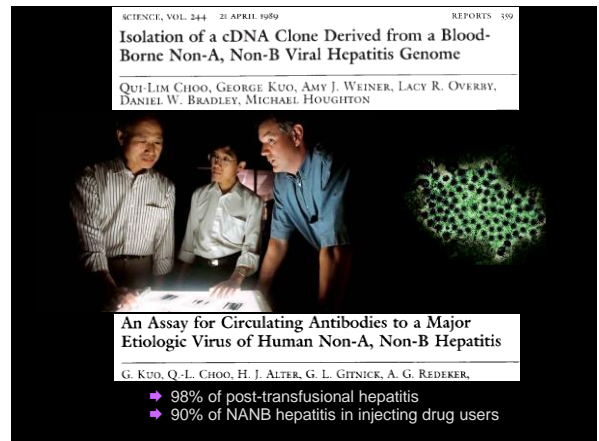


## Using DAA therapy to eliminate HCV Dream Or Reality?



Ed Gane  
NZLTU, Auckland City Hospital



### The Life cycle of an Infectious Disease

1. Discovery ✓
2. Reliable diagnostic test ✓
3. Effective therapy ✓
4. Protective vaccination
5. Control of disease burden
6. Elimination of infection
7. Global eradication of infection

### Control vs. Elimination vs. Eradication

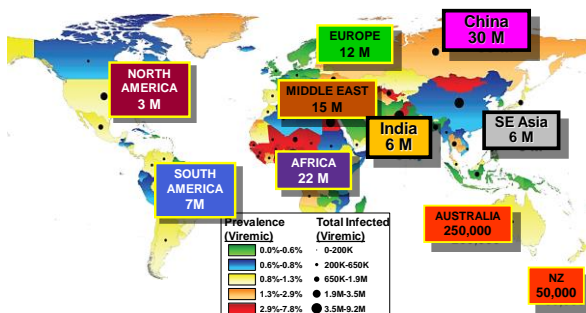
**Control:** reduction in prevalence, morbidity/mortality of an infectious disease to a locally acceptable level.

**Elimination:** reduction to zero of the incidence of disease or infection in a defined geographical area, but requires continued measures to prevent re-establishment of transmission (e.g. measles, polio)

**Eradication:** permanent reduction to zero of the worldwide incidence of infection, with no further control measures required (e.g. smallpox).

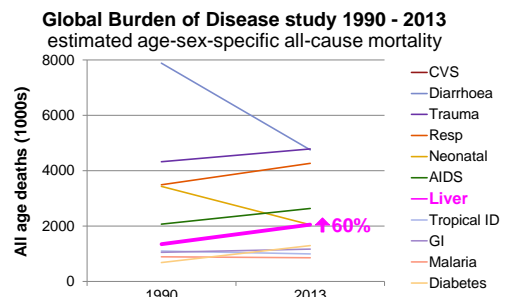
### Hepatitis C is silent global epidemic of 21<sup>st</sup> Century

- 1.1% i.e. 80 million (62-103) infected



Gower, E., Estes C., Hindman, S., Razavi-Shearer, K., Rizzin, T. Global epidemiology and genotype distribution of the hepatitis C virus. *Journal of Hepatology* 2014.

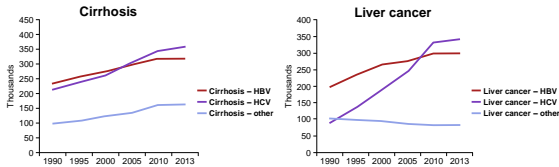
### Global burden from liver disease is increasing more rapidly than any other disease



Cowie BC, et al. EASL 2015; Poster #P1250.  
Global Burden of Disease 2015. *Lancet* 2016;386:117-71

HCV is now the leading cause of liver-related morbidity and mortality

Global Burden of Disease study 1990 - 2013  
estimated age-sex-specific all-cause mortality

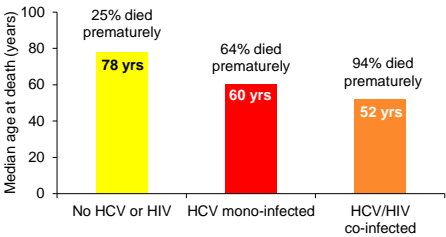


Deaths due to HCV more than doubled between 1990–2013;  
Liver cancer deaths due to HCV increased 300%

