# Viva La Revolución: Options to Combat Hepatitis C

**Andrew I. Aronsohn, MD**
Associate Professor of Medicine
The University of Chicago Medicine
Chicago, Illinois

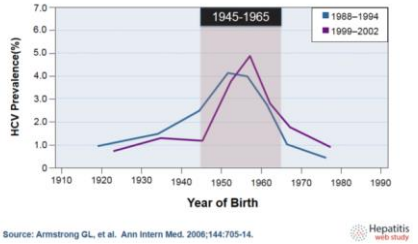
IAS–USA

## 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 and retreatment

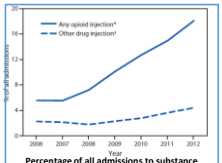
## Incidence of HCV: Age



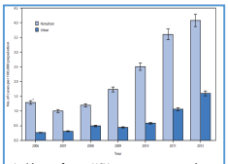

Source: Armstrong GL, et al. Ann Intern Med. 2006;144:705-14.

Hepatitis web study

## Changing Epidemiology of HCV



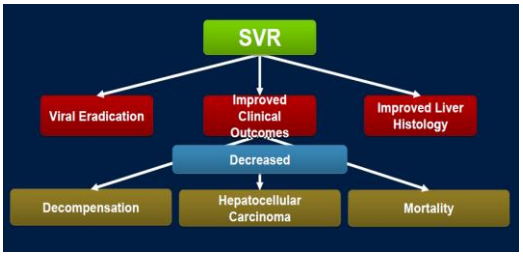

Percentage of all admissions to substance abuse treatment centers by persons aged 12–29 years attributed to the injection of opioids and other drugs, by year — Kentucky, Tennessee, Virginia, and West Virginia,



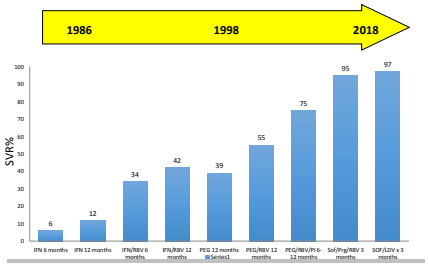
Incidence of acute HCV among persons aged ≤30 years, by urbanicity and year — Kentucky, Tennessee, Virginia, and West Virginia

*Zibbell et al MMWR 2015*

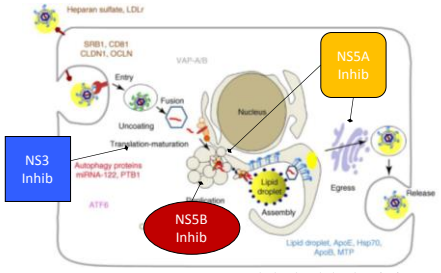
## Treatment Outcomes after Sustained Virologic Response (Cure)




## Timeline of HCV Therapeutics

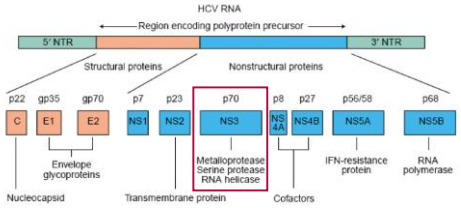


## Overview of HCV life-cycle and antiviral targets

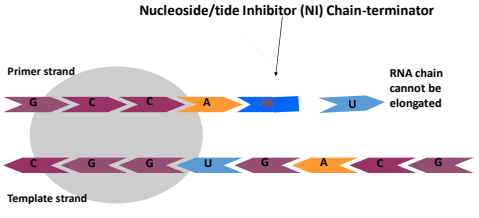



Georgel et al. Trends in Molecular Medicine 16(2010) 277-286. Moradpour D. Nat Rev 2007.

