AETC AIDS Education & Training Center Program Mountain West

Hepatitis C Treatment Update

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Disclosures

I have served on Advisory Board for Gilead Sciences (not hep C related), the P& T Cmte for Premera Blue Cross, and data adjudication cmte for Novo Nordisk.

Agenda

- Epidemiology update
- Review new AASLD/IDSA practice guidelines
- What to do with treatment interruptions
- Pregnancy and HCV therapy

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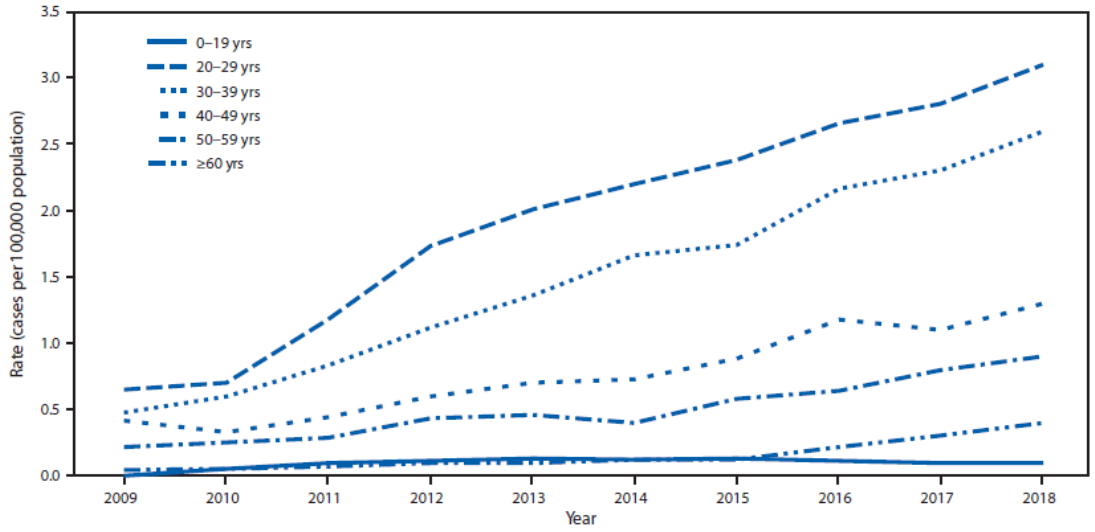
Epidemiology: HCV still increasing

- During 2018, a total of 3,621 cases of acute hepatitis C were reported, representing an estimated 50,300 cases (95% CI = 39,800–171,600)
- During 2009–2018, the number of reported acute hepatitis C cases per 100,000 population increased threefold, from 0.3 in 2009 to 1.2 in 2018.

