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Hepatitis C in 2017

Part 2: Hepatitis C treatment

Acknowledgment to Country

We are committed to supporting reconciliation between Indigenous and non-Indigenous Australian people. In keeping with the spirit of Reconciliation, we acknowledge the Aboriginal and Torres Strait Islander Peoples as the Traditional Owners of the lands. We wish to pay respect to their Elders – past, present and emerging – and acknowledge the important role Aboriginal and Torres Strait Islander people continue to play within our community.

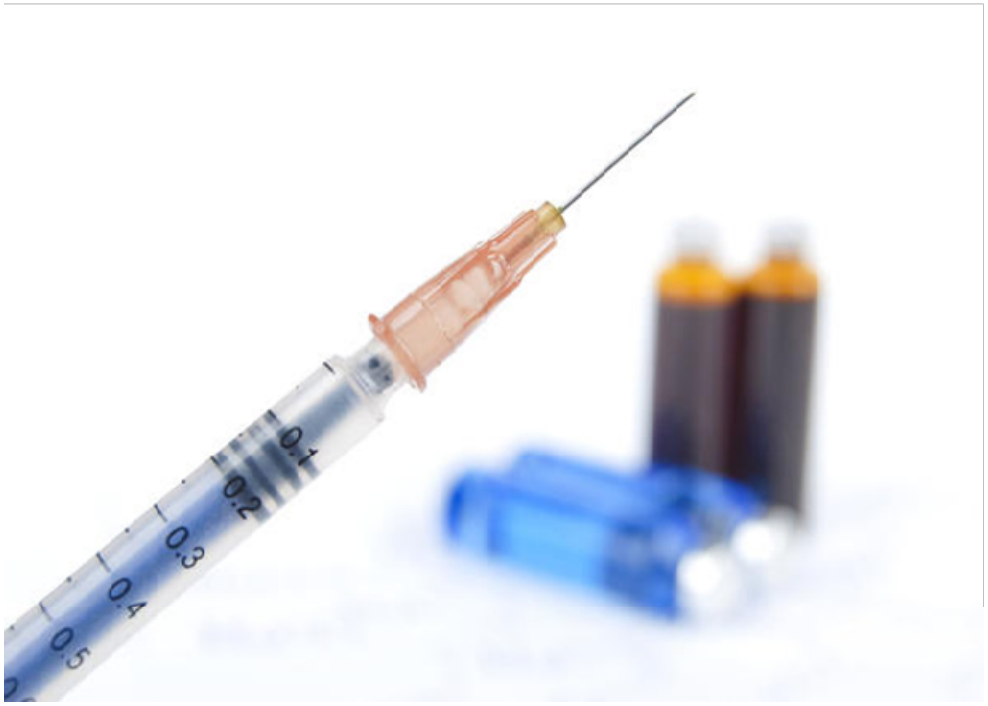
PHN Acknowledgment

This webinar has been developed by Eastern Melbourne PHN on behalf of the Victorian PHN Alliance, which is the collective platform for the six PHNs in Victoria.

Eastern Melbourne PHN does not take responsibility arising from the use of, or reliance on, this webinar by a third party. Any such use or reliance is the sole responsibility of that party. This webinar does not constitute medical advice. If you require medical advice, please consult an appropriate medical professional.

Information contained in this presentation is current as at June 2017

Setting the scene …

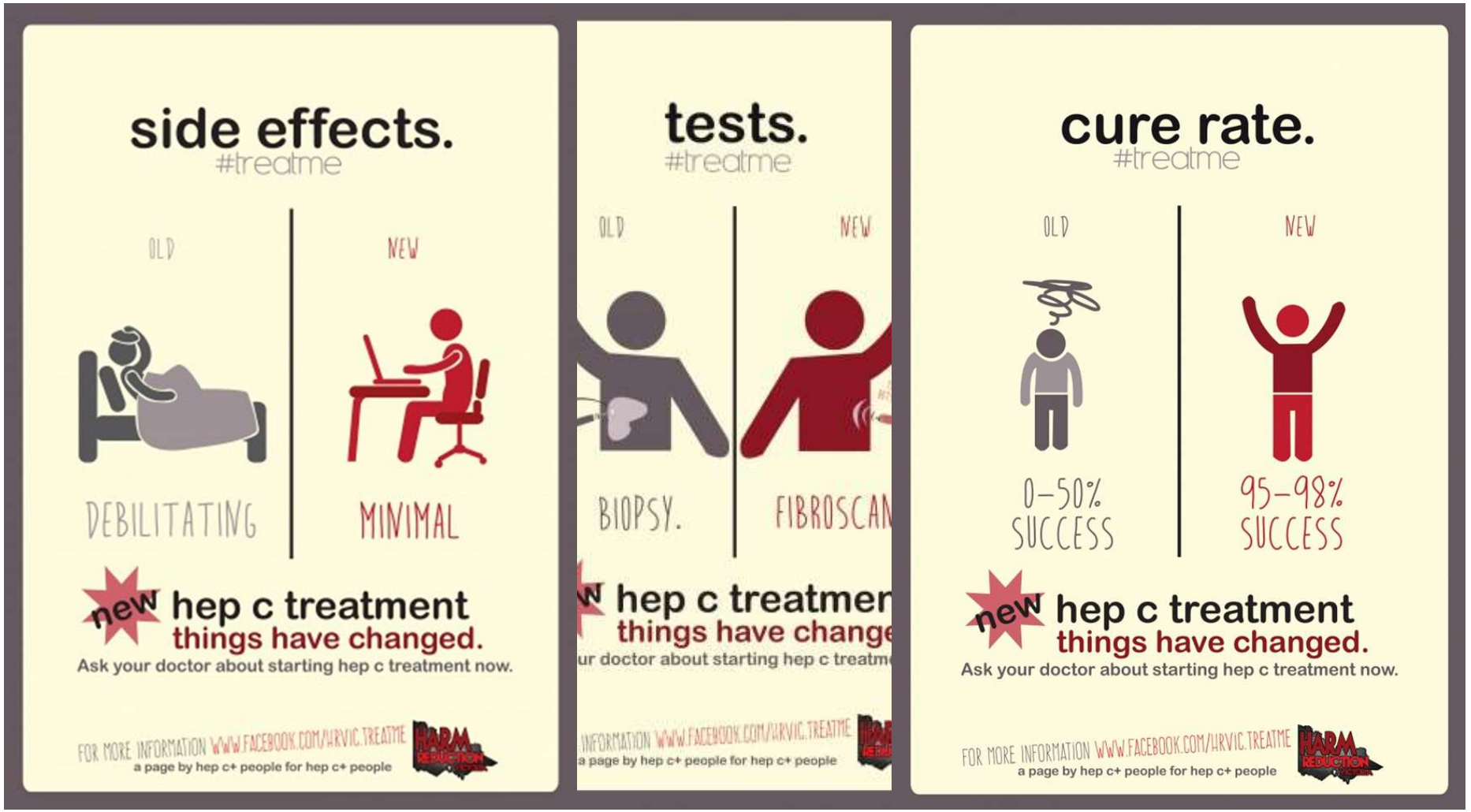


Hepatitis C treatment in 2016 and beyond

Australian Government

"..no matter what their condition or how they contracted it…"

