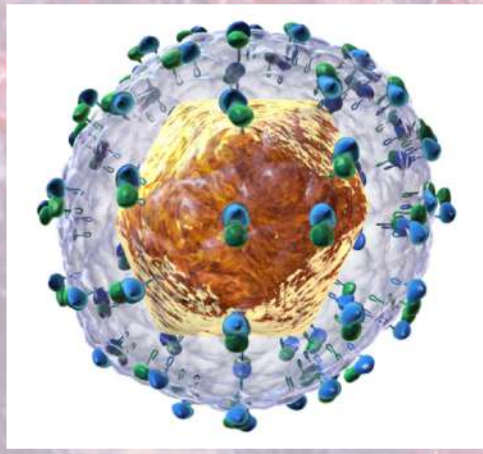
Otago Spotlight Series

Infectious Disease Research

Hepatitis C: Time for Elimination?



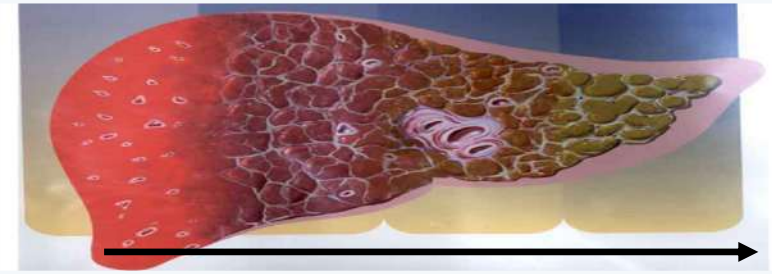
Catherine Stedman

Clinical Associate Professor of Medicine

University of Otago, Christchurch
Gastroenterology Department,
Christchurch Hospital

What is hepatitis C?

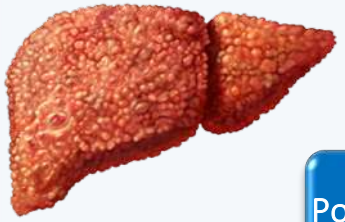
- Hepatitis C is a blood-borne virus that infects the liver and causes inflammation.
- Infection with Hepatitis C virus is often undiagnosed, and acute infections clear spontaneously in 25% of patients.
- Chronic infection can damage the liver, and progress to fibrosis, cirrhosis, liver failure, hepatocellular carcinoma, and death.
- HCV has been shown to double the risk of all-cause mortality.

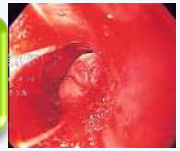
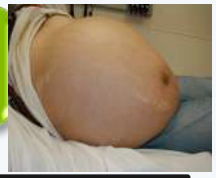


In most patients, the virus also has effects beyond the liver, causing cardiovascular, renal, metabolic, neurological, and immune disorders.

1 CDC. Hepatitis C Questions and Answers for the Public. Available at https://www.cdc.gov/hepatitis/hcv/cfaq.htm. Accessed July 2018.
2 Cacoub P, et al. Ther Adv Infect Dis 2016; Feb; 3(1): 3-14.

Complications of cirrhosis



- Portal hypertension
  - Varices
    
    
  - Hepatic encephalopathy (HE)
  - Ascites
    
    - Hepatorenal syndrome (HRS)
    - Spontaneous bacterial peritonitis (SBP)
  - Hepatocellular carcinoma (HCC)
    
- Hepatic insufficiency
  - Jaundice
    

10 – 20% of patients will progress to cirrhosis which is associated with significant morbidity and mortality

Healthline. **Cirrhosis and Hepatitis C: Their Connection, Prognosis, and More**. Available at https://www.healthline.com/health/cirrhosis-and-hepatitis-c. Accessed July 2018

Hepatitis C in New Zealand

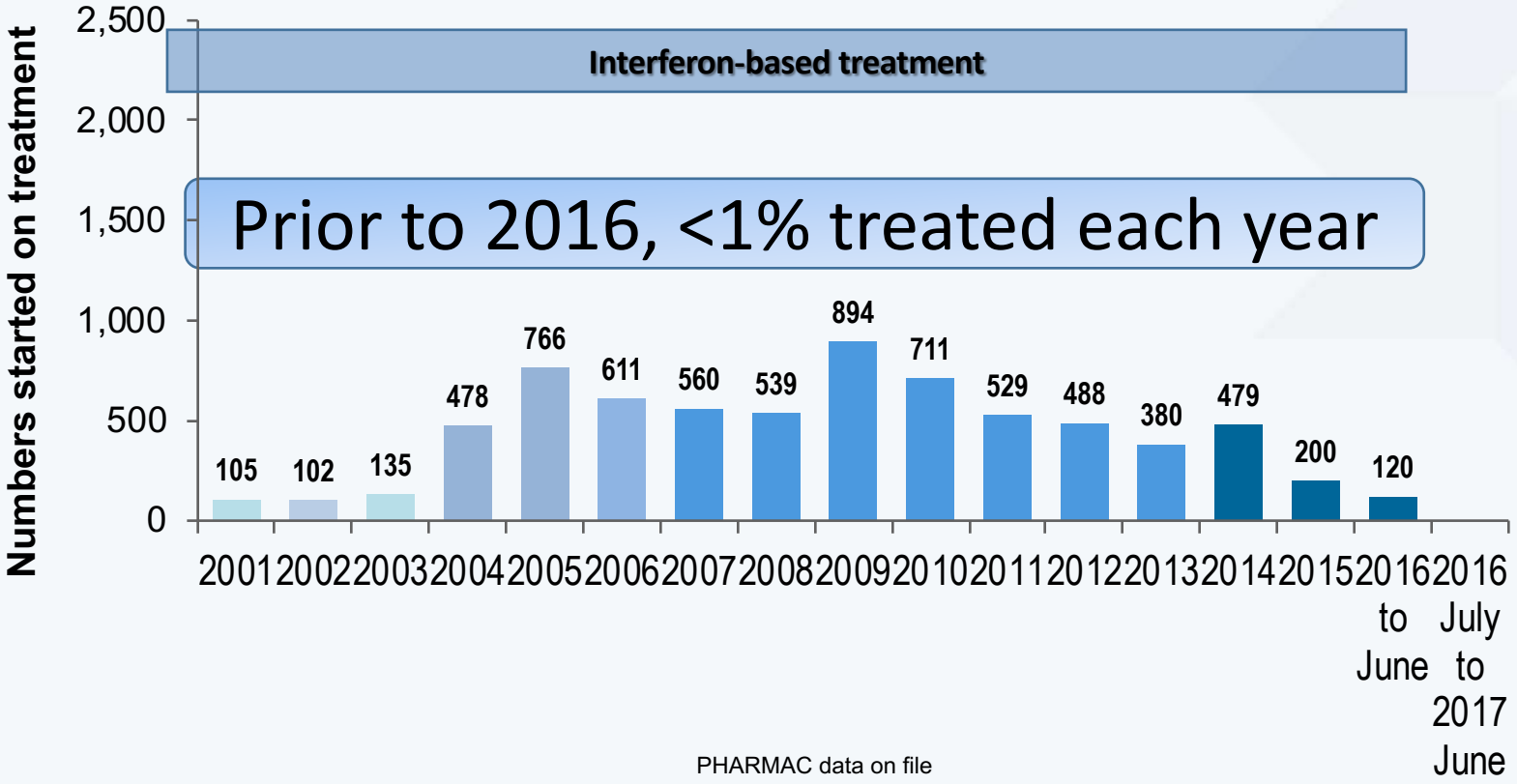
In NZ, more than **50,000 people** are estimated to have chronic infection with the hepatitis C virus (HCV).

