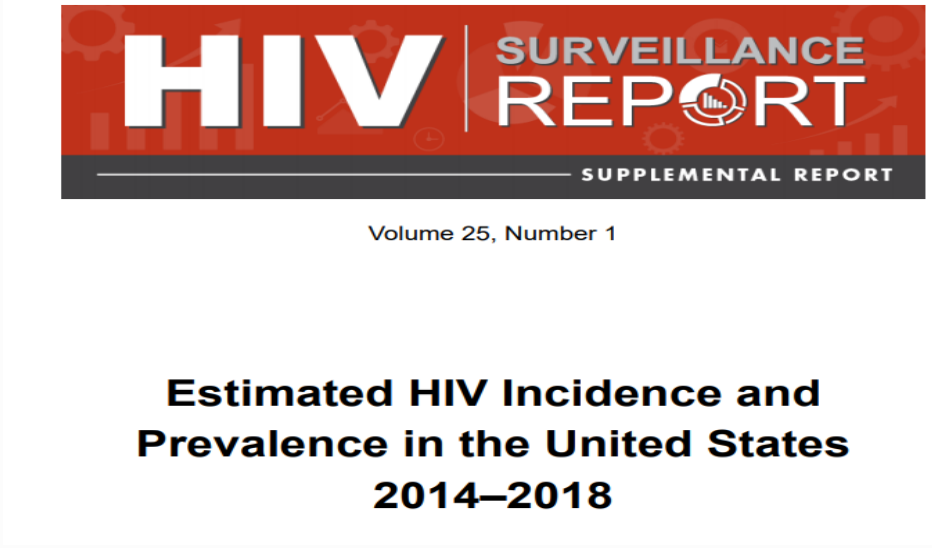
AETC AIDS Education & Training Center Program Southeast

Monthy 1st and 3rd Wednesday and
12:00pm-1:00pm EST
11:00am-12:00pm CST
09:00am-10:00am PST

4th Wednesday
12:00pm-1:00pm CST
01:00pmpm-2:00pm EST
10:00am-11:00am PST

South East Viral Hepatitis Interactive Case Conference

- HCV/HIV/HBV Telehealth- 3 Wednesdays a month
- HIV PrEP Telehealth – 2nd Wednesday at noon



- US population- 330 million
- HIV -estimated 1.2 million aged 13 and older
- Thus HIV prevalence **>1/330 Americans**
  - Males- 0.7% (1/150 male Americans)
  - Females-0.2%

United States Preventive Services Task Force recommendations

GRADE A for HIV

Recommendation Summary

Population	Recommendation	Grade
Pregnant persons	The USPSTF recommends that clinicians screen for HIV infection in all pregnant persons, including those who present in labor or at delivery whose HIV status is unknown.	A
Adolescents and adults aged 15 to 65 years	The USPSTF recommends that clinicians screen for HIV infection in adolescents and adults aged 15 to 65 years. Younger adolescents and older adults who are at increased risk of infection should also be screened. See the Clinical Considerations section for more information about assessment of risk, screening intervals, and rescreening in pregnancy.	A

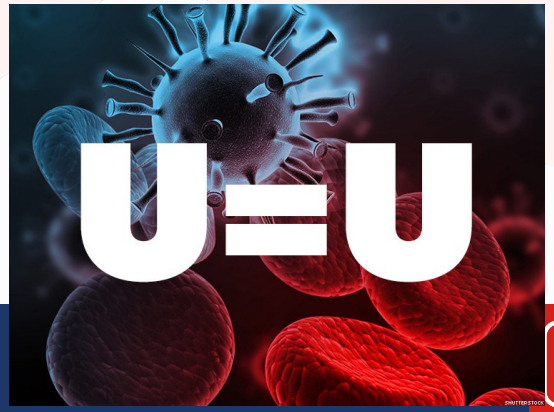
GRADE B for BREAST CANCER SCREEING

Recommendation Summary

Population	Recommendation	Grade
Women aged 50 to 74 years	The USPSTF recommends biennial screening mammography for women aged 50 to 74 years.	B
Women aged 40 to 49 years	The decision to start screening mammography in women prior to age 50 years should be an individual one. Women who place a higher value on the potential benefit than the potential harms may choose to begin biennial screening between the ages of 40 and 49 years.	C

Recommendations for Initiating ART for an HIV infected person

- ART (Antiretroviral therapy or HIV medications) is recommended for all HIV-infected individuals to reduce the risk of disease progression.
- Effective ART reduces transmission to almost **“0”**
- HIV is easier to treat than Diabetes, COPD, CHF
- Undetectable= Untransmissible



DHHS Guidelines: Recommended Regimens for **First-line HIV Antiretroviral Therapy**

Class	Regimen
INSTI	▪ BIC/TAF/FTC (Biktarvy®) ▪ DTG/ABC/3TC (Triumeq®) ▪ DTG + (TAF or TDF)/FTC (Tivicay®+ Descovy® or Truvada®) ▪ RAL + (TAF or TDF)/FTC (Isentress®+Descovy® or Truvada®)

IAS-USA now lists EVG/COBI/TAF/FTC and RAL + TAF/FTC as alternative regimens owing to their lower resistance barriers and, respectively, more drug interactions and higher pill burden

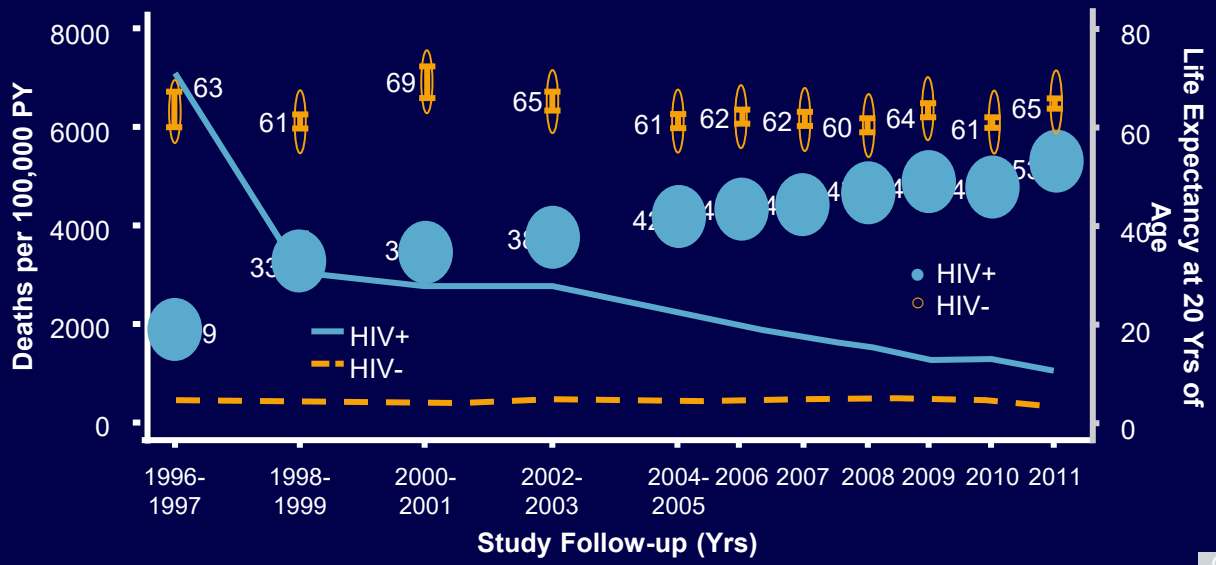
DHHS Guidelines. 2019.

