Hepatitis C epidemiology, screening and treatment

Date: Wednesday 29 August 2018: 7.00-8.00pm
Presenter: Professor Greg Dore

This education activity has been developed in association with:
• Kirby Institute, UNSW & St Vincent’s Hospital
• Aboriginal Health and Medical Research Council of NSW and NSW Health

Acknowledgement of Country

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

We pay our respects to Elders past and present.
Hepatitis C epidemiology, screening and treatment

Professor Greg Dore
Program Head, Viral Hepatitis Clinical Research Program, Kirby Institute, UNSW Sydney
Infectious Diseases Physician, St Vincent's Hospital, Sydney
NHMRC Practitioner Fellow

Learning Outcomes

• Identify risk factors and increase appropriate screening strategies for Hepatitis C within a community setting.

• Discuss barriers to effective implementation of Hepatitis C diagnosis and treatment.

• Outline the role of general practitioners (GPs) and other health practitioners in the context Hepatitis C treatment for Aboriginal and Torres Strait Islander people.

• Discuss the importance of harm reduction for prevention of Hepatitis C, including following successful treatment (reinfection).
Session outline

- Introduction to hepatitis C
- Identify priority populations for hepatitis C testing
- Interpret test results for hepatitis C
- Primary care based management and specialist referral
- Pre-treatment assessment, including liver fibrosis
- Treatment of hepatitis C and post-treatment monitoring

Introduction to hepatitis C
Global HCV burden: 2016 chronic HCV

Core message:
- Viral Hepatitis C in the world
- 71 million people globally
- Distribution by region

Natural history of HCV infection:
1. Acute HCV
   - Symptomatic in only 10-20%
2. HCV RNA+ Chronic infection
3. HCV RNA- HCV clearance
4. Normal ALT
5. Fibrosis 1-3
6. Cirrhosis
   - 20 years
   - 10-20%
Testing for HCV infection

There are two blood tests:

- **Ab**: Antibody test EVER come into contact with HCV
- **RNA**: Infected with the virus NOW

<table>
<thead>
<tr>
<th>Ab</th>
<th>RNA</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>Infected with HCV NOW</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>Infected with HCV in the PAST</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>NEVER infected with HCV</td>
</tr>
</tbody>
</table>

Spontaneous clearance OR Treatment-induced clearance

HCV transmission risk levels

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Level of risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular IDU (lifetime)</td>
<td>50-60%</td>
</tr>
<tr>
<td>Regular IDU (&lt; 3 years)</td>
<td>20-40%</td>
</tr>
<tr>
<td>Occasional IDU</td>
<td>10-20%</td>
</tr>
<tr>
<td>Born in highly endemic country</td>
<td>10-20% Egypt, 5% SEA</td>
</tr>
<tr>
<td>Infant of HCV+ mother</td>
<td>3-5%</td>
</tr>
<tr>
<td>Infant of HIV/HCV+ mother</td>
<td>10-15%</td>
</tr>
<tr>
<td>Heterosexual partner of HCV+</td>
<td>&lt;1% over 10-20 years</td>
</tr>
<tr>
<td>HIV- MSM</td>
<td>1%</td>
</tr>
<tr>
<td>HIV+ MSM (+/- IDU)</td>
<td>10-15%</td>
</tr>
</tbody>
</table>
Screening for HCV infection

Populations to consider for a HCV screening test:

- People who inject drugs or who have ever injected drugs
- People in custodial settings
- People with tattoos or body piercing
- Aboriginal and Torres Strait Islander peoples
- People who received a blood transfusion or organ transplantation before 1990
- Children born to HCV-infected mothers
- Sexual partners of an HCV-infected person (individuals at higher risk of sexual transmission include men who have sex with men and people with HCV–HIV coinfection)
- People infected with human immunodeficiency virus or hepatitis B virus
- People with evidence of liver disease, such as elevated alanine aminotransferase level
- People who have had a needle-stick injury
- Migrants from high-prevalence regions (Egypt, Pakistan, Mediterranean and Eastern Europe, Africa and Asia)

HCV notifications: 15-24 years

Rate per 100,000

- Indigenous
- Non-Indigenous

NINDSS 2018

Indigenous
Non-Indigenous

2013 2014 2015 2016 2017
0 20 40 60 80 100 120
**Needle syringe sharing (last month): ANSPS**

![Graph showing needle syringe sharing (last month): ANSPS]

