AETC AIDS Education & Training Center Program
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A Case Based Approach to Treatment of HCV and Treatment Failure in People with HIV

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Disclosures

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Learning Objectives

- By the end of this session, each participant will be able to:
  - Describe recent changes to the AASLD/IDSA HCV Guidance and manage patients co-infected with HIV-HCV according to these guidelines.
  - Identify important drug-drug interactions between ART and DAAs used to treat HCV.
  - Discuss monitoring strategies for HCV treatment-naïve co-infected patients on DAAs.
  - Manage HCV treatment non-adherence and failure in patients co-infected with HIV and HCV

Case 1

A 30 year old male well-controlled HIV initiates care at your clinic. His CD4 is 450 cells/µL and plasma HIV-1 RNA is undetectable on bictegravir / emtricitabine / tenofovir alafenamide. On his intake labs, HCV Ab is positive and HBSAg is negative. Review of his outside records reveals that he tested HCV Ab positive last year with an HCV RNA of 1.5 million IU/mL but has never been treated. Which of the following statements is true?

A. HIV infection is a contraindication to a simplified HCV treatment approach
B. His HCV can be treated according to a simplified treatment approach as long as he does not have cirrhosis.
C. His HCV can be treated according to a simplified treatment approach as long as he does not have decompensated cirrhosis.

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C. **His HCV can be treated according to a simplified treatment approach as long as he does not have decompensated cirrhosis.**

- AASLD/IDSA HCV guidance was updated in in October 2022 to **remove HIV co-infection as a contraindication to the simplified treatment approach**
- There are simplified treatment guidelines for HCV treatment-naïve adults without and with compensated cirrhosis
- Patients with decompensated cirrhosis should be referred to a liver specialist

AASLD/IDSA Simplified Treatment Guidelines for Treatment Naïve Adults (without cirrhosis)

Who Is NOT Eligible	Who is Eligible
▪ Prior Hepatitis C treatment ▪ Cirrhosis (can receive simplified treatment for adults with cirrhosis) ▪ HBSAg positive (untreated Chronic HBV) ▪ Current pregnancy ▪ Known or suspected hepatocellular carcinoma ▪ Prior liver transplantation ▪ **HIV+ on TDF-containing regimen with eGFR<60 ml/min**	▪ Adults with chronic Hepatitis C (any genotype), including those co-infected with HIV, who do not have cirrhosis and have not previously received treatment

AASLD-IDSA. Simplified HCV Treatment for Treatment-Naïve Adults Without Cirrhosis. Recommendations for testing, managing, and treating hepatitis C. https://www.hcvguidelines.org/treatment-naive/simplified-treatment

Case 1

The patient has not had any pre-treatment assessment. Which of the following pre-treatment tests should be done initially to assess risk for cirrhosis?

A. Transient elastography (FibroScan)
B. Liver ultrasound
C. Fib-4 score
D. Liver biopsy

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D. Liver biopsy

Pre-treatment Assessment: Cirrhosis Assessment

- Calculate Fib-4 score (age, ALT, AST, platelets)
  - https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4

Cirrhosis presumed if FIB-4 score is >3.25 OR if prior testing concerning for cirrhosis

- Transient elastography (FibroScan) stiffness >12.5kPa
- Noninvasive serologic (e.g. FibroSure, Enhanced Liver Fibrosis Test) above the cutoff for cirrhosis
- Evidence of cirrhosis on imaging (nodularity and/or splenomegaly)
- Platelets <150,000 mm^3
- Liver biopsy with cirrhosis

AASLD-IDSA. Simplified HCV Treatment for Treatment-Naïve Adults Without Cirrhosis. Recommendations for testing, managing, and treating hepatitis C. https://www.hcvguidelines.org/treatment-naive/simplified-treatment

Fib-4 Score and Advanced Fibrosis

- Fib-4 <1.45 has a NPV 90%
- Fib 4 >3.25 has 97% specificity & PPV 65%
- ~70% of patients will have values <1.45 or >3.25

https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4

Complete blood count (CBC)
Hepatic function panel
Calculated glomerular filtration rate (eGFR)

- Within 6 months before treatment initiation

Quantitative HCV RNA (HCV viral load)
HIV Ag /Ab test in patients who are negative
Hepatitis B Surface Antigen