Of these only around 40% have been diagnosed.

People who are undiagnosed may not yet be experiencing symptoms, or they may have mild or non-specific symptoms such as fatigue, nausea, or depression.

Gane E, Stedman et al. *NZ Med J* 2014;127(1407):61–74.
Cacoub P, etal. Ther Adv Infect Dis 2016 Feb; 3(1):3-14.
Ministry of Health. Hepatitis C. 2016 www.health.govt.nz/your-health/conditions-and-treatments/diseases-and-illnesses/hepatitis-c.

Hepatitis C:
interferon-based treatment rates



PHARMAC data on file

Otago Spotlight Series

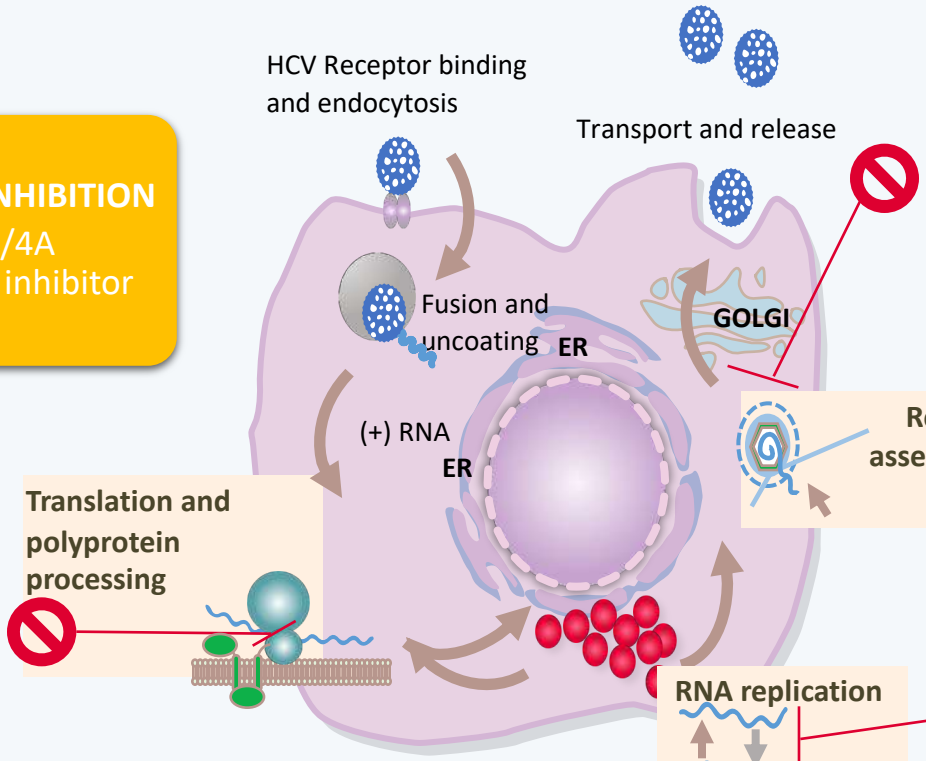
Infectious Disease Research

Exploring interferon-free therapy for HCV

- Collaboration with Prof Ed Gane, University of Auckland
- >60 trials over 10 years
- >25 publications; ~2000 citations

New Drugs for Hepatitis C:

Direct Acting Antivirals inhibit viral replication



1. EARLY INHIBITION
NS3/4A protease inhibitor

3. MID-/LATE LIFECYCLE INHIBITION
NS5A inhibitor

2. MID-LIFECYCLE INHIBITION
non-nucleoside NS5B polymerase inhibitor

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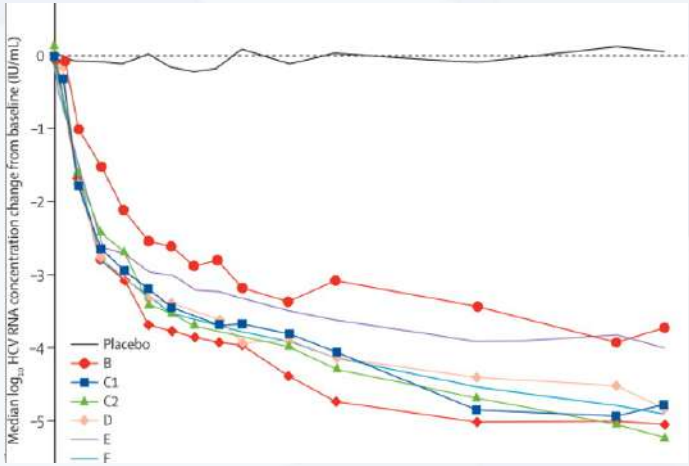
Lindenbach & Rice. Nature 2005:436;933–38.

Proof of Concept HCV Studies

INFORM-1 Study

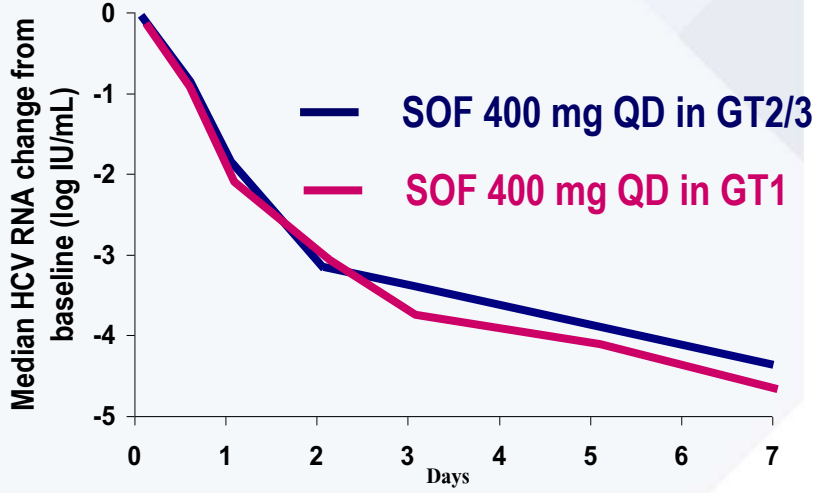
- Dual HCV oral antivirals (danoprevir + miracitabine) can suppress Hepatitis C and prevent resistance



Gane, Roberts, Stedman et al Lancet 2010

ELECTRON Study

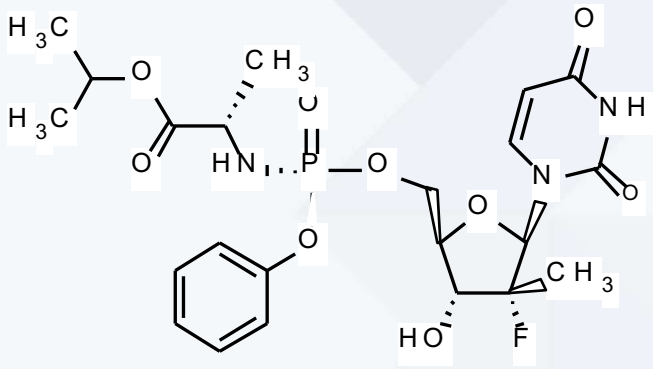
- Proof of concept that HCV can be cured in interferon-free regimen of sofosbuvir + ribavirin