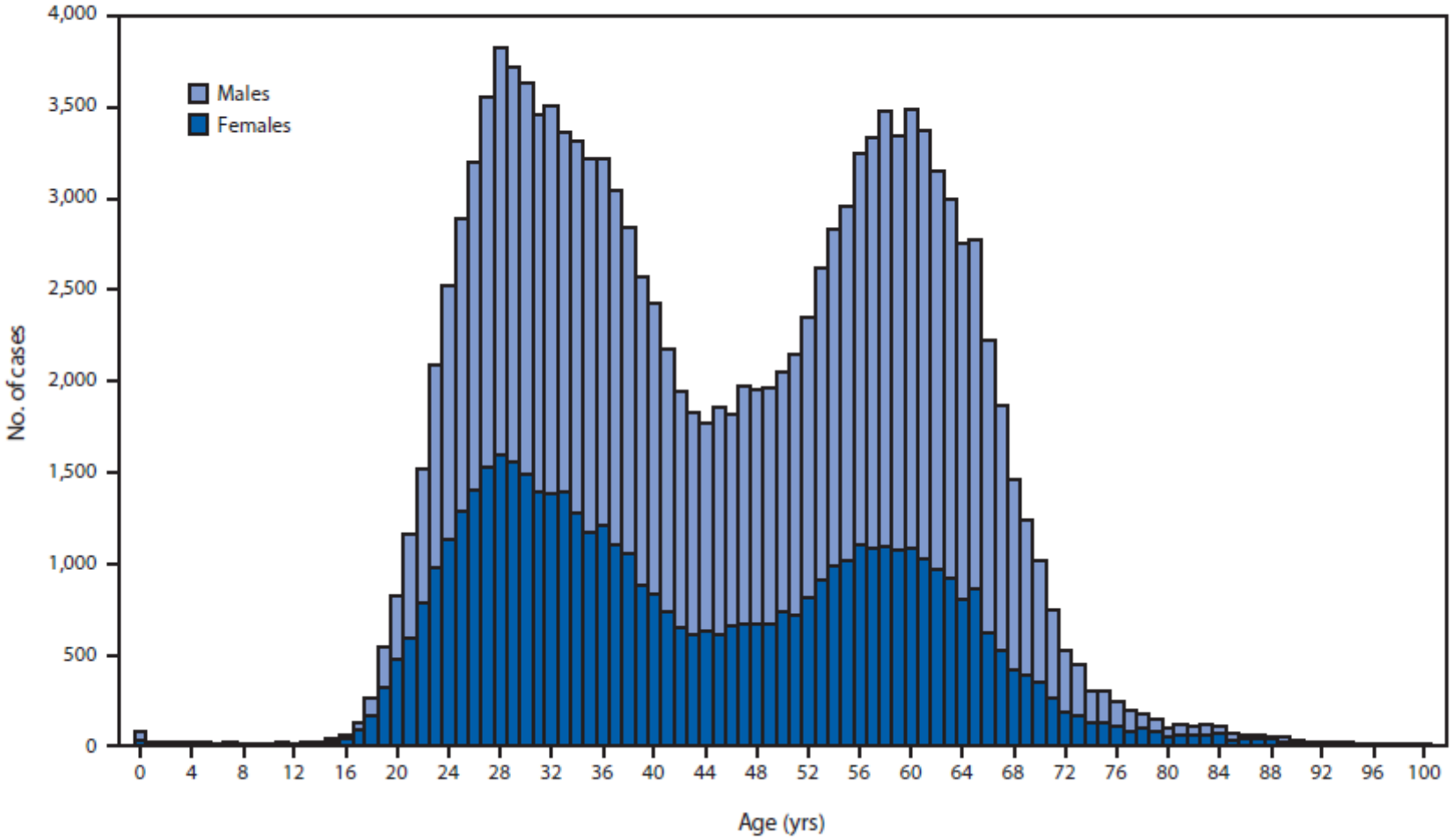
FIGURE 1. Rate* of reported† acute hepatitis C cases,§ by year and age group — National Notifiable Diseases Surveillance System, United States, 2009–2018



Source: Ryerson AB, et al. MMWR 2020; 69(14):399-404.

Millennials now outnumber Baby Boomers

FIGURE 2. Number of newly reported* chronic hepatitis C cases,† by sex and age — National Notifiable Diseases Surveillance System, United States, 2018



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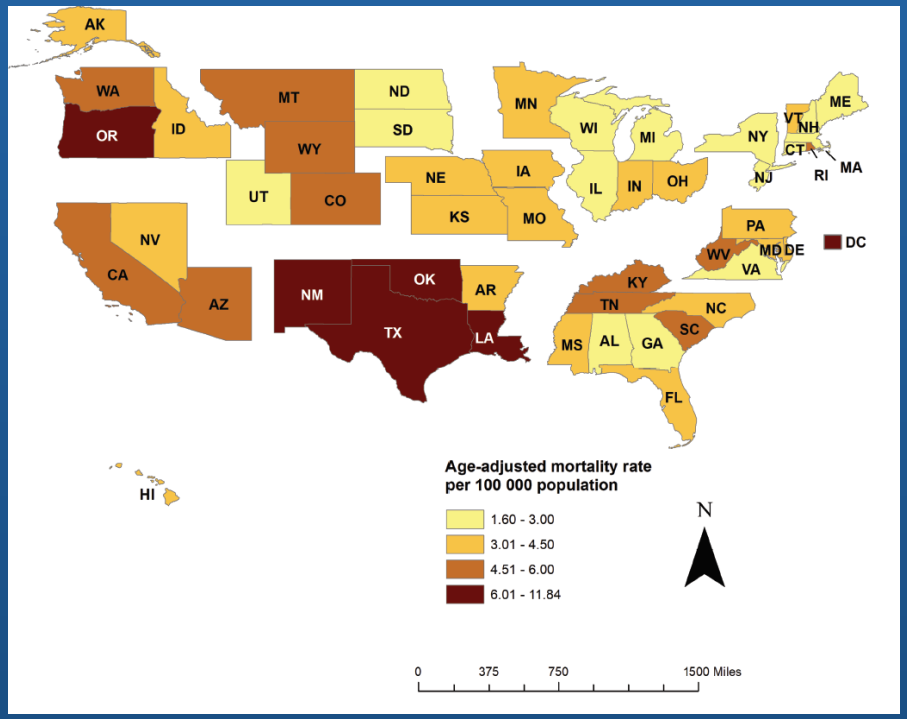
HCV is the #11 cause of death in 2017