- Anytime prior to treatment initiation

Serum pregnancy testing and counseling regarding pregnancy risks of HCV medications in women of childbearing age

- Shortly before treatment initiation

AASLD-IDSA. Simplified HCV Treatment for Treatment-Naïve Adults Without Cirrhosis. Recommendations for testing, managing, and treating hepatitis C. https://www.hcvguidelines.org/treatment-naive/simplified-treatment

Additional pre-treatment assessment

- Medication reconciliation and assessment for drug-drug interactions
  - University of Liverpool Hepatitis Drug Interactions: https://www.hep-druginteractions.org/checker
- Education about medication administration & adherence
- Education on prevention of reinfection

Case 1

- The patient's FIB-4 score is <1.45 and eGFR is 70 ml/min. He is on bictegravir / emtricitabine / tenofovir alafenamide. He takes no other medications. What are the firstline direct acting antivirals recommended to treat this patient?

Case 1

- The patient's FIB-4 score is <1.45 and eGFR is 70 ml/min. He is on bictegravir / emtricitabine / tenofovir alafenamide. He takes no other medications. What are the first-line direct acting antivirals (DAAs) recommended to treat this patient?

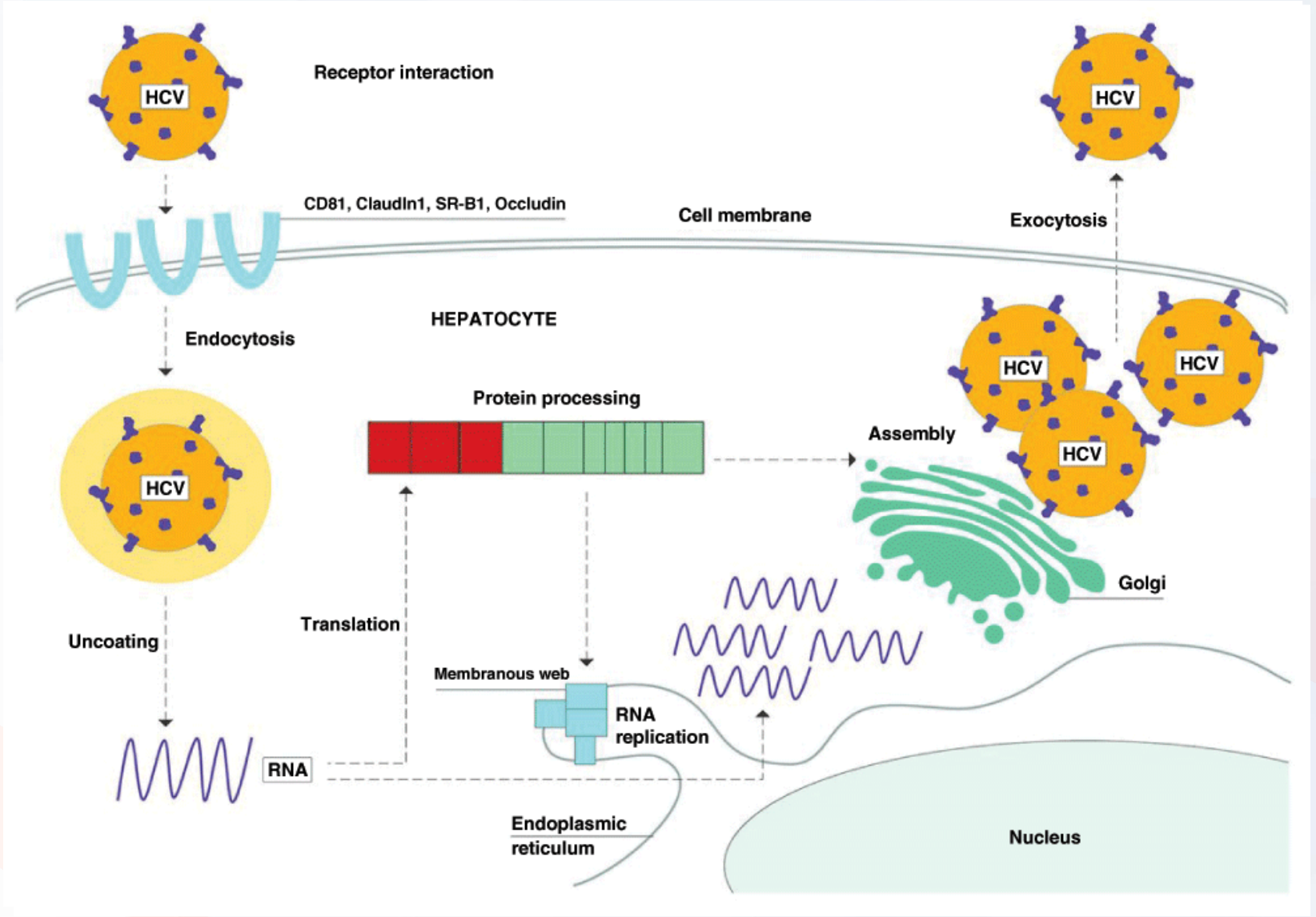
Glecaprevir 100 mg/pibrentasvir 40 mg, 3 tablets daily for 8 weeks OR