Cowie BC, et al. EASL 2015; Poster #P1256;  
Global Burden of Disease 2013. Lancet 2015;385:117–71

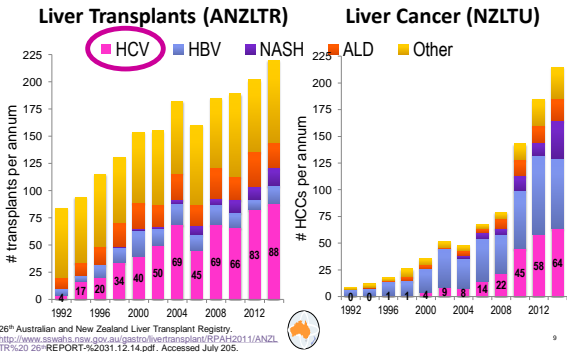
Live expectancy reduced in HCV-infected adults

Premature death (<65 years) and median age at death among all deaths, NYC (2000–2011)



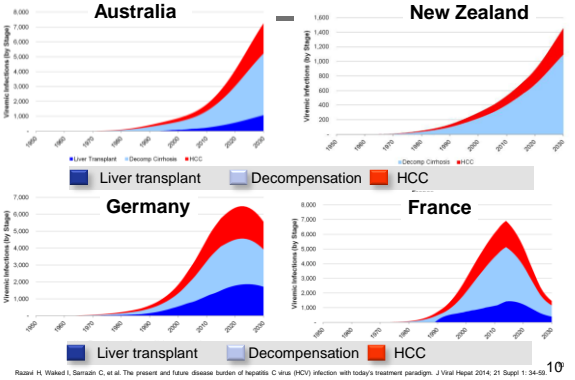
Pinchoff J, et al. Clin Infect Dis 2014;58:1047–54

Disease burden from hepatitis C is increasing as the infected population gets older



26<sup>th</sup> Australian and New Zealand Liver Transplant Registry.  
<http://www.ssiashs.new.gov.au/gastro/livertxplant/REPORT2011/ANZLTR%20REPORT%2031.12.14.pdf>. Accessed July 2015.

Disease burden from hepatitis C will continue to increase as the infected population gets older



Razavi H, Wakefield J, Sarrazin C, et al. The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm. J Viral Hepat 2014; 21 Suppl 1: S4-S9.

The Life cycle of an Infectious Disease

1. Discovery
2. Reliable diagnostic test
3. Effective therapy
4. Protective vaccination
5. Control of disease burden

6. Elimination of infection
7. Global eradication of infection

Can Vaccination eradicate HCV?  
Best candidates in development

Approach	Antigen	Company	Subjects	Efficacy
Recombinant proteins	gpE1; gpE2	Chiron; CSL Innogenetics	Chimps Humans	N N
	Core	Novartis	Chimps	N
	NS3-core	Globeimmune	Humans	
Peptides	T-cell epitopes	InterCell AG	Humans (HLA-A2+)	N
Viral vectors	Adenovirus	Okairos; NIH	Chimps Humans	Y ?
	Vaccinia	Transgene; NYBC	Chimps	Y
Virus-like particles	Core-E1E2	NIH	Chimps	Y
DNA vaccine with electroporation	HCV NS3, 4a, 4b, 5a	Triprep; VGX/Inovio	Humans	?

## Can Vaccination eradicate HCV?

Many barriers to successful vaccine development

### HCV FACTORS

- HCV genomic diversity
  - Anti-E1/E2 escape mutants
  - CD4+/CD8+ escape mutants
- T cell exhaustion
- Impaired DC maturation
- HCV NS3/5A inhibits IFN

### PATIENT FACTORS

- Host genomic diversity
  - IL28B SNP
  - Limited TCR repertoire
  - MHC Class 1 restriction
- Aging population
- HIV co-infection

### OTHER FACTORS

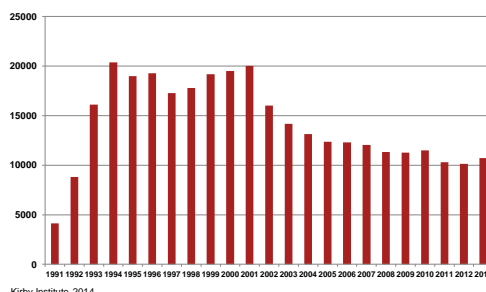
- Chimpanzee is the only animal model for vaccine
- Preclinical results not translate to humans
- Reduced interest in need for prophylaxis
- Vaccinating PWID may not be practical

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## Can Public Health interventions eradicate HCV?

