Hepatitis C

1. About hepatitis C – natural history and disease progression
2. Public Health Issues – HCV
3. HCV Diagnosis and management
4. Current and Future treatment Options

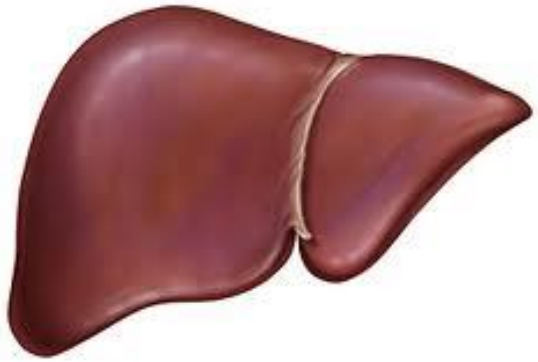
About hepatitis C – natural history and disease progression

Jenny Bourke CNS/Nurse Manager

Hepatitis C Community Clinic

Christchurch

About Hepatitis C ?



- 'Hepatitis' is a general term that means inflammation of the liver
- Hepatitis C (HCV) is a blood-borne virus that replicates in the liver. Over time the virus can cause significant damage to the livers parenchyma due to inflammation and chronic fibrosis. This damage may be accelerated by alcohol & cannabis use or if infected with other viruses – viruses such as hepatitis B or HIV
- HCV was first identified in 1989 when the virus was able to be enlarged through PCR. This differentiated HCV from hepatitis A and B
- There are 6 different strains or genotypes of hepatitis C. Most in NZ are 1, 2 or 3.
- There are also sub strains (subtypes) a-e

How is hepatitis C different from hepatitis A and B?

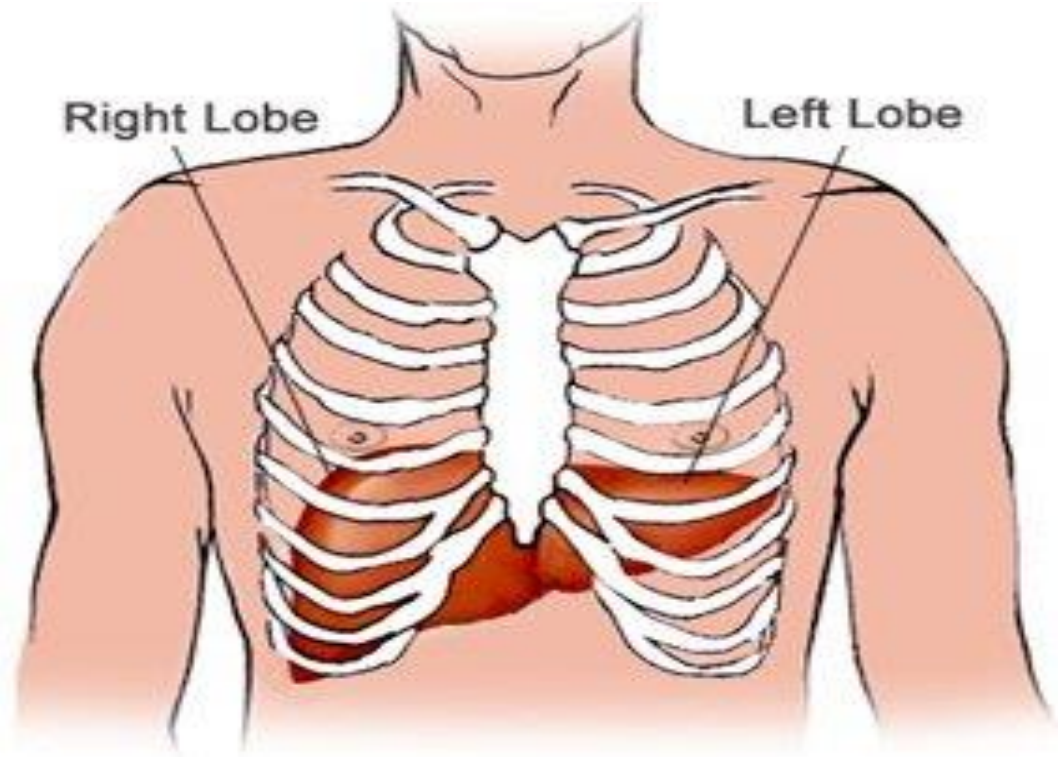
Virus Type	Profile	Transmission	Vacc'n	Treatment
Hep A (HVA)	Usually a mild disease that is self-limiting with no long lasting consequences	Faecal/oral route. Usually through water or food contaminated by faecal matter	Yes	No specific treatment
Hep B (HBV)	A DNA virus that can be acute or chronic. Less than 5% of adults exposed contract HBV	•Blood-blood (PWID) •Mother to baby (vertical transmission) •Sexual transmission) •More often transmitted in childhood	Yes	Life-long antiviral therapy Post exposure prophylaxis available
Hep C (HCV)	An RNA virus. Likely to become chronic in 75% of those exposed	Transmitted when infected blood from one person enters the blood stream of another (blood to Blood). Less than 5% vertical tx or sexual contact. Can NOT be transmitted by hugging or toilet seats!	No	HCV genotype 1 can be cured through antiviral therapy. Limited treatment options for genotypes 2 & 3 in NZ currently

Two other hepatitis viruses; D (delta) and E have been isolated, but both are rare in NZ

About the liver

- The liver is the largest internal organ in the body
- It is located under the ribs on the right hand side – RUQ
- The liver filters blood & other substances to be used or excreted by the body
- The liver is responsible for
  - breaking down food, chemicals and medications
  - making bile to help digest food
  - storing vitamins and minerals
  - manufacturing proteins & nutrients
  - converting nutrients into energy
  - storing sugar and controlling level of sugar in the blood
  - regulating fat storage
  - Regulating blood clotting
- Unique ability of being able to regenerate cells

Position of liver in the body



Acute hepatitis C

- Most people (80%) who develop acute HCV will have no symptoms
- Those with symptoms may experience vague abdominal discomfort, nausea, vomiting, fatigue and possible jaundice.
- The **window period** or incubation period for HCV - most people develop detectable HCV antibodies within 8 to 12 weeks after becoming infected.
- Only acute hep C is notifiable (to public health)
- Need to have obvious signs or have test HCV ab+ with a recorded ab- test in previous year
- 75% of people fail to spontaneously clear the virus in the acute phase and go on to have chronic hepatitis C.
- Liver function enzymes may be elevated

LFT results – Acute Hepatitis C

	Example patient		Normal Range
Protein	80	g/L	64 - 83
Albumin	40	g/L	32 – 48
Bilirubin	13	umol/L	2 – 20
Alkaline Phosphatase	111	U/L	30 – 150
GGT	89*	U/L	10 – 35
AST	284*	U/L	10 – 50
ALT	642*	U/L	0 – 30

Transaminases may elevate into the 1000's. If no decrease and patient becomes increasingly unwell – hospitalise.

In chronic HCV the enzymes may still be elevated or may return to normal range

Chronic hepatitis C

Acute phase

Cleared spontaneously-25%

No immunity

-test again if in window period

Chronic HCV-75%

(after 6mths)

25% stable

Cirrhosis 10% - 20% over 20 years

HIV

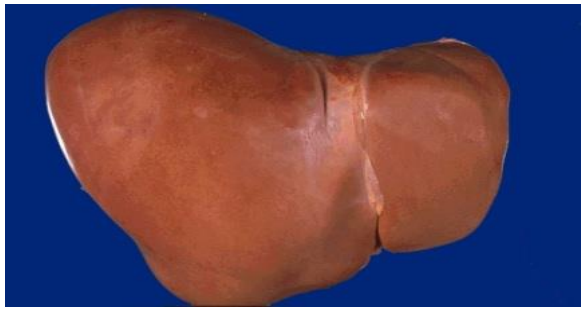
HBV

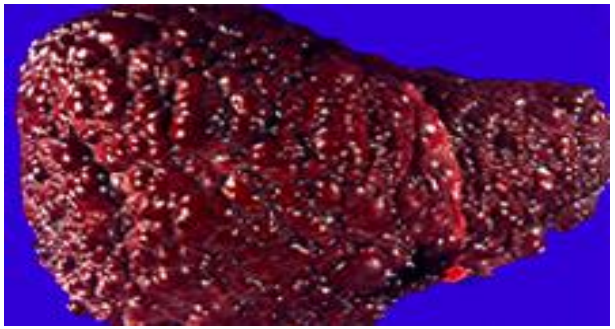
alcohol

cannabis

Decompensated cirrhosis, 5 year survival rate – 50%

HCC 1-4% per year





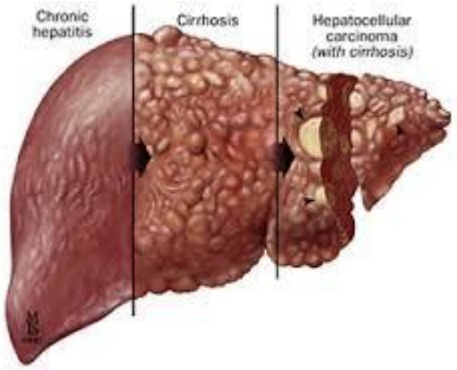
Signs and symptoms HCV

Only about 25% of people may experience:

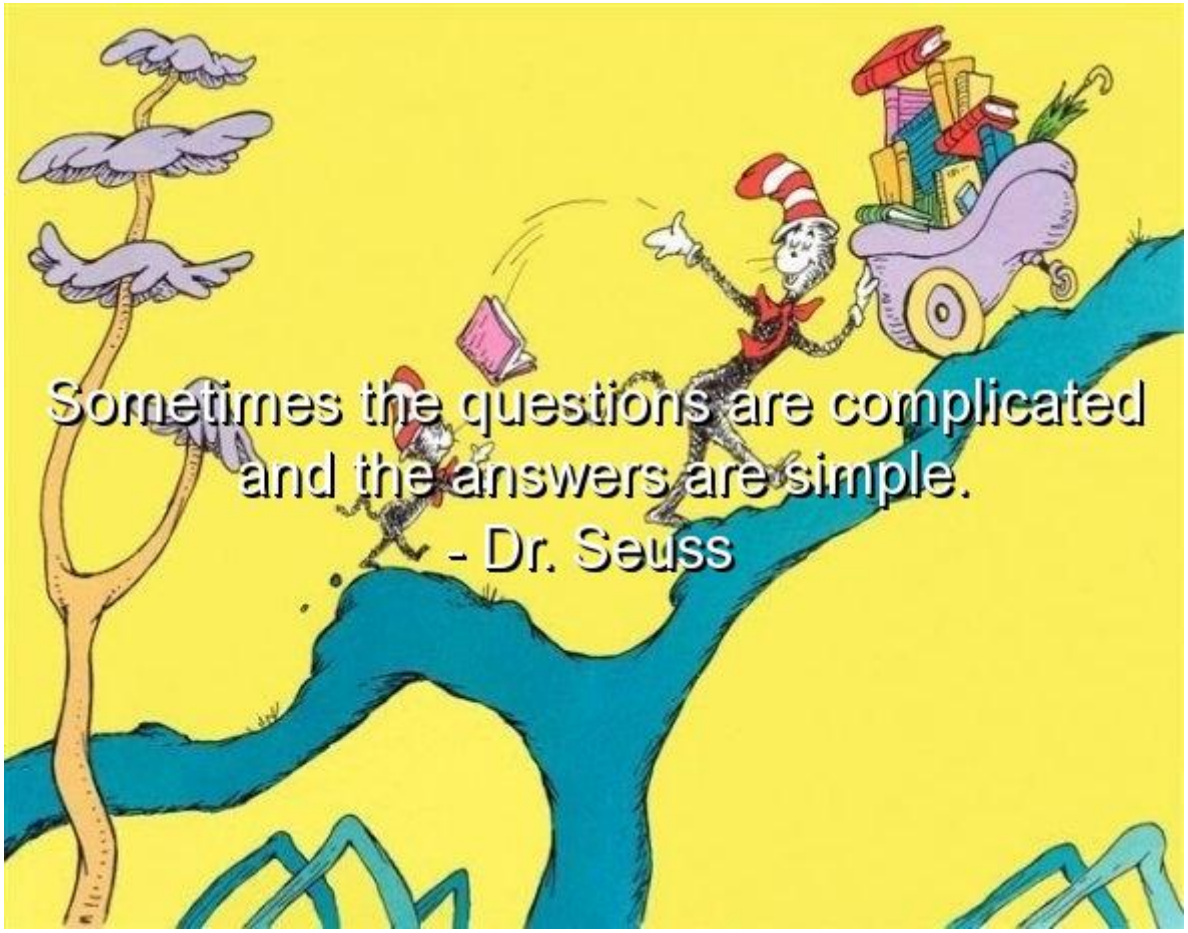
- Fatigue
- Muscle and/or joint pain
- Loss of appetite
- Brain fog – blunted thinking
- Headaches
- Flu-like symptoms

Most symptoms of chronic hepatitis C don't appear until cirrhosis develops and the liver begins to fail:

- Weakness
- Weight loss
- Abdominal swelling
- Blood clotting problems



Just ask!

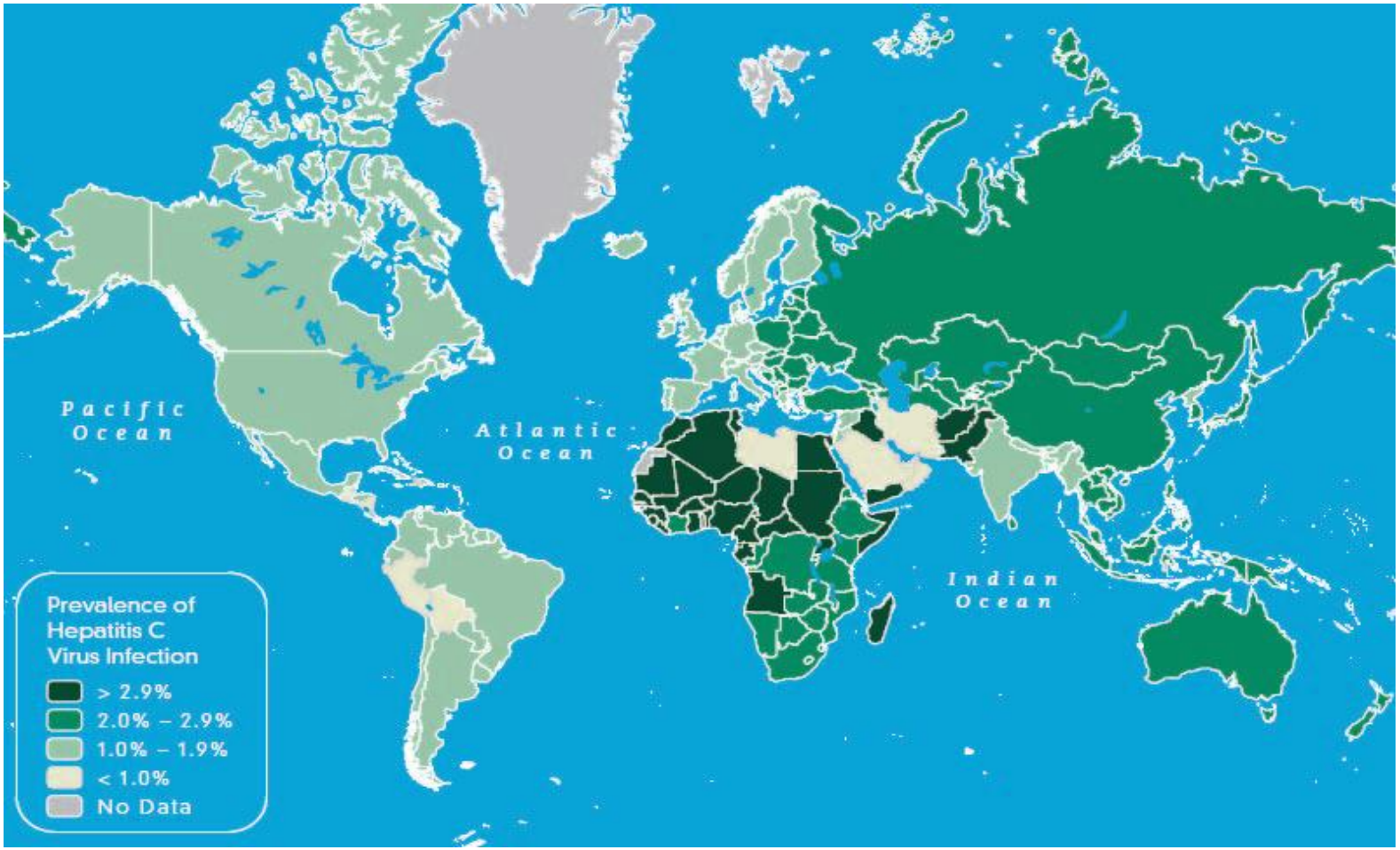

Sometimes the questions are complicated
and the answers are simple.
- Dr. Seuss

Public Health Issues - HCV

Prevalence of hepatitis C

- **Worldwide,** about **200 million** people have been infected with hepatitis C (as opposed to 35 million with HIV) – this includes more than **54,000 in New Zealand.**
- Of 50,000 people in New Zealand infected with HCV, **30%** are unaware they have the virus and only **5%** have accessed treatment.
- There are 1000 new infections every year

Global prevalence hepatitis C



Risk Factors - Highest Risk

- Using a needle or syringe that has been used by someone else
- Sharing other injecting equipment – cookers, filters and water