Dolutegravir controversy in pregnancy
Tsepamo Birth Outcomes Surveillance Study(Botswana)

- **May 2018:**
  - Unplanned analysis of Tsepamo birth outcomes surveillance study found increase in NTD incidence among women who conceived on DTG[1]
  - DTG vs non-DTG ART: 0.94% (95% CI: 0.37-2.4) vs 0.12% (95% CI: 0.07-0.21)
- **April 2019:**
  - NTD prevalence among women who received DTG at conception lower than previous analysis, but still higher than other exposure groups[2]
  - DTG vs non-DTG ART: 0.30% (95% CI: 0.13-0.69) vs 0.10% (95% CI: 0.06-0.17)
- **April 2020:**
  - Updated NTD prevalence
  - DTG vs non-DTG ART: 0.19% vs 0.11%

1. Zash. NEJM. 2018; 379:979. 2. Zash. IAS 2019. Abstr MOAX0105LB. 3. Zash. AIDS 2020. Abstr OAXLB01.

Life Expectancy in Patients With HIV Is Increasing: The "Graying" of the HIV Epidemic



Marcus JL, et al. J Acquir Immune Defic Syndr. 2016;73:39-46.

Slide credit: clinicaloptions.com

Hepatitis C Screening Recommendations

Population	Recommendation	Grade (What's This?)
Adults aged 18 to 79 years	The USPSTF recommends screening for hepatitis C virus (HCV) infection in adults aged 18 to 79 years.	B

One-Time Hepatitis C Testing

Recommendations for One-Time Hepatitis C Testing	
RECOMMENDED	RATING
One-time, routine, opt out HCV testing is recommended for all individuals aged 18 years and older.	I, B
One-time HCV testing should be performed for all persons less than 18 years old with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV infection (see below).	I, B
Periodic repeat HCV testing should be offered to all persons with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV exposure (see below).	IIa, C
Annual HCV testing is recommended for all persons who inject drugs and for HIV-infected men who have unprotected sex with men.	IIa, C

Hepatitis C

- The most important risk factor for HCV infection is past or current injection drug use
  - The estimated prevalence of chronic HCV infection is approximately 1.0% (2013 to 2016)

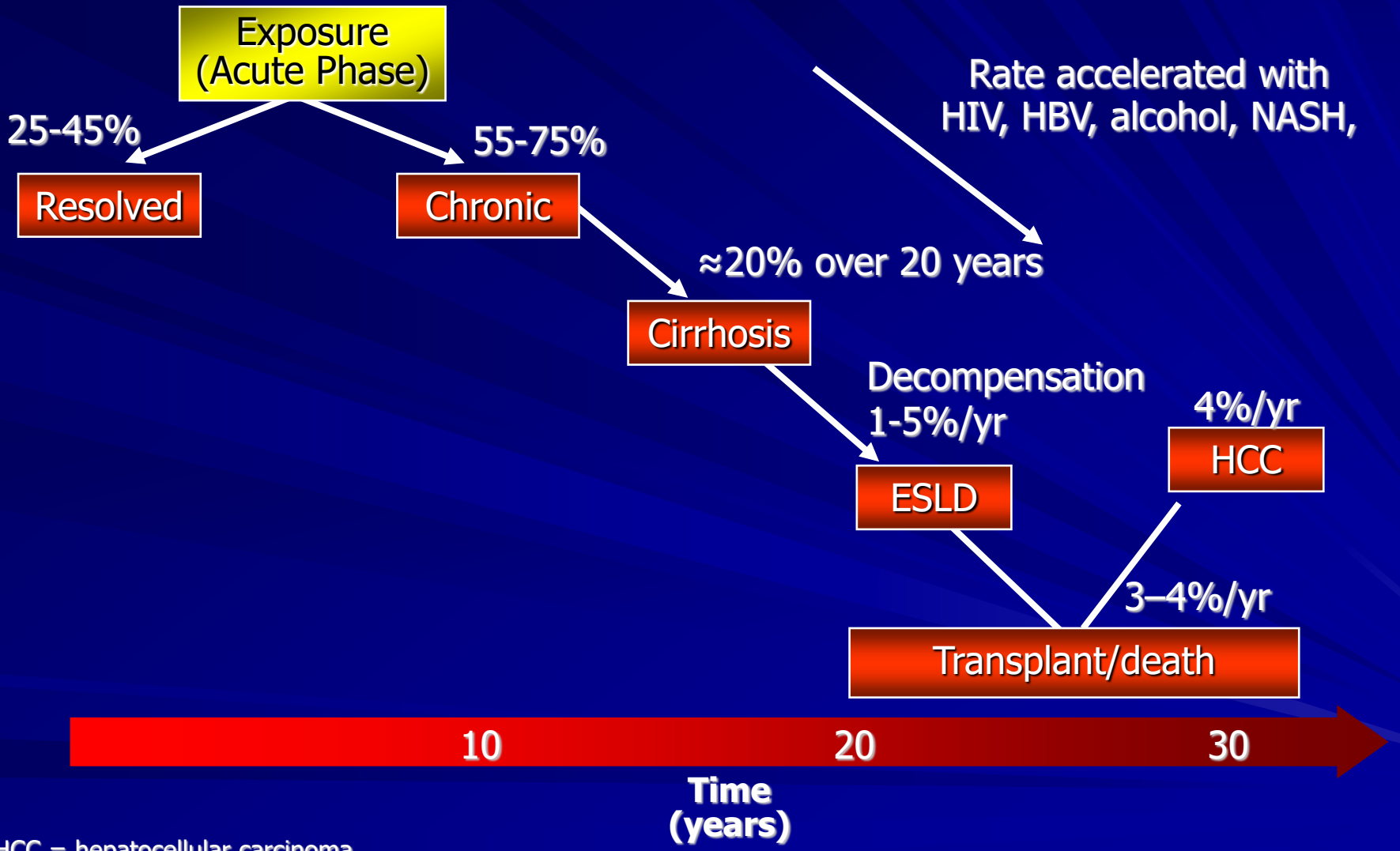
    Hofmeister MG, Hepatology. 2019;69(3):1020-1031
- In the US, an estimated 4.1 million persons have past or current HCV infection
  - Positive for the anti-HCV antibody
- Approximately 2.4 million have current infections
  - Based on testing with molecular assays for HCV RNA.