Past vs present…



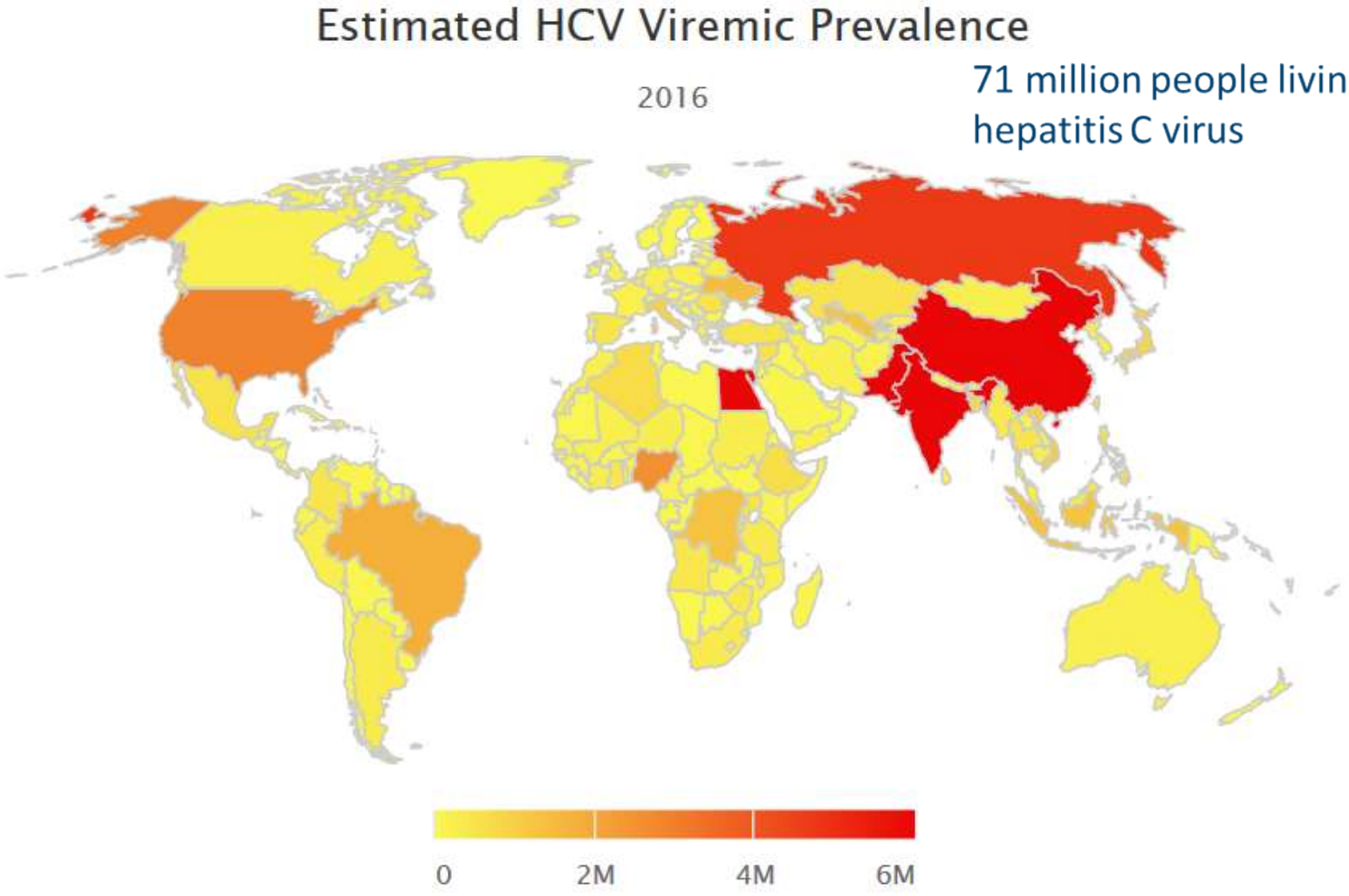
Overview

- Hepatitis C epidemiology
  - Global and local
  - Genotypes
- New era of hepatitis C treatment
  - Direct Acting Antivirals
  - Clinical Guidelines for hepatitis C treatment
  - Clinical monitoring
- Treatment uptake in Australia

Learning objectives

1. Identify treatment options for your patients with hepatitis C.
2. Describe the monitoring requirements for your patients undergoing treatment for hepatitis C.