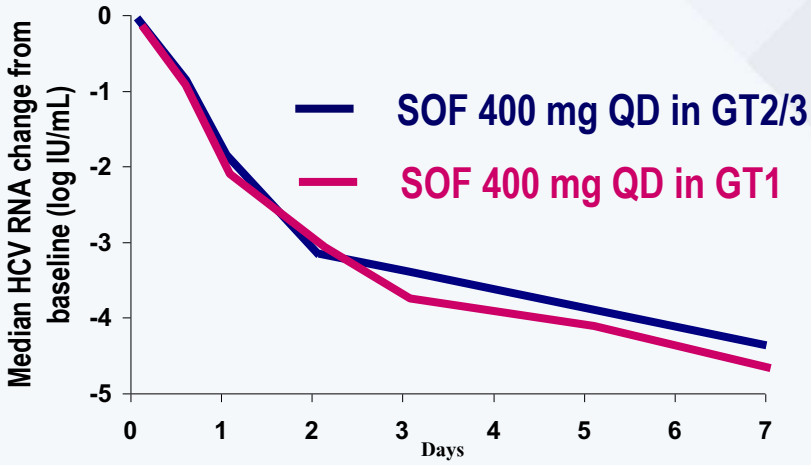


Gane E, Stedman C et al. N Engl J Med 2013

Sofosbuvir (Solvaldi™, GS-7977)

- HCV-specific NS5B polymerase inhibitor
- Potent pan-genotypic antiviral activity against HCV GT1–6
- Simple dosing regimen
  - Once-daily 400mg tablet
  - No impact of BMI, sex, race
  - No hepatic CYP450 metabolism
    - Limited drug interactions
- Safe and well tolerated
  - No toxicity in >5000 patients
- High barrier to resistance





Gane E, Stedman C et al. N Engl J Med 2013;368:34-44

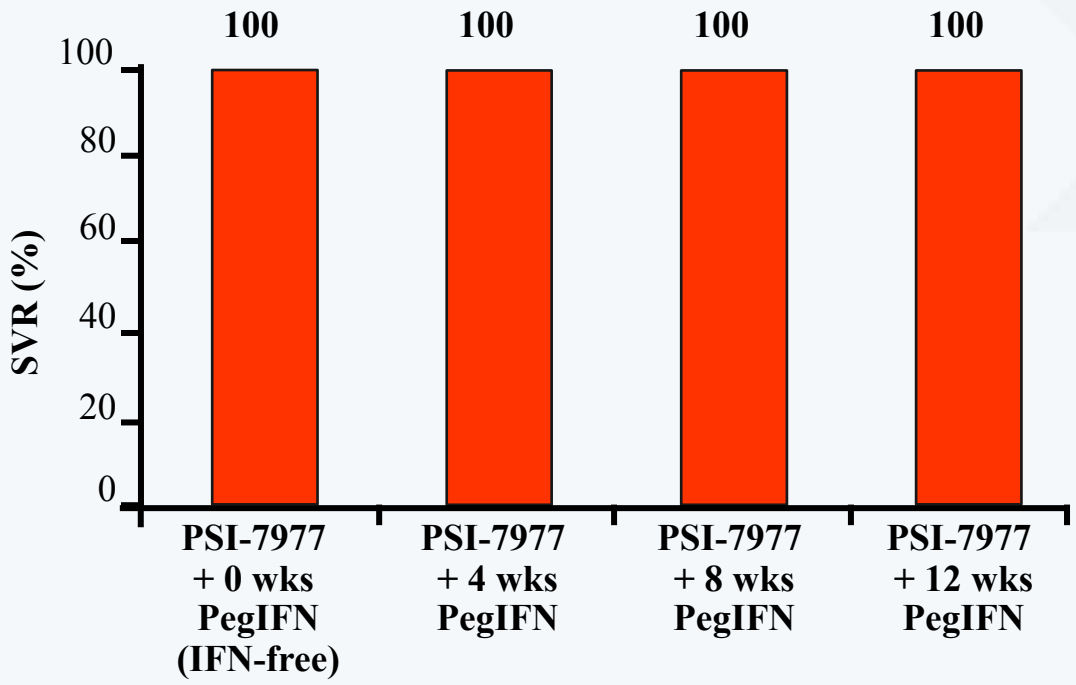
Gane E, et al. N Engl J Med 2013;368:34-44

Lawitz E, et al J Hepatol 2011

ELECTRON:

Sofosbuvir + ribavirin for 12 weeks in HCV genotypes 2/3

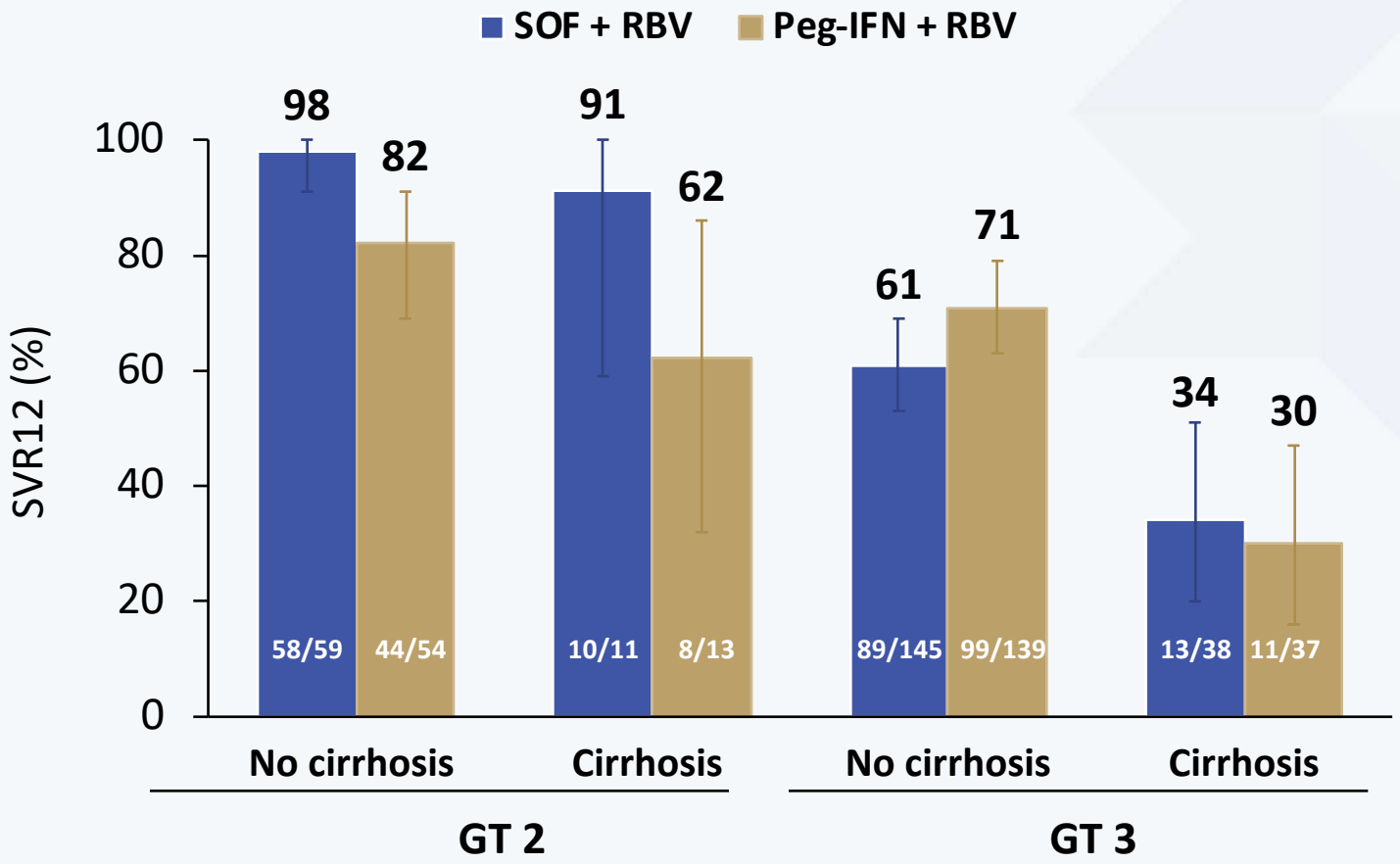
- PegIFN included for 0, 4, 8, or 12 wks



Gane EJ, Stedman C, NEJM 2013.