    Chou R, Dana Agency for Healthcare Research and Quality; 2020. AHRQ publication

Genotypes

- **HCV- 6 major genotypes**
  - GT 1 -60-75% (most common in US, Europe, Latin America)
  - GT 2- 13%
  - GT 3-12%;
    - GT 4 -1%
    - GT 5 and GT 6 < 1%
  - *Germer JJ,et al: J Clin Microbiol. 2011;49(8):3040–3043.*
- GT3
  - Common in India, Far East, Australia
  - Increase in worldwide prevalence of GT 3 in IVDUs
  - *Kanwal F, et al. Hepatology. 2014;60(1):98–105.*
- There are 67 subtypes
  - GT1 that cannot be subtyped should be treated as genotype 1a infection.

Natural History of HCV Infection



HCC = hepatocellular carcinoma

ESLD = end-stage liver disease

Modified from Di Bisceglie A, et al. *Hepatology*. 2000;31:1014-1018.

FULL TEXT ARTICLE

Prevalence of Spontaneous Clearance of Hepatitis C Virus Infection Doubled From 1998 to 2017

- Spontaneous clearance occurs in approximately 25%-45% of acute infections
  - Higher spontaneous clearance in younger patients

- Detectable HCV RNA -within 1–2 weeks of exposure
- Anti-HCV Antibody- 8–11 weeks after exposure

Fibrosis Assessment:

- **Transient elastography**
  - > 12.5 KPa = cirrhosis
- **Serum tests**
  - FibroTest (0.75 = cirrhosis)
  - **APRI or FIB-4 – very attractive, can be done anywhere by any provider**
    - Very good **negative predictive value – rule out cirrhosis**
- **Ultrasound – not needed in all patients**
  - **Insensitive for cirrhosis – only needed if cirrhotic to exclude HCC before treatment**
- Biopsy rarely needed

HIV/HCV Co-infection

- All persons living with HIV should be screened for HCV
  - Those at high risk of HCV should be screened annually
  - MSM, PWID
- HIV is independently associated with the progression of HCV (liver fibrosis and cirrhosis)
  - ART may slow the progression of liver disease
  - All HIV/HCV co-infected patients should be treated with HIV ART
- Similar effectiveness of HCV DAAs in HIV/HCV co-infection

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. IDSA. 2018. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.
Bersoff-Matcha et al. *Ann Intern Med*. 2017;166(11):792-798..
Wang C et al. *Clin Gastroenterol Hepatol*. 2017;15(1):132-136..

Liver Fibrosis progression - HIV/HCV coinfection

- Observational cohort from Baltimore, Maryland
  - 1176 current and former IVDU.
- Factors associated with progression of liver fibrosis
  - High HIV Viral Loads
  - Low nadir CD4 counts
  - Alcohol use

Kirk GD,Ann Intern Med. 2013;158:658–666.

- Meta-analysis of 8 studies
  - More rapid progression of liver fibrosis in HIV/HCV co-infected
  - Adjusted relative risk (RR) - 2.92 (progression to cirrhosis)

Graham CS, et al. Clin Infect Dis. 2001

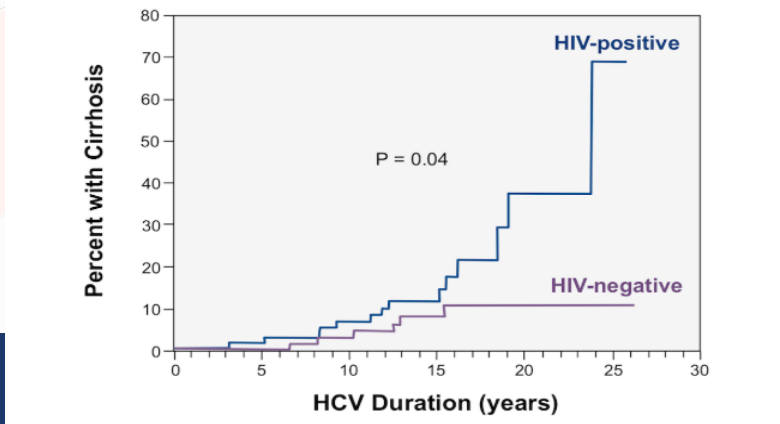


Figure 1 - Progression to Cirrhosis in Patients with HCV Monoinfection and HIV-HCV Coinfection

Benefits of treating HIV/HCV coinfected patients

- HIV Antiretroviral therapy:
  - Slows the rate of HCV disease progression

  Thein HH, et al. a meta-analysis; Hepatology 2008

- HCV DAA treatment : regression of liver stiffness post SVR
  - 129 patients HCV/HIV coinfected /85 patients monoinfected
  - ≥30% regression of liver stiffness in almost 50%
  - In mono-infected and co-infected groups

Malin JJ, et al. Liver stiffness regression after successful hepatitis C treatment :HIV Med. 2019

HCV treatment in HIV-infected patients - should be a priority for providers, payers, and patients.

Treatment of Chronic HCV

- Goal of Treatment is - Sustained Virological Response(SVR)
  - SVR-undetectable HCV viral Load ≥12 weeks after treatment completion
- Current DAAs have SVR > 98% in
- Treatment is recommended for ALL pts with chronic hepatitis C infection
  - Exception: life expectancy likely to be < 6 months despite treatment or transplantation

Pan-genotypic Regimens

Sofosbuvir/Velpatasvir (Epclusa®)

Glecaprevir/Pibrentasvir (Mavyret™)

Reserved for treatment experienced

Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi®)

HCV Direct Acting Antivirals

	GT 1	GT 2	GT 3	GT 4	GT 5	GT 6
GZR/EBR (Zepatier®)	✓			✓		
***GLE/PIB (Mavyret®)**	✓	✓	✓	✓	✓	✓
SOF/LDV (Harvoni®)	✓			✓	✓	✓
***SOF/VEL (Epclusa®)**	✓	✓	✓	✓	✓	✓
***SOF/VEL/VOX (Vosevi®)**	✓	✓	✓	✓	✓	✓

***Pan-genotypic**

Treatment options for GT1

4 highly potent DAA combination regimens available

Baseline genotypic drug resistance testing is not recommended for most of the first-line DAA regimens

Except elbasvir-grazoprevir.

