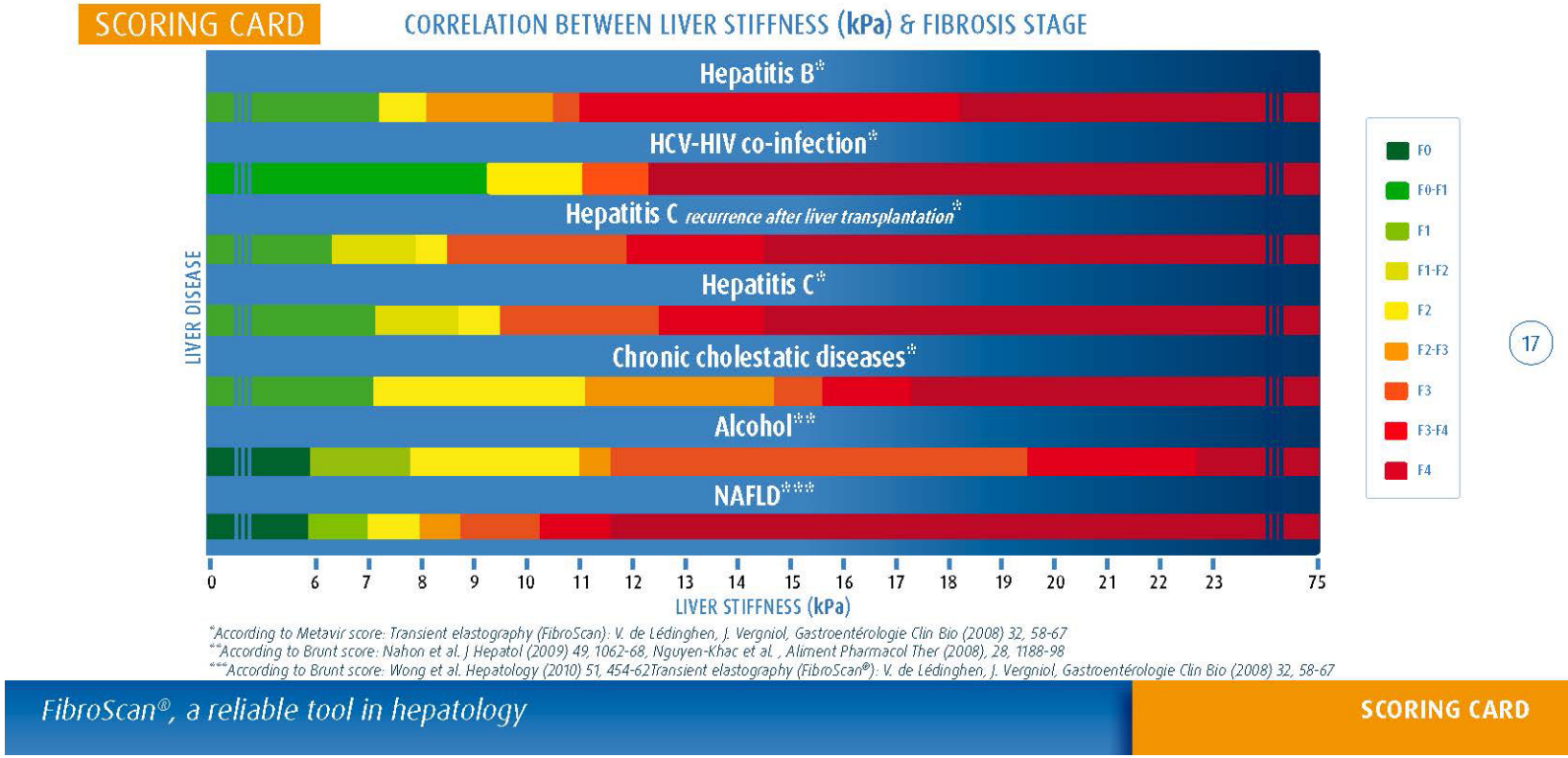
- MAVIRET is indicated for adult patients with HCV genotypes 1-6 with or without compensated cirrhosis (Child-Pugh A)
    - includes patients with HCV/HIV-1 co-infection, any stage of renal impairment (including those on dialysis), and HCV/HBV co-infection
- Dosing is 3 tablets taken orally, once daily; there is no dose adjustment for MAVIRET itself
- In phase 2 and 3 clinical studies, the adverse events observed in ≥5% of approximately 2,300 patients were headache, fatigue, and nausea
- Many drug interactions are not clinically relevant, or can be managed by monitoring and /or dose adjustment. Others are contraindicated, and should be stopped or switched to alternatives