Other Risk Factors

- Mother to baby < 7%
- Household < 5%
- Sexual < 5%
- Being/been in prison

- Tattooing/piercing
- Snorting drugs
- Blood transfusions
- Acupuncture, cosmetic injection
- Overseas procedures
- Occupational exposure

Prison Population and HCV

- Drug use continues in prison
- Needles are shared in prison
- Unsterile tattooing in prison
- MSM in prison
- Fights and bites in prison

Burden of hepatitis C

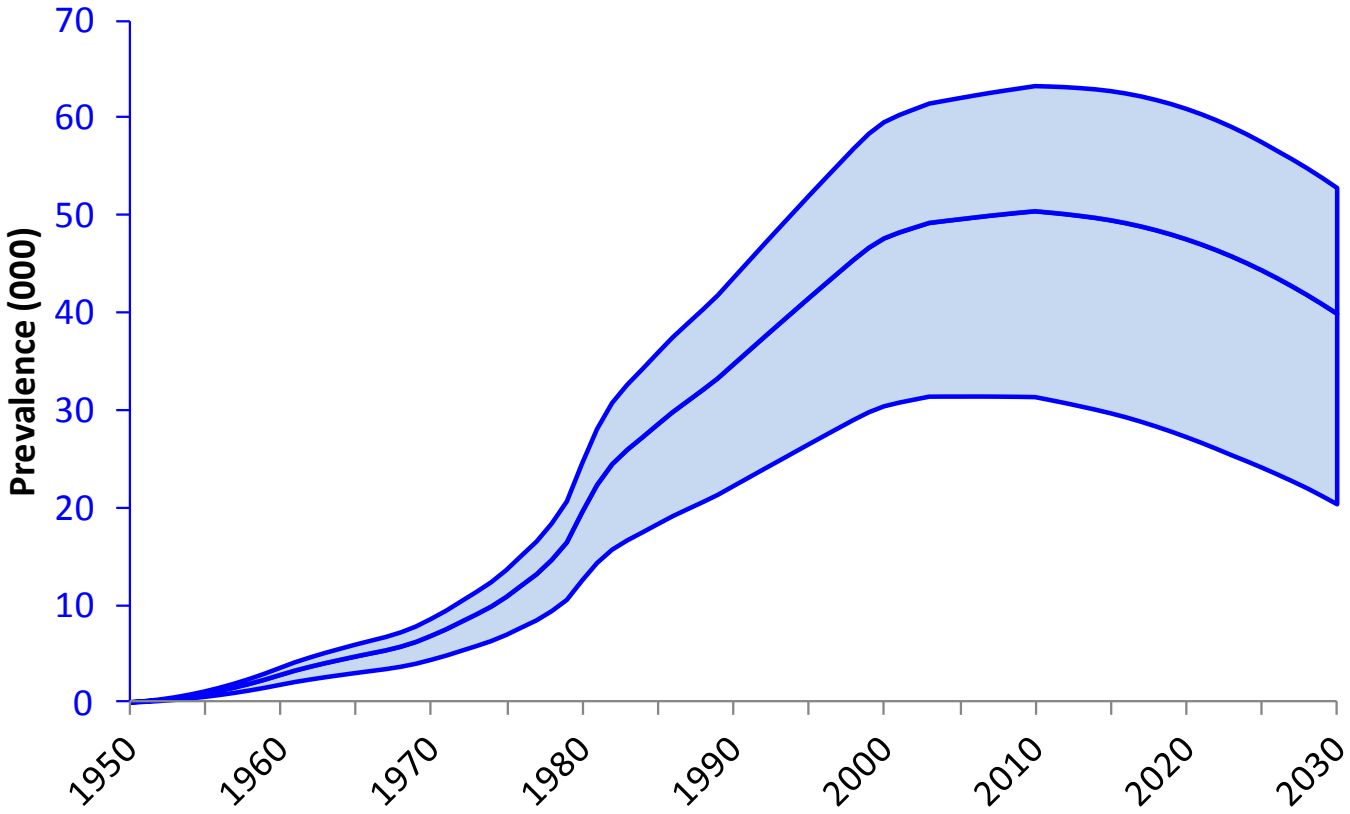
- Incidence of HCV high during 1960s – 1980's
- Most chronic infections are now in the 40 – 60 years age group
- Due to the low rate of treatment uptake – cirrhosis, liver failure & liver cancer on the rise
- Leading to increase in liver related deaths and increased number of liver transplants

Updated estimates

	Number	Range
HCV infections	**66,980**	**(36,240 - 96,630)**
Viraemic	**50,000**	**(27,050- 72,130)**
Diagnosed	**20,000**	
New infections	**1,020 per year**	
Rate	**22.6/100,000**	

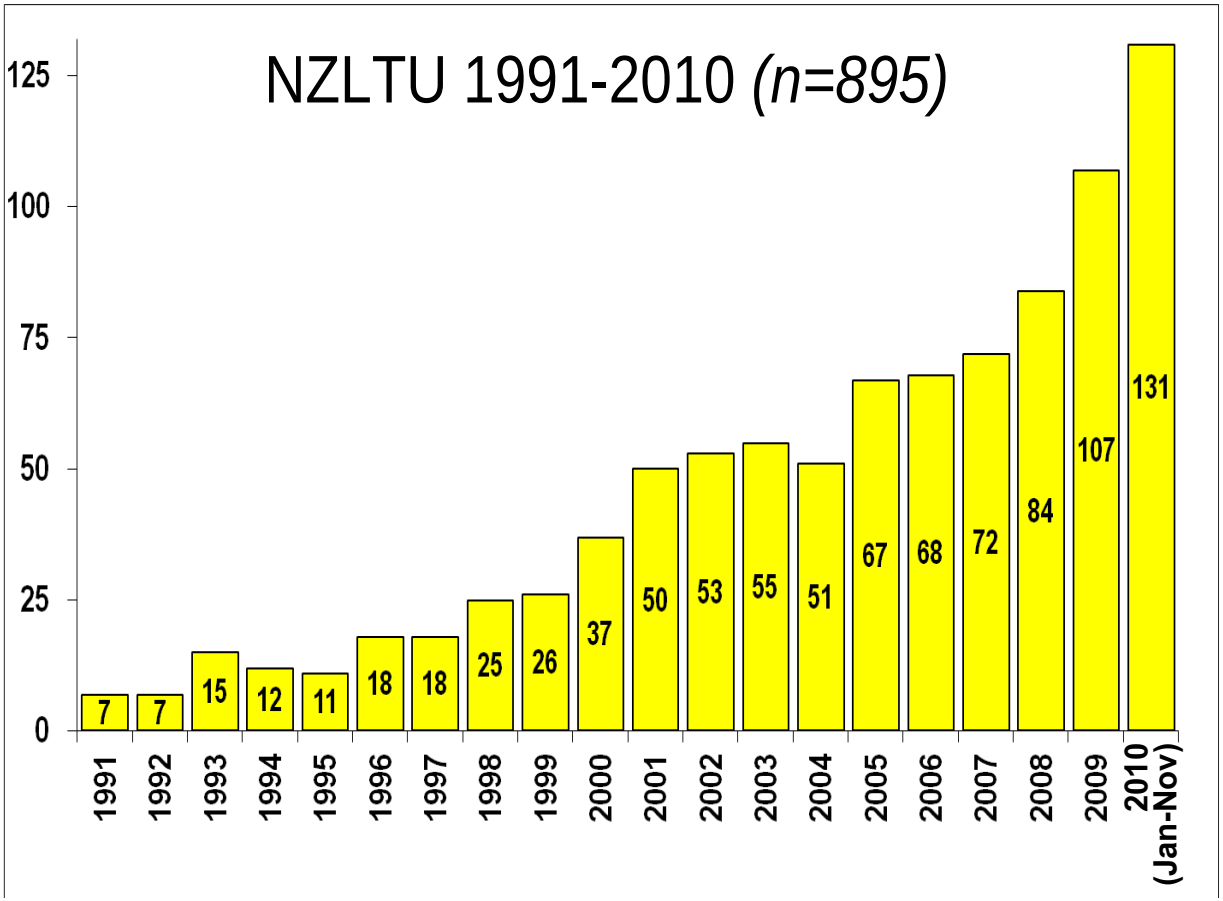
Gane, Stedman, Brunton, Radke, Henderson, Estes & Razavi (2014)

Total viraemic population



HCV Epidemiology and Trends

Increasing Liver Cancer in NZ



Cost

- It will cost NZ $0.5 billon over the next 20 years
- In 2010 it was estimated the cost of a liver transplant cost $296,000 - ? Now
- Indirect cost – lost wages, dental costs, OPD/hospitalisations, transport

Implication of models

- Prevalence of HCV infection peaked in 2010 (50,480 cases)
- Peak prevalence of cirrhosis and HCC will occur after 2030
- Increased treatment uptake and efficacy will help prevent advance liver disease and deaths
- Continued efforts to reduce disease transmission are still required – OST, NEX and harm reduction