Sofosbuvir 400 mg/velpatasvir 100 mg, 1 tablet daily for 12 weeks

These agents are pangenotypic = no genotype needed

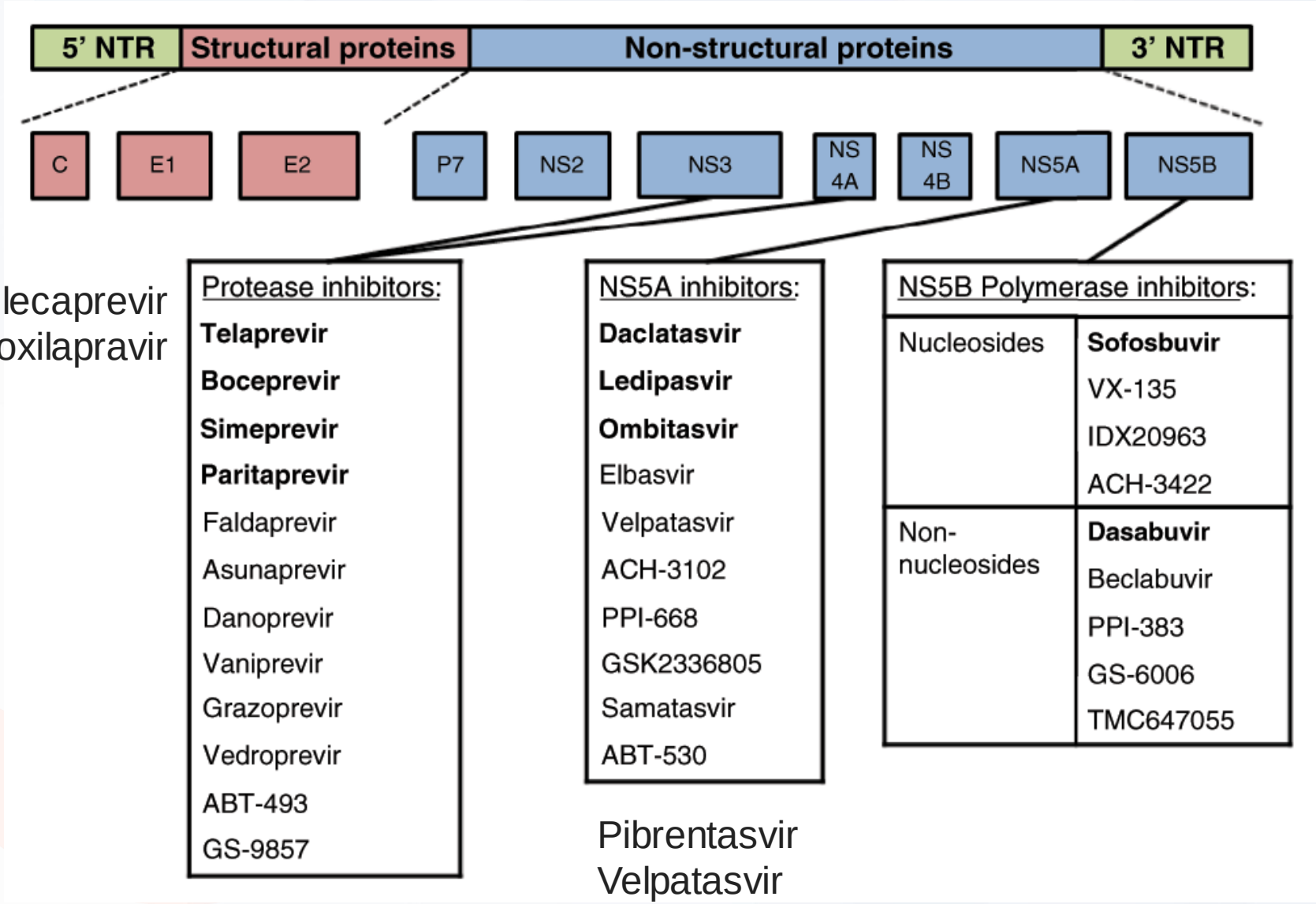
AASLD-IDSA. Simplified HCV Treatment for Treatment-Naïve Adults Without Cirrhosis. Recommendations for testing, managing, and treating hepatitis C. https://www.hcvguidelines.org/treatment-naive/simplified-treatment

