Recommendations for the Management of HCV infection: Australian (and International) Guidelines

Professor Alex Thompson
St Vincent's Hospital Melbourne
30th September 2016

ST VINCENT'S HEALTH AUSTRALIA
UNDER THE STEWARDSHIP OF MARY AIKENHEAD MINISTRIES

THE UNIVERSITY OF MELBOURNE

GESA Gastroenterological Society of Australia
ala Australian Liver Association

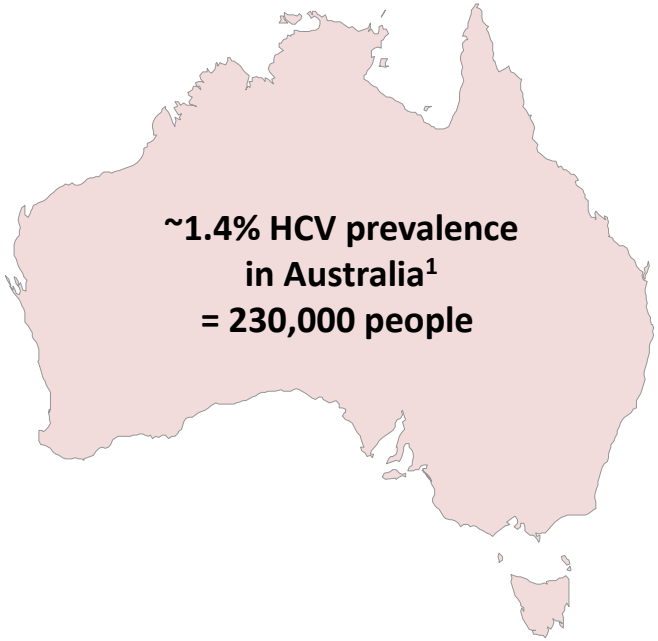
Acknowledgement to Country

- We recognise the traditional custodians of the land and sea on which we live and work

Disclosures

- Advisory board member - Gilead, Abbvie, Bristol-Myers Squibb (BMS), Merck, and Roche Diagnostics
- Speaker - Gilead, Janssen, Merck, BMS, Abbvie
- PI - Gilead, Merck, Roche, BMS, Janssen, Spring Bank
- Research / grant support – Gilead, Merck, BMS, Abbvie
- My presentation includes discussion of drugs which are not approved for clinical use

HCV in Australia, 2013

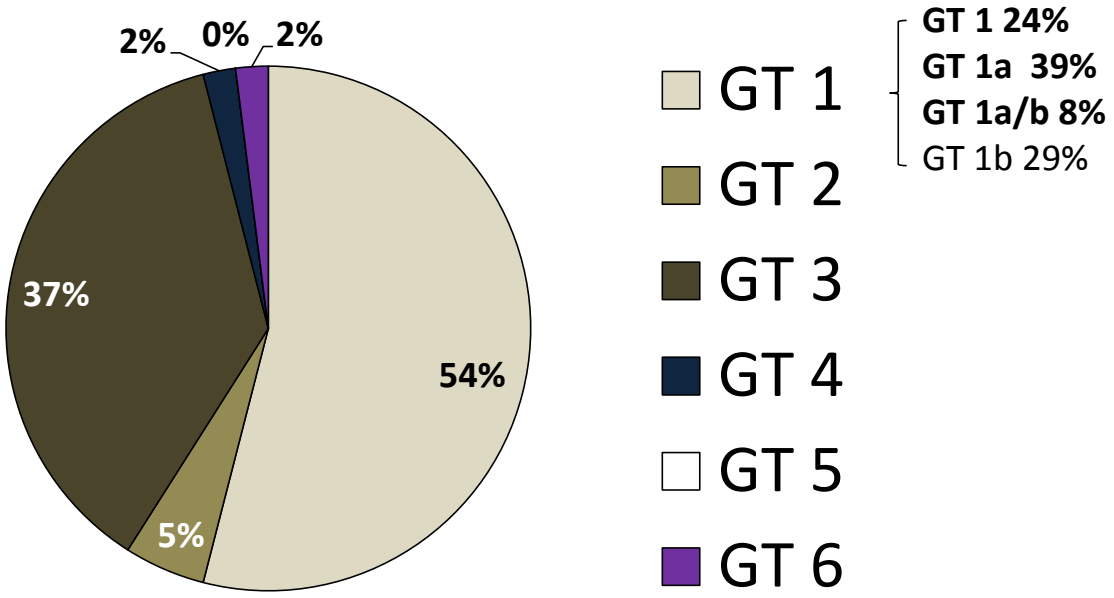


ST VINCENT'S HEALTH AUSTRALIA

Sievert, J Gastro Hep, 2014;
HIV, viral hepatitis and sexually transmissible infections in Australia. Annual surveillance report, Kirby Institute, 2013.

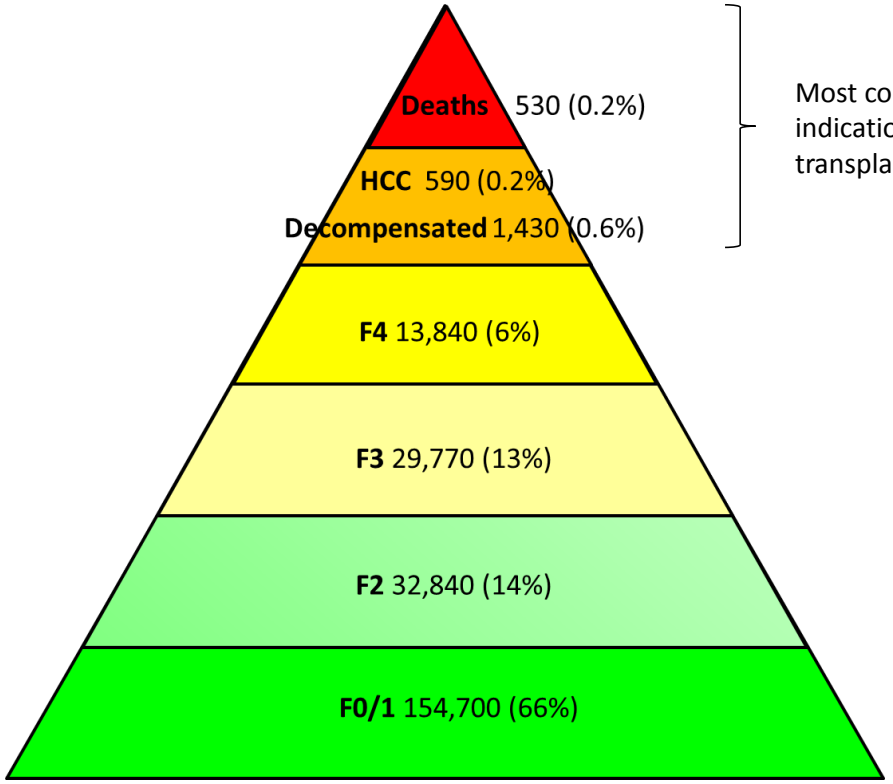
HCV Genotypes in Australia

Data from >10,000 patients at VIDRL in Melbourne



(VIDRL data on file)

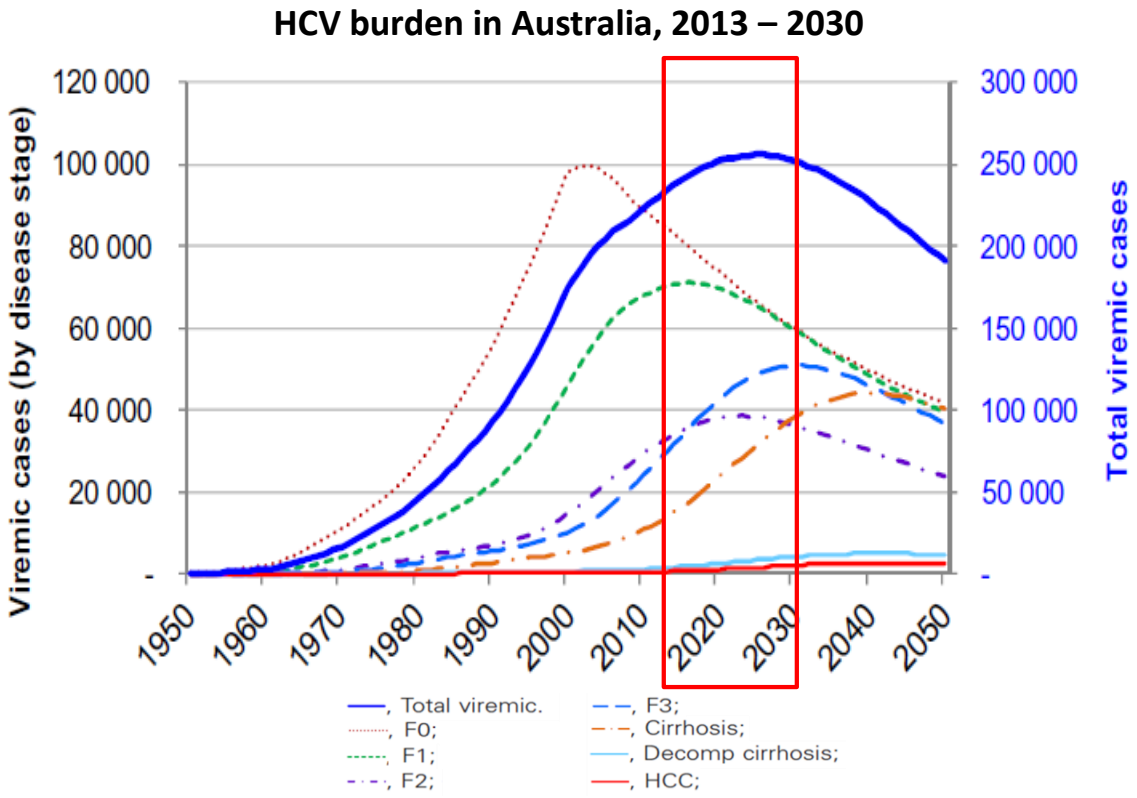
HCV Burden in Australia, 2013



ST VINCENT'S HEALTH AUSTRALIA

Sievert, J Gastro Hep, 2014;
ALA report, The economic cost and health burden of liver diseases in Australia, 2013

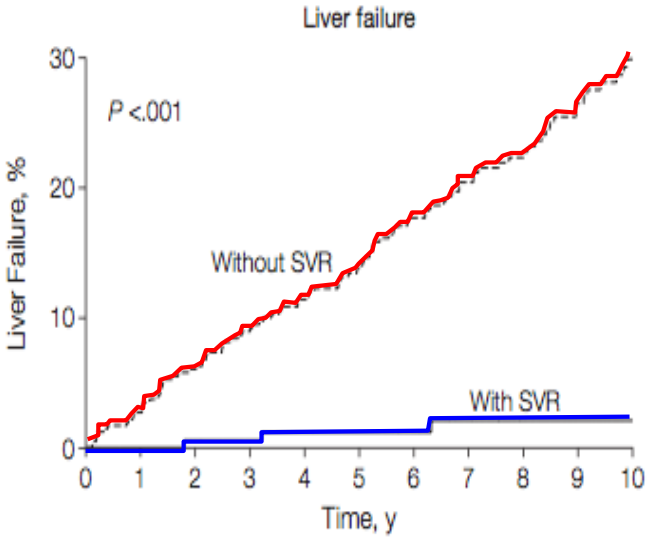
The Burden of HCV is Increasing

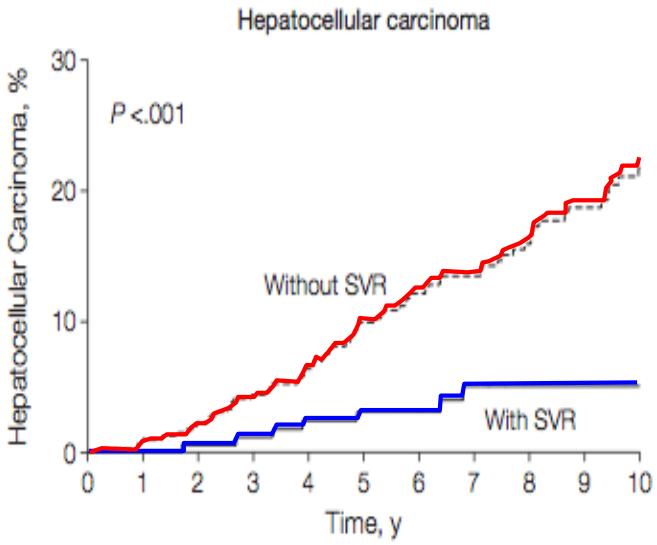


ST VINCENT'S HEALTH AUSTRALIA

Sievert, J Gastro Hep, 2014;
ALA report, The economic cost and health burden of liver diseases in Australia, 2013