## Structure of HCV Genome: Protease Inhibitors
## Ex: voxilaprevir / glecaprevir

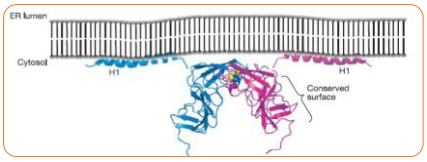



## Nucleoside/tide Polymerase Inhibitors Mechanism of Action
## Ex: Sofosbuvir



## HCV NS5a Replication Complex: Another Therapeutic Target

**Ex: Velpatasvir / Pibrentasvir**



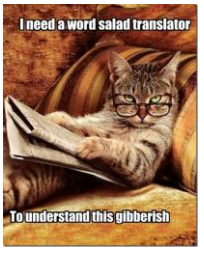

- Large phosphoprotein
- Associates at least as a dimer
- Binds RNA
- Amphipathic helix (H) at amino terminus promotes membrane association

- Essential component of HCV RNA ER-membrane–associated replication complex
- Modulates cellular systems involved in IFN resistance

Tellinghuisen TL, et. al. Nature. 2005;435(7040):374-379.
Love RA, et al. J Virol. 2009;83(9):4395–4403.

## Lots of Words

- **- previr** = protease inhibitor
  - Grazoprevir, Simeprevir
- **- asvir** = NS5A inhibitor
  - Daclatasvir, Ledipasvir
- **- buvir** = polymerase inhibitor
  - Sofosbuvir




## Currently Available DAA's

| DAA Class | Sofosbuvir/ Velpatasvir | Sofosbuvir/ Ledipasvir | Sofosbuvir/ Velpastasvir/ Voxilaprevir | Elbasvir/ Grazoprevir | Glecaprevir/ Pibrentasvir |
|---|---|---|---|---|---|
| Protease Inhibitor | | | X | X | X |
| NS5A inhibitor | X | X | X | X | X |
| Nucleoside Polymerase Inhibitor | X | X | X | | |

www.hcvguidelines.org

1)Genotype

2)Treatment Experienced?

3)Cirrhotic?

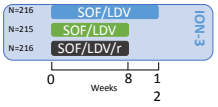

ARS Question 1: Eight weeks of LDV/SOF is not recommended for which patient population with GT1 and an HCV RNA <6 million? (AASLD/IDSA Guidelines)

1. Patients without cirrhosis
2. Black patients
3. Female patients
4. Male patients
5. Genotype 1a subtype

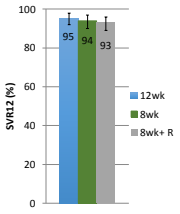
## Sofosbuvir / Ledipasvir

- **Genotype 1, 4, 5,6**
- **Effective in cirrhosis (including decompensation)**
- **GFR >30**
- **8 weeks for some**
- **Amiodarone contraindicated**

## SOF/LDV: 8 vs. 12 weeks for treatment naïve GT1




- Cirrhosis excluded
- Relapses
  - 4-5% in 8 week arms
    - 20/23 in 8 week arms
  - 1% in 12 week arm
- Post-hoc analyses
  - HCV RNA <6 million
    - 2% relapse in 8 and 12 weeks arms
  - 99% SVR women
  - 91% SVR Black



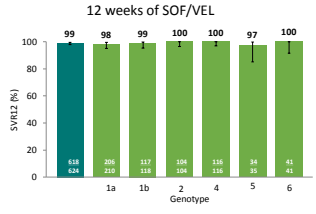

**HCV Guidelines**

8 week recommendation
Non-black
HIV uninfected
HCV RNA <6 million

## Sofosbuvir / Velpatasvir

- **Pangenotypic**
- **Safe / Effective in Cirrhosis (including decompensation)**
- **GFR > 30**
- **Amiodarone contraindicated**

## ASTRAL-1: SOF/VEL for 12 weeks



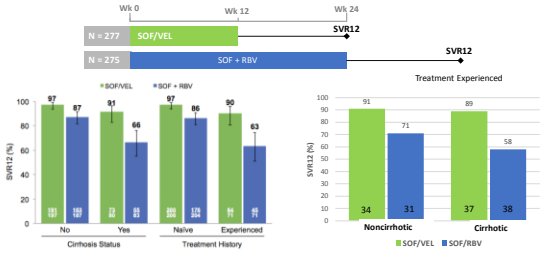

2 virologic failures:
- 1a, TN, NC, IL28 *CT* with Q30R
- 1b, TE, Cirr, IL28 *TT* with Q30R/L31M