FISSION: HCV Genotypes 2 & 3

12weeks Sofosbuvir +RBV vs
24 weeks pegIFN/RBV



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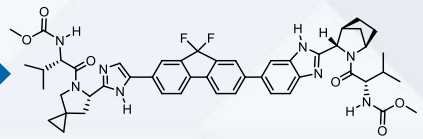
Lawitz et al NEJM 2013; 368;20:1878-86

Fixed Dose Combinations:

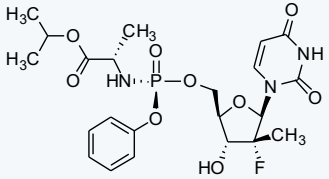
Ledipasvir/sofosbuvir

- **Ledipasvir**
  - Picomolar potency against HCV GT 1a and 1b[1]
  - Effective against NS5B RAV S282T[2]
  - Once daily, oral, 90 mg

LDV NS5A inhibitor



- **Sofosbuvir**
  - Potent antiviral activity against HCV GT 1–6
  - High barrier to resistance
  - Once-daily, oral, 400-mg tablet approved for use with other agents to treat HCV infection



SOF nucleotide polymerase inhibitor

- **Ledipasvir/Sofosbuvir FDC**
  - Once-daily, oral, fixed-dose (400/90 mg) combination tablet
  - No food effect
  - >2000 patients treated

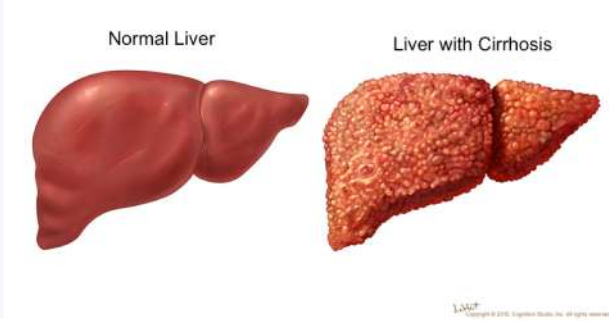
LDV NS5A inhibitor + **SOF nucleotide polymerase inhibitor**

1. Lawitz E, et al. EASL 2011, poster 1219; 2. Cheng G, et al. EASL 2012, poster 1172.

Ledipasvir/sofosbuvir:

Multiple hypotheses/situations tested

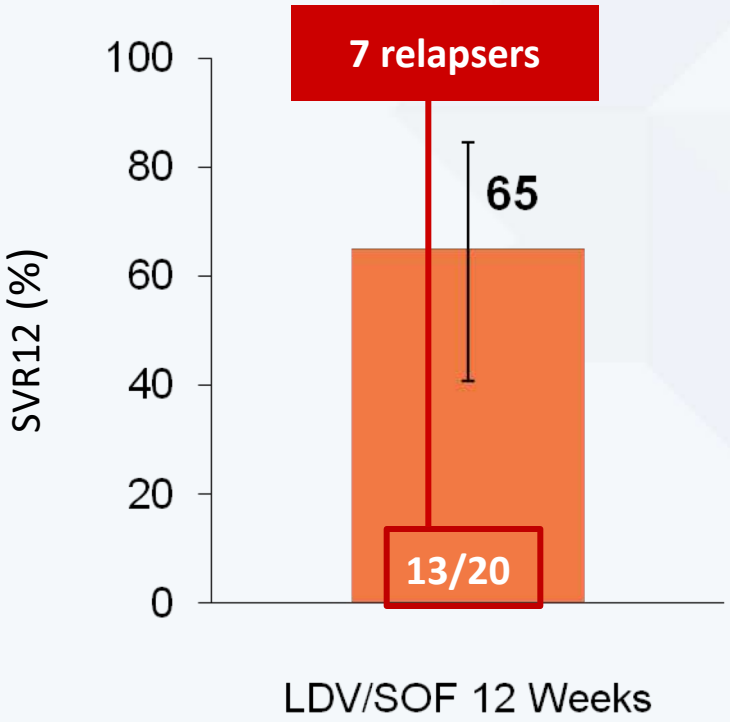
- Different **genotypes** HCV (GT1,2,3,4,6)
- **Treatment** experienced/treatment naïve
- Explored different treatment **durations**
  - 4 weeks too short…..12 wk optimal for many situations
- **Patient subgroups**:
  - Coinfections e.g. HBV
  - Haemophilia
  - HIV
- **Non cirrhotic vs cirrhotic**



ELECTRON-2 Results:

Patients with decompensated Child Pugh B Cirrhosis

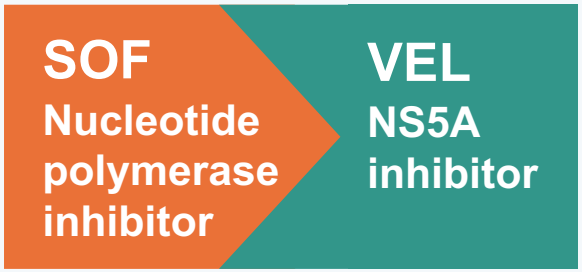
	GT 1 CPT Class B
Median total bilirubin, mg/dL (range)	1.5 (0.7-3.7)
Median serum albumin, g/dL (range)	3.1 (2.3-3.8)
Median INR (range)	1.2 (1.0-3.0)
Ascites, n (%)	4 (20)
Hepatic encephalopathy, n (%)	6 (30)
Median platelet count, $10^3/\mu L$ (range)	84 (44-162)



Stedman C et al DDW 2016

Error bar represents the 95% confidence interval.

Further fixed dose combinations:
Sofosbuvir/ velpatasvir
Sobosbuvir/ velpatasvir/ voxilaprevir



+

- **Sofosbuvir (SOF)/Velpatasvir (VEL; GS-5816)**
  - Once-daily, oral, FDC (400/100 mg)
  - Potent antiviral activity against HCV GT 1–6

♦ **GS-9857**

– Pangenotypic HCV NS3/4A PI with potent antiviral activity against HCV GT 1–6[1, 2]