Figure 2. Life cycle of the hepatitis C virus.



Maan R and van der Meer AJ. Recent advances in managing chronic HCV infection: focus on therapy in patients with severe liver disease [version 1]. F1000Research 2016, 5:367 (doi: 10.12688/f1000research.7399.1).

Figure 1. The hepatitis C virus (HCV) genome.



Maan R and van der Meer AJ. Recent advances in managing chronic HCV infection: focus on therapy in patients with severe liver disease [version 1]. F1000Research 2016, 5:367 (doi: 10.12688/f1000research.7399.1).

Case 1

- How would we approach this patient differently if their ART regimen was:
  - Darunavir/cobicistat/emtricitabine/tenofovir alafendamide?
  - Efavirenz/emtricitabine/tenofovir disoproxil fumarate?

Drug-Drug Interactions

HIV Antiretrovirals	Glecaprevir/Pibrentasivir	Sofosbuvir/Velpatasvir
Efavirenz, Etravirine, Nevirapine, other strong CYP-3A4 and P-gp inducers	↓ concentrations of both DAAs AVOID	↓velpatasvir AVOID
Ritonivir or cobicistat boosted PI; unboosted atazanavir	↑ concentrations of both DAAs AVOID	May ↑ velpatasvir but no adverse effect in trials Coadministration okay
Tenofovir disoproxil fumarate, Tenofovir alafenamide	Coadministration okay	TAF preferred; If TDF used with boosted Pis AND eGFR <60, ↑TDF & monitoring recommended
Rilpivirine, Doravorine, Elvitegravir-cobicistat, Raltegravir, Bictegravir, Dolutegravir, Abacavir, Emtricitabine, Lamivudine, Maraviroc	Coadministration okay	Coadminstration okay

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/hepatitis-c-virus?view=full

How to approach drug-drug interactions

- ART should never be held to treat with DAAs
- In patients taking a contraindicated HIV antiretroviral, often the best approach is to modify ART regimen prior to initiating DAAs
  - Delay initiation of the DAA regimen by ≥ 2 weeks
- If resuming prior ART regimen, wait until ≥ 2 weeks after completing DAAs

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/coinfections-hepatitis-c-virus-hcv

Case 1

- The patient starts treatment with sofosbuvir/velpatasvir for 12 weeks. What type monitoring should be done during and post-treatment?
  - A. CBC, hepatic function panel, eGFR and HCV RNA at 4 weeks and HCV RNA + hepatic function panel at end of therapy and 12 weeks after completing therapy
  - B. HCV RNA and hepatic function panel at end of therapy and 12 weeks after completing therapy
  - C. HCV RNA and hepatic function panel at 12 weeks after completing therapy

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  - B. HCV RNA and hepatic function panel at end of therapy and 12 weeks after completing therapy
  - **C. HCV RNA and hepatic function panel at 12 weeks after completing therapy**

Monitoring in simplified HCV treatment

On treatment monitoring

- Often no laboratory monitoring required
- Can schedule in-person or telehealth visits as needed
- Monitor patients on DM medications for symptomatic hypoglycemia
- Monitor patients on warfarin for subtherapeutic anticoagulation

Post-treatment follow-up

- Assess for SVR by checking HCV RNA to confirm it is undetectable 12 weeks (SVR12) or later after treatment
- Also check hepatic function panel for normalization of transaminases

AASLD-IDSA. Simplified HCV Treatment for Treatment-Naïve Adults Without Cirrhosis. Recommendations for testing, managing, and treating hepatitis C. https://www.hcvguidelines.org/treatment-naive/simplified-treatment

