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Saturday, August 13, 2016

(Room 10)

7:00 - 8:00 Abbvie Breakfast Session

1. Joining the Dots in Psoriatic Arthritis; 2. Reaching for a Cure for Hep C

Newly funded treatments for NZ patients with genotype 1 hepatitis C

Associate Professor Catherine Stedman

University of Otago, Christchurch

Christchurch Hospital

This is an educational meeting designed to share clinical data and promote scientific exchange.

This slide set is intended to be read as a whole without modification.

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AbbVie Limited, Wellington, NZ. NZ-HCV-2016-66. August 2016.

DISCLOSURES:

Catherine Stedman

Clinical Trials, Consulting and Advisory Boards for Abbvie, MSD and Gilead Sciences

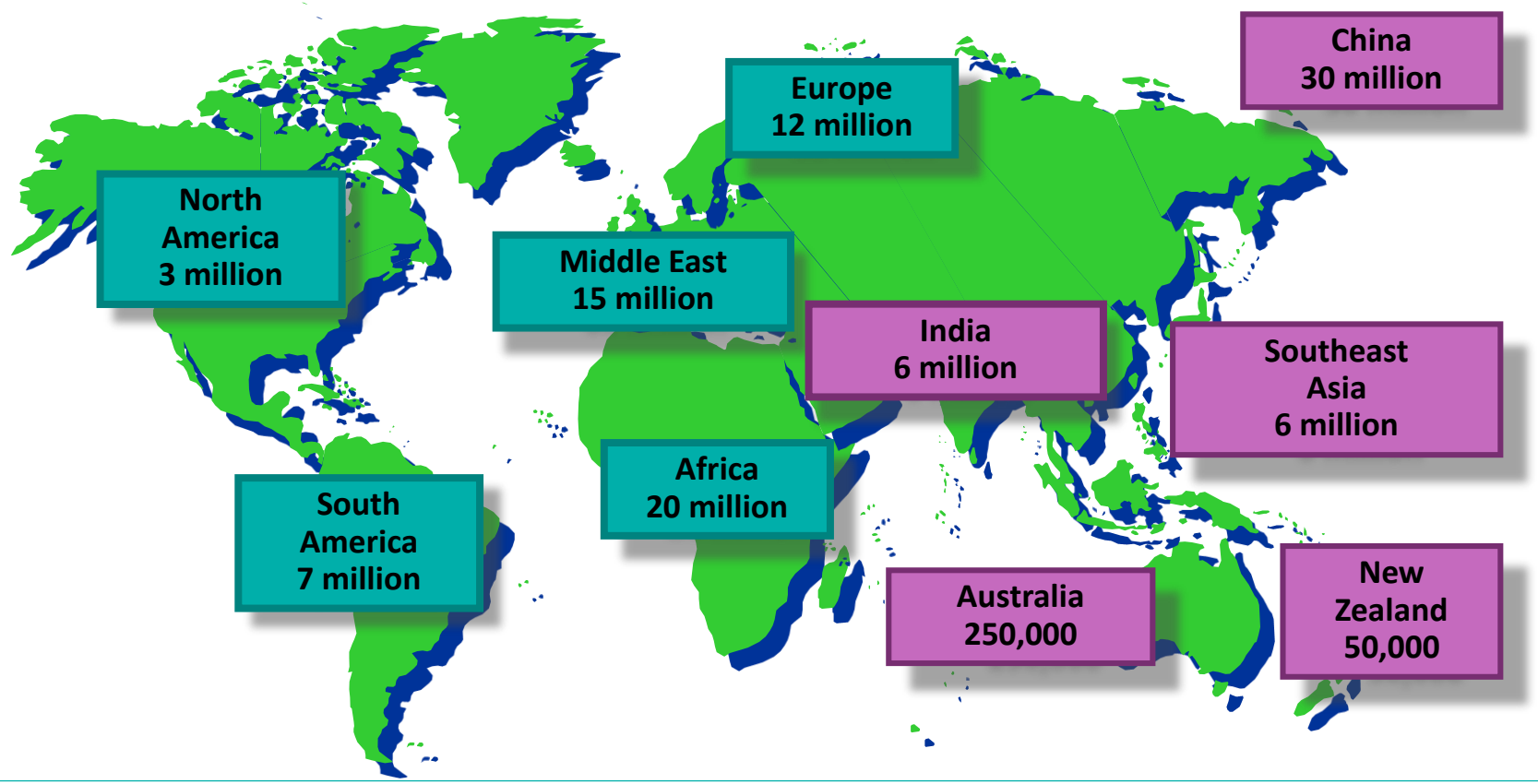
Canterbury District Health Board
Te Poari Hauora o Waitaha

University of Otago
Te Whare Wānanga o Otāgo
New Zealand

Gastroenterology and Endoscopy Specialists

Hepatitis C is the silent global epidemic of the 21st Century

110–170 million people are now living with chronic hepatitis C (HCV) – most of these people live within the Asia Pacific region



Gower E et al. *Journal of Hepatology* 2014. 61(1 Suppl):S45-57.

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Risk factors for HCV infection in New Zealand

Transmission through blood products

- Since screening (1992 in NZ) no post-transfusion hepatitis
- Immigrants from countries where HCV is endemic may have been exposed via this route

~90% of transmission of HCV occurs through injecting drug use in NZ

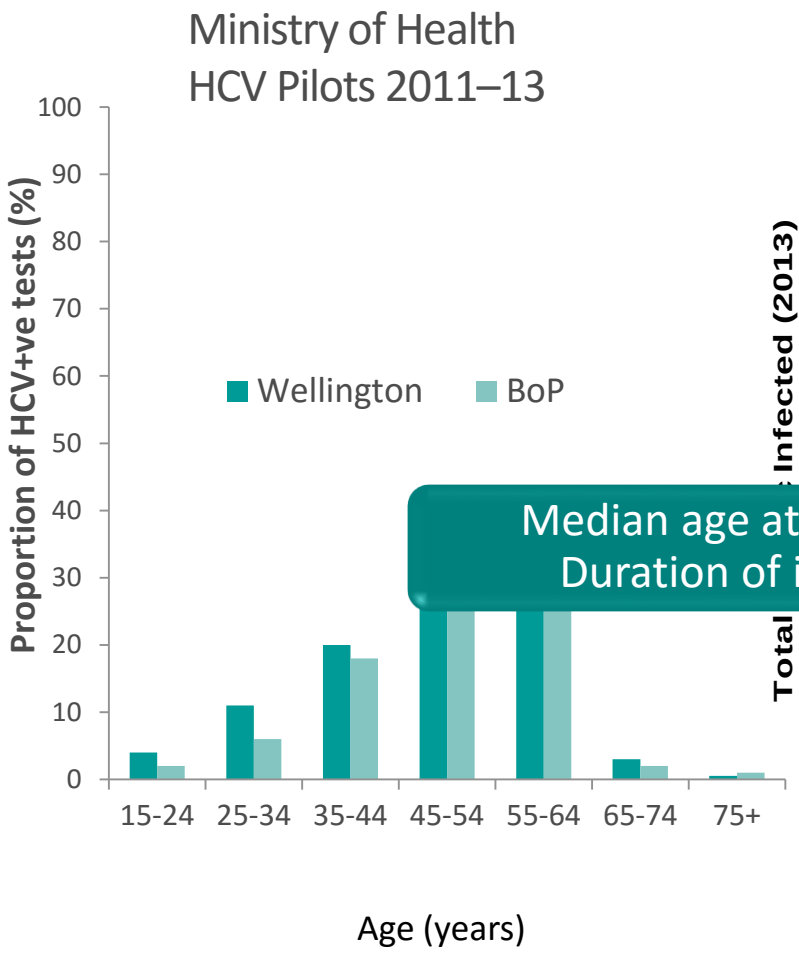
- » Peak age of infection 15–25 years
- » Peak incidence 1970–1990

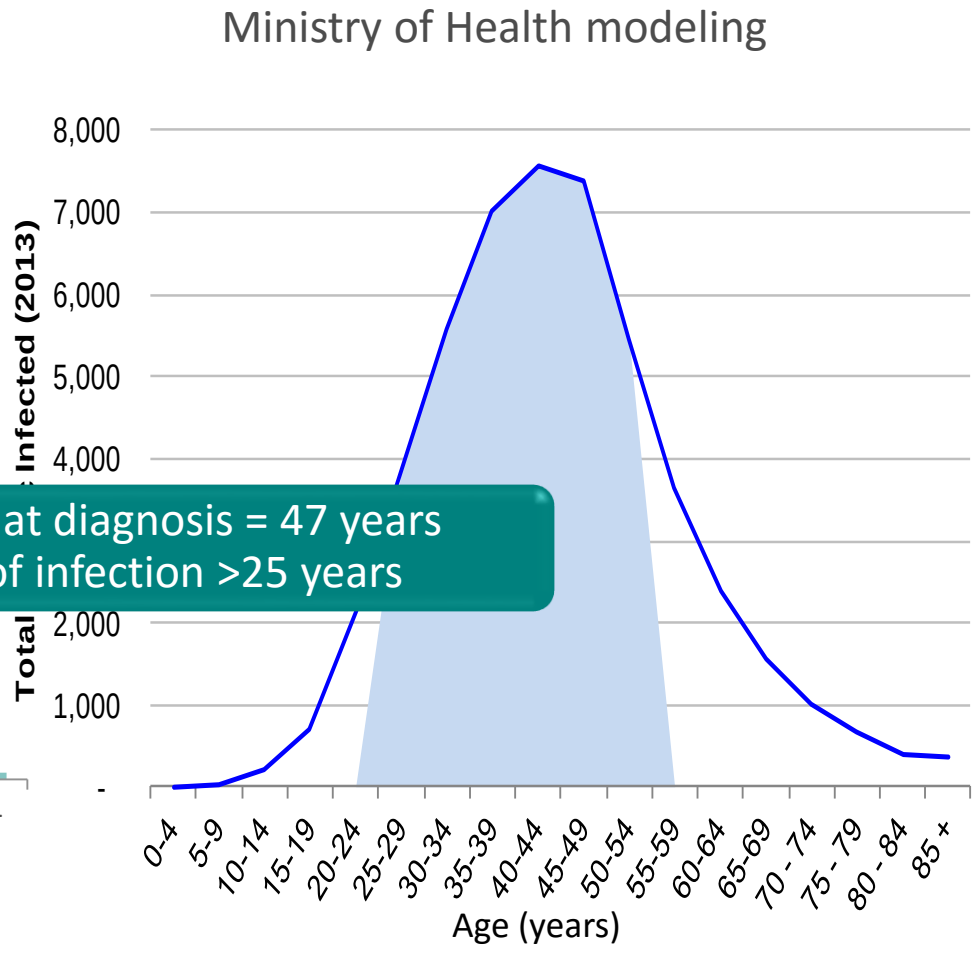
Small numbers of people are also infected via unsafe tattooing or body piercing

Total number infected >50,000
Estimated undiagnosed = 40–50%

Gane E, et al. *NZ Med J* 2014. 127; 1407:61–74.

Age of NZ patients with chronic HCV





Median age at diagnosis = 47 years
Duration of infection >25 years

Hepatitis Foundation Report Nov 2014.

Gane E, et al. *NZ Med J* 2014. 127; 1407:61–74.

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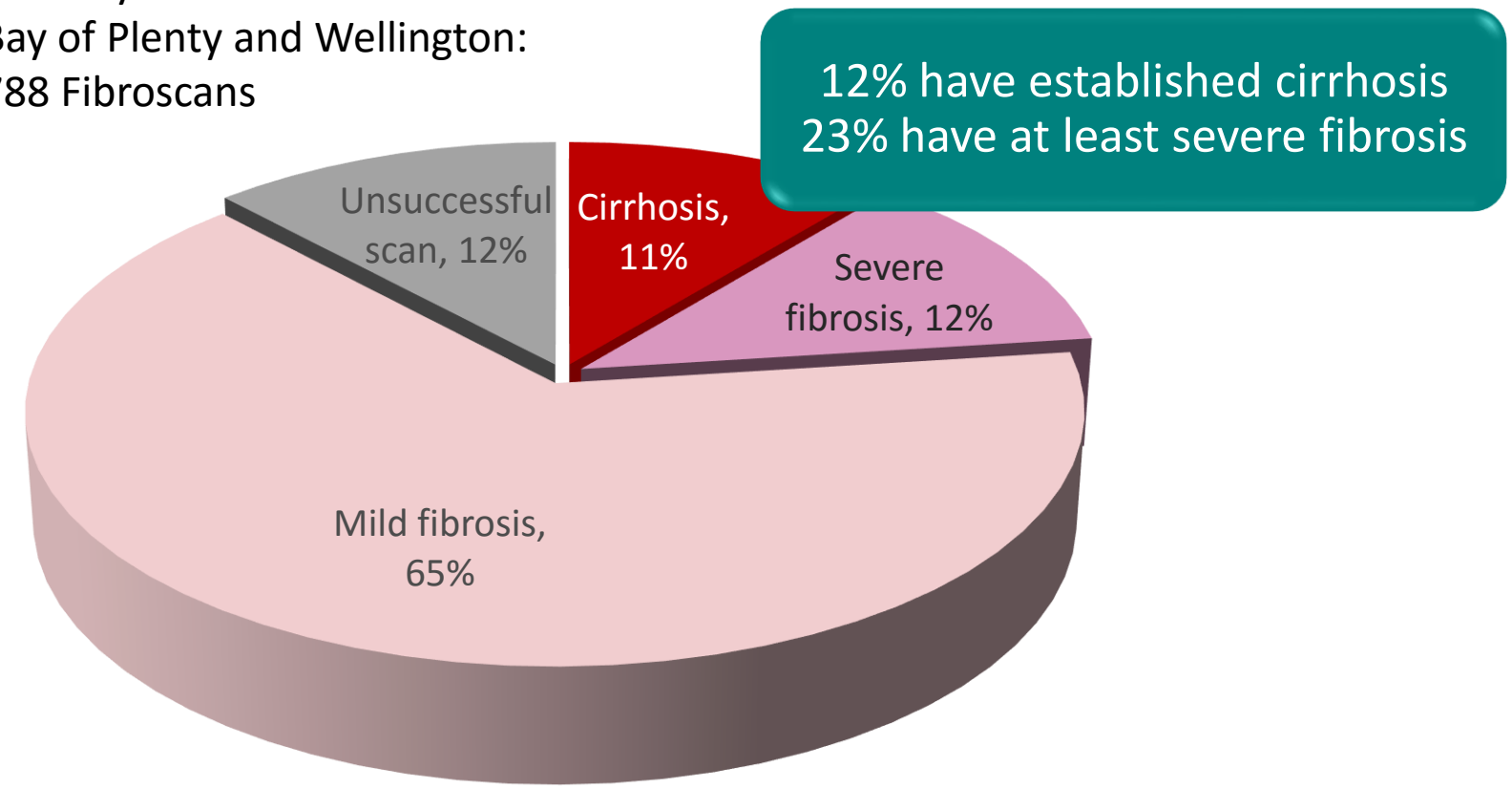
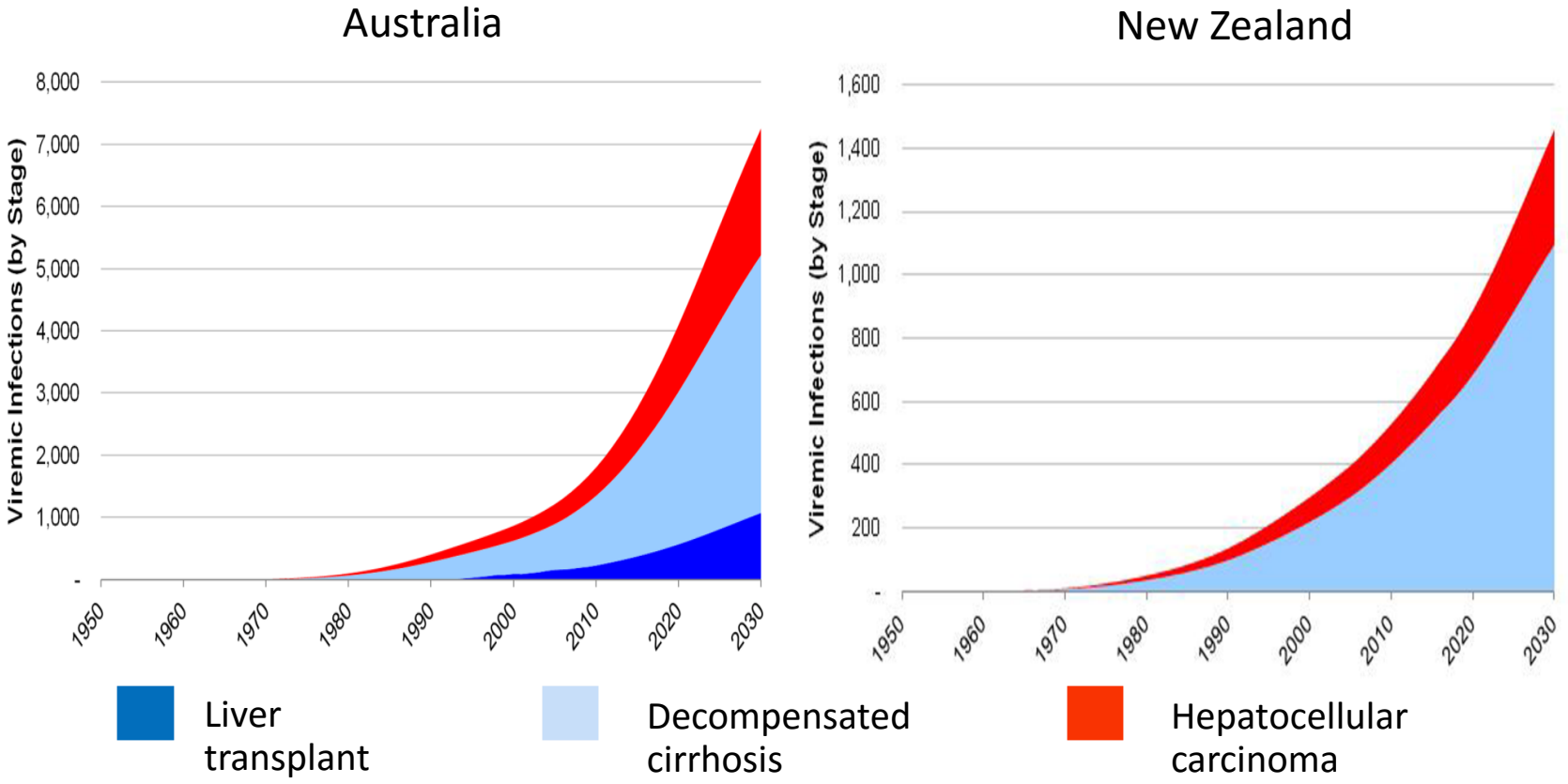
Fibrosis stage of NZ patients with chronic HCV