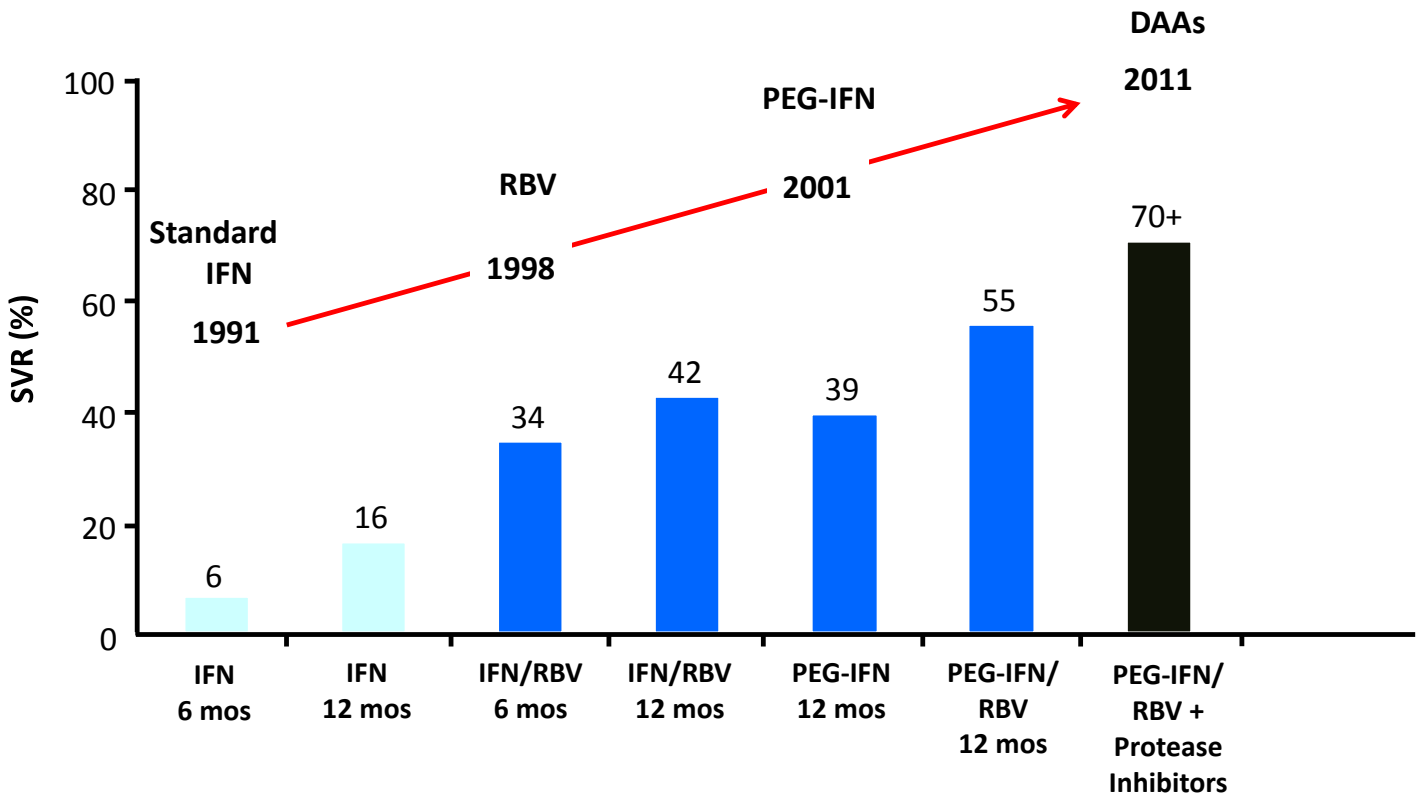
Cure (SVR) Improves Outcome





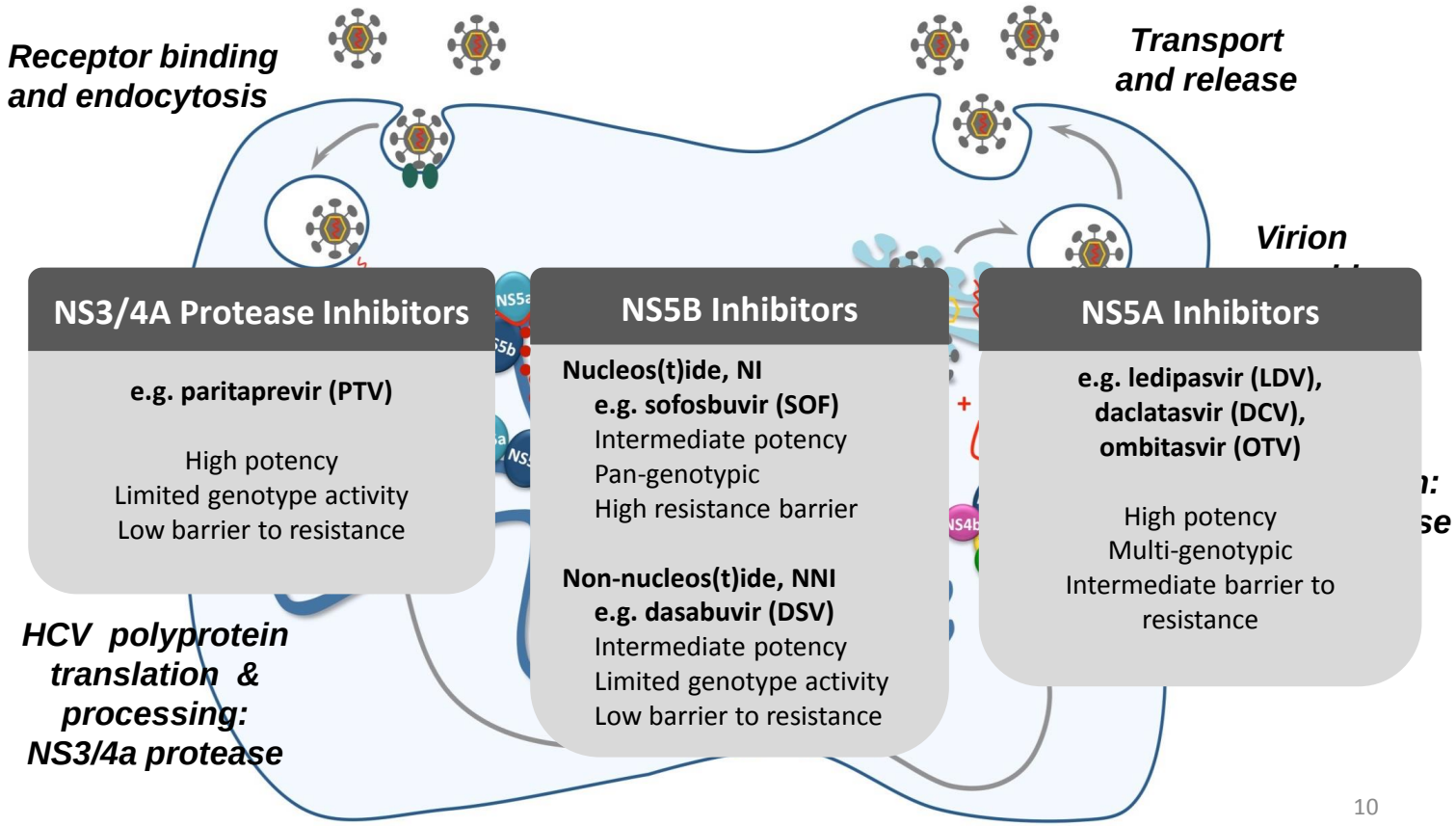
Van der Meer A, et al. JAMA 2012

Evolution of HCV treatment to 2015



Adapted from the US FDA, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring, MD.

Moving beyond Interferon:
Direct Acting Antivirals (DAAs) Target HCV Life Cycle



THE HON SUSSAN LEY MP
MINISTER FOR HEALTH
MINISTER FOR AGED CARE
MINISTER FOR SPORT

20 December 201

…all Australians with HCV…

The Turnbull Go ccess to
breakthrough cur

In a "watershed lia would
become one of t 00,000 –
for the nation's entire population of Hep C sufferers, no matter what their condition or how they contracted it.

Australia leads the world

- All Australians with HCV have access to DAAs
- This is unique globally, and the major distinction between Australian and International HCV policy
- The policy provides the platform for HCV elimination in Australia

Genotype 1

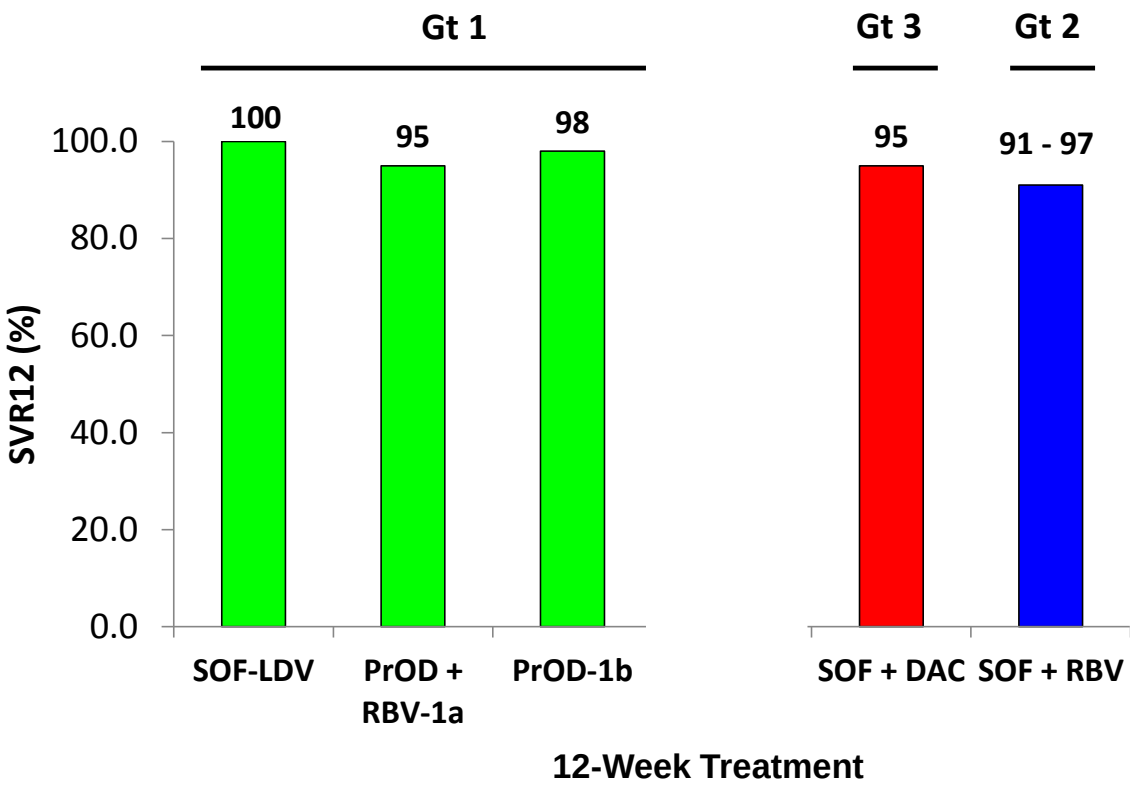
Genotype 3

Genotype 2

(Genotype 1/4)