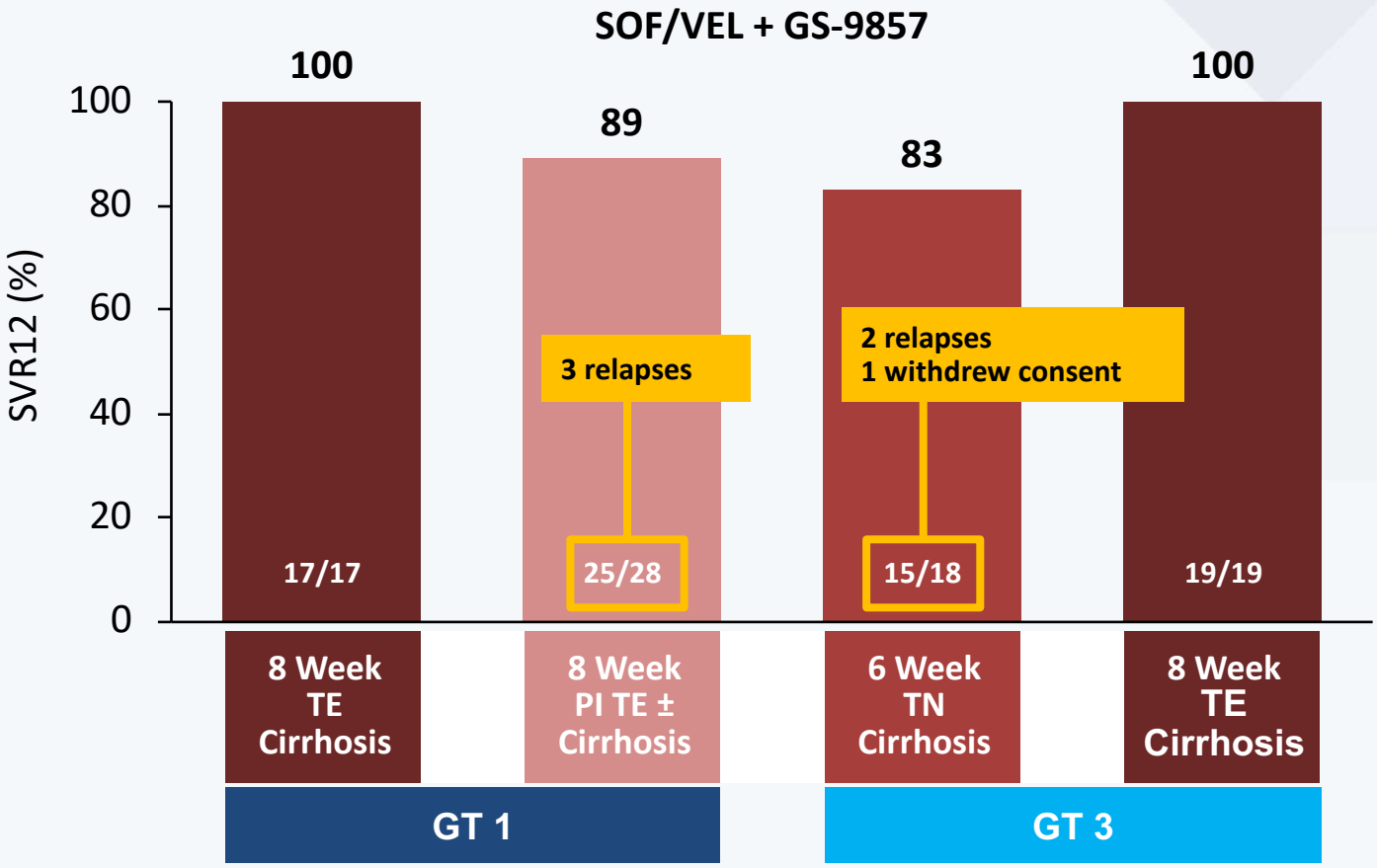
– 100 mg monotherapy for 3 days resulted in maximal viral load reductions of >3 log10 IU/mL in patients infected with HCV GT 1–4[2]

– Improved resistance profile compared with first generation HCV PIs[1, 3]

FDC, fixed dose combination; PI, protease inhibitor

1. Taylor JG, et al. EASL 2015, Poster 899; 2. Rodriguez-Torres, M, et al. EASL 2015, Poster 901; 3. Lawitz E, et al. AASLD 2015, Poster 718.

Sofosbuvir/ velpatasvir/ GS9857 in HCV Genotypes 1 & 3



Gane & Stedman Gastroenterology 2016

TE, PEG + RBV treatment experienced; PI TE, protease inhibitor treatment experienced; TN, treatment naïve.

Conclusions:

- Hepatitis C is now a curable disease in the vast majority of people (>97%)
- Other companies (especially Abbvie) have also developed excellent pangenotypic regimens
- But treatment does come at a price

Gilead initial price for Ledipasvir/sofosbuvir $ 1000 US per tablet

Hepatitis C: from Virus Discovery to Plans for Elimination in 30 years

1989: Identification of HCV

Science 21.4.1989

Isolation of a cDNA Clone Derived from a Blood-Borne Non-A, Non-B Viral Hepatitis Genome

Qui-Lim Choo, George Kuo, Amy J. Weiner, Lacy R. Overby, Daniel W. Bradley, Michael Houghton

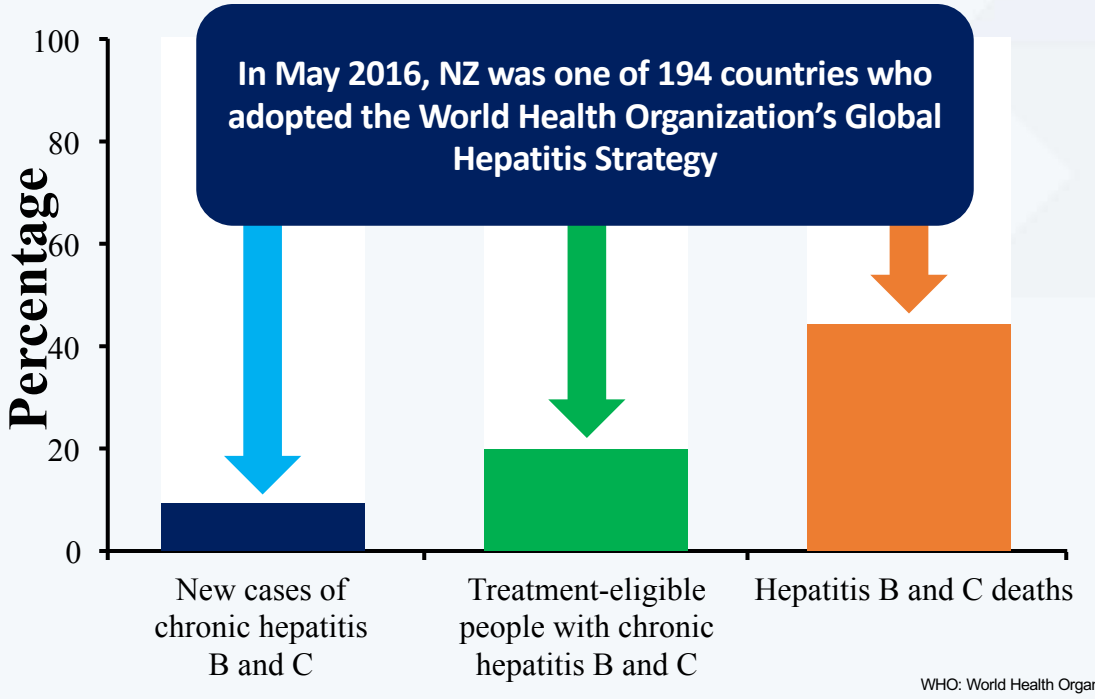
2016: The WHO Global Health Sector established the goal of HCV elimination as a major public heath target by 2030

WHO has set ambitious global targets to control viral hepatitis by 2030

90% reduction in new cases of Hep C

80% eligible people receive Hep C treatment

65% reduction in deaths from Hep C



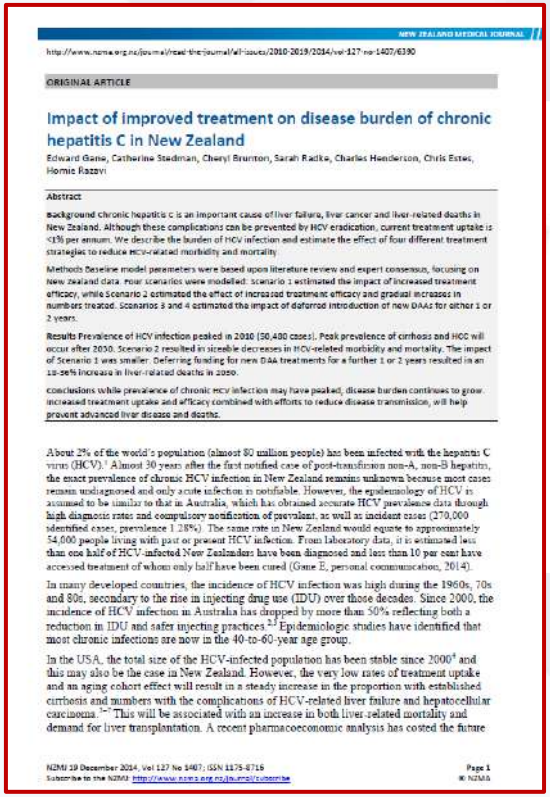
WHO: World Health Organization

WHO global health sector strategy on viral hepatitis. Available at: http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf?ua=1 (accessed April 2017)

How many New Zealanders have Hepatitis C?