Recent decrease in Incidence of HCV infection

### HCV notifications in Australia: 1991-2013

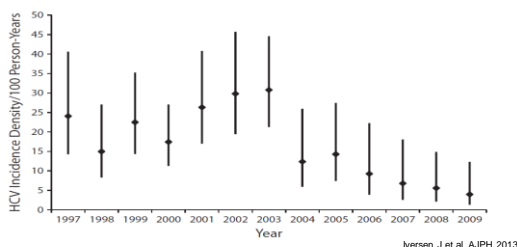


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## Can Public Health measures eradicate HCV?

HCV Prevention through Harm Reduction

### HCV incidence among PWID in Australian NSP Survey

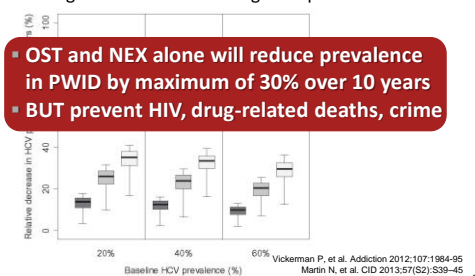


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## Can Public Health measures eradicate HCV?

Harm reduction cannot eliminate HCV in isolation

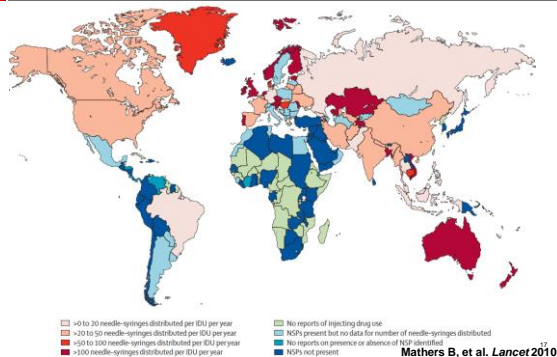
- UK model of the impact of increasing opioid substitution coverage and needle exchange from current baseline
  - Decreasing benefit with increasing HCV prevalence in PWID



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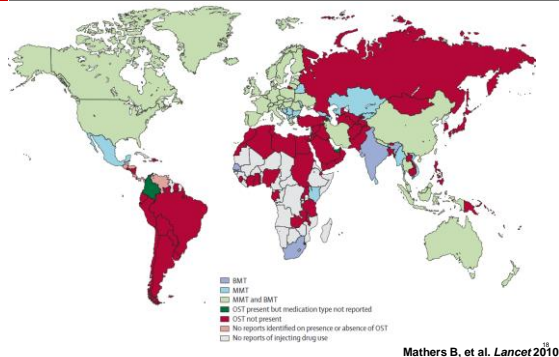
## Can Public Health measures eradicate HCV?

Only 41% countries have needle syringe programmes



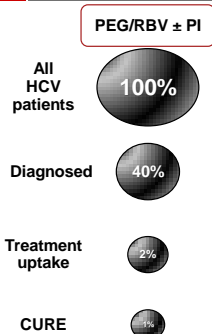
## Can Public Health measures eradicate HCV?

Only 35% countries have opioid substitution therapy



## Could HCV be eliminated through antiviral therapy?

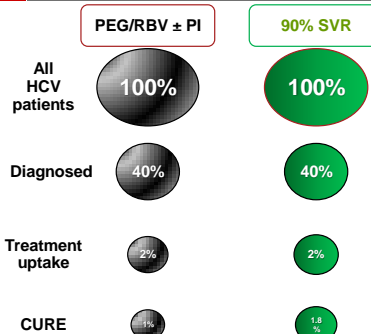
### Current situation



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## Could HCV be eliminated through antiviral therapy?