ACTG A5360 (MINMON) Study

- 399 participants with chronic HCV, compensated cirrhosis included
- 166 participants co-infected with HIV
- Limited baseline testing
- Provided with entire 12 week supply of sofosbuvir/velpatasvir
- No lab monitoring or in person visits on treatment
- SVR 12 weeks after treatment 95% (95% CI, 92.4-96.7%)
- Similar proportions of patients with and without HIV had SVR

Solomon SS, et al. A minimal monitoring approach for the treatment of hepatitis C virus infection (ACTG A5360 [MINMON]): a phase 4, open-label, single-arm trial. Lancet Gastroenterol Hepatol. 2022 Apr;7(4):307-317. doi: 10.1016/S2468-1253(21)00397-6.

AASLD/IDSA Simplified Treatment Guidelines for Treatment Naïve Adults (with cirrhosis)

Who Is NOT Eligible	Who is Eligible
▪ Current/prior episode of decompensated cirrhosis ▪ Prior Hepatitis C treatment ▪ End stage renal disease (eGFR <30 ml/min/m^2) ▪ HBSAg positive (untreated Chronic HBV) ▪ Current pregnancy ▪ Known or suspected hepatocellular carcinoma ▪ Prior liver transplantation ▪ HIV+ on TDF-containing regimen with eGFR<60 ml/min/m^2	▪ Adults with chronic Hepatitis C (any genotype), including those co-infected with HIV, who have compensated cirrhosis (Child Pugh A) and have not previously received treatment ▪ Liver biopsy not required ▪ Presumed cirrhosis is based on FIB-4 >3.25 or previous testing (FibroScan >12.5 kPa; non-invasive serologic test above cutoff e.g. FibroSure; liver nodularity/splenomegaly on imaging; platelest <150,000/mm^3; prior liver biopsy with cirrhosis)

AASLD-IDSA. Simplified HCV Treatment for Treatment-Naïve Adults With Compensated Cirrhosis. Recommendations for testing, managing, and treating hepatitis C. https://www.hcvguidelines.org/treatment-naive/simplified-treatment-compensated-cirrhosis

Child-Turcott-Pugh Score (CTP score)

- https://www.hepatitisc.uw.edu/page/clinical-calculators/ctp
- Hepatic encephalopathy, ascites, total bilirubin, albumin, INR
- Score ≥7 indicates decompensated cirrhosis

Differences with the non-cirrhosis guidance

CTP score in addition to FIB-4

Liver US to rule out HCC or subclinical ascites

Genotype

Labs within 3 rather than 6 months prior

CBC, hepatic function panel, eGFR, ***INR***

Genotype 1-6: Glecaprevir / pibrentasvir x 8 wks

Genotype 1, 2, 4, 5, 6: Sofosbuvir/velpatasvir x 12 weeks

Genotype 3: Baseline NS5A resistance-associated substitution (RAS) testing. If no Y93H, then can use sofosbuvir / velpatasvir x 12 weeks

On treatment may monitor hepatic function periodically; monitor for liver related symptoms

Check HCV RNA, LFTs 12 weeks post-treatment

Follow-up after SVR:

Liver US surveillance for HCC +/- AFP q6 monts

EGD to assess for varices as per AASLD guidance

AASLD-IDSA. Simplified HCV Treatment for Treatment-Naïve Adults With Compensated Cirrhosis. Recommendations for testing, managing, and treating hepatitis C. https://www.hcvguidelines.org/treatment-naive/simplified-treatment-compensated-cirrhosis

Case 2

- A 38 year old male with HIV and chronic HCV (without cirrhosis) is on treatment with glecapravir/pibrentasvir. The patient calls you and says he took most of his doses for the first 4 weeks, he just missed " a couple of times". He had to leave town unexpectedly for a family emergency and was unable to pick up his refill. He has missed 5 days. What are the next steps?

A. Restart glecaprevir/pibrentasvir immediately and complete the 8 week course as planned. Check for SVR 12 weeks after completion.

B. Restart glecaprevir/pibrentasvir immediately. Check HCV RNA now and if undetectable continue 8 week course as planned. If detectable, stop glecaprevir/pibrentasvir and manage as a retreatment.