Cure > 95%

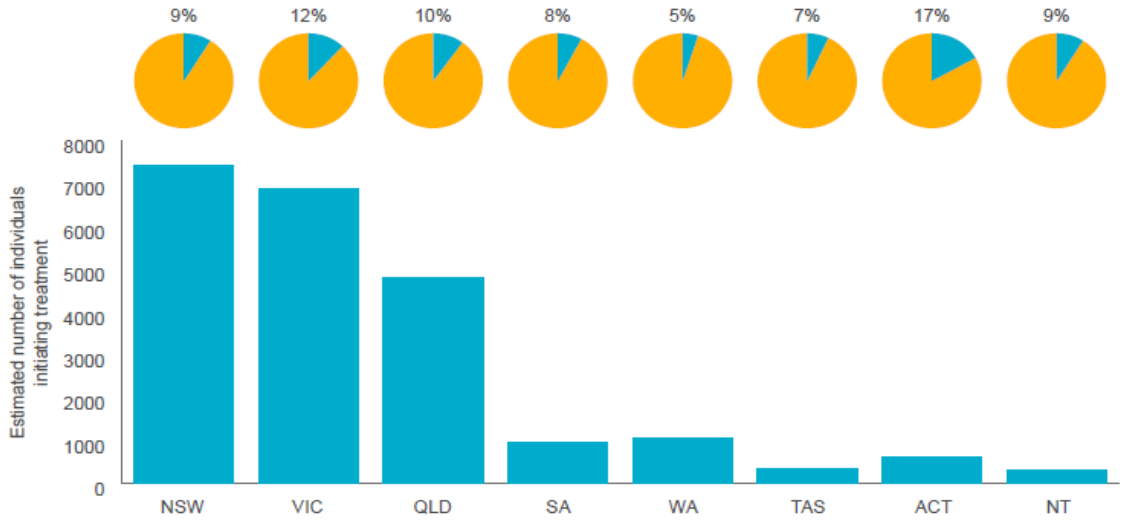
Patients with no cirrhosis



Afdhal N et al. NEJM 2014; Kowdley J et al. NEJM 2014; Afdhal N et al. NEJM 2014; Feld JJ et al. NEJM 2014; Ferenci P et al. NEJM 2014; Nelson D et al Hepatology 2015; Zeuzem s et al. NEJM 2014

Treatment Uptake, Mar-Jun 2016
n = 22,470 (!)

Figure 1: The estimated number of individuals initiating HCV DAA treatment (bar charts) and the proportion of individuals living with chronic HCV who initiated DAA treatment (pie charts) during March to June 2016, by jurisdiction[2]



NSW: New South Wales; VIC: Victoria; QLD: Queensland; SA: South Australia; WA: Western Australia; ATC: Australian Capital Territory; TAS: Tasmania; NT: Northern Territory

The Kirby Institute. Monitoring hepatitis C treatment uptake in Australia (Issue 3). The Kirby Institute, UNSW, Sydney, Australia, July 2016 (http://kirby.unsw.edu.au/research-programs/vhcrp-newsletters)

Australian Recommendations for the Management of HCV Infection: a Consensus Statement 2016

The Consensus Statement was prepared by an expert panel representing:

- the Gastroenterological Society of Australia (Australian Liver Association)
- the Australasian Society for Infectious Diseases
- the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine
- the Australasian Hepatology Association
- Hepatitis Australia
- the Royal Australian College of General Practitioners

Australian recommendations for the management of hepatitis C virus infection: a consensus statement 2016

GESA Gastroenterological Society of Australia
ala Australian Liver Association
ASID
AUSTRALASIAN HEPATOLOGY ASSOCIATION
ashm Supporting the HIV, Viral Hepatitis and Sexual Health Workforce
hepatitis australia

www.gesa.org.au

Thompson AJ, Med J Aust 2016; 204 (7): 268-272

SCREENING AND PREVENTION

Screening & Risk factors for HCV infection
People who inject drugs or who have ever injected drugs
Sex workers
People in custodial settings
Tattooing or body piercing
People who received a blood transfusion / organ transplant prior to 1990
Children born to HCV-infected mothers
Sexual partners of an HCV-infected person
People infected with human immunodeficiency virus or hepatitis B virus
People with evidence of liver disease (persistently elevated ALT level)
People who have had a needle-stick injury
Migrants from high prevalence regions (Egypt, Pakistan, Mediterranean and Eastern Europe, Africa and Asia)

- Annual* HCV serological testing is recommended for seronegative individuals with ongoing risk factors for HCV transmission
- For individuals who are seropositive but have undetectable HCV RNA (past infection), annual HCV RNA testing is recommended in the setting of ongoing risk factors for HCV transmission

Prevention

- Holistic care includes harm reduction strategies
  - opioid substitution therapy
  - needle and syringe programs
  - education and discussion about strategies to prevent parenteral or sexual transmission of HCV
- Treating PWID may reduce HCV transmission (treatment as prevention)

PRE-TREATMENT ASSESSMENT

Checklist for pre-treatment assessment		
	HCV virology: • Anti-HCV (serology) • HCV RNA level (quantitative) • HCV genotype	 • Indicates HCV exposure • Confirms HCV infection • Determines treatment regimen
	HCV treatment history — previous regimen and response	Determines treatment regimen and duration
	Potential for non-adherence?	Consider medical and social issues that may be barriers to medication adherence
	Alcohol intake history	Cofactor for cirrhosis
	Weight and body mass index	Non-alcoholic fatty liver disease (NAFLD) — cofactor for cirrhosis
	Pregnancy discussion*	
	Check for drug–drug interactions	**www.hep-druginteractions.org** Includes prescribed, over-the-counter, complementary/herbal, illicit drugs
	Signs of chronic liver disease	
	FBE	• Baseline haemoglobin level • Low platelets are a marker of portal hypertension
	LFTs and INR	Low albumin, raised bilirubin, raised INR identify liver synthetic dysfunction and suggest advanced cirrhosis
	U&Es and eGFR	• Sofosbuvir is not recommended if eGFR < 30 mL/min/1.73m² • Ribavirin is renally cleared and needs dose reduction if eGFR < 50 mL/min/1.73m²
	Fasting glucose and lipids	Diabetes and hyperlipidaemia are associated with NAFLD
	HBV (HBsAg, anti-HBc, anti-HBs), HIV, HAV serology	If seronegative, vaccinate against HAV, HBV
	Cirrhosis assessment • FibroScan • APRI	Determines treatment regimen and duration Thresholds consistent with no cirrhosis: • Liver stiffness < 12.5 kPa • APRI < 1.0
	If cirrhosis present: • Specialist referral recommended • MELD and Child–Pugh scores • Liver ultrasound • Gastroscopy • Bone densitometry scan	 • Prognostic scores indicating liver decompensation • Screen for HCC, portal hypertension • Screen for oesophageal varices • Screen for osteoporosis
	Electrocardiogram if ribavirin therapy planned and patient is aged > 50 years OR has cardiac risk factors	Screen for ischaemic heart disease

* As there are no safety data for the use of any direct-acting antiviral regimen during pregnancy, treatment of pregnant women is not recommended. Ribavirin (Category X) and peginterferon-alfa are contraindicated during pregnancy. Both women and men should be counselled about the risk of teratogenicity and the importance of avoiding pregnancy during treatment, and for 6 months after ribavirin treatment. Women treated with paritaprevir–ritonavir, ombitasvir and dasabuvir should avoid ethinyl estradiol-containing contraceptives.

HCV – hepatitis C virus. FBE – full blood examination. LFT – liver function test. INR – international normalised ratio. U&E – urea and electrolyte. eGFR – estimated glomerular filtration rate. HBV – hepatitis B virus. HAV – hepatitis A virus. HBsAg – hepatitis B surface antigen. anti-HBc – hepatitis B core antibody. anti-HBs – hepatitis B surface antibody. APRI – aspartate aminotransferase to platelet ratio index. MELD – Model for End-Stage Liver Disease. HCC – hepatocellular carcinoma.

Thompson AJ, Med J Aust 2016; 204 (7): 268-272

The KISS principle…

- 5 key issues to consider:
  - HCV genotype
  - Is cirrhosis present?
    - Clinical, FibroScan, other
  - HCV treatment history
  - Concomitant medications
    - www.**hep-druginteractions**.org
  - eGFR

Is cirrhosis present?

NON-INVASIVE methods for excluding cirrhosis		
Method	**Formula**	**Key threshold for excluding cirrhosis**
Transient elastography	**FibroScan**	LSM < 12.5
APRI	= (AST [IU/L] / AST upper normal limit [IU/L] * 100) / platelet count (x 10^9/L) http://www.hepatitisc.uw.edu/page/clinical-calculators/apri	APRI < 1.0
Hepascore	Patented formula combining bilirubin, GGT, hyaluronate, α-2-macroglobulin, age and gender	HS < 0.80
FibroGENE	Patented formula based on age, platelet count, AST, GGT and IFNL3 (rs12979860) genotype http://www.fibrogene.com/viral_hepatitis.html	Threshold not published but online calculator available
ELF test	Patented formula combining age, hyaluronate, MMP-3 and TIMP-1	ELF < 9.8

Note - these thresholds have good performance characteristics for excluding the presence of cirrhosis. Patients in whom results exceed these thresholds should be referred for further assessment for the presence of cirrhosis by a with experience in assessing liver disease severity and managing patients with advanced liver disease. These thresholds alone should not be used to diagnose cirrhosis.

Note – the performance of Hepascore and APRI for predicting the presence of cirrhosis may be less accurate in people with HIV coinfection than in people with HCV mono-infection (be aware of false positive results due to HIV-induced thrombocytopaenia – APRI or ART-related hyperbilirubinaemia – Hepascore).

Thompson AJ, Med J Aust 2016; 204 (7): 268-272

Is cirrhosis present?

NON-INVASIVE methods for excluding cirrhosis		
Method	**Formula**	**Key threshold for excluding cirrhosis**
Trans elast		
APRI		
Hepa		
Fibro		**nline**
ELF t		
Note -		**resholds**

Cirrhosis assessment MUST occur BEFORE treatment

should be referred for further assessment for the presence of cirrhosis by a with experience in assessing liver disease severity and managing patients with advanced liver disease. These thresholds alone should not be used to diagnose cirrhosis.

Note – the performance of Hepascore and APRI for predicting the presence of cirrhosis may be less accurate in people with HIV coinfection than in people with HCV mono-infection (be aware of false positive results due to HIV-induced thrombocytopaenia – APRI or ART-related hyperbilirubinaemia – Hepascore).

Thompson AJ, Med J Aust 2016; 204 (7): 268-272

Why is cirrhosis important?