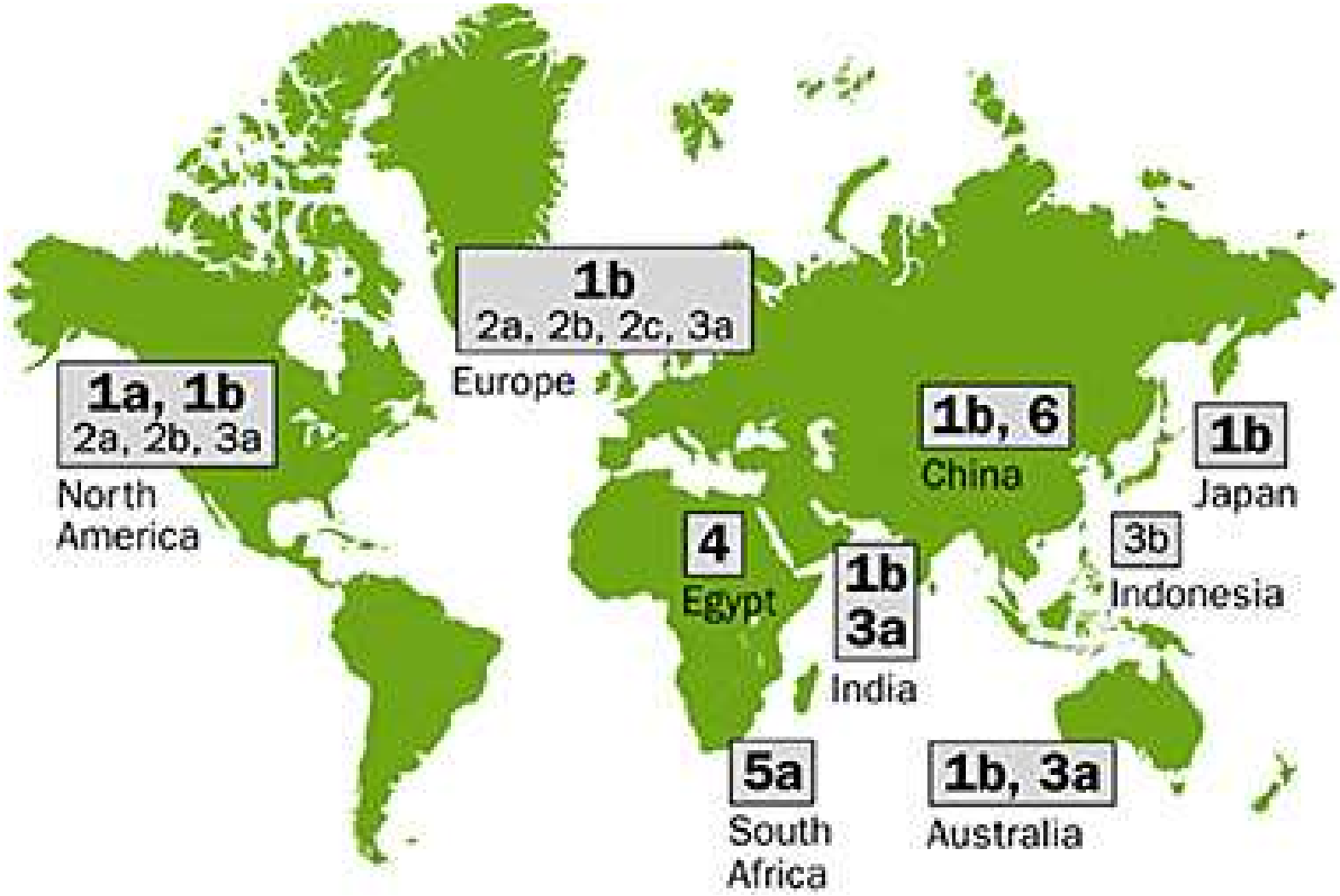
Global hepatitis C epidemiology



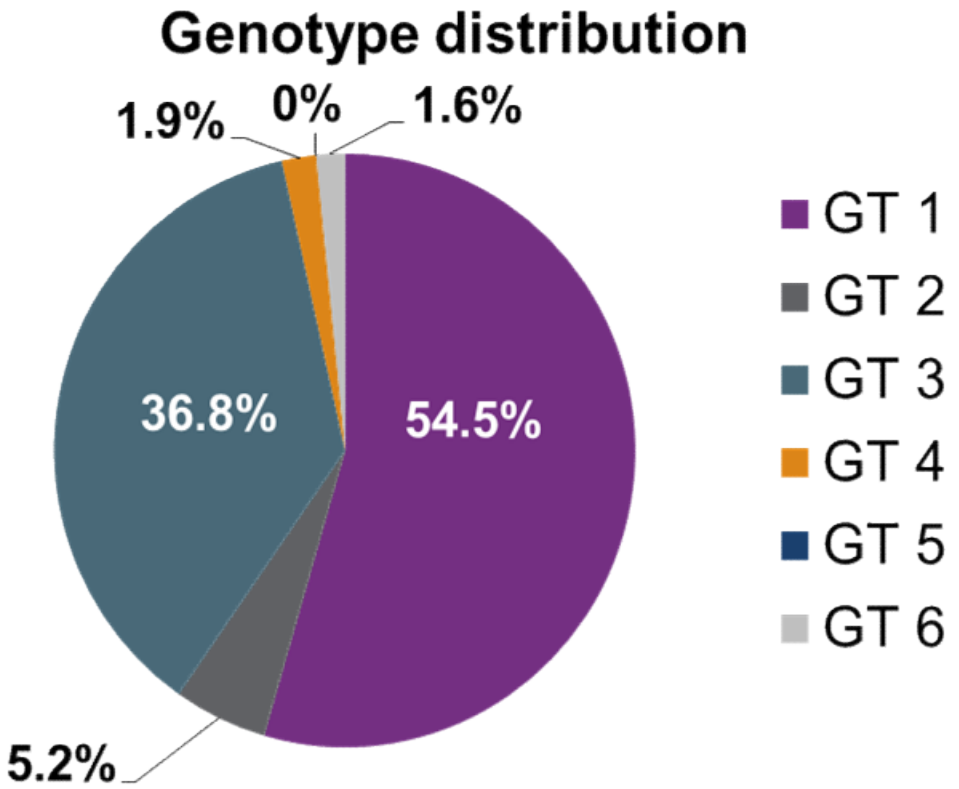
Hepatitis C in Australia

- ~227,306 people were living with hepatitis C at the end of 2015
  - 29,070 had severe fibrosis
  - 17,149 had hepatitis C-related cirrhosis
  - 818 deaths were attributable to hepatitis C
- 65,000 Victorians living with hepatitis C