C. Do not restart glecaprevir/pibrentasvir. Assess for SVR12 and if HCV RNA is not undetetable, manage as a retreatment.

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C. Do not restart glecaprevir/pibrentasvir. Assess for SVR12 and if HCV RNA is not undetetable, manage as a retreatment.

- Treatment interruptions to glecaprevir/pibrentasvir or sofosbuvir/velpatasvir in first 28 days

Missed ≤ 7 days	Missed ≥ 8 days
Restart same DAA therapy immediately	Restart same DAA therapy immediately
Complete the original duration (8 – 12 weeks)	Check HCV RNA now.
Check SVR 12	HCV RNA undetectable: complete original course; extend 4 weeks if genotype 3 and/or cirrhosis. Check SVR 12.
	HCV RNA detectable or not obtained: extend treatment by 4 weeks. Check SVR12.

AASLD-IDSA. Incomplete adherence. Recommendations for testing, managing, and treating hepatitis C. https://www.hcvguidelines.org/evaluate/monitoring#incomplete-adherence

- Treatment interruptions to glecaprevir/pibrentasvir or sofosbuvir/velpatasvir after 28 days or more

Missed ≤ 7 days	Missed ≥ 8 days	Missed ≥ 21 days
Restart same DAA therapy immediately	Restart same DAA therapy immediately	Stop treatment and assess SVR12
Complete the original duration (8 – 12 weeks)	Check HCV RNA now.	If SVR 12 not achieved, retreat
Check SVR 12	HCV RNA undetectable: complete original course; extend 4 weeks if genotype 3 and/or cirrhosis. Check SVR 12.	
	HCV RNA detectable or not obtained: stop therapy, manage as retreatment	

Case 3

- A 40 y/o F with HIV and chronic HCV with compensated cirrhosis, genotype 1a, completed 12 weeks of sofosbuvir/velpatasvir. However at her SVR12 measurement, HCV RNA was detectable. The patient thinks she missed a dose about once/week. What is the best next step?

A. Retreat with sofosbuvir/velpatasvir for another 12 weeks.

B. Treat with glecaprevir/pibrentasvir for 8 weeks

C. Treat with sofosbuvir /velpatasvir/voxilaprevir for 12 weeks

D. Send testing for NS5A RAS (resistance associated substitutions)

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C. Treat with sofosbuvir /velpatasvir/voxilaprevir for 12 weeks

D. Send testing for NS5A RAS (resistance associated substitutions)

Sofosbuvir-Based Treatment Failure

- Managed the same in patients with and without compensated cirrhosis
- Sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg x 12 weeks
- Alternative: Glecaprevir 300 mg/pibrentasvir 120 mg x 16 weeks
  - Avoid in patients with prior exposure to combination NS5A inhibitor and NS3/4 protease inhibitor such as elbasvir/grazoprevir
  - Avoid in genotype 3 infection with sofosbuvir/NS5A inhibitor experience.

AASLD-IDSA. Sofosbuvir-based and elbasvir/grazoprevir treatment failures. Recommendations for testing, managing, and treating hepatitis C. https://www.hcvguidelines.org/treatment-experienced/sof-and-elb-grz-failures

Glecaprevir/Pibrentasvir Treatment Failure

- Managed the same in patients with and without compensated cirrhosis
  - Glecaprevir 300 mg/pibrentasvir 120 mg plus daily sofosbuvir 400 mg and weight-based ribavirin x 16 weeks
  - Sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg x 12 weeks (add weight based ribavirin for patients with compensated cirrhosis)

AASLD-IDSA. Glecaprevir/pibrentasvir treatment failures. Recommendations for testing, managing, and treating hepatitis C. https://www.hcvguidelines.org/treatment-experienced/g-p-failures

HCV Resistance to DAAs

- Like HIV, HCV is an RNA virus that replicates rapidly, 1-3 errors per replication cycle
- Resistance associated substitutions (RAS)
- Usually occur in setting of subtherapeutic drug levels
- Subset of patients have baseline RAS (for instance, ~13% with NS5A resistance mutations)
- Most of the clinically significant RASs involve NS5A

Wang, G.P., Terrault, N., Reeves, J.D. *et al.* Prevalence and impact of baseline resistance-associated substitutions on the efficacy of ledipasvir/sofosbuvir or simeprevir/sofosbuvir against GT1 HCV infection. *Sci Rep* **8**, 3199 (2018). https://doi.org/10.1038/s41598-018-21303-2

Clinical significance of RASs

- Regimen (co-drugs)
- Patient characteristics affecting treatment response like cirrhosis
- Fold-change decline in potency
- Genotype (1a, 1b, 3)
- Proportion of virus with the RAS (present in ≥15% to potentially affect SVR)

AASLD-IDSA. HCV Resistance Primer. Recommendations for testing, managing, and treating hepatitis C. https://www.hcvguidelines.org/evaluate/resistance

- When is resistance testing recommended?

