C 型肝炎治療的臨床實務

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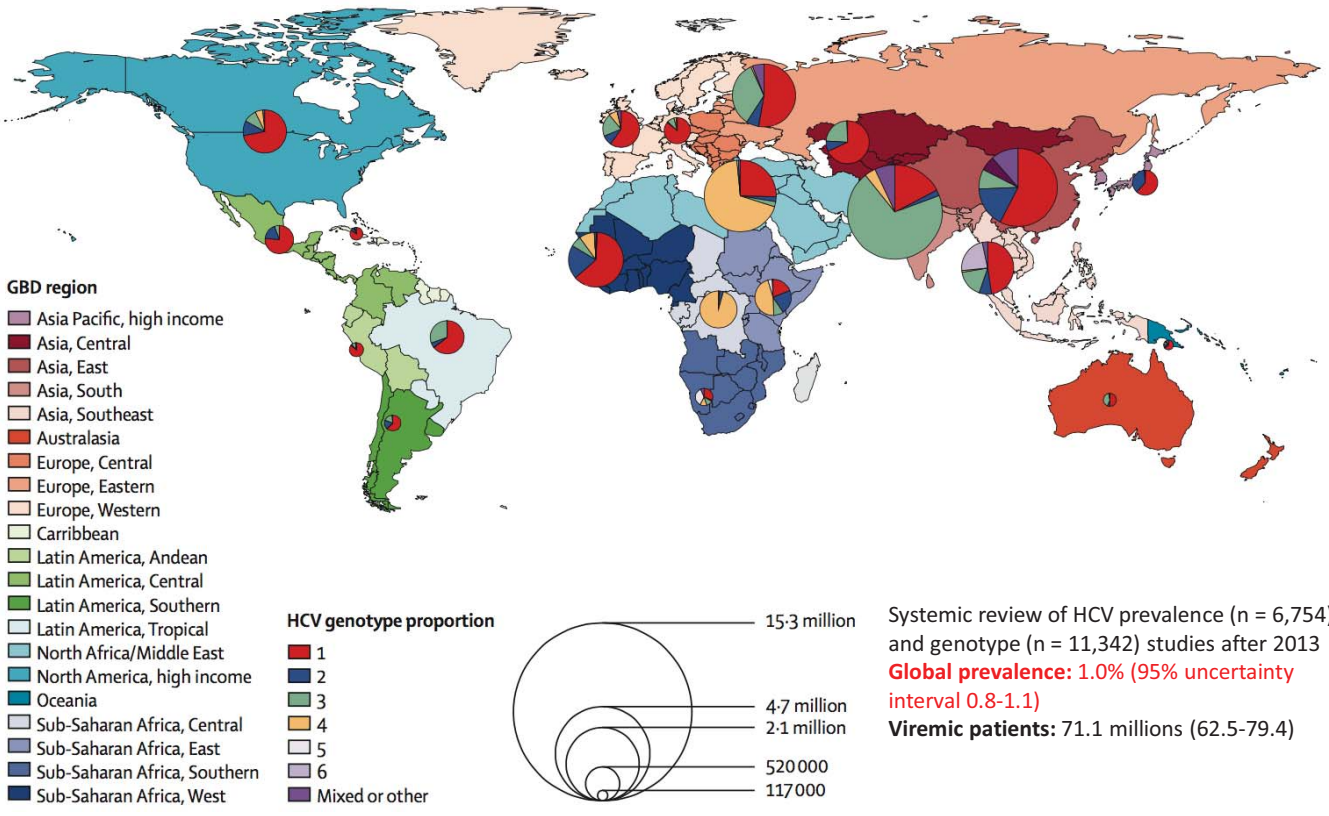
1	2	3	4	5	6
Epidemiology Natural history	**Diagnosis**	**Implications of SVR**	**DAA treatment**	**DDI**	**Public health**
Global & Local	**Flow Tool**	**Viral cure Health outcome**	**Concept Usual & Special Population**	**Concept Red flag DDI**	**WHO goal Barriers**

1

Epidemiology
Natural history

Global & Local

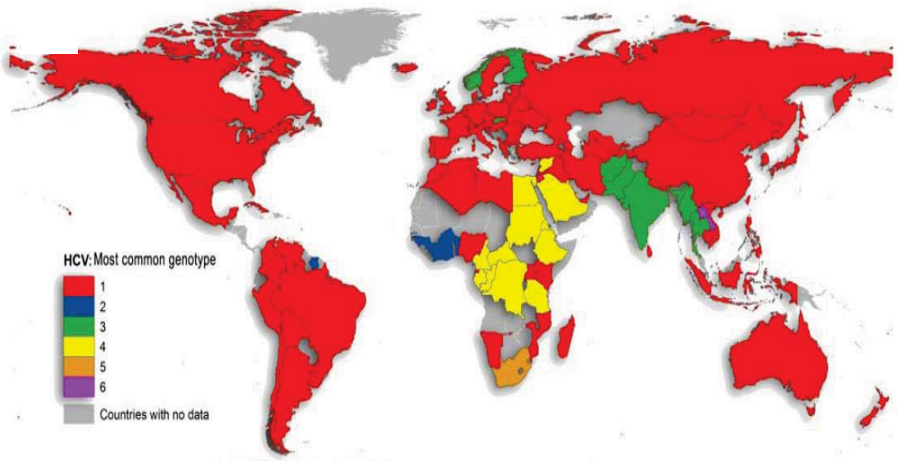
Global Prevalence and Genotype Distribution of HCV in 2015



Systemic review of HCV prevalence (n = 6,754) and genotype (n = 11,342) studies after 2013
Global prevalence: 1.0% (95% uncertainty interval 0.8-1.1)
Viremic patients: 71.1 millions (62.5-79.4)

Polaris Observatory HCV Collaborators. Lancet Gastroenterol Hepatol 2017;2:161-76

Most Common HCV Genotype Among Different Countries

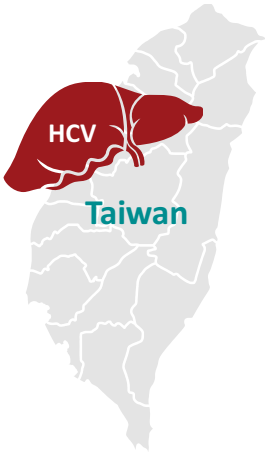


Genotype	Region
1	Worldwide, especially United States, North Europe
2	Worldwide, especially Northern Europe, Japan
3	India
4	Middle East, Africa
5	South Africa
6	Hong Kong, Southeast Asia
7	Canada , Belgium, and possibly infected in Central Africa

Messina JP, et al. Hepatology 2015;61:77-87

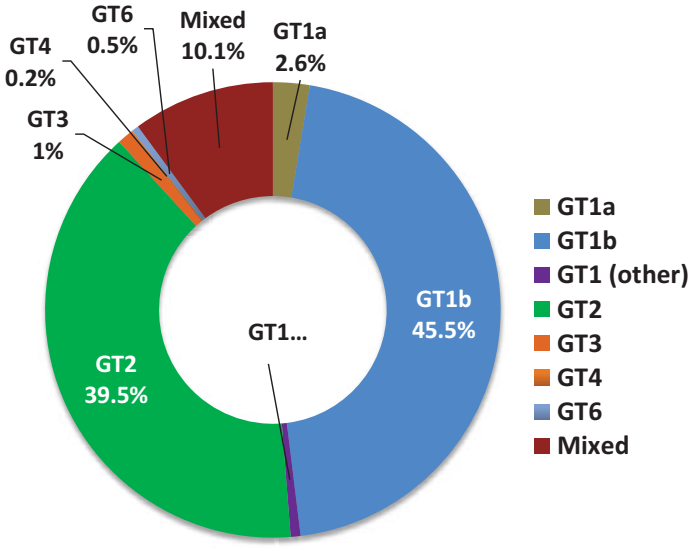
HCV Prevalence and Genotypes Distribution in Taiwan: Global Survey Polaris 2015

HCV infection is one of the leading causes of chronic hepatitis, liver cirrhosis, and HCC worldwide



HCV viremic population
489,000 [310,000-877,000]

HCV viremic prevalence
2.1% [1.3%-3.7%]

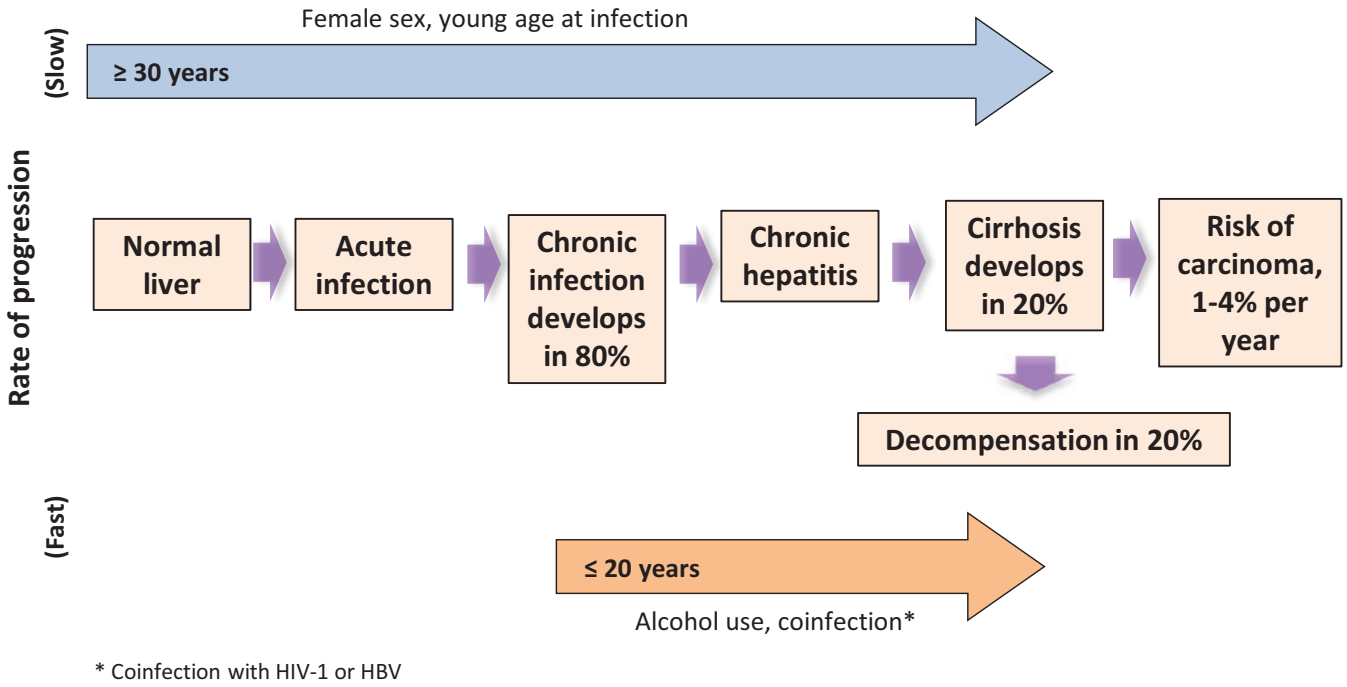


Dominant GT in Taiwan: GT1b & GT2

- Mixed types: 10.1%
- GT6 is increasing due to increasing immigrants

Polaris Observatory HCV Collaborators. Lancet Gastroenterol Hepatol 2017;2:161-76

Disease Progression in HCV



* Coinfection with HIV-1 or HBV

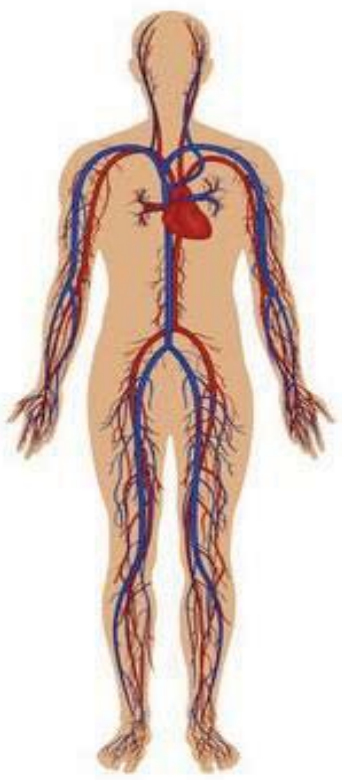
Lauer GM, et al. N Engl J Med 2001;345:41-52

Extrahepatic Manifestation of HCV Infection

CNS disorders
Chronic fatigue, subclinical cognitive impairment, psychomotoric deceleration , symptoms of depression, neurocognitive disorders, peripheral neuropathy, Parkinson's disease

Cardiovascular diseases
Cardiomyopathy, myositis

Rheumatologic disorders
Mixed cryoglobulinemia, , cryoglobulinemic vasculitis, rheumatoid arthritis, oligopolyarthritis, rheumatoid factor positivity, Sicca syndrome, uveitis



Endocrine disorders
Autoimmune thyroidopathies, CREST syndrome, insulin resistance, diabetes mellitus, growth hormone and vitamin D insufficiencies

Renal disorders
Glomerulonephritis, nephrotic syndrome

Hematologic disorders
Lymphoproliferative disorders, non-Hodgkin's lymphoma, immune thrombocytopenic purpura, monoclonal gammopathies, autoimmune hemolytic anemia, aplastic anemia

Dermatologic disorders
Palpable purpura, porphyria cutanea tarda, lichen planus, pruritus, cutaneous necrotizing vasculitis

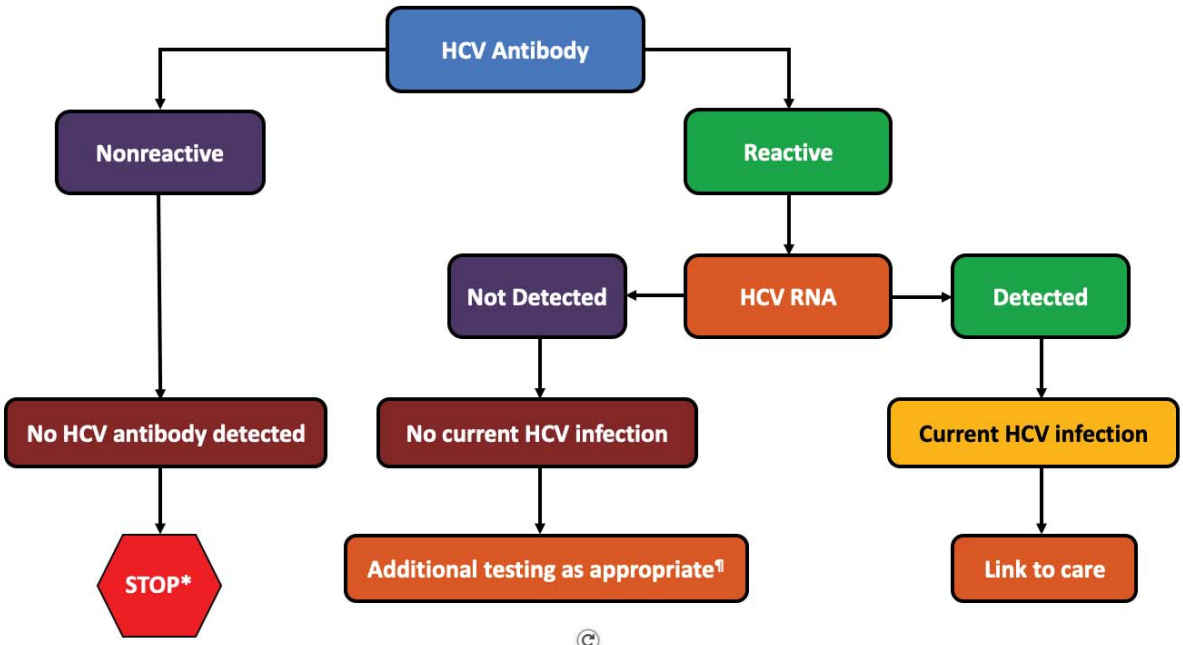
2

Diagnosis

Flow

Tool

Recommended HCV Testing Sequence for Identifying Current HCV infection



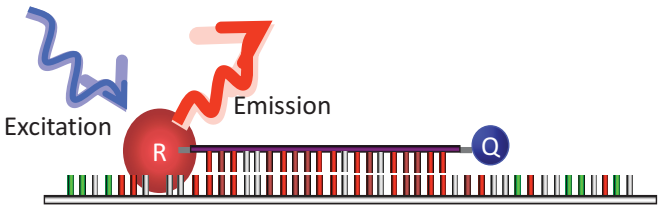
* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommend. For persons who are immunocompromised, testing for HCV RNA can be considered.

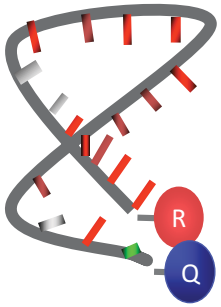
¶ To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Centers for Disease Control and Prevention (CDC). MMWR 2013;62:362–5

Commonly Used Molecular HCV RNA and Genotyping Tests

HCV RNA Assay	Limit of detection (LOD)	Dynamic range of quantification
Cobas Taqman HCV v2.0 with high pure system	10 IU/mL	25-390,000,000 IU/mL
Abbott RealTi*me* HCV assay	12 IU/mL	12-100,000,000 IU/mL
HCV Genotyping Assay	**Identifiable genotypes/subgenotypes**	
Abbott RealTi*me* HCV Genotype II	Genotype 1-6 (1a, 1b)	
Cobas HCV GT	Genotype 1-6 (1a, 1b)	





3

Implications of SVR

Viral cure

Health outcome

Goal of HCV Therapy: Straightforward !

Sustained Virologic Response (SVR)
Short term surrogate marker [off-therapy 12-24 weeks]

Functional cure
Biochemical/hematological marker improvement
Hepatic fibrosis regression
Quality of life improvement
Extra-hepatic outcome improvement

Complete cure / Sterilizing cure
Rare late relapsers following SVR
High durability (> 99%) even if at patients' immunosuppressive state
Improved survival by reducing overall mortality and morbidity

Sustained Virologic Response (SVR): A Surrogate Marker of Virologic Cure

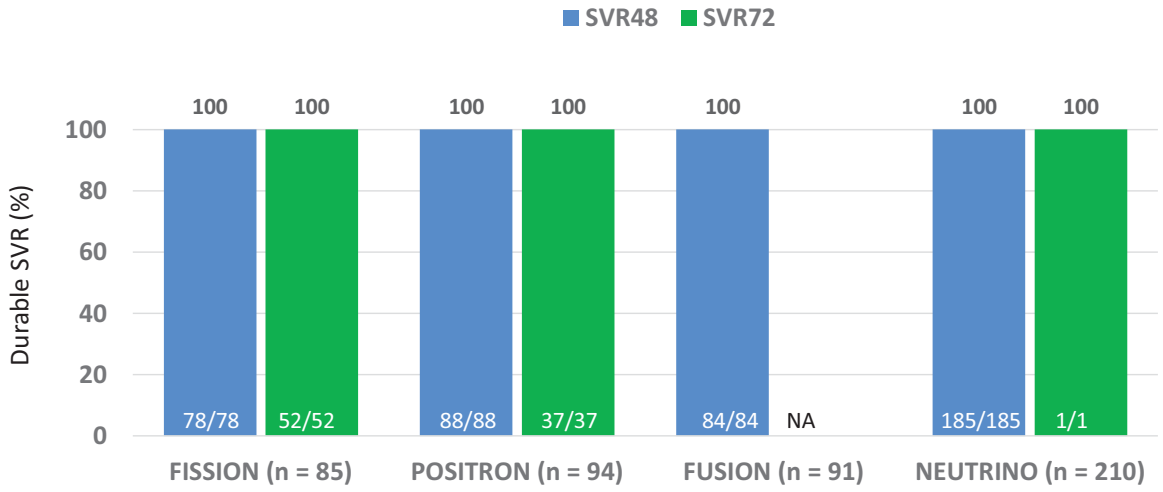
Step 1	Step 2	Step 3
		 SVR
Antiviral therapy • IFN-based: 16-72 weeks • DAA-based: 8-24 weeks	**Off-therapy HCV RNA testing** • off-therapy 12-24 weeks	 non-SVR

IFN: interferon; DAA: direct acting antiviral

SVR: sustained virologic response

- **HCV RNA testing:** by sensitive qualitative (< 50 IU/mL) or quantitative (12-15 IU/mL) tests
- **SVR_{12}:** undetectable HCV RNA 12 weeks off therapy
- **SVR_{24}:** undetectable HCV RNA 24 weeks off therapy

Long-Term Follow-Up of Patients Treated with SOF in Phase 3 Studies FISSION, POSITRON, FUSION, and NEUTRINO



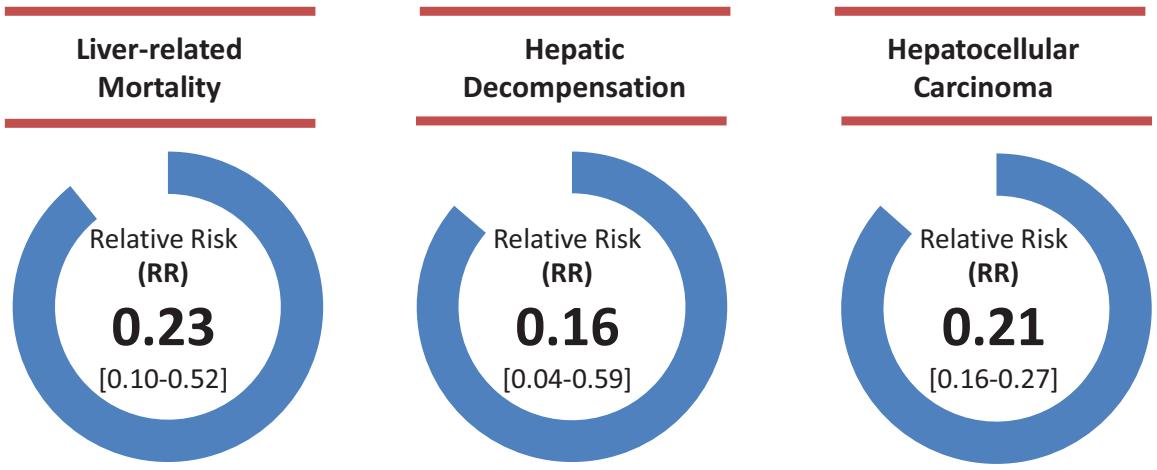
Median time of follow-up: 170 d (~24 wk) after SVR24

- 435 (91%) and 90 (19%) had post-treatment Week 48 and 72 data, respectively

Cheng W, et al. EASL 49th Annual Meeting, London, UK, 2014

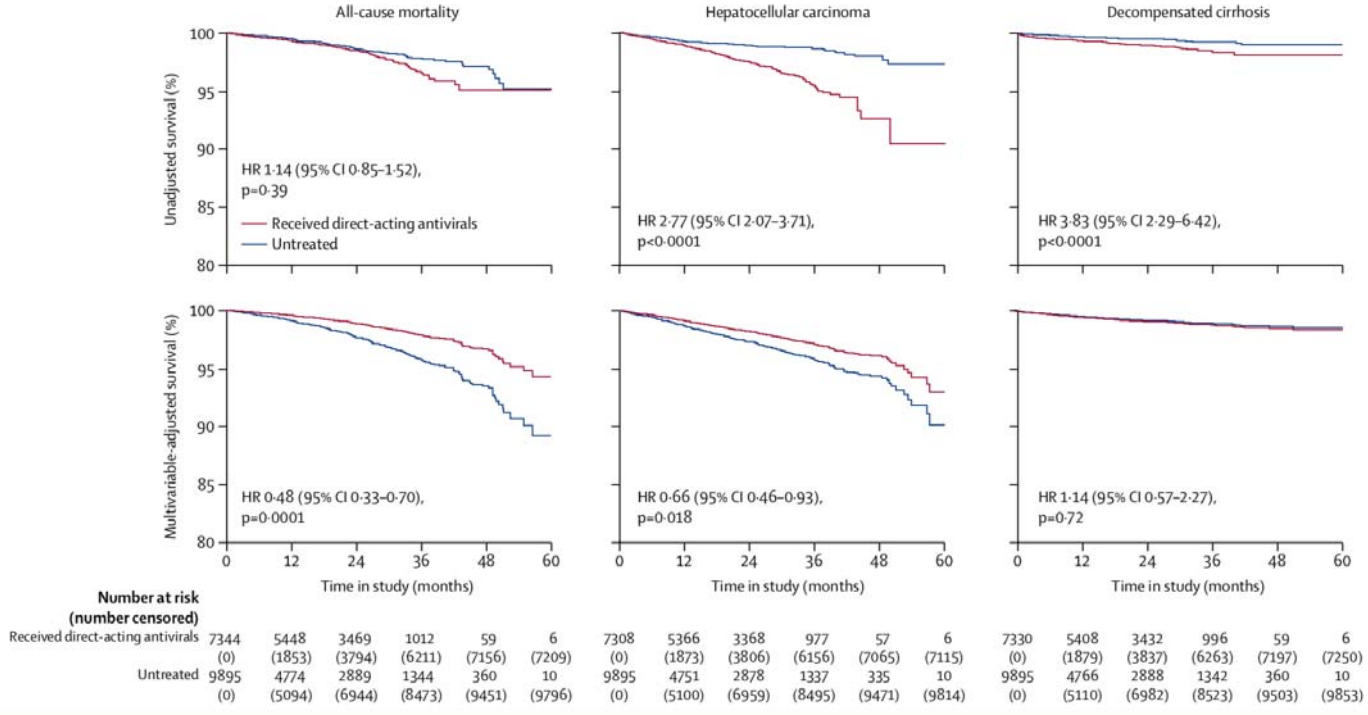
SVR is Associated with Reduced Liver-Related Morbidity and Mortality in Patients with CHC (Meta-analysis)

- **Study design:** meta-analysis of 26 studies from initial 2,276 potentially related articles
- **Relative risk (RR):** for patients with SVR, compared to those without SVR



Singal AG, et al. Clin Gastroenterol Hepatol 2010;8:280-8

Clinical Outcome in Patients with HCV after DAA Treatment: Prospective Cohort Study



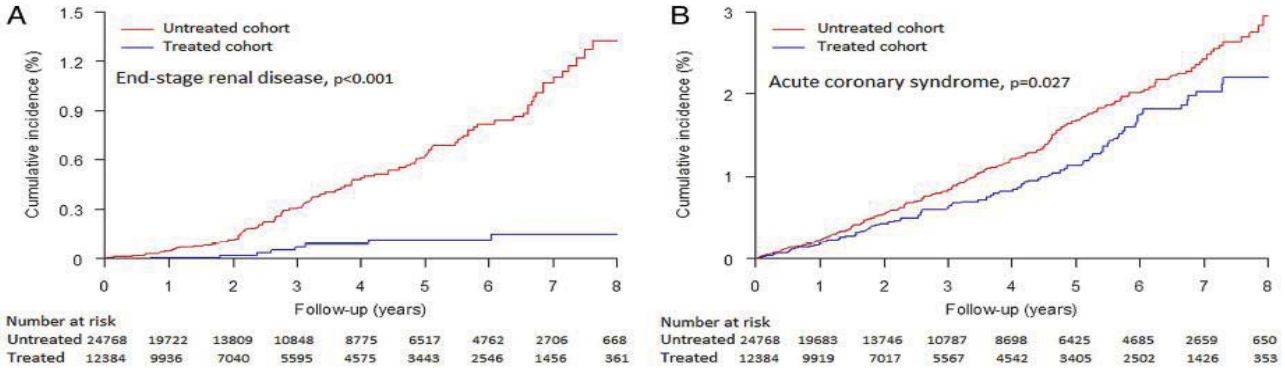
Number at risk (number censored)

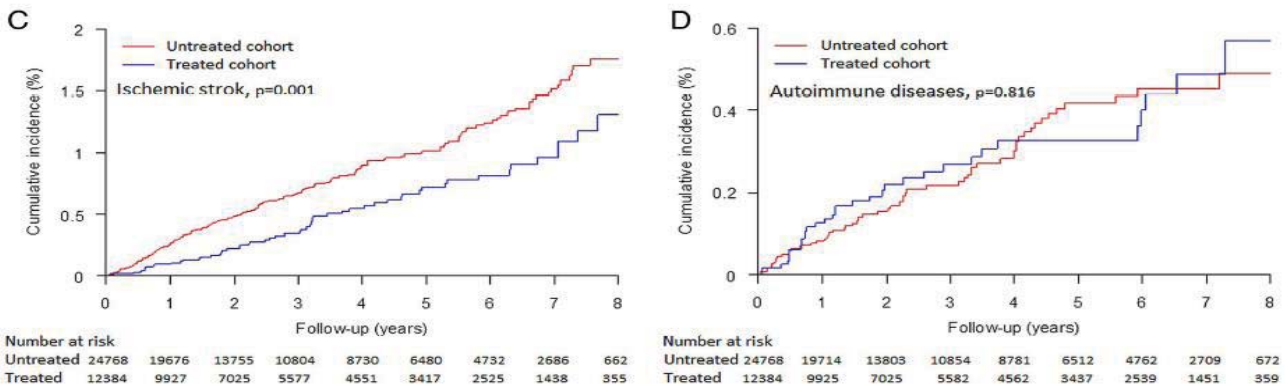
Received direct-acting antivirals	7344	5448 (1853)	3469 (3794)	1012 (6211)	59 (7156)	6 (7209)	7308	5366 (1873)	3368 (3806)	977 (6156)	57 (7065)	6 (7115)	7330	5408 (1879)	3432 (3837)	996 (6263)	59 (7197)	6 (7250)
Untreated	9895	4774 (5094)	2889 (6944)	1344 (8473)	360 (9451)	10 (9796)	9895	4751 (5100)	2878 (6959)	1337 (8495)	335 (9471)	10 (9814)	9895	4766 (5110)	2888 (6982)	1342 (8523)	360 (9503)	10 (9853)

Adjusted: age, sex, BMI, geographic origin, infection route, fibrosis score, HCV TN, HCV GT, alcohol consumption, DM, HTN, biological variables, and MELD in cirrhotic patients

Carrat F, et al. Lancet 2019;393:1453-64

Association of Antiviral Therapy and Extrahepatic Outcomes in Patients with HCV Infection





Hsu YC, et al. Gut 2015;64:495-503

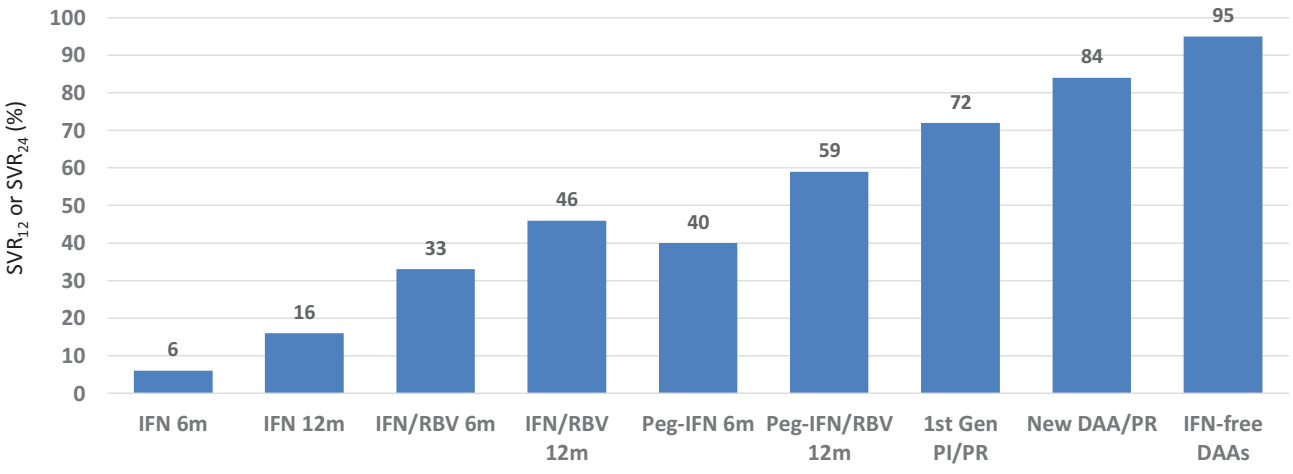
4

DAA treatment

Concept

Usual & Special Population

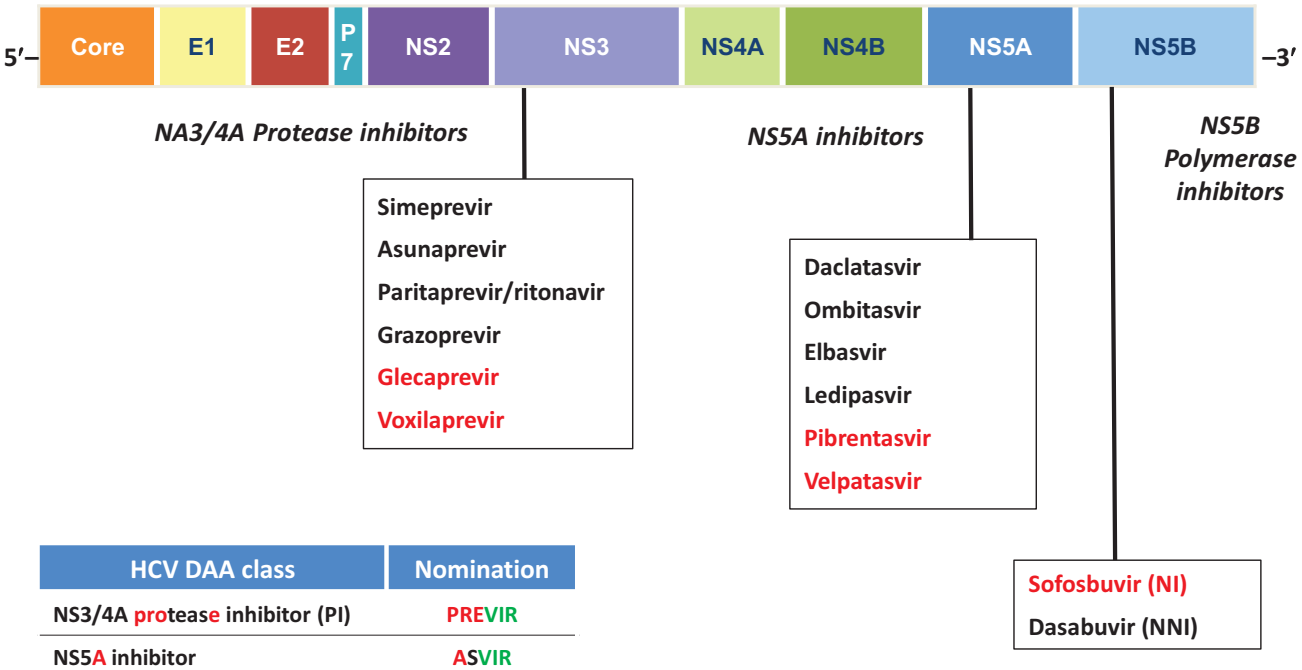
Milestones of Antiviral Therapy for Hepatitis C Virus Infection



Response-guided therapy (RGT): 2004 **IL28B genotypes: 2009** **Direct-acting antiviral agents (DAAs): 2011**
Pangenotypic IFN-free DAAs: 2016

1992-2000 ---------- 2001-2010 ---------- 2011-2013 ---------- ~ 2013

Therapeutic Targets of Licensed DAAs for HCV (Licensed)



HCV DAA class	Nomination
NS3/4A protease inhibitor (PI)	PREVIR
NS5A inhibitor	ASVIR
NS5B polymerase inhibitor	BUVIR

Cocktail combination therapy is required and mandatory !

Spectrum of Genotype/Subtype Coverage for Various Reimbursed IFN-free DAAs

DAA regimen	HCV Genotype Coverage						
Daclatasvir Asunaprevir	1a	1b	2	3	4	5	6
Paritaprevir/ritonavir Ombitasvir Dasabuvir	1a	1b	2	3	4	5	6
Grazoprevir Elbasvir	1a	1b	2	3	4	5	6
Sofosbuvir Ribavirin	1a	1b	2	3	4	5	6
Sofosbuvir Ledipasvir	1a	1b	2	3	4	5	6
Sofosbuvir Velpatasvir	1a	1b	2	3	4	5	6
Sofosbuvir Velpatasvir Voxilaprevir	1a	1b	2	3	4	5	6
Glecaprevir Pibrentasvir	1a	1b	2	3	4	5	6

The Ideal All-Oral Regimens for HCV Infection

- **Super:** excellent sustained virologic response (SVR) rates
- **Safe:** few adverse events (AEs), few drug-drug interaction
- **Simple:** low pill burden, and no complex treatment regimens
- **Shorter:** at best within weeks
- **Save:** affordable to every patient

4

DAA treatment

Concept

Usual & Special Population

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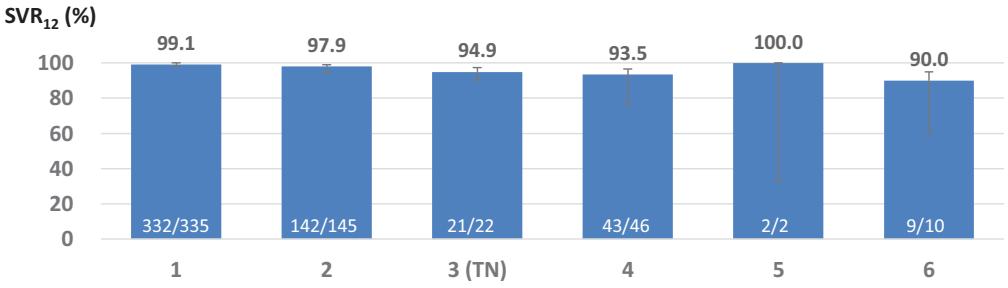
Glecaprevir Pibrentasvir	1a	1b	2	3	4	5	6

Glecaprevir/Pibrentasvir for HCV-1 to 6

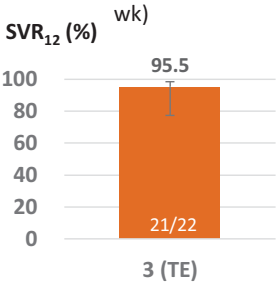
ENDURANCE-1, 3; SURVEOR-II [Part 4]

No LC; HCV-1, 2, 4, 5, 6 (TN/TE) and HCV-3 (TN) (G/P 8 wk)



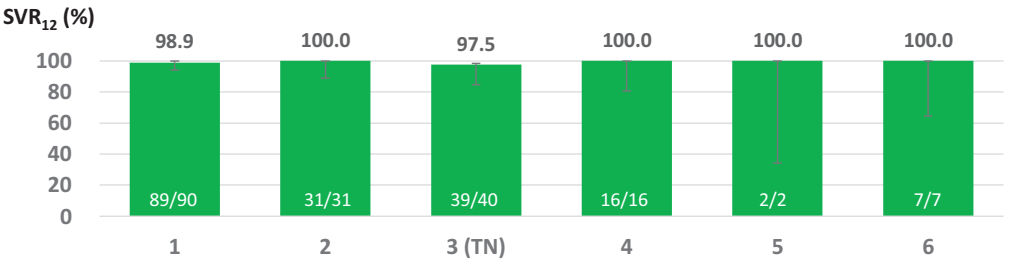
SURVEOR-II [Part 3]

No LC; HCV-3 (TE) (G/P 16 wk)



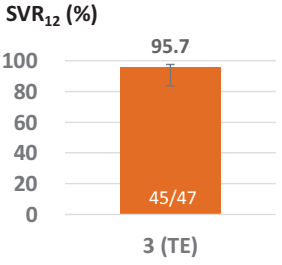
EXPEDITION-1; SURVEOR-II [Part 4]

LC; HCV-1, 2, 4, 5, 6 (TN/TE) and HCV-3 (TN) (G/P 12 wk)



SURVEOR-II [Part 3]

LC; HCV-3 (TE) (G/P 16 wk)

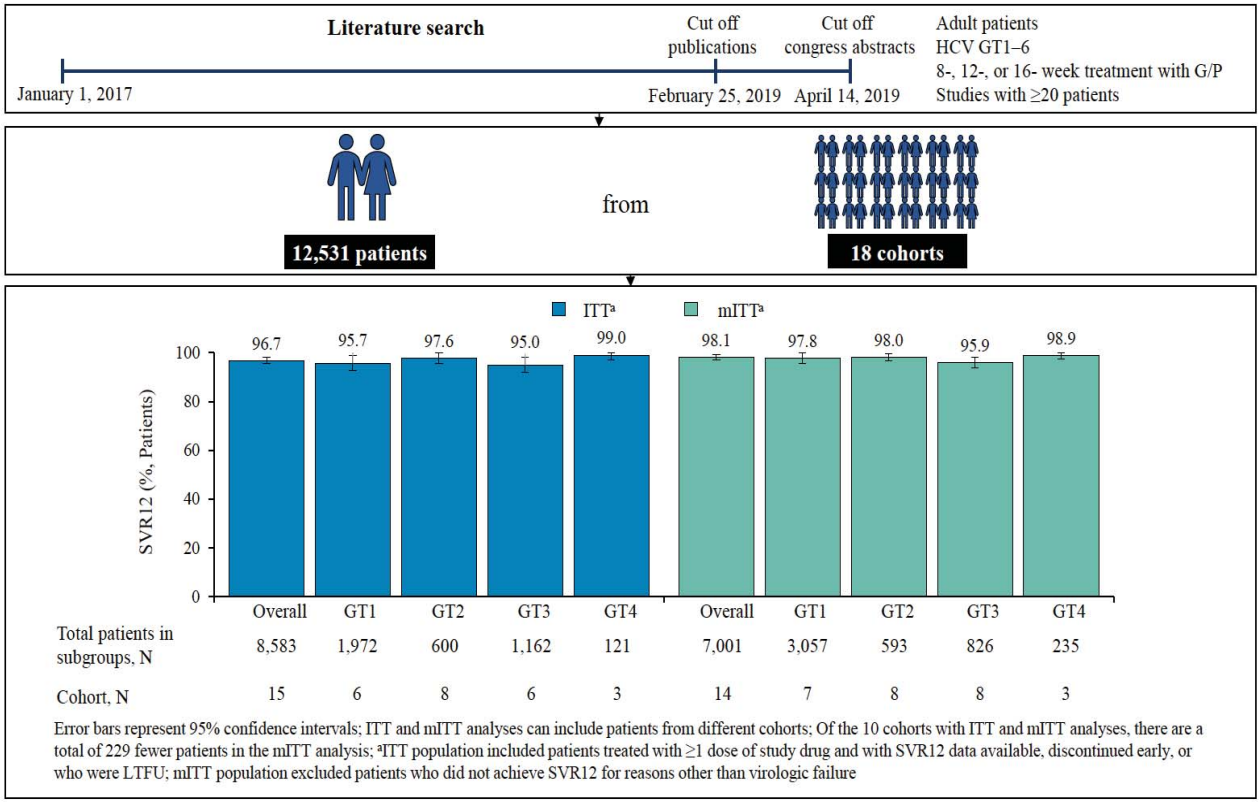


Zeuzem S, et al. N Engl J Med 2018;378:354-69

Asselah T, et al. Clin Gastroenterol Hepatol 2018;16:417-26

Wyles D, et al. Hepatology 2018;67:514-23

Real-World Effectiveness and Safety of GLE/PIB for HCV: Meta-analysis



Error bars represent 95% confidence intervals; ITT and mITT analyses can include patients from different cohorts; Of the 10 cohorts with ITT and mITT analyses, there are a total of 229 fewer patients in the mITT analysis; [a]ITT population included patients treated with ≥1 dose of study drug and with SVR12 data available, discontinued early, or who were LTFU; mITT population excluded patients who did not achieve SVR12 for reasons other than virologic failure

Lampertico P, et al. J Hepatol 2020;72:1112-21

Spectrum of Genotype/Subtype Coverage for Various Reimbursed IFN-free DAAs

DAA regimen	HCV Genotype Coverage						
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Sofosbuvir Velpatasvir Voxilaprevir	1a	1b	2	3	4	5	6
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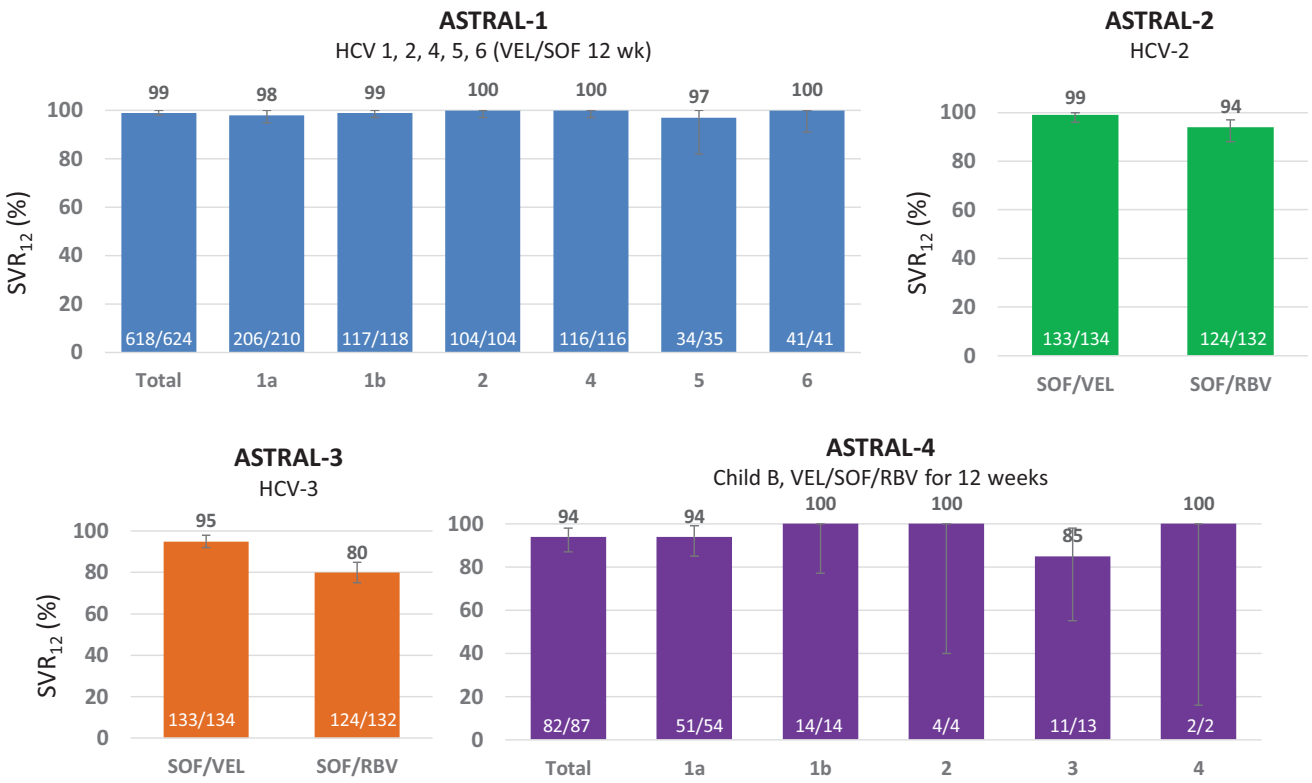
Velpatasvir/Sofosbuvir ± RBV for HCV-1 to 6

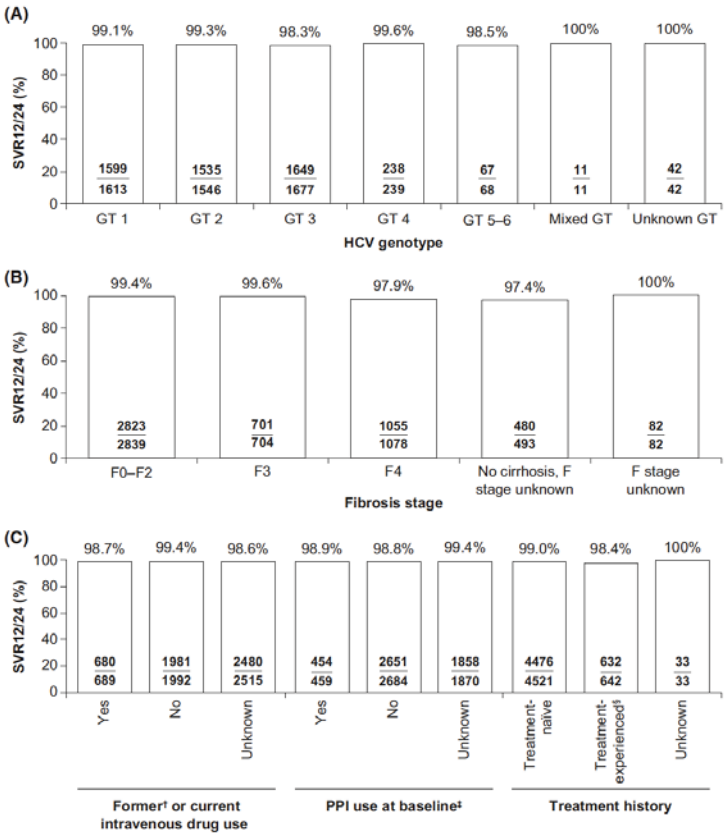


Feld JJ, et al. N Engl J Med 2015;373:2599-607

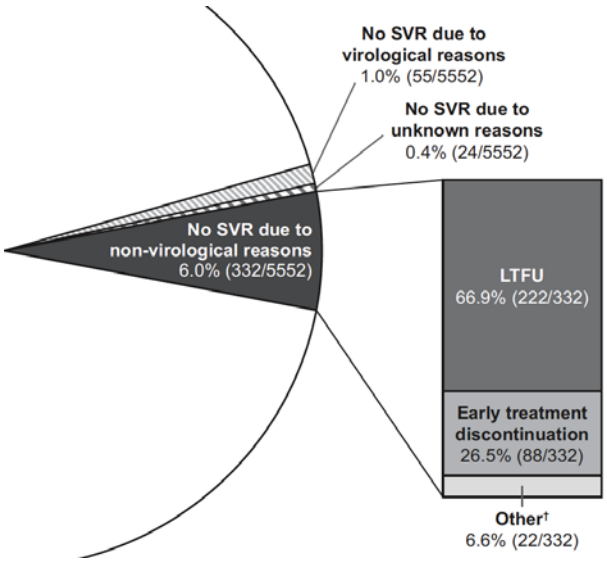
Foster GR, et al. N Engl J Med 2015;373:2608-17

Curry MP, et al. N Engl J Med 2015;373:2018-28

Global Real-World Evidence of Sofosbuvir/Velpatasvir: Analysis of 12 Practice Cohorts



Overall $SVR_{12/24}$: 92.6% (5141/5552)



Mangia A, et al. Liver Int 2020;40:1841-52

Recommended DAA Regimens for HCV

Characteristics	Sofosbuvir/Velpatasvir (SOF/VEL, Epclusa)	Glecaprevir/Pibrentasvir (GLE/PIB, Maviret)
DAA class	NS5A NS5B NUC	NS3 NS5A
Genotype coverage	1-6	1-6
DAA Daily pills	1	3
Treatment duration (wk)	12	8-16
DAA Daily pills	1	3
Contraindication	-	Child-Pugh B/C cirrhosis
Regimen (based on fibrosis)		
F0-3	SOF/VEL 12 wk	GLE/PIB 8 wk
F4 (Child-Pugh A)	SOF/VEL 12 wk	GLE/PIB 8 wk (TN) GLE/PIB 12 wk (TN)
F4 (Child-Pugh B/C)	SOF/VEL + RBV 12 wk	-
Special interest for GLE/PIB		
GT-3, TE (F0-F4 Child-Pugh A)	-	GLE/PIB 16 wk
GT-1, DAA failure, NS5A-containing only	-	GLE/PIB 16 wk
Overall SVR_{12}	95%-99%	95%-100%
Tolerability	Excellent	Good to excellent
Drug-drug interaction	Lower	Higher

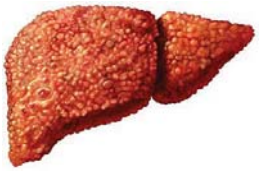
4

DAA treatment

Concept

Usual & Special Population

Challenges with Treating Decompensated Cirrhosis



Child-Pugh B or C cirrhosis

- **Poor 5-year survival:** approximately only 50%
- **Shortage of graft donation**
- **Recurrent HCV infection after transplantation**
- **SVR attained:** improved clinical outcome, irrespective of transplantation or not
- **NS3/4A protease inhibitors (DAA)**
  - Watchful use and frequent monitoring of decompensation in Child-Pugh A cirrhosis
  - **Contraindicated** in Child-Pugh B/C cirrhosis

Mauss S, et al. Hepatology: A Clinical Textbook. 8th Ed. Medizin Fokus Verlag, 2017
Gamboto M, et al. J Hepatol 2014;61:S120-31

Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis: ASTRAL-4 Study

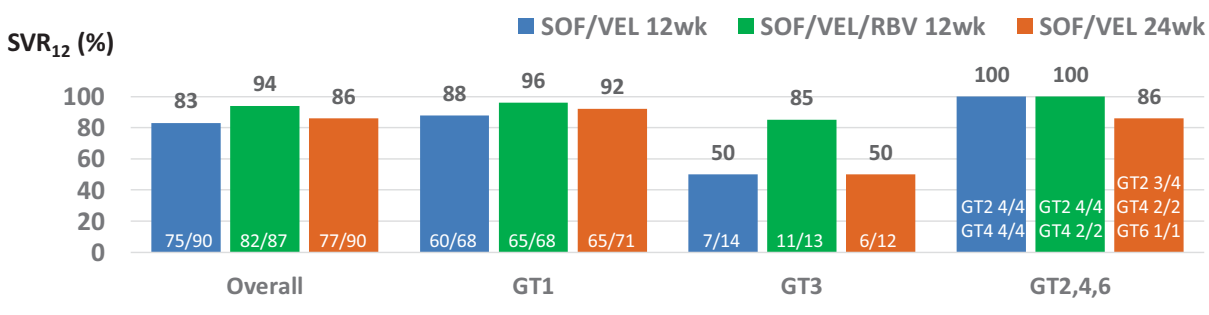
267 **HCV GT 1-6 Child B cirrhosis**

Phase 3, open-label, randomized study SOF/VEL for 12 wk (n = 90) or 24 wk (n = 90), or SOF/VEL +weight-based RBV for 12 wk (n = 87)

Non-SVR$_{12}$

- **Virologic failure**
  - SOF/VEL 12 wk: 11/90 (12%)
  - SOF/VEL/RBV 12 wk: 3/87 (3%)
  - SOF/VEL 24 wk: 8/90 (9%)

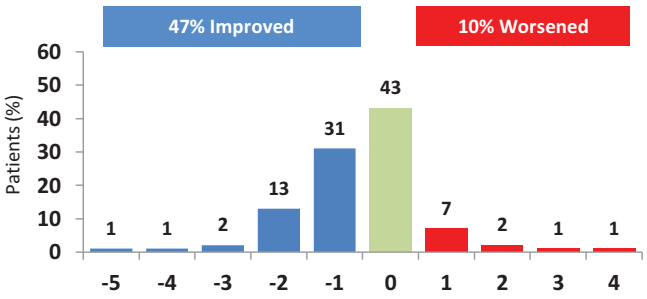
- **SVR$_{12}$ rate**
- **Child-Pugh or MELD score improvement**



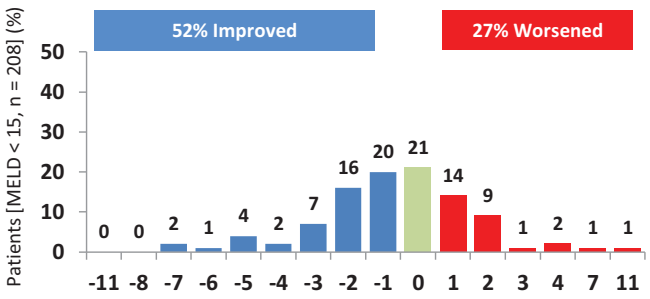
Curry MP, et al. N Engl J Med 2015;373:2018-28

Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis: ASTRAL-4 Study

CPT Score Change: Baseline to FU Week 12 (Patients with SVR12*)



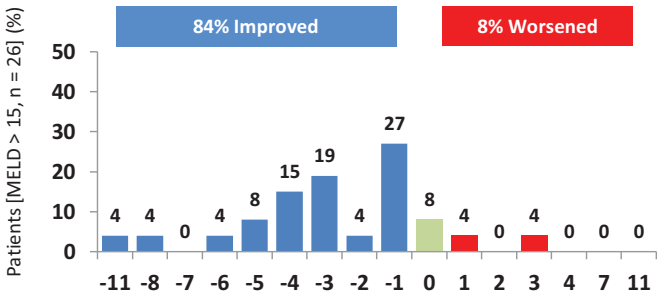
MELD Change: Baseline to FU Week 12 (Patients with SVR12*)



		FU Week 12, % (n/n)		
		CPT A	CPT B	CPT C
Baseline	CPT A	71 (10/14)	29 (4/14)	0 (0/14)
	CPT B	17 (34/205)	81 (167/205)	2 (4/205)
	CPT C	10 (1/10)	50 (5/10)	40 (4/10)

n = 234, 5 patients had no FU

MELD Change: Baseline to FU Week 12 (Patients with SVR12*)

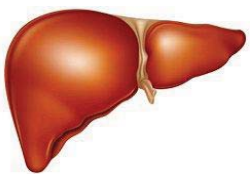


Curry MP, et al. N Engl J Med 2015;373:2018-28

Liver Transplant Patients: the Challenge

HCV+ Recipient

HCV+/- Donor



- **Recurrence:** universal in patients who are HCV-positive at the time of transplant
- **Course after recurrence:** accelerated
  - 30% of patients with chronic recurrent disease will develop cirrhosis within 5 years post-transplant
  - 40% of patients with cirrhosis post-transplant will experience graft loss within a year
- **Treatment regimens:** complex, drug-drug interactions (DDIs) between HCV NS3/4A protease inhibitors and calcineurin inhibitors (need for frequent dose monitoring and adjustment)

Forman LM, et al. Gastroenterology 2002; 122:889–96
Garcia-Retortillo M, et al. Hepatology 2002; 35:680–7
Gonzalez S. Gastroenterol Hepatol 2010; 6:637–45
Gambato M, et al. J Hepatol 2014; 61:S120–31

Glecaprevir/Pibrentasvir for Liver or Renal Transplant Adults with HCV Genotype 1-6 Patients: MAGELLAN-2

100 recurrent HCV GT 1-6 liver or renal transplant patient
Phase 3, open-label study of GLE/PIB for 12 weeks

- SVR_{12} rate
- Safety

DAA-related serious AEs: 2 (2%)

Discontinuation due to DAA-related AE: 0 (0%)

1.0% **T-BIL ≥ 3.0 × ULN**

1.0% **ALT ≥ 3.0 × ULN**

2.0% **CrCL < 30 mL/min/1.73m²**

SVR_{12} [ITT] 98% (98/100)

SVR_{12} [mITT] 99% (98/99)

Non-SVR_{12}

- Relapse (n = 1): 3a
- LTFU (n = 8)

Reau N, et al. Hepatology 2018;68:1298-307

Sofosbuvir/Velpatasvir for HCV Genotype 1-4 Liver Transplant Recipients

79 recurrent HCV GT 1-4 liver transplant patient
Phase 3, open-label study of SOF/VEL for 12 weeks

- SVR_{12} rate
- Safety

DAA-related serious AEs: 0 (0%)

Discontinuation due to AE: 1 (1%), hyperglycemia

SVR_{12} [ITT] 96% (76/79)

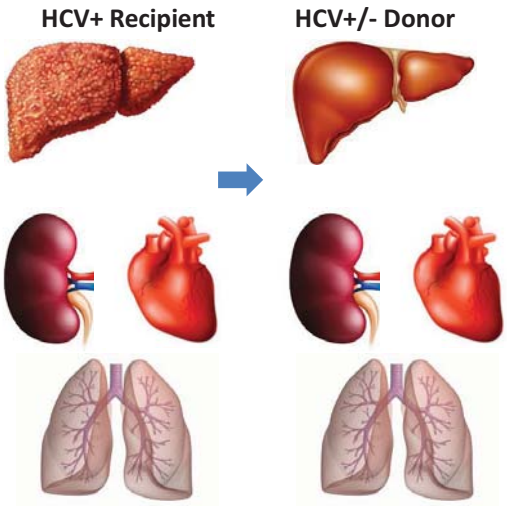
Non-SVR_{12}

- Relapse (n = 2): 1a and 3
- Discontinue (n = 1): 1b

Agarwal K, et al. J Hepatol 2018;69:603-7

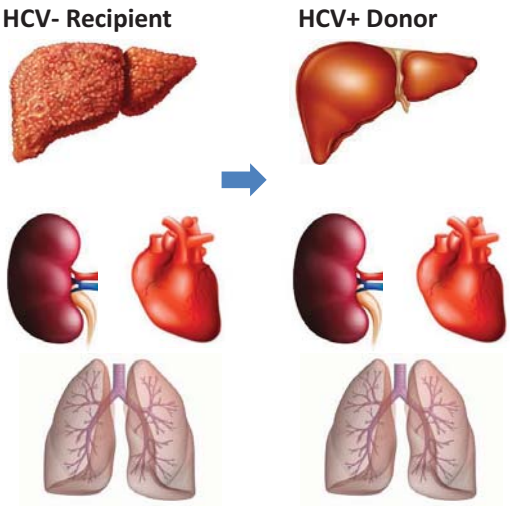
Potential Role of DAAs in Solid Organ Transplantation

Recurrent HCV Infection
HCV Superinfection



Recurrent infection (acute): prophylaxis (?), preemptive (?) DAAs (level III)
Recurrent infection (chronic): DAA (level I)
HCV superinfection: DAAs (level I)

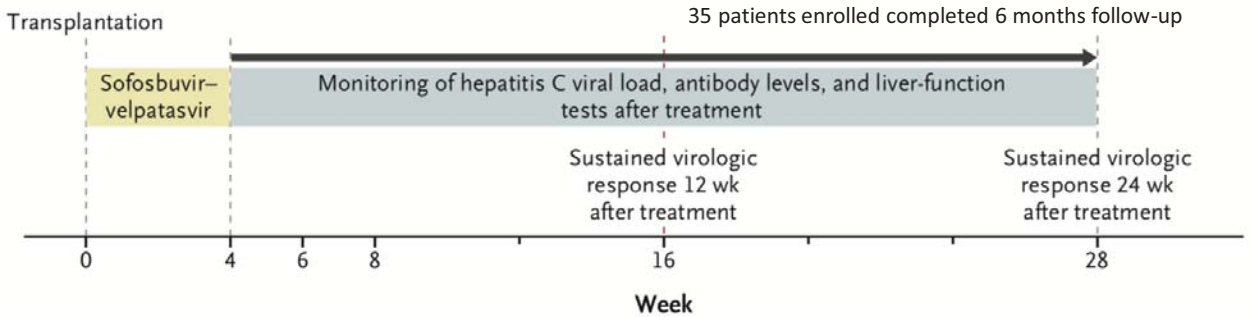
***De novo* HCV Infection**

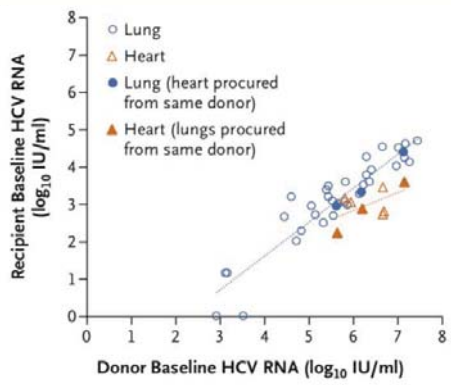


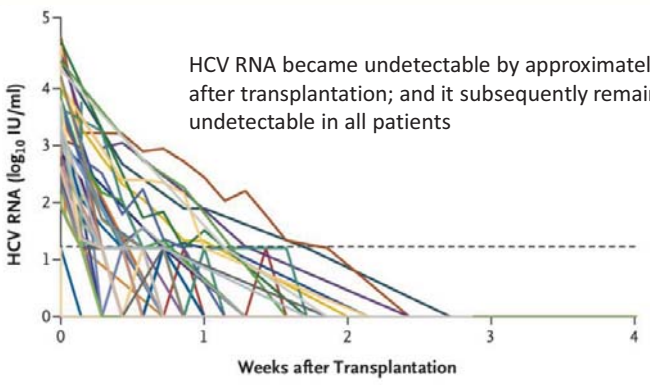
De novo infection (acute): prophylaxis (?), preemptive (?) DAAs (level III)
De novo infection (chronic): DAA (level I)

Heart and Lung Transplant from HCV Infected Donors to Uninfected Recipients: DONATE HCV Trial

- **Design (N = 44):** pre-emptive sofosbuvir/velpatasvir for 4 weeks, a few hours after heart (n = 8) and lung (n = 36) transplantation



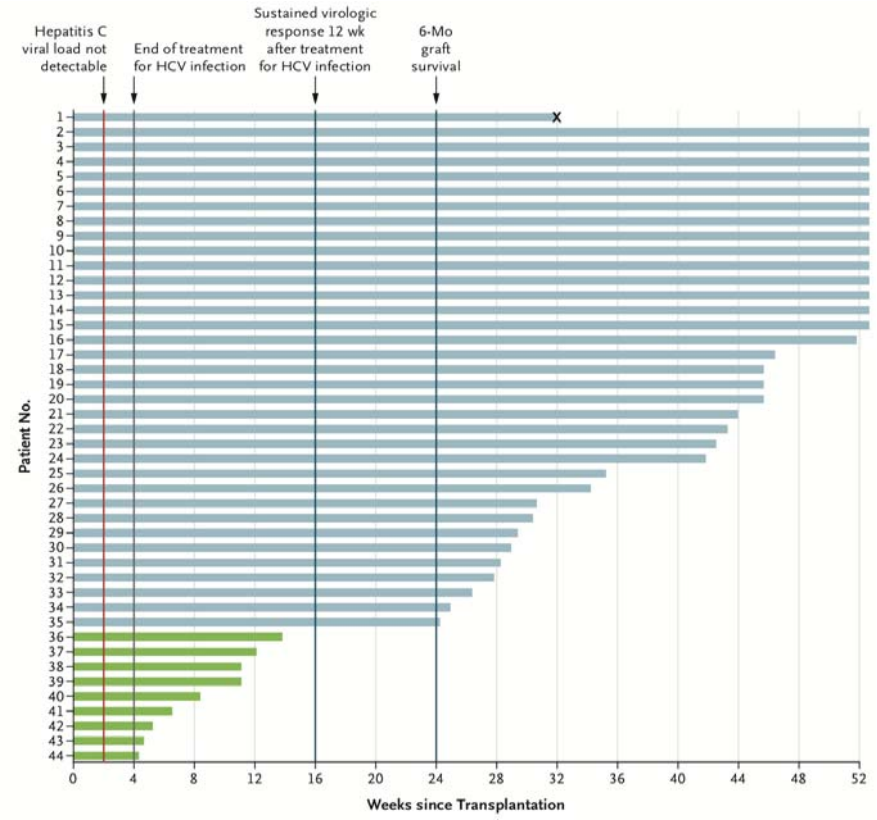




HCV RNA became undetectable by approximately 2 weeks after transplantation; and it subsequently remained undetectable in all patients

Woolley AE, et al. N Engl J Med 2019;380:1606-17

Heart and Lung Transplant from HCV Infected Donors to Uninfected Recipients: DONATE HCV Trial



Results of Patient Follow-up after Transplantation

The black X indicates that Patient 1 died at week 32. The green bars represent patients who had not completed 16 weeks of follow-up by July 31, 2018

SVR_{12}: 35/35 (100%) [95% CI: 90-100]

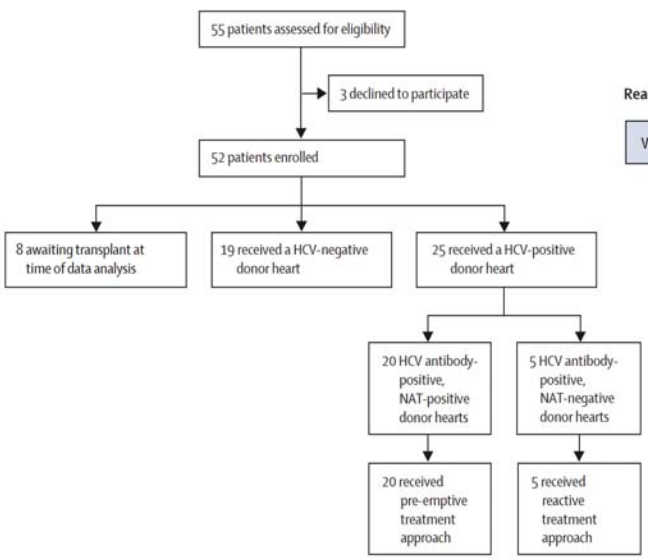
Safety:

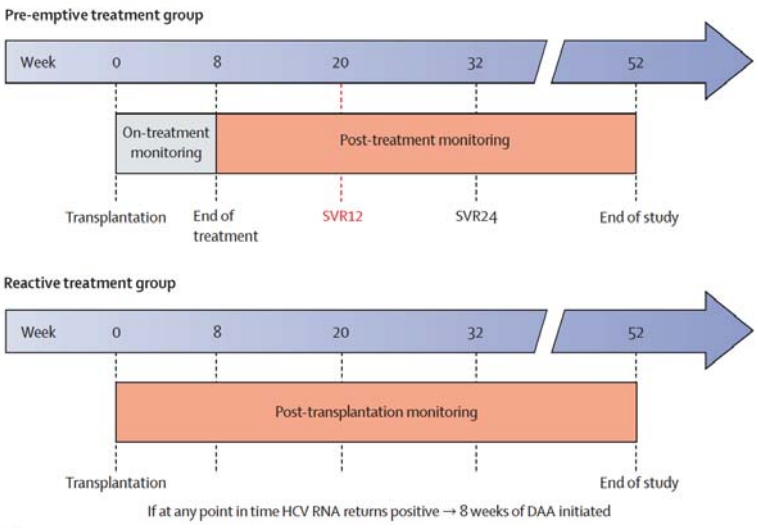
1) No treatment-related serious adverse events identified.
2) More cases of acute cellular rejection in lung-transplant recipients receiving SOF/VEL, but the difference was not significant after adjustment for possible confounders.

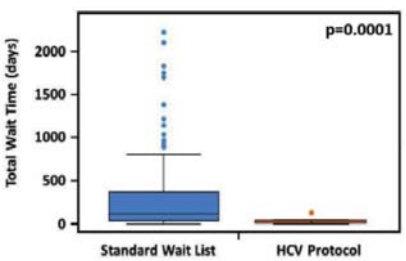
Woolley AE, et al. N Engl J Med 2019;380:1606-17

Preemptive DAA Therapy in Donor HCV-Positive to HCV-Negative Cardiac Transplantation

- **Design:** open-label, single arm, proof of concept study; G/P treatment before being transported to operation room, total DAA treatment 8 weeks; NAT (+) donors to HCV-negative recipients







- **HCV protocol: 20 days (IQR: 8-57)**
- **Standard wait list: 113 days (IQR: 40-366)**

Bethea E, et al. Lancet Gastroenterol Hepatol 2019;4:771-80

Preemptive DAA Therapy in Donor HCV-Positive to HCV-Negative Cardiac Transplantation

	eGFR (mL/min per 1·73 m²)	Time from HCV-positive consent to transplantation (days)	Donor NAT	Donor genotype	Donor viral load (IU/mL)	Peak recipient viral load (IU/mL)	Time to unquantifiable or undetectable viral load (days)	SVR12*
1	50	20	+	1a	36 000	0	0	Yes
2	>60	10	+	1a	13 000 000	1100	3	Yes
3	45	8	–	NA	Undetectable (NAT–)	Undetectable (NAT–)	Undetectable (NAT–)	NA
4	38	79	+	1a	7 640 000	458	1	Yes
5	45	83	+	3	2 540 000	0	0	Yes
6	47	1	+	1a	6 070 000	498	8	Yes
7	12†	2	+	1a	3 760 000	213	7	Yes
8	>60	9	+	1a	2 450 000	1060	9	Yes
9	>60	37	+	1a	4 620 000	409	7	Yes
10	>60	130	+	1	1 010 000	0	0	Yes
11	35	1	+	Indeterminant	232	0	0	Yes
12	>60	1	+	3	446 000	0	1	Yes
13	28	27	–	NA	Undetectable (NAT–)	Undetectable (NAT–)	Undetectable (NAT–)	NA
14	39	25	+	Indeterminant	9 930 000	7300	14	Yes
15	42	10	–	NA	Undetectable (NAT–)	Undetectable (NAT–)	Undetectable (NAT–)	NA
16	20	17	–	NA	Undetectable (NAT–)	Undetectable (NAT–)	Undetectable (NAT–)	NA
17	30†	41	+	1a	4200000	643	14	Yes
18	28	2	–	NA	Undetectable (NAT–)	Undetectable (NAT–)	Undetectable (NAT–)	NA
19	>60	57	+	Indeterminant	420	0	0	Yes
20	>60	60	+	1b	>100 000 000	5110	14	Yes
21	>60	78	+	Indeterminant	5 610 000	892	4	Yes
22	>33	2	+	1a	1 060 000	123	7	Yes
23	>60	264	+	1a	3 210 000	0	0	Yes
24	40	14	+	1a	1930	0	0	Yes
25	>60	37	+	1a	37 000 000	2190	17	Yes

- No treatment-related AE or HCV-attributable AEs or SAEs
- No drug reactions or interactions have necessitated a relapse or cessation of therapy
- Patient and allograft survival: 100% at a median follow-up of 10.7 months [range 6.5-10.8]

Bethea E, et al. Lancet Gastroenterol Hepatol 2019;4:771-80

Glecaprevir/Pibrentasvir for HCV GT 1-6 Patients with Renal Impairment: EXPEDITION-4

104 HCV GT 1-6 patient with CKD stage 4 or 5
Phase 3, open-label study of GLE/PIB for 12 weeks

- SVR_{12} rate
- Safety

DAA-related serious AEs: 0 (0%)

Discontinuation due to AE: 4 (4%)

0% **T-BIL ≥ 3.0 × ULN**

1.0% **ALT ≥ 3.0 × ULN**

SVR_{12} [ITT]: 98% (102/104)

SVR_{12} [mITT]: 100% (102/102)

Non-SVR_{12}

- Discontinue (n = 1)
- LTFU (n = 1)

Gane E, et al. N Engl J Med 2017;377:1448-55

Sofosbuvir/Velpatasvir for 12 Weeks in Patients on Dialysis

59 **HCV GT 1-6 patient with CKD stage 5 on HD or PD**
Phase 2, open-label study of SOF/VEL for 12 weeks

- **SVR_{12} rate**
- **Safety**

DAA-related serious AEs: 0 (0%)

Discontinuation due to AE: 0 (0%)

Death: 2 (3%)

- Suicide at SVR_4
- Metastatic lung cancer after SVR_{12}

SVR_{12} [ITT] 95% (56/59)

SVR_{12} [mITT] 97% (56/58)

Non-SVR_{12}

- Relapse (n = 2)
- Suicide (n = 1)

Borgia SM, et al. J Hepatol 2019;71:660-5

Sofosbuvir/Ledipasvir for Patients with Chronic Hepatitis C and B Coinfection

111 **HCV GT 1 or 2 patient with HBV/HCV confection**
Phase 3, open-label study of SOF/LDV for 12 weeks in Taiwan

- **SVR_{12} rate**
- **Safety**

DAA-related serious AEs: 0 (0%)

Discontinuation due to AE: 4 (4%)

HBV reactivation: 70 (63%)

- **4.5% ALT > 2.0 × ULN**

SVR_{12} [ITT] 100% (111/111)

Predictor of HBV reactivation

(HBV DNA > 1 $\log_{10}$ increase and ALT > 2X ULN)

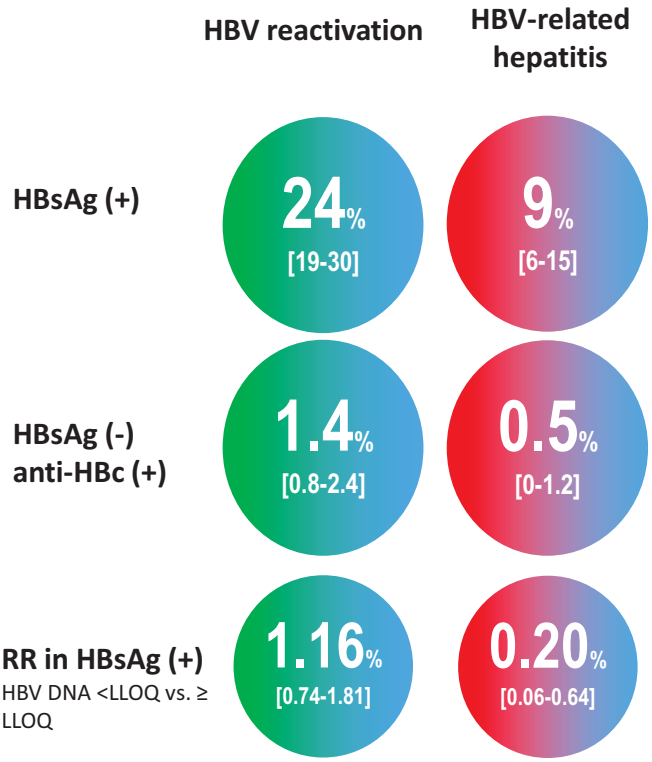
- **Mean baseline ALT**
- **Mean baseline HBV DNA**

Liu CJ, et al. Gastroenterology 2018;154:989-97

HBV Reactivation during DAA Therapy for Hepatitis C: Systemic Review and Meta-Analysis

1,621 HCV patient with HBV/HCV confection (242 HBsAg +; 1,379 resolved HBV infection) from 17 studies

- **HBV reactivation**
  - **HBsAg (+):** increase ≥ $2\log_{10}$ HBV DNA or > 100 IU/mL with baseline undetectable level
  - **HBsAg (-)/anti-HBc (+):** reverse HBsAg seroconversion or detectable HBV DNA
- **HBV-related hepatitis**
  - ALT ≥ 2X ULN in combination with molecular reactivation



Mücke MM, et al. Lancet Gastroenterol Hepatol 2018;3:172-80

Glecaprevir/Pibrentasvir for HCV GT 1-6/HIV-1 Co-Infected Patients: EXPEDITION-2

153 HCV GT 1-6 patient with HIV-1 coinfection
Phase 3, open-label study of GLE/PIB for 8 (n = 137) or 12 (n = 16) weeks

- SVR_{12} rate
- Safety

SVR_{12} [ITT]: 98% (150/153)

SVR_{12} [mITT]: 99% (150/151)

DAA-related serious AEs: 0 (0%)

Discontinuation due to AE: 1 (0.7%)

0.7% **T-BIL ≥ 3.0 × ULN**

0% **ALT ≥ 5.0 × ULN**

Non-SVR_{12}

- Breakthrough (n = 1): 3a, cirrhosis
- Discontinue (n = 1)
- LTFU (n = 1)

Rockstroh JK, et al. Clin Infect Dis 2018;67:1010-7

Sofosbuvir/Velpatasvir in Patients Coinfected with HCV & HIV-1: ASTRAL-5

106 HCV GT 1-6 patient with HIV-1 coinfection
Phase 3, open-label study of SOF/VEL for 12 weeks

- SVR_{12} rate
- Safety

DAA-related serious AEs: 0 (0%)

Discontinuation due to AE: 2 (2%)

Death: 0 (0%)

SVR_{12} [ITT]: 97% (103/106)

SVR_{12} [mITT]: 98% (103/105)

Non-SVR_{12}

- Relapse (n = 2): 1a
- Withdrew consent (n = 1)

Wyles D, et al. Clin Infect Dis 2017;65:6-12

SOF/VEL/VOX for 12 Weeks in NS5A Inhibitor-Experienced HCV GT 1-6: POLARIS-1

263 HCV GT 1-6 patient with prior NS5A DAA failure
Phase 3, open-label, randomized study of SOF/VEL/VOX (n = 263) or placebo (n = 152) for 12 weeks

- SVR_{12} rate
- Safety

Serious AEs: 5 (2%)

Discontinuation due to AE: 1 (< 1%)

Death: 0 (0%)

SVR_{12} [ITT]: 96% (253/263)

99% (140/142) Non-cirrhosis

93% (113/121) Cirrhosis

Non-SVR_{12}

- Breakthrough (n = 1)
- Relapse (n = 6)
- LTFU (n = 1)
- Withdrew consent (n = 2)

Bourliere M, et al. N Engl J Med 2017;376:2134-46

Glecaprevir/Pibrentasvir for Adolescents with Chronic Hepatitis C: DORA Part 1 Study

47 HCV GT 1-4 patient aged 12-17 years
Phase 2/3, open-label study of GLE/PIB as adults

SVR_{12} [ITT]

100% (47/47)

- SVR_{12} rate
- Safety

Pharmacokinetic studies for GLE/PIB

(adolescents vs. adults)

- **GLE: comparable**
- **PIB: comparable**

DAA-related serious AEs: 0 (0%)

Discontinuation due to AE: 2 (2%)

0% T-BIL ≥ 3.0 × ULN

0% ALT ≥ 5.0 × ULN

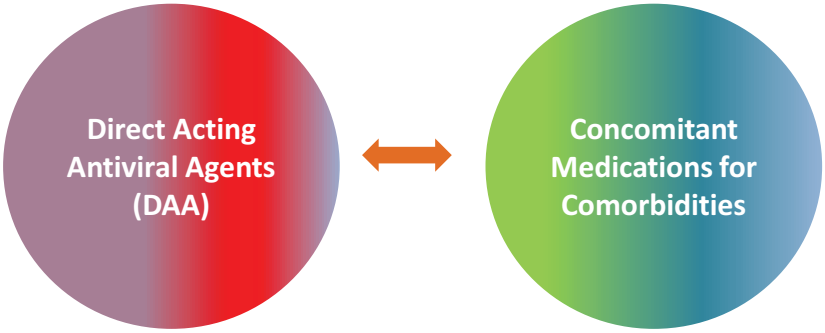
Jonas MM, et al. Hepatology 2020;71:456-62

5

DDI

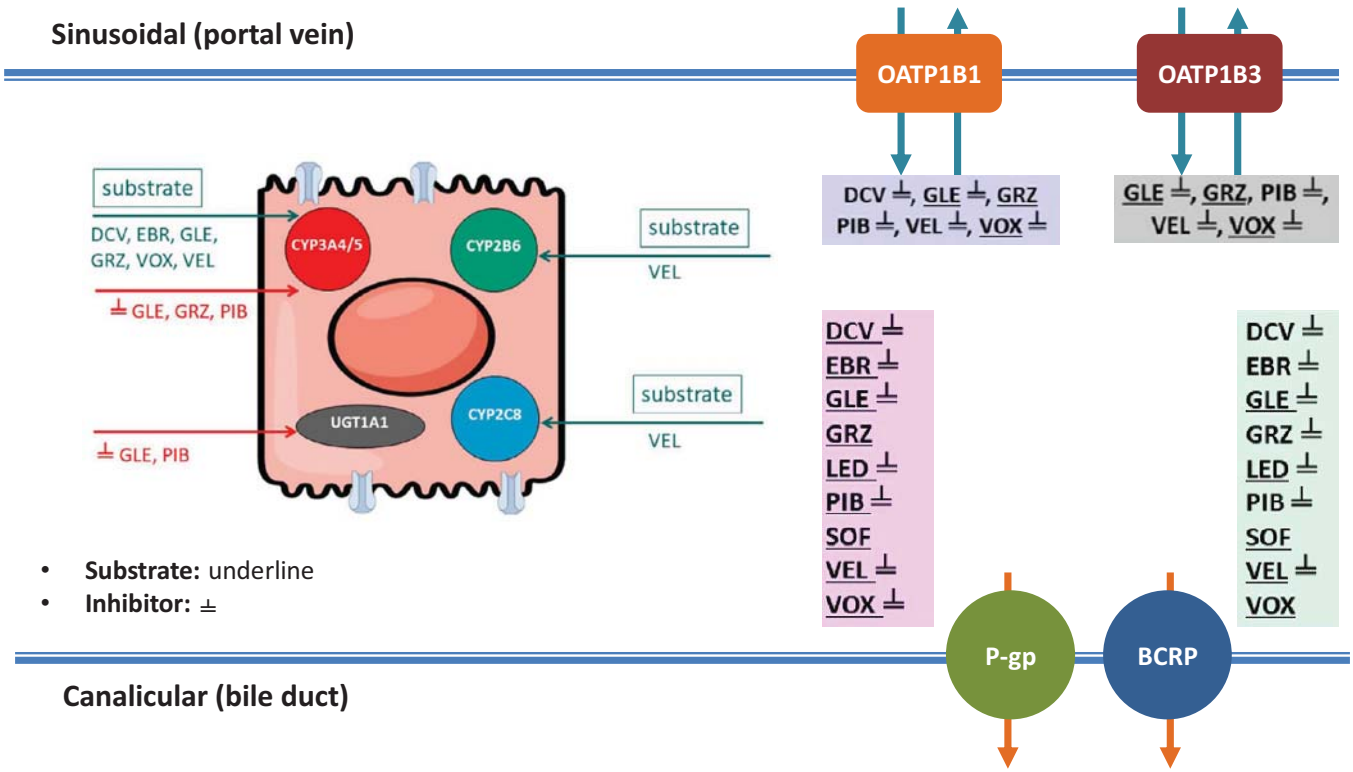
Concept
Red flag DDI

Potential Interactions of DAAs for HCV and Concomitant Medications



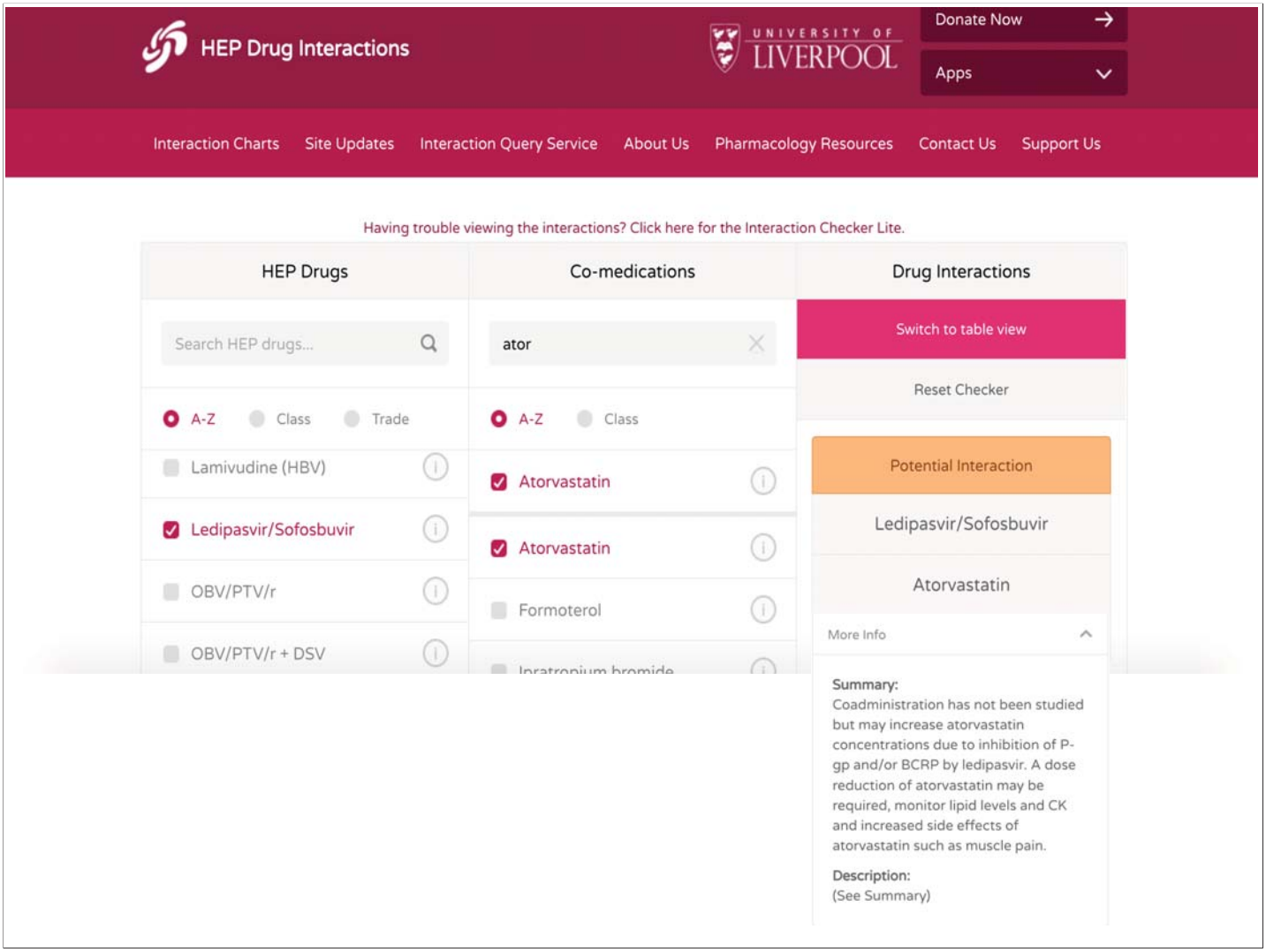
Mechanism	Effects		Effects
Enzyme induction	DAA-induced		↓ Drug level
Enzyme inhibition			↑ Drug level
Enzyme induction	↓ Drug level		Co-medication-induced
Enzyme inhibition	↑ Drug level		
Substrate	↑ Drug level		↑ Drug level

Transmembrane Transport and Metabolism of DAAs



- **Substrate:** underline
- **Inhibitor:** ⊥

Ing Lorenzini K, Girardin F. Liver Int 2020;40:32-44



Glecaprevir/Pibrentasvir and Sofosbuvir/Velpatasvir: Red-Flag DDI

Class	Glecaprevir/Pibrentasvir	Sofosbuvir/Velpatasvir
Anti-arrhythmia	-	amiodarone, dronedarone
Anticoagulant, antiplatelet	dabigatran, eltrombopag	-
Heart failure, pulmonary hypertension	aliskiren, bosentan	bosentan
Lipid lowering agent	atorvastatin, lovastatin, simvastatin	-
Anticonvulsant	carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone	carbamazepine, eslicabazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, rufinamide
Antipsychotics	pimozide	-
Anxiolytics	amobarbital	amobarbital
Anti-TB	rifampin, rifabutin, rifapentine	rifampin, rifabutin, rifapentine
HIV-NNRTI	efavirenz, nevirapine, etravirine	efavirenz, nevirapine, etravirine
HIV-PI	all	tipranavir
Herbals	St. John's wart	St. John's wart
Contraceptives	ethinylestradiol	-
Anti-cancer	vinblastine, vincristine	-

6

Public health

WHO goal

Barriers

WHO Target for Viral Hepatitis Elimination

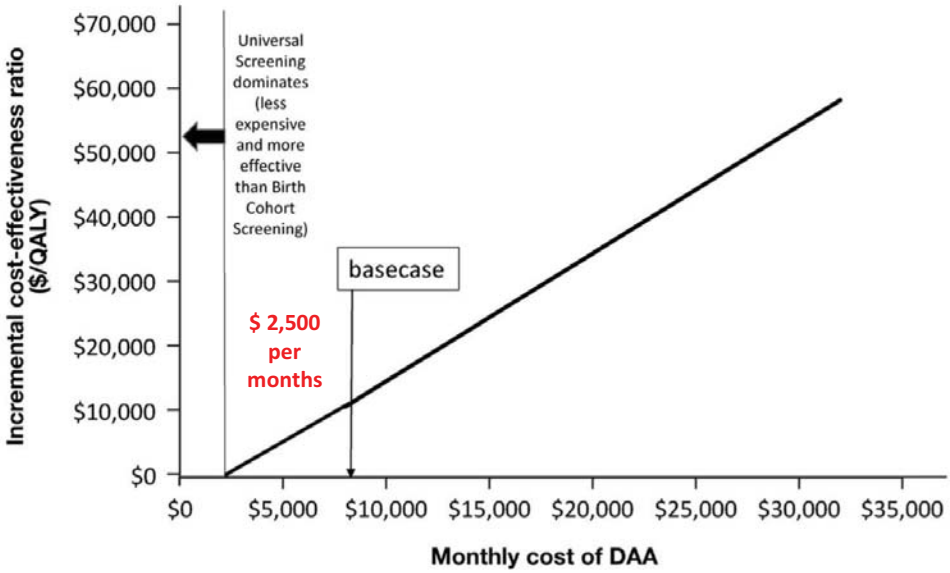
Target areas				Baseline 2015	2020 target	2030 target
Service coverage	Prevention	1 Three-dose hepatitis B vaccine for infants (coverage %)		82%	90%	90%
		2 Prevention of mother-to-child transmission of HBV: hepatitis B birth-dose vaccination or other approaches (coverage %)		38%	50%	90%
		3 Blood and injection safety (coverage %)	Blood safety: donations screened with quality assurance	89%	95%	100%
			Injection safety: use of engineered devices	5%	50%	90%
		4 Harm reduction (sterile syringe/needle set distributed per person per year for people who inject drugs [PWID])		20	200	300
	5 Treatment	5a. Diagnosis of HBV and HCV (coverage %)		<5%	30%	90%
		5b. Treatment of HBV and HCV (coverage %)		<1%	5 million (HBV) 3 million (HCV)	80% eligible treated
Impact leading to elimination	Incidence of chronic HBV and HCV infections			6–10 million	30% reduction	90% reduction
	Mortality from chronic HBV and HCV infections			1.46 million	10% reduction	65% reduction

Key Elements in Macro-elimination of HCV

1	2	3	4	5
Awareness	**Access to Testing**	**Link to Care**	**Access to Medicine**	**Post-Tx Care**
- Mass screening - Patient education (prognosis, therapy) - Avoid stigma associated with HCV infection	- Efficient testing process - Simple testing process	- Efficient referral systems in place - Identifying prior diagnosed patients (retrieval programs)	- Convenient treatment system - Simplified treatment regimen - Unrestricted treatment program - Budget support	- Ongoing hepatic surveillance - Reinfection surveillance and treatment - Ongoing disease assessment by Re-Tx for Tx failure

Kåberg M, et al. Liver Int 2020;40:61-6

Cost-Effectiveness of Universal Screening for HCV in the Era of Pangenotypic DAA Regimens

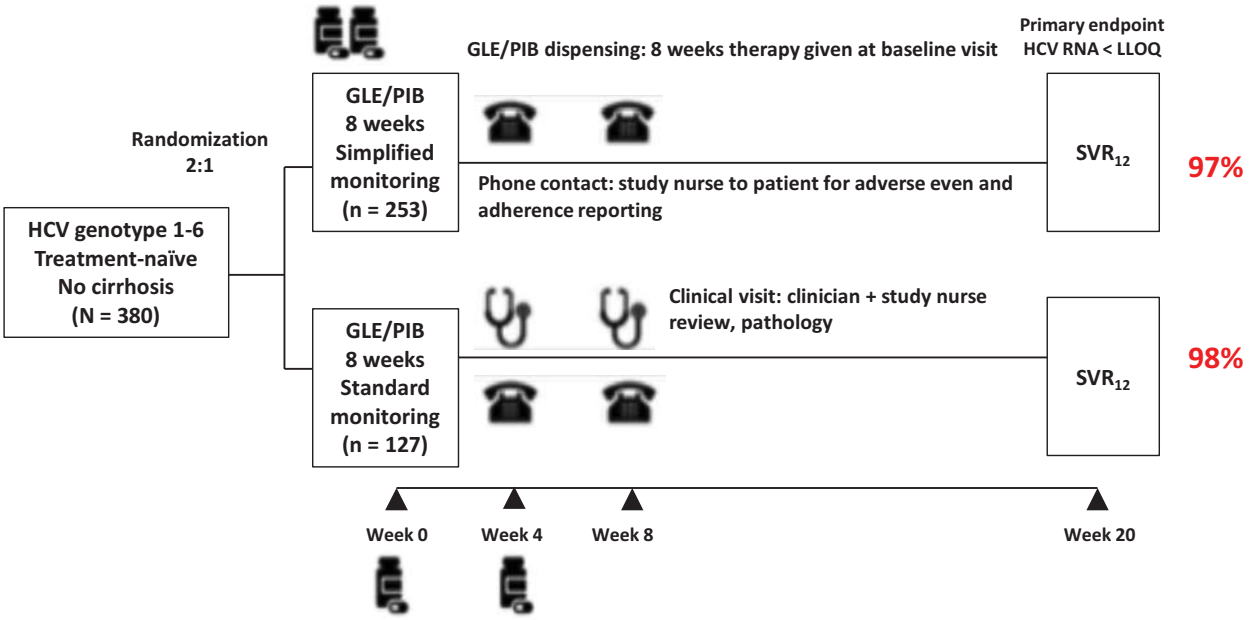


One-way sensitivity analysis examining monthly cost of DAA agent. The base-case value for the parameter is $ 8,090. Below a monthly cost of roughly $ 2,500 universal screening dominates, being less costly and more effective than birth cohort screening.

Eckman MH, et al. Clin Gastroenterol Hepatol 2019;17:930-9

Standard vs. Simplified Monitoring of Initial Treatment of GLE/PIB: SMART-C

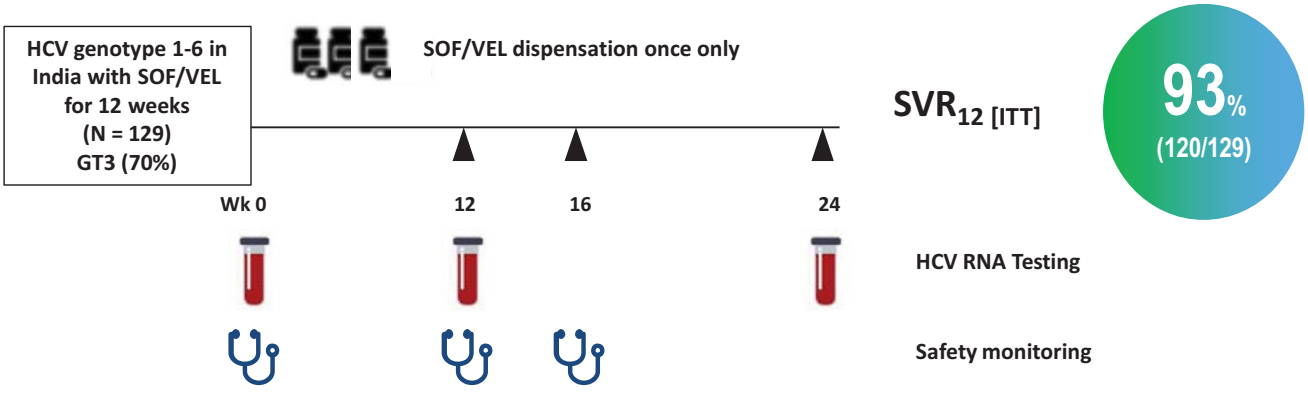
- **Design:** investigator-initiated, open-label phase 3b, randomized controlled trial



Adherence > 95%: 98% standard vs 96% simplified

Dore GJ, et al. J Hepatol 2020;72:431-40

Sofosbuvir/Velpatasvir in a Setting with Minimal Monitoring



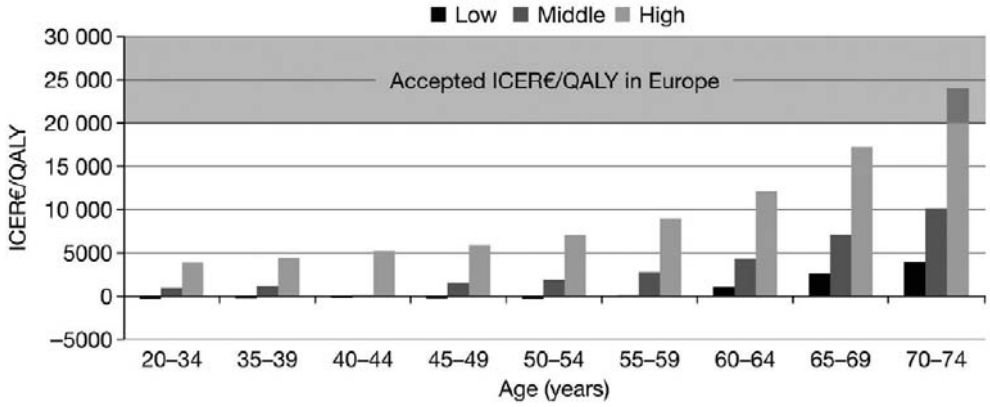
Non-SVR$_{12}$ due to virologic failure

- On-treatment failure (n = 1)
- Relapse (n = 2)

- No discontinuation due to AEs and no deaths during the study period
- 12 patients (9%) had Grade 3-4 laboratory abnormalities and none were considered as drug-related

Sood A, et al. Hepatol Int 2019;13:173-9

Cost-Effective Elimination Policy of Universal Access to DAAs in Spain



Age cohort[a]	ICER €/QALY	ICER€/QALY screening and treatment
20-34	-930	Cost saving
35-39	-913	Cost saving
40-44	-864	Cost saving
45-49	-770	Cost saving
50-54	-604	Cost saving
55-59	-324	125
60-64	141	961
65-69	936	2651
70-74	2329	3904

Cost-effectiveness of screening and treatment (ICER €/QALY) by age group for the screening and according to three possible DAA prices

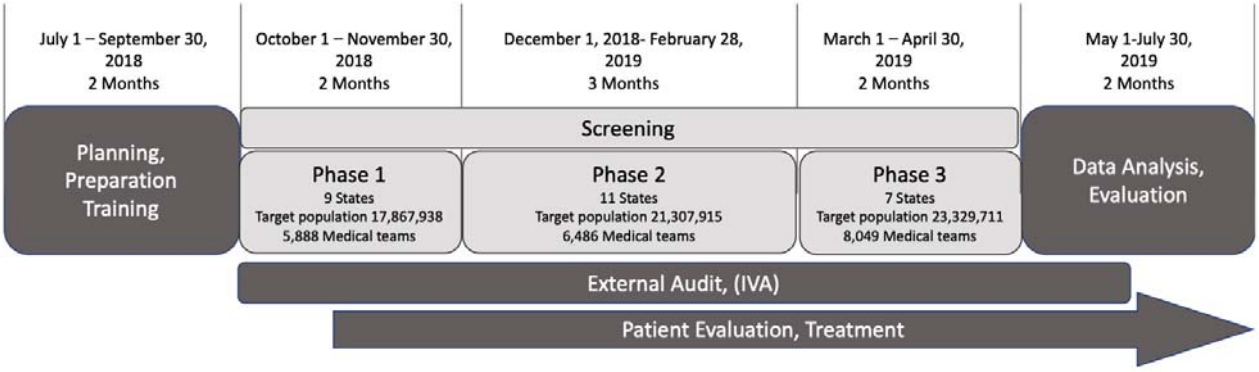
- Low, €7000
- Middle €14 000
- High €30 000

Crespo J, et al. J Viral Hepat 2020;27:360-70

Screening and Treatment Program to Eliminate Hepatitis C in Egypt

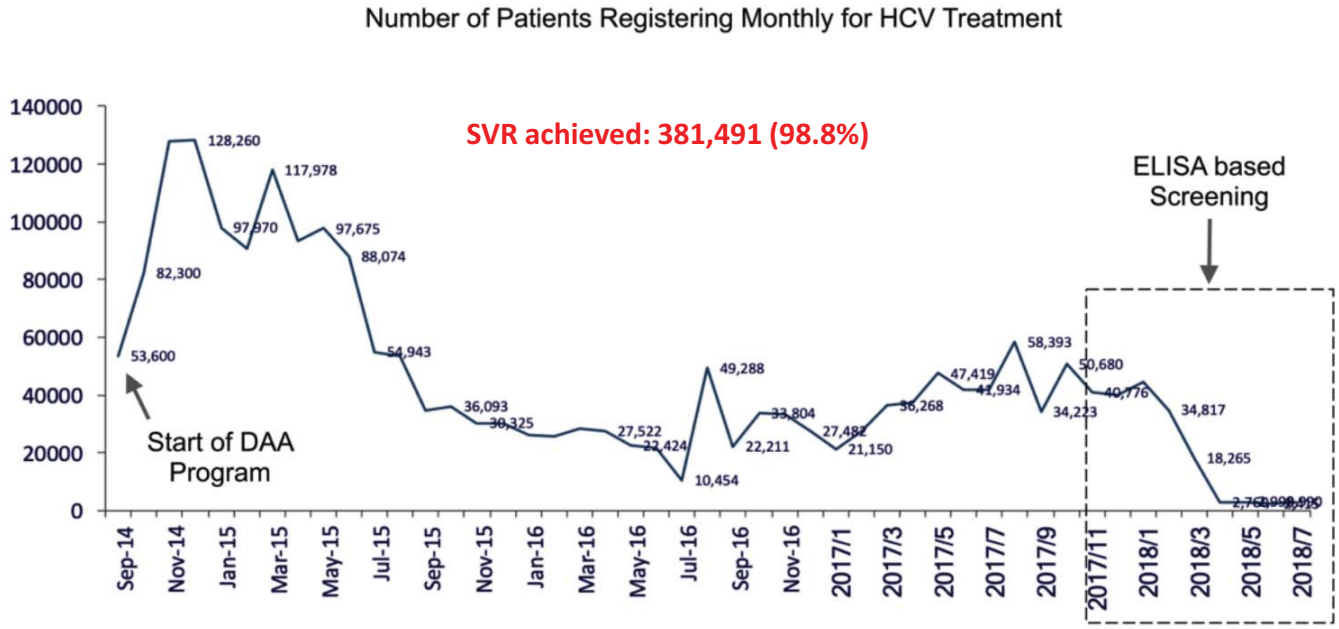
- **Egypt:** HCV antibody seroprevalence 9% and viremic 7% [5.5 million carriers] due to unsafe IV injection among 1950-1980 for Schistosomiasis
- **Scale up treatment:** from 2015, now 2 million people treated (40%) with cure rate > 90%
- **Cost of DAAs:** SOF plus DCV for 12 weeks [$1,650 in 2015] to local generics [$85 in 2018]

Timeline for the screening campaign



Waked I, et al. N Engl J Med 2020;382:1166-74

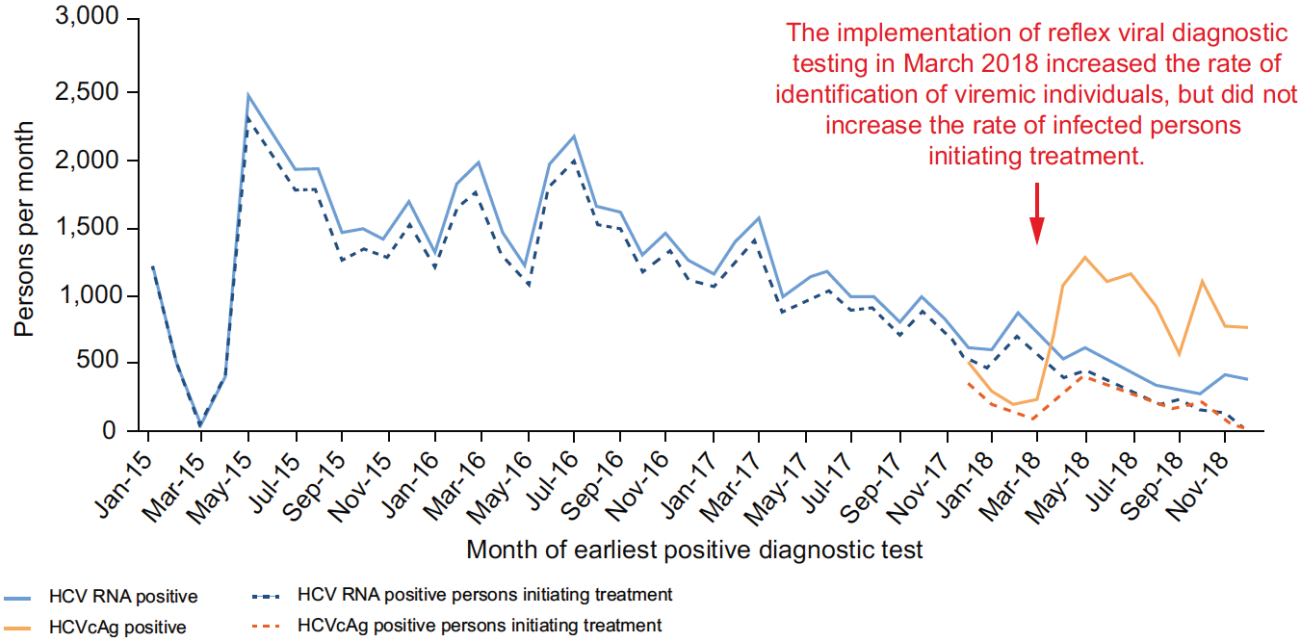
Screening and Treatment Program to Eliminate Hepatitis C in Egypt



Waked I, et al. N Engl J Med 2020;382:1166-74

Progress and Challenges of a Pioneering HCV Elimination Program in the Country of Georgia

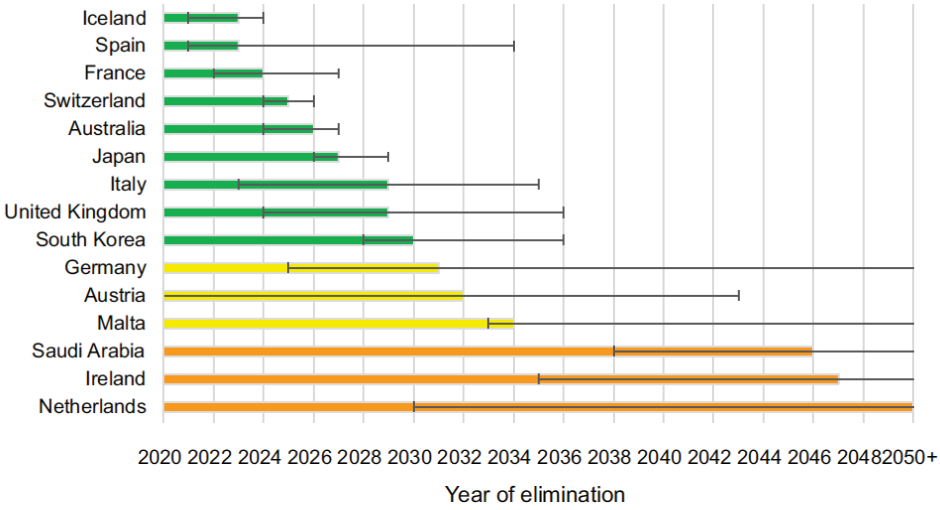
Hepatitis C virus RNA (HCV RNA) or HCV core antigen (HCVcAg) diagnostic testing and initiation of treatment by test method and month of diagnosis
Georgia hepatitis C elimination program, January 2015 – December 2018



Averhoff F, et al. J Hepatol 2020;72:680-7

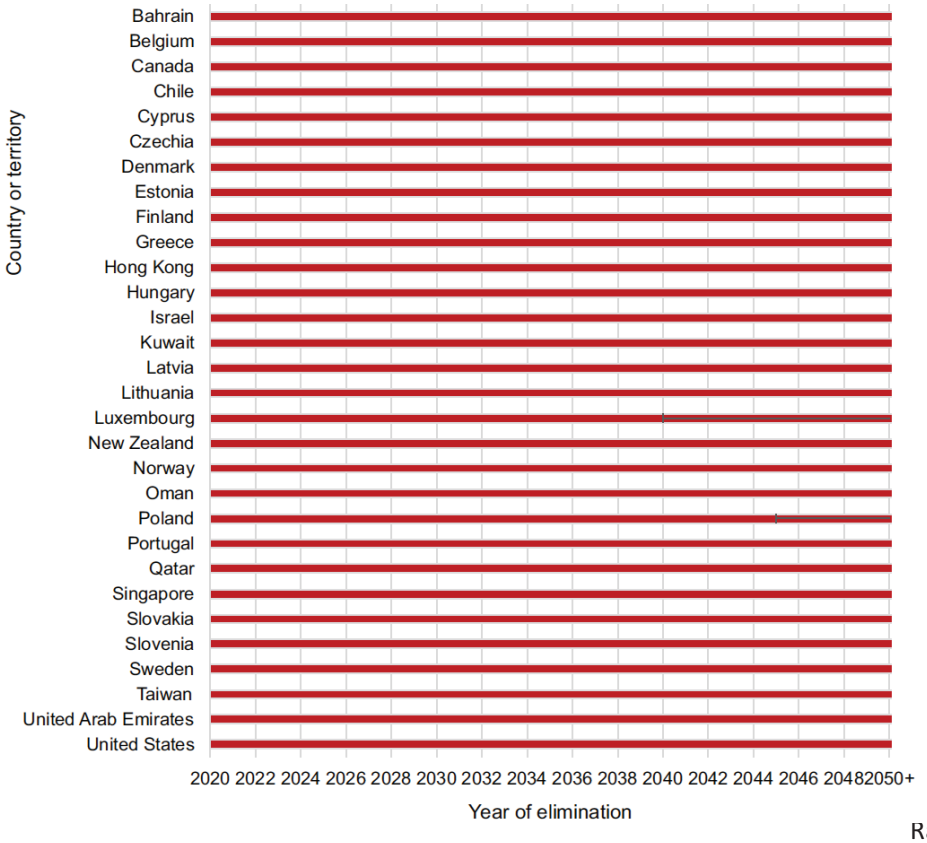
Global Timing of Hepatitis C Virus Elimination in High-Income Countries

- **Design:** Markov disease progression model for 45 high-income countries



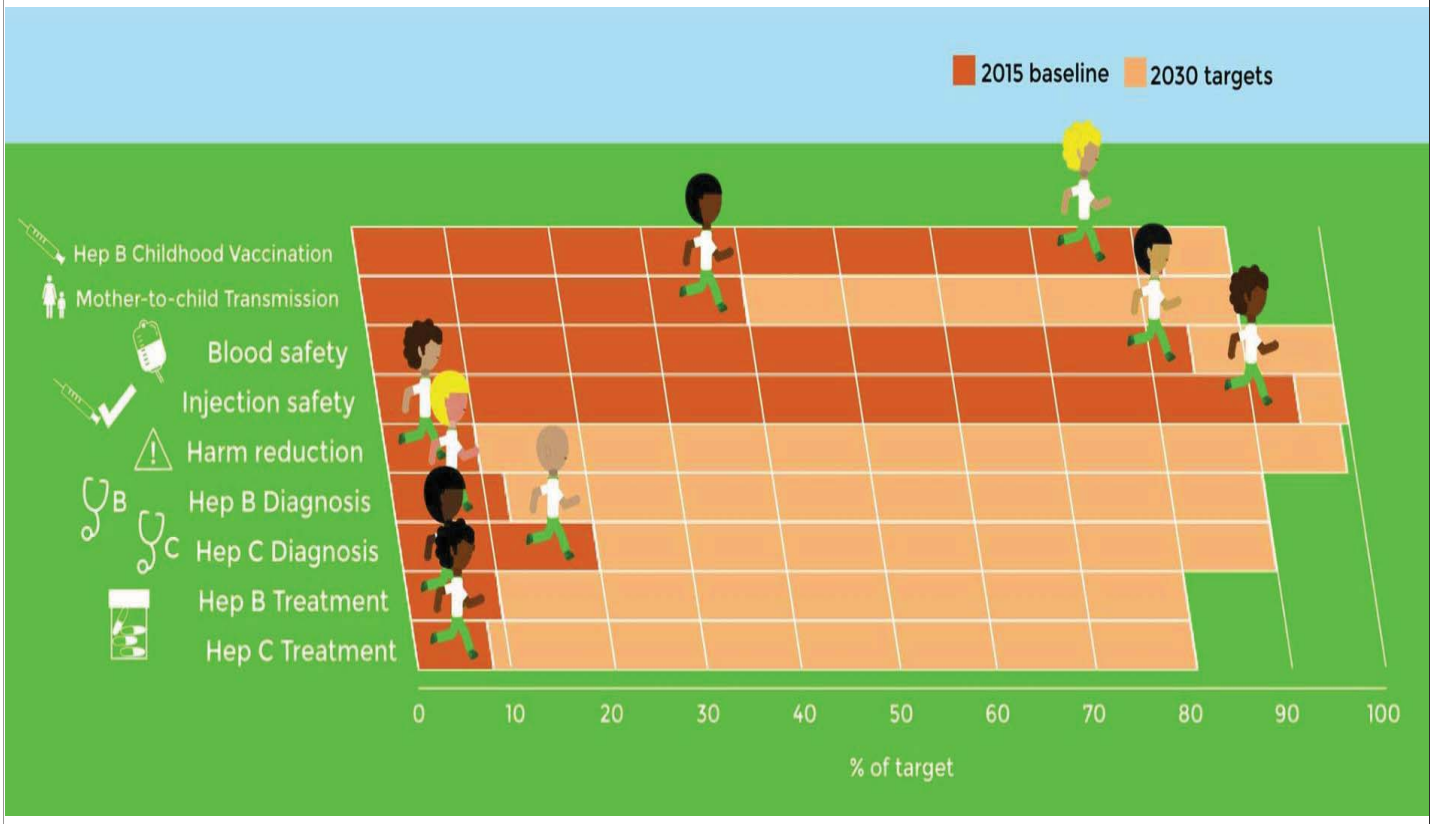
Razavia H, et al. Liver Int 2020;40:522-9

Global Timing of Hepatitis C Virus Elimination in High-Income Countries



Razavia H, et al. Liver Int 2020;40:522-9

Targets for Eliminating Chronic Viral Hepatitis C



Thank You for Your Attention

At the Core of HCV Research