- In 2017, there were 17,253 HCV-associated deaths
- HCV-associated death rate of 4.13 per 100k
- 29% listed HCV as underlying cause of death
- For situation where HCV was a contributor but not underlying cause, the top 3 causes of death were HCC, alcoholic cirrhosis and other neoplasm of liver
- Decline of 6.6% vs. 2016



Source: Ly KN, et al. Deaths Associated With Hepatitis C Virus Infection Among Residents in 50 States and the District of Columbia, 2016–2017. *Clin Infect Dis* 2020; 71(5):1149–60.

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Changes to AASLD/IDSA Guidelines

- Simplification and streamlining
- Updates on workup labs, treatment monitoring, SOF/VEL/VOX failures

Initial Labs and Workup

Initial HCV Testing and Follow-Up

Recommendations for Initial HCV Testing and Follow-Up	
RECOMMENDED	RATING
HCV-antibody testing with reflex HCV RNA polymerase chain reaction (PCR) testing is recommended for initial HCV testing.	I, A
Among persons with a negative HCV-antibody test who were exposed to HCV within the prior 6 months, HCV-RNA or follow-up HCV-antibody testing 6 months or longer after exposure is recommended. HCV-RNA testing can also be considered for immunocompromised persons.	I, C
Among persons at risk of reinfection after previous spontaneous or treatment-related viral clearance, HCV-RNA testing is recommended because a positive HCV-antibody test is expected.	I, C
Quantitative HCV-RNA testing is recommended prior to initiation of antiviral therapy to document the baseline level of viremia (ie, baseline viral load).	I, A
HCV genotype testing may be considered for those in whom it may alter treatment recommendations.	I, A
Persons found to have a positive HCV-antibody test and negative results for HCV RNA by PCR should be informed that they do not have evidence of current (active) HCV infection but are not protected from reinfection.	I, A

<u>Liver Fibrosis Assessment:</u>

- CBC, LFTs, INR, Cr
- AST:platelet ratio (APRI)
- FIB-4
- Transient elastography (Fibroscan)
- Fibrosure
- Imaging (CT or u/s)
- Liver biopsy (rarely required)

<u>Additional Labs:</u> urine pregnancy test (if woman of childbearing potential), HIV, Hep A and B serologies

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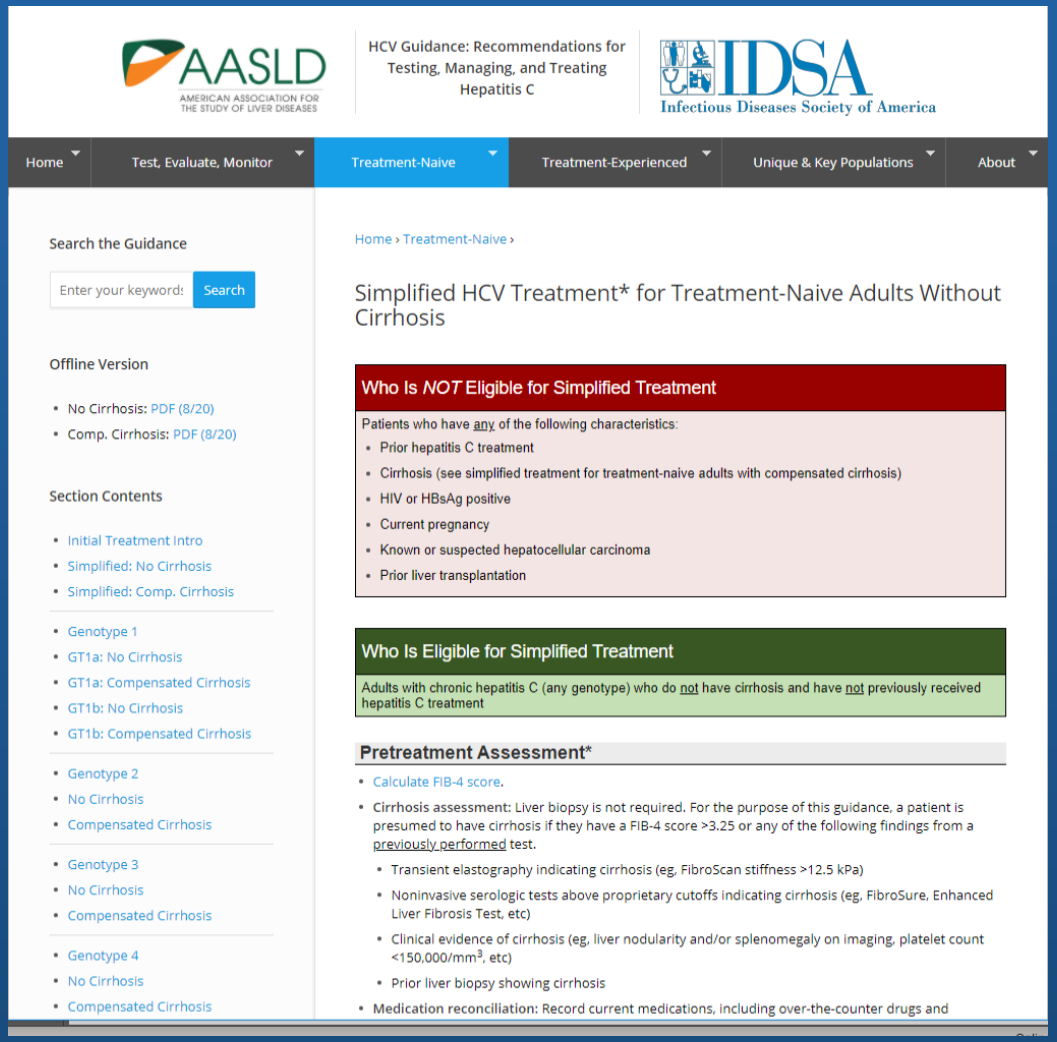
Simplified HCV Therapy: No Cirrhosis



AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

Home | Test, Evaluate, Monitor | Treatment-Naive | Treatment-Experienced | Unique & Key Populations | About

Search the Guidance

Enter your keyword: Search

Offline Version

- No Cirrhosis: PDF (8/20)
- Comp. Cirrhosis: PDF (8/20)

Section Contents

- Initial Treatment Intro
- Simplified: No Cirrhosis
- Simplified: Comp. Cirrhosis
- Genotype 1
- GT1a: No Cirrhosis
- GT1a: Compensated Cirrhosis
- GT1b: No Cirrhosis
- GT1b: Compensated Cirrhosis
- Genotype 2
- No Cirrhosis
- Compensated Cirrhosis
- Genotype 3
- No Cirrhosis
- Compensated Cirrhosis
- Genotype 4
- No Cirrhosis
- Compensated Cirrhosis

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Simplified HCV Treatment* for Treatment-Naive Adults Without Cirrhosis

Who Is *NOT* Eligible for Simplified Treatment

Patients who have any of the following characteristics:

- Prior hepatitis C treatment
- Cirrhosis (see simplified treatment for treatment-naive adults with compensated cirrhosis)
- HIV or HBsAg positive
- Current pregnancy
- Known or suspected hepatocellular carcinoma
- Prior liver transplantation

Who Is Eligible for Simplified Treatment

Adults with chronic hepatitis C (any genotype) who do not have cirrhosis and have not previously received hepatitis C treatment

Pretreatment Assessment*

- Calculate FIB-4 score.
- Cirrhosis assessment: Liver biopsy is not required. For the purpose of this guidance, a patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 or any of the following findings from a previously performed test.
  - Transient elastography indicating cirrhosis (eg, FibroScan stiffness >12.5 kPa)
  - Noninvasive serologic tests above proprietary cutoffs indicating cirrhosis (eg, FibroSure, Enhanced Liver Fibrosis Test, etc)
  - Clinical evidence of cirrhosis (eg, liver nodularity and/or splenomegaly on imaging, platelet count <150,000/mm^3, etc)
  - Prior liver biopsy showing cirrhosis
- Medication reconciliation: Record current medications, including over-the-counter drugs and

- First-Line DAAs:
- Glecaprevir/pibrentasvir (Mavyret) x 8 wks
- Sofosbuvir/velpatasvir (Epclusa) x 12 wks

