Initial Treatment of the Hepatitis C Virus-Infected Patient

Kristen Marks, MD
Assistant Professor of Medicine
Weill Cornell Medical College
New York, New York

IAS–USA

Off-Label Warning

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

Slide 2 of 83

Learning Objectives

After attending this presentation, learners will be able to:

- Recognize diagnostic testing strategies for HCV and when to do testing for HCV resistance
- List treatment options for treatment naïve patients
- Identify the advantages and limitations of newly approved HCV treatment regimens

Slide 4 of 83

Learning Objectives

- Initial treatment recommendations
- Initial treatment simplification
- Initial treatment of PLWH
- Initial treatment of PWID

Slide 5 of 83

IDSA/AASLD
www.hcvguidelines.org



EASL
http://www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/easl-recommendations-on-treatment-of-hepatitis-c-2018



ARS Question #1: Which of the following patients does the CDC currently recommend should be offered HCV testing?

1. 45 W on hemodialysis
2. 54 midwestern M with normal liver enzymes
3. 33 pregnant W from Egypt
4. 41 M with HIV acquired through sex
5. All of the above
6. All but #2 and #3
7. All but #3

Slide 7 of 83

Current CDC recommendations for HCV Testing

Test once (no risk assessment):

- **Adults born 1945-1965**

Uncertain

- Long term sexual partner of HCV+
- STIs or multiple sex partners
- Intranasal drug use
- Tattooing/bodypiercing

Not recommended

- Health-care, emergency medical, and public safety workers
- *Pregnant women*
- Household (nonsexual) contacts of HCV-positive persons
- *General population*

Test based on risk for exposure:

- Currently injecting drugs
- Ever injected drugs
- Have certain medical conditions, including :
  - received clotting factor pre 1987
  - long-term hemodialysis
  - with persistently abnormal alanine aminotransferase levels (ALT)
  - who have HIV infection
- Were prior recipients of transfusions or organ transplants, including persons who:
  - were notified that they received blood from a donor who later tested positive for HCV infection
  - Pre July 1992

Test based on a recognized exposure:

- Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood
- Children born to HCV-positive women

Slide 8 of 83 https://www.cdc.gov/hepatitis/hcv/guidelinesc.htm

Recommendation for Universal Hepatitis C Screening in Pregnancy

RECOMMENDED	RATING
All pregnant women should be tested for HCV infection (see *Recommendations for Initial HCV Testing and Follow-Up*), ideally at the initiation of prenatal care.	IIb, C

Recommendation Regarding HCV Treatment and Pregnancy

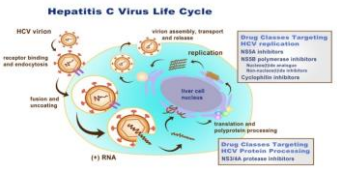
RECOMMENDED	RATING
For women of reproductive age with known HCV infection, antiviral therapy is recommended before considering pregnancy, whenever practical and feasible, to reduce the risk of HCV transmission to future offspring.	I, B

Not Recommended Regarding HCV Treatment and Pregnancy

NOT RECOMMENDED	RATING
Treatment during pregnancy is not recommended due to the lack of safety and efficacy data.	IIb, C

Slide 9 of 83

Strategy for Initial HCV therapy: Direct acting antivirals target life cycle



---**PR**EVIR
Protease inhibitors
e.g. *telaprevir, boceprevir,* faldaprevir, simeprevir, danoprevir, asunaprevir, paritaprevir, grazoprevir, voxilaprevir, glecaprevir

---BUVIR
Polymerase inhibitors
- Nucleos(t)ide analogs: e.g. tegobuvir, sofosbuvir,
- Non-nucs: e.g. deleobuvir, dasabuvir

---**AS**VIR
NS**5A** inhibitors
e.g. daclatasvir, ledipasvir, ombitasvir, elbasvir, velpatasvir, pibrentasvir

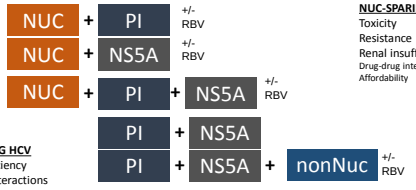
Slide 10 of 83

ARS Question #2: Which of the following represents the BEST strategy for treating HCV?