- **2014 MoH Epidemiology Working Group**
  - Assume Australian prevalence rates
    - 1.1% are HCV RNA +

⇨ Estimated 50,000 currently infected



NEW ZEALAND MEDICAL JOURNAL

http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2014/vol-127-no-1407/6390

ORIGINAL ARTICLE

Impact of improved treatment on disease burden of chronic hepatitis C in New Zealand

Edward Gane, Catherine Stedman, Cheryl Brunton, Sarah Radke, Charles Henderson, Chris Estes, Homie Razavi

Abstract

Background Chronic hepatitis C is an important cause of liver failure, liver cancer and liver-related deaths in New Zealand. Although these complications can be prevented by HCV eradication, current treatment uptake is <1% per annum. We describe the burden of HCV infection and estimate the effect of four different treatment strategies to reduce HCV-related morbidity and mortality.

Methods Baseline model parameters were based upon literature review and expert consensus, focusing on New Zealand data. Four scenarios were modelled. Scenario 1 estimated the impact of increased treatment efficacy, while Scenario 2 estimated the effect of increased treatment efficacy and gradual increases in numbers treated. Scenarios 3 and 4 estimated the impact of deferred introduction of new DAAs for either 1 or 2 years.

Results Prevalence of HCV infection peaked in 2010 (50,400 cases). Peak prevalence of cirrhosis and HCC will occur after 2030. Scenario 2 resulted in sizeable decreases in HCV-related morbidity and mortality. The impact of Scenario 1 was smaller. Deferring funding for new DAA treatments for a further 1 or 2 years resulted in an 18-36% increase in liver-related deaths in 2050.

Conclusions While prevalence of chronic HCV infection may have peaked, disease burden continues to grow. Increased treatment uptake and efficacy combined with efforts to reduce disease transmission, will help prevent advanced liver disease and deaths.

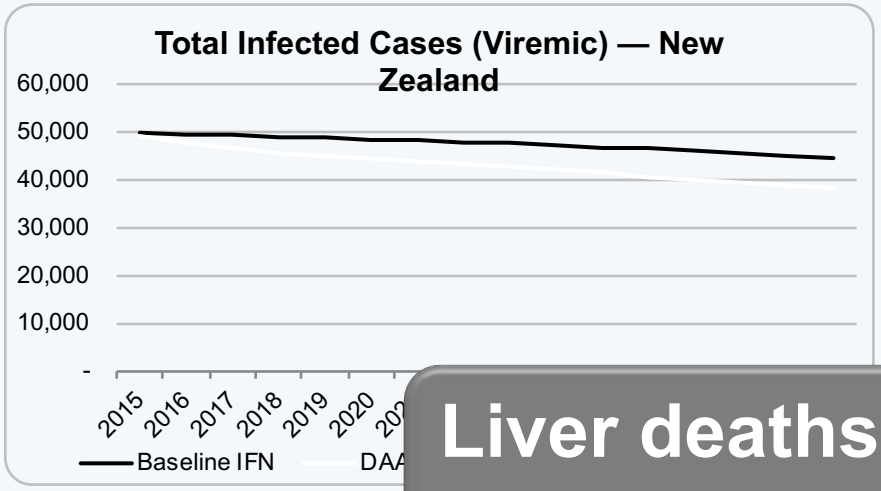
About 2% of the world's population (almost 80 million people) has been infected with the hepatitis C virus (HCV).[1] Almost 30 years after the first notified case of post-transfusion non-A, non-B hepatitis, the exact prevalence of chronic HCV infection in New Zealand remains unknown because most cases remain undiagnosed and only acute infection is notifiable. However, the epidemiology of HCV is assumed to be similar to that in Australia, which has obtained accurate HCV prevalence data through high diagnostic rates and compulsory notification of prevalent, as well as incident cases (270,000 identified cases, prevalence 1.28%). The same rate in New Zealand would equate to approximately 54,000 people living with past or present HCV infection. From laboratory data, it is estimated less than one half of HCV-infected New Zealanders have been diagnosed and less than 10 per cent have accessed treatment of whom only half have been cured (Gane E, personal communication, 2014).

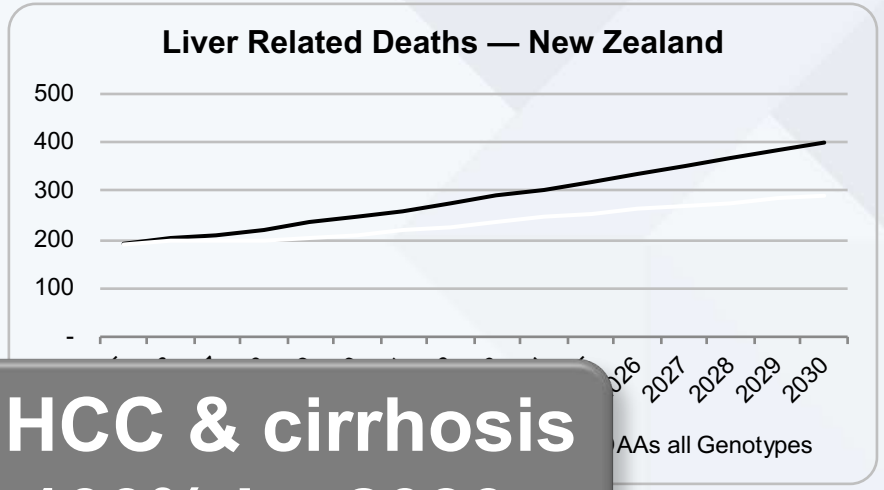
In many developed countries, the incidence of HCV infection was high during the 1960s, 70s and 80s, secondary to the rise in injecting drug use (IDU) over those decades. Since 2000, the incidence of HCV infection in Australia has dropped by more than 50% reflecting both a reduction in IDU and safer injecting practices.[2,3] Epidemiologic studies have identified that most chronic infections are now in the 40-to-60-year age group.