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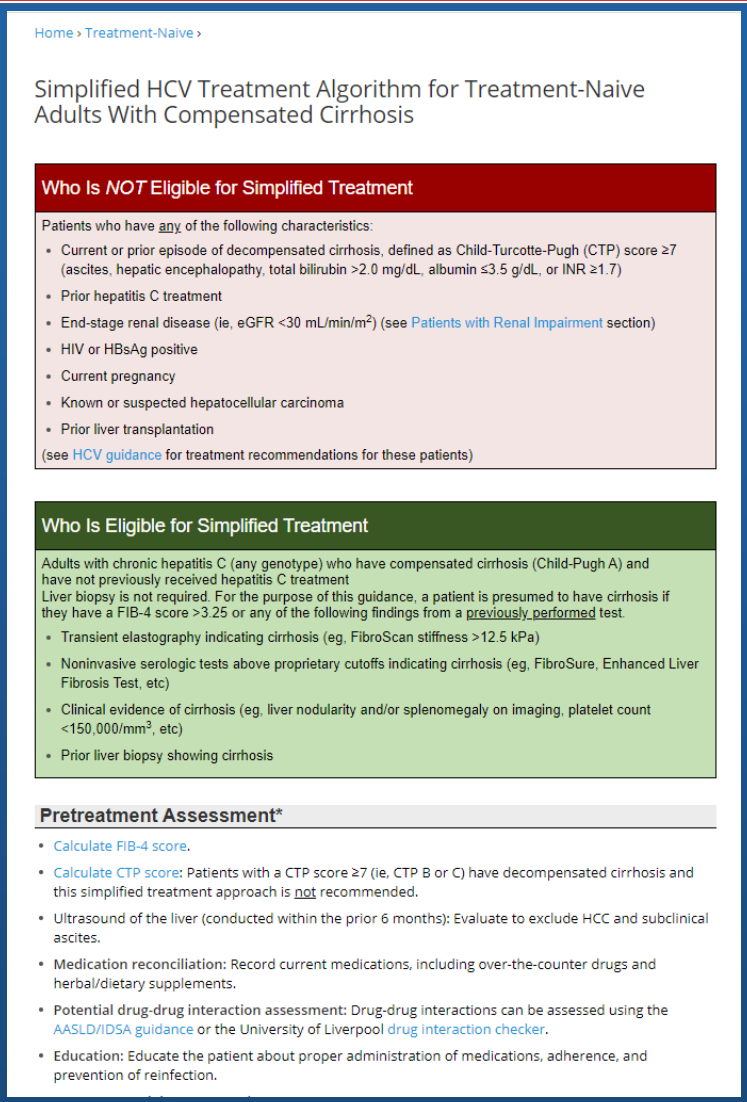
Simplified HCV Therapy: Cirrhosis



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Simplified HCV Treatment Algorithm for Treatment-Naive Adults With Compensated Cirrhosis

Who Is *NOT* Eligible for Simplified Treatment

Patients who have any of the following characteristics:

- Current or prior episode of decompensated cirrhosis, defined as Child-Turcotte-Pugh (CTP) score ≥7 (ascites, hepatic encephalopathy, total bilirubin >2.0 mg/dL, albumin ≤3.5 g/dL, or INR ≥1.7)
- Prior hepatitis C treatment
- End-stage renal disease (ie, eGFR <30 mL/min/m^2) (see Patients with Renal Impairment section)
- HIV or HBsAg positive
- Current pregnancy
- Known or suspected hepatocellular carcinoma
- Prior liver transplantation

(see HCV guidance for treatment recommendations for these patients)

Who Is Eligible for Simplified Treatment

Adults with chronic hepatitis C (any genotype) who have compensated cirrhosis (Child-Pugh A) and have not previously received hepatitis C treatment
Liver biopsy is not required. For the purpose of this guidance, a patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 or any of the following findings from a previously performed test.

- Transient elastography indicating cirrhosis (eg, FibroScan stiffness >12.5 kPa)
- Noninvasive serologic tests above proprietary cutoffs indicating cirrhosis (eg, FibroSure, Enhanced Liver Fibrosis Test, etc)
- Clinical evidence of cirrhosis (eg, liver nodularity and/or splenomegaly on imaging, platelet count <150,000/mm^3, etc)
- Prior liver biopsy showing cirrhosis

Pretreatment Assessment*

- Calculate FIB-4 score.
- Calculate CTP score: Patients with a CTP score ≥7 (ie, CTP B or C) have decompensated cirrhosis and this simplified treatment approach is not recommended.
- Ultrasound of the liver (conducted within the prior 6 months): Evaluate to exclude HCC and subclinical ascites.
- Medication reconciliation: Record current medications, including over-the-counter drugs and herbal/dietary supplements.
- Potential drug-drug interaction assessment: Drug-drug interactions can be assessed using the AASLD/IDSA guidance or the University of Liverpool drug interaction checker.
- Education: Educate the patient about proper administration of medications, adherence, and prevention of reinfection.