1. 3 drugs for 8 weeks
2. 2 drugs for 8 weeks
3. 2 drugs for 12 weeks
4. 3 drugs for 12 weeks

Slide 11 of 83

Currently used combinations of DAA classes



NUC-SPARING HIV
Toxicity
Resistance
Renal insufficiency
Drug-drug interactions
Affordability

NUC-SPARING HCV
Renal insufficiency
Drug-drug interactions
Duration
Affordability/Access
Toxicity
Resistance

Slide 12 of 83

Approved Drug Regimens for Initial Treatment

	PEG RBV SOF	RBV SOF	RBV SMV SOF	LDV SOF	DAC SOF	RBV PTV/r OMV DAS	GZR EBV	VEL SOF	GLE PBV
Interferon	PegIFN								
Ribavirin	ribavirin	ribavirin	+/-ribavirin			+/-ribavirin			
Nucs	sofosbuvir	sofosbuvir	sofosbuvir	sofosbuvir	sofosbuvir			sofosbuvir	
Protease inhibitors			simeprevir			Paritaprevir /ritonavir	grazoprevir	velpatasvir	glecaprevir
NS5A				ledipasvir	daclatasvir	ombitasvir	elbasvir		pibrentasvir
Non-Nucs						dasabuvir			
G1	x	x	X	X	X	X	X	X	X
G2	x	X			x			X	X
G3	X	x			X			X	X
G4	x	X	x	X	x	X	X	X	X

Slide 13 of 83

First-line HCV Therapy: Distinguishing Among Recommended Options

EBR/GZR - QD single tablet
12 wks, GT 1 or 4
Requires RAS testing for GT1a
Contains PI: *do not use* if decompensated
Can be used in stage 4/5 CKD
DDI highlights: glucocorticoids, statins, PDE inhibitors, rifampin

DDIs are drug specific and there are many more to consider than are listed here. Always check! https://www.hep-druginteractions.org/

AASLD/IDSA. HCV guidance. September 2017.

Slide 14 of 83

Slide credit: clinicaloptions.com

First-line HCV Therapy: Distinguishing Among Recommended Options

EBR/GZR - QD single tablet
12 wks, GT 1 or 4
Requires RAS testing for GT1a
Contains PI: *do not use* if decompensated
Can be used in stage 4/5 CKD
DDI highlights: glucocorticoids, statins, PDE inhibitors, rifampin

GLE/PIB - QD 3 tablets with food
8 wks no cirrhosis, 12 wks if cirrhosis, GT 1-6
No RAS testing
Contains PI: *do not use* if decompensated
Can be used in stage 4/5 CKD
DDI highlights: statins, rifampin

DDIs are drug specific and there are many more to consider than are listed here. Always check! https://www.hep-druginteractions.org/

AASLD/IDSA. HCV guidance. September 2017.

Slide 15 of 83

Slide credit: clinicaloptions.com

First-line HCV Therapy: Distinguishing Among Recommended Options

EBR/GZR - QD single tablet
12 wks, GT 1 or 4
Requires RAS testing for GT1a
Contains PI: *do not use* if decompensated
Can be used in stage 4/5 CKD
DDI highlights: glucocorticoids, statins, PDE inhibitors, rifampin

GLE/PIB - QD 3 tablets with food
8 wks no cirrhosis, 12 wks if cirrhosis, GT 1-6
No RAS testing
Contains PI: *do not use* if decompensated
Can be used in stage 4/5 CKD
DDI highlights: statins, rifampin

LDV/SOF - QD single tablet
8-12 wks, GT 1, 4, 5, or 6
No RAS testing
Safe in decompensation
Not recommended for stage 4/5 CKD
DDI highlights: acid-reducing agents, statins, rifampin

DDIs are drug specific and there are many more to consider than are listed here. Always check! https://www.hep-druginteractions.org/

AASLD/IDSA. HCV guidance. September 2017.

