Hepatitis C in 2018: From Evolution to Revolution

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Learning Objectives

After attending this presentation, learners will be able to:

- List the available drugs and regimens for treating hepatitis C and their viral targets
- Describe the efficacy of treatments, by virus genotype, for initial therapy

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Off-Label Disclaimer

I will discuss the following off-label use in this presentation:
Treatment of acute HCV infection

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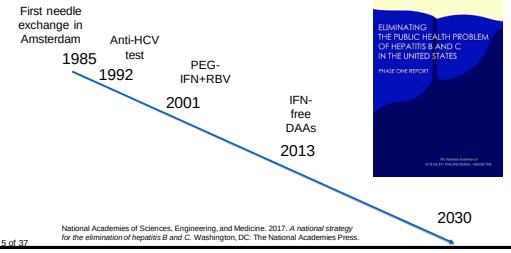
Will we be able to move towards elimination?



National Academies of Sciences, Engineering, and Medicine. 2017. *A national strategy for the elimination of hepatitis B and C*. Washington, DC: The National Academies Press.

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AASLD | HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C | IDSA Infectious Diseases Society of America

Goal of Treatment

The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response.

Recommendations for When and in Whom to Initiate Treatment

Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert.

Adapted from http://hcvguidelines.org

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Audience Response Question 1

Chronic HCV infection is associated with approximately how many years of lost life expectancy?

1. 1-5 years
2. 6-8 years
3. 15-25 years

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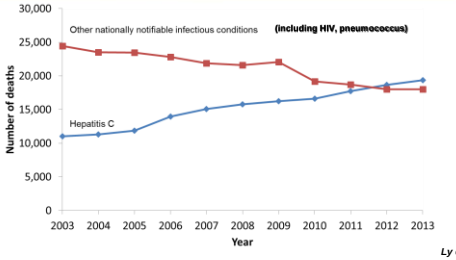
HCV deaths exceed those from 60 infectious conditions (death certificate data)



Ly et al. CID 2016

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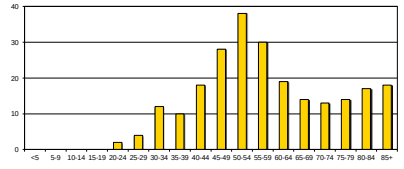
Death Rates Among HCV Cases in Massachusetts, by age at death, 2000-2009

The highest average annual mortality rate for those with HCV was among the 50 to 54 year age group, with 38 deaths per 100,000



HCV data Source: MDPH Office of Integrated Surveillance and Informatics Services, data as of 2/10/12
HCV diagnosis date is the earliest known date of documented HCV infection

Slide courtesy: Dan Church, MA DPH

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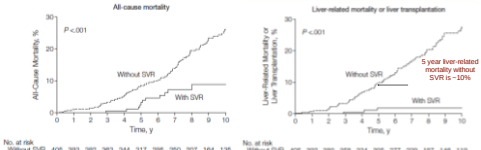
SVR Reduces All-Cause and Liver-Related Mortality



Outcomes	With SVR: Events, No.	With SVR: Observation Period, Person-Years	With SVR: Rate per 100 Person-Years (95% CI)	Without SVR: Events, No.	Without SVR: Observation Period, Person-Years	Without SVR: Rate per 100 Person-Years (95% CI)	P Value[b]
Any event[a]	18	1260	1.43 (0.77-2.09)	169	2921	5.79 (4.91-6.66)	<.001
All-cause mortality	13	1283	1.01 (0.46-1.56)	100	3410	2.93 (2.36-3.51)	<.001
Liver-related mortality or liver transplantation	3	1283	0.23 (<0.01-0.50)	103	3120	3.30 (2.58-3.82)	<.001

...er A. JAMA. 2013

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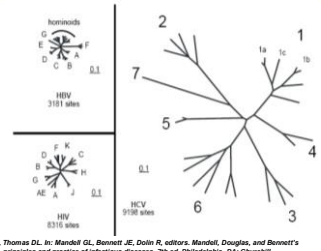
HCV Sequence Diversity Relative to Hepatitis B and HIV



Ray SC, Thomas DL. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases, 7th ed. Philadelphia, PA: Churchill Livingstone/Elsevier; 2010.