Ministry of Health HCV Pilot in Bay of Plenty and Wellington: 788 Fibroscans



Hepatitis Foundation Report Nov 2014.

Disease burden from hepatitis C: projected to treble in Australia and NZ by 2030



Razavi H, et al. J Viral Hepat 2014; 21 Suppl 1: 34-59.

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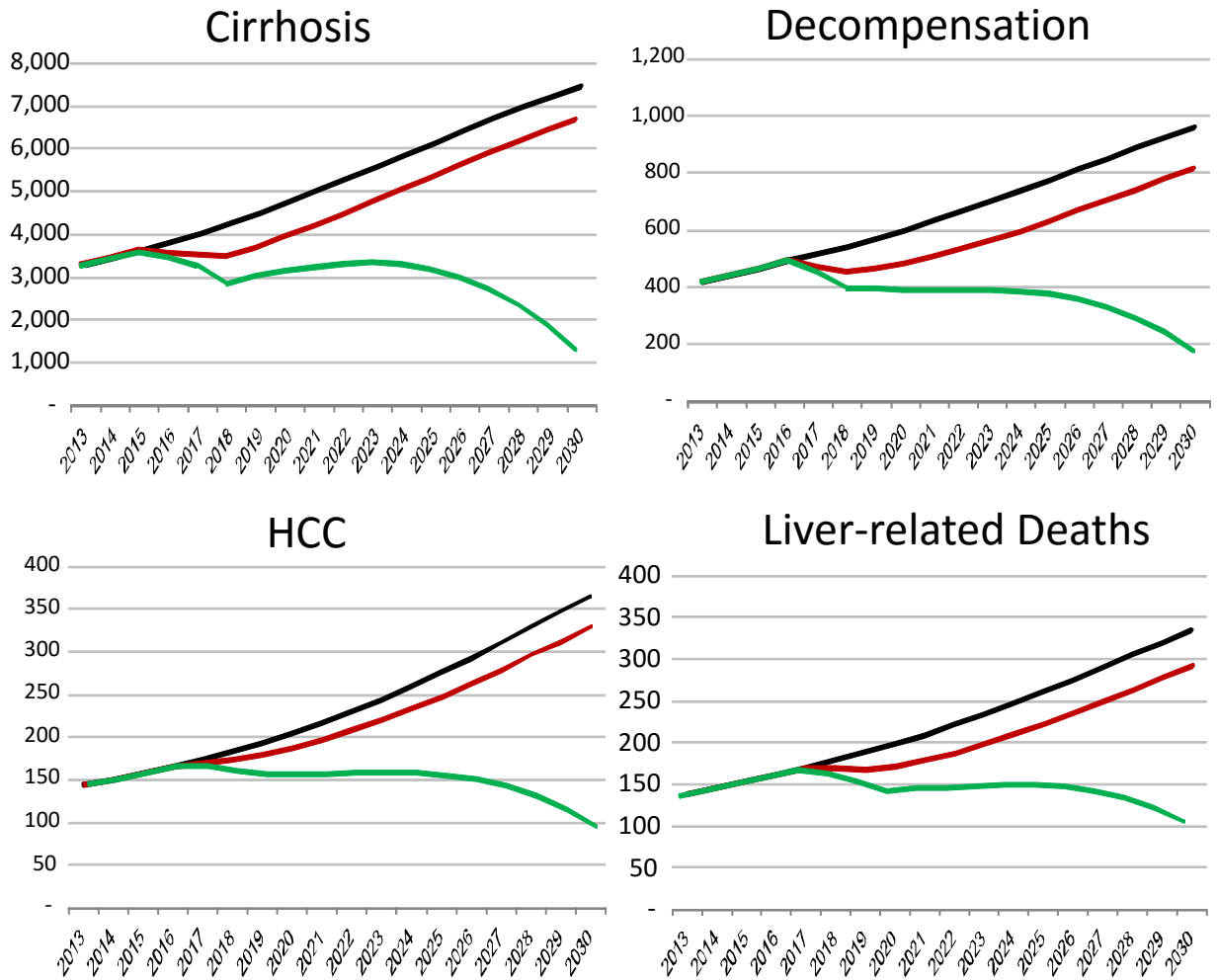
New direct-acting antivirals should enable increased rates of treatment and cure



Most patients are untreated, and waiting for all-oral therapy

1% treated
→50% cured

2% treated
(i.e. only cirrhotics)
→90% cured

10% treated
→ 90% cured

Gane E, et al. *NZ Med J* 2014. 127; 1407:61–74.

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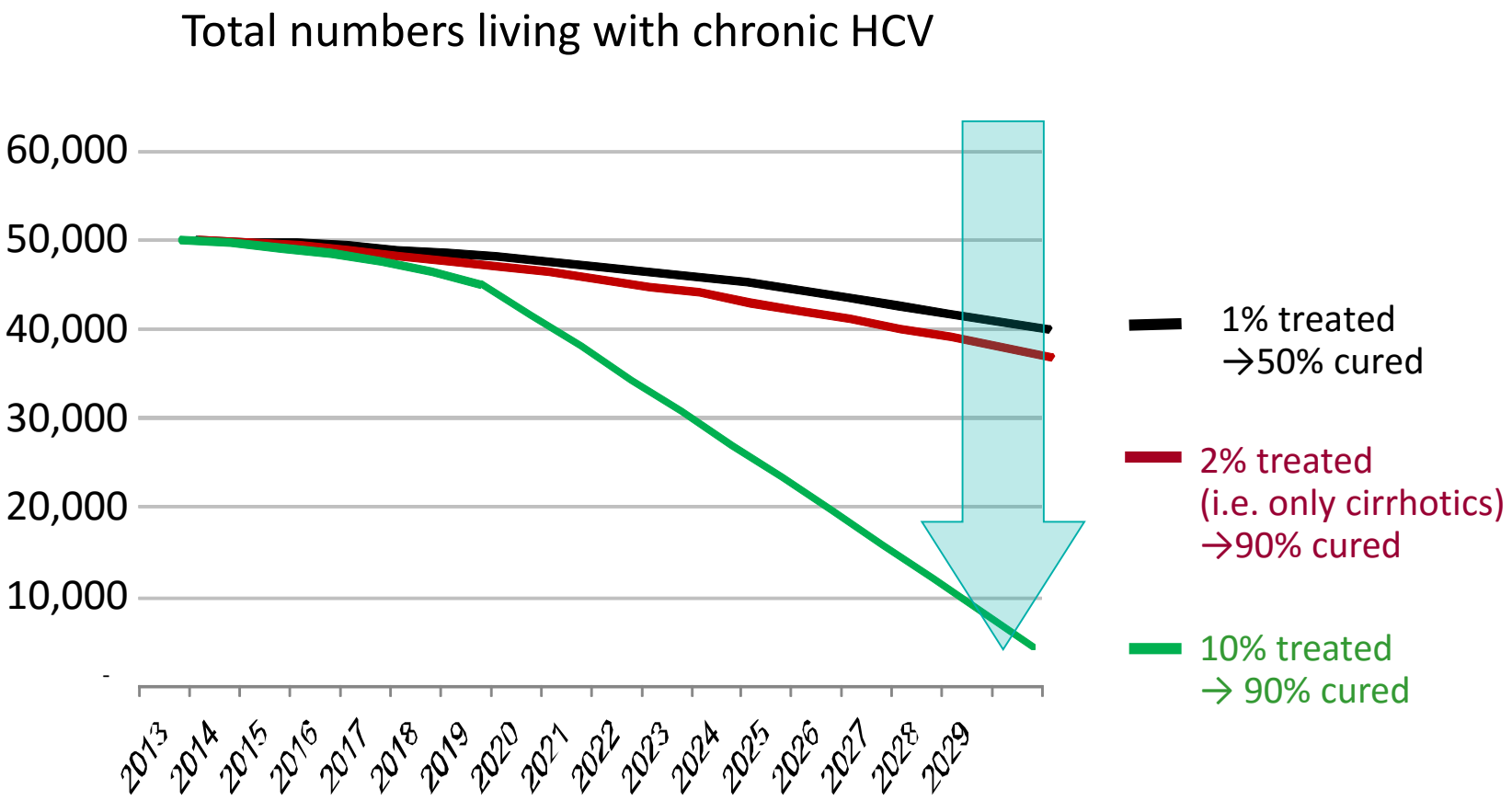
New treatments should eliminate HCV in New Zealand within 15 years



Gane E, et al. *NZ Med J* 2014. 127; 1407:61–74.

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What will it take to eliminate HCV from NZ?

Total number infected >50,000
Estimated undiagnosed = 40–50%

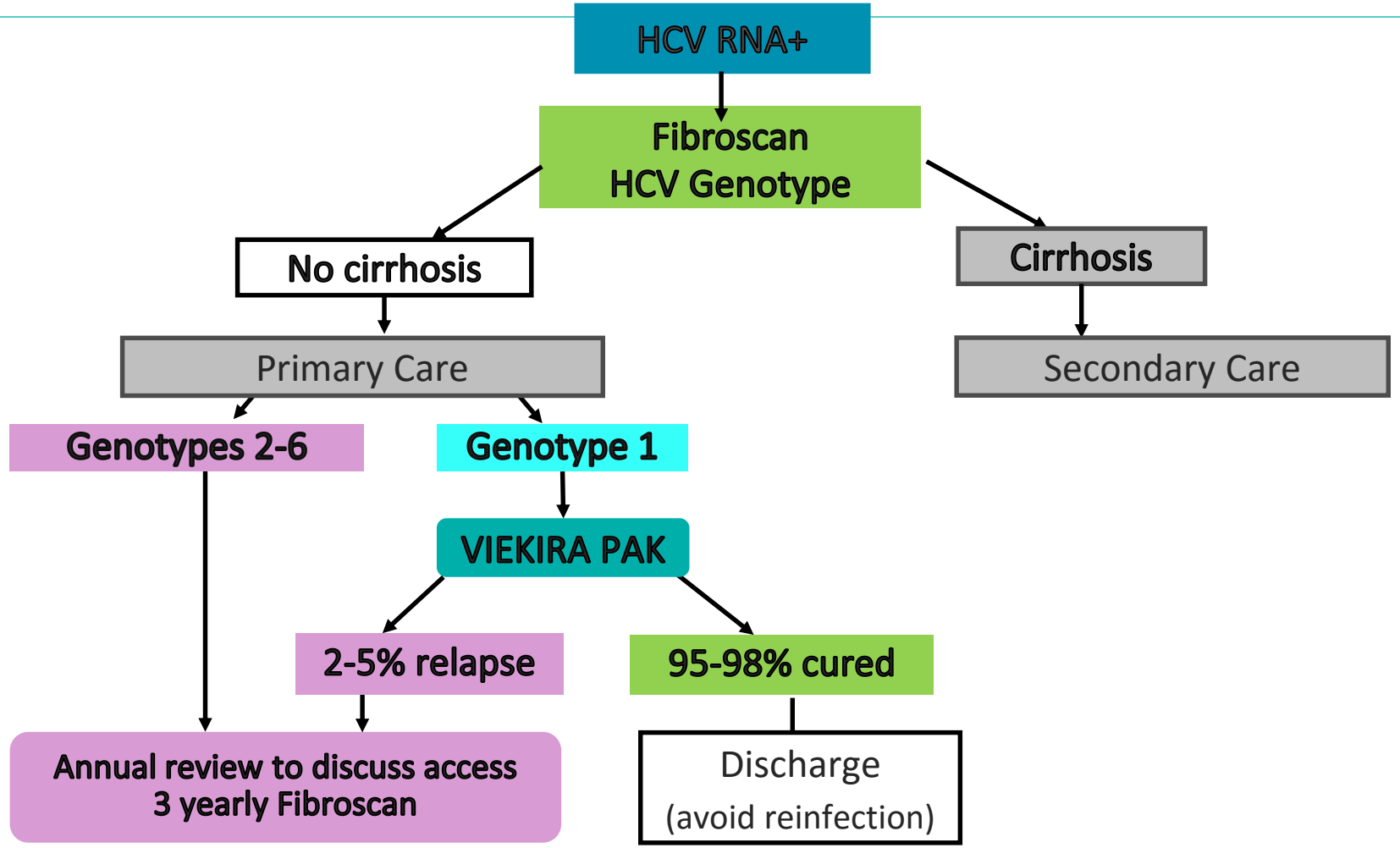
Identify those who remain undiagnosed

- Targeted testing in Primary Care
- Point-of-care testing in Prisons, Needle Exchange (NEX), Community Alcohol and Drug Services (CADS)