Pill not actual size

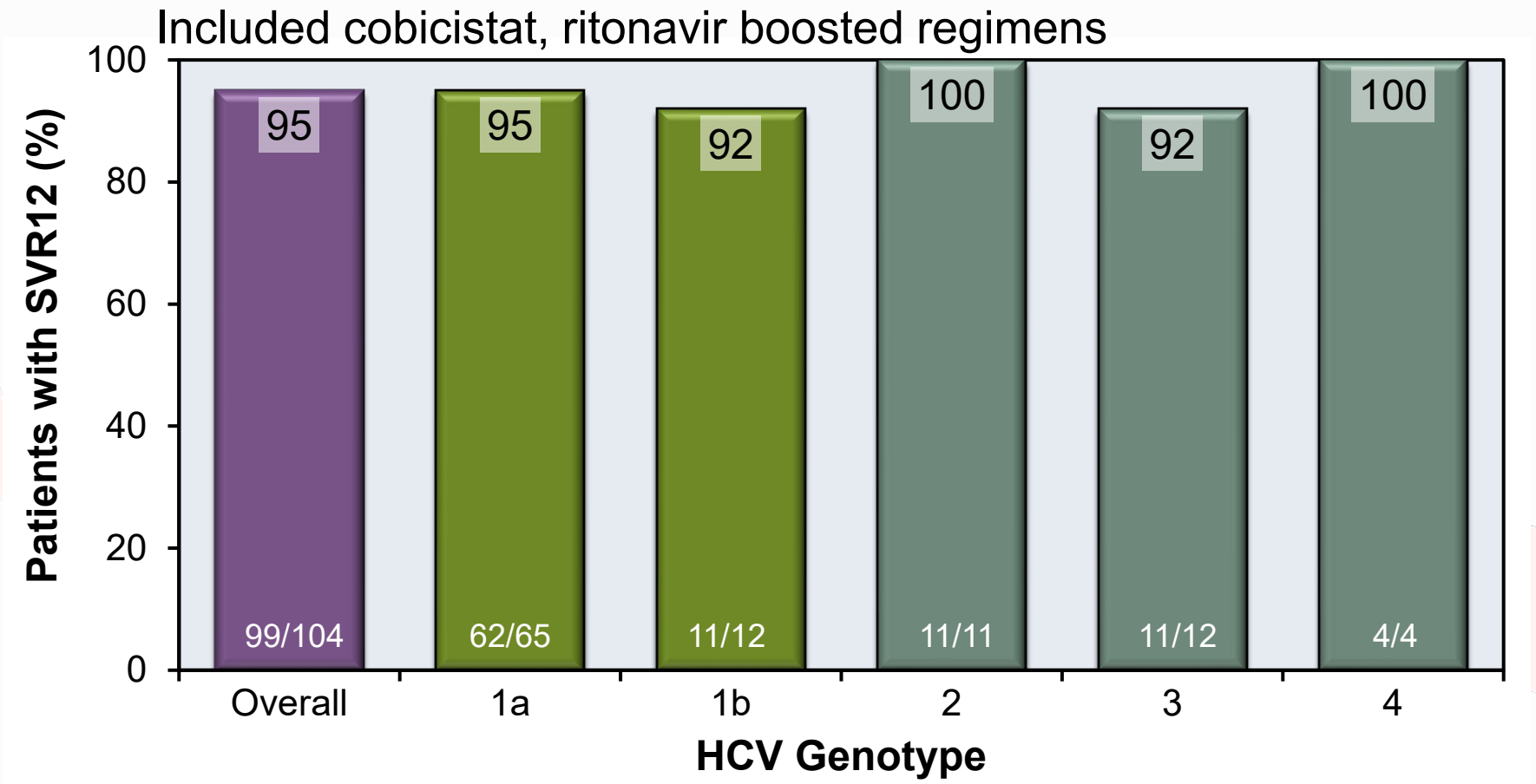
Sofosbuvir/Velpatasvir
(Approved July 2016)

Pill not actual size

- EPCLUSA :Fixed-dose combination of
  - Sofosbuvir (400 mg)- NS5B polymerase inhibitor
  - Velpatasvir (100 mg) - HCV NS5A inhibitor
- Indicated for the treatment of adult patients with
  - Chronic HCV genotypes - 1, 2, 3, 4, 5, or 6
    - Baseline resistance testing required only for GT 3
- One tablet once daily with or without food

Sofosbuvir-Velpatasvir in HIV-HCV Coinfected Patients ASTRAL-5:

ASTRAL-5: SVR12 Results by Genotype



Source: Wyles D, et al. EASL 2016, Abstract PS104.

Glecaprevir/ Pibrentasvir (Mavyret)

- Pangenotypic
- Coformulated into single tablet
  - Glecaprevir 300mg/ Pibrentasvir 120mg= target dose
  - Formulated as Glecaprevir 100mg/Pibrentasvir 40mg
  - 3 pills a day, with food
- Approved August 2017

Glecaprevir/pibrentasvir HIV/Hepatitis C coinfection

- **EXPEDITION-2** study- HIV/HCV coinfection
- 8 weeks of GLE/PBV -137 adults without cirrhosis
- 12 weeks of GLE/PIB - 16 with compensated cirrhosis.
  - Either antiretroviral naive with a CD4 ≥500/mm^3
  - Or on ART regimen for 8 weeks with a CD4 ≥200/mm^3.
  - ART drugs included (**raltegravir, dolutegravir, rilpivirine**)- tenofovir disoproxil fumarate, tenofovir alafenamide, abacavir, emtricitabine, and lamivudine.
- Overall SVR12 was 98%