Hepatitis C genotypes

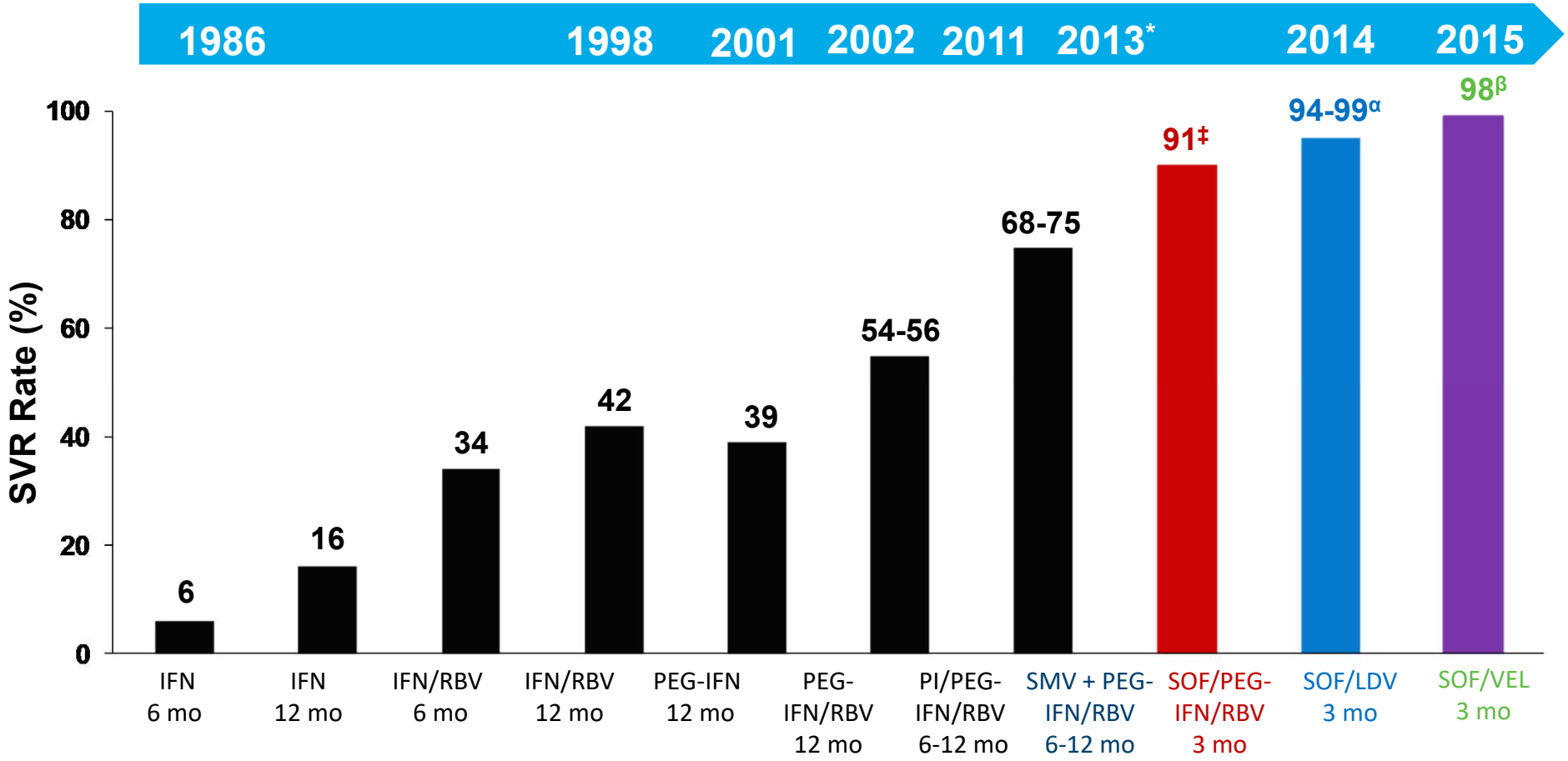


Hepatitis C genotypes in Australia



Of those with GT1 infection:
~ 40% have GT1a
~ 32% GT1b

Cure rates in patients with hepatitis C (genotype 1)



*Year of presentation of QUEST-1, QUEST-2, and NEUTRINO
‡SVR12 rate of 90% among GT 1 patients in the Phase 3 NEUTRINO trial (12 weeks of SOF+PEG-IFN+RBV)
αSVR12 rate of 95-99% among GT 1 patients in the Phase 3 ION-1, ION-2 & ION-3 trials (12 weeks of SOF/LDV)
βSVR12 rate of 98% among GT 1 patients in the Phase 3 ASTRAL-1 trial (12 weeks of SOF/VEL)

Adapted from Strader DB, et al. *Hepatology* 2004;39:1147-71. INCIVEK [PI]. Cambridge, MA: Vertex Pharmaceuticals; 2012. VICTRELIS [PI]. Whitehouse Station, NJ: Merck & Co; 2011. Jacobson I, et al. EASL 2013. Amsterdam. The Netherlands. Poster # 1425. Manns M, et al. EASL 2013. Amsterdam. The Netherlands. Oral #1413. Lawitz E, et al. APASL 2013. Singapore. Oral #LB-02; Afdhal N, et al. *N Engl J Med* 2014;370:1889–98; Kowdley KV, et al. *N Engl J Med* 2014;370:1879–88; Afdhal N, et al. *N Engl J Med* 2014;370:1483–93; Feld JJ, et al. *N Engl J Med*. 2015;373:2599-607.

New era of hepatitis C treatment

- 1st March 2016, Australia publicly subsidised through the Pharmaceutical Benefits Scheme (PBS) curative Direct Acting Antiviral (DAA) regimens for all people with hepatitis C
  - No restrictions on stage of liver disease
  - No restrictions on alcohol or drug use
  - No restrictions on the number of times a person can be treated

$1 billion over five years…

Australian consensus recommendations (2017)

- www.gesa.org.au
- Best practice guidelines for the management of hepatitis C
- Focuses on primary care management of hepatitis C

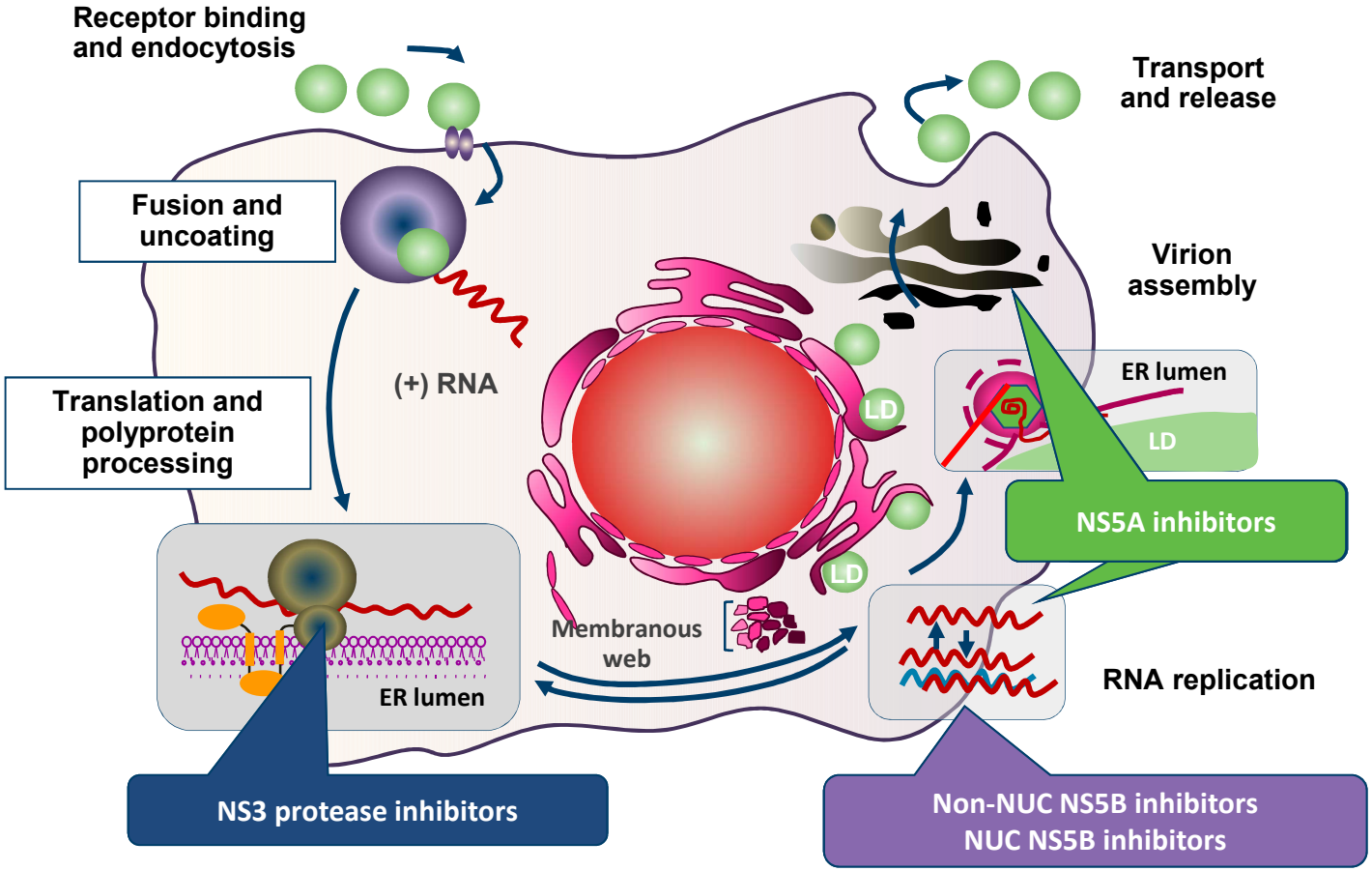
New era of hepatitis C treatment

- Daklinza® (daclatasvir)
- Harvoni® (sofosbuvir + ledipasvir)
- Ibavyr® (ribavirin)
- Sovaldi® (sofosbuvir)
- Viekira Pak® (paritaprevir + ritonavir + ombitasvir + dasabuvir)
- Viekira Pak RBV® (paritaprevir + ritonavir + ombitasvir + dasabuvir + ribavirin)
- Zepatier® (elbasvir + grazoprevir)