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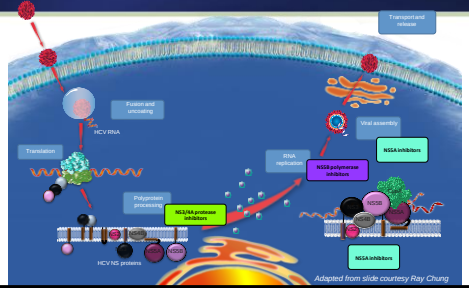
Potential Therapeutic Targets in the HCV Replication Cycle



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Combining Agents with Nonoverlapping Resistance Profiles Increases the Barrier to Resistance

Target	Variant	NS3 Linear	NS3 Macrocyclic	NS5A inhibitor	NS5B nucleoside	NS5B Palm	NS5B Thumb	NS5B Finger	IFN	RBV
NS3 Protease	V36M	R	S	S	S	S	S	S	S	S
	T54A	R	S	S	S	S	S	S	S	S
	R155K	R	R	S	S	S	S	S	S	S
	A156T	R	R	S	S	S	S	S	S	S
	D168V	S	R	S	S	S	S	S	S	S
NS5A	L28V	S	S	R	S	S	S	S	S	S
	Y93H	S	S	R	S	S	S	S	S	S
NS5B	S282T	S	S	S	R	S	S	S	S	S
	C316Y	S	S	S	S	R	S	S	S	S
	M414T	S	S	S	S	R	S	S	S	S
	R422K	S	S	S	S	S	R	S	S	S
	M423T	S	S	S	S	S	R	S	S	S
	P495S	S	S	S	S	S	S	R	S	S

S = Susceptible (< 4 fold shift in HCV replicon EC50)

R = Resistant (>4 fold increase in EC50)

Possible combinations of HCV treatments then are applied to different viral genotypes

PEG IFN

RBV

BOC

TLV

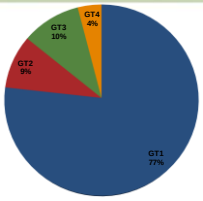
SMV VOX PRVir GZR GLE

LDV VEL OBV DCV EBR PIB

DSV

SOF

SOF



Abbreviations: GT = genotype; PEG IFN = pegylated interferon; RBV = ribavirin
PIs: BOC = boceprevir, TLV = telaprevir, SMV = simeprevir; VOX = voxilaprevir; PRV = paritaprev
GZR = grazoprevir; GLE = glecaprevir. Pharmacologic booster: r = ritonavir; NS5A: LDV = ledipas
VEL = velpatasvir; OBV = ombitasvir; DCV = daclatasvir; EBR = elbasvir; PIB = pibrentasvir;
NS5B nonnucleoside: DSV = dasabuvir; NS5B nucleotide: SOF = sofosbuvir

Predictors of relapse to sofosbuvir-based regimens

RBV SOF

12 week FISSION POSITRON FUSION VALENCE n=285

RBV SOF

24 week VALENCE n=247

PEG RBV SOF

12 week ATOMIC NEUTRINO n=339

Who will do poorly with currently-available SOF-based regimens?

SVR12= undetectable HCV RNA at 12 weeks after cessation of therapy

SVR12 Rates by Number of Negative Predictors

Derived From Multivariate Analysis (combined dataset)

Six factors associated with relapse:

Treatment-experienced
IL28B non-CC
Male sex
Weight > 75 kg
Cirrhosis
High viral load >800,000 IU/mL

Foster et al. EASL 2014 Abstract 66

Antiviral HCV treatments (FDA-approved as of August, 2017)

Monotherapies

- IFN-2a
- IFN-2b
- PEG-IFN 2a
- PEG-IFN 2b

Combination Therapies

- IFN-2a + Ribavirin
- IFN-2b + Ribavirin
- PEG-IFN 2a + Ribavirin*
- PEG-IFN 2b + Ribavirin
- PEG-IFN + ribavirin plus either:
  - Boceprevir (GT1)
  - Telaprevir (GT1)
  - Simeprevir (GT1)
- In combination with other agents:
  - Sofosbuvir