- % Sharing in previous month
- 0 to 30
- 2008 to 2017
- Indigenous vs. Non-Indigenous

**HCV in Australia: 2015 cascade of care**

![Bar chart showing HCV in Australia: 2015 cascade of care]

- Living with chronic HCV: 227,310
- Diagnosed living with chronic HCV: 186,760
- Ever received HCV treatment: 50,170
- HCV cured: 32,140

82% 22% 14%

HCV in Australia: 2015 by genotype

227,000
Australians live with chronic HCV infection

HCV genotype 1
HCV genotype 3
Other

HCV liver disease progression

Normal Liver → Cirrhosis → HCC

Disease State Factors
- Liver fibrosis stage
- Inflammation grade
- Persistently elevated ALT levels

Patient/Viral Factors
- Male gender
- Age
- Obesity, diabetes
- HIV, HBV coinfection
- Immunosuppression
- Hepatic steatosis
- Iron overload
- Genotype 3

Lifestyle Factors
- Heavy alcohol use
- Tobacco use
- Daily cannabis use

Evolution of HCV therapy

Dore GJ & Feld J. CID 2015 (revised)

Australian PBS listed HCV treatments

Gilead Sciences, SOVALDI Australian PI, March 2015; Gilead Sciences, HARVONI Australian PI, June 2015 Bristol-Myers Squibb, DAKLINZA Australian PI, August 2016; AbbVie, VIEKIRA PAK-RBV PI, August 2016 Merck Sharp & Dohme, ZEPATIER ARTG August 2016; Gilead Sciences, EPCLUSA Australian PI August 2017
### Australian PBS listed HCV treatments

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1, 3</td>
<td>Sofosbuvir + Daclatasvir</td>
</tr>
<tr>
<td>Genotype 1, 4</td>
<td>Grazoprevir/Elbasvir</td>
</tr>
<tr>
<td>Genotype 1, 4</td>
<td>Grazoprevir/Elbasvir</td>
</tr>
<tr>
<td>Genotype 1-6</td>
<td>Sofosbuvir/Velpatasvir, Glecaprevir/Pibrentasvir</td>
</tr>
</tbody>
</table>

**Advantages of DAA Therapy**

- All oral options
- High cure rates (SVR)
- Few side-effects
- Little monitoring while on treatment
- Short course of treatment

Increasing number of candidates for treatment

+ Guidelines to follow: Australian Recommendations for the Management of Hepatitis C Virus Infection: a Consensus Statement
## Rationale for universal HCV treatment

### Cure

**HCV eradication**
- Societal benefits:
  - ↓ transmission of HCV
  - ↓ health service usage and costs
  - ↑ allocation of liver transplants to non-HCV patients

**Non cirrhotic patients**
- ↓ Progression to cirrhosis
- ↑ Overall survival

**Cirrhotic patients**
- ↓ Clinical decompensation and variceal bleeding
- ↓ Cirrhosis regression
- ↑ Liver related survival

**Decompensated patients**
- ↓ Cirrhosis
- ↓ Decompensation
- ↓ Transplantation
- ↓ HCV Recurrence post liver transplant
- Better post liver transplant outcomes

**Extrahepatic**
- ↓ All-cause mortality
- Improved QoL
- ↓ Neurocognitive function
- ↓ Fatigue
- ↓ Insulin resistance, diabetes
- ↓ Cardiovascular disease
- ↓ Renal disease
- ↓ Cryoglobulinaemia
- ↓ Malignancy: lymphoma

**Improved clinical outcomes**
- Hepatic
- ↓ Progression to cirrhosis
- ↑ Overall survival

**Cirrhotic patients**
- ↓ Clinical decompensation and variceal bleeding
- ↓ Cirrhosis regression
- ↑ Liver related survival

**Decompensated patients**
- ↓ Cirrhosis
- ↓ Decompensation
- ↓ Transplantation
- ↓ HCV Recurrence post liver transplant
- Better post liver transplant outcomes

**Societal benefits**
- ↓ transmission of HCV
- ↓ reinfection of HCV
- ↓ health service usage
- ↑ allocation of liver transplants to non-HCV patients

---


---

## PBS requirements for DAA treatment

### Population criteria:
Patient must be aged 18 years or older.

### Treatment criteria:
Must be treated by a medical practitioner or an authorised nurse practitioner 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.