Fund direct-acting antiviral therapy, and quadruple numbers treated by 2020 (2,000 patients per annum) by moving treatment out to the community

- Primary care
- NEX, CADS, Prisons → “treatment as prevention”

Suggested algorithm for community treatment



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

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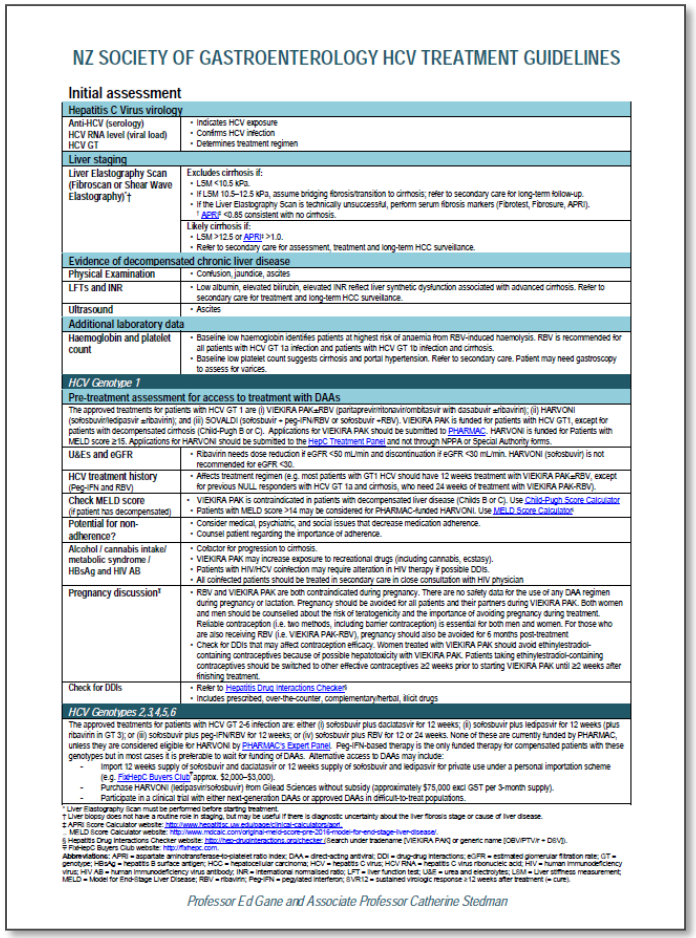
Treatment guidelines for NZ



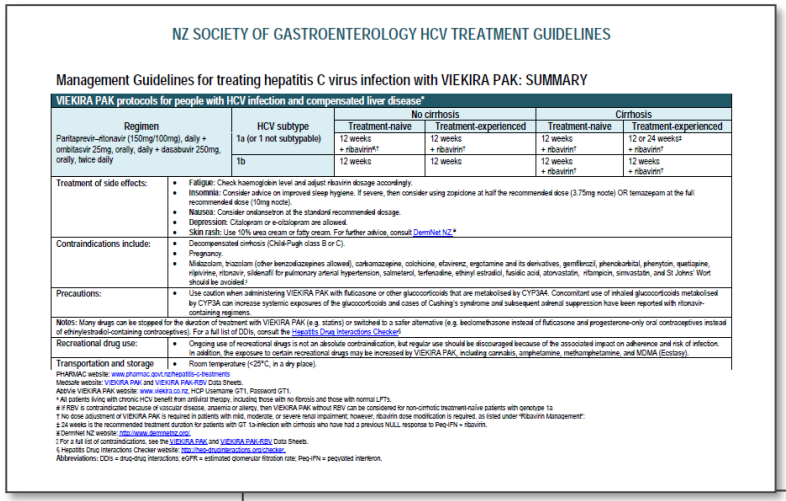
NZ SOCIETY OF GASTROENTEROLOGY HCV TREATMENT GUIDELINES

Initial assessment

Hepatitis C Virus virology	
Anti-HCV (serology) HCV RNA level (viral load) HCV GT	• Indicates HCV exposure • Confirms HCV infection • Determines treatment regimen
Liver staging	
Liver Elastography Scan (Fibroscan or Shear Wave Elastography)*†	Excludes cirrhosis if: • LSM <10.5 kPa. • If LSM 10.5–12.5 kPa, assume bridging fibrosis/transition to cirrhosis; refer to secondary care for long-term follow-up. • If the Liver Elastography Scan is technically unsuccessful, perform serum fibrosis markers (Fibrotest, Fibrosure, APRI). ‡ APRI <0.85 consistent with no cirrhosis. Likely cirrhosis if: • LSM >12.5 or APRI‡ >1.0. • Refer to secondary care for assessment, treatment and long-term HCC surveillance.
Evidence of decompensated chronic liver disease	
Physical Examination	• Confusion, jaundice, ascites
LFTs and INR	• Low albumin, elevated bilirubin, elevated INR reflect liver synthetic dysfunction associated with advanced cirrhosis. Refer to secondary care for treatment and long-term HCC surveillance.
Ultrasound	• Ascites
Additional laboratory data	
Haemoglobin and platelet count	• Baseline low haemoglobin identifies patients at highest risk of anaemia from RBV-induced haemolysis. RBV is recommended for all patients with HCV GT 1a infection and patients with HCV GT 1b infection and cirrhosis. • Baseline low platelet count suggests cirrhosis and portal hypertension. Refer to secondary care. Patient may need gastroscopy to assess for varices.
HCV Genotype 1	
Pre-treatment assessment for access to treatment with DAAs	
The approved treatments for patients with HCV GT 1 are (i) VIEKIRA PAK+RBV (paritaprevir/ritonavir/ombitasvir with dasabuvir ±ribavirin); (ii) HARVONI (sofosbuvir/ledipasvir ±ribavirin); and (iii) SOVALDI (sofosbuvir + peg-IFN/RBV or sofosbuvir +RBV). VIEKIRA PAK is funded for patients with HCV GT1, except for patients with decompensated cirrhosis (Child-Pugh B or C). Applications for VIEKIRA PAK should be submitted to PHARMAC. HARVONI is funded for Patients with MELD score ≥15. Applications for HARVONI should be submitted to the HepC Treatment Panel and not through NPPA or Special Authority forms.	
U&Es and eGFR	• Ribavirin needs dose reduction if eGFR <50 mL/min and discontinuation if eGFR <30 mL/min. HARVONI (sofosbuvir) is not recommended for eGFR <30.
HCV treatment history (Peg-IFN and RBV)	• Affects treatment regimen (e.g. most patients with GT1 HCV should have 12 weeks treatment with VIEKIRA PAK+RBV, except for previous NULL responders with HCV GT 1a and cirrhosis, who need 24 weeks of treatment with VIEKIRA PAK-RBV).
Check MELD score (if patient has decompensated)	• VIEKIRA PAK is contraindicated in patients with decompensated liver disease (Childs B or C). Use Child-Pugh Score Calculator • Patients with MELD score >14 may be considered for PHARMAC-funded HARVONI. Use MELD Score Calculator
Potential for non-adherence?	• Consider medical, psychiatric, and social issues that decrease medication adherence. • Counsel patient regarding the importance of adherence.
Alcohol / cannabis intake/ metabolic syndrome / HBsAg and HIV AB	• Cofactor for progression to cirrhosis. • VIEKIRA PAK may increase exposure to recreational drugs (including cannabis, ecstasy). • Patients with HIV/HCV coinfection may require alteration in HIV therapy if possible DDIs. • All coinfected patients should be treated in secondary care in close consultation with HIV physician
Pregnancy discussion‖	• RBV and VIEKIRA PAK are both contraindicated during pregnancy. There are no safety data for the use of any DAA regimen during pregnancy or lactation. Pregnancy should be avoided for all patients and their partners during VIEKIRA PAK. Both women and men should be counselled about the risk of teratogenicity and the importance of avoiding pregnancy during treatment. Reliable contraception (i.e. two methods, including barrier contraception) is essential for both men and women. For those who are also receiving RBV (i.e. VIEKIRA PAK+RBV), pregnancy should also be avoided for 6 months post-treatment. • Check for DDIs that may affect contraception efficacy. Women treated with VIEKIRA PAK should avoid ethinylestradiol-containing contraceptives because of possible hepatotoxicity with VIEKIRA PAK. Patients taking ethinylestradiol-containing contraceptives should be switched to other effective contraceptives ≥2 weeks prior to starting VIEKIRA PAK until ≥2 weeks after finishing treatment.
Check for DDIs	• Refer to Hepatitis Drug Interactions Checker§ • Includes prescribed, over-the-counter, complementary/herbal, illicit drugs
HCV Genotypes 2,3,4,5,6	
The approved treatments for patients with HCV GT 2-6 infection are: either (i) sofosbuvir plus daclatasvir for 12 weeks; (ii) sofosbuvir plus ledipasvir for 12 weeks (plus ribavirin in GT 3); or (iii) sofosbuvir plus peg-IFN/RBV for 12 weeks; or (iv) sofosbuvir plus RBV for 12 or 24 weeks. None of these are currently funded by PHARMAC, unless they are considered eligible for HARVONI by PHARMAC's Expert Panel. Peg-IFN-based therapy is the only funded therapy for compensated patients with these genotypes but in most cases it is preferable to wait for funding of DAAs. Alternative access to DAAs may include: - Import 12 weeks supply of sofosbuvir and daclatasvir or 12 weeks supply of sofosbuvir and ledipasvir for private use under a personal importation scheme (e.g. FixHepC Buyers Club¶ approx. $2,000–$3,000). - Purchase HARVONI (ledipasvir/sofosbuvir) from Gilead Sciences without subsidy (approximately $75,000 excl GST per 3-month supply). - Participate in a clinical trial with either next-generation DAAs or approved DAAs in difficult-to-treat populations.	

* Liver Elastography (can must be performed before starting treatment.
† Liver biopsy does not have a routine role in staging, but may be useful if there is diagnostic uncertainty about the liver fibrosis stage or cause of liver disease.
‡ APRI Score Calculator website: http://www.hepatitisc.uw.edu/page/clinical-calculators/apri.
MELD Score Calculator website: http://www.mdcalc.com/original-meld-score-pre-2016-model-for-end-stage-liver-disease/
§ Hepatitis Drug Interactions Checker website: http://hep-druginteractions.org/checker (search under tradename [VIEKIRA PAK] or generic name [OBV/PTV/r + DSV]).
¶ FixHepC Buyers Club website: http://fixhepc.com.
Abbreviations: APRI = aspartate aminotransferase-to-platelet ratio index; DAA = direct-acting antiviral; DDI = drug-drug interactions; eGFR = estimated glomerular filtration rate; GT = genotype; HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HCV RNA = hepatitis C virus ribonucleic acid; HIV = human immunodeficiency virus; HIV AB = human immunodeficiency virus antibody; INR = international normalised ratio; LFT = liver function test; U&E = urea and electrolytes; LSM = Liver stiffness measurement; MELD = Model for End-Stage Liver Disease; RBV = ribavirin; Peg-IFN = pegylated interferon; SVR12 = sustained virologic response ≥12 weeks after treatment (= cure).

Professor Ed Gane and Associate Professor Catherine Stedman

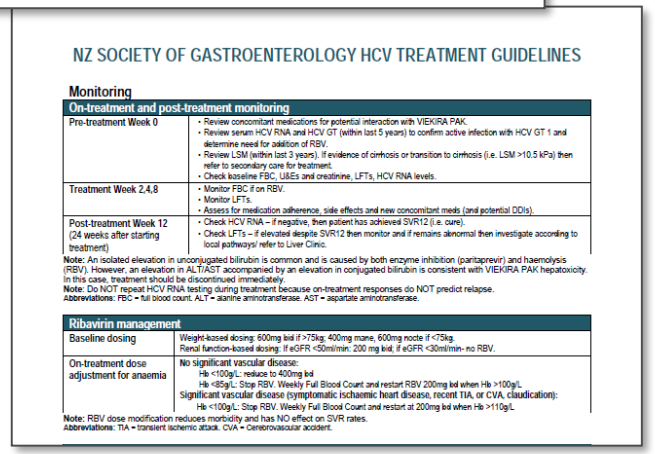


NZ SOCIETY OF GASTROENTEROLOGY HCV TREATMENT GUIDELINES

Management Guidelines for treating hepatitis C virus infection with VIEKIRA PAK: SUMMARY

VIEKIRA PAK protocols for people with HCV infection and compensated liver disease*						
			No cirrhosis		Cirrhosis	
Regimen	HCV subtype		Treatment-naive	Treatment-experienced	Treatment-naive	Treatment-experienced
Paritaprevir–ritonavir (150mg/100mg), daily + ombitasvir 25mg, orally, daily + dasabuvir 250mg, orally, twice daily	1a (or 1 not subtypable)		12 weeks + ribavirin†^	12 weeks + ribavirin†	12 weeks + ribavirin†	12 or 24 weeks‡ + ribavirin†
	1b		12 weeks	12 weeks	12 weeks + ribavirin†	12 weeks + ribavirin†
Treatment of side effects:	• **Fatigue:** Check haemoglobin level and adjust ribavirin dosage accordingly. • **Insomnia:** Consider advice on improved sleep hygiene. If severe, then consider using zopiclone at half the recommended dose (3.75mg nocte) OR temazepam at the full recommended dose (10mg nocte). • **Nausea:** Consider ondansetron at the standard recommended dosage. • **Depression:** Citalopram or e-citalopram are allowed. • **Skin rash:** Use 10% urea cream or fatty cream. For further advice, consult DermNet NZ§					
Contraindications include:	• Decompensated cirrhosis (Child-Pugh class B or C). • Pregnancy. • Midazolam, triazolam (other benzodiazepines allowed), carbamazepine, colchicine, efavirenz, ergotamine and its derivatives, gemfibrozil, phenobarbital, phenytoin, quetiapine, rifampicin, ritonavir, sildenafil for pulmonary arterial hypertension, salmeterol, terfenadine, ethinyl estradiol, fusidic acid, atorvastatin, rifampicin, simvastatin, and St Johns' Wort should be avoided‖.					
Precautions:	• Use caution when administering VIEKIRA PAK with fluticasone or other glucocorticoids that are metabolised by CYP3A4. Concomitant use of inhaled glucocorticoids metabolised by CYP3A can increase systemic exposures of the glucocorticoids and cases of Cushing's syndrome and subsequent adrenal suppression have been reported with ritonavir-containing regimens.					
Notes: Many drugs can be stopped for the duration of treatment with VIEKIRA PAK (e.g. statins) or switched to a safer alternative (e.g. beclomethasone instead of fluticasone and progesterone-only oral contraceptives instead of ethinylestradiol-containing contraceptives). For a full list of DDIs, consult the Hepatitis Drug Interactions Checker¶						
Recreational drug use:	• Ongoing use of recreational drugs is not an absolute contraindication, but regular use should be discouraged because of the associated impact on adherence and risk of infection. In addition, the exposure to certain recreational drugs may be increased by VIEKIRA PAK, including cannabis, amphetamine, methamphetamine, and MDMA (Ecstasy).					
Transportation and storage	• Room temperature (<25°C, in a dry place).					