- Required for PBS approval
- Determines treatment duration
- Indicates the need for specialist referral
  - Hepatocellular cancer (HCC) screening
  - Portal hypertension screening

TREATING HCV

Genotype 1

Genotype 3

Genotype 2

(Genotype 1/4)

Treatment protocols for people with hepatitis C virus (HCV) infection and compensated liver disease, including people with HCV/HIV coinfection

Regimen	HCV genotype	No cirrhosis		Cirrhosis	
		Treatment-naive	Treatment-experienced*	Treatment-naive	Treatment-experienced*
Sofosbuvir 400 mg, orally, daily + Ledipasvir 90 mg, orally, daily	1a/b	8 or 12 weeks†	12 weeks	12 weeks	24 weeks
Sofosbuvir 400 mg, orally, daily + Daclatasvir 60 mg, orally, daily‡ ± Ribavirin 1000/1200 mg, orally, daily§	1a/b	12 weeks	12 weeks OR 24 weeks¶	12 weeks + ribavirin OR 24 weeks (no ribavirin)	12 weeks + ribavirin OR 24 weeks (no ribavirin)
Paritaprevir–ritonavir (150 mg/100 mg), orally, daily + Ombitasvir 25 mg, orally, daily + Dasabuvir 250 mg, orally, twice daily ± Ribavirin 1000/1200 mg, orally, daily§	1a	12 weeks + ribavirin	12 weeks + ribavirin	12 weeks + ribavirin	12 or 24 weeks + ribavirin**
	1b	12 weeks	12 weeks	12 weeks	12 weeks
Sofosbuvir 400 mg, orally, daily + Ribavirin 1000/1200 mg, orally, daily§	2	12 weeks	12 weeks	12 weeks	12 weeks
Sofosbuvir 400 mg, orally, daily + Daclatasvir, 60 mg, orally, daily‡	3	12 weeks	12 weeks	24 weeks	24 weeks
Sofosbuvir 400 mg daily + Ribavirin 1000/1200 mg daily§	3	24 weeks	24 weeks	24 weeks	24 weeks
Sofosbuvir 400 mg, orally, daily + Peginterferon-alfa, subcutaneously, weekly + Ribavirin 1000/1200 mg, orally, daily§	3, 4, 5, 6	12 weeks	12 weeks	12 weeks	12 weeks

* Treatment experience generally refers to peginterferon-**alfa** plus ribavirin ± first-generation protease inhibitors (see full consensus statement). † 8 weeks may be considered if HCV RNA < 6 × 10^6 IU/mL in people with no cirrhosis who are treatment-naive. ‡ Daclatasvir dose modification is required when used in combination with specific antiretroviral therapies for HIV (see full consensus statement). § Ribavirin dosing is weight-based; recommended dose is 1000 mg for people weighing < 75 kg and 1200 mg for people weighing ≥ 75 kg. ¶ Recommended treatment duration for sofosbuvir plus daclatasvir (no ribavirin) for people who have failed treatment with a protease inhibitor + peginterferon + ribavirin is 24 weeks, including people with cirrhosis and people with no cirrhosis; recommended treatment duration for people with no cirrhosis who have previously failed peginterferon + ribavirin is 12 weeks. ** Recommended treatment duration for paritaprevir–ritonavir, ombitasvir, dasabuvir (PrOD) plus ribavirin in people with genotype 1a HCV and cirrhosis who have had a previous null response to peginterferon-alfa and ribavirin therapy is 24 weeks. PrOD therapy is not recommended for people who did not respond to previous therapy that included an HCV protease inhibitor or an NS5A inhibitor.

Notes: Sofosbuvir is not recommended for patients with an estimated glomerular filtration rate < 30 mL/min/1.73m². At the time of writing, the combination of PrOD ± ribavirin was approved by the Therapeutic Goods Administration but not yet available for prescription under the Pharmaceutical Benefits Scheme; this treatment regimen should be used with caution in people with cirrhosis and is contraindicated in people with decompensated liver disease. Dose reduction or dose interruption of direct-acting antiviral therapy is not recommended. Dose reduction of ribavirin for the management of symptomatic anaemia according to the product information is appropriate and will not reduce the likelihood of SVR (sustained virological response at least 12 weeks after treatment [cure]).
The recommended treatment regimens differ in the setting of decompensated liver disease (Child–Pugh score ≥ B7) (see full consensus statement).

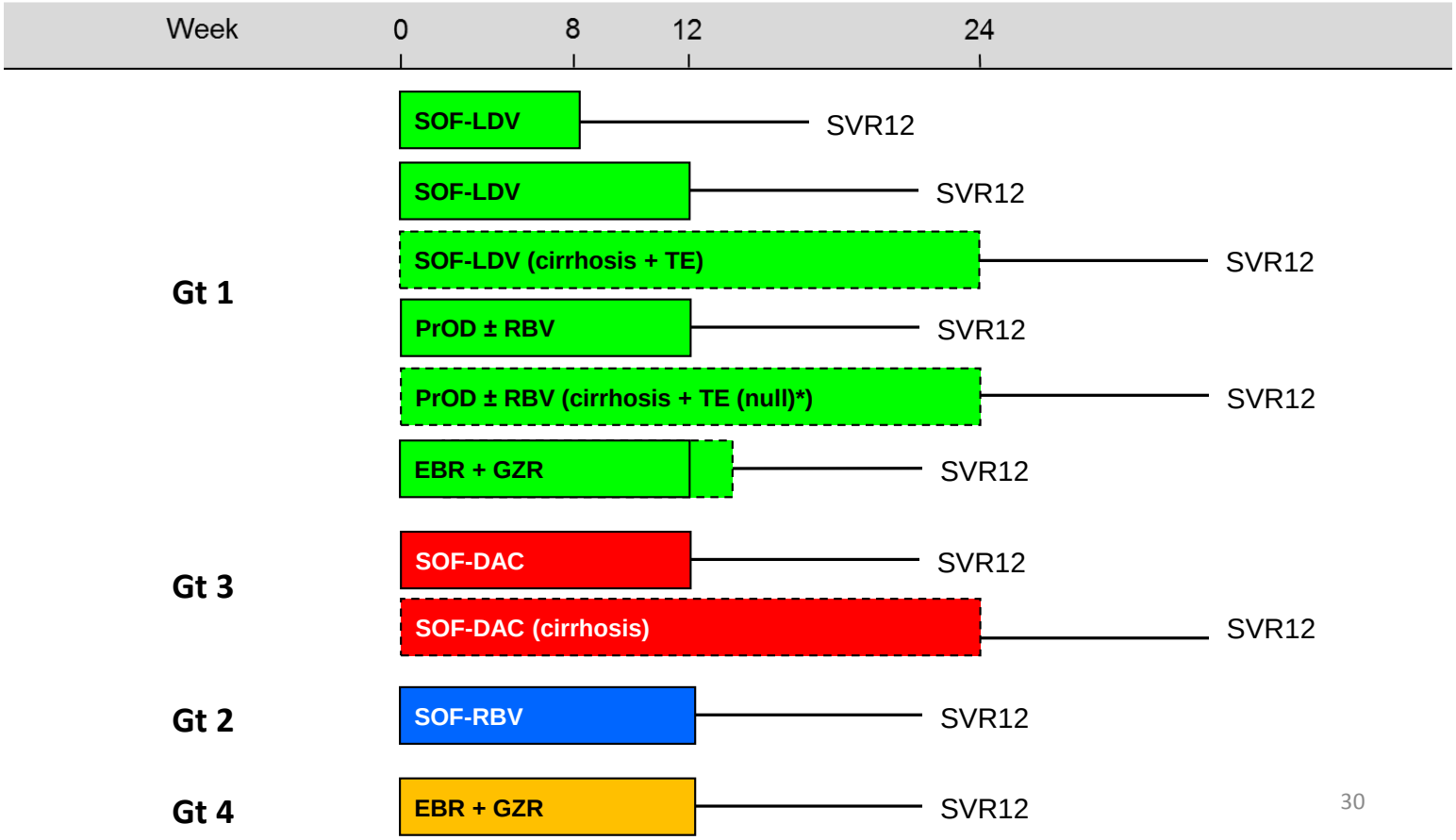
GESA Gastroenterological Society of Australia
ala Australian Liver Association
AUSTRALASIAN HEPATOLOGY ASSOCIATION
ASID
ashm Supporting the HIV, Viral Hepatitis and Sexual Health Workforce
hepatitis australia