Regimen	Testing
Elbasvir/grazoprevir	NS5A RAS testing for genotype 1a treatment naïve or experienced patients. Consider different regimen if clinically significant RAS present (M28A/T, Q30H/R, L31M/V, Y93C/H/N)
Ledipasvir/sofosbuvir	Consider NS5A RAS testing in treatment experienced patients with genotype 1a. If resistance conferring >100x change in vitro EC_{50} to ledipasvir consider different regimen. (Q30R, L31M/V, Y93H/N)
Sofosbuvir/velpatasvir	NS5A RAS testing for treatment-naïve genotype 3 & cirrhosis and treatment-experienced patients (without cirrhosis) if planning 12 weeks of this regimen. If Y93H is detected, add weight-based ribavirin or use different regimen

AASLD-IDSA. HCV Resistance Primer. Recommendations for testing, managing, and treating hepatitis C. https://www.hcvguidelines.org/evaluate/resistance

Case 4

- A 55 y/o female with HIV and chronic HCV, as well history of HTN and IVDU initiates care with your clinic. She was diagnosed with HIV 5 years ago but failed to engage in care. She recently completed an inpatient rehab program followed by sober living and her OUD has been in remission for 1 year. At the rehab she was started on dolutegravir/lamivudine. HIV VL is undetectable.
- Labs:
  - BMP wnl; ALT 75, AST 58; albumin 4; T. bili 0.8; coags wnl
  - CBC wnl except for PTL 135K
  - HBsAg neg, Anti-HBc pos, Anti-HBs neg
- US shows hepatomegaly, no nodules
- Elastography: stage 3 fibrosis

Case 4

She is highly motivated to treat her chronic HCV. In this situation:

A. HCV treatment proceeds as usual per compensated cirrhosis guidance
B. Patient needs treatment for both HBV and HCV
C. HBV treatment is initiated first, followed by HCV treatment
D. Additional work up is needed

Case 4

She is highly motivated to treat her chronic HCV. In this situation:

A. HCV treatment proceeds as usual per compensated cirrhosis guidance
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Case report | Open Access | Open Peer Review

Fulminant hepatitis B reactivation leading to liver transplantation in a patient with chronic hepatitis C treated with simeprevir and sofosbuvir: a case report

Alexander R. Ende, Nina H. Kim, Matthew M. Yeh, Jason Harper and Charles S. Landis