- Do not use an HCV protease in Child's class B or C cirrhosis

- First Line DAAs:
- Glecaprevir/pibrentasvir (Mavyret) x 8 wks
- Sofosbuvir/velpatasvir (Epclusa) x 12 wks

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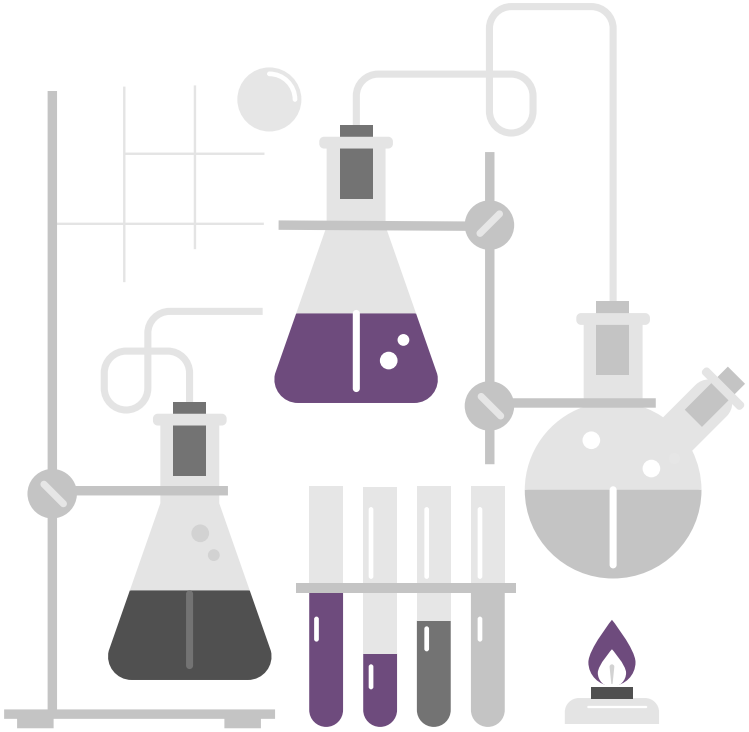
On-Treatment Monitoring



- For patients with cirrhosis and Hep B, monthly LFTs
- For all others, monthly check-in (either in person, phone or telemedicine) regarding side effects and adherence
- Pregnancy test monthly for women of child-bearing potential
- NO VIRAL LEVEL TESTING

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Treatment Interruptions

- Threshold Duration of Therapy
  - ≤ 4 weeks (non- cirrhosis) and ≤ 8 weeks (cirrhosis)
  - Non cirrhosis : <4 weeks: 50% (n = 2/4) v s. 99.1% (n = 109/110) for ≥4 weeks
  - Cirrhosis: <8 weeks: 83.3% (n = 25/30) v s. 94.6%(n = 209/221) for ≥8 weeks
- Other groups also used 4 week threshold
  - One study evaluated any missed doses in the prior 7 days early and late in treatment→ no correlation b/w adherence and SVR
    - at 4 ± 2 weeks (early)
    - 2-3 weeks prior to end of treatment (late)
  - HIV/HCV study
    - Adherence decreased significantly from early (bl-wk 4) vs late (wks 8-12)
      - 95% also had SVR

Source: Fabbiani, J Viral Hepat 20201. Serper, JGIM 2020. Slide courtesy D Bhattacharya