"People say nothing's impossible,
but I do nothing everyday."
-Winnie the Pooh

HCV Diagnosis and Management

Testing for hepatitis C

Four main blood tests

- HCV antibody test – indicates exposure to HCV (this is NOT a diagnostic test – it is an immune response)
- HCV RNA/Viral load – confirms if there is virus in the blood (normally in number form)
- Genotype – the strain & sub strains of HCV
- Liver function tests - (LFT's) to determine possible extent of damage serologically

There may be other tests that help build a picture of the virus on an individual basis

Interpretation of testing

Antibody test

- If positive – more testing required
- If negative – CONGRATULATIONS – keep up the good work! Plus ongoing harm reduction messages

Viral Load/RNA

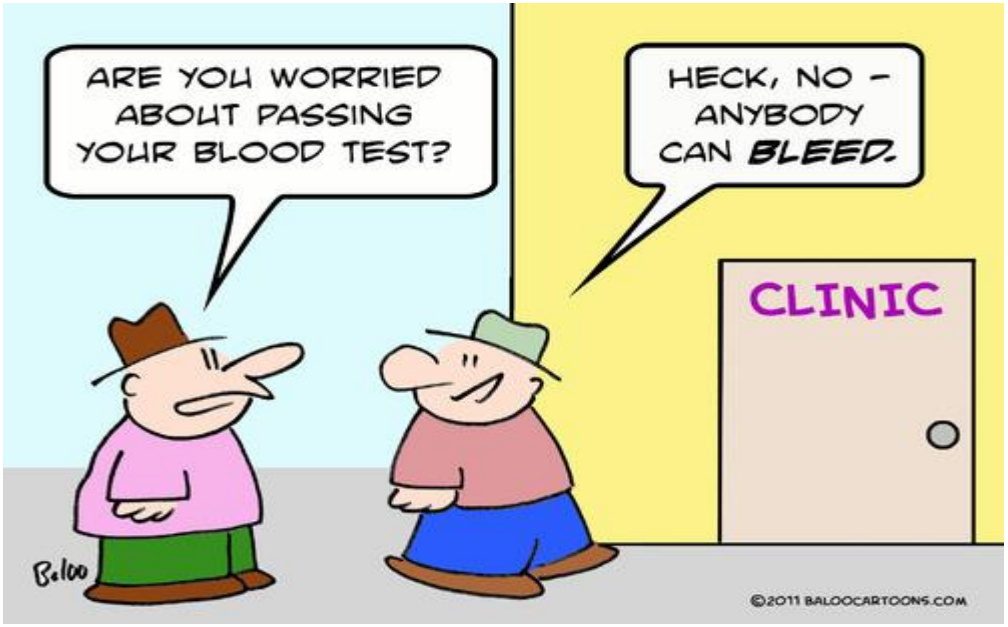
- Indicates chronic infection. Only likely to be 'RNA not detected' following treatment or if cleared spontaneously. If high (millions) does NOT indicate liver is worse than those with lower V/L. However can be more infective.

Genotype

- There is no 'worse' genotype, in terms of faster progression of disease. Those with genotype 3 may be more prone to 'fatty' liver (as are those who are obese) and are harder to treat with new DAA's.

Liver Function Tests

- May show the level of inflammation
- Give an indication of alcohol use
- Can give ‘a hint’ of damaged liver (together with other blood tests)



Example of blood results that may indicate advanced liver disease

Blood Count

(Patient example)		(Normal Range)	
Haemoglobin	127 g/L	130 – 175	L
Platelets	103x10(9)/L	150 – 400	L

LFTs

Albumin	23 g/L	32 – 48	L
Bilirubin	50 umol/L	2 – 20	H
GGT	108 U/L	10 – 50	H
ALT	109 U/L	0 – 40	H
AST	147 U/L	10 – 50	H

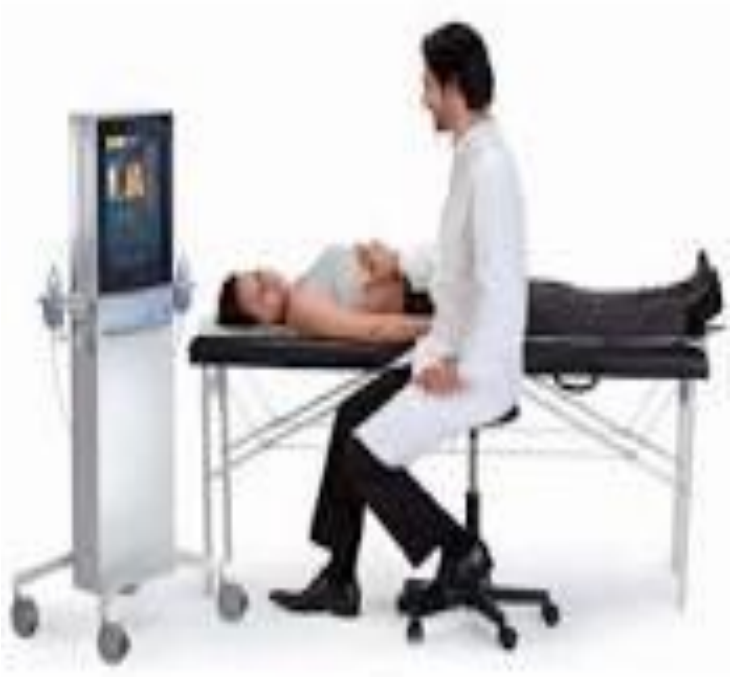
Coagulation Studies

INR	1.3	0.8 - 1.2	H

Other Investigations

- A fibroscan will determine the amount of scarring in the liver and is used to assess for possible cirrhosis

- Ultrasound (US) has a major role in the diagnostic and prognostic information as well as detecting complications such as hepatocellular carcinoma (HCC) and portal hypertension



Barriers to Accessing Primary Health Care, IDU

- stigma and discrimination
- chaotic lifestyle
- procuring and using drugs
- immediate survival needs take precedence over healthcare
- cost

But wait there's more…

- Stigma/confidentiality concerns
- Limited awareness: providers and patients/clients
- Lack of tailored service provision (testing & treatment in community settings)

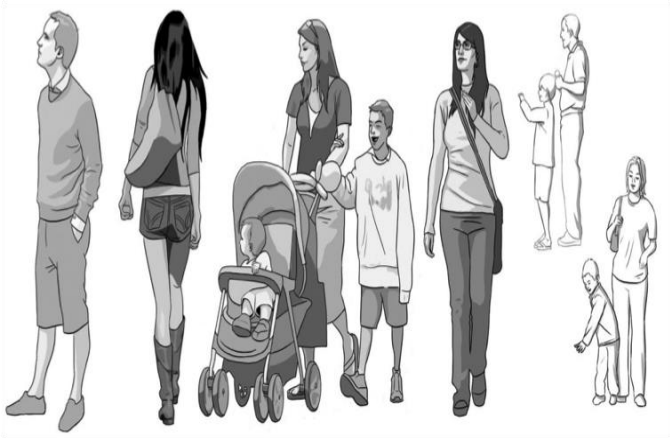
Testing

- Belief that not at risk/not offered test
- Belief that already tested/lack of awareness or understanding HCV tests
- Venous access concerns/ difficult access
- Fear of diagnosis/belief not eligible for treatment

Hepatitis C is more than a medical diagnosis

Recurring themes

PWID
Court
Poor health
Dental problems
Depression
Prison
Poor/No housing
Co-existing mental health
Low/no income/benefit
TBI
Little family support
Cannabis/ synthetics
OST
Transport



Lifestyle factors

Advice for all!!!!

- Maintain a healthy diet
- Mind/manage your weight
- Alcohol use – one size does not fit all
- Reduce cannabis use
- Stay hydrated
- Reduce stress/anxiety where possible
- Regular exercise
- Take advice on ‘over the counter’ therapies
- Always ask about medications (specialist – HCV)

GOOD LUCK!

BUT nurses are awesome!