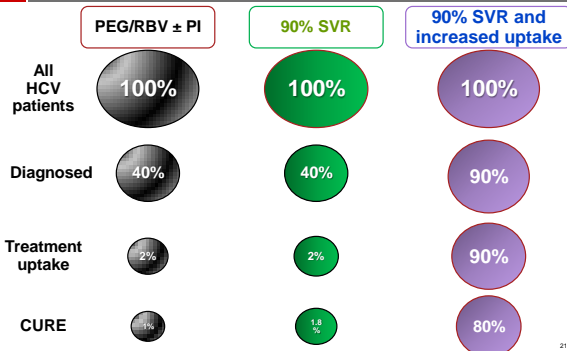
### DAA therapies with higher SVR rates



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## Could HCV be eliminated through antiviral therapy?

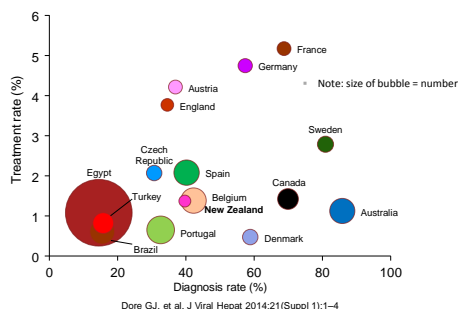
### DAA therapies combined with increased uptake



21

## Treatment and Diagnosis Rate by Country, 2013

Estimated HCV prevalence, diagnosis and treatment rates in 2013




22

**SIMPLE**

- Short duration
- Low pill burden
- Minimal monitoring
- Minimal drug-drug interactions

**EFFECTIVE**

Pangenotypic  
>95% Cure rates  
Improved survival  
Improved QoL



**SAFE**

NO Interferon  
No Ribavirin  
No toxicity  
No DDIs

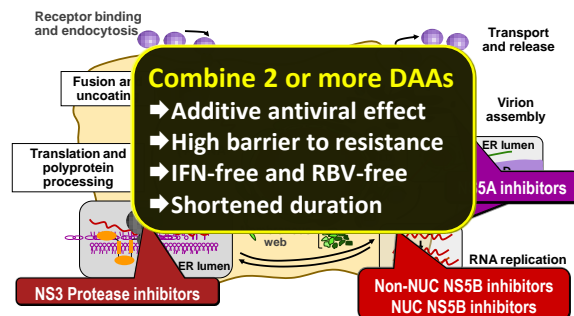
**SPECIAL POPS**

Elderly  
Liver failure  
Renal failure  
HIV co-infection

**AFFORDABLE**  
all populations

## DAA's offer a new treatment paradigm for HCV

### More effective and safer therapies



Lindenbach BD, Rice CM. Nature 2005;436(Suppl):933-8

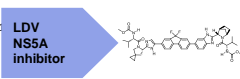
ER: endoplasmic reticulum; LD: luminal domain

## Ledipasvir plus Sofosbuvir (Harvoni™) 1<sup>st</sup> IFN and RBV-free Single Tablet Regimen



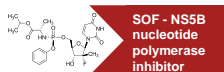
### ■ Ledipasvir (LDV)

- Picomolar potency against GT 1a and 1b
- Effective against NS5B RAV S282T<sup>2</sup>
- Once-daily, oral, 90 mg



### ■ Sofosbuvir (SOF)

- Potent antiviral activity against GT 1–6
- Effective against NS5A RAVs<sup>3</sup>
- High barrier to resistance
- Once-daily, oral, 400-mg tablet



### ■ Ledipasvir/Sofosbuvir STR

- Once-daily, oral fixed-dose (90/400 mg) combination tablet
- >2000 patients treated in clinical trials
- >200,000 treated in real world

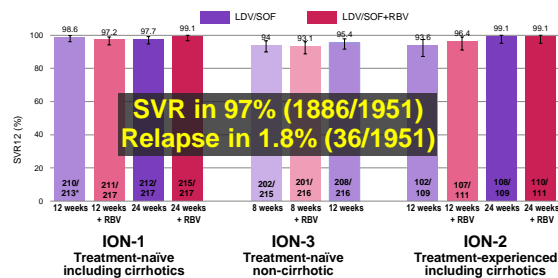


FDA Approval 10 October 2014  
European Approval 18 November 2014

1. Laveit E, et al. EASL 2011, poster 1210; 2. Cheng G, et al. EASL 2012, poster 1172; 3. SOVALD™ (DSFPC) GlaxoSmithKline, Inc. EMA, 2014