www.gesa.org.au

Thompson AJ, Med J Aust 2016; 204 (7): 268-272

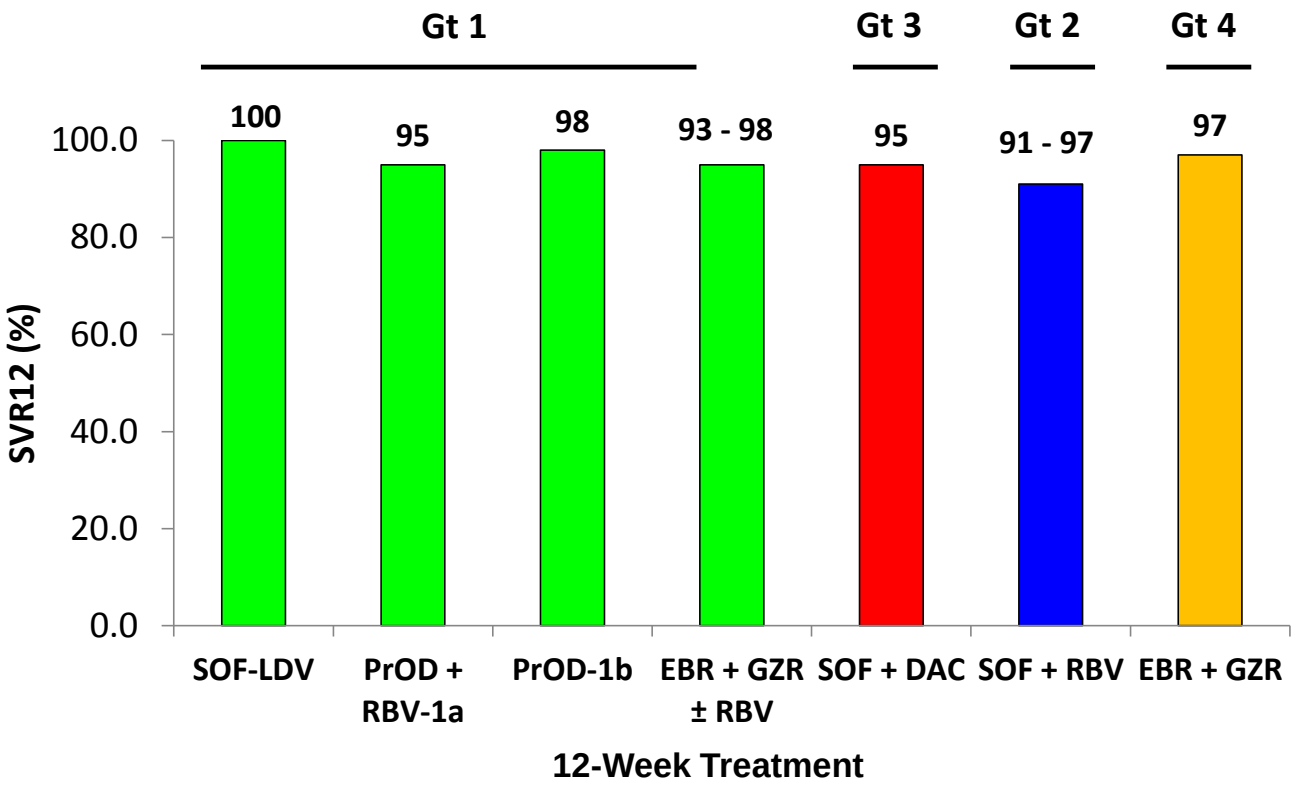
12 Weeks Treatment Duration for Most

Longer – cirrhosis, prior treatment failure



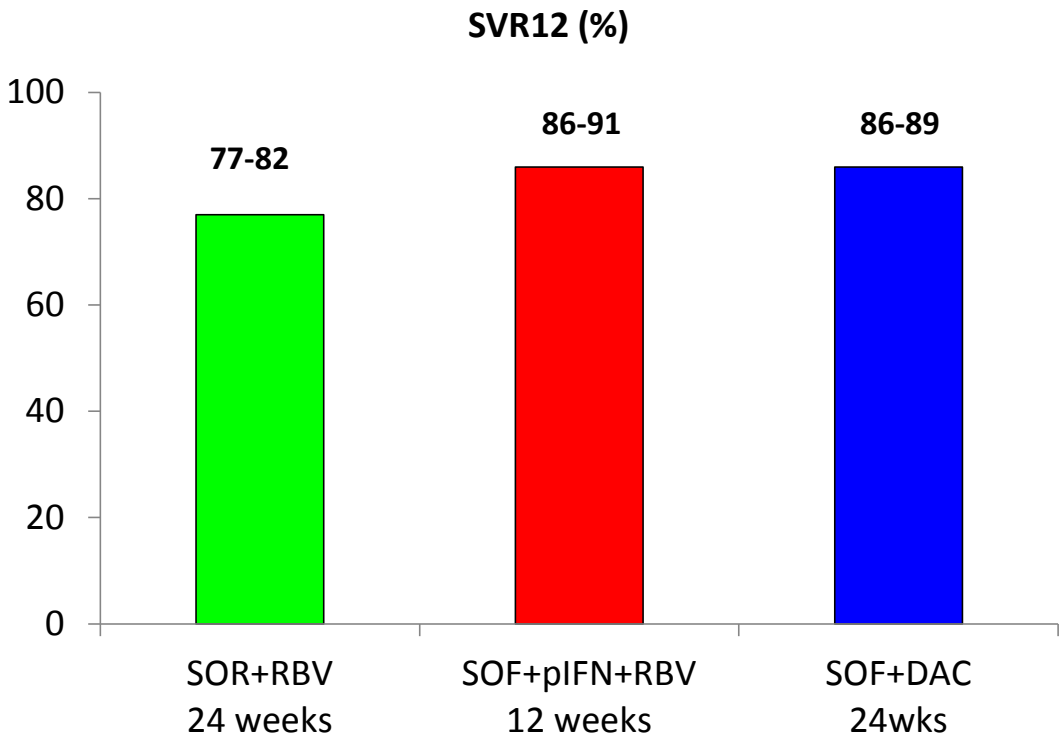
Cure > 95%

Patients with no cirrhosis



Afdhal N et al. NEJM 2014; Kowdley J et al. NEJM 2014; Afdhal N et al. NEJM 2014; Feld JJ et al. NEJM 2014; Ferenci P et al. NEJM 2014; Nelson D et al Hepatology 2015; Zeuzem s et al. NEJM 2014

Gt 3 + Cirrhosis remains Harder to Cure



Zeuzem S et al. NEJM 2014; Foster G et al. NEJM 2015; Leroy V et al. Hepatology 2015

DAAs are well tolerated

Adverse Effects with Sofosbuvir + Ledipasvir Reported in ≥5% of Subjects			
	Ledipasvir-Sofosbuvir		
	8 Weeks	12 Weeks	24 Weeks
	N=215	N=539	N=326
Fatigue	16%	13%	18%
Headache	11%	14%	17%
Nausea	6%	7%	9%
Diarrhea	4%	3%	7%
Insomnia	3%	5%	6%

Note. Mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C).

- No dose adjustment of HARVONI is required

Note. Sofosbuvir is renally excreted

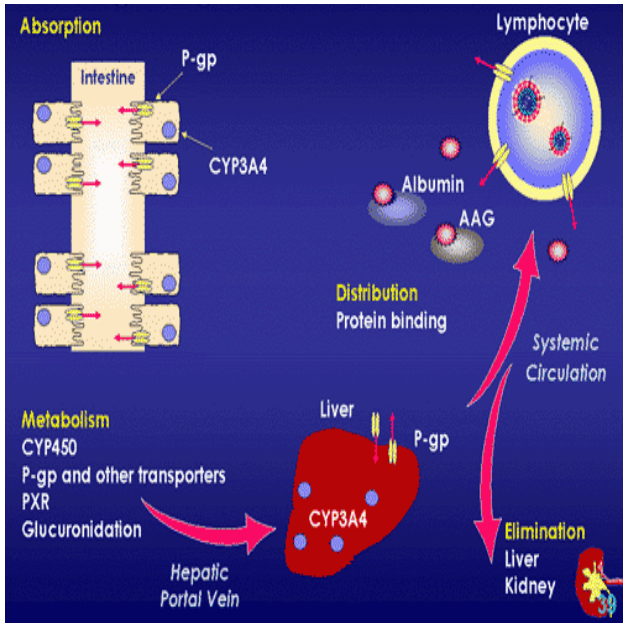
- **not recommended in patients with eGFR <30 mL/min/1.73m^2**

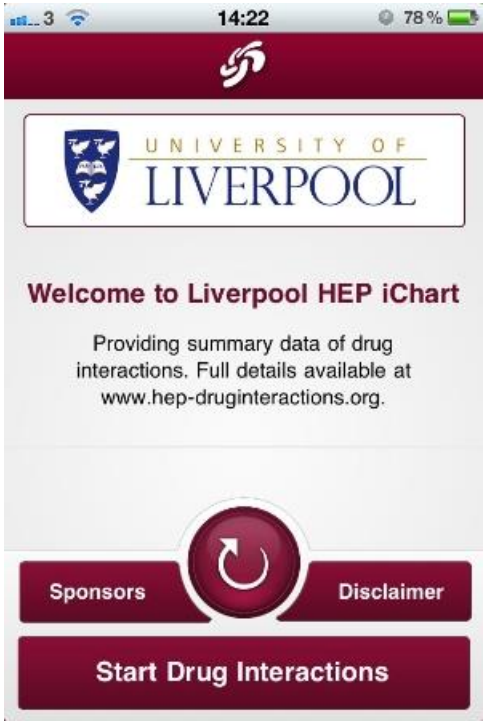
FDA Label

Ribavirin is used rarely but has side effects

- Hemolysis
  - Median Hb reduction 2g/dL
- Other – 15-20%
  - Pruritus
  - Nausea, diarrhoea
  - Cough, dyspnoea
  - Difficulty concentrating (ribavirin “fog”)
- Teratogenic
  - 2 forms of contraceptives recommended
- Renally excreted
  - Dose reduce if eGFR < 50mL/min/1.73m^2

Drug-Drug Interactions





www.**hep-druginteractions**.org

www.medscape.com

Drug-Drug Interactions

- SOF / LDV
  - Not recommended
    - rosuvastatin
    - omeprazole >20mg (PPI class effect – reduces LDV absoprtion)
    - amiodarone*
    - potent P-gp inducers (e.g. rifampicin, St John's Wort)
  - No significant DDI
    - OCP, HIV ARV, antacids, opiates, immunosuppressive agents

- PrOD is more complicated
  - Protease inhibitors have more DDIs
  - Protease inhibitor is ritonavir boosted

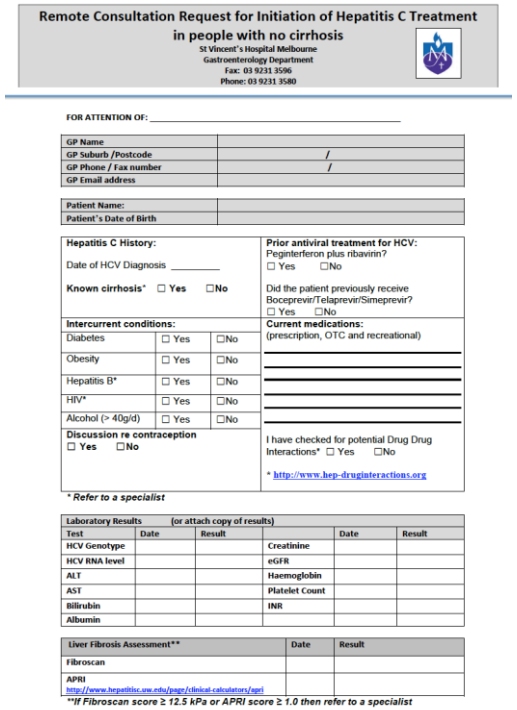
GP prescribing

Population criteria: Patient must be aged 18 years or older.
Treatment criteria: Must be treated by a gastroenterologist, hepatologist or infectious diseases physician experienced in the treatment of chronic hepatitis C infection; or in consultation with a gastroenterologist, hepatologist or infectious diseases physician experienced in the treatment of chronic hepatitis C infection.
The following information must be provided at the time of application: a) the hepatitis C virus genotype; and b) the patient's cirrhotic status (non-cirrhotic or cirrhotic) The following information must be documented in the patient's medical records: a) evidence of chronic hepatitis C infection (repeatedly antibody to hepatitis C virus (anti-HCV) positive and hepatitis C virus ribonucleic acid (HCV RNA) positive); and b) evidence of the hepatitis C virus genotype

* PBS authority approval from the Department of Human Services (Medicare) — via written or telephone channels — will be required for each prescription; the medicines will not be available under streamlined authority.

“In consultation”

- means that a GP must consult with one of the specified specialists by phone, fax, mail, email or videoconference in order to meet the prescriber eligibility requirements
- **most suitable for people with no cirrhosis**



Remote Consultation Request for Initiation of Hepatitis C Treatment in people with no cirrhosis

St Vincent's Hospital Melbourne
Gastroenterology Department
Fax: 03 9231 3596
Phone: 03 9231 3580

FOR ATTENTION OF: _____

GP Name	
GP Suburb /Postcode	/
GP Phone / Fax number	/
GP Email address	

Patient Name:	
Patient's Date of Birth	

Hepatitis C History:

Date of HCV Diagnosis _____

Known cirrhosis* ☐ **Yes** ☐**No**

Prior antiviral treatment for HCV:
Peginterferon plus ribavirin?
☐ Yes ☐No

Did the patient previously receive Boceprevir/Telaprevir/Simeprevir?
☐ Yes ☐No

Intercurrent conditions:

Diabetes	☐ Yes	☐No
Obesity	☐ Yes	☐No
Hepatitis B*	☐ Yes	☐No
HIV*	☐ Yes	☐No
Alcohol (> 40g/d)	☐ Yes	☐No

Discussion re contraception
☐ **Yes** ☐**No**

Current medications:
(prescription, OTC and recreational)

I have checked for potential Drug Drug Interactions* ☐ Yes ☐No

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

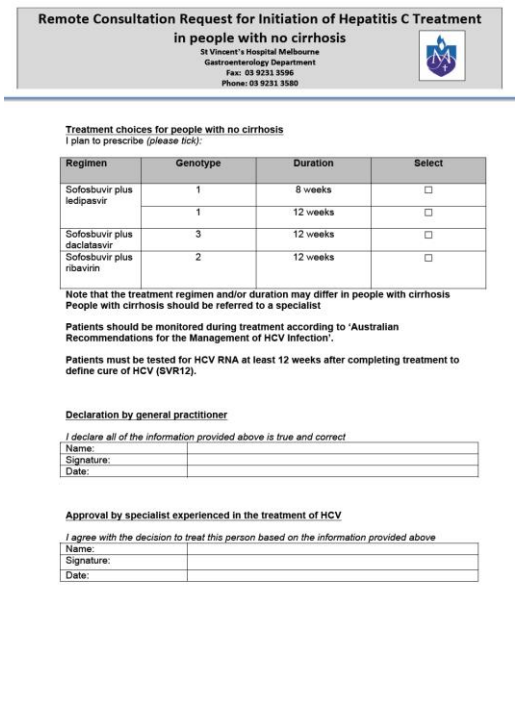
** Refer to a specialist*

Laboratory Results (or attach copy of results)

Test	Date	Result		Date	Result
HCV Genotype			Creatinine		
HCV RNA level			eGFR		
ALT			Haemoglobin		
AST			Platelet Count		
Bilirubin			INR		
Albumin					

Liver Fibrosis Assessment**	Date	Result
Fibroscan		
APRI http://www.hepatitisc.uw.edu/page/clinical-calculators/apri		

***If Fibroscan score ≥ 12.5 kPa or APRI score ≥ 1.0 then refer to a specialist*



Remote Consultation Request for Initiation of Hepatitis C Treatment in people with no cirrhosis

St Vincent's Hospital Melbourne
Gastroenterology Department
Fax: 03 9231 3596
Phone: 03 9231 3580

Treatment choices for people with no cirrhosis
I plan to prescribe *(please tick)*:

Regimen	Genotype	Duration	Select
Sofosbuvir plus ledipasvir	1	8 weeks	☐
	1	12 weeks	☐
Sofosbuvir plus daclatasvir	3	12 weeks	☐
Sofosbuvir plus ribavirin	2	12 weeks	☐

Note that the treatment regimen and/or duration may differ in people with cirrhosis
People with cirrhosis should be referred to a specialist

Patients should be monitored during treatment according to 'Australian Recommendations for the Management of HCV Infection'.