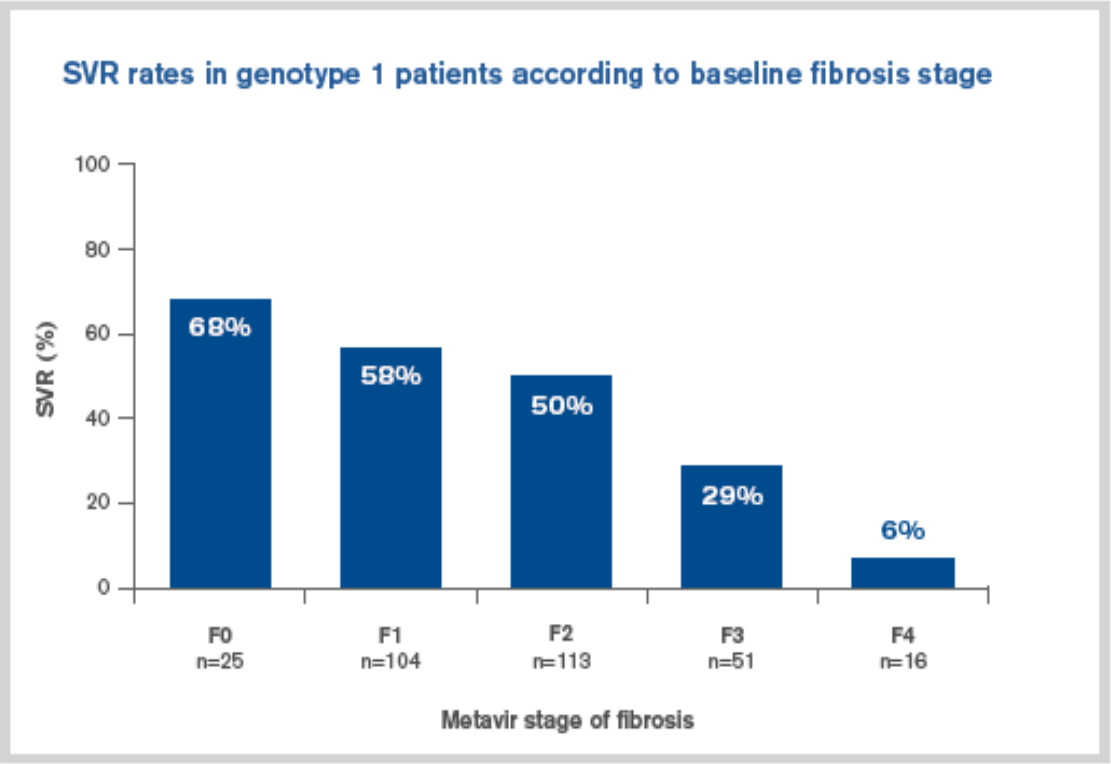
Nurses can play an integral role in the management and care of people who have or are affected by hepatitis C.

- **Awareness of risk factors** – many people are unaware of their HCV due to asymptomatic nature of virus
- **Encourage testing** – even if they 'know they've got it'!
- **Asking difficult questions using non-judgemental language** – tattoos?
- **Testing & diagnosis** – use of rapid testing in primary care or rural areas
- **Educate on harm reduction factors** (alcohol, lifestyle factors, sharing IDU equipment)
- **Supporting patients by informing of treatment options**
- **Treatment** – possible primary care/community availability


You can't stay in your corner of the forest waiting for others to come to you. You have to go to them sometimes.
-winnie the pooh-
rinnyy/tumblr-

Current and Future Treatment Options

Peginterferon α/ ribavirin treatment for HCV



Based on a randomised controlled trial including 438 genotype 1 patients treated with Pegasys (180mcg/week) and ribavirin (1000/1200 mg/day) for 48 weeks.

Adapted from Roberts SK *et al* 2009[3]

- Poor tolerability Peg/RBV
  - Flu-like syndrome
  - Anorexia, weight loss
  - Insomnia
  - Bone marrow suppression
  - Depression
  - Contraindicated in some patients
  - Refused by many patients
  - Many have failed treatment

New Treatment for HCV

- for genotype 1(a,b,c)

Approval of funding for hepatitis C treatments

PHARMAC is pleased to announce that, from 1 July 2016:

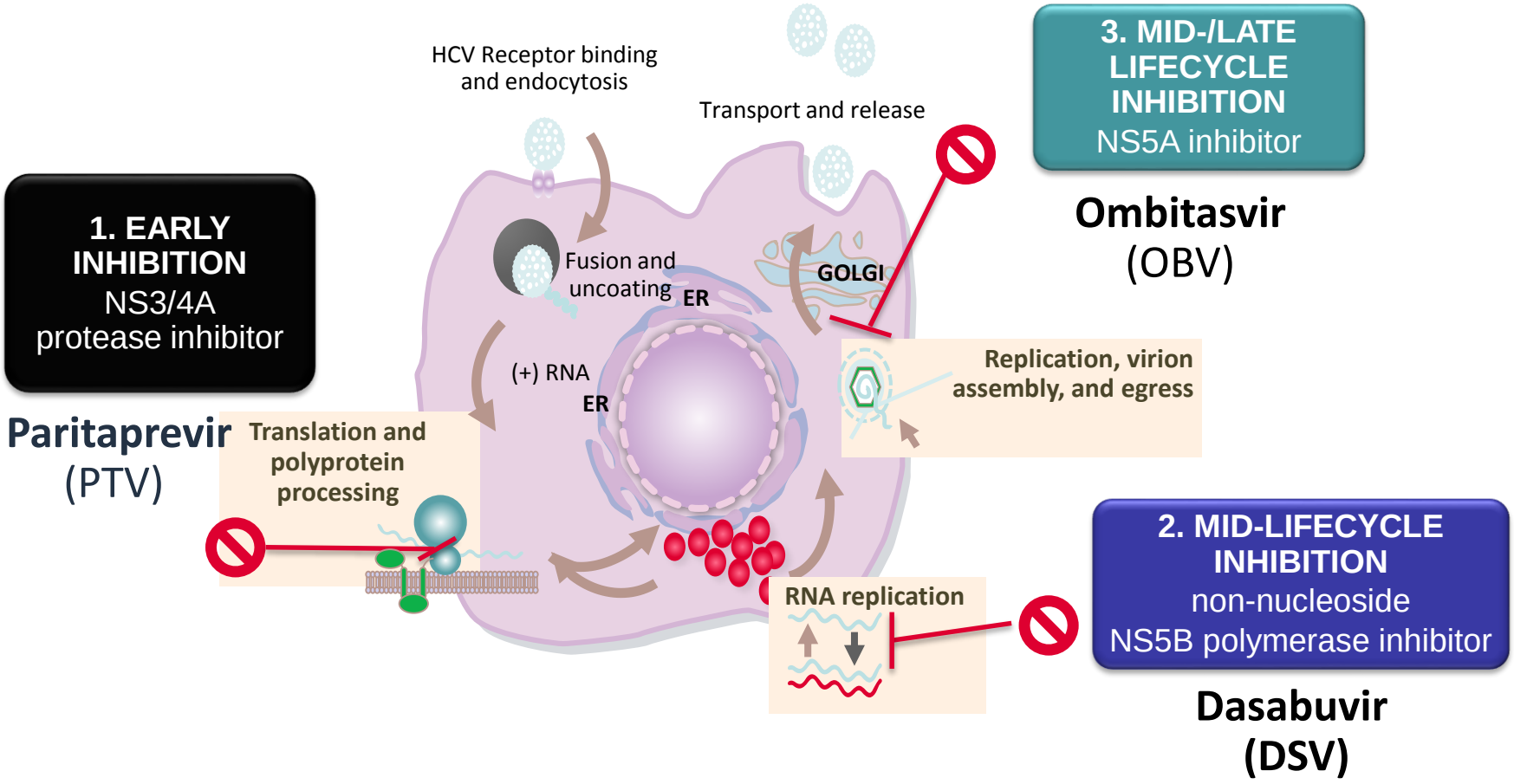
- Ledipasvir with sofosbuvir (Harvoni) will be funded in the community and DHB hospitals for the treatment of hepatitis C for patients with severe liver disease, subject to restrictions; and
- Paritaprevir with ritonavir and ombitasvir copackaged with dasabuvir (Viekira Pak) and paritaprevir with ritonavir and ombitasvir copackaged with dasabuvir and ribavirin (Viekira Pak-RBV) will be funded in the community and DHB hospitals for the treatment of hepatitis C.