In the USA, the total size of the HCV-infected population has been stable since 2000[4] and this may also be the case in New Zealand. However, the very low rates of treatment uptake and an aging cohort effect will result in a steady increase in the proportion with established cirrhosis and numbers with the complications of HCV-related liver failure and hepatocellular carcinoma.[5–7] This will be associated with an increase in both liver-related mortality and demand for liver transplantation. A recent pharmacoeconomic analysis has costed the future

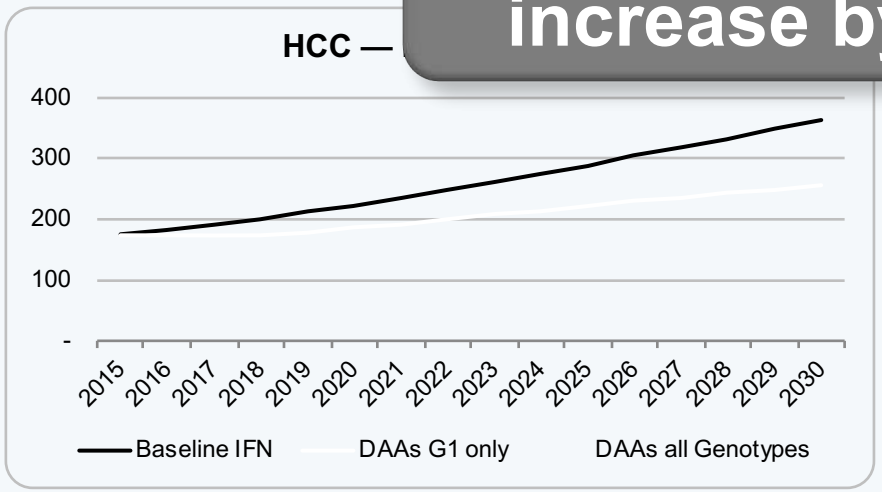
Gane E, et al. *NZ Med J* 2014;127(1407):61–74.
Ministry of Health. Hepatitis C. 2016 www.health.govt.nz/your-health/conditions-and-treatments/diseases-and-illnesses/hepatitis-c.
Arlo Upton (Personal Communication)

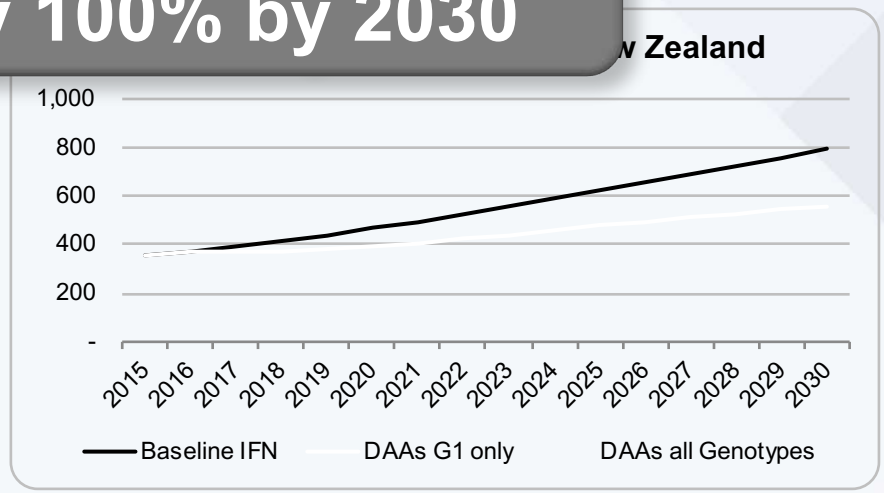
If we continued to treat with PEG/RBV (600 pts/year; 65% SVR) and diagnose only 900 new cases per annum





Liver deaths, HCC & cirrhosis increase by 100% by 2030





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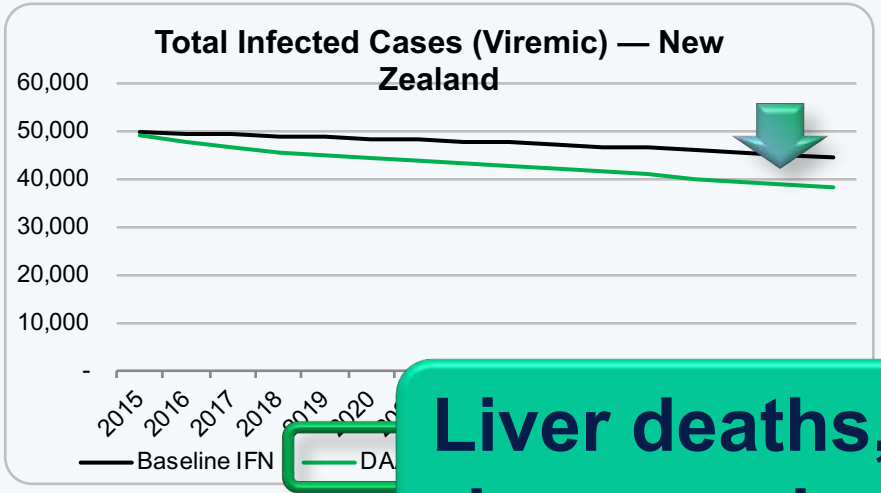
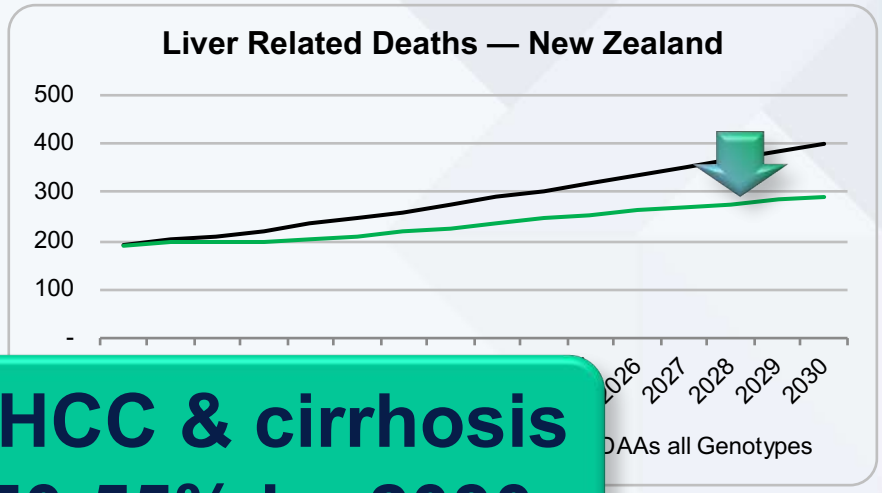
CDA Center for Disease Analysis

SKLLR Hong Kong, Nov 2017

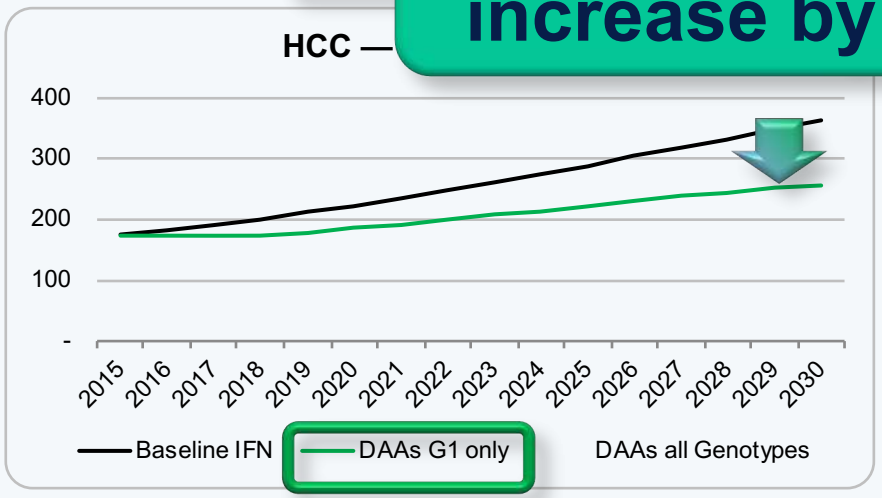
2016-2018 Scenario: VIEKIRA PAK for G1, HARVONI for decompensated liver disease