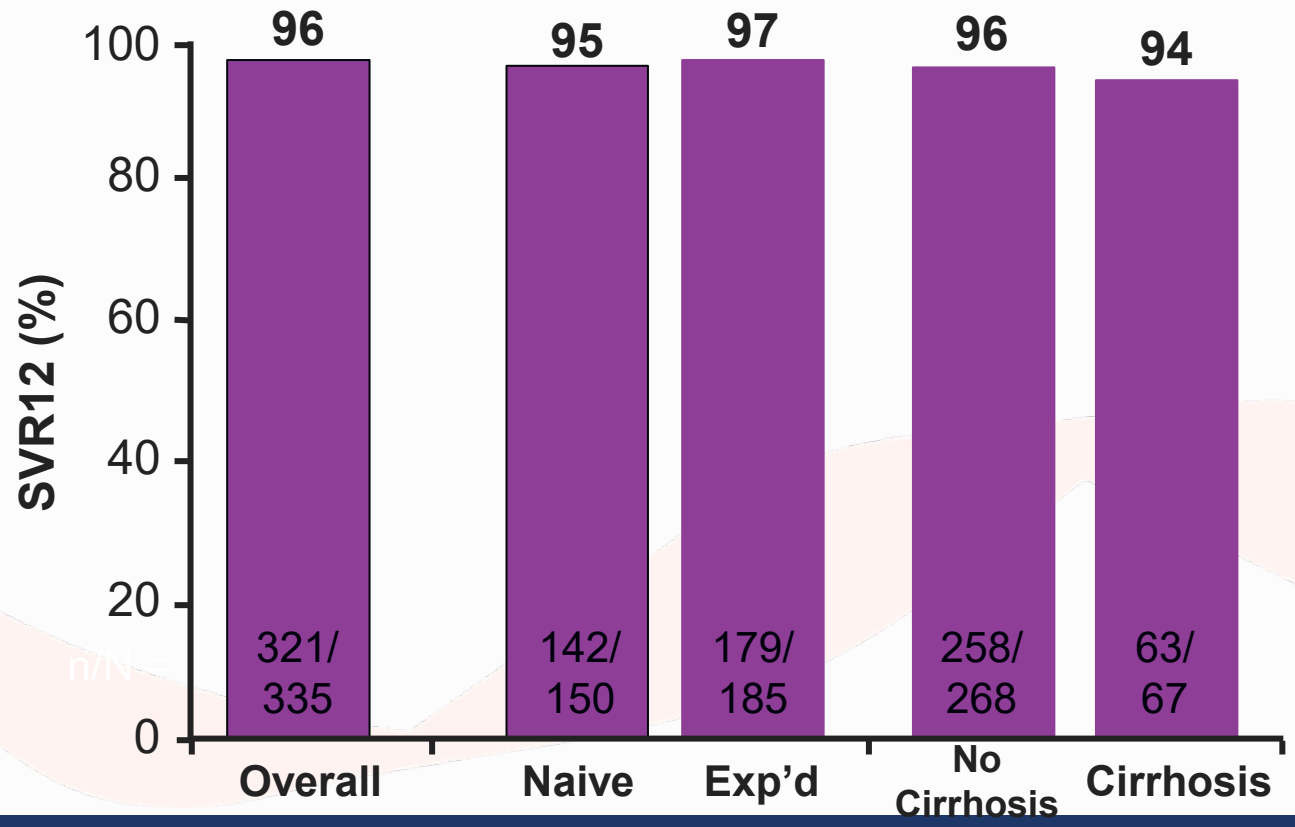
ION-4:

ORIGINAL ARTICLE

Ledipasvir and Sofosbuvir for HCV in Patients Coinfected with HIV-1

Susanna Naggie, M.D., M.H.S., Curtis Cooper, M.D., Michael Saag, M.D., Kimberly Workowski, M.D., Peter Ruane, M.D., William J. Towner, M.D., Kristen Marks, M.D., Anne Luetkemeyer, M.D., Rachel P. Baden, M.D., Paul E. Sax, M.D., Edward Gane, M.D., Jorge Santana-Bagur, M.D., et al., for the ION-4 Investigators*

- 12 weeks of LDV/SOF
- GT1 or 4 HCV, 20% with compensated cirrhosis, 55% treatment experienced



Treating HIV/HCV GT1 Co infection

- Ledipasvir/Sofosbuvir (Harvoni®)
  - Ledipasvir increases tenofovir levels when given as TDF
  - Avoid in patients with an eGFR <60 mL/min.
- Sofosbuvir/Velpatasvir (Epclusa®)
- Elbasvir/Grazoprevir (Zepatier®)
  - NS5A resistance testing needed
- Glecaprevir/Pibrentasvir (Mavyret®) x 8 weeks if non cirrhotic
  - Compounds that inhibit P-gp, BCRP, or OATP1B1/3 may increase glecaprevir and pibrentasvir concentrations.
    - Like Cobicistat which is in Genvoya
    - Monitor LFTs at 4 weeks if on a cobicistat based regimen
  - Drugs that induce P-gp/CYP3A may decrease glecaprevir and pibrentasvir concentrations
    - Like Efavirenz and Etravirine
  - Mavyret not approved for 8 weeks for HIV/HCV coinfected patients with cirrhosis
    - Expedition 8 did not have any HIV/HCV co-infected patients

HCV Therapy Highly Effective in HIV/HCV-Coinfected

	Study	Population	HCV Regimens	SVR12, %
HARVONI	ION-4 ERADICATE	N = 335; GT1 (98%) or GT4 N=50	LDV/SOF 12 wks	**96** **100**
ZEPATIER	C-EDGE CO-INFECTION	N = 218; GT1, 4, 6	EBR/GZR 12 wks	**96**
EPCLUSA	ASTRAL-5	N = 106;18 % cirrhosis GT1-4	SOF/VEL 12 wks	**95**
MAVYRET	EXPEDITION-2 All patients had CD4 > 200	N = 163; GT1-6 137- no cirrhosis 16 comp cirrhosis	GLE/PIB for 8 wks for without cirrhosis and 12 wks with cirrhosis	**98**

1.
3.

Selected ART and HCV DAA Drug Interactions

HCV Regimen	Do NOT Use With:
EBR/GZR (Zepatier®)	**COBI, EFV,** ETV, NVP, or any **HIV PI**
GLE/PIB (Mavyret®)	**ATV, RTV, EFV,** or ETV
SOF/VEL (Epclusa®)	**EFV,** ETV, or NVP
SOF/VEL/VOX (Vosevi®)	**ATV/RTV, EFV**, ETV, or NVP

Existing data with Bictegravir suggests co-administration is safe

"Patients With HIV/HCV Coinfection: HCV Guidance." Patients With HIV/HCV Coinfection | HCV Guidance, 24 May 2018.
Ahmed, Aijaz, et al. "Drug-Drug Interactions in Hepatitis C Virus Treatment: Do They Really Matter?" AASLD, John Wiley & Sons, Ltd, 30 Nov. 2017, aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/cld.668.

Benefits of Sustained Virologic Response (SVR)

- In a review of 3,010 treatment-naive patients
- **40% to 73%** of participants who achieved SVR had improvement in liver fibrosis and necrosis.
  - Cirrhosis resolved in 49% of the cases
    - Portal hypertension, splenomegaly, and other clinical manifestations of advanced liver disease also improved

  Poynard T, et al. Gastroenterology. 2002;122(5):1303-1313.