Direct Acting Antivirals

Increasingly, we must ask: are we witnessing the approaching 'end of history' with regard to HCV therapy, which would be a scenario in which we have the weapons we need to cure just about everybody? – Jacobson (2015)

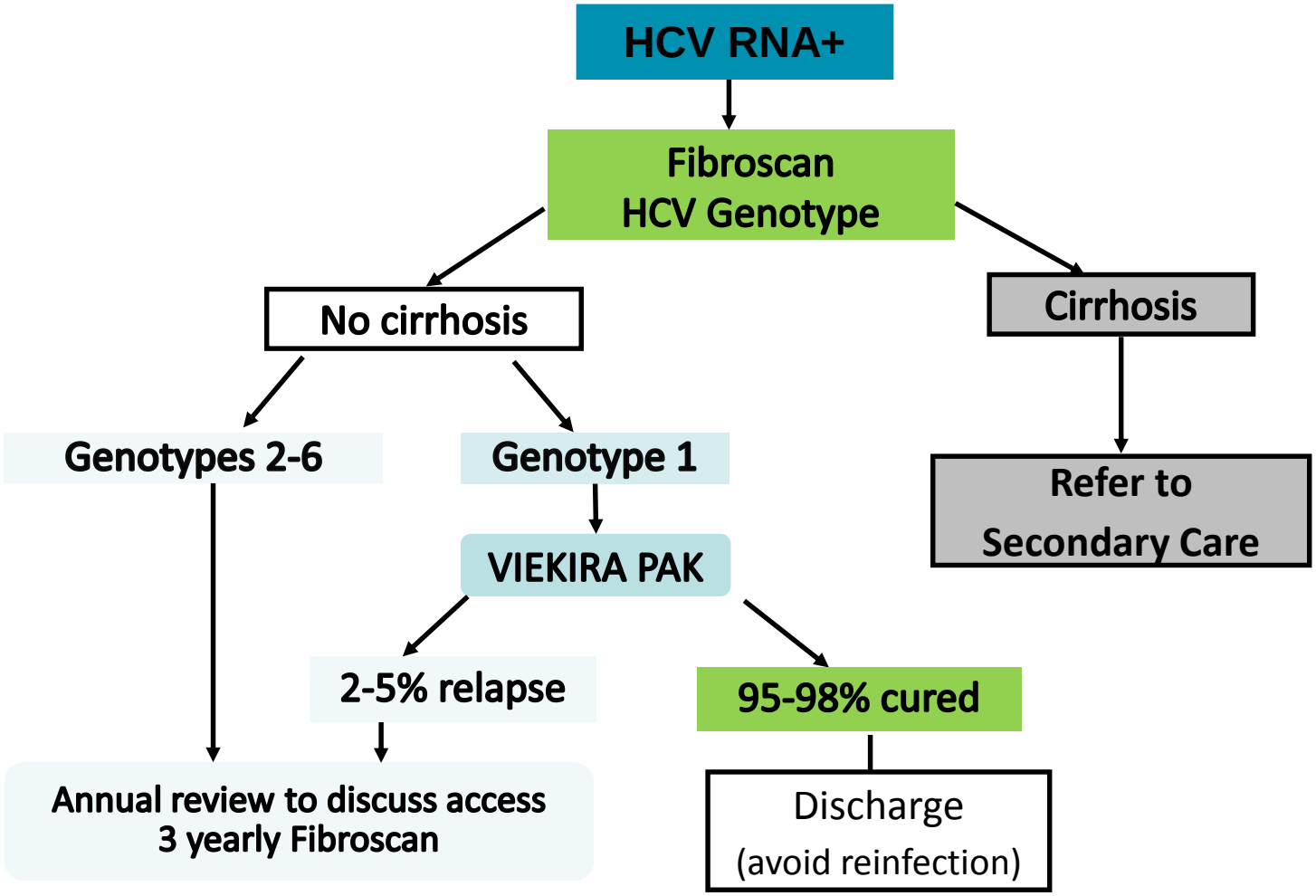
- Work by inhibiting viral replication at different phases
- All oral
- Limited side effects
- Greater chance of cure
- Shorter treatment times

VIEKIRA PAK: mode of action



Lindenbach & Rice. Nature 2005:436;933–38.
AbbVie Limited. VIEKIRA PAK and VIEKIRA PAK-RBV Data Sheets. Medsafe New Zealand; May 2016.

Suggested community treatment algorithm



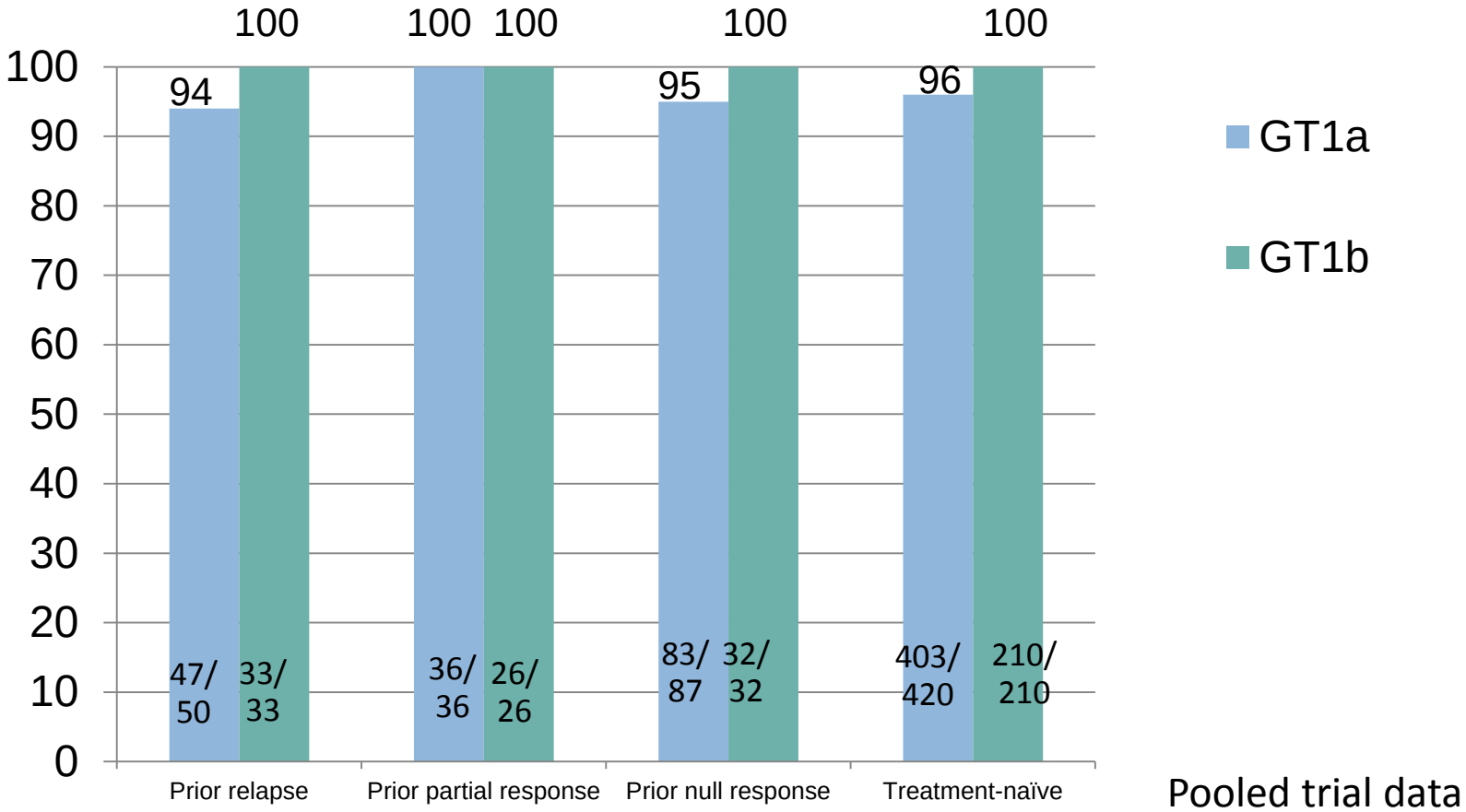
Ministry of Health HCV Implementation Committee. Clinical pathway for hepatitis C. June 2016.

VIEKIRA PAK and **VIEKIRA PAK-RBV**
are indicated for the treatment of genotype 1 chronic hepatitis C, including patients with compensated cirrhosis.

Duration of therapy and addition of ribavirin are dependent on patient population.

AbbVie Limited. VIEKIRA PAK and VIEKIRA PAK-RBV Data Sheets. Medsafe New Zealand; May 2016.

Non-cirrhotic patients: efficacy with NZ's recommended regimen



Pooled trial data

Previous treatment with peg IFN/RBV

AbbVie Limited. VIEKIRA PAK and VIEKIRA PAK-RBV Data Sheets. Medsafe New Zealand; May 2016.

Pre-treatment assessment for VIEKIRA PAK

Tests	Rationale
Antibody (serology) **HCV RNA** (PCR)	HCV antibodies indicate exposure to virus. Positive viral load confirms **current HCV**.
HCV Genotype	VIEKIRA PAK is indicated for patients with **Genotype 1**; regimen differs for GT1a and 1b

Genotype - may need to repeat if >5 years old or not subtyped

*__VIEKIRA PAK__ can be considered for non-cirrhotic patients with genotype 1a.

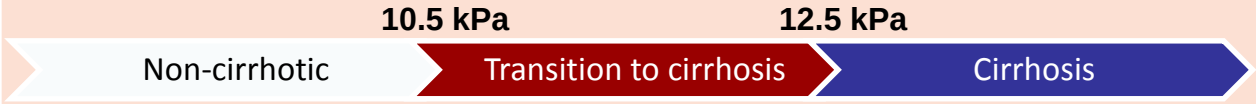
Non-cirrhotic patients

Genotype	Treatment	Duration
GT1a (or unknown or mixed GT1)	**VIEKIRA PAK-RBV***	12 weeks
GT1b	**VIEKIRA PAK**	12 weeks

Gane, Stedman. NZSG Treatment Guidelines. 2016. Available at http://www.nzsg.org.nz/cms2/uploads/Hepatitis%20C%20Guidance_FINAL%20July%2011.pdf

AbbVie Limited. VIEKIRA PAK and VIEKIRA PAK-RBV Data Sheets. Medsafe New Zealand; May 2016.