Slide 16 of 83

Slide credit: clinicaloptions.com

First-line HCV Therapy: Distinguishing Among Recommended Options

EBR/GZR - QD single tablet 12 wks, GT 1 or 4 Requires RAS testing for GT1a Contains PI: *do not use* if decompensated Can be used in stage 4/5 CKD DDI highlights: glucocorticoids, statins, PDE inhibitors, rifampin	GLE/PIB - QD 3 tablets with food 8 wks no cirrhosis, 12 wks if cirrhosis, GT 1-6 No RAS testing Contains PI: *do not use* if decompensated Can be used in stage 4/5 CKD DDI highlights: statins, rifampin
LDV/SOF - QD single tablet 8-12 wks, GT 1, 4, 5, or 6 No RAS testing Safe in decompensation *Not recommended* for stage 4/5 CKD DDI highlights: acid-reducing agents, statins, rifampin	SOF/VEL - QD single tablet 12 wks, GT 1-6 Requires RAS testing for some GT 3 Safe in decompensation *Not recommended* for stage 4/5 CKD DDI highlights: acid-reducing agents, rifampin

DDIs are drug specific and there are many more to consider than are listed here.
Always check! https://www.hep-druginteractions.org/

AASLD/IDSA. HCV guidance. September 2017.

Slide 17 of 83

Slide credit: clinicaloptions.com

Previously Challenging Clinical Scenarios – SVR now >95%

- Black patients
- ESRD
- HIV/HCV
- Post-liver transplant
- G3 + cirrhosis

Slide 18 of 83

CASE 1 – Initial Treatment and when to do resistance testing

26 y.o. Caucasian Woman with HCV Geno 1b, no cirrhosis , HCV RNA 1.2 mil IU/mL

HCV Hx:

Diagnosed during last pregnancy
Risk factor IVD last use 26 mos ago
Treatment naïve
Fibrosure F0

Other med hx includes:

Seizure disorder on keppra

Slide 19 of 83

ARS Question #3: Which of the following regimens would NOT be recommended for this patient with HCV g1b and no cirrhosis?

1. Sofosbuvir/velpatasvir/voxilaprevir x 8 wks
2. Sofosbuvir/velpatasvir x 12 wks
3. Sofosbuvir/ledipasvir x 8 wks
4. Glecaprevir/pibrentasvir x 8 wks

Slide 20 of 83

Minimum to Know Pre-Treatment

- HCV genotype/subtype
- HCV resistance (sometimes)
- Stage of fibrosis
  - Cirrhosis - yes/no
    - If yes, decompensated? (e.g., ascites, encephalopathy, etc)
      - If yes, **don't use PIs**!
  - Method?
    - Liver biopsy
    - Transient elastography
    - Laboratory biomarkers
    - Imaging
- Prior HCV treatment?
  - Response?
  - DAA used?
- Medications
  - To check for drug interactions
- Comorbidities
  - Renal function
  - HIV status
  - Life expectancy < 1yr non-liver causes?
- Patient preference
- Child-bearing potential of patient/partner
  - Ribavirin is a teratogen

HIV/Hepatitis C helpline
1-866-637-2342

Slide 21 of 83

G1b Initial Treatment Recommended Regimens

IDSA/AASLD

www.hcvguidelines.org

NO CIRRHOSIS:	CIRRHOSIS:
Elbasvir/grazoprevir x 12 w	Elbasvir/grazoprevir x 12 w
Glecaprevir/pibrentasvir x 8 w	Glecaprevir/pibrentasvir x 12 w
Ledipasvir/sofosbuvir x 8* or 12 w	Ledipasvir/sofosbuvir x 12 w
Sofosbuvir/velpatasvir x 12 w	Sofosbuvir/velpatasvir x 12 w

*8 wk not recommended for Black patients or HIV-infected. Only recommended when RNA< 6 million IU/ml

Slide 22 of 83

CASE 1 – cont

26 y.o. Caucasian Woman with HCV Geno 1b, no cirrhosis (F0) HCV RNA 1.2 mil IU/mL on leviteracetam prescribed 8 weeks of sofosbuvir/ledipasvir.

ARS Question #4: True or false? Resistance testing should be performed prior to treatment.