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Stuttering Adherence

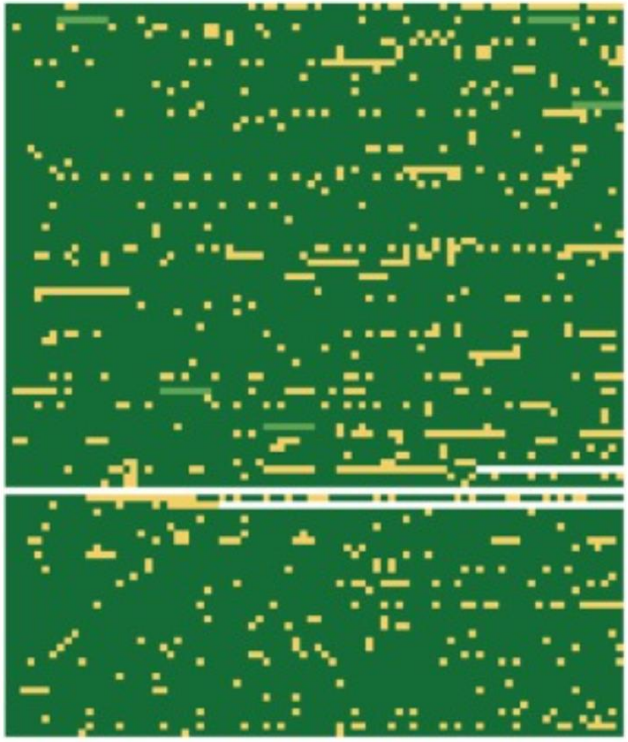

Table 2
Treatment adherence and dosing patterns among all participants in the SIMPLIFY study.

Variable	Overall (n = 103) n (%)
Treatment completion	100 (97)
Missed doses of sofosbuvir/velpatasvir as measured by electronic blister-pack, n (%)	
No missed doses (100%)	12 (12)
1-4 missed doses (95- < 100%)	36 (35)
5-8 missed doses (90- < 95%)	20 (19)
9-17 missed doses (80- < 90%)	17 (17)
≥18 missed doses (< 80%)	18 (17)
Longest episode of non-adherence[a]	
1 day	44 (43)
2 days	19 (18)
3 days	3 (3)
4 days	9 (9)
5 days	2 (2)
6 days	3 (3)
≥7 days	11 (11)
Median on-treatment sofosbuvir/velpatasvir adherence percent	
Patient report	99 (98-100)
Blister-pack, weekly	98 (94-100)
Blister-pack, daily	94 (88-98)
Dose timing[a]	
Morning (5:00AM-11:59AM)	42 (41)
Afternoon (12:00PM-4:59PM)	42 (41)
Evening (5:00PM-12:00AM)	17 (17)
Night (12:00AM-4:59AM)	1 (1)
Consistency in dose timing (standard deviation in minutes)[a]	
< 120	24 (24)
≥ 120- < 240	43 (42)
≥ 240	35 (34)

[a] Among those with available blister-pack data (n = 102).

No difference in SVR among those with sofosbuvir/velpatasvir adherence ≥90% (94%, 66 of 70)

as compared to those with sofosbuvir/velpatasvir adherence of < 90% (94%, 31 of 33,P= 0.944).

Daily adherence to sofosbuvir/velpatasvir therapy as measured by weekly-administered electronic blister-packs. Rows represent individual participants and columns represent days of therapy.
Green boxes represent a dose received, with light green boxes indicating a damaged blister-pack where clinical pill count data was used.
Yellow boxes represent no dose received on that treatment day and white boxes represent early treatment discontinuation or death.

Source: Cunningham Int J Drug Policy 2018

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Potential Scenarios and My Advice

1

If missed <7 d, re-start regimen and finish out course

2

If missed >7 d, check HCV RNA. If negative, re-start regimen and finish out course. If positive, do not re-start. Obtain RAS testing and tailor therapy based on results.

3

If patient stops or has adherence issues after 10 wks, don't worry. Probably sufficient to just re-start therapy and finish out course.

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2020 Sep;1(5):e200-e208. doi: 10.1016/S2666-5247(20)30062-8. Epub 2020 Jul 27

A PHASE ONE STUDY OF LEDIPASVIR/SOFOSBUVIR IN PREGNANT WOMEN WITH HEPATITIS C VIRUS

Catherine A. Chappell, Elizabeth E. Krans, Katherine Bunge, Ingrid Macio, Debra Bogen, Kimberly K. Scarsi, Leslie A. Meyn, Sharon L. Hillier

CROI 2019 and *Lancet Microbe*, 2020. e200-08.

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Study Design

12 week treatment course

Enrollment 23-24 weeks gestation

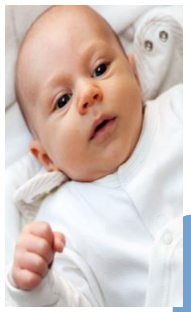
PK-visit 1 25-26 weeks gestation

PK-visit 2 29-30 weeks gestation

PK-visit 3 33-34 weeks gestation

Delivery

Sustained viral response (SVR)12 visit (post-partum)



HCV viral load and adverse events

Follow-up is ongoing

Delivery

Visit 1 (8w)

Visit 2 (6m)

Visit 3 (12m)

HCV viral load, adverse events, physical exam, growth and neurodevelopmental assessment