Pre-treatment assessment for VIEKIRA PAK

Tests	Rationale
Antibody (serology) **HCV RNA** (PCR)	HCV antibodies indicate exposure to virus. Positive viral load confirms **chronic HCV**.
HCV Genotype	VIEKIRA PAK is indicated for patients with **Genotype 1**; regimen differs for GT1a and 1b.
Liver staging (Fibroscan, Shear wave elastography, or APRI score)	Patients with liver stiffness measurement (LSM) >10.5 kPa, or APRI score (AST to Platelet Ratio Index) ≥1.0: **refer to secondary care** 
Blood count	Low **platelet count** (<90 cells x10^9L) suggests portal hypertension: **refer to secondary care**
Medicines review	Consider potential **drug interactions** between VIEKIRA PAK and other medications
Treatment history (pegIFN/RBV)	Determines length of treatment regimen - 24 weeks of VIEKIRA PAK are recommended for a subgroup of cirrhotic patients with genotype 1a who had a previous null response to Rx with pegIFN/RBV

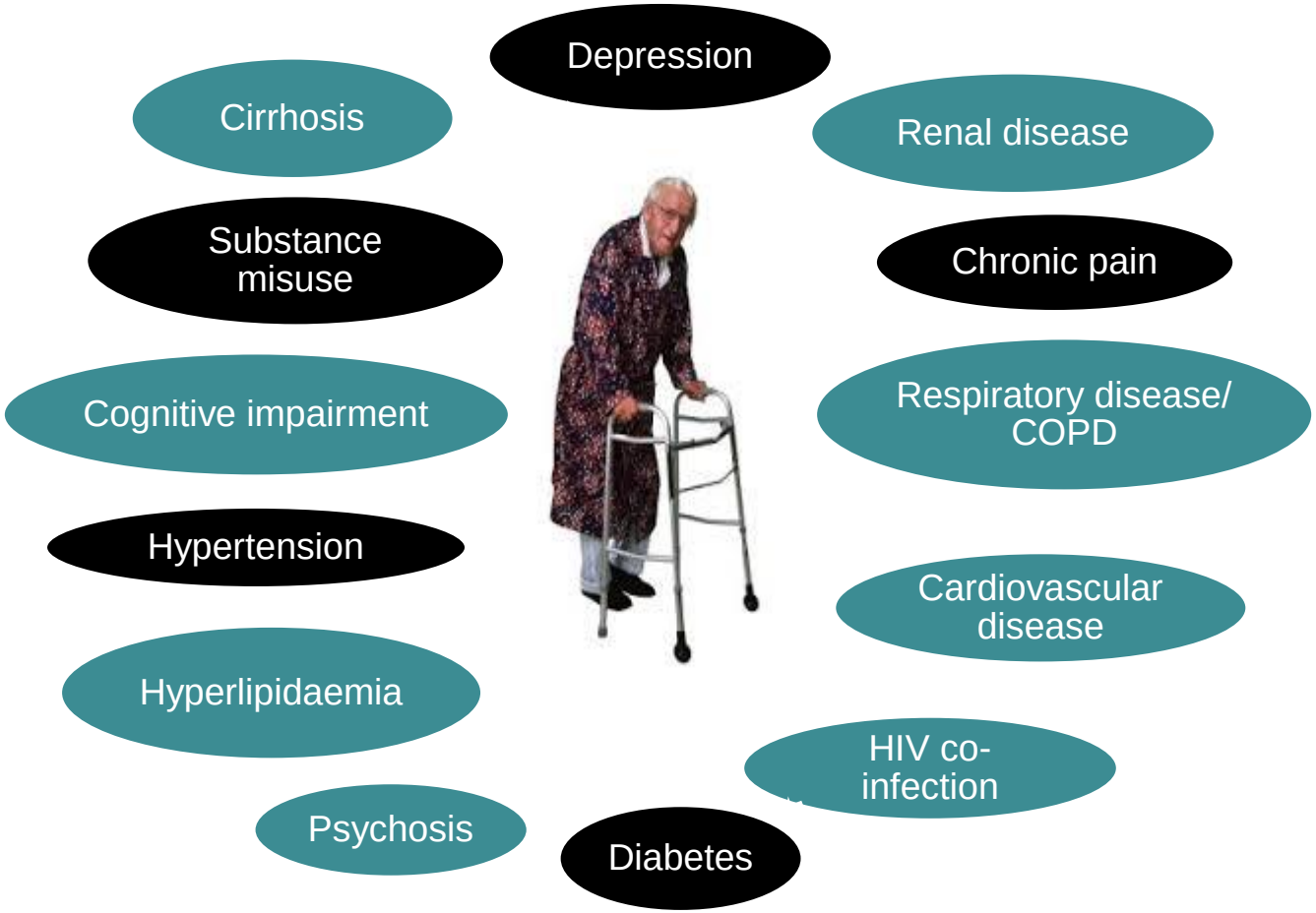
Gane, Stedman. NZSG Treatment Guidelines. 2016. Available at http://www.nzsg.org.nz/cms2/uploads/Hepatitis%20C%20Guidance_FINAL%20July%2011.pdf
AbbVie Limited. VIEKIRA PAK and VIEKIRA PAK-RBV Data Sheets. Medsafe New Zealand; May 2016.

Drug–Drug Interactions

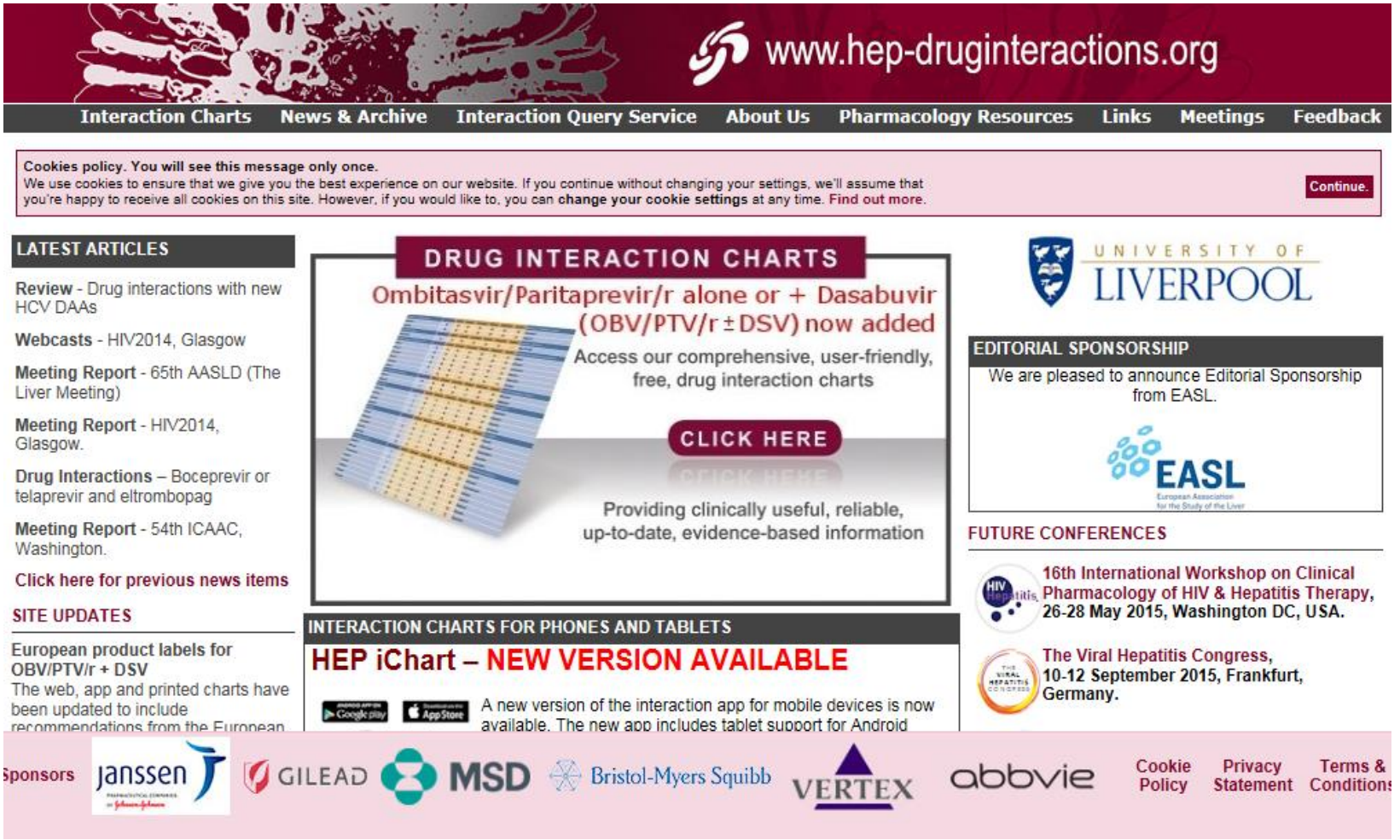
- All direct-acting antivirals interact with drug metabolising enzymes or transporters. Ribavirin is associated with additional drug interactions.
- DDIs between HCV DAAs and concomitant medications could reduce clinical efficacy and lead to unwanted adverse events.
- **All patients with hepatitis C should undergo a careful medicines review before treatment**. Need to check not just what patient reports
- Ask about OTC, recreational and herbal supplements e.g. St Johns wort
- Most potential drug interactions can be managed by careful monitoring and adjustment of dose. No dose adjustment is needed for VIEKIRA PAK itself.
- Some medications are contraindicated, and must be stopped, or substituted with alternatives, during treatment.
- Patients should be monitored throughout their treatment for any potential adverse reactions.