PHARMAC website: www.pharmac.govt.nz/hepatitis-c-treatments
Medsafe website: VIEKIRA PAK and VIEKIRA PAK-RBV Data Sheets.
Abbvie VIEKIRA PAK website: www.viekira.co.nz, HCP Username GT1, Password GT1.
* All patients living with chronic HCV benefit from antiviral therapy, including those with no fibrosis and those with normal LFTs.
# If RBV is contraindicated because of vascular disease, anaemia or allergy, then VIEKIRA PAK without RBV can be considered for non-cirrhotic treatment-naïve patients with genotype 1a
† No dose adjustment of VIEKIRA PAK is required in patients with mild, moderate, or severe renal impairment; however, ribavirin dose modification is required, as listed under "Ribavirin Management".
‡ 24 weeks is the recommended treatment duration for patients with GT 1a-infection with cirrhosis who have had a previous NULL response to Peg-IFN + ribavirin.
§ DermNet NZ website: http://www.dermnetnz.org/
‖ For a full list of contraindications, see the VIEKIRA PAK and VIEKIRA PAK-RBV Data Sheets.
¶ Hepatitis Drug Interactions Checker website: http://hep-druginteractions.org/checker.
Abbreviations: DDIs = drug-drug interactions; eGFR = estimated glomerular filtration rate; Peg-IFN = pegylated interferon.



NZ SOCIETY OF GASTROENTEROLOGY HCV TREATMENT GUIDELINES

Monitoring

On-treatment and post-treatment monitoring	
Pre-treatment Week 0	• Review concomitant medications for potential interaction with VIEKIRA PAK. • Review serum HCV RNA and HCV GT (within last 5 years) to confirm active infection with HCV GT 1 and determine need for addition of RBV. • Review LSM (within last 3 years). If evidence of cirrhosis or transition to cirrhosis (i.e. LSM >10.5 kPa) then refer to secondary care for treatment. • Check baseline FBC, U&Es and creatinine, LFTs, HCV RNA levels.
Treatment Week 2,4,8	• Monitor FBC if on RBV. • Monitor LFTs. • Assess for medication adherence, side effects and new concomitant meds (and potential DDIs).
Post-treatment Week 12 (24 weeks after starting treatment)	• Check HCV RNA – if negative, then patient has achieved SVR12 (i.e. cure). • Check LFTs – if elevated despite SVR12 then monitor and if remains abnormal then investigate according to local pathways/ refer to Liver Clinic.

Note: An isolated elevation in unconjugated bilirubin is common and is caused by both enzyme inhibition (paritaprevir) and haemolysis (RBV). However, an elevation in ALT/AST accompanied by an elevation in conjugated bilirubin is consistent with VIEKIRA PAK hepatotoxicity. In this case, treatment should be discontinued immediately.
Note: Do NOT repeat HCV RNA testing during treatment because on-treatment responses do NOT predict relapse.
Abbreviations: FBC = full blood count. ALT = alanine aminotransferase. AST = aspartate aminotransferase.

Ribavirin management	
Baseline dosing	Weight-based dosing: 600mg bid if >75kg; 400mg mane, 600mg nocte if <75kg. Renal function-based dosing: If eGFR <50ml/min: 200 mg bid; if eGFR <30ml/min- no RBV.
On-treatment dose adjustment for anaemia	**No significant vascular disease:** Hb <100g/L: reduce to 400mg bd Hb <85g/L: Stop RBV. Weekly Full Blood Count and restart RBV 200mg bd when Hb >100g/L **Significant vascular disease (symptomatic ischaemic heart disease, recent TIA, or CVA, claudication):** Hb <100g/L: Stop RBV. Weekly Full Blood Count and restart at 200mg bd when Hb >110g/L

Note: RBV dose modification reduces morbidity and has NO effect on SVR rates.
Abbreviations: TIA = transient ischemic attack. CVA = Cerebrovascular accident.

Gane, Stedman. NZ Society of Gastroenterology HCV Treatment Guidelines. 2016. Available at: http://www.nzsg.org.nz/cms2/uploads/Hepatitis%20C%20Guidance_FINAL%20July%2011.pdf Accessed July 2016.

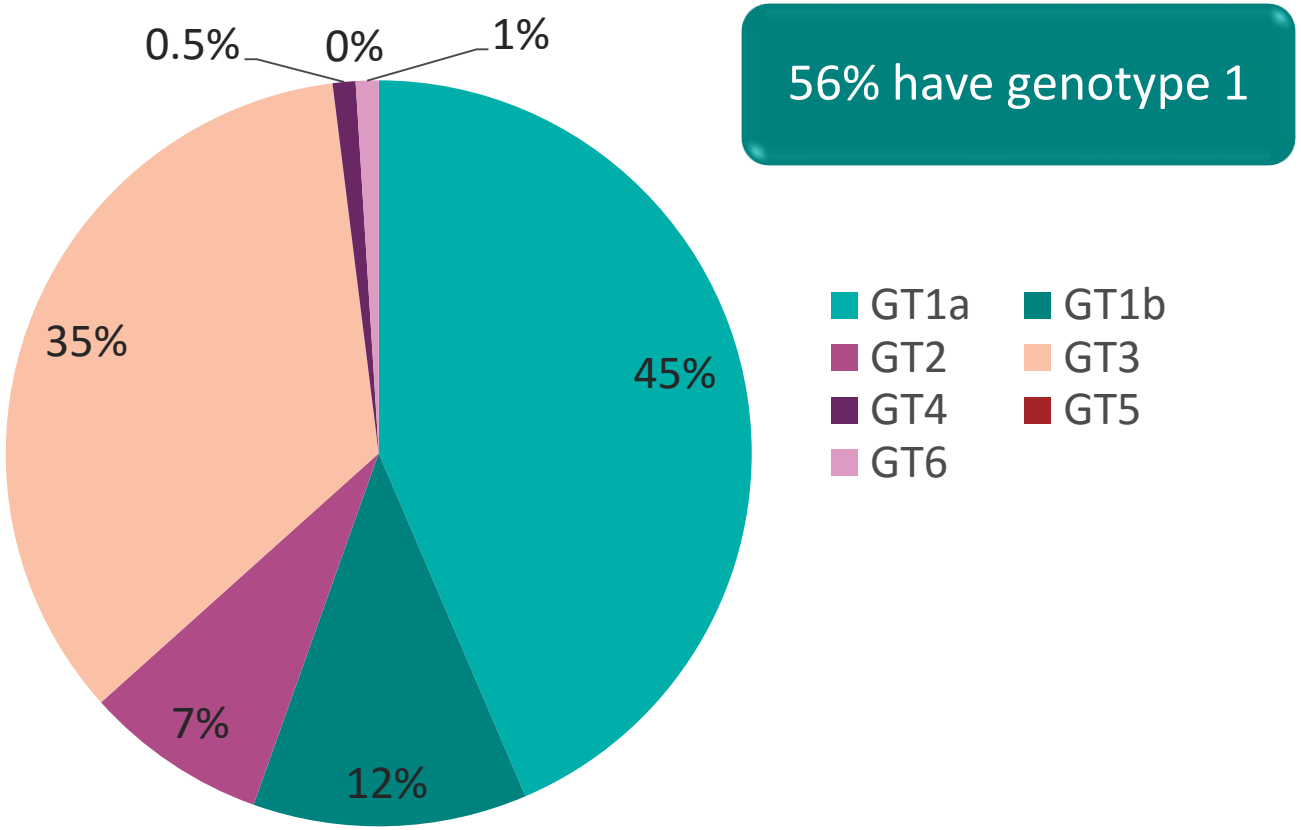
Pre-treatment assessment for VIEKIRA PAK: virology

Tests	Rationale
Antibody (serology) **HCV RNA** (PCR)	• **HCV antibodies** indicate **exposure** to virus • **Positive viral load** confirms current **chronic HCV** • Perform if - no result within past 5 years - previous acute hepatitis (i.e. jaundice or ALT >10xULN) - previous treatment
HCV Genotype and Subtype (1a vs 1b)	• VIEKIRA PAK is indicated only for patients with **Genotype 1** (55% of total) • Regimen differs for genotypes 1a and 1b • Perform if no result within past 5 years (old assays misclassified genotypes 1 and 6, and were unable to subtype 20% of GT1)

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

Genotype distribution among NZ patients with chronic HCV

6130 patients genotyped at LabPlus (2005–2014)



Gane E, et al. *NZ Med J* 2014. 127; 1407:61–74.

Indication

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.

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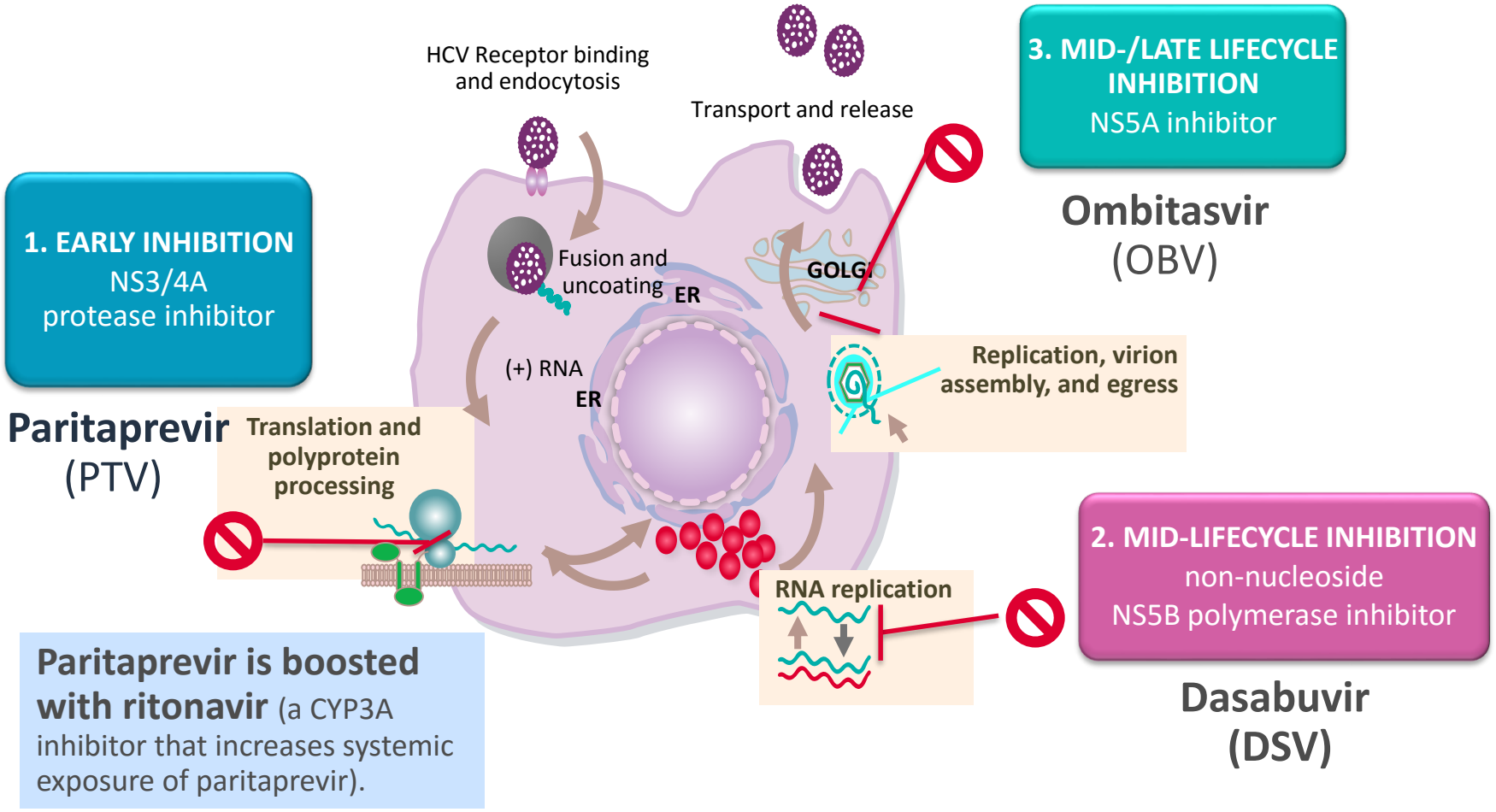
VIEKIRA PAK: mode of action



Paritaprevir is boosted with ritonavir (a CYP3A inhibitor that increases systemic exposure of paritaprevir).

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

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NZ Medsafe-approved regimen: non-cirrhotic patients

Type of hepatitis C (HCV)	Treatment	Duration
Genotype 1a (or mixed/unsubtypeable GT1)	**VIEKIRA PAK-RBV***	12 weeks
Genotype 1b	**VIEKIRA PAK**	12 weeks

*__VIEKIRA PAK__ can be considered for non-cirrhotic treatment-naïve patients with genotype 1a; however, addition of RBV is recommended for most GT1a patients to maximise antiviral efficacy.

Note: this regimen is the same as that approved in Australia, Canada, and Switzerland, but differs from the USFDA label.

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

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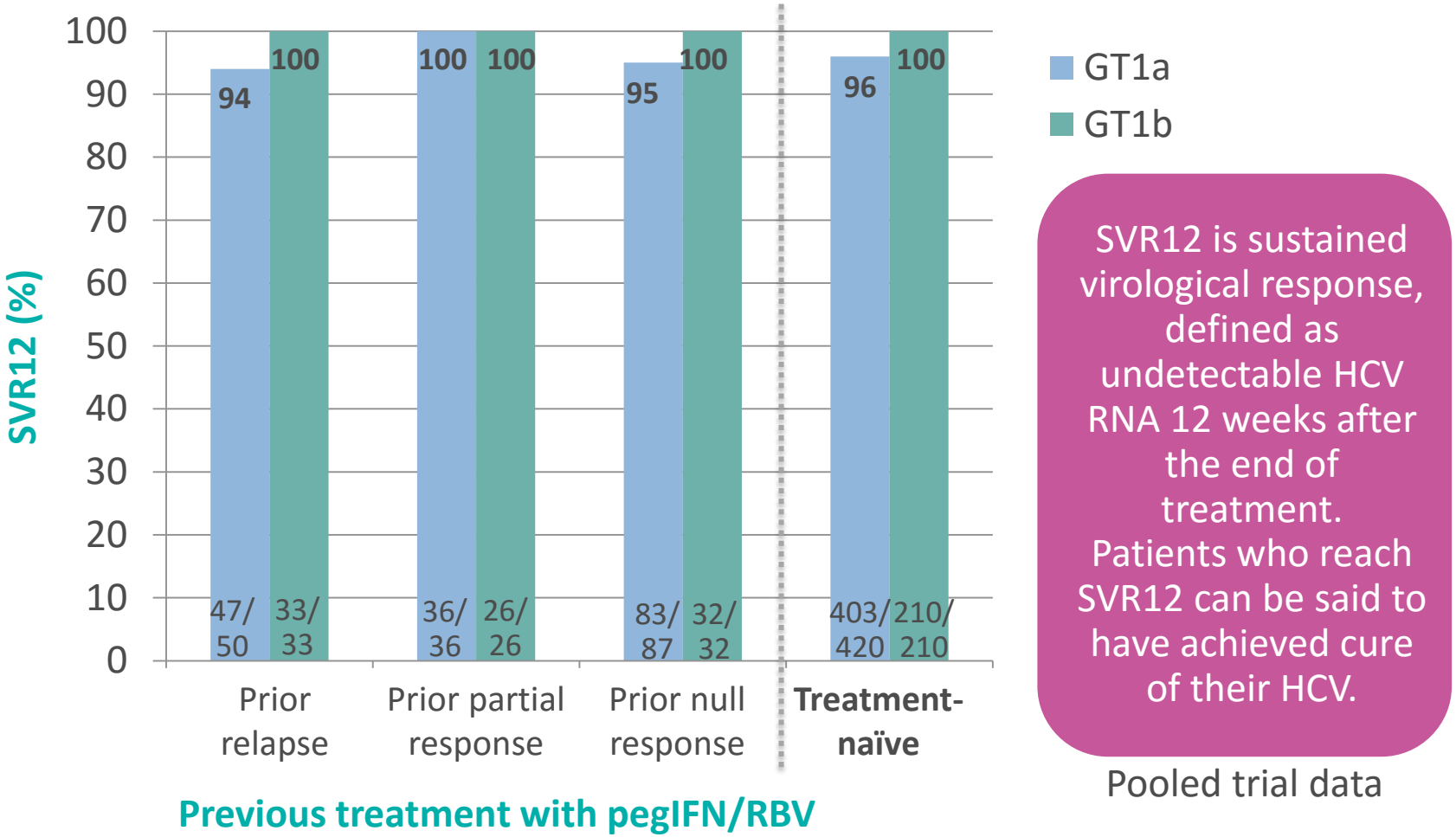
Non-cirrhotic patients: efficacy with NZ's recommended regimen



SVR12 is sustained virological response, defined as undetectable HCV RNA 12 weeks after the end of treatment. Patients who reach SVR12 can be said to have achieved cure of their HCV.