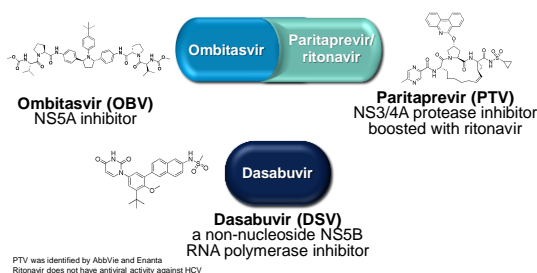
25

## Ledipasvir/Sofosbuvir in HCV GT 1 Overall Efficacy across the Phase 3 Program



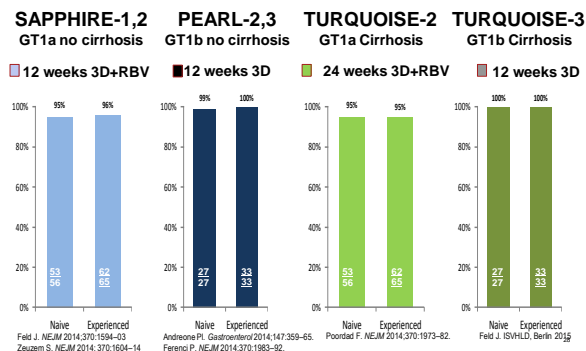
Abdel N, et al. N Engl J Med 2014; 370: 1885-90; Abdel N, et al. N Engl J Med 2014; 370: 1483-93; Roudot N, et al. N Engl J Med 2014; 370: 1879-88. Data on File, GlaxoSmithKline, Inc.

## AbbVie Multi-Targeted 3-DAA (3D) Regimen



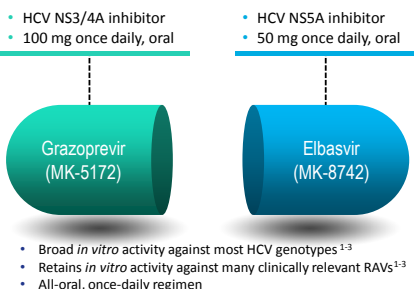
27

## AbbVie-3D Phase III Trials in HCV GT-1



Feld J. NEJM 2014;370:1594-03; Zeuzem S. NEJM 2014; 370:1604-14; Andreone P. Gastroenterol 2014;147:359-65; Ferenci P. NEJM 2014;370:1983-92.

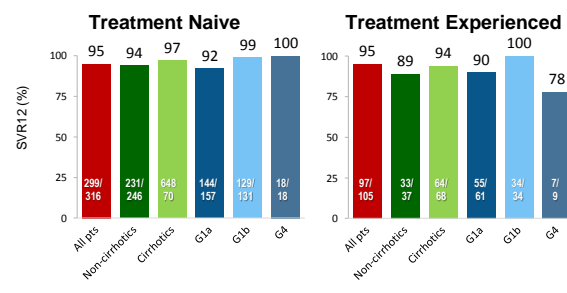
## Merck MK2 regimen in HCV GT 1, 4,5 and 6: Grazoprevir/Elbasvir Fixed Dose Combination



1. Summa V, et al. Antimicrobial Agent Chemother. 2012;56: 4161-67.  
2. Coburn CA, et al. ChemMedChem. 2013;8: 1930-40.  
3. Harper S, et al. ACS Med Chem Lett. 2012;Mar 2; 3(4):332-6.