- SVR is associated with
  - >70% reduction in the risk of HCC
  - 90% decrease in liver-related mortality & liver transplantation

  Van der Meer AJ, et al. JAMA. 2012;308(24):2584-2593

AASLD: New Simplified HCV Treatment Approach

Eligible Patients:
Chronic hepatitis C without cirrhosis and no previous HCV therapy

- Assess cirrhosis (liver biopsy not required)
  - Treat as though cirrhotic if any of the following suggest cirrhosis
  - FIB-4 > 3.25, platelet count < 150,000/mm^3, APRI > 2.0, *FibroScan* > 12.5 kPa
- Record medications and supplements, assess DDIs
- Conduct recommended baseline labs
- Provide patient education

Treatment Options:
GLE/PIB 3 pills/day for 8 wks (with food) or SOF/VEL 1 pill/day for 12 wks

AASLD Guidance. November 2019.

Simplified Treatment algorithm:

Not applicable to HIV-HCV co-infected patients

- Treating HIV-HCV co-infected patients has as good SVR rates as treating HCV mono-infected patients
- But caution with Drug interactions

Exclusions to Simplified Treatment

- Prior hepatitis C treatment
- End-stage renal disease
- HIV or HBsAg positive
- Current pregnancy
- Known or suspected hepatocellular carcinoma
- Prior liver transplantation
- Decompensated cirrhosis

AASLD/IDSA HCV Guidelines. 2019.

On-Treatment Monitoring

- Monitor blood glucose
  - Diabetics have the potential for hypoglycemia.
- Monitor INR if on Warfarin
- No laboratory monitoring is required for other patients.
- Consider an in-person or telehealth/phone visit for patient support and adherence

Post-Treatment Assessment of Cure (SVR)

- ≥ 12 weeks after finishing DAA Treatment
  - Quantitative HCV RNA
  - LFT
    - If Liver enzymes persistently elevated then assessment for other causes of liver disease is recommended

Follow-Up After Achieving Virologic Cure (SVR)

- For patients without Cirrhosis who achieve SVR
  - No liver-related follow-up is recommended
- For patients with ongoing risk IVDU, MSM engaging in unprotected sex
  - Risk Reduction Counseling
  - Annual testing for HCV RNA.
- Advise patients to avoid excess alcohol use.

CASE PRESENTATIONS

Case 215 – Dr. Ada Stewart

Baseline Demographics					
Age: 69	**Race:** African American	**Gender: Female**		**Primary Insurance:** Medicare	
PMH/Comorbidities/Substance Use: Depression/1ppd x 50-year smoking history					
Pertinent Clinical Findings: N/A					
Weight (kg):	86.8	**Serum Albumin:**	4.3	**ALT:**	11
Hgb:	11.9	**Total bilirubin:**	0.2	**AST:**	14
PLT:	229	**INR:**	1.0	**SCr/CrCl:**	0.98/74mL/min

Case 215 – Dr. Ada Stewart

HCV Evaluation					
Ultrasound: Pending	**CT:** Not done				**MRI:** Not done
Signs of Cirrhosis:	no				
Staging Modality:	**Results:**	**Interpretation:**		**APRI:**	0.15
Fibroscan/Transient Elastography:	Not done	-----		**FIB-4:**	1.27
Fibrosure:	0.36	F1-F2			
Treatment Naïve?:	Yes	**If no, previous treatment:**		**HIV Antibody:**	Positive, 4th gen test – reactive, VL <20
HCV Genotype:	**1b**	**HCV RNA:**	723,000	**HAV | Total Ab:**	Positive
HBV | sAb: *Not on therapy*	Negative	**HBV | sAg:**	Positive	**HBV | Total cAb:**	Reactive
Requested Regimen:	Epclusa x 12 weeks				

Case 215 – Dr. Ada Stewart

- Medication List:
  - Mirtazapine 30mg daily
  - Sertraline 50mg daily
  - Hydroxyzine daily
  - HCTZ 12.5 mg daily
  - Alprazolam 0.5mg
  - Omeprazole – will hold (acknowledged by provider)

- **Clinical considerations:**
  - **GT1b**
  - **Treatment naïve**
  - **Metavir- F1-F2**
  - **HBV Co-infection**
  - **HIV-1 Co-infection?**
  - Positive HIV-1 Ab (4/27/20)
    - Reactive 4th-generation +
    - Indeterminant HIV-1 Ab (8/28/20 and 9/10/20)
    - HIV VL < 20

HBV Evaluation

- Ensure adequate HBV evaluation prior to initiating HCV therapy
- HBV viral load needed to then address treatment plan and laboratory evaluation

Marker	Interpretation	Acute Infection	Window Period	Chronic Infection	Remote Infection	Immunization	Inactive Chronic Carrier
HBcAb	Exposure	+	+	+	+	–	+
HBsAg	Infection	+	–	+	–	–	–
HBsAb	Immunity	–	–	–	+	+	–

Risk for HBV Reactivation

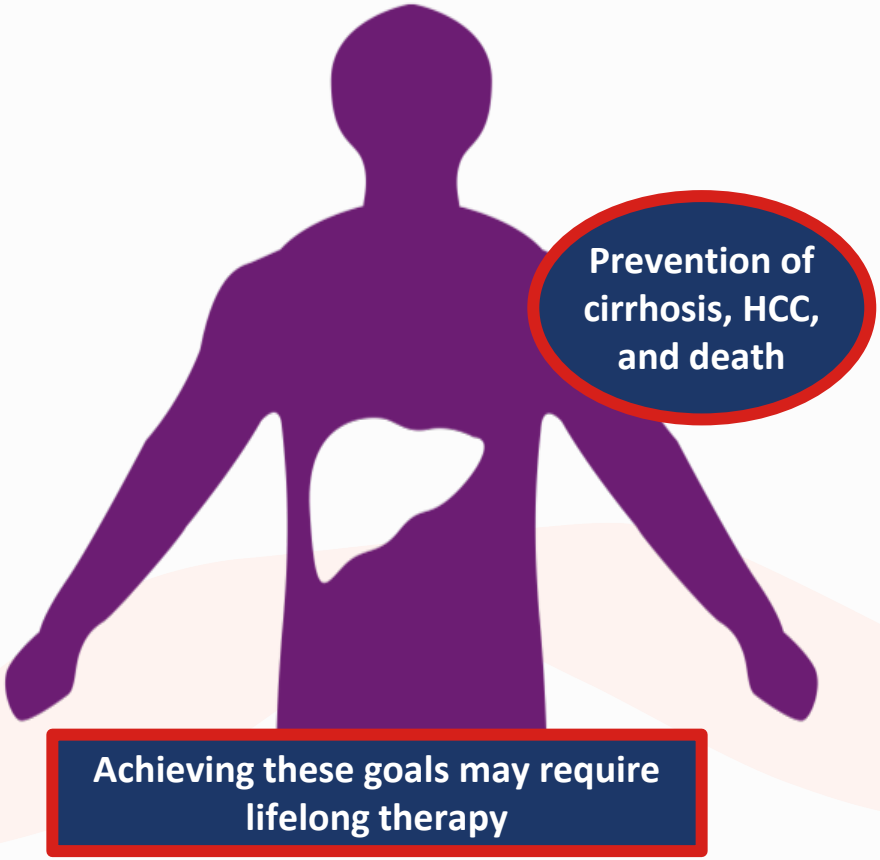
- All HIV patients starting HCV medications should be assessed for HBV co-infection
  - HBsAg, anti-HBs, and anti-HBc testing
  - If Anti-HBs negative → administer anti-HBV vaccination