1. True
2. False

Slide 23 of 83

RAS Testing prior to Treatment

- NS5A RASs are relatively common (10-15%)
- Significance of NS5A RASs may depend on the RAV, the genotype, the regimen used and whether prior NS5A treatment
- In initial treatment, use resistance testing prior to:
  - Treatment with grazoprevir/elbasvir for 1a
  - Treatment with sofosbuvir/velpatasvir for G3 with cirrhosis

Table: Clinically Significant NS5A Resistance-Associated Variants (RAVs)

Wild-type Amino Acid (sensitive)	Position	Variant Amino Acid (reduced EBR activity)
M	28	A/G/T
Q	30	D/E/H/G/K/L/R
L	31	F/M/V
Y	93	C/H/N/S



Slide 24 of 83

G1a Initial Treatment Recommended Regimens

IDSA/AASLD

www.hcvguidelines.org

NO CIRRHOSIS:

- Elbasvir/grazoprevir x 12 w if no hi level NS5A resistance
- Glecaprevir/pibrentasvir x 8 w
- Ledipasvir/sofosbuvir x 8* or 12 w
- Sofosbuvir/velpatasvir x 12 w

*8 wk not recommended for Black patients or HIV-infected

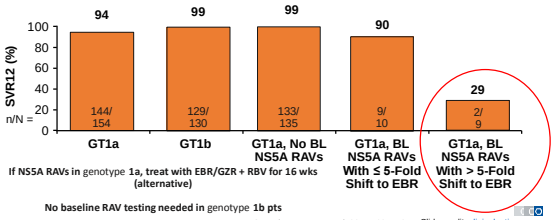
CIRRHOSIS:

- Elbasvir/grazoprevir x 12 w if no hi level NS5A resistance
- Glecaprevir/pibrentasvir x 12 w
- Ledipasvir/sofosbuvir x 12 w
- Sofosbuvir/velpatasvir x 12 w

Slide 25 of 83

Impact of Baseline NS5A RAVs:

SVR12 With 12 Wks of Grazoprevir/Elbasvir for initial treatment



If NS5A RAVs in genotype **1a, treat with EBR/GZR + RBV for 16 wks (alternative)**

No baseline RAV testing needed in genotype **1b pts**

Zeuzem S, et al. Ann Intern Med. 2015;163:1-13. Slide credit clinicaloptions.com

Slide 26 of 83

Team Approach to HCV Treatment
Pre-treatment, Pre-approval

My Contribution

- Work with patient to pick regimen
- Clearly describe in plan ANY indications for treatment
  - E.g. HCV st 2 fibrosis, woman of child bearing potential, cryoglobulins, DM, etc.
- Clearly describe in my plan the indications for this SPECIFIC regimen
  - E.g. G1a, Tx-naïve, cirrhosis – LDV/SOF x 12 wks
  - If unusual choice - cite study or guidance document
- Clearly describe in my plan the reasons other regimens NOT a good option
  - E.g. current darunavir/r use precludes use of PrOD
- Confirm discussed medication interactions and address any specific ones
- Document no barriers to adherence evidenced by HIV control, etc

Contribution of Hepatitis Nurses +/or Pharmacy

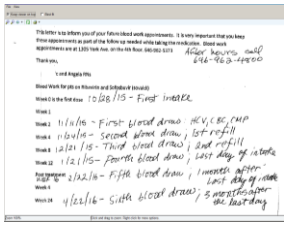
- Complete specialty pharmacy referral
- Print any relevant lab/imaging documentation
- Fax to specialty pharmacy
  - File and Track progress
- Help draft letters for Appeals
  - File and Track progress
- Stay in communication with patient
- Patient assistance connections when needed
  - Copay programs
  - Charity

Slide 27 of 83

Team Approach to HCV Treatment
Pre-treatment, Post-approval

Meet with Hepatitis Nurses only

- Drugs usually delivered to our clinic
- Review any new medications
- Education about medications
- Discussion of side effects and management
- Create monitoring plan schedule
- Book appointments for monitoring visits
  - Local Quest lab if cannot make to our clinic
- Review how to take and usually take first dose