## Merck MK2 Phase III Trials in HCV GT-1/4/6 12 weeks GZR/EBR without RBV: C-EDGE Studies

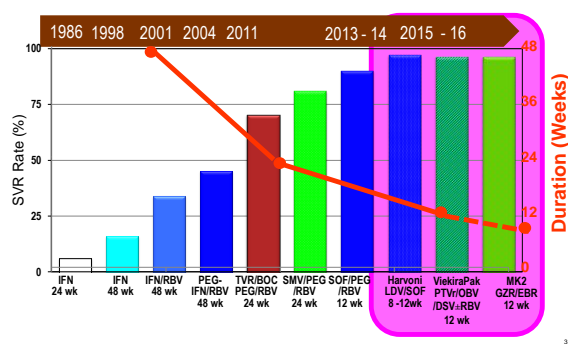


Zeuzem S, et al. EASL 2015, Vienna. #G07

Kwo P, et al. EASL 2015, Vienna. #P0886

30

## SVR Rates in Compensated HCV GT 1



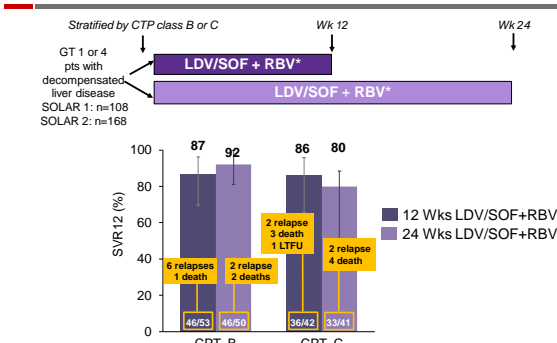
31

## AbbVie Viekira Pak, Gilead Harvoni and Merck MK2 Oral DAA therapies in HCV GT 1

- In clinical trials and real world studies, IFN-free DAA regimens are well tolerated with >95% SVR after 8-12 weeks in treatment-naïve GT 1
- What about other “difficult-to-cure” populations
  - Patients with decompensated cirrhosis
  - Patients with HIV co-infection
  - Patients infected with other HCV genotypes

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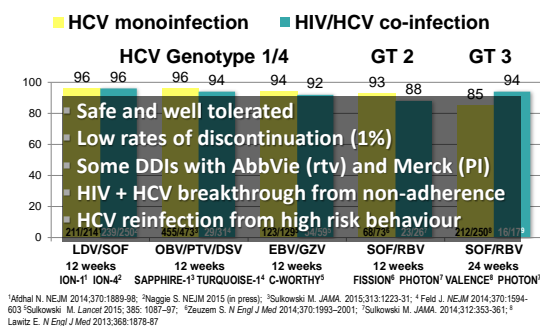
## Safe & effective therapy in decompensated cirrhosis SOLAR Studies of 12 and 24 wks Harvoni + RBV



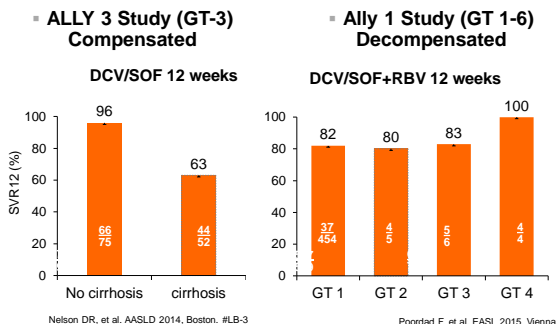
Charlton M, et al. Gastroenterology 2015;149:649-659  
Ganev E, et al. DOW 2015

33

## Safe & effective therapy in HIV co-infection No longer a baseline predictor of response?



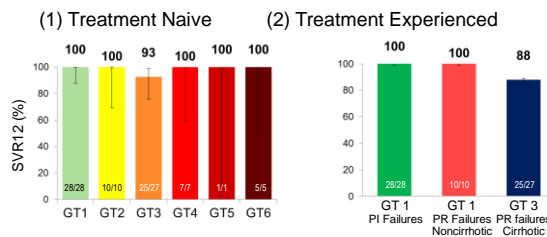
## Pan-genotypic Regimen NUC + NS5AI Sofosbuvir + Daclatasvir in GT 1 - 6



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## Pan-genotypic Regimen: NUC + 2<sup>nd</sup> Wave NS5AI Sofosbuvir + Velpatasvir (GS-5816) in GT 1 - 6

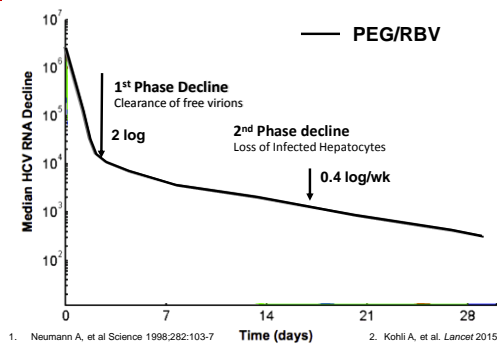
Phase 2, open-label studies of GS-5816/SOF±RBV for 12 weeks