- Persons with HCV/HIV coinfection and active HBV infection (HBsAg positive) should receive ART that includes **two agents** with anti-HBV activity prior to initiating HCV therapy

AASLD/IDSA HCV Guidelines. 2018.

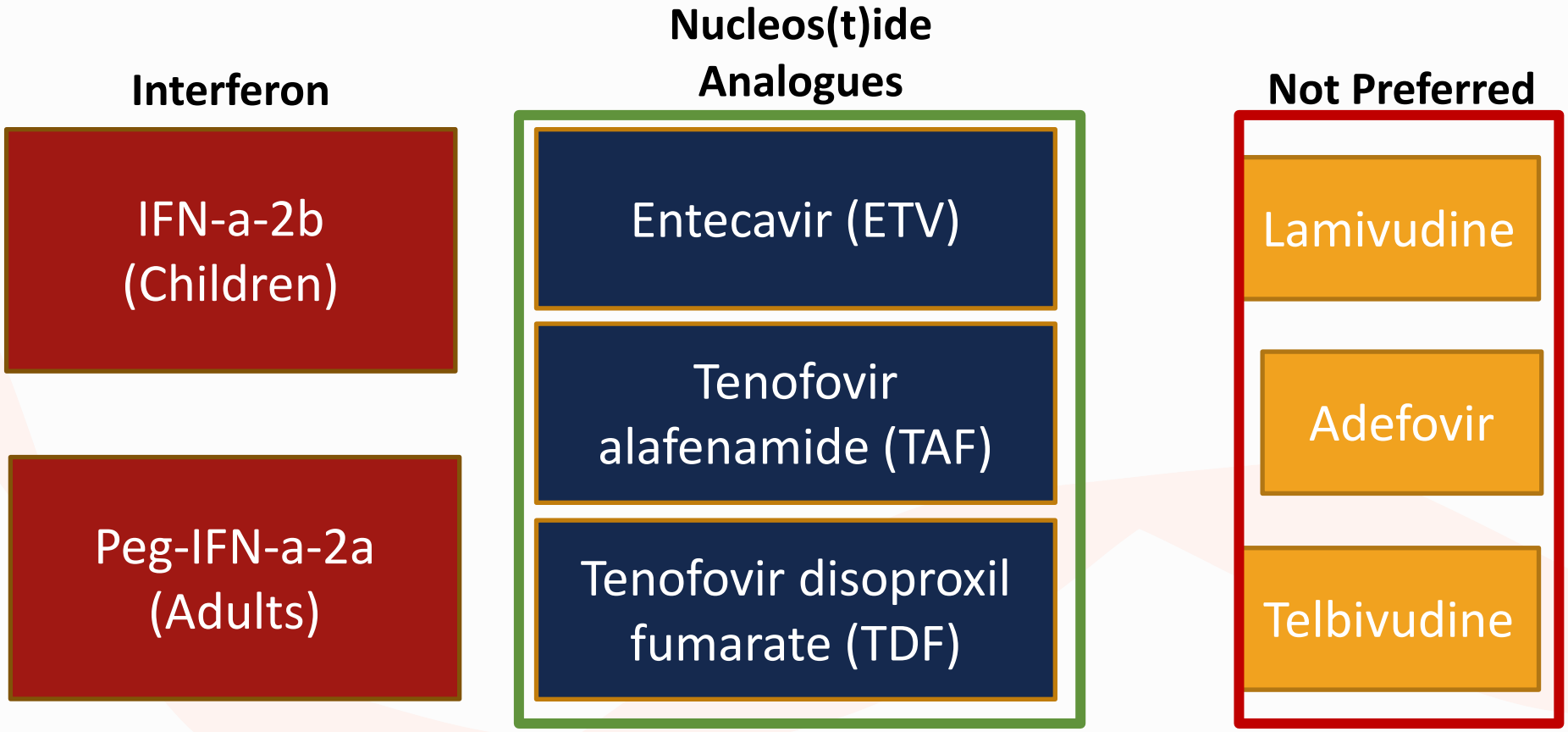
Goals of Therapy for HBV

- Liver Histology Improves
- Seroconversion (HBeAg ↓, anti-HBe ↑, HBsAg ↓)
- Serum HBV DNA ↓
- ALT Normalization