Slide 28 of 83

Initial Treatment Algorithm

Algorithm

- HCV genotype/subtype & resistance
- HIV status
- Cirrhosis - yes/no - duration
  - If yes, decompensated? (e.g., ascites, encephalopathy, etc)
    - If yes, **don't use PIs**!
- Renal function
  - Avoid Sof if CrCl <30
- Medications
  - Address drug interactions
  - Ribavirin is a teratogen
- On treatment/Follow up specifics

Our case patient

- 1b, no need for resistance testing, choose from 4 recommended regimens
- HIV neg
- Cirrhosis – No
  - Could use 8 wk regimen if meet criteria
- CrCl nl
- Medications: PPI qd
  - Elbasvir/grazoprevir – no interaction
  - Glecaprevir/pibrentasvir (limit dose)
- Follow up: h/o IVD, rescreen and ensure adequate supportive services (psych, harm reduction)

Slide 29 of 83

CASE 2 – What to use in patient with ESRD

45 y.o. African American M with HCV Geno2 and cirrhosis, HCV RNA 221,000 IU/mL

HCV Hx:

- Treatment naïve
- Cirrhotic based on transient elastography measurement of 17 kpa
  - No decompensation events
  - EGD no varices
  - Sono mildly nodular, no HCC

Other med hx includes:

- HTN, high cholesterol
- ESRD on hemodialysis
- Mild GERD on PPI qD
- HBV sAg+ cAb+ sAb-, HBV DNA negative

Slide 30 of 83

G2 INITIAL TREATMENT RECOMMENDED REGIMENS

IDSA/AASLD/IAS-USA

www.hcvguidelines.org

NO CIRRHOSIS:

- Glecaprevir/pibrentasvir x 8 w
- Sofosbuvir/velpatasvir x 12 wks

CIRRHOSIS:

- Glecaprevir/pibrentasvir x 12 w
- Sofosbuvir/velpatasvir x 12 wks

Slide 31 of 83

ARS Question #5: Prior to treatment, you recommend which following additional evaluation?

1. Hepatitis B genotype
2. HCV resistance test
3. MRI to evaluate for Hepatocellular carcinoma
4. Transplant center referral

Slide 32 of 83

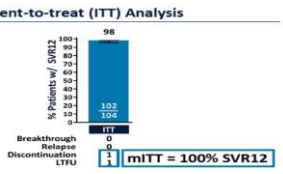
ARS Question #6: Your patient is not interested in kidney transplant at this time. Which of the following treatments do you recommend?

1. Elbasvir/grazoprevir x 12 w
2. Glecaprevir/pibrentasvir x 8w
3. Glecaprevir/pibrentasvir x 12w
4. Sofosbuvir/velpatasvir x 12 wks

Slide 33 of 83

Glecaprevir/pibrentasvir: Renal Impairment

- GT 1-6 for 12 weeks
- Stage 4 or 5 CKD
  - GFR<30 including HD
  - 82% on HD
- TN or TE (42%) with IFN, P/R or SOF+P/R
- Including compensated cirrhosis (19%)
- GT1a 22%, GT1b 28%, GT2 16%, GT3 11%, GT4 19%, GT5 1, GT6 11



Gane et al. EASL 2017

Slide 34 of 83

Recommended regimens listed by evidence level and alphabetically for:

Patients With CKD Stage[a] 4 or 5 (eGFR <30 mL/min or End-Stage Renal Disease)

RECOMMENDED	GENOTYPE	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	1a, 1b, 4	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	1, 2, 3, 4, 5, 6	8 to 16 weeks[c]	I, B[c]

[a] Chronic kidney disease (CKD) stages: 1 = normal (eGFR >90 mL/min); 2 = mild CKD (eGFR 60-89 mL/min); 3 = moderate CKD (eGFR 30-59 ml/min); 4 = severe CKD (eGFR 15-29 mL/min); 5 = end-stage CKD (eGFR <15 mL/min)
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] Patients in this group should be treated as would patients without CKD. Duration of glecaprevir/pibrentasvir should be based on presence of cirrhosis and prior treatment experience (please refer to appropriate section). As such, strength of rating may be lower for certain subgroups.