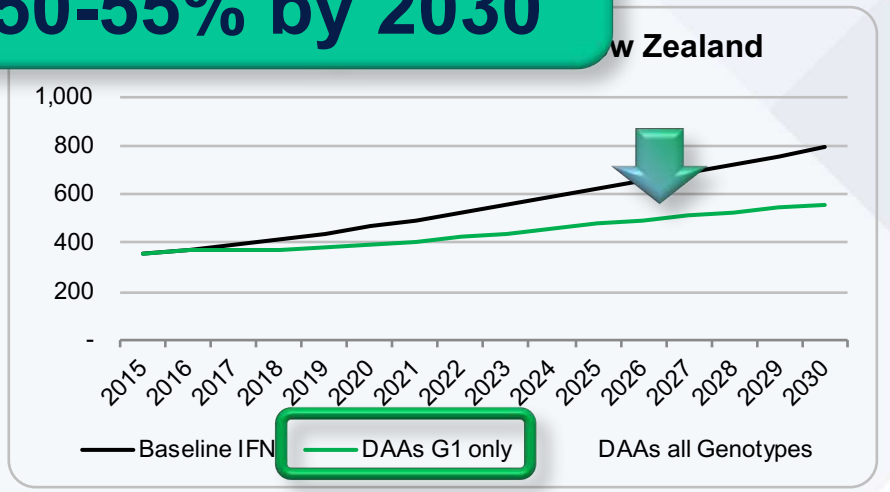
Liver deaths, HCC & cirrhosis increase by 50-55% by 2030





Liver deaths, HCC & cirrhosis increase by 50-55% by 2030





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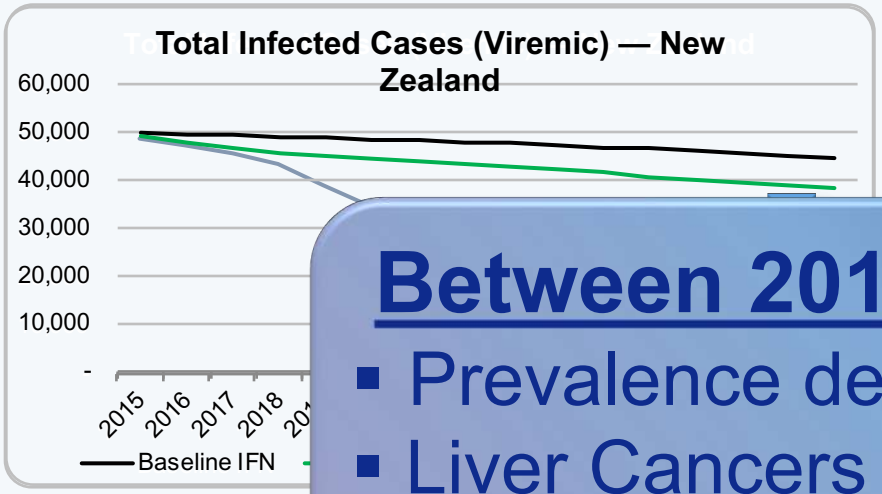
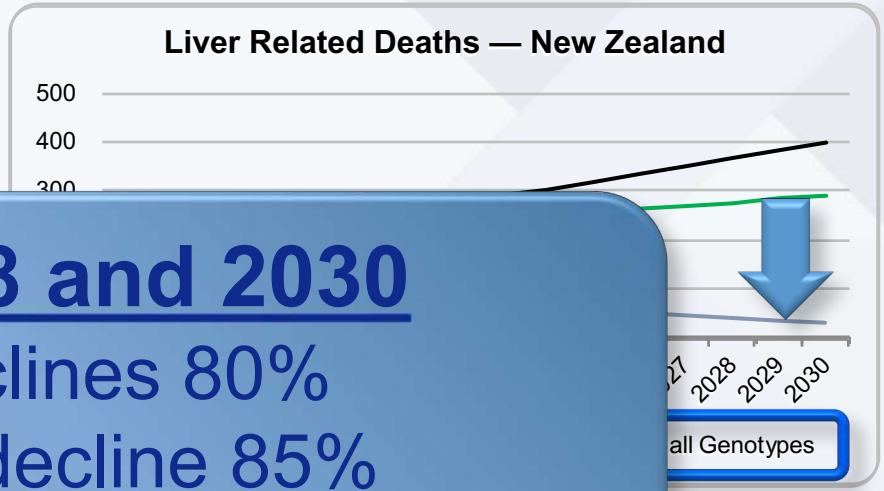
CDA Center for Disease Analysis

2018 or 2019 Scenario: Pangenotypic DAA Therapy combined with doubling of current diagnosis rates (to 2000/year)

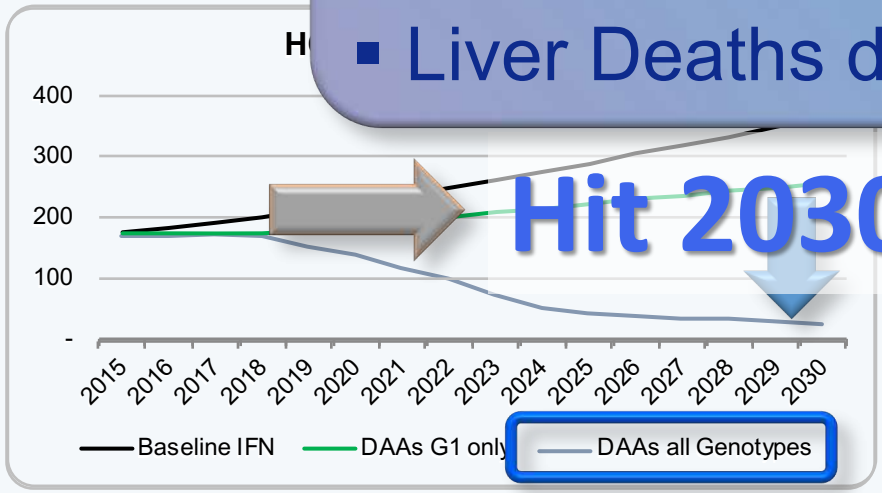


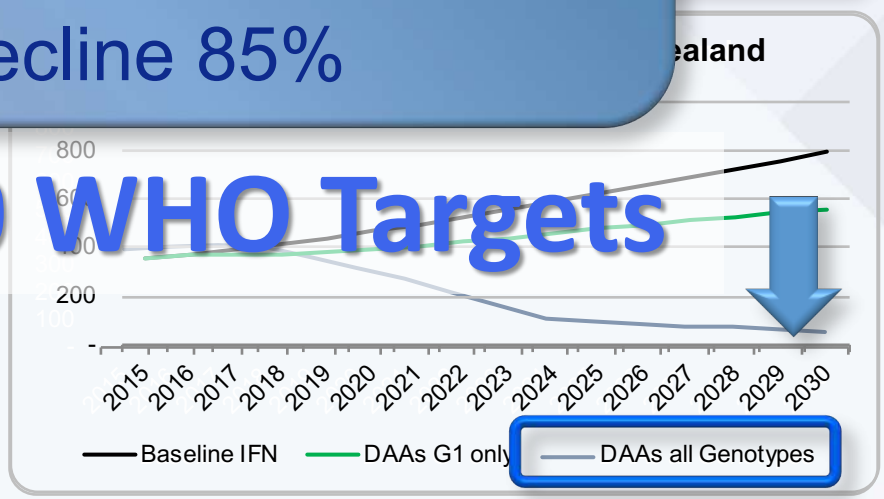


Between 2018 and 2030

- Prevalence declines 80%
- Liver Cancers decline 85%
- Liver Deaths decline 85%

Hit 2030 WHO Targets





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CDA Center for Disease Analysis

SKLLR Hong Kong, Nov 2017

Can New Zealand reach 2030 WHO targets towards HCV "elimination"?

Only with major changes……..

- We must **broaden funding/access to care so that all genotypes are treated** with highly effective DAA regimens
- We must **increase diagnosis rates and improve linkage to care** by delivering treatment in community
- We need to embrace "treatment as prevention"
- Effective strategies for **managing treatment failures** are essential
- Treatment must be coupled with harm minimisation to reduce reinfections