New era of hepatitis C treatment

- DAA treatment:
  - Highly effective (95% cure rate)
  - All oral tablets for 8-12 weeks (no cirrhosis), up to 24 weeks for patients with cirrhosis
  - Few side effects

DAAs target different stages of the hepatitis C virus lifecycle



Adapted from Lindenbach BD, Rice CM. *Nature* 2005;436(Suppl):933–8.

DAA: direct acting antiviral; ER: endoplasmic reticulum; LD: luminal domain; NUC: nucleotide

Treatment for people with genotype 1 (G1)

- Treatment choices:
  - sofosbuvir + ledipasvir (Harvoni®)
  - sofosbuvir + daclatasvir ± ribavirin
  - paritaprevir (ritonavir-boosted) + ombitasvir + dasabuvir ± ribavirin (Viekira Pak RBV®)
  - elbasvir + grazoprevir (Zepatier®) ± ribavirin
- All well tolerated; efficacy≥ 95% across all patient groups, including people with cirrhosis and those who have not responded previously to Pegylated Interferon (pegIFN) + ribavirin

Table 3. Treatment protocols for people with compensated liver disease and hepatitis C virus (HCV) genotype (Gt) 1 infection, including people with HCV–HIV coinfection

Regimen	HCV Gt	Treatment duration				Efficacy (SVR)
		No cirrhosis		Cirrhosis		
		Treatment-naive	Treatment-experienced*	Treatment-naive	Treatment-experienced*	
Sofosbuvir 400 mg, orally, daily + Ledipasvir 90 mg, orally, daily	1a/b	8 weeks OR 12 weeks‡	12 weeks§	12 weeks	24 weeks§	≥ 95%
Sofosbuvir 400 mg, orally, daily + Daclatasvir 60 mg, orally, daily† ± Ribavirin 1000/1200 mg, orally, daily (weight-based)††	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)¶	≥ 95%
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 (weight-based)††	1a	12 weeks + ribavirin	12 weeks + ribavirin	12 weeks + ribavirin	12 weeks + ribavirin**	≥ 95%
	1b	12 weeks	12 weeks	12 weeks	12 weeks	
Elbasvir, 50 mg, orally, daily + Grazoprevir, 100 mg, orally, daily ± Ribavirin 1000/1200 mg, orally, daily (weight-based)††	1a	12 weeks	12 weeks (relapser) OR 16 weeks + ribavirin (on-treatment virological failure)	12 weeks	12 weeks (relapser) OR 16 weeks + ribavirin (on-treatment virological failure)	≥ 95%
	1b	12 weeks	12 weeks	12 weeks	12 weeks	

Treatment for people with Genotype 3 (G3)

- Genotype 3 is harder to cure than Gt 1 and 2 using DAA therapy
  - Particularly in people with cirrhosis and prior non-responders to pegIFN + ribavirin
  - Sofosbuvir + daclatasvir for 12 or 24 weeks
  - Sofosbuvir + ribavirin for 24 weeks

Table 4. Treatment protocols for people with compensated liver disease and hepatitis C virus (HCV) genotype (Gt) 2 or 3 infection, including people with HCV–HIV coinfection

		Treatment duration				
		No cirrhosis		Cirrhosis		
Regimen	HCV Gt	Treatment-naive	Treatment-experienced*	Treatment-naive	Treatment-experienced*	Efficacy (SVR)
Sofosbuvir 400 mg, orally, daily + Ribavirin 1000/1200 mg, orally, daily (weight-based)†	2	12 weeks	12 weeks	12 weeks	12 weeks	> 90%
Sofosbuvir 400 mg, orally, daily + Daclatasvir, 60 mg, orally, daily‡ ± Ribavirin 1000/1200 mg, orally, daily (weight-based)†	3	12 weeks	12 weeks	12 weeks + ribavirin OR 24 weeks	12 weeks + ribavirin OR 24 weeks	> 85%
Sofosbuvir 400 mg, orally, daily + Ribavirin 1000/1200 mg, orally, daily (weight-based)†	3	24 weeks	24 weeks	24 weeks	24 weeks	58%–95%§
Sofosbuvir 400 mg, orally, daily + PegIFN, subcutaneously, weekly + Ribavirin 1000/1200 mg, orally, daily (weight-based)†	3	12 weeks	12 weeks	12 weeks	12 weeks	> 85%

Treatment for people with Genotype 4 (G4)

- The combination of elbasvir + grazoprevir ± ribavirin is PBS-listed for the treatment of people with Gt 4

Treatment for people with Genotypes 5 and 6

- Combination of sofosbuvir + pegIFN and ribavirin for 12 week
  - SVR rates of 96%–100%

Another change is around the corner …

Pangenotypic regimen: EPCLUSA

- Sofosbuvir/Velpatasvir
  - One pill, once a day
  - Clinical trials included patients with GT1-6
  - Overall, 98% of patients achieve an SVR12 (GT1 99%, GT2, 99%, GT3 95%, GT4 97%, GT5 100%, GT6 100%)
  - Most common adverse events were headache, fatigue, nausea and nasopharangitis
- Awaiting PBS listing

Pre-treatment assessment

- Patient's history
  - Identify threats and supports for adherence
- What medication is the patient taking?
  - Prescription, over-the-counter, illicit, herbal
  - Develop a comprehensive list so a DDI check can be done
- Physical examination
  - Signs of cirrhosis (e.g. spider naevi)
- Virology
- Investigations (FBE, LFTs, INR)
- Fibrosis assessment

Liver fibrosis assessment

- Serum biomarker
  - APRI = aspartate aminotransferase (AST) to platelet ratio index
  - A result <1 indicates that cirrhosis is unlikely
- Non-invasive test such as transient elastography (e.g. FibroScan®)
- Formal evaluation for cirrhosis with a non-invasive test is recommended for all people with hepatitis C

Prevalence of hepatitis C-related cirrhosis

- Bloom et al. (2016) assessed the prevalence of liver disease in patients with hepatitis C or B, aged 18-80 years, who had not been assessed by a liver specialist (<18 months), but were attending high case load primary care practices in Melbourne
  - 15.9% estimated to have cirrhosis and 40.6% with significant fibrosis in people with hepatitis C
  - High rates of cirrhosis in patients not engaged with specialist liver health care is of significant concern