Pooled trial data

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

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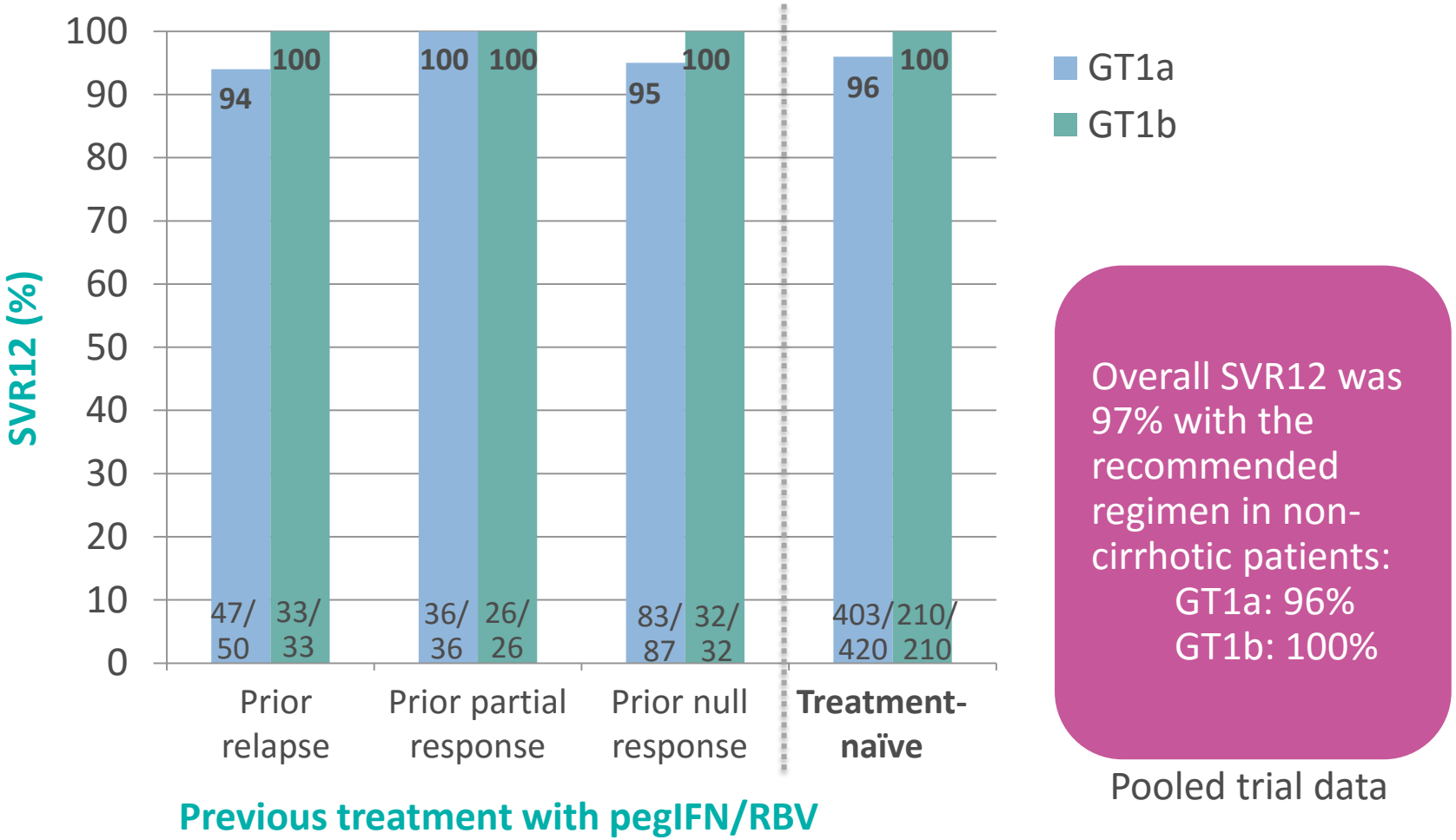
Non-cirrhotic patients: efficacy with NZ's recommended regimen



Overall SVR12 was 97% with the recommended regimen in non-cirrhotic patients:
GT1a: 96%
GT1b: 100%

Pooled trial data

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

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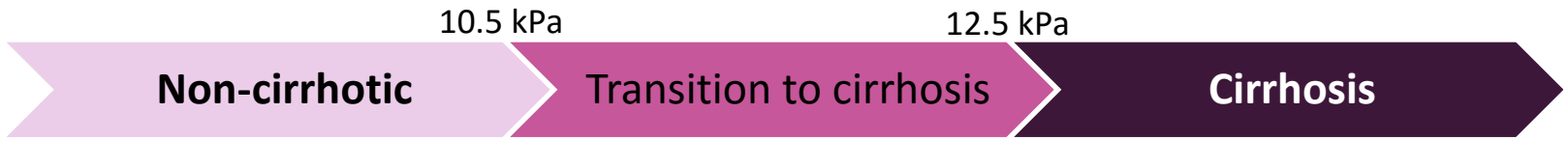
Pre-treatment assessment for VIEKIRA PAK

Tests	Rationale
Medicines review	Consider potential **drug interactions** between VIEKIRA PAK and other medications
Treatment history (pegIFN/RBV)	Determines length of treatment regimen
Comorbidities	RBV dose should be adjusted for patients with renal dysfunction or severe vascular disease.
Liver staging (Fibroscan, Shear wave, or APRI score)	Patients with liver stiffness measurement (LSM) >10.5 kPa, or APRI score (AST to Platelet Ratio Index) >0.85: ***refer to secondary care***
Blood count	Low **platelet count** (<90 cells x10^9L) suggests portal hypertension and risk of AEs: ***refer to secondary care***



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.

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Pre-treatment assessment for VIEKIRA PAK: Patients with cirrhosis

- All patients with cirrhosis should be referred to secondary care.
- A specialist will calculate a Child-Pugh score for every cirrhotic patient, based on bilirubin, serum albumin, INR, and any signs of ascites or hepatic encephalopathy.

Stage of cirrhosis	VIEKIRA PAK
Child-Pugh A / compensated cirrhosis	**Indicated:** ***should be treated in secondary care, with long-term follow-up for HCC.***
Child-Pugh B / decompensated cirrhosis/ moderate hepatic impairment	**Not recommended**
Child-Pugh C / decompensated cirrhosis/ severe hepatic impairment	**Contraindicated**

INR= International Normalised Ratio

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.

Check: contraindications for VIEKIRA PAK

- **Severe hepatic impairment** (Child-Pugh C).
- **Co-administration with drugs** that are highly dependent on CYP3A for clearance, are moderate or strong inducers of CYP3A, or are strong inducers or inhibitors of CYP2C8.
- **Hypersensitivity** to components or excipients.

Additional contraindications for VIEKIRA PAK-RBV

- **Pregnancy** (including of a partner). Use two forms of contraception to avoid pregnancy, and continue for 6 months after end of treatment. Category X.
- History of **severe, unstable, or uncontrolled cardiac disease** in previous 6 months
- **Haemoglobinopathies** (e.g. thalassaemia, sickle-cell anaemia).

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

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Drug–drug interactions

All direct-acting antivirals interact with drug metabolising enzymes or transporters.

Ribavirin is associated with additional drug interactions.

Drug interactions could reduce clinical efficacy and/or cause adverse events.

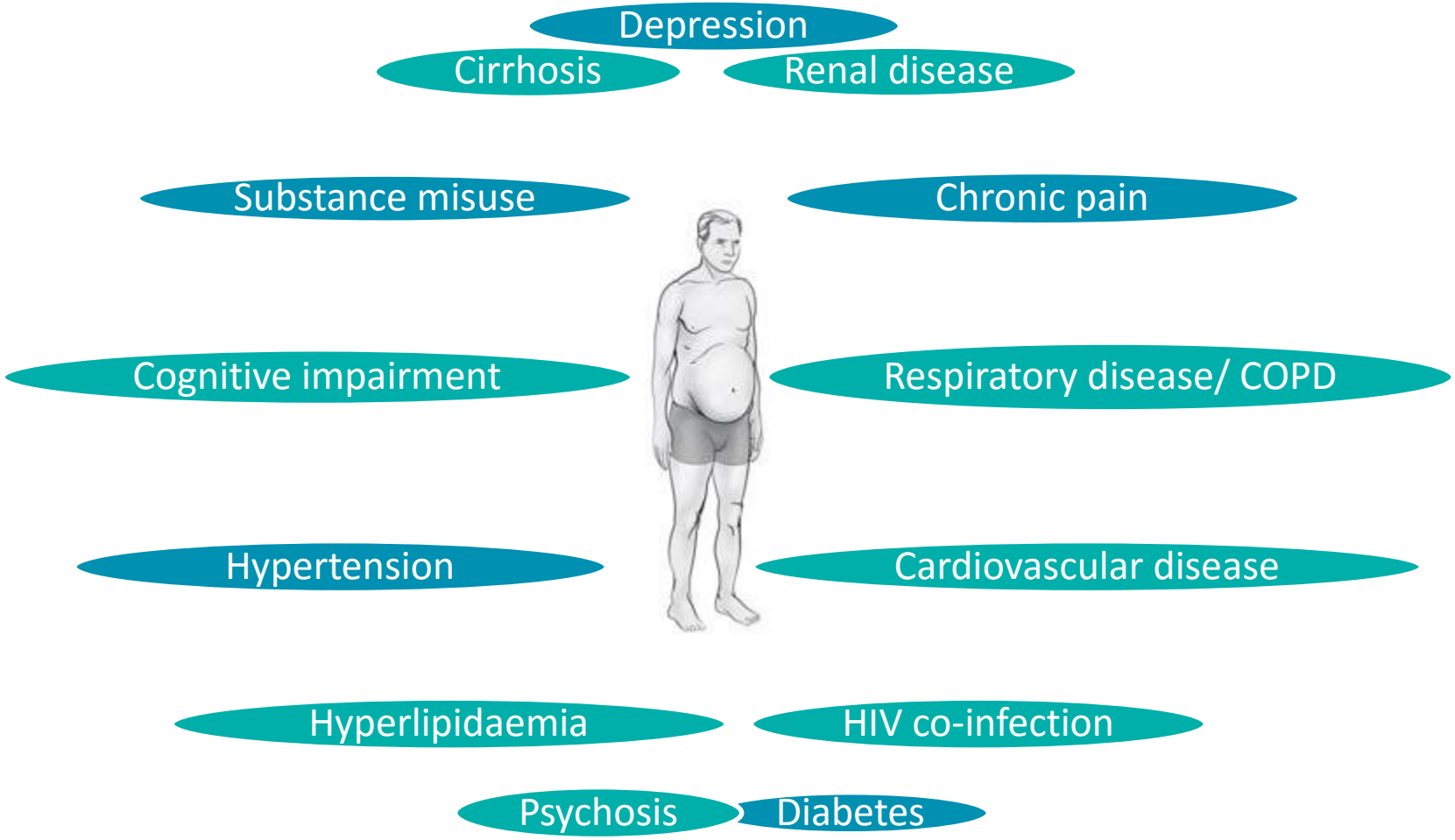
All patients need a careful medicines review before treatment.

Most potential drug interactions can be managed by adjustment of dose and/or monitoring during treatment for any potential adverse reactions. No dose adjustment is needed for VIEKIRA PAK itself.

Some medications are contraindicated, and must be stopped, or substituted with alternatives, during treatment.

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

Patients with hepatitis C often have many comorbidities… with associated medications



Louie, KS. *BMC Infect Dis*. 2012; 12: 86.

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Where to find information on interactions

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

2. **University of Liverpool website**: http://hep-druginteractions.org/
   - Searchable by alphabetical list of drugs or by drug class.
   - Mobile apps are available.

3. **AbbVie Medical Information:** 0800 900 030, medinfoanz@abbvie.com
   - AbbVie can answer questions based on 'Data on File', built up through the clinical development programme and post-marketing experience.

NZ Data Sheet: drug interactions with VIEKIRA PAK

No restrictions	Caution / dose adjustment / clinical monitoring[a]	Contraindicated/ not recommended
Abacavir	Alprazolam	Atorvastatin†
Buprenorphine	Amiodarone	Carbamazepine
Dolutegravir[b]	Amlodipine	Colchicine in renal or hepatic impairment
Duloxetine	Atazanavir	Efavirenz
Emtricitabine	Cyclosporine	Ergotamine and its derivatives
Escitalopram	Darunavir	Ethinyloestradiol-containing products
Lamivudine	Diazepam	Fusidic Acid
Metformin	Digoxin	Gemfibrozil
Methadone	Fluticasone	Oral Midazolam
Naloxone	Flecainide	Phenobarbital
Norethisterone[c]	Furosemide	Phenytoin
Paracetamol	Ketoconazole	Quetiapine
Raltegravir	Lidocaine (systemic)	Rifampicin
Sulfamethoxazole	Mexiletine	Rilpivirine[b]
Tenofovir	Omeprazole	Ritonavir
Trimethoprim	Pravastatin	Sildenafil[e]
	Propafenone	Simvastatin
	Rosuvastatin	Salmeterol
	Tacrolimus	St. John's Wort *(Hypericum Perforatum)*
	Warfarin	Terfenadine
		Triazolam

[a]Refer to Medsafe-approved Data Sheets. [b]Registered but not reimbursed in NZ. [c]NZ spelling for Norethindrone. [d]Alfuzosin, astemizole, bepridil, blonanserin, carisoprodol, cisapride, cyclobenzaprine, disopramide, hydrocodone, lovastatin, pimozide, and quinidine are also listed in the Data Sheets as drug-interactions, but are not registered or reimbursed in NZ. [e]Contraindicated for treatment of pulmonary arterial hypertension; for erectile dysfunction, reduced dose frequency is recommended. †Liverpool website but not NZ Data Sheet.