Comorbidities common to patients with hepatitis C

- may have multiple comedications



Drug-drug interactions: “Liverpool app”



University of Liverpool HIV & HEPATITIS Pharmacology Group. Hepatitis Drug Interactions. www.hep-druginteractions.org (Accessed Feb 2016).

NZ Data Sheet: drug interactions with VIEKIRA PAK

No restrictions
Abacavir
Buprenorphine
Dolutegravir
Duloxetine
Emtricitabine
Escitalopram
Lamivudine
Metformin
Methadone
Naloxone
Norethisterone
Paracetamol
Raltegravir
Sulfamethoxazole
Tenofovir
Trimethoprim

Caution / dose adjustment / clinical monitoring
Alprazolam
Amiodarone†
Amlodipine
Atazanavir
Atorvastatin†
Cyclosporine
Darunavir
Diazepam
Digoxin
Fluticasone
Flecainide
Furosemide
Ketoconazole†
Lidocaine (systemic)
Mexiletine
Omeprazole
Pravastatin
Propafenone
Rosuvastatin
Tacrolimus
Quetiapine†

Contraindicated/ not recommended
Carbamazepine
Colchicine in renal or hepatic impairment
Efavirenz
Ergotamine and its derivatives
Ethinyloestradiol-containing products
Fusidic Acid
Gemfibrozil
Oral Midazolam
Phenobarbital
Phenytoin
Rifampicin
Rilpivirine
Ritonavir
Sildenafil*
Simvastatin
Salmeterol
St. John's Wort *(Hypericum Perforatum)*
Terfenadine
Triazolam

*Contraindicated for treatment of pulmonary arterial hypertension; for erectile dysfunction, reduced dose frequency is recommended.
†Contraindicated in Liverpool website but not NZ Data Sheet.

Refer to the Data Sheets and the University of Liverpool website for full information

AbbVie Limited. VIEKIRA PAK and VIEKIRA PAK-RBV Data Sheets. Medsafe New Zealand; May 2016.
University of Liverpool website: http://hep-druginteractions.org/

Hepatitis C Community Clinic

Viekira Treatment Checklist

Name: _____ NHI: _____

Check when last seen by consultant	☐ _____
Print off latest report	☐ _____
Check when/if next hospital appt	☐ _____
Contact client & discuss Rx	☐ _____
Appointment made	☐ _____
Update bloods & medications (check – blood sugar, lipids, HIV, HBV)	☐ _____
Check for DDI's (print out)	☐ _____
Contraception discussion (sos)	☐ _____
Referral to GP (med review sos)	☐ _____
ECG > 50 years old (1a)	☐ _____
Fibroscan	☐ _____
Weight	☐ _____
Request for oversight form/re-referral	☐ _____

Consultant clinic visit/scripting/fibroscan

Monitoring for a 12-week course in a patient without cirrhosis

Do NOT repeat HCV RNA testing during treatment; on-treatment responses do NOT predict relapse.

Week:	Baseline	2	4	8	12	24
PCR test Serum HCV RNA/ viral load	Genotype, RNA					RNA – **SVR12**
Patients with Genotype 1a given VIEKIRA PAK-RBV	Hb	Hb	Hb	Hb		
Patients with Genotype 1b given VIEKIRA PAK	-	-	-	-		

During treatment, assess adherence, side effects and new comedications (with potential interactions).

Guidelines recommend that liver function tests (alanine transaminase, albumin, and bilirubin) should be monitored in patiens with cirrhosis. Elevations in unconjugated bilirubin are common (caused by both enzyme inhibition and haemolysis). **Discontinue treatment if an elevation in conjugated bilirubin is accompanied by an elevation in ALT/AST.**

Best Practice Guidelines. 2016. Available at www.bpac.org.nz
Gane, Stedman. NZSG Treatment Guidelines. 2016. Available at www.nzsg.org.nz/cms2/uploads/Hepatitis%20C%20Guidance_FINAL%20July%2011.pdf

Monitoring: ribavirin

Ribavirin (RBV) can cause dose-related haemolysis and anaemia

Dose reduction is recommended as follows:

- If Hb <100g/L, reduce RBV to 600mg/day
- If Hb <85g/L, discontinue RBV

In Phase 3 clinical trials with VIEKIRA PAK-RBV, 8.5% patients required RBV dose to be reduced due to anaemia; there was no reduction in SVR rates in these patients.

Additional precautions are required for patients with renal dysfunction, cardiac disease, or severe vascular disease. These patients should be treated in secondary care.

VIEKIRA PAK and VIEKIRA PAK-RBV Data Sheets. Medsafe New Zealand; May 2016.

AbbVie VIEKIRA PAK Antiviral Therapy
Paritaprevir/ritonavir/Ombitasvir/Dasabuvir (PrOD) +/-Ribavirin

Patient name/NHI

On-treatment monitoring

Blood test

Start of treatment	**Day 1**	No blood test required	
26/07/2016			
	Week 2	9/08/2016	
	Week 4	23/08/2016	**Collect repeat medications**
	Week 8	20/09/2016	**Collect repeat medications**
End of treatment	**Week 12**	No blood test required	
18/10/2016			
12 weeks post treatment	**Week 24**	10/01/2017	
NOTES:	Blood tests should be done a day or two before this date, or at least first thing that day.		

Treatment side effects of patients in the Gastroenterology Department over the last 18 months

- *Mind shift (away from lengthy treatment with protracted side effects)*
- Mild anaemia
- No worsening of thrombocytopenia or neutropenia
- Bilirubin elevation in patients with cirrhosis – inhibition of bilirubin transporters by paritaprevir
  - Check conjugated bilirubin if elevations in total bilirubin
- Mild nausea
- Mild headache
- Mild sleep disturbance – sleep hygiene
- Dry itchy skin and mucous membranes
  - 10% urea cream

Management of side effects

Fatigue: Check haemoglobin level and adjust ribavirin dosage accordingly.

Nausea: Consider ondansetron at the standard recommended dosage.

Skin rash: Use 10% urea cream or fatty cream. Consult DermNet NZ.

Insomnia: Consider advice on improved sleep hygiene. If severe, then consider using temazepam (10mg nocte) or zopiclone (3.75mg nocte) when required.

Gane, Stedman. NZSG Treatment Guidelines. 2016. Available at http://www.nzsg.org.nz/cms2/uploads/Hepatitis%20C%20Guidance_FINAL%20July%2011.pdf

Summary: VIEKIRA PAK and VIEKIRA PAK-RBV

High certainty of cure*	• EFFICACY: SVR12 = 97% for patients with genotype 1 HCV, including cirrhotics and those who previously failed with pegIFN/RBV.
Low rates of failure	• RESISTANCE PROFILE: Low rates of virologic failure (<2%)
Low rates of discontinuation	• SAFETY: Well-tolerated regimen, with low rates of discontinuations due to adverse events (1.0%)

**Cure defined as ≤25 IU/mL HCV RNA 12 weeks after end of treatment (SVR12). SVR12 for VIEKIRA PAK and VIEKIRA PAK-RBV was 97% in patients with GT1 HCV (with or without cirrhosis; pooled analysis Phase III trial cohorts; n=1096).*

AbbVie Limited. VIEKIRA PAK and VIEKIRA PAK-RBV Data Sheets. Medsafe New Zealand; May 2016.

Conclusions

- Hepatitis C genotype 1 is now curable in 12-week all-oral interferon-free regimens that are relatively free of side effects


UNLESS someone like
YOU cares a whole
awful lot, NOTHING
is going to get better.
It's NOT.
The Lorax by Dr. Seuss
Dr. Seuss

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