SVR with baseline NS5A RASs*: 99% (255/257)

*RASs at >1%, all genotypes

32% treatment experienced (99% SVR12); 19% cirrhosis (99% SVR12)

## ASTRAL-3: SOF/VEL for genotype 3 infection



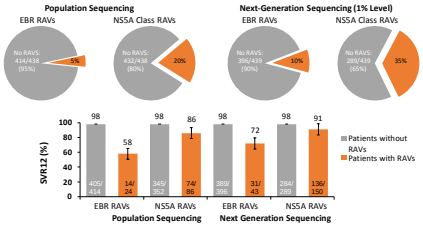

Foster GR, et al. N Engl J Med. 2015;373:2608-2617.

## Elbasvir / Grazoprevir

- **Genotype 1 and 4**
- **Safe / Effective in cirrhosis (NOT for CTP B and C)**
- **Safe / Effective CKD including dialysis**
- **Need to watch for RAS in GT 1a**

## Impact of Baseline NS5A RAVs in Pts With GT1a HCV Treated With EBR/GZR

- Analysis of pts with GT1a HCV treated with GZP/EBR in phase II/III trials (naive/relapsers)

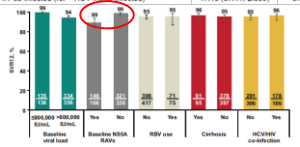



Jacobson I, et al. AASLD 2015. Abstract LB-22.

## GZR/EBR Efficacy in GT1a HCV: Resistance is all that matters!

- Analysis of PEP* of TN pts with GT1a HCV treated with GZP/EBR in phase II/III trials

| Multivariable logistic regression model | OR (95% CI) | P value |
|---|---|---|
| Baseline HCV >800,000 IU/mL (ref = ≤800,000) | 0.091 (0.012, 0.695) | 0.0208 |
| With baseline NS5A RAVs (ref = no baseline NS5A RAVs) | 0.111 (0.040, 0.309) | <0.0001 |
| RBV use (ref = no RBV use) | 0.709 (0.218, 2.300) | 0.5663 |
| Cirrhotic (ref = noncirrhotic) | 1.659 (0.518, 5.315) | 0.3942 |
| HCV/HIV co-infected (ref = HCV mono-infected) | 1.113 (0.441, 2.809) | 0.8205 |




*PEP = pooled efficacy population.

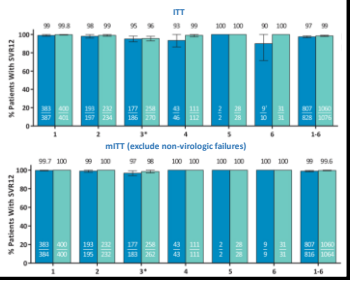
Zeuzem S, et al. AASLD 2015. Abstract 700.


## Glecaprevir / Pibrentasvir

- **Pangenotypic**
- **Safe / Effective in cirrhosis (Not to be used in CTP B and C)**
- **Safe / Effective for CKD including dialysis**
- **8 weeks for some (noncirrhotics)**
- **Efficacy in DAA Experienced**

## Integrated analysis of G/P in non-cirrhotics

- Pooled analysis across phase 2/3 studies
  - G/P 8 wk vs 12 wk
- Non-cirrhotic
- GT3 were also treatment naïve

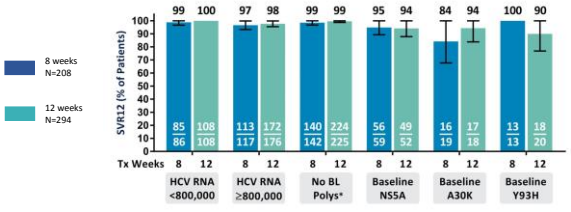



10/13 virologic failures were GT3

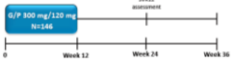
0.6% discontinued prematurely (same in 8 and 12 wk arms)

Pol S. SAT-233. EASL 2017.