### Information that must be provided on application:
- a) the hepatitis C virus genotype; and
- b) the patient’s cirrhotic status (non-cirrhotic or cirrhotic)

### The patient’s medical records must document:
- a) evidence of chronic hepatitis C infection; and
- b) evidence of the hepatitis C virus genotype

---

1. Medicines for the treatment of hepatitis C are listed for prescribing by authorised nurse practitioners under the General Schedule only.
**Specialist approval: remote consultation**

The **REACH-C study** aims to evaluate uptake and real world outcomes of HCV DAA therapy in Australia.

As part of the REACH-C study, ASHM and the Kirby Institute have developed an **online form** that medical practitioners can complete to gain specialist approval to initiate DAA therapy.

**The turnaround time for specialist approval is 24 hours.**

*By completing the online form, the medical practitioner is giving approval for the de-identified data entered to be collected for the REACH-C Study.*


---

**HCV treatment in Australia**

![Graph showing HCV treatment in Australia from 1997 to 2017]

- **IFN-free DAA = 58,000**
- **(26% chronic HCV)**

*Dore GJ & Hajarizadeh B. ID Clinics 2018*
**HCV treatment uptake among current PWID**

<table>
<thead>
<tr>
<th>Year</th>
<th>Active Infection</th>
<th>Treatment-induced Clearance</th>
<th>Ever Initiated Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>96%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>2016</td>
<td>80%</td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td>2017</td>
<td>68%</td>
<td>33%</td>
<td>0%</td>
</tr>
</tbody>
</table>

- *Non Indigenous*
- *Indigenous*

* Treatment eligible respondents: Ever exposed excluding those with spontaneous clearance

---

**High DAA efficacy across all sub-populations**

**REACH-C study: Per protocol analysis** *(n=3,204)*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Overall</th>
<th>Positive</th>
<th>Negative</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR (%)</td>
<td>96.3%</td>
<td>98.2%</td>
<td>93.8%</td>
<td>92.3%</td>
<td>97.6%</td>
<td>92.2%</td>
<td>96.8%</td>
<td>96.6%</td>
<td>95.4%</td>
<td>96.6%</td>
<td>96.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Treatment eligible respondents: Ever exposed excluding those with spontaneous clearance

---

Iversen J, et al. AVHC 2018

Yee J, et al. GHS 2018 (P1-062); Kirby Institute 2018
HCV in Australia: 2017 by disease stage

182,000
Australians live with chronic HCV infection

Pre-cirrhosis, naive
Pre-cirrhosis, experienced
Cirrhosis

A diverse range of models of HCV care

- Need to bring HCV care to the community where patients access services

Sexual health
Drug and alcohol clinics
Primary health care / GPs
Tertiary care hospital
Community health centres
Prisons
Needle and syringe programmes
Pharmacies
Primary care pivotal to HCV response

- Primary care is first line of engagement for majority of patients
- Primary care is central to management of chronic disease
- HIV treatment by GPs provides an important precedent
- Large number of GPs involved in addiction medicine, so able to reach critical population for HCV elimination
- Primary care is best suited to treat because HCV should not be treated in isolation but in the context of the whole person
  - Allows co-management of HIV, drug use disorders, psychiatric disease, and other chronic diseases

DAA prescriber distribution in Australia

The Kirby Institute. Monitoring hepatitis C treatment uptake in Australia (Issue 9). The Kirby Institute, UNSW Sydney, Sydney, Australia, July 2018
Pre-treatment Assessment including Liver Fibrosis

Pre-treatment assessment in primary care

- Test for hepatitis C genotype and viral load, FBC, urea, electrolytes and creatinine, glucose, liver function, hepatitis A, B, and HIV serology
- Exclude cirrhosis
- Establish prior treatment experience and select appropriate treatment regimen
- Check for drug-drug interactions
- Monitor on treatment and check for SVR12
- Follow-up according to recommended guidelines

Adapted from Managing hepatitis C in general practice. Australian Prescriber Volume 40 : Number 2 : April 2017
Assessment for liver fibrosis

**History**
- Length of infection
- Presence of co-morbidities such as alcohol use

**Physical examination**
- Jaundice, ascites, varices, encephalopathy

**Laboratory tests**
- Liver tests, platelet count, coagulation profile
- APRI, FIB-4, Hepascore
- Fibroscan, shear wave elastography

**Imaging**
- US, CT, MRI

**Liver biopsy**

It is a PBS requirement that you know the patient’s cirrhotic status (non-cirrhotic or cirrhotic)