Harvoni

- For Decompensated Liver Disease
- Managed in secondary care

From 1 July 2016 until 12 June 2017, access to HARVONI was restricted to patients with decompensated cirrhosis with a Model for End-Stage Liver Disease (MELD) score of 15 or greater patients who were pre or post liver transplant and patients with cryoglobulinaemia. On 12 June 2017, the MELD threshold for patients with decompensated cirrhosis to access HARVONI was lowered from 15 to 12 in order to further widen access for this special population and increase salvage from death or transplantation. In December 2017, the criteria were widened further to include any patient who has decompensated cirrhosis (Child-Pugh class B or C) regardless of MELD score. To date, 161 patients with decompensated cirrhosis have been treated with HARVONI±RBV.

Fibroscan

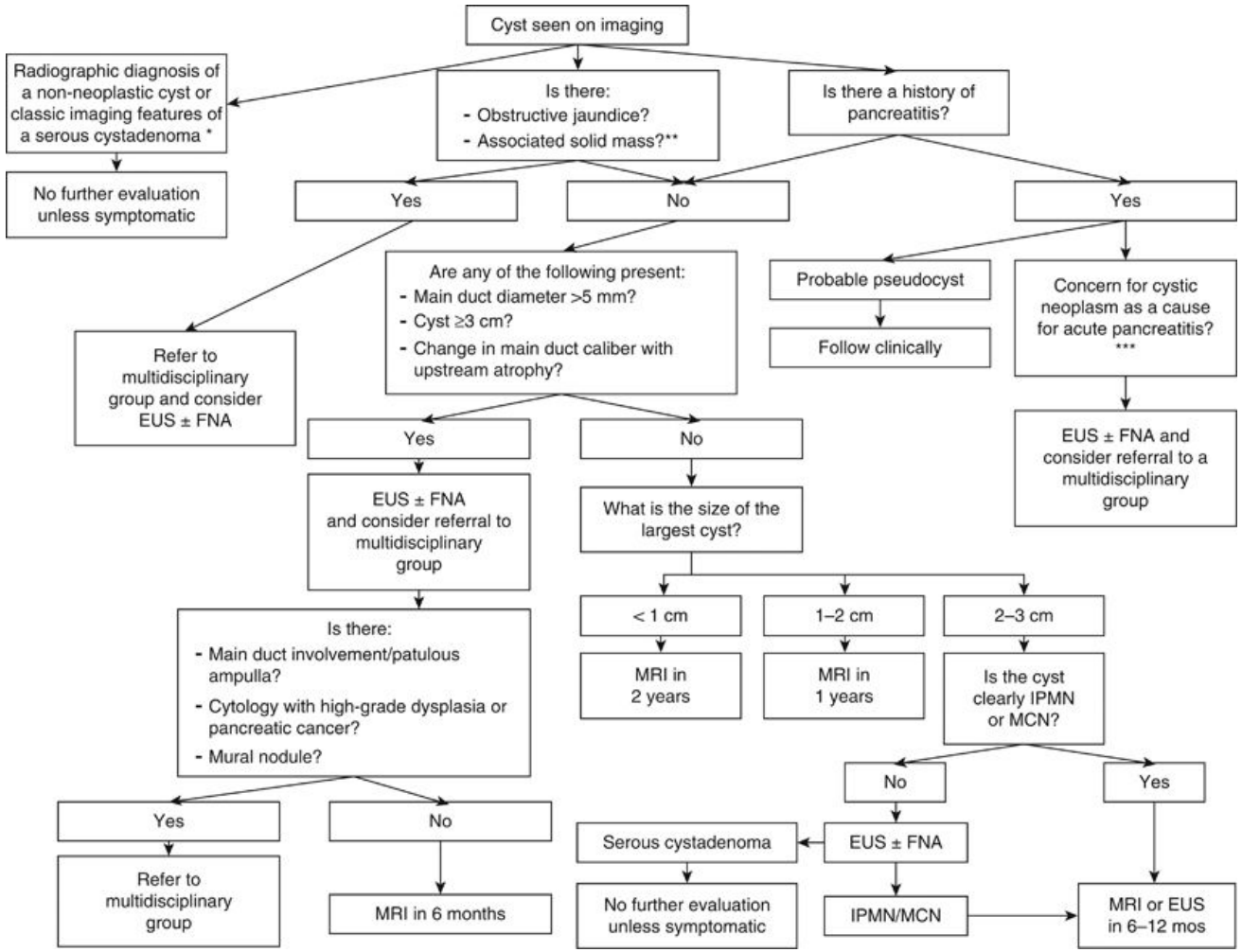


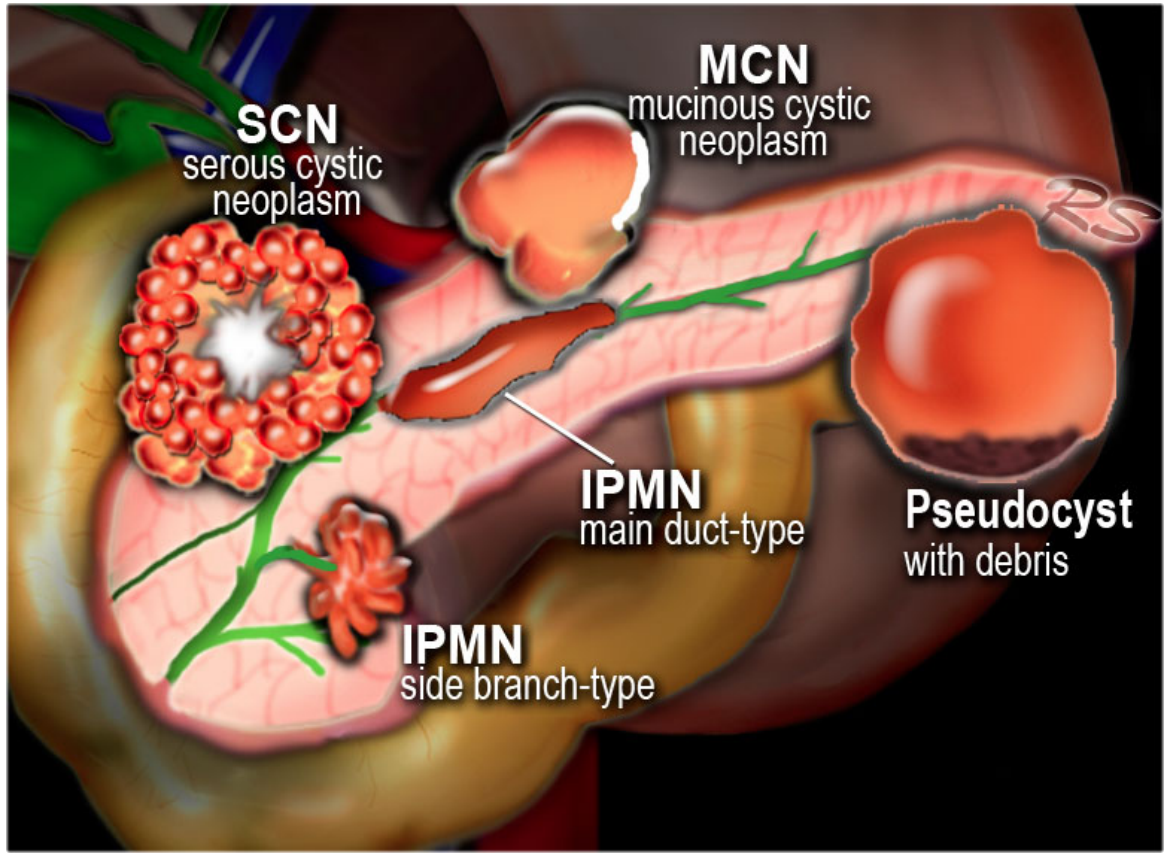
- $350
- Covered by all insurance companies except Southern Cross

Treatment

- Normal LSM
- Treated with 8 weeks of Maviret
- Dispensed at certain pharmacies

Pancreatic Cysts





Endoscopic Ultrasound