IFN-free Combination Therapies

- Daclatasvir (DCV) + Sofosbuvir (SOF) (GT1,3)*§
- Elbasvir (EBR) / Grazoprevir (GZR) (FDC GT1,4)*
- Glecaprevir (GLE) / Pibrentasvir (PIB) / (FDC All GTs)
- Ledipasvir (LDV) / Sofosbuvir (SOF) (FDC, GT1,4,5,6)*§
- Paritaprevir / ritonavir / ombitasvir (FDC) + dasabuvir PrOD (GT1)
- Paritaprevir / ritonavir/ ombitasvir (FDC) PrO (GT4)
- Simeprevir (SMV) + Sofosbuvir (SOF) (GT1)
- Sofosbuvir (SOF) / Velpatasvir (VEL) (FDC, All GTs)*
- Sofosbuvir (SOF) / Velpatasvir (VEL) /Voxilaprevir (VOX) (FDC, Retreatment)

*approved for HIV/HCV coinfection
§approved for GT1 - decompensated and post-liver transplant
•approved for decompensated

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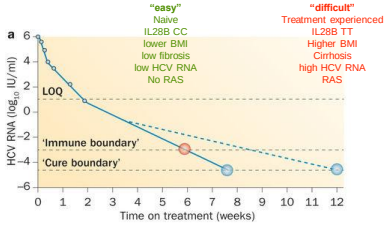
Viral decay
Predictions from modeling studies



Perelson & Guedj Nature Reviews Gastroenterology & Hepatology 2015(12):437–445

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Differences in the barrier to resistance by drug class, subtype, and generation

	NS3/4A Protease Inhibitors	NS5B Nucleos(t)ide Polymerase Inhibitors	NS5B Nonnucleoside Polymerase Inhibitors	NS5A Inhibitors
Drugs in Class	Simeprevir Paritaprevir Grazoprevir Voxilaprevir Glecaprevir	Sofosbuvir	Dasabuvir	Ledipasvir Ombitasvir Daclatasvir Elbasvir Pibrentasvir
Barrier to resistance	Variable (1a lower barrier than 1b)	Extremely High (1a=1b)	Very low (1a lower barrier than 1b)	Variable (1a lower barrier than 1b)
Comments	2nd and 3rd generation PIs have higher barrier, pangenotypic	Single target Active site	Allosteric Many targets	Multiple antiviral Mechanism of Action

Modified from Schaefer EA, et al. Gastroenterology. 2012

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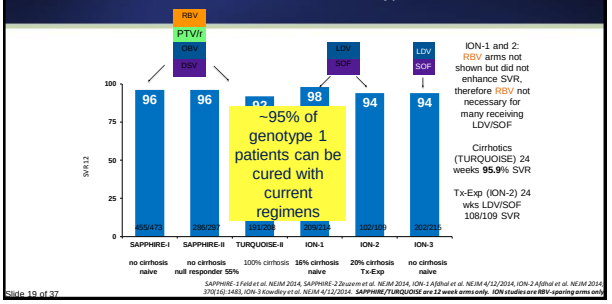
>90% cure rates for Genotype 1



ION-1 and 2: RBV arms not shown but did not enhance SVR, therefore RBV not necessary for many receiving LDV/SOF

Cirrhotics (TURQUOISE) 24 weeks **95.9**% SVR

Tx-Exp (ION-2) 24 wks LDV/SOF 108/109 SVR

SAPPHIRE-1 Feld et al. NEJM 2014, SAPPHIRE-2 Zeuzem et al. NEJM 2014, ION-1 Afdhal et al. NEJM 4/12/2014, ION-2 Afdhal et al. NEJM 2014; 370(16):1483, ION-3 Kowdley et al. NEJM 4/12/2014. ***SAPPHIRE/TURQUOISE are 12 week arms only. ION studies are RBV-sparing arms only***

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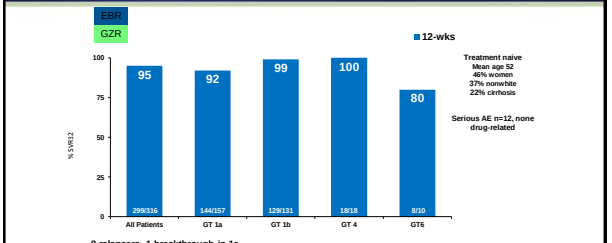
C-EDGE: elbasvir/grazoprevir is a RBV and nucleoside/nucleotide sparing 12- week regimen for GT 1/4/6 HCV