Assessment for liver fibrosis: APRI Score

APRI = \( \frac{\text{AST (IU/L)}}{\text{AST ULN (IU/L)} \times 100} \times \text{platelet count (x10^9/L)} \)

Use an online calculator, such as: [https://www.hepatitisc.uw.edu/page/clinical-calculators/apri](https://www.hepatitisc.uw.edu/page/clinical-calculators/apri)

Fluctuating AST and/or platelet count impacts on reliability of APRI
- If APRI >1: need further assessment to exclude cirrhosis

Critical to assess for advanced fibrosis or cirrhosis
- Informs when specialist referral needed
- Indicates need for post-SVR HCC monitoring
- Affects HCV regimen selection

RACGP
Royal Australian College of General Practitioners

Healthy Profession. Healthy Australia.
DAA treatment guidelines in Australia

Current PBS listed treatments and management recommendations

General Statement for Drugs for the Treatment of Hepatitis C

www.pbs.gov.au

(Always up to date)

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


(Note: updates re new DAAs may be delayed)
**DAA treatment algorithm: GT1 (ASHM)**

<table>
<thead>
<tr>
<th>HCV genotype 1 regimen</th>
<th>Treatment- naive</th>
<th>Treatment- experienced***</th>
<th>Cirrhosis</th>
<th>Treatment- naive</th>
<th>Treatment- experienced***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir / velpatasvir ± Ribavirin</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks (+ Ribavirin)</td>
<td>12 wks (+ Ribavirin)</td>
<td></td>
</tr>
<tr>
<td>Gileadvi/ pibrentasvir</td>
<td>8 wks</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks (+ Ribavirin)</td>
</tr>
<tr>
<td>Sofosbuvir + ledipasvir</td>
<td>8 or 12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
<td>24 wks</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir + daclatasvir ± Ribavirin</td>
<td>12 wks</td>
<td>12 or 24 wks</td>
<td>12 wks + ribavirin</td>
<td>24 wks</td>
<td>12 wks + ribavirin</td>
</tr>
<tr>
<td>Grazoprevir/Elebavir ± Ribavirin</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
<td></td>
</tr>
</tbody>
</table>

Healthy Profession.
Healthy Australia.

**DAA treatment algorithm: GT2/3 (ASHM)**

<table>
<thead>
<tr>
<th>HCV genotype 2 regimen</th>
<th>Treatment- naive</th>
<th>Treatment- experienced***</th>
<th>Cirrhosis</th>
<th>Treatment- naive</th>
<th>Treatment- experienced***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir / velpatasvir ± Ribavirin</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks (+ Ribavirin)</td>
<td>12 wks (+ Ribavirin)</td>
<td></td>
</tr>
<tr>
<td>Gileadvi/ pibrentasvir</td>
<td>8 wks</td>
<td>8 wks</td>
<td>12 wks</td>
<td>12 wks</td>
<td></td>
</tr>
</tbody>
</table>

**HCV genotype 3 regimen**

<table>
<thead>
<tr>
<th>HCV genotype 3 regimen</th>
<th>Treatment- naive</th>
<th>Treatment- experienced***</th>
<th>Cirrhosis</th>
<th>Treatment- naive</th>
<th>Treatment- experienced***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir / velpatasvir ± Ribavirin</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks (+ Ribavirin)</td>
<td>12 wks (+ Ribavirin)</td>
<td></td>
</tr>
<tr>
<td>Gileadvi/ pibrentasvir</td>
<td>8 wks</td>
<td>16 wks</td>
<td>12 wks</td>
<td>16 wks</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir + daclatasvir ± Ribavirin</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks + ribavirin</td>
<td>24 wks</td>
<td>12 wks + ribavirin</td>
</tr>
</tbody>
</table>

Healthy Profession.
Healthy Australia.
Drug to drug interaction

- Review all prescription and OTC meds, herbal supplements and other complementary medications
- Be alert for interactions with common drugs such as:
  - Statins
  - Proton pump inhibitors
  - Antiepileptic drugs (e.g. carbamazepine)
  - Birth control preparation (e.g. ethinyl oestradiol)
  - Some herbal – esp. St John’s Wort
- Remember: patients rarely tell you all the pills they are taking