Options for HBV Treatment

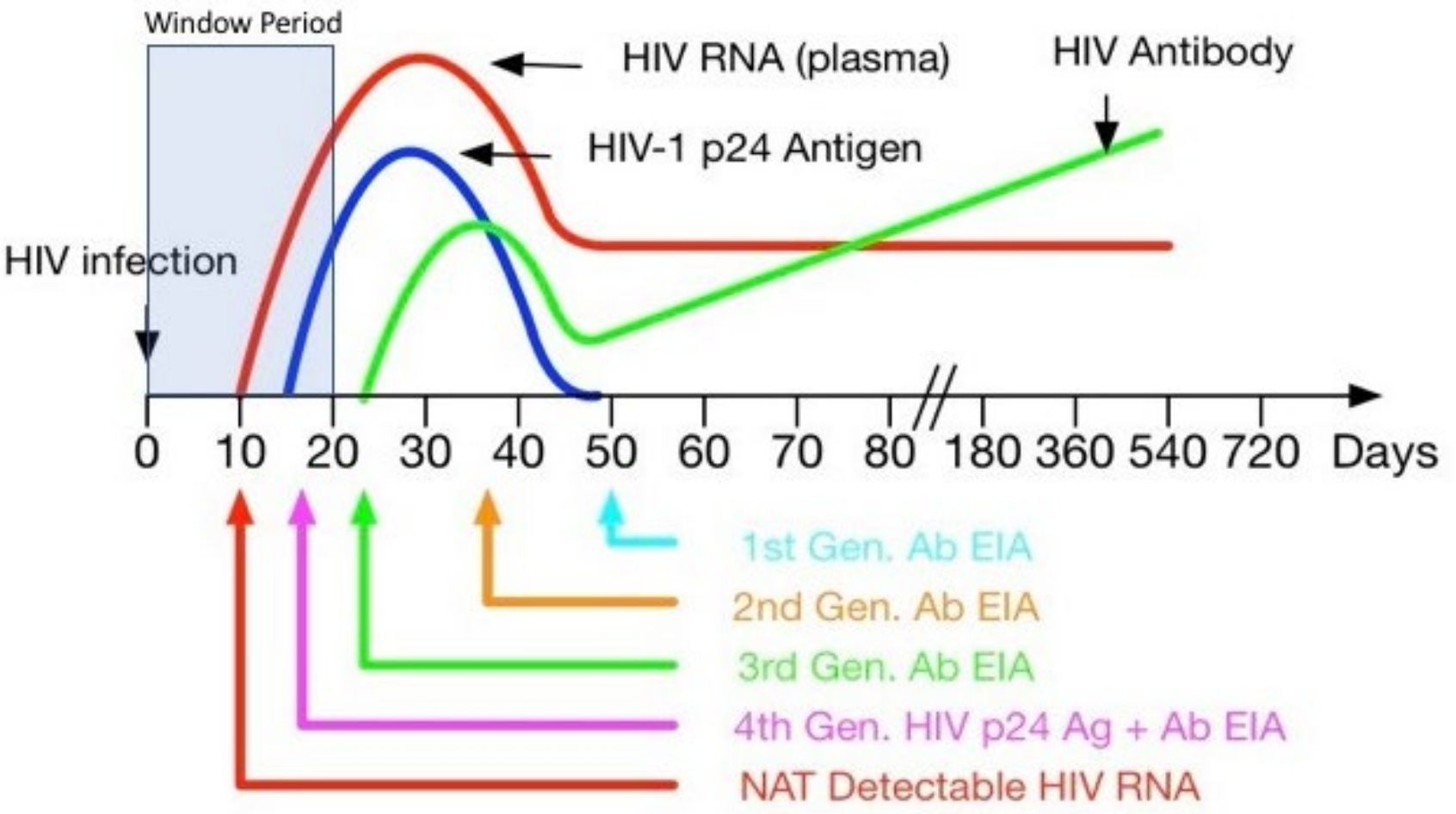
Dual therapy in HIV/HBV Co-infection



EASL. J Hepatol. 2017;67:370. Terrault. Hepatology. 2018;67:1560.

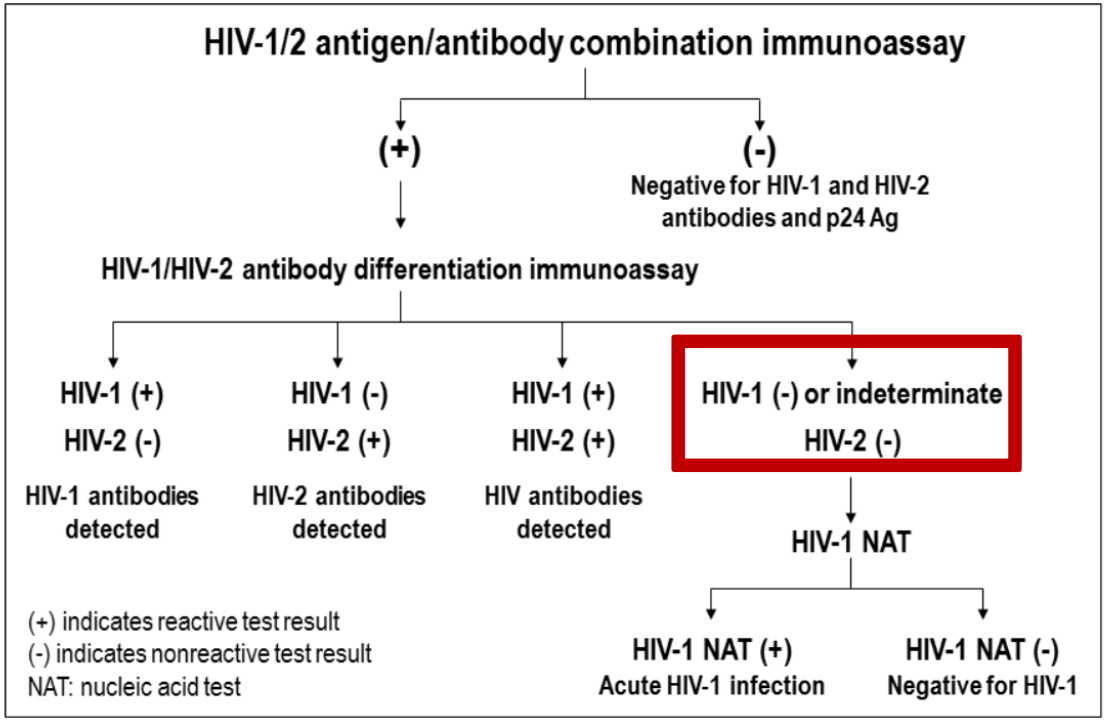
- FOR A DETAILED DISCUSSION OF HIV and HBV Co-infection
- Please join the Telehealth program at 1EST/12 CST next Wednesday (10/14/20)

HIV testing


Window Period
HIV RNA (plasma)
HIV Antibody
HIV-1 p24 Antigen
HIV infection
0 10 20 30 40 50 60 70 80 180 360 540 720 Days
1st Gen. Ab EIA
2nd Gen. Ab EIA
3rd Gen. Ab EIA
4th Gen. HIV p24 Ag + Ab EIA
NAT Detectable HIV RNA

HIV Evaluation

- Patients who receive a positive 4th generation HIV1/2 and p24 Ag combination immunoassay with indeterminate Ab should receive the HIV-1 NAT (PCR)
- HIV-1 NAT tests for the presence of HIV-1 RNA and should be performed as soon as possible



2014 Laboratory testing for the diagnosis of HIV: updated recommendations. CDC

Indeterminate HIV test results

- The initial test is a combination Ag/Ab immunoassay
  - The Ag disappears very quickly once Ab develops as the Ag and Ab form immune complexes
- If the HIV antibody differentiation assay is negative or indeterminate- check HIV-1 NAT