Patients must be tested for HCV RNA at least 12 weeks after completing treatment to define cure of HCV (SVR12).

Declaration by general practitioner

I declare all of the information provided above is true and correct

Name:	
Signature:	
Date:	

Approval by specialist experienced in the treatment of HCV

I agree with the decision to treat this person based on the information provided above

Name:	
Signature:	
Date:	

Modified from an original template designed for the ALA by Prof Simone Strasser

MONITORING ON-TREATMENT

A. Monitoring of patients ON-TREATMENT AND POST-TREATMENT for virological response	
Routine monitoring for a 12 week treatment regimen:	
Week 0	• FBE, LFTs, U&Es, eGFR, INR, HCV RNA level (quantitative)
Week 4	• FBE, LFTs*

Week 12 ± 24 (EOT)	• FBE, LFTs, HCV PCR (qualitative)
	  • At each on-treatment visit assess for :
	  ○ medication adherence
	  ○ treatment adverse effects
	  ○ drug to drug interactions

Week 12 post-treatment (SVR12)	• FBE, LFTs, HCV PCR (qualitative)

Note:

- **Routine on-treatment HCV RNA testing is not mandated but may be considered where there is a clinical concern about non-compliance with treatment, especially in people with cirrhosis.**
- **The need for increased frequency of review should be individualized.**
- **Patients taking ribavirin may require FBE at week 2 and week 4 and then every 4 weeks.**
- **Patients with cirrhosis require monitoring every 4 weeks including FBE, LFTs and assessment for hepatic decompensation. A quantitative HCV RNA level is recommended at weeks 4, 12 ± 24 on-treatment in patients with cirrhosis.**
- **Patients with decompensated liver disease require close monitoring with review every 2-4 weeks.**
- **Abbrev. EOT = end-of-treatment; SVR12 = cure**

Thompson AJ, Med J Aust 2016; 204 (7): 268-272

A. Monitoring of patients ON-TREATMENT AND POST-TREATMENT for virological response	
Routine monitoring for a 12 week treatment regimen:	
Week 0	• FBE, LFTs, U&Es, eGFR, INR, HCV RNA level (quantitative)
Week 4	• FBE, LFTs*

Week 12 ± 24 (EOT)	• FBE, LFTs, HCV PCR (qualitative)
	  • At each on-treatment visit assess for :
	  ○ medication adherence
	  ○ treatment adverse effects
	  ○ drug to drug interactions

Week 12 post-treatment (SVR12)	• FBE, LFTs, HCV PCR (qualitative)

Note:

- **Routine on-treatment HCV RNA testing is not mandated but may be considered where there is a clinical concern about non-compliance with treatment, especially in people with cirrhosis.**
- **The need for increased frequency of review should be individualized.**
- **Patients taking ribavirin may require FBE at week 2 and week 4 and then every 4 weeks.**
- **Patients with cirrhosis require monitoring every 4 weeks including FBE, LFTs and assessment for hepatic decompensation. A quantitative HCV RNA level is recommended at weeks 4, 12 ± 24 on-treatment in patients with cirrhosis.**
- **Patients with decompensated liver disease require close monitoring with review every 2-4 weeks.**
- **Abbrev. EOT = end-of-treatment; SVR12 = cure**

Thompson AJ, Med J Aust 2016; 204 (7): 268-272

A. Monitoring of patients ON-TREATMENT AND POST-TREATMENT for virological response	
Routine monitoring for a 12 week treatment regimen:	
Week 0	• FBE, LFTs, U&Es, eGFR, INR, HCV RNA level (quantitative)
Week 4	• FBE, LFTs*

Week 12 ± 24 (EOT)	• FBE, LFTs, HCV PCR (qualitative)
	  • At each on-treatment visit assess for :
	  ○ medication adherence
	  ○ treatment adverse effects
	  ○ drug to drug interactions

Week 12 post-treatment (SVR12)	• FBE, LFTs, HCV PCR (qualitative)

Note:

- **Routine on-treatment HCV RNA testing is not mandated but may be considered where there is a clinical concern about non-compliance with treatment, especially in people with cirrhosis.**
- **The need for increased frequency of review should be individualized.**
- **Patients taking ribavirin may require FBE at week 2 and week 4 and then every 4 weeks.**
- **Patients with cirrhosis require monitoring every 4 weeks including FBE, LFTs and assessment for hepatic decompensation. A quantitative HCV RNA level is recommended at weeks 4, 12 ± 24 on-treatment in patients with cirrhosis.**
- **Patients with decompensated liver disease require close monitoring with review every 2-4 weeks.**
- **Abbrev. EOT = end-of-treatment; SVR12 = cure**

Thompson AJ, Med J Aust 2016; 204 (7): 268-272

A. Monitoring of patients ON-TREATMENT AND POST-TREATMENT for virological response

Routine monitoring for a 12 week treatment regimen:

Week 0	• FBE, LFTs, U&Es, eGFR, INR, HCV RNA level (quantitative)
Week 4	• FBE, LFTs*
(Week 8)	• (LFTs required for one regimen – EBR+GZR)
~~**Week 12 ± 24 (EOT)**~~	• ~~FBE, LFTs, HCV PCR (qualitative)~~ • At each on-treatment visit assess for : ○ medication adherence ○ treatment adverse effects ○ drug to drug interactions
Week 12 post-treatment (SVR12)	• FBE, LFTs, HCV PCR (qualitative)

Note:

- **Routine on-treatment HCV RNA testing is not mandated but may be considered where there is a clinical concern about non-compliance with treatment, especially in people with cirrhosis.**
- **The need for increased frequency of review should be individualized.**
- **Patients taking ribavirin may require FBE at week 2 and week 4 and then every 4 weeks.**
- ~~**Patients with cirrhosis require monitoring every 4 weeks including FBE, LFTs and assessment for hepatic decompensation. A quantitative HCV RNA level is recommended at weeks 4, 12 ± 24 on-treatment in patients with cirrhosis.**~~
- **Patients with decompensated liver disease require close monitoring with review every 2-4 weeks. A quantitative HCV RNA level is recommended at weeks 4, 12 ± 24 on-treatment in patients with cirrhosis.**
- **Abbrev. EOT = end-of-treatment; SVR12 = cure**

POST-TREATMENT

Cirrhosis?
Second liver disease?

B. Monitoring POST-SVR12

- **SVR12, no cirrhosis, and normal LFTs (males: ALT < 30 U/mL; females ALT < 19 U/mL)**

- Patients who are cured do not require clinical follow-up for HCV

- **SVR12 and abnormal LFTs (males: ALT ≥ 30 U/mL; females ALT ≥ 19 U/mL)**

- Patients with persistently abnormal LFTs require evaluation for other liver diseases and should be referred for gastroenterology review.
- Investigations to consider include: Fasting glucose, fasting lipid levels, iron studies, ANA, ASMA, anti-LKM antibodies, total IgG and IgM, AMA, coeliac serology, copper, caeruloplasmin, and α-1-antitrypsin levels.

- **SVR12, cirrhosis**

- Patients with cirrhosis require long-term monitoring; enrol in screening programs for:
    - hepatocellular carcinoma, HCC (liver ultrasound)
    - oesophageal varices (gastroscopy)
    - osteoporosis (bone mineral densitometry)

Thompson AJ, Med J Aust 2016; 204 (7): 268-272

B. Monitoring POST-SVR12

- **SVR12, no cirrhosis, and normal LFTs (males: ALT < 30 U/mL; females ALT < 19 U/mL)**

- Patients who are cured do not require clinical follow-up for HCV

- **SVR12 and abnormal LFTs (males: ALT ≥ 30 U/mL; females ALT ≥ 19 U/mL)**

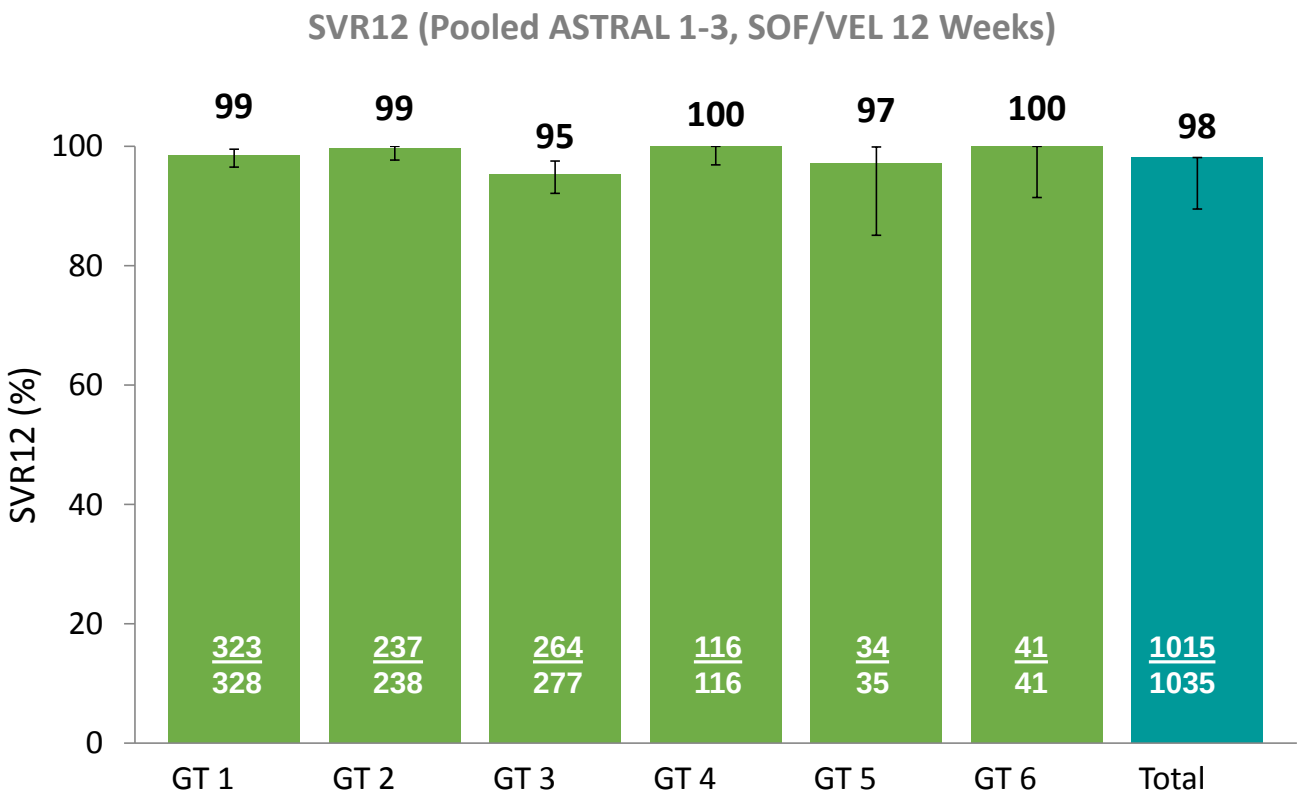
- Patients with persistently abnormal LFTs require evaluation for other liver diseases and should be referred for gastroenterology review.
- Investigations to consider include: Fasting glucose, fasting lipid levels, iron studies, ANA, ASMA, anti-LKM antibodies, total IgG and IgM, AMA, coeliac serology, copper, caeruloplasmin, and α-1-antitrypsin levels.