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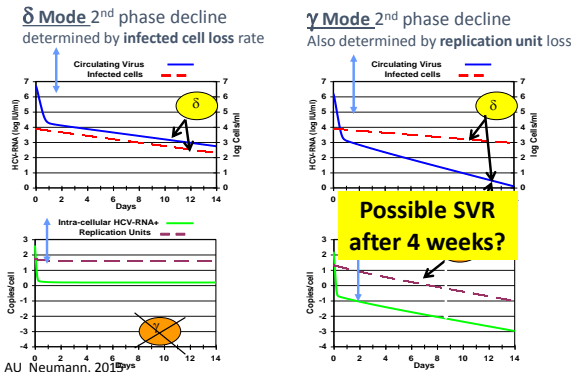
The regimen which is the shortest duration possible

What DURATION of treatment is needed to eradicate HCV without Interferon?

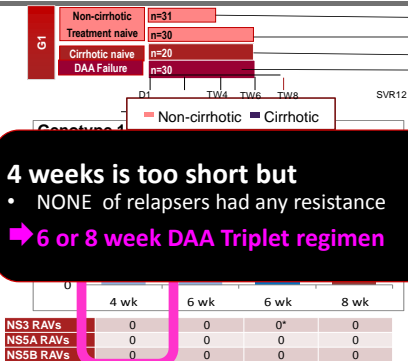


1. Neumann A, et al Science 1998;282:103-7 2. Kohli A, et al. Lancet 2015; 385: 1107-15

What DURATION of treatment is needed?  
New 3 Phase Model with Intra-cellular dynamics



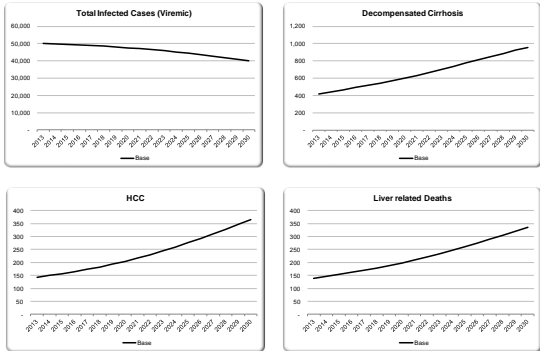
What DURATION of treatment is needed?  
LEPTON: GS-5816/SOF + GS-9857 in GT 1 and 3



Poordad F, et al EASL 2015

Can these new therapies be used to eliminate HCV?

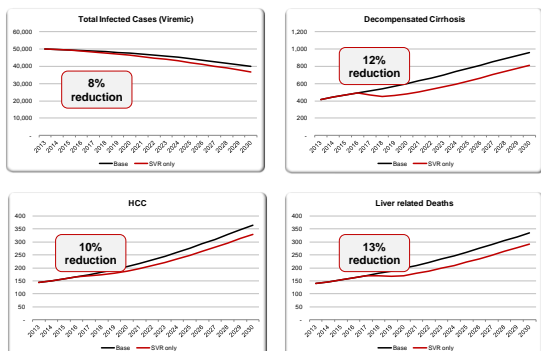
No increase in SVR or in numbers treated will result in continued rise in liver-related complications



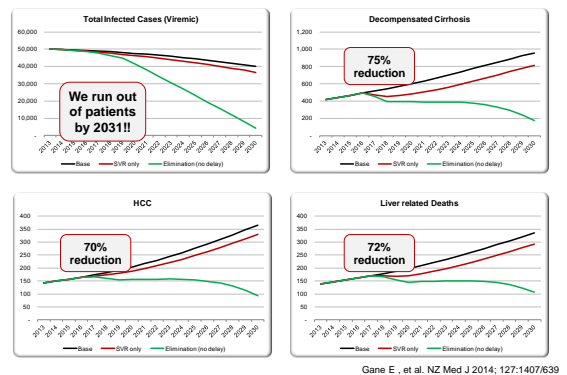
Gane E, et al. NZ Med J 2014; 127:1407/639