Slide 35 of 83

CASE 2 – cont

45 y.o. African American M with HCV Geno2 and compensated cirrhosis, HCV RNA 221,000 IU/mL, ESRD, prescribed glecaprevir/pibrentasvir x 12 weeks.
Four weeks into treatment, he comes in for labs and complains of some malaise. Exam unchanged with no evidence of ascites or edema.

Labs reveal:
HCV RNA not detected
AST 120 IU/ml (baseline 35)
ALT 155 IU/ml (baseline 33)
Bili 1.9 mg/dl (baseline 1.0)

Slide 36 of 83

ARS Question #7: What do you do next?

1. Immediately discontinue his HCV treatment and admit to hospital
2. Discontinue HCV treatment and order labs
3. Continue HCV treatment and order labs

Slide 37 of 83

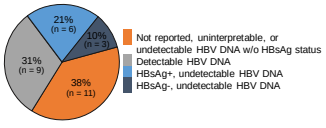
Some potential explanations:

- Hepatitis B reactivation
- Hepatic decompensation from HCV protease inhibitor
- Another viral infection
- Drug-induced liver injury

Slide 38 of 83

HBV Reactivation in Pts Receiving HCV DAAs: Postmarketing Cases Reported to FDA

- 29 confirmed cases of HBV reactivation in HCV DAA recipients in ~ 3 yrs (November 2013 to October 2016)
  - Most cases occurred within 4-8 wks of initiation



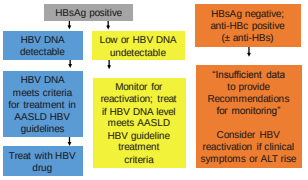
- Outcome:
  - Transplant (n = 1)
  - Death (n = 2)
  - Hospitalization (n= 3)
  - Other (n = 20)

Bersoff-Matcha SJ, et al. AASLD 2016. Abstract LB-17.

Slide 39 of 83

HBV Testing/Monitoring During HCV DAA Therapy

- Test all pts initiating HCV therapy for HBsAg, anti-HBc, and anti-HBs
  - Vaccinate if no HBV markers; follow flow chart below if HBV markers present



AASLD/IDSA. HCV Guidelines 2016. Graphic adapted from Ira M. Jacobson, MD.

Slide credit: clinicaloptions.com

Slide 40 of 83

Initial Treatment Algorithm

Algorithm

- HCV genotype/subtype & resistance
- HIV status
- Cirrhosis - yes/no - duration
  - If yes, decompensated? (e.g., ascites, encephalopathy, etc)
    - If yes, **don't use PIs**!
- Renal function
  - Avoid Sof if CrCl <30
- Medications
  - Address drug interactions
  - Ribavirin is a teratogen
- On treatment/Follow up

Our case patient

- 2, no need for resistance testing, start with 2 recommended regimens
- HIV neg
- Cirrhosis – yes
  - No 8 wk regimens
  - Compensated so ok to use PIs
- CrCl <30, no regimens w/ sofosbuvir
- Medications: PPI qd
  - Elbasvir/grazoprevir – no interaction
  - Glecaprevir/pibrentasvir (limit dose)
- Cirrhosis needs monitoring, HBV sAg+ needs monitoring

Slide 41 of 83

Summary : Is this as good as it gets?

- Remarkable advances in terms of HCV treatment tolerability & efficacy
  - SVRs for HIV/HCV now mirror monoinfection
  - Continued refinement of therapies that can be used in varied populations (ESRD with G2 and G3, G3+cirrhosis, acute HCV)
  - Still drug interaction issues, but valuable resources to help manage
- RAV testing prior to initial treatment if:
  - G1a and planned grazoprevir/elbasvir
  - G3 & cirrhosis
- Successful treatment prevents cirrhosis, end stage liver disease, and hepatocellular cancer
- Post SVR – continue liver disease management/HCC screening, monitor HBV reactivation, and consider HCV screening if ongoing risk

Slide 42 of 83

Optimizing Initial Treatment: Case Session 2

Kristen M. Marks, MD
Assistant Professor
Weill Cornell Medical College
New York, NY

Slide 43 of 83