- **SVR12, cirrhosis**

- Patients with cirrhosis require long-term monitoring; enrol in screening programs for:
    - hepatocellular carcinoma, HCC (liver ultrasound)
    - oesophageal varices (gastroscopy)
    - osteoporosis (bone mineral densitometry)
- **Consider repeat LSM at 3 months and 12 months**

WHAT'S NEXT – PAN-GENOTYPIC DAAs

Sofosbuvir + velpatasvir (FDC), 12 wks is a pangenotypic regimen



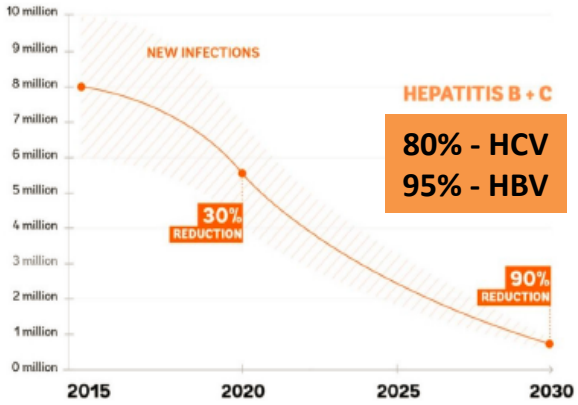
Gilead dataset, AASLD 2015

ELIMINATING HCV

Increasing treatment uptake
Treatment as prevention

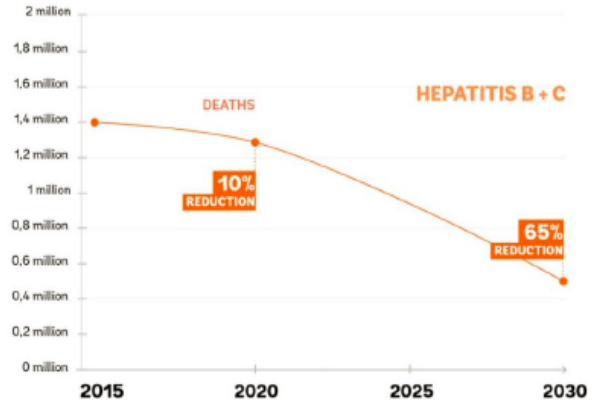
WHO Targets for Elimination of Viral Hepatitis

90% reduction in new cases of of chronic HBV and HCV infection



6-10 million infections (in 2015) to 900,000 infections (by 2030)

65% reduction in deaths from chronic HBV and HCV



1.4 million deaths (in 2015) to under 500,000 deaths (by 2030)

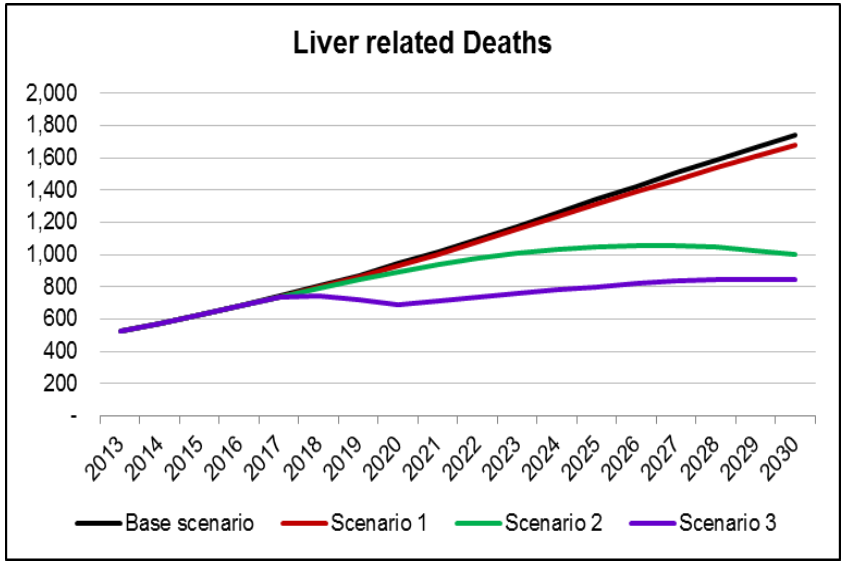
World Health Organization

Hirnschall G, WHO, 2015

100% SVR is Not Enough

Increasing Treatment Uptake is Critical to Reduce Prevalence and Burden of HCV

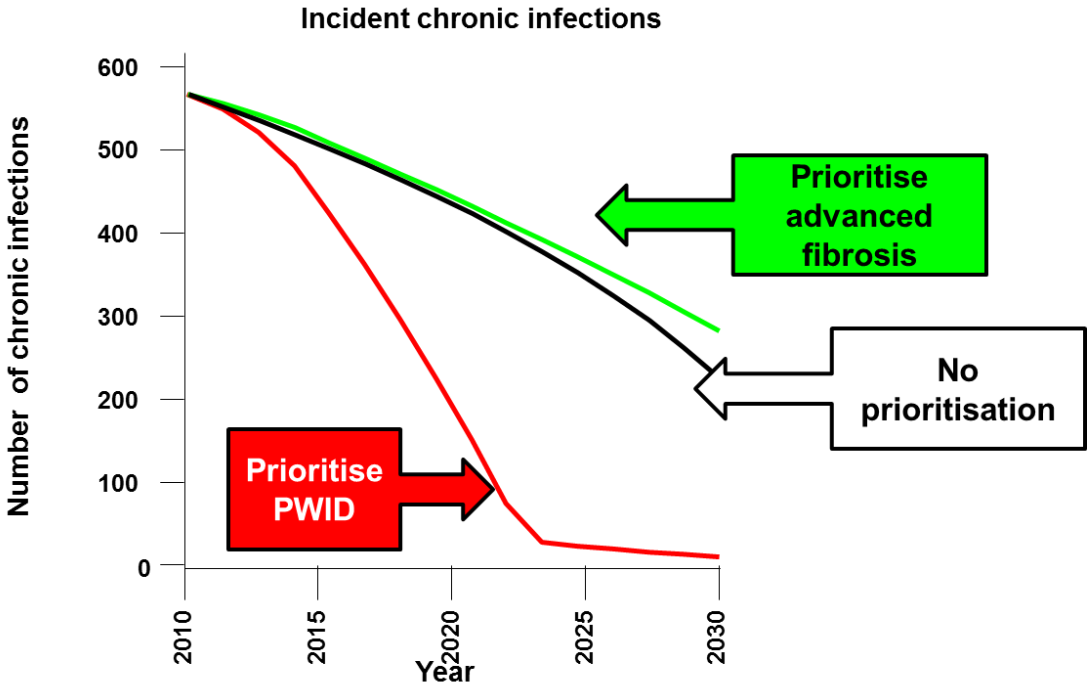
Projected burden of disease: liver-related deaths, 2013–2030



Scenario 1: *increase sustained virological response (SVR) only, with no increase in annual treated population and treatment eligibility not restricted by fibrosis stage.*
Scenario 2: *increase SVR and annual treated population, with treatment eligibility not restricted by fibrosis stage.*
Scenario 3: *increase SVR and annual treated population, restricted to fibrosis stage ≥ F3 in 2015–2017, then unrestricted (all stages ≥ F0) from 2018.*[5]

Sievert, Razavi, Estes, Thompson et al, JGH, 2014

To Reduce Prevalence, High Incidence Groups Should Be Prioritised

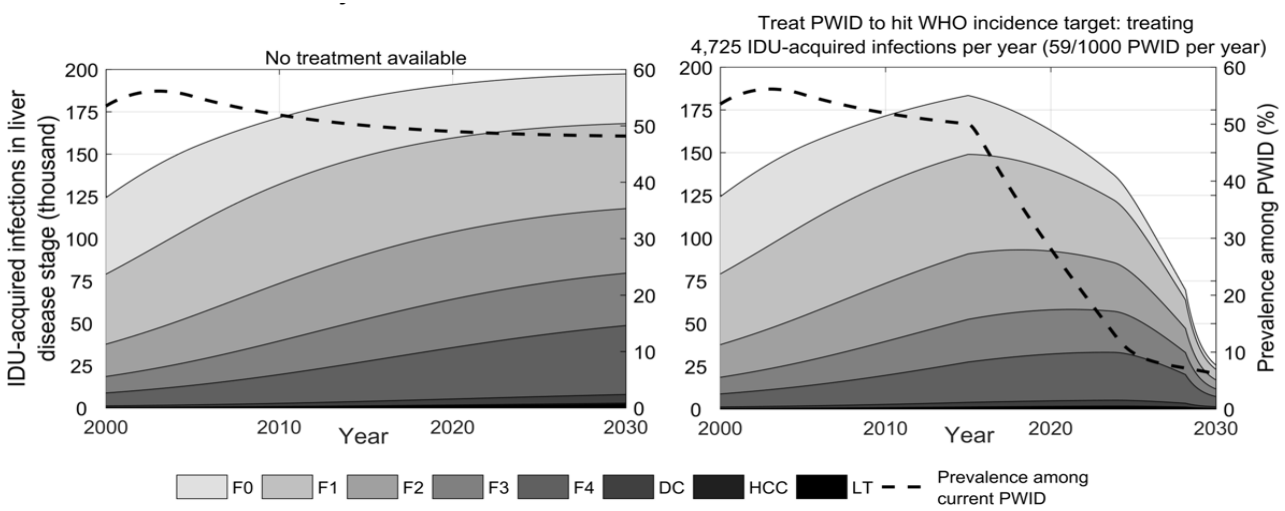


Innes H, et al. Gut 2014; doi:10.1136/gutjnl-2014-308166

Targets to reduce incidence of HCV in Australia by 80% by 2030

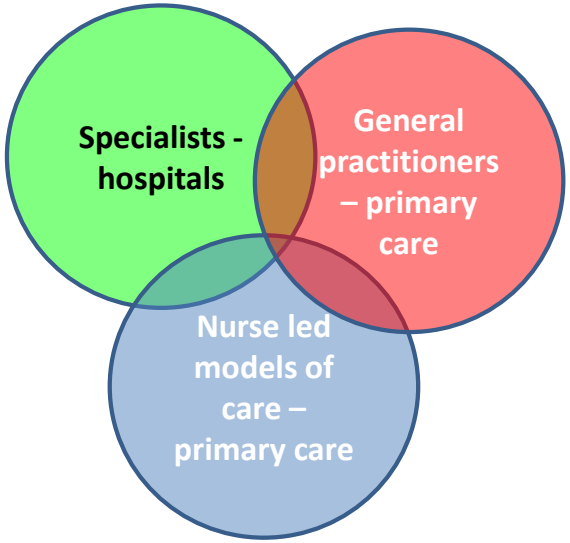
In Victoria, there are an estimated 15 – 25,000 PWID with ~ 50% chronically HCV RNA detectable). Modelling by our group suggests that treating 58/1000 PWID/yr will achieve the WHO transmission targets of an 80% reduction in new HCV infections by 2030

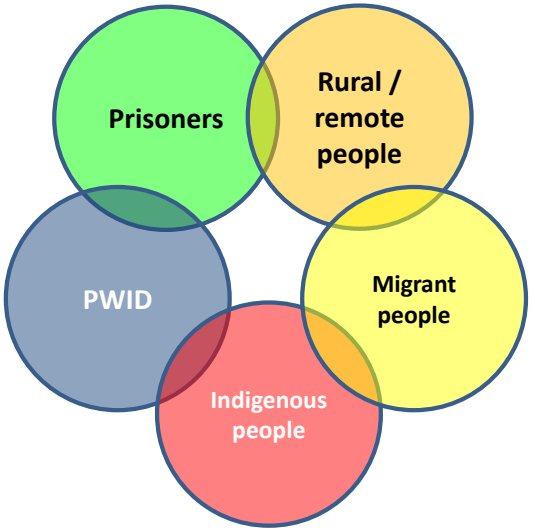
Victoria – treat 1,000 PWID/yr



Data courtesy of Margaret Hellard, Burnet Institute, Melbourne

Models of care






EC Partnership
#EliminatingHepC
TRANSMISSION
IN VICTORIA
BY 2030.