## Integrated analysis of 8 vs. 12 weeks in GT3

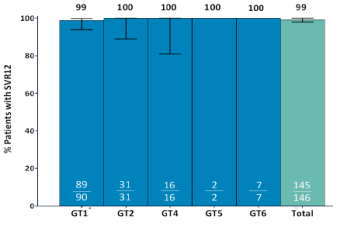



## EXPEDITION-I: GT1, 2, 4-6 with cirrhosis




25% Treatment experienced
8% SOF experienced

20% with PLT <100,000




1 VF: Y93N at baseline→→ Y93N + Q30R + H58D

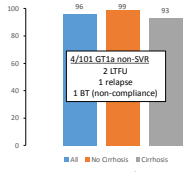
## Sofosbuvir / Velpatasvir / Voxilaprevir

- **Pangenotypic**
- **High SVR in DAA Failures**
- **Effective in cirrhosis (Not to be used with CTP B and C)**
- **Amiodarone contraindicated**
- **GFR >30**

## Triple DAA therapy for re-treatment

Regimen: SOF/VEL/VOX for 12 weeks

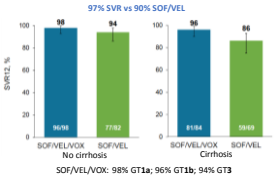
POLARIS-1 (n=263)
NS5A experienced
46% cirrhosis




SVR12: 96% GT**1a**; 100% GT**1b**; 95% GT**3**

POLARIS-4 (n=182)
NO NS5A exposure
46% cirrhosis

97% SVR vs 90% SOF/VEL




SOF/VEL/VOX: 98% GT**1a**; 96% GT**1b**; 94% GT**3**
SOF/VEL: 89% GT**1a**; 95% GT**1b**; 85% GT**3**

Bourliere M. NEJM 2017.

## DAA experienced: What do the labels say?

| | Prior treatment | SOF/VEL/VOX | GLE/PIB |
|---|---|---|---|
| GT1 | NS5A (+/- SOF) | 12 (also 2-6) | 16 |
| GT1 | NS3 (+/- SOF) | 12 (1a only) | 12 |
| GT1-6 | NS3+NS5A | 12 | NR |
| GT3 | SOF (no NS5A) | 12 | 16 |

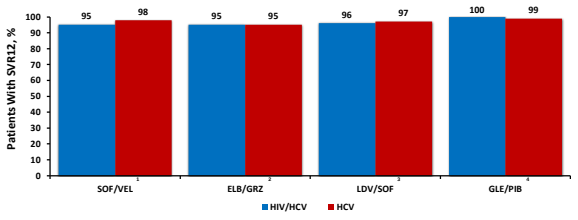
**AASLD/IDSA Guidelines: GT3 NS5A-experienced with compensated cirrhosis**

| RECOMMENDED | DURATION | RATING |
|---|---|---|
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/ voxilaprevir (100 mg) | 12 weeks | I, A |
| For patients with prior NS5A inhibitor failure and cirrhosis, weight-based ribavirin is recommended. | 12 weeks | IIa, C |

**Reminder: HCV PIs (including VOX and GLE) are either not recommended or contraindicated in CTP B/C cirrhosis**

## Treatment of HCV in HIV/HCV Coinfection

*Same Regimens, Same Efficacy as in HCV Monoinfection*




## Cliffs notes for DAA therapy


- Use hcvguidlines.org
- Check for HIV and HBV
- OK to use EBV/ GRZ and G/P in Renal disease
- Don't use protease inhibitors (previrs) in decompensated cirrhosis
- Never use amiodarone with sofosbuvir
- G/P, SOF/VEL/VOX for DAA experienced
- (almost) never need RBV or resistance testing
- HIV same as monoinfected

## Take home points

- Tremendous advances in antiviral treatment of HCV have been realized in the last 5 years
- SVR >95% is attainable in all populations with 8-12 weeks of therapy
- From a treatment efficacy standpoint there are no more "special populations"
- There is a very limited role for resistance testing or the use of ribavirin
- Diagnosis, access and coverage limitations are now the most significant barriers to HCV cure

## 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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