### Increasing SVR >90% without change in numbers treated has small impact on morbidity & mortality



### Increasing SVR >90% with increase in numbers treated 5-fold out could eliminate HCV by 2030



### What would it take to reduce disease burden in ANZ

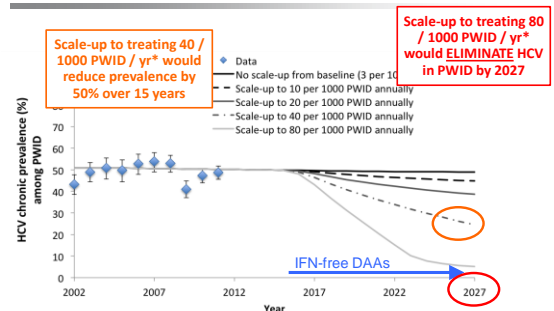
- Funding of new oral therapies for all cirrhotics
- Access to Fibrosan to identify cirrhotics
- Capacity to treat 2%/year (100% increase)

### What would it take to eliminate HCV from ANZ

- Funding of the new oral therapies for everyone
- Community testing to identify the 60,000 Australians and New Zealanders who remain undiagnosed
- Capacity to treat 10%/year (1000% increase)
- Treat those who are transmitting HCV (PWID, prisoners) i.e. "treatment as prevention"



### HCV treatment as prevention: Melbourne



### What barriers still remain to national elimination and global eradication of Hepatitis C?

- 1. Low diagnosis rates**
  - » Targeted testing, Point-Of-Care tests in community
  - » Community access to Fibrosan
- 2. Low treatment uptake**
  - » Wide access to DAA Therapy
    - Simplified referral and treatment algorithms
    - Test and treat in the community
- 3. High cost of DAA**
  - » Government investment in High Income countries
  - » Donor access programs in Low Income countries

### What would it take to eliminate HCV from ANZ PBAC recommendations: March 2015

GT 1	Harvoni (LDV/SOF) SOF/PEG/RBV SOF + Daclatasvir Viekira Pak (AbbVie-3D)	12 weeks
GT 2	SOF + RBV	12-16 weeks
GT 3	SOF + Daclatasvir	12 weeks

- **ALL STAGES** of liver disease
- **S85 PRESCRIBING:** Community Pharmacy & GPs

➡ **POSSIBLE PBS LISTING DEC 2015 OR EARLY 2016**



## What would it take for global eradication of HCV? DAA Access Programmes

**FIERCEPHARMA** (<http://www.fiercepharma.com>)

### Gilead in talks with Indian drugmakers to sell Sovaldi at cut-rate prices

February 4, 2014 | By Tracy Staton

"We are going to give license[s] to Indian companies,"

Gilead is aiming for a price on Sovaldi of about **\$2,000 for a treatment course**, he said. The U.S. sticker price is \$84,000 for a 12-week cycle.

### GILEAD OFFERS EGYPT NEW HEPATITIS C DRUG AT 99 PERCENT DISCOUNT

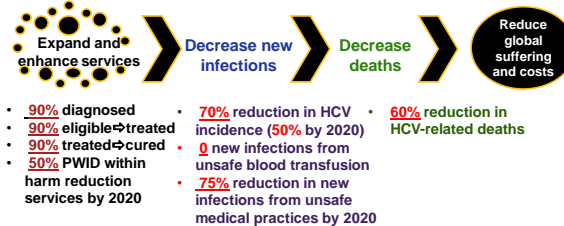
BY MAGGIE FICK CAIRO/LONDON Fri Mar 21, 2014 4:10pm EDT

(Reuters) - Sovaldi, has offered to supply the medicine to Egypt at a 99 percent discount to the U.S. price.

While the drug will still cost **\$900 for a 12-week course of treatment**, that is a fraction of the \$84,000 charged for a course of treatment in the United States.

## What would it take for global eradication of HCV? World Health Organisation Targets for 2030

WHO Resolution on Viral Hepatitis (WHA67.6) May 22<sup>nd</sup> 2014



WHO Global Health Sector Strategy on viral hepatitis, 2016–2021. Available at [http://www.who.int/hiv/draft-hep-strategy-2016-2021\\_en.pdf](http://www.who.int/hiv/draft-hep-strategy-2016-2021_en.pdf) (accessed June 2015)

PWID: people who inject drugs;  
WHO: World Health Organization