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

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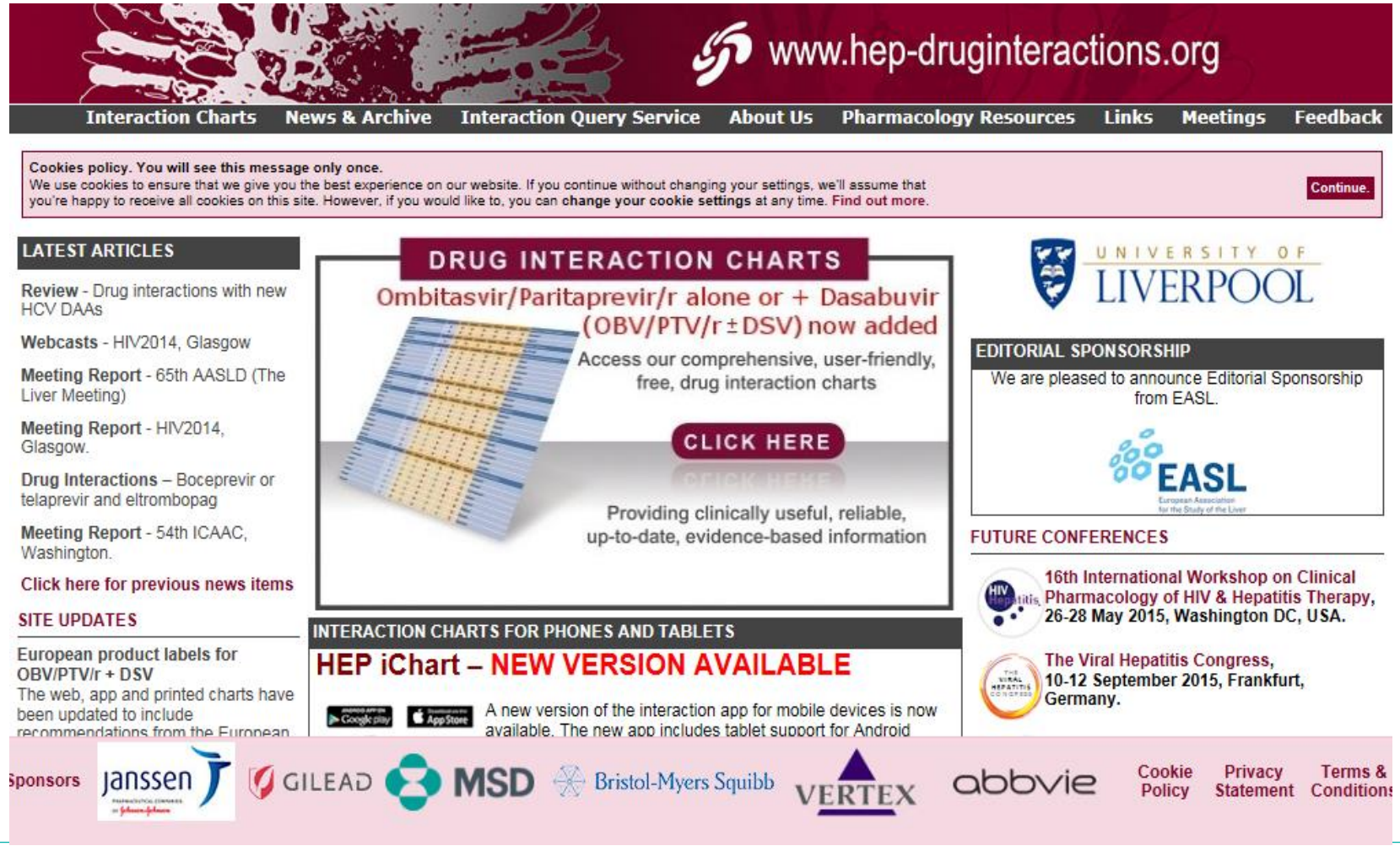
Drug interactions: University of Liverpool website



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

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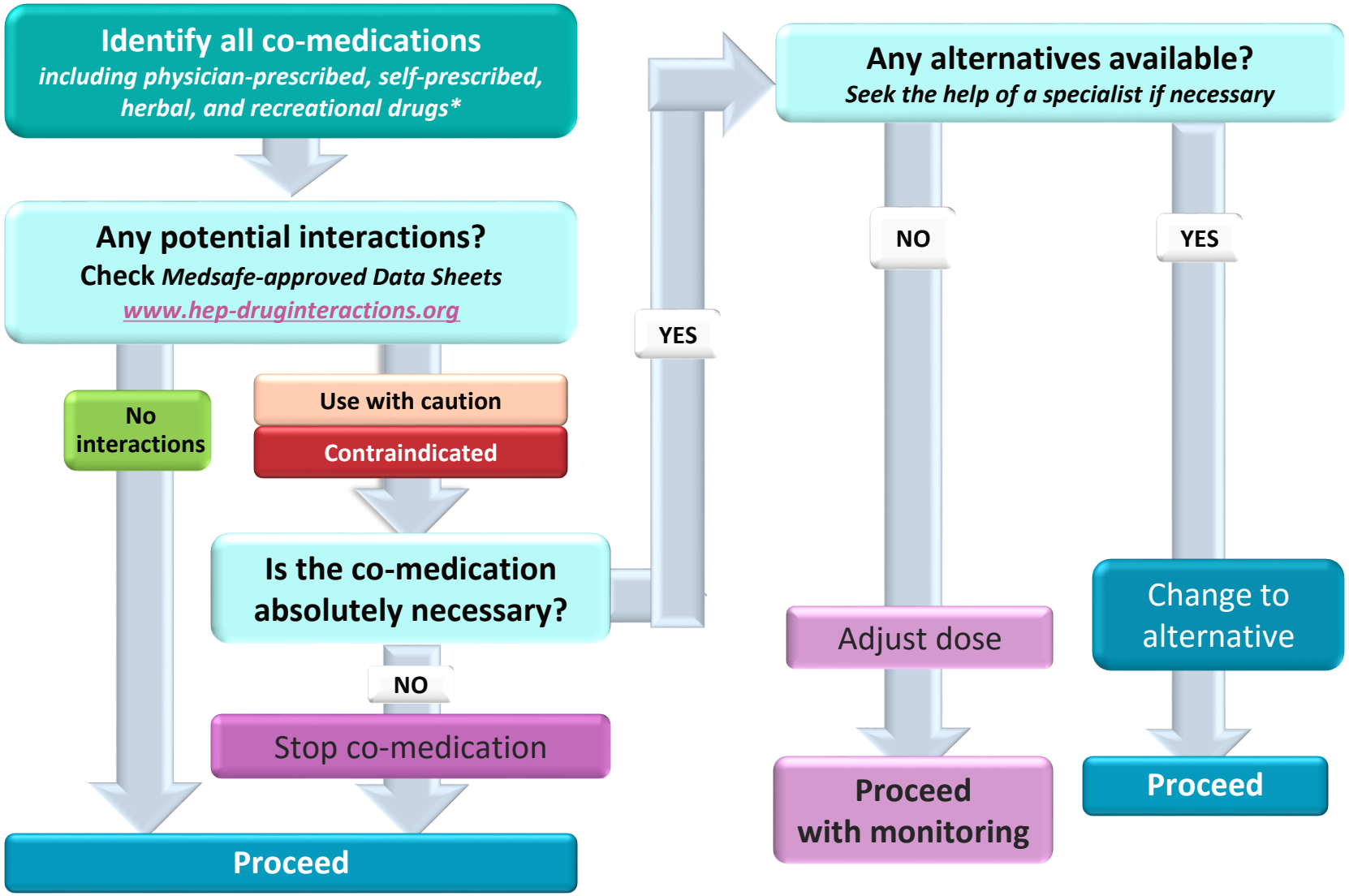
Management of drug interactions



Adapted from Professor David Back, University of Liverpool

Pre-treatment assessment for VIEKIRA PAK±RBV: baseline tests

HCV Ab (confirm +ve)
PCR test for RNA (confirm **chronic HCV**)
HCV Genotype and subtype (redo if older than 5 years)
Liver staging. Patients with **LSM >10.5 kPa** (Fibroscan or Shear-wave elastography; repeat if older than 5 years) or APRI score >0.85: ***refer to secondary care for assessment, treatment, and follow-up***
Full Blood count: Low Hb suggests susceptible to anaemia, monitor Hb carefully. Low **platelet count** (<90 x10^9L) suggests portal hypertension: ***refer to secondary care.***
Check treatment history (any previous treatment with pegIFN/RBV?)
Comorbidities (e.g. reduce RBV and monitor in renal dysfunction, gout, or cardiac disease)
Medicines review: Consider potential **drug interactions** with VIEKIRA PAK
Pregnancy: RBV is **contraindicated** in pregnancy, and VIEKIRA PAK is also not recommended
Comorbidities: RBV is **contraindicated** in severe or unstable cardiac disease or with haemoglobinopathies

LSM= liver stiffness measurement; APRI = AST to Platelet Ratio Index.

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

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Constituents of VIEKIRA PAK

Co-formulated paritaprevir/ritonavir (PTV/r) 75 mg/50 mg plus ombitasvir (OBV) 12.5 mg tablets

Dasabuvir (DSV) 250 mg tablets

VIEKIRA PAK is taken with food, as three tablets in the morning and one in the evening.

Paritaprevir is boosted with ritonavir (a CYP3A inhibitor that increases systemic exposure of paritaprevir).

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

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Constituents of VIEKIRA PAK-RBV

Co-formulated paritaprevir/ritonavir (PTV/r) 75 mg/50 mg plus ombitasvir (OBV) 12.5 mg tablets

Dasabuvir (DSV) 250 mg tablets

Ribavirin, weight-based dose, 200 mg tablets

Example: 1000mg RBV dose (patient ≤ 75kg)

Ribavirin is a synthetic nucleoside analogue with HCV antiviral activity.

Most patients should start on 1000 or 1200 mg, depending on bodyweight.

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

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Safety monitoring during a 12-week course: uncomplicated non-cirrhotic patients

	Week 2	Week 4	Week 8	Week 12
GT1a	Hb, LFT	Hb, LFT	Hb, LFT	-
GT1b	LFT	LFT	LFT	-

During treatment, check adherence, ask about side effects, and look up any new comedications (for potential DDIs).

★ End of treatment

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

Hb = haemoglobin. LFT = liver function tests.

Safety monitoring during a 12-week course: uncomplicated non-cirrhotic patients

	Week 2	Week 4	Week 8	Week 12	Week 24
GT1a	Hb, LFT	Hb, LFT	Hb, LFT	-	**TEST VIRAL LOAD** Undetectable virus = SVR12 = CURE
GT1b	LFT	LFT	LFT	-	

During treatment, check adherence, ask about side effects, and look up any new comedications (for potential DDIs).

★ End of treatment

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

Hb = haemoglobin. LFT = liver function tests.

Safety monitoring: ribavirin

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

The starting dose of RBV dose should be reduced for patients with severe vascular disease, renal dysfunction, cardiac disease, and post-transplant patients.

Dose reduction is recommended during treatment:

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

In Phase 3 clinical trials with VIEKIRA PAK-RBV, 8.5% of patients required RBV dose to be reduced due to anaemia.

The rate of SVR12 in these patients was 99% (i.e. dose reduction did not affect effectiveness).

**RBV should be used with caution in patients with significant vascular disease (symptomatic ischaemic heart disease, recent TIA, or CVA, claudication). Please refer to Data Sheets and Guidelines for recommendations on dose reduction and discontinuation in these patients.*

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

Non-cirrhotic patients: adverse events

Adverse Event	SAPPHIRE I and II trials	
	VIEKIRA PAK-RBV N = 770	*Placebo N = 255*
Fatigue	**263 (34%)**	***67 (26%)***
Nausea	**172 (22%)**	***38 (15%)***
Pruritus	**121 (16%)**	*11 (4%)*
Insomnia	**108 (14%)**	*19 (7%)*
Asthenia	**104 (13%)**	*17 (7%)*
Anaemia	41 (5%)	*0*

This is a side-by-side tabulation of pooled adverse event rates in Phase 3 trials, based on adverse events that occurred 5% more often with VIEKIRA PAK-RBV than with placebo.

AbbVie Limited. VIEKIRA PAK and VIEKIRA PAK-RBV Data Sheets. Medsafe New Zealand; December2015. Table 14, pp45-46.

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Non-cirrhotic patients: adverse events

Adverse Event	SAPPHIRE I and II trials		PEARL II, III and IV trials	
	VIEKIRA PAK-RBV N = 770	*Placebo N = 255*	VIEKIRA PAK-RBV N = 401	VIEKIRA PAK N = 509
Fatigue	**263 (34%)**	***67 (26%)***	**120 (30%)**	**135 (27%)**
Nausea	**172 (22%)**	***38 (15%)***	**63 (16%)**	43 (8%)
Pruritus	**121 (16%)**	*11 (4%)*	**48 (12%)**	31 (6%)
Insomnia	**108 (14%)**	*19 (7%)*	**49 (12%)**	26 (5%)
Asthenia	**104 (13%)**	*17 (7%)*	36 (9%)	20 (4%)
Anaemia	41 (5%)	*0*	30 (7%)	1 (0.2%)

This is a side-by-side tabulation of pooled adverse event rates in Phase 3 trials, based on adverse events that occurred 5% more often with VIEKIRA PAK-RBV than with placebo.

AbbVie Limited. VIEKIRA PAK and VIEKIRA PAK-RBV Data Sheets. Medsafe New Zealand; December2015. Table 14, pp45-46.

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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, pinetarsol, or fatty cream. Consult DermNet NZ.

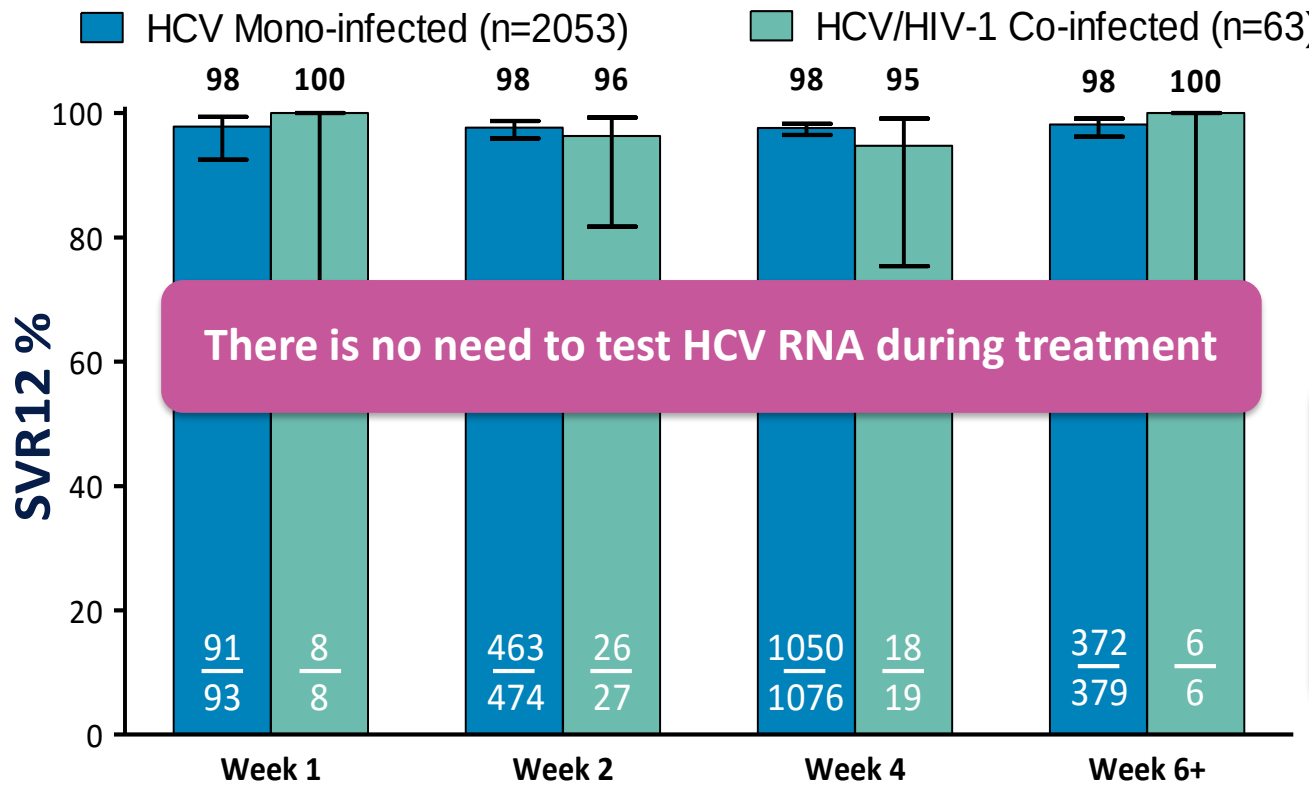
Insomnia: Consider advice on improved sleep hygiene. If severe, then consider using intermittent zopiclone at half the recommended dose (3.75mg nocte) OR temazepam at the full recommended dose (10mg nocte).