ELIMINATION IS THE GOAL
AUSTRALIA-HEP C FREE

SUMMARY

Prescribing DAAs for HCV

- Key issues to consider:
  - HCV genotype
  - Is cirrhosis present?
    - Clinical, FibroScan, other
  - HCV treatment history
  - Concomitant medications
    - www.**hep-druginteractions**.org
  - eGFR

Australian recommendations for the management of hepatitis C virus infection: a consensus statement 2016

www.gesa.org.au

Thompson AJ, Med J Aust 2016; 204 (7): 268-272

Treatment protocols for people with hepatitis C virus (HCV) infection and compensated liver disease, including people with HCV/HIV coinfection

Regimen	HCV genotype	No cirrhosis		Cirrhosis	
		Treatment-naive	Treatment-experienced*	Treatment-naive	Treatment-experienced*
Sofosbuvir 400 mg, orally, daily + Ledipasvir 90 mg, orally, daily	1a/b	8 or 12 weeks†	12 weeks	12 weeks	24 weeks
Sofosbuvir 400 mg, orally, daily + Daclatasvir 60 mg, orally, daily‡ ± Ribavirin 1000/1200 mg, orally, daily§	1a/b	12 weeks	12 weeks OR 24 weeks¶	12 weeks + ribavirin OR 24 weeks (no ribavirin)	12 weeks + ribavirin OR 24 weeks (no ribavirin)
Paritaprevir–ritonavir (150 mg/100 mg), orally, daily + Ombitasvir 25 mg, orally, daily + Dasabuvir 250 mg, orally, twice daily ± Ribavirin 1000/1200 mg, orally, daily§	1a	12 weeks + ribavirin	12 weeks + ribavirin	12 weeks + ribavirin	12 or 24 weeks + ribavirin**
	1b	12 weeks	12 weeks	12 weeks	12 weeks
Sofosbuvir 400 mg, orally, daily + Ribavirin 1000/1200 mg, orally, daily§	2	12 weeks	12 weeks	12 weeks	12 weeks
Sofosbuvir 400 mg, orally, daily + Daclatasvir, 60 mg, orally, daily‡	3	12 weeks	12 weeks	24 weeks	24 weeks
Sofosbuvir 400 mg daily + Ribavirin 1000/1200 mg daily§	3	24 weeks	24 weeks	24 weeks	24 weeks
Sofosbuvir 400 mg, orally, daily + Peginterferon-alfa, subcutaneously, weekly + Ribavirin 1000/1200 mg, orally, daily§	3, 4, 5, 6	12 weeks	12 weeks	12 weeks	12 weeks

* Treatment experience generally refers to peginterferon-**alfa** plus ribavirin ± first-generation protease inhibitors (see full consensus statement). † 8 weeks may be considered if HCV RNA < 6 × 10^6 IU/mL in people with no cirrhosis who are treatment-naive. ‡ Daclatasvir dose modification is required when used in combination with specific antiretroviral therapies for HIV (see full consensus statement). § Ribavirin dosing is weight-based; recommended dose is 1000 mg for people weighing < 75 kg and 1200 mg for people weighing ≥ 75 kg. ¶ Recommended treatment duration for sofosbuvir plus daclatasvir (no ribavirin) for people who have failed treatment with a protease inhibitor + peginterferon + ribavirin is 24 weeks, including people with cirrhosis and people with no cirrhosis; recommended treatment duration for people with no cirrhosis who have previously failed peginterferon + ribavirin is 12 weeks. ** Recommended treatment duration for paritaprevir–ritonavir, ombitasvir, dasabuvir (PrOD) plus ribavirin in people with genotype 1a HCV and cirrhosis who have had a previous null response to peginterferon-alfa and ribavirin therapy is 24 weeks. PrOD therapy is not recommended for people who did not respond to previous therapy that included an HCV protease inhibitor or an NS5A inhibitor.

Notes: Sofosbuvir is not recommended for patients with an estimated glomerular filtration rate < 30 mL/min/1.73m². At the time of writing, the combination of PrOD ± ribavirin was approved by the Therapeutic Goods Administration but not yet available for prescription under the Pharmaceutical Benefits Scheme; this treatment regimen should be used with caution in people with cirrhosis and is contraindicated in people with decompensated liver disease. Dose reduction or dose interruption of direct-acting antiviral therapy is not recommended. Dose reduction of ribavirin for the management of symptomatic anaemia according to the product information is appropriate and will not reduce the likelihood of SVR (sustained virological response at least 12 weeks after treatment [cure]).
The recommended treatment regimens differ in the setting of decompensated liver disease (Child–Pugh score ≥ B7) (see full consensus statement).

GESA Gastroenterological Society of Australia
ala Australian Liver Association
AUSTRALASIAN HEPATOLOGY ASSOCIATION
ASID
ashm
Supporting the HIV, Viral Hepatitis and Sexual Health Workforce
hepatitis australia

www.gesa.org.au

Thompson AJ, Med J Aust 2016; 204 (7): 268-272

Checklist for pre-treatment assessment		
	HCV virology: • Anti-HCV (serology) • HCV RNA level (quantitative) • HCV genotype	 • Indicates HCV exposure • Confirms HCV infection • Determines treatment regimen
	HCV treatment history — previous regimen and response	Determines treatment regimen and duration
	Potential for non-adherence?	Consider medical and social issues that may be barriers to medication adherence
	Alcohol intake history	Cofactor for cirrhosis
	Weight and body mass index	Non-alcoholic fatty liver disease (NAFLD) — cofactor for cirrhosis
	Pregnancy discussion*	
	Check for drug–drug interactions	**www.hep-druginteractions.org** Includes prescribed, over-the-counter, complementary/herbal, illicit drugs
	Signs of chronic liver disease	
	FBE	• Baseline haemoglobin level • Low platelets are a marker of portal hypertension
	LFTs and INR	Low albumin, raised bilirubin, raised INR identify liver synthetic dysfunction and suggest advanced cirrhosis
	U&Es and eGFR	• Sofosbuvir is not recommended if eGFR < 30 mL/min/1.73m² • Ribavirin is renally cleared and needs dose reduction if eGFR < 50 mL/min/1.73m²
	Fasting glucose and lipids	Diabetes and hyperlipidaemia are associated with NAFLD
	HBV (HBsAg, anti-HBc, anti-HBs), HIV, HAV serology	If seronegative, vaccinate against HAV, HBV
	Cirrhosis assessment • FibroScan • APRI	Determines treatment regimen and duration Thresholds consistent with no cirrhosis: • Liver stiffness < 12.5 kPa • APRI < 1.0
	If cirrhosis present: • Specialist referral recommended • MELD and Child–Pugh scores • Liver ultrasound • Gastroscopy • Bone densitometry scan	 • Prognostic scores indicating liver decompensation • Screen for HCC, portal hypertension • Screen for oesophageal varices • Screen for osteoporosis
	Electrocardiogram if ribavirin therapy planned and patient is aged > 50 years OR has cardiac risk factors	Screen for ischaemic heart disease

* As there are no safety data for the use of any direct-acting antiviral regimen during pregnancy, treatment of pregnant women is not recommended. Ribavirin (Category X) and peginterferon-alfa are contraindicated during pregnancy. Both women and men should be counselled about the risk of teratogenicity and the importance of avoiding pregnancy during treatment, and for 6 months after ribavirin treatment. Women treated with paritaprevir–ritonavir, ombitasvir and dasabuvir should avoid ethinyl estradiol-containing contraceptives.

HCV – hepatitis C virus. FBE – full blood examination. LFT – liver function test. INR – international normalised ratio. U&E – urea and electrolyte. eGFR – estimated glomerular filtration rate. HBV – hepatitis B virus. HAV – hepatitis A virus. HBsAg – hepatitis B surface antigen. anti-HBc – hepatitis B core antibody. anti-HBs – hepatitis B surface antibody. APRI – aspartate aminotransferase to platelet ratio index. MELD – Model for End-Stage Liver Disease. HCC – hepatocellular carcinoma.

On-treatment and post-treatment monitoring for virological response	
Routine monitoring for a 12-week treatment regimen:	
Week 0	• FBE, U&Es, LFTs, INR, HCV RNA level (quantitative)
Week 4	• FBE, LFTs
Week 12 ± 24 (EOT)	• FBE, LFTs, HCV PCR (qualitative)
	• At each on-treatment visit, assess for: ▸ medication adherence ▸ treatment adverse effects ▸ drug–drug interactions
Week 12 after EOT (SVR)	• FBE, LFTs, HCV PCR (qualitative)

Routine on-treatment HCV RNA testing is not mandated but may be considered where there is a clinical concern about non-adherence to treatment, especially in people with cirrhosis. The need for increased frequency of review should be individualised. People taking ribavirin may require FBE at Week 2 and Week 4 and then every 4 weeks. People with cirrhosis require monitoring every 4 weeks, including FBE, LFTs and assessment for hepatic decompensation. Measurement of quantitative HCV RNA level is recommended at Weeks 4, 12 ± 24 on-treatment in patients with cirrhosis. People with cirrhosis who are treated with the combination of paritaprevir–ritonavir, ombitasvir, dasabuvir ± ribavirin should have LFTs checked at Week 2 as well as Week 4. People with decompensated liver disease require close monitoring, with review every 2–4 weeks.

EOT – end of treatment. SVR – sustained virological response at least 12 weeks after treatment (cure). FBE – full blood examination. U&E – urea and electrolyte. LFT – liver function test. INR – international normalised ratio. HCV – hepatitis C virus. PCR – polymerase chain reaction.

Ongoing monitoring of people after successful hepatitis C treatment outcome (SVR)
SVR, no cirrhosis, and normal LFT results (males, ALT < 30 U/L; females, ALT < U/L): • People who are cured do not require clinical follow-up for hepatitis C
SVR and abnormal LFT results (males, ALT ≥ 30 U/L; females, ALT ≥ 19 U/L): • People with persistently abnormal LFT results require evaluation for other liver diseases and should be referred for gastroenterology review. Investigations to consider include: fasting glucose level, fasting lipid levels, iron studies, ANA, ASMA, anti-LKM antibodies, total IgG and IgM, AMA, coeliac serology, copper, caeruloplasmin, and α-1-antitrypsin levels.
SVR, cirrhosis: • People with cirrhosis require long-term monitoring and should be enrolled in screening programs for: ▸ hepatocellular carcinoma ▸ oesophageal varices ▸ osteoporosis

SVR – sustained virological response at least 12 weeks after treatment (cure). LFT – liver function test. ALT – alanine aminotransferase. ANA – anti-nuclear antibodies. ASMA – anti-smooth muscle antibodies. LKM – liver–kidney microsome. AMA – anti-mitochondrial antibody.

People who do not respond to hepatitis C treatment
• Specialist referral recommended

GESA Gastroenterological Society of Australia
ala Australian Liver Association
AUSTRALASIAN HEPATOLOGY ASSOCIATION
ASID
ashm Supporting the HIV, Viral Hepatitis and Sexual Health Workforce
hepatitis australia

www.gesa.org.au

Thompson AJ, Med J Aust 2016; 204 (7): 268-272

"Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning"

Winston Churchill, 1942

Victory over Hep C