Treatment naive
Mean age 52
46% women
37% nonwhite
22% cirrhosis

Serious AE n=12, none drug-related

9 relapsers, 1 breakthrough in 1a
Similar SVR for n=218 HIV co-infected individuals on DTG/RAL/RPV

Zeuzem et al. Ann Intern Med 2015; Rockstroh et al. Lancet HIV 2015

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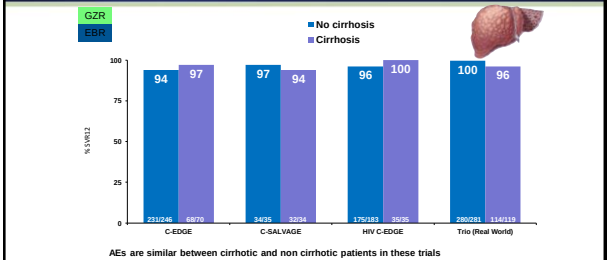
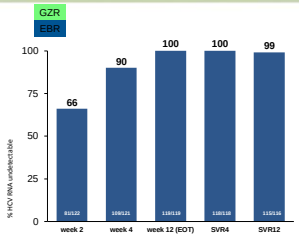
High efficacy for cirrhotic patients for EBR/GZR



AEs are similar between cirrhotic and non cirrhotic patients in these trials

Slide 21 of 37 Zeuzem et al. Ann Intern Med 2015; Rockstroh et al. Lancet HIV 2015; Buti et al. CID 2016; Jacobson et al. AASLD 2015; Flamm et al. Alimentary Pharm & Therapeutics 2018

EBR/GZR - C-SURFER established safety and efficacy in patients with chronic kidney disease (CKD) stage 4/5



Treatment naive and experienced
Mean age 56
~6% cirrhosis

Hypertension or diabetes were primary etiologies
Prior renal transplant n=17

SAE 14.4% in treatment
SAE 16.8% in deferred

Roth et al. Lancet 2015

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Broad Cross-resistance With "Early Generation" NS5As

Fold-change	1a				1b	
	M28T	Q30R	L31M/V	Y93H/N	L31V	Y93H/N
Ledipasvir	20x	>100x	>100x/ >100x	>1,000x/ >10,000		>100x/--
Ombitasvir	>1000x	>100x	<3x/ >100x	>10,000x/ >10,000x	<10x	20x/50x
Daclatasvir	>100x	>1000x	>100x/ >1000x	>1,000x/ >10,000x	<10x	20x/50x
Elbasvir	20x	>100x	>10x/ >100x	>1,000x/ >1,000x	<10x	>100x/--
Velpatasvir	<10x	<3x	20x/50x	>100x/ >1000x		<3x/--
ACH-3102	30x	20x	<10x	>100x/>100x		<3x/<3x
Pibrentasvir	<3x	<3x	<3x	<10x/<10x	<3x	<3x/<3x
MK-8408	<10x	<10x	<10x	<10x	<10x	<10x

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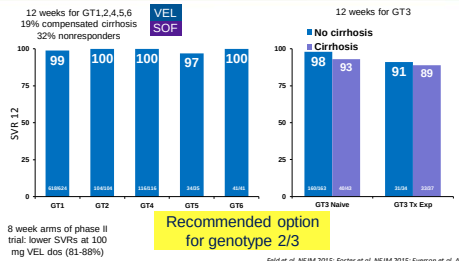
Wang C. AAC 2012; Cheng G. #1172. EASL 2012; Zhao Y. #A845 EASL 2012; Yang G. EASL 2013; Ng T. #639 CROI 2014; Asante-Appiah E. AASLD 2013

Response rates for pangenotypic regimen: Genotypes 1-6



8 week arms of phase II trial: lower SVRs at 100 mg VEL dos (81-88%)

Recommended option for genotype 2/3

Feld et al. NEJM 2015; Foster et al. NEJM 2015; Everson et al. Ann Intern Med 2015

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Audience Response Question 2

Which statement is NOT true of the newly-approved glecaprevir/pibrentasvir (G/P) regimen?