Management of comorbidities

Depression: Citalopram or escitalopram are allowed.

Gane, Stedman. NZ Society of Gastroenterology HCV Treatment Guidelines. 2016. Available at: http://www.nzsg.org.nz/cms2/uploads/Hepatitis%20C%20Guidance_FINAL%20July%2011.pdf Accessed July 2016.

Monitoring: HCV RNA levels



Active IDU, prisoners and HIV-positive patients should be monitored for reinfection

Time on treatment until HCV RNA undetectable

Pooled analysis: 2116 patients treated with VIEKIRA PAK in Phase II/III studies

Wyles D, et al. CROI 2015

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Summary: VIEKIRA PAK and VIEKIRA PAK-RBV

High certainty of cure*	• EFFICACY: SVR12 = 97% for patients with genotype 1 HCV, with or without cirrhosis, including previous null responders to 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.

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Thank you

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VIEKIRA PAK and VIEKIRA PAK-RBV are fully funded Prescription Medicines on the Pharmaceutical Schedule with an alternative Xpharm distribution; prescribing is restricted to Gastroenterologists, ID physicians and Hepatologists until 1 October. Please review full Data Sheets before prescribing.
These are available from AbbVie Limited at www.viekira.co.nz and from Medsafe at www.medsafe.govt.nz.

VIEKIRA PAK is a combination therapy containing paritaprevir/ritonavir/ombitasvir (75/50/12.5 mg) tablets and dasabuvir (250 mg) tablets. VIEKIRA PAK-RBV contains VIEKIRA PAK, plus ribavirin (200 mg*) tablets.

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

CONTRAINDICATIONS: VIEKIRA PAK: Severe hepatic impairment (Child-Pugh C); Hypersensitivity to components or excipients of VIEKIRA PAK or VIEKIRA PAK-RBV; Concomitant administration with: astemizole, carbamazepine, colchicine (in renal or hepatic impairment), efavirenz, ergotamine and its derivatives, ethinyloestradiol-containing medicines (e.g. oral contraceptives), fusidic acid, gemfibrozil, oral midazolam, phenobarbital, phenytoin, rifampicin, St. John's Wort (Hypericum perforatum), salmeterol, sildenafil (when used for pulmonary arterial hypertension), simvastatin, terfenadine, or triazolam. Please refer to the full Data sheets for a complete list. VIEKIRA PAK-RBV As above, and Pregnancy, including men whose partners are pregnant (Cat X); History of severe cardiac disease in previous 6 months; Haemoglobinopathies (e.g. thalassaemia, sickle-cell anaemia).

PRECAUTIONS: VIEKIRA PAK: Moderate hepatic impairment (Child-Pugh B); For patients with compensated cirrhosis, monitor for clinical signs and symptoms of hepatic decompensation or failure, and discontinue treatment in patients who develop evidence of hepatic decompensation; HCV genotypes other than 1; Not studied in patients previously treated with VIEKIRA PAK or other direct-acting antiviral agents; Not studied in patients younger than 18 or older than 70; Pregnancy (B3); Discontinue breastfeeding prior to initiation; See Data Sheets for concomitant medicines for which dose adjustment or monitoring is recommended; Monitor changes in laboratory parameters including bilirubin and alanine transaminase (ALT). VIEKIRA PAK-RBV: As above, and Use two forms of contraception to avoid pregnancy; Monitor haemoglobin in patients with pre-existing cardiac disease; Monitor uric acid in patients predisposed to gout; Reduce dose of ribavirin and monitor haemoglobin in patients with renal impairment.

INTERACTIONS: See Data Sheets for medicines for which dose adjustment and/or monitoring should be considered. ADVERSE EFFECTS: VIEKIRA PAK: Fatigue, nausea, pruritus, insomnia and asthenia. VIEKIRA PAK-RBV: As above, and: anaemia, diarrhoea, vomiting, decreased appetite, dizziness, headache, sleep disorder, cough, dyspnoea, dry skin, and rash. DOSAGE AND ADMINISTRATION: VIEKIRA PAK: recommended dose is two paritaprevir/ritonavir/ombitasvir (75/50/12.5 mg) tablets once daily (in the morning) and one dasabuvir (250 mg) tablet taken with food twice daily (morning and evening) for 12 weeks. VIEKIRA PAK-RBV: As above, for 12 or 24 weeks, with ribavirin. The recommended dose of ribavirin depends on a patient's bodyweight (<75 kg = 1000 mg; ≥75 kg = 1200 mg), and should be taken with food in two doses (morning and evening). Ribavirin monotherapy is not effective and ribavirin must only be used in combination with VIEKIRA PAK. See full Data Sheets for additional information on duration of therapy and use in special populations.

*Other presentations, including ribavirin 400 mg and/or 600 mg tablets, are not currently available in New Zealand.

Back-up slides

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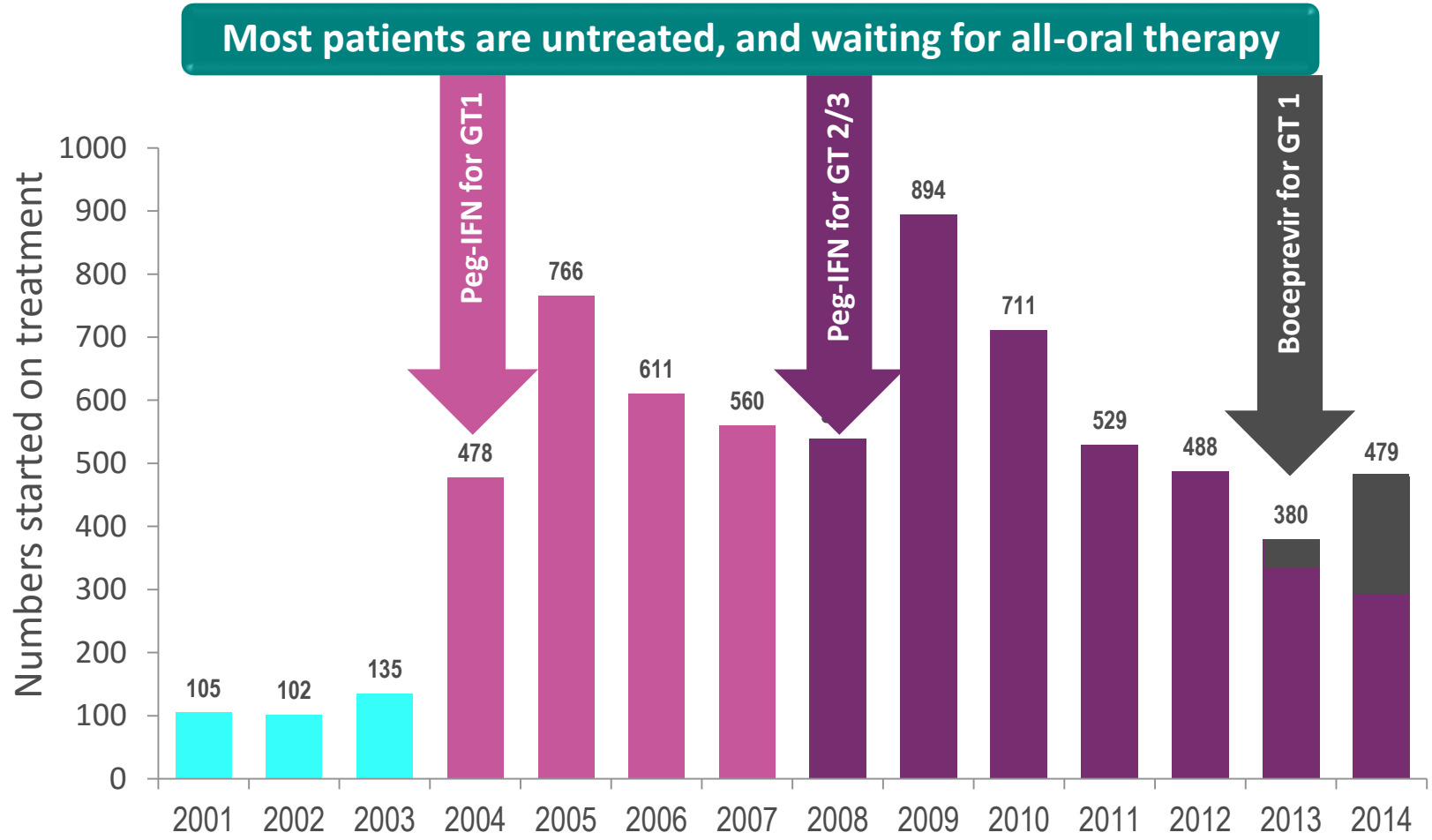
Treatment rate by year in New Zealand



PHARMAC; Data on file. Auckland Clinical Studies, Christchurch Clinical Studies; Data on file.

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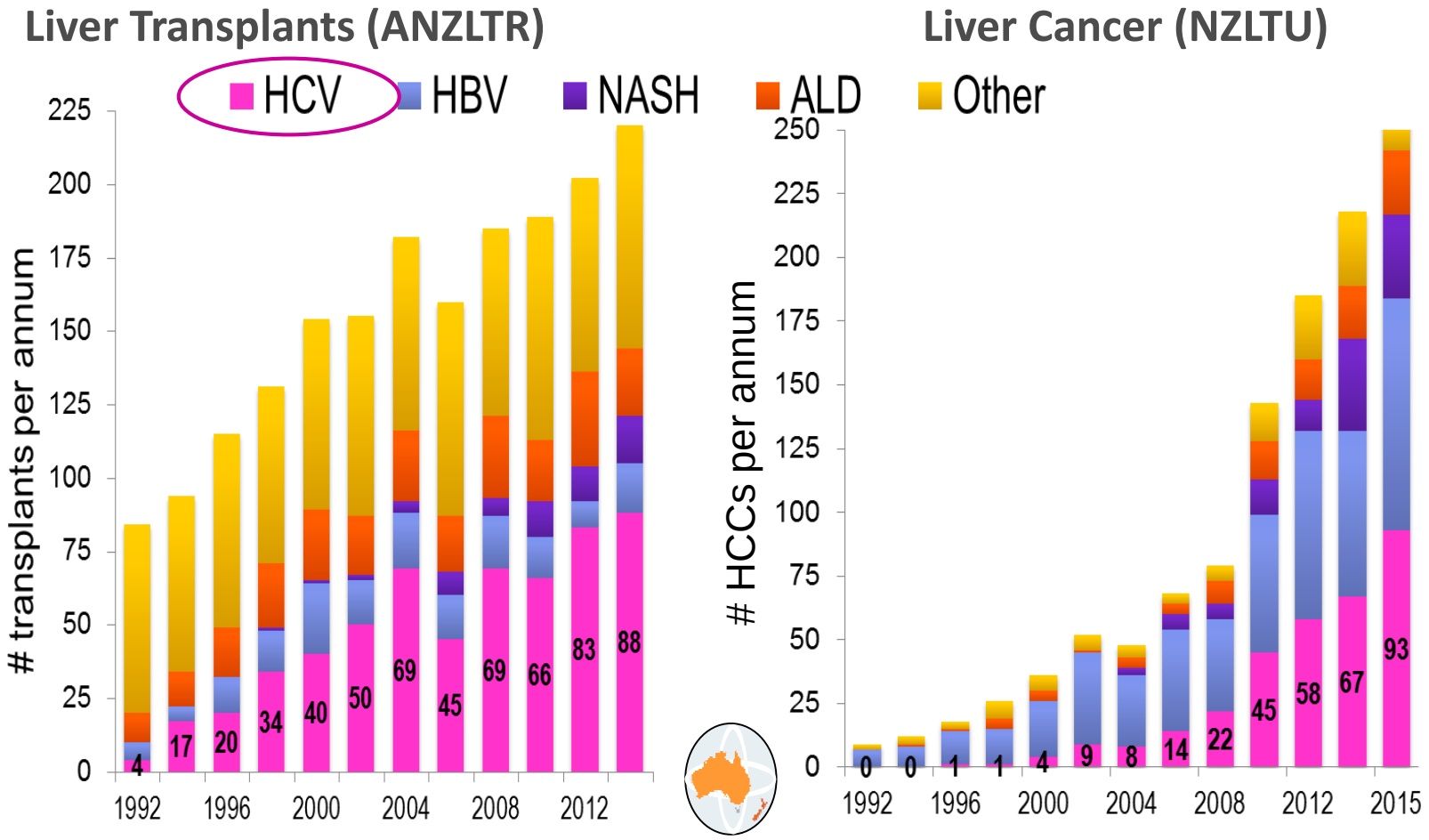
Disease burden from hepatitis C



26th Australian and New Zealand Liver Transplant Registry. http://www.sswahs.nsw.gov.au/gastro/livertransplant/RPAH2011/ANZLTR%2026thREPORT-%2031.12.14.pdf . Accessed July 2015.