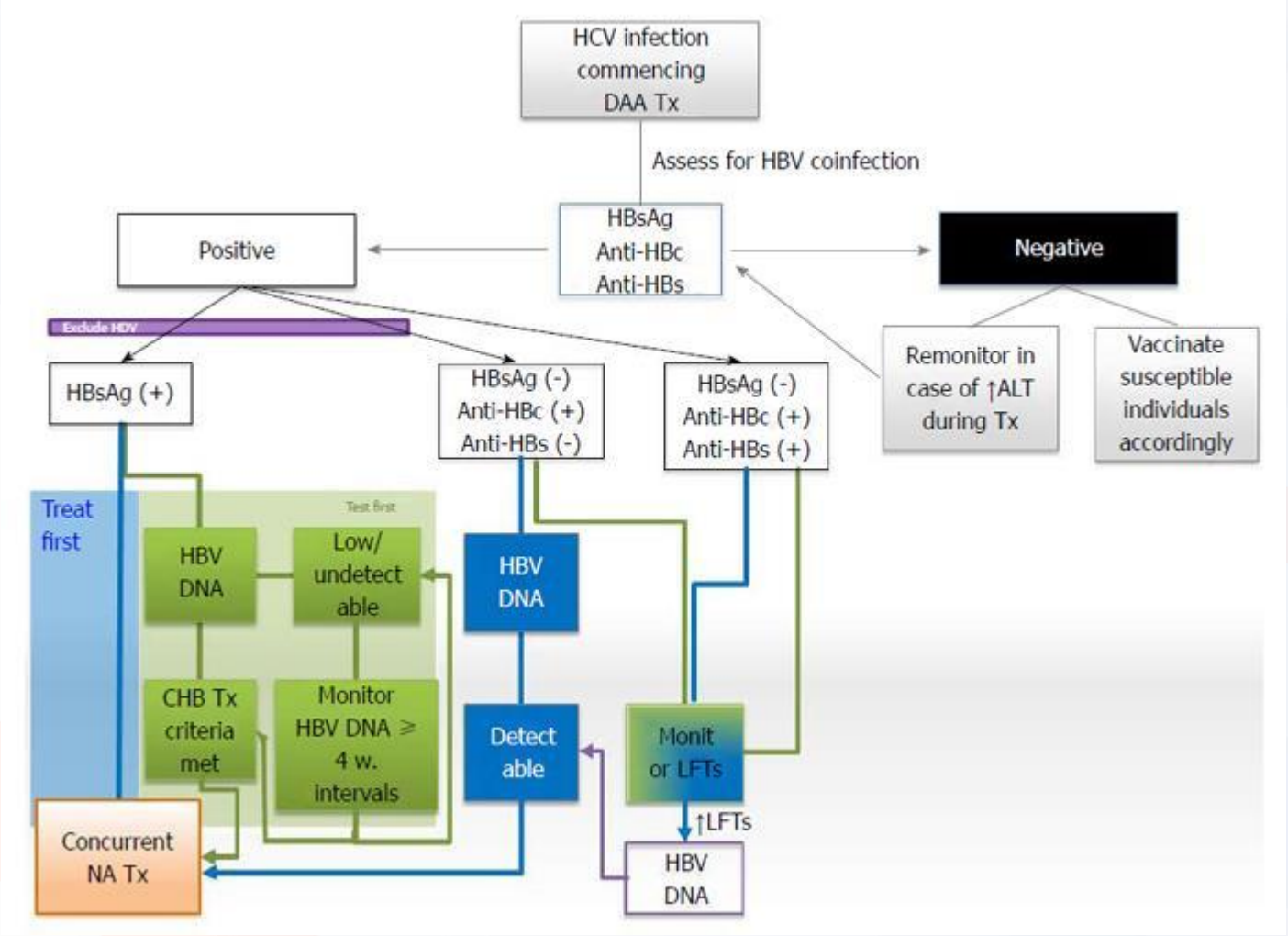
Journal of Medical Case Reports 2015 9:164
https://doi.org/10.1186/s13256-015-0630-8
Received: 16 December 2014 | **Accepted:** 29 May 2015 | **Published:** 28 July 2015

Open Peer Review reports

- 59-year-old female with HCV GT1b
- Isolated hepatitis B core antibody positive
- Treated with simeprevir, sofosbuvir, and ribavirin
- Fulminant hepatic failure at week 11 of a planned 12-week course (hepatitis B reactivation)
- Required liver transplantation
- Fortunately, unremarkable post-transplant clinical course

Week 11 labs
ALT 2263U/L
AST 2870U/L
TB 9.1mg/dL
INR 1.9
Pos HBsAg
VL 29,000,000IU/mL

Treatment algorithm in HBV-HCV co-infection



Aggeletopoulou I, Konstantakis C, Manolakopoulos S, Triantos C. Risk of hepatitis B reactivation in patients treated with direct-acting antivirals for hepatitis C. *World J Gastroenterol* 2017; 23(24): 4317-4323 [PMID: 28706414 DOI: 10.3748/wjg.v23.i24.4317]

Take Away Points

- Co-infection with HIV is no longer a contraindication to the simplified treatment approach for chronic in for treatment-naïve patients without cirrhosis or with compensated cirrhosis.
- Most treatment-naïve patients without cirrhosis or with compensated cirrhosis require minimal monitoring while on DAAs.
- Many patients who experience treatment interruptions are able to resume the same regimen and complete their original course as planned.
- Patients can often be retreated after treatment failure without the need for resistance testing
- Patients with positive HBsAg indicating chronic HBV are at risk for fulminant liver failure if HCV is treated but HBV is not. In rare cases, patients with isolated HBcAb have reactivated HBV with fulminant liver failure.

Thank you! Any comments or questions?