Drug-drug interactions (DDIs)

- DDIs are a potential issue for all DAA regimens
- Important drugs to consider for potential interactions with DAAs include:
  - proton pump inhibitors
  - Statins
  - St John's wort
  - Antimicrobials
  - anti-epileptic agents
  - amiodarone,
  - immunosuppressive agents including cyclophilin inhibitors and mammalian target ofrapamycin (mTOR) inhibitors, and antiretroviral agents
- University of Liverpool's Hepatitis Drug Interactions website www.hep-druginteractions.org

Adherence to DAAs

Patient Preference and Adherence

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Open Access Full Text Article

ORIGINAL RESEARCH

The Australasian Hepatology Association consensus guidelines for the provision of adherence support to patients with hepatitis C on direct acting antivirals

This article was published in the following Dove Press journal:
Patient Preference and Adherence
13 December 2016
Number of times this article has been viewed

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Background: Hepatitis C is a blood-borne virus primarily spread through sharing of drug-injecting equipment. Approximately 150 million people worldwide and 230,000 Australians are living with chronic hepatitis C infection. In March 2016, the Australian government began subsidizing direct acting antivirals (DAAs) for the treatment of hepatitis C, which are highly effective (95% cure rate) and have few side effects. However, there is limited evidence to inform epatitis C on DAAs including the level of medication adherence required to achieve a cure.

www.dovepress.com/the-australasian-hepatology-association-consensus-guidelines-for-the-p-peer-reviewed-article-PPA

Adherence to DAAs

- High adherence is a process, not an isolated event
- Adherence support needs to be integrated into the practice of all members of the interdisciplinary team
- Primary health carers have an important role in supporting adherence to DAAs

1. Optimal adherence to the hepatitis C DAAs is yet to be determined. Therefore, it is recommended that every effort is made to support patients to be 100% adherent to DAAs.
2. The patient-centered approach underpins the delivery of DAA adherence support.
3. All patients are at risk of nonadherence (intentional and/or unintentional).
4. Patients benefit from receiving holistic care from members of the interdisciplinary team.
5. All patients should have the opportunity to engage in a pretreatment assessment with a health professional knowledgeable about hepatitis C.
6. All patients should have the opportunity to discuss their readiness to commence DAA treatment with a health professional knowledgeable about hepatitis C.
7. The decision to commence DAA treatment is shared between the patient with hepatitis C and their treating clinician.
8. Where possible, people with hepatitis C should have the opportunity to choose the clinical setting where they access DAA treatment (excluding patients with complex comorbidities, such as, but not limited, to cirrhosis).
9. Pretreatment education should adopt a patient-centered approach incorporating the patient's health literacy and cultural needs.
10. Using a patient-centered approach pretreatment education should include a discussion about harm minimization strategies to reduce the risk of reinfection.

Treatment monitoring

- On-treatment monitoring is usually not necessary but should be assessed on a case-by-case basis to:
  - Optimise adherence
  - Assess adverse events
  - Potential drug–drug interactions
  - Monitor blood test results necessary for patient safety
- All patients should be provided with the contact details of the treating clinician

Treatment monitoring

- For most people one assessment at Week 4 of treatment will be sufficient during an 8-week or 12-week treatment course
  - Patients taking Zepatier need LFTs performed during treatment (week 4 or 8) for 12 or 16 weeks' duration
- PCR at 12 weeks after treatment completion
  - No need for PCR tests during treatment
- HCC surveillance is recommended at baseline for all people living with cirrhosis
  - Ongoing surveillance recommended every 6 months – including after treatment

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

- People treated with elbasvir plus grazoprevir should have LFTs at Week 8 to screen for hepatotoxicity. The Week 8 LFTs may be done as an alternative to Week 4 LFTs.
- 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.
- Patients taking ribavirin may require FBE at Week 2 and Week 4 and then every 4 weeks.
- Patients with cirrhosis require HCC screening with liver ultrasound every 6 months.
- Patients with decompensated liver disease require close monitoring, with review every 2–4 weeks. Measurement of quantitative HCV RNA level is recommended at Weeks 4, 12 ± 24 on-treatment in these patients to confirm viral suppression.

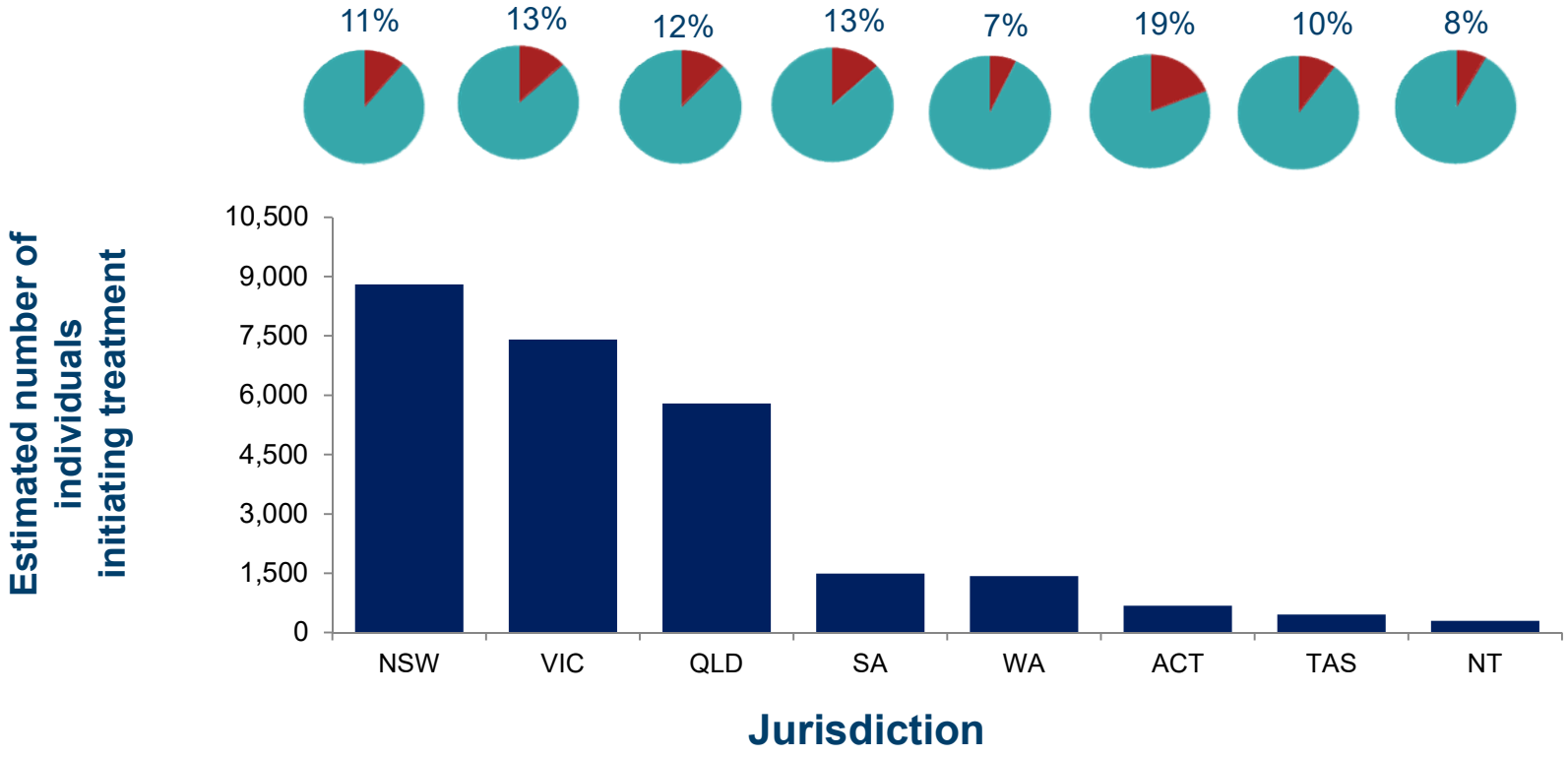
B. Monitoring after SVR
SVR, no cirrhosis and normal LFT results (males, ALT < 30 U/L; females, ALT < 19 U/L):
• Patients who are cured do not require clinical follow-up for HCV
SVR and abnormal LFT results (males, ALT ≥ 30 U/L; females, ALT ≥ 19 U/L):
• Patients with persistently abnormal LFT results 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 level, caeruloplasmin level and α-1-antitrypsin level
SVR and cirrhosis:

Treatment uptake in Australia

- An estimated 25,890 individuals initiated DAA therapy between March and September 2016
  - 33,390 people initiated treatment March-Dec 2016
- 11% of people living with hepatitis C in Australia
- Most commonly prescribed regimens:
  - Sofosbuvir/ledipasvir (Harvoni), 57%
  - Sofosbuvir/daclatasvir, 38%
- % of individuals receiving GP prescriptions increased from 4% in March to 19% in Sept

Australian uptake DAA March–July 2016, by jurisdiction

The estimated number of people initiating DAA treatment (bar charts) and the proportion of individuals with hepatitis C who initiated DAA treatment (pie charts) during March–July 2016, by jurisdiction



Monitoring hepatitis C uptake in Australia. Available at: http://www.ashm.org.au/Documents/Kirby_HepC_Newsletter_Issue5_2.pdf (accessed December 2016)

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

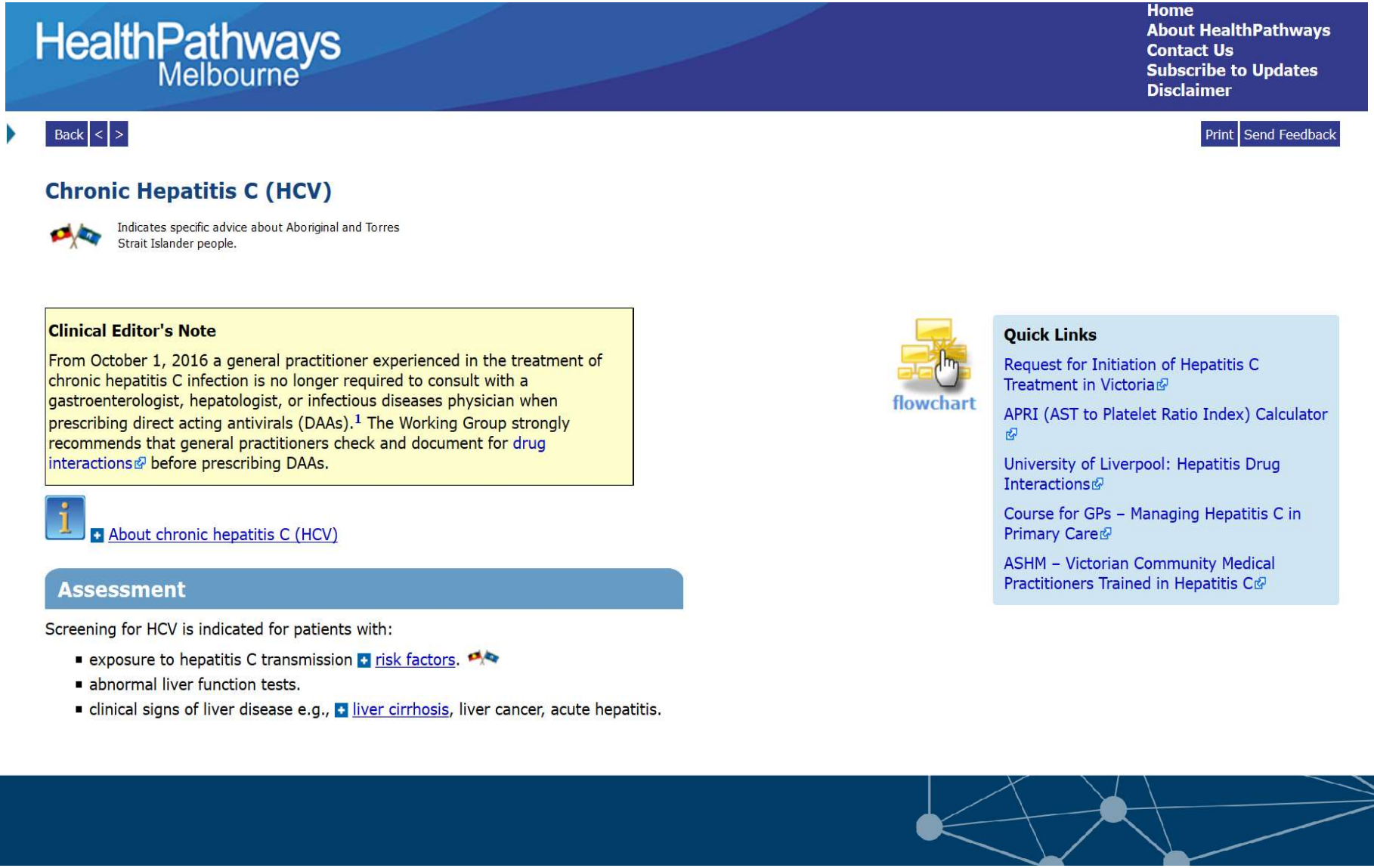
Treatment access in Australia

- DAAs are available through the PBS General Schedule (Section 85) and the Section 100 (S100) Highly Specialised Drugs Program
  - S85 prescriptions are filled at community pharmacies
  - S100 prescriptions are filled at hospital pharmacies
    - Allows access for people in custodial settings

Prescribers

- The PBAC recommendation was updated on the 1st November 2016:
  - DAAs can be prescribed by any medical practitioner experienced in the treatment of chronic hepatitis C infection, or in consultation with a gastroenterologist, hepatologist or infectious diseases physician experienced in treating chronic hepatitis C infection
  - Nurse practitioners have also just been approved as prescribers

melbourne.healthpathways.org.au



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Note: HCV RNA testing – about 20% of patients will spontaneously resolve their infection within the first year. This group is anti-HCV positive, but HCV RNA negative. They do not have ongoing infection, only past (resolved) infection.

Management

Advise patients to cease all complementary and alternative medicines during the treatment period with DAAs to optimise the likelihood of cure.

Initial management to determine eligibility for DAAs

Initiating treatment with DAAs

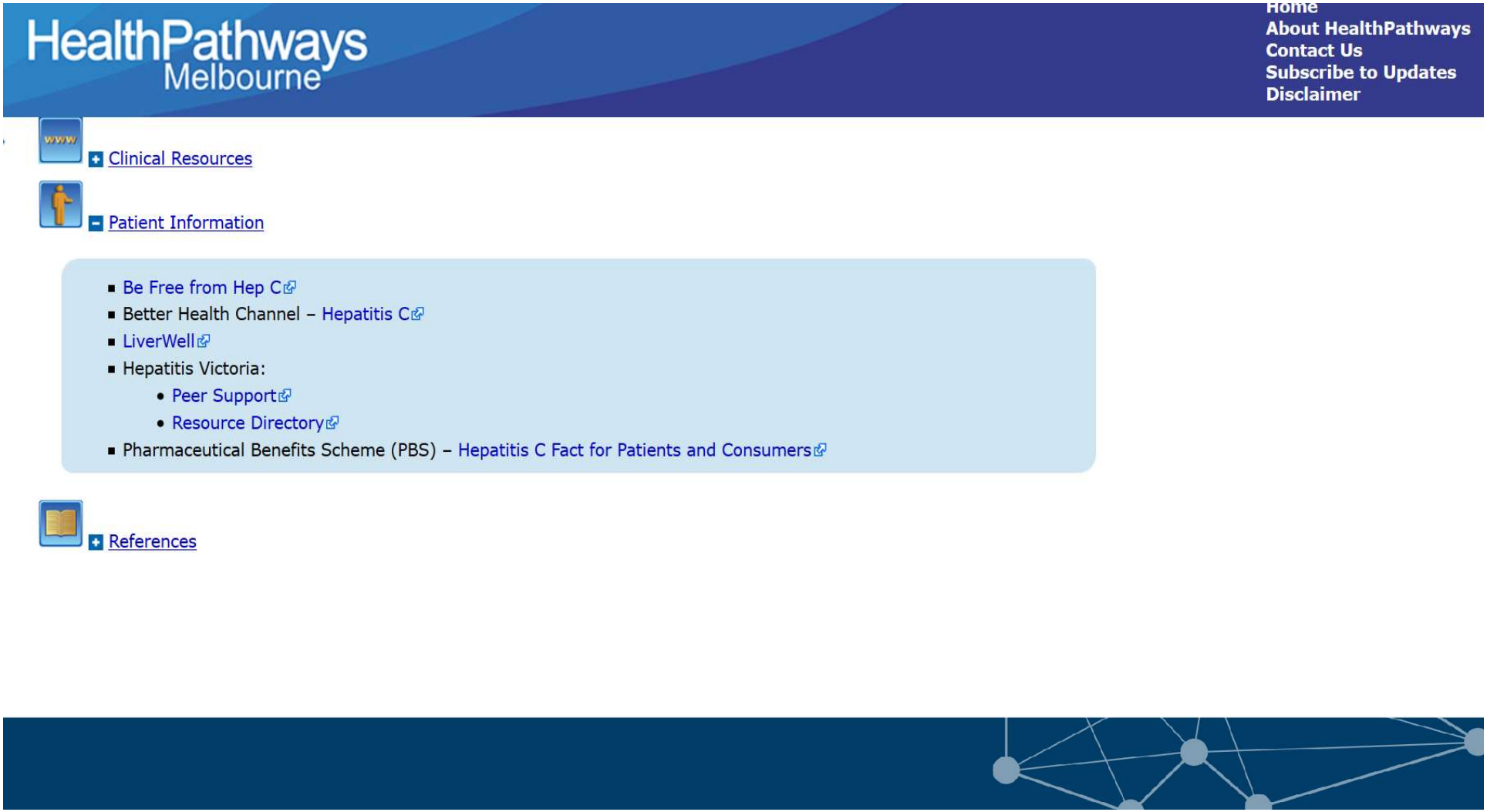
Monitoring treatment with DAAs

Long-term management

Referral

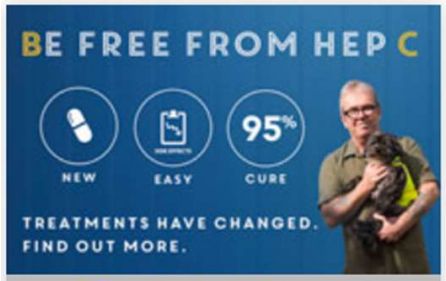
- If patient is eligible for treatment with DAAs, and for new prescribers, refer for specialist consultation and approval for treatment.
- Refer patient for urgent liver assessment or gastroenterology assessment, especially in patients with:
  - cirrhosis.
  - coexisting liver diseases, including hepatitis B.
  - complicated comorbidities.
  - new suspicious liver lesion (HCC).
  - worsening liver function.
- Consider infectious diseases assessment (if available locally) for those patients with concomitant infections, including HIV or hepatitis B.
- Complete a Request for Initiation of Hepatitis C Treatment in Victoria for initiation of hepatitis C treatment.

melbourne.healthpathways.org.au



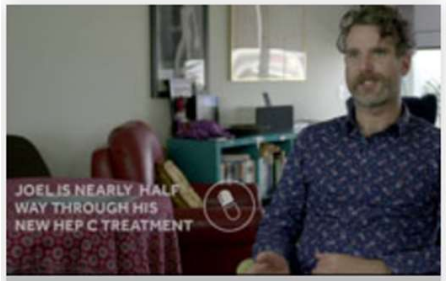
Be free from Hepatitis C campaign

www.befreefromhepc.org.au



Watch the full story

Watch Billy's story



Watch Joel's story

Watch Julie's story

Watch Jane's treatment diary

Watch Amanda's story

Summary

- There have been significant changes to the treatment of hepatitis C infection
- Primary health care has a significant role in:
  - Pre treatment assessment including liver fibrosis assessment using APRI and if indicated FibroScan®
  - GP and Nurse Practitioner prescribing
  - Linking with community pharmacies for dispensing of the DAAs

Eliminating hepatitis C from Victoria

- Partnership between the Burnet Institute, St Vincent's Hospital, Department of Health Victoria and Gilead Sciences
- https://www.burnet.edu.au/centres/24_eliminate_hep_c

Thank you for watching and listening

Feedback or further support regarding this webinar should be directed to your local PHN.

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