Demographic and Clinical Characteristics

Demographic	Number (%) or Median
Age	31 (25, 38)
White Race	9 (100%)
Insurance	
Public	8 (89%)
Military	1 (11%)
Education	
>High school	6 (67%)
High School	1 (11%)
<High School	2 (22%)

Clinical Characteristic	Number (%)
Tobacco Use	7 (78%)
Opioid Therapy	4 (44%)
Methadone	2 (22%)
Buprenorphine	2 (22%)
Route of HCV acquisition	
IV Drug Use	8 (89%)
Perinatal	1 (11%)
HCV RNA >6 million copies/mL at Enrollment	1 (11%)
HCV Genotype 1	9 (100%)

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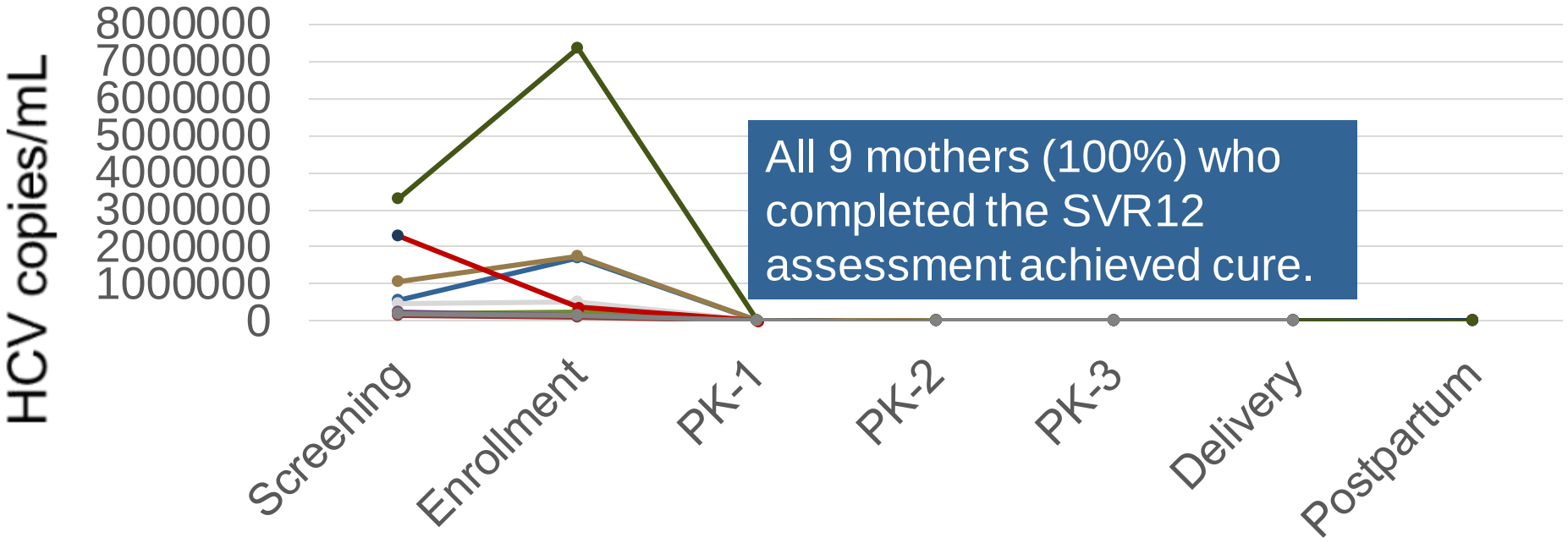
HCV Viral Response to LDV/SOF During Pregnancy (HCV RNA copies/mL median [low, high])



Visit	Screening	Enrollment	PK-1	PK-2	PK-3	Delivery	SVR12
HCV	4.9 (1.7, 33.0)x10^5	5.2 (1.0, 73.5)x10^5	12 (0, 49)	0 (0, 12)	0 (0, 0)	0 (0, 12)	0 (0,0)

12 weeks of treatment

12 weeks after finishing course
Undetectable = cure

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Pregnancy and Delivery Outcomes

Outcome	N (%) or Median (High, Low)
Maternal Related Adverse Events	5 (56%)
Maternal Related Adverse Events >Grade 2	0 (0%)
Vaginal Delivery	5 (56%)
Gestational age at delivery (weeks + days)	39+2 (36+6, 41+0)
Birth weight (g)	3,290 (2,600, 4,160)
Infant Length of Hospital Stay (days)	3 (2, 12)
Infant Related Adverse Events	0 (0%)
Infant HCV RNA at Last Visit (copies/mL)	0 (0, 0)

Questions?

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