Medsafe-approved regimen: cirrhotic patients

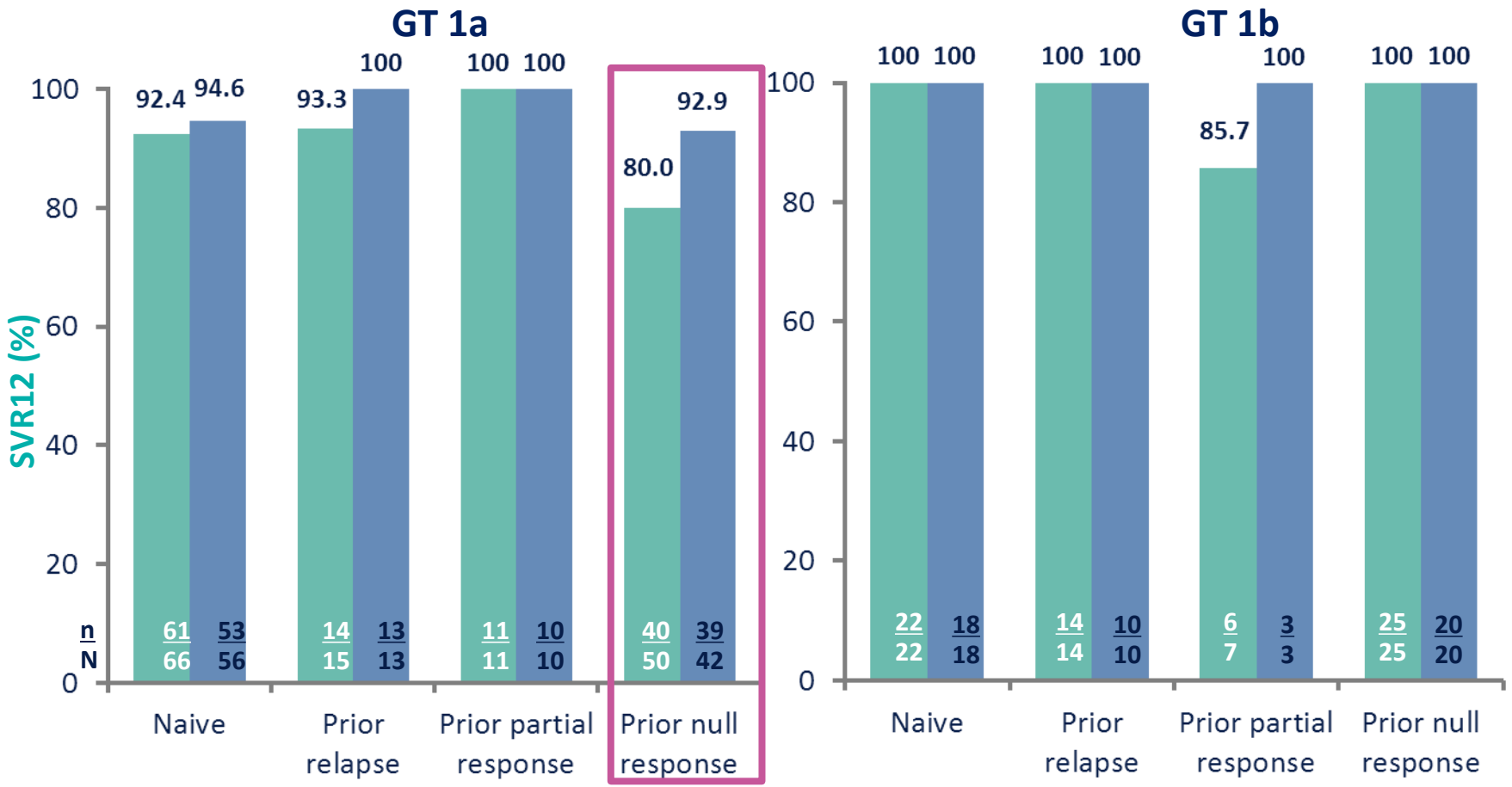
Patient Population	Treatment	Duration
GT1a	VIEKIRA PAK-RBV	12 weeks†
GT1b	VIEKIRA PAK-RBV	12 weeks

†24 weeks of **VIEKIRA PAK-RBV** are recommended for cirrhotic patients with genotype 1a who had a previous null response to treatment with pegIFN/RBV.

Note: this regimen is the same as that approved in Australia, Canada, and Switzerland, but differs from the USFDA label.

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

Patients with compensated cirrhosis: efficacy by treatment duration, subtype, and treatment history



Poordad F et al. *N Engl J Med* 2014:370;1973–82.

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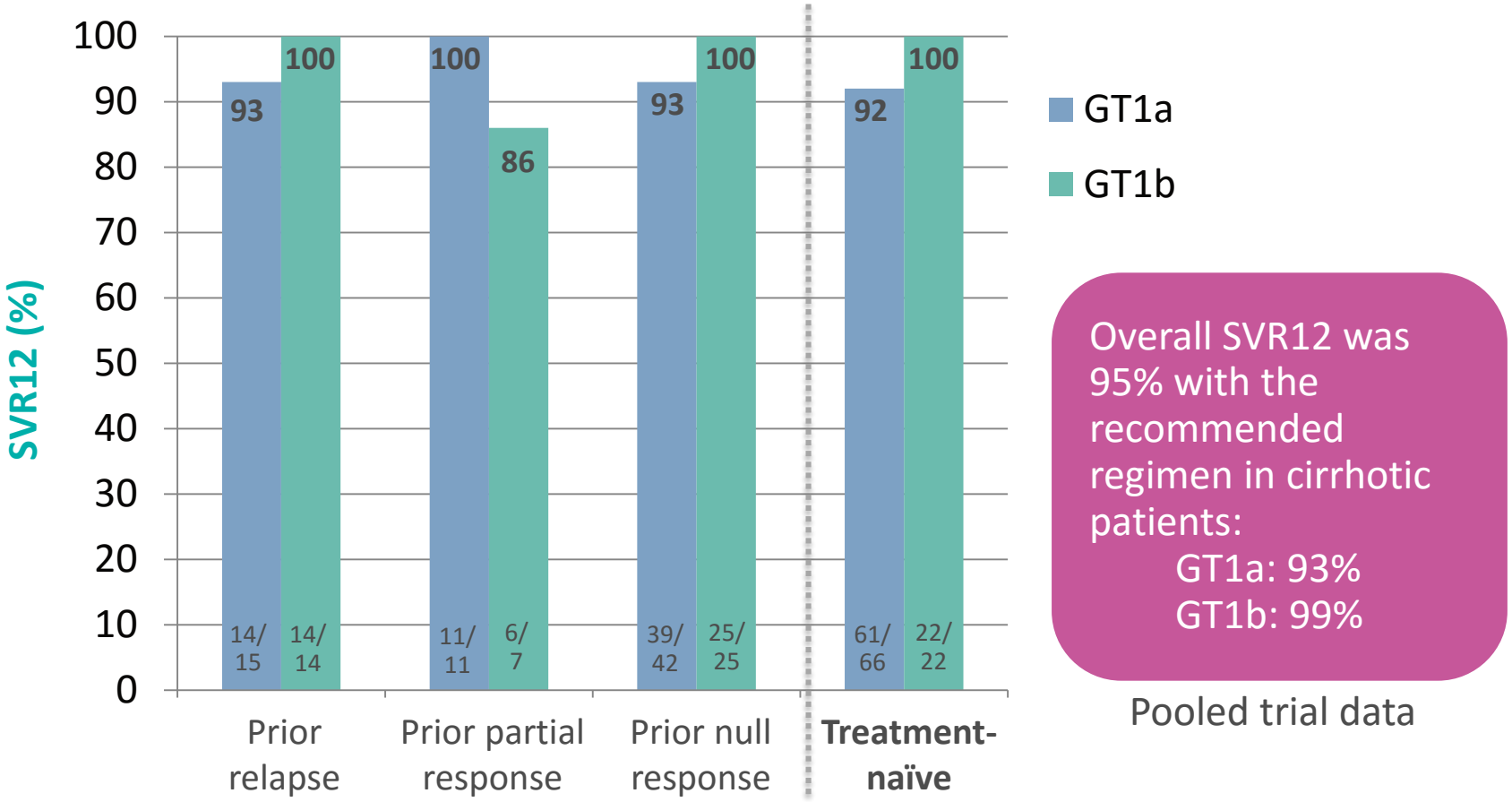
Cirrhotic patients: Efficacy with NZ's recommended regimen



Overall SVR12 was 95% with the recommended regimen in cirrhotic patients:

GT1a: 93%

GT1b: 99%

Pooled trial data

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

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Patients with compensated cirrhosis (Child-Pugh A): safety

In a pooled analysis of 1066 patients from the clinical trials of VIEKIRA PAK (±RBV):

- **Overall, treatment was well-tolerated**:
  - 23/1066 patients (2.2%) **discontinued treatment** due to an adverse event[1]
  - 13/1066 patients (1.2%) had **adverse events consistent with hepatic decompensation.*** Most of these events resolved with continuing treatment (9/13; 69%), and 77% (10/13) achieved SVR12[1]
- **The rate of hepatic decompensation in patients with compensated cirrhosis** (Child-Pugh A), **was similar to the baseline rate of decompensation** in untreated patients with HCV and compensated cirrhosis[1-3]

**Ascites, oesophageal varices haemorrhage, hepatic failure, hepatorenal syndrome, hypoalbuminaemia, hepatic encephalopathy, or jaundice, or increased bilirubin. 5/13 discontinued treatment, and 1 died (pneumonia, multiple organ failure).*

1 Poordad F et al. OPTIMIZE Workshop, 12 April 2016, Barcelona, Spain. 2 Alazawi W, et al. Aliment Pharmacol Ther. 2010;32:344–55. 3 D'Amico G, et al. J Hepatol. 2006;44:217−31.

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Pooled safety assessment from Clinical Trials: patients with compensated cirrhosis (Child-Pugh A)

Baseline characteristic	AE of interest*	
	No N = 1053	Yes N = 13
Child-Pugh score, n (%)		
5	886 (86.3)	5 (38.5)
6	122 (11.9)	8 (61.5)†
>6		
Missing or		
Platelet count, n (%)		
<90 cells × 10³/L	185 (17.6)	6 (46.2)‡
Missing	1	0
Albumin, n (%)		
<35 g/L	83 (7.9)	5 (38.5)§

Patients who had adverse events consistent with hepatic decompensation had higher Child-Pugh scores, lower levels of platelets or albumin, and prior evidence of varices.

Poordad F et al. OPTIMIZE Workshop, 12 April 2016, Barcelona, Spain.

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Real-world evaluation of VIEKIRA PAK in cirrhotic patients (Australian REV1TAL Study)

Compassionate-access programme in 269 patients; most (91%) had Child- Pugh A cirrhosis, but investigators included 9% with Child-Pugh B cirrhosis*

- Treatment discontinuation in 6%
- Grade 4 bilirubin elevation in 4%
- Hepatic decompensation in 2%

Predictors for serious adverse events were: low platelets, low albumin, age >70 years, and previous decompensation

Proportion of patients with serious adverse events

		Platelets	
		>111 cells x10^9L	<111 cells x10^9L
Albumin	>35 g/L	7%	15%
	<35 g/L	27%	**33%**

Lubel JS, *et al. EASL* 2016 ; #SAT-182

*Note: VIEKIRA PAK±RBV is not recommended for use in patients with Child Pugh B cirrhosis.

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Adverse events: cirrhotic and non-cirrhotic patients

Adverse Event	Non-cirrhotic patients (PEARL II, III and IV trials)		Cirrhotic patients (TURQUOISE II trial)
	VIEKIRA PAK-RBV N = 401	**VIEKIRA PAK** N = 509	**VIEKIRA PAK-RBV** N = 380
Fatigue	120 (30%)	135 (27%)	148 (39%)
Nausea	63 (16%)	43 (8%)	72 (19%)
Pruritus	48 (12%)	31 (6%)	71 (19%)
Insomnia	49 (12%)	26 (5%)	63 (17%)
Asthenia	36 (9%)	20 (4%)	51 (13%)
Anaemia	30 (7%)	1 (0.2%)	34 (9%)

This is a side-by-side tabulation of pooled adverse event rates in Phase 3 trials, based on adverse events that occurred 5% more often with VIEKIRA PAK-RBV than with placebo.

AbbVie Limited. VIEKIRA PAK and VIEKIRA PAK-RBV Data Sheets. Medsafe New Zealand; December2015. Table 14, pp45-46.

Safety monitoring: liver function

Bilirubin

- In the Phase 3 clinical trials, 0.4% of the patients given VIEKIRA PAK and 5% of patients given VIEKIRA PAK-RBV experienced bilirubin elevations (>3 x ULN).
- Bilirubin elevations were transient (peaked by first week), mainly indirect bilirubin, and not linked to ALT elevations.
- Mechanism is haemolysis (ribavirin) and inhibition of the bilirubin transporters OATP1B1/1B3 (paritaprevir).

Alanine aminotransferase (ALT)

- ALT elevations >5xULN were seen in less than 1% of non-cirrhotic patients in the Phase 3 clinical trials, and most were due to ethinyloestradiol, which is now contraindicated.
- Treatment should be discontinued if ALT elevation is accompanied by signs or symptoms of liver inflammation, or increasing conjugated bilirubin, alkaline phosphatase, or INR.

ULN= upper limit of normal. INR = international normalised ratio.

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

Liver function during VIEKIRA PAK±RBV: alanine aminotransferase (ALT)

	Non-cirrhotic patients		Cirrhotic patients
CTCAE Grade*	VIEKIRA PAK N = 301	VIEKIRA PAK-RBV N = 589/593†	VIEKIRA PAK-RBV N = 202
1	64 (21.3%)	95 (16.1%)	91 (45%)
2	2 (0.7%)	4 (0.7%)	4 (2.0%)
3	0	4 (0.7%)	3 (1.5%)
4	0	2 (0.3)	1 (0.5%)

* Common Terminology Criteria for Adverse Events. Grade 1 = < 3 x ULN, Grade 2 = 3.0-5.0 x ULN, Grade 3 = 5.0-20 x ULN, Grade 4 = >20 x ULN, where ULN = upper limit of normal. † number of patients with post baseline value.

Gane et al. Efficacy and safety of ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin, in adults treated with the regimen approved in Australia, Canada, New Zealand and Switzerland. Presented at the International Liver Congress, April 13–17, 2016, Barcelona, Spain.

Hyperbilirubinaemia on therapy

CTCAE Grade*	Non-cirrhotic patients		Cirrhotic patients
	VIEKIRA PAK N = 301	VIEKIRA PAK-RBV N = 589/593†	VIEKIRA PAK-RBV N = 202
1	33 (11%)	129 (21.9%)	62 (30.7%)
2	17 (5.6%)	126 (21.4%)	58 (28.7%)
3	1 (0.3%)	13 (2.2%)	22 (10.9%)
4	0	0	0

* Common Terminology Criteria for Adverse Events. Grade 1 = < 1.5 x ULN, Grade 2 = 1.5-3.0 x ULN, Grade 3 = 3.0-10 x ULN, Grade 4 = >10 x ULN, where ULN = upper limit of normal. † number of patients with post baseline value.

Gane et al. Efficacy and safety of ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin, in adults treated with the regimen approved in Australia, Canada, New Zealand and Switzerland. Presented at the International Liver Congress, April 13–17, 2016, Barcelona, Spain.

Summary: safety and tolerability

Overall, adverse events were frequent, but mild and manageable.

Non-cirrhotic patients

- Adverse events were generally mild (grade 1).
- The most common AEs overall were fatigue, nausea, pruritus, and insomnia.
- Rates of serious adverse events were very low, with fewer than 1% discontinuations overall (similar to placebo).

Cirrhotic patients

- Adverse events were generally mild or moderate.
- Serious adverse events occurred in 4.5% of patients with cirrhosis.
- 1% discontinued due to an adverse event.

Gane et al. Efficacy and safety of ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin, in adults treated with the regimen approved in Australia, Canada, New Zealand and Switzerland. Presented at the International Liver Congress, April 13–17, 2016, Barcelona, Spain.

Illicit/ recreational drugs

www.hep-druginteractions.org

Drug		Interaction
Benzodiazepines	Midazolam (oral) and triazolam	CONTRAINDICATED
	Alprazolam, clonazepam, diazepam, estazolam, flurazepam, lorazepam, lormetazepam, midazolam (parenteral), oxazepam, quazepam, zaleplon, zopiclone	Monitor Consider dose reduction
	Temazepam, zolpidem	No clinically significant interaction
Amphetamine		
Cannabis		
Cocaine		
Gamma-hydroxybutyrate		
Lysergic acid diethylamide (LSD)		
MDMA (Ecstasy)		
Methamphetamine		
Phencyclidine		
Codeine		
Diamorphine / Heroin		
Diazepam		
Methylphenidate		
Morphine		

University of Liverpool. www.hep-druginteractions.org.

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Missed doses of VIEKIRA PAK

Missed dose of PTV/r/OBV (OD dosing)

- ≤12 hours, take prescribed dose
- >12 hours, missed dose should not be taken. Instead take the next dose as per the usual dosing schedule

Missed dose of DSV (BD Dosing)

- ≤6 hours, take prescribed dose
- >6 hours, missed dose should not be taken. Instead take the next dose as per the usual dosing schedule

Missed dose of RBV (BD Dosing)

- Take the next dose as per the usual dosing schedule.

Patients should <u>not</u> take more than their prescribed dose of VIEKIRA PAK or VIEKIRA PAK-RBV to make up a missed dose*

**A missed dose should be reported as an adverse event.*

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

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