HBV reactivation during DAA Therapy

- Patients at risk: prior, resolved, or active HBV infection
- HBV reactivation (during or after DAA therapy) has been reported in HCV/HBV coinfected patients not on HBV therapy
  - Severity: mild to severe fulminant liver injury (life threatening)
  - Frequency: low to very low
- Seen with different HCV genotypes and DAA combinations
- Mechanism of reactivation unknown
- Important to screen for HBV prior to starting HCV treatment: HBsAg, HBcAb, HBsAb

<table>
<thead>
<tr>
<th></th>
<th>HBsAg</th>
<th>Anti-HBc</th>
<th>Anti-HBs</th>
<th>Recommended action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic HBV</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Consult specialist</td>
</tr>
<tr>
<td>Unexposed</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Vaccinate</td>
</tr>
<tr>
<td>Immune - prior infection</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Nil needed</td>
</tr>
<tr>
<td>Prior infection - resolved</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Consult specialist (low risk of HBV reactivation)</td>
</tr>
<tr>
<td>Immune – prior vaccination</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Nil needed</td>
</tr>
</tbody>
</table>
When to consult a specialist

- Patients with advanced fibrosis or cirrhosis
- Patients with extrahepatic manifestations
- Patients with complex co-morbidities
- Patients with renal impairment
- Patients with HIV/HCV or HBV/HCV coinfection
- Patients who failed first line DAA
- Patients with acute HCV

Australian Recommendations for the Management of HCV Infection: A Consensus Statement 2018

Post-treatment follow up: liver disease and reinfection monitoring
**Confirming cure post-treatment**

- **SVR12** = undetectable HCV RNA 12 weeks post treatment completion
  - Don’t need another repeat SVR after SVR12 (=cure) but consider on a case by case basis – if significant risk of reinfection, annual HCV RNA testing recommended

- Note that **HCV antibody tests will remain positive after cure and should not be repeated**
  - Important to warn patients that this can happen in case the test is repeated by another doctor

- **Treatment failure** = detectable HCV RNA 12 weeks post treatment completion

---

**Post-treatment follow-up**

**No cirrhosis, normal LFTs at SVR12**
- Patients who are cured do not require clinical follow-up for HCV
- Discussion around moving on as “hepatitis C free”
- Ongoing HCV monitoring (annual LFTs and HCV RNA) if potential risk of re-exposure (PWID, HIV+ MSM) or if LFTs become abnormal

**Abnormal LFTs at SVR12**
- Patients with persistently abnormal LFTs require evaluation for other liver diseases and should be referred for gastroenterology review.
- Check for other causes of liver disease including alcohol, metabolic syndrome

---

[Diagram]

- SVR
- Fibrosis stage prior to treatment
  - Early liver fibrosis (stage 0-2)
  - Advanced fibrosis or cirrhosis (stage 3-4)

Australian Consensus Statement 2018 (www.hepcguidelines.org.au)
Hepatitis C online learning

- ASHM eLearning:  https://lms.ashm.org.au

Hepatitis C web resources

- ASHM:  http://www.ashm.org.au
- ASID:  https://www.asid.net.au/

Patient Support and Resources

- National hepatitis Information Line:  1800 437 222
- Provide information and support services to people affected by hepatitis (primarily hepatitis C) and to support the reduction of hepatitis C transmission:
Hepatitis NSW

Directory of local doctors prescribing HCV and dispensing pharmacies: [https://www.hep.org.au/](https://www.hep.org.au/)

---

**Summary**

**T**
- Screen all people at risk for hepatitis C. Hepatitis C infection can be cured
- Test for HCV to confirm current infection (= anti-HCV +ve and HCV RNA +ve)
- All people with HCV infection should be considered for treatment, including people who inject drugs

**R**
- Assess for liver fibrosis and other co-morbidities
- Refer patients with cirrhosis, renal failure, HBV or HIV coinfection to a specialist

**E**
- Evaluate for DDIs at [http://hep-druginteractions.org](http://hep-druginteractions.org)
- Select appropriate treatment regimen, assess adherence

**A**
- Approval from a specialist to prescribe (using a remote consultation request form or similar) is required if GPs are not experienced in HCV treatment
- Dispensing of S85 scripts are from a community pharmacy

**T**
- Monitor on treatment and check for SVR 12 weeks after treatment completion
- Tailor post-treatment follow-up according to treatment outcome, liver disease stage, reinfection risk
- Patients with cirrhosis need ongoing lifetime surveillance for liver cancer
- Re-treatment should be offered to people who become reinfected