1. Most patients will receive 12 weeks
2. It is a single daily-dosed pill
3. It should not be used for genotype 4 patients
4. It should not be used for CKD 4-5 patients
5. It has demonstrated safety for decompensated patients

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Glecaprevir and pibrentasvir (G/P): Fixed-dose combination 3 pills once daily

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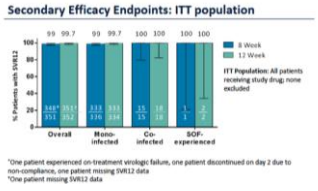
Glecaprevir and pibrentasvir (G/P): novel pangenotypic regimen

- ENDURANCE-1 examined 8 versus 12 weeks in GT1 non-cirrhotic patients with or without HIV



- 8 weeks G/P achieved 95% SVR in non cirrhotic genotype 3 patients in ENDURANCE-3

Zeuzem et al. AASLD 2016; EASL 2017

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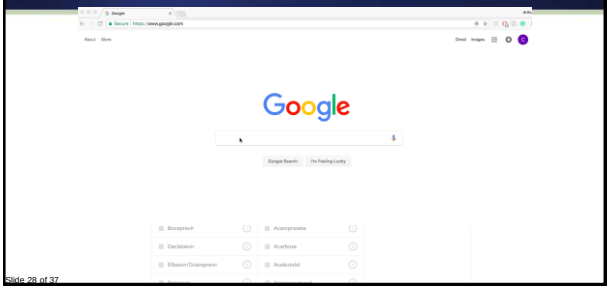
Don't forget drug interactions!



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A menu of options

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Prix fixe menus?

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Barriers to addressing & treating HCV

Biologic
~~Genotype~~
~~High viral loads~~
~~Fibrosis / cirrhosis~~
~~Prior treatment failure~~
~~Viral resistance mutations~~
~~HIV~~
~~Renal disease~~

Medications
~~Side effects of treatment~~
Drug Interactions

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Barriers to addressing & treating HCV

Psychosocial
Stigma
Lack of awareness
Fear of evaluation and treatment
Substance abuse
Neuropsychiatric comorbidities
Poor adherence to treatment
Imprisonment
Unstable housing

Provider/Structural
Dearth of providers
Lack of provider knowledge
Lack of insurance
Access restrictions
- fibrosis
- substance use
- provider credentials

High cost

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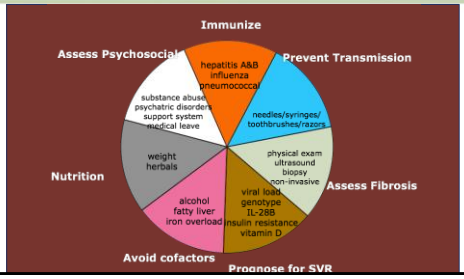
Components of HCV care



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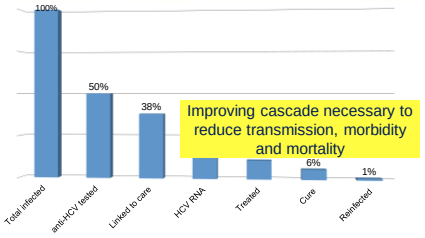
The continuum of care in HCV infection in the U.S.
At least 3 million persons infected



Improving cascade necessary to reduce transmission, morbidity and mortality

Adapted from Holmberg et al. NEJM 2013

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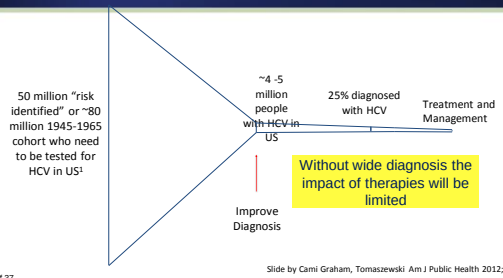
Need for improved diagnosis



Without wide diagnosis the impact of therapies will be limited

Slide by Cami Graham, Tomaszewski Am J Public Health 2012; 102 (11):e101

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Take-home points from this workshop

- Increased screening critical
  - Groups at risk - women of childbearing age, people who inject drugs, HIV MSM
- Simplification of fibrosis staging
- Simplification of treatment
  - Primary treatments for all genotypes
  - Free of interferon and (mostly) free of ribavirin
- Virtually all HCV should be treated

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Question-and-Answer

Remember to raise your hand and wait until you have the microphone before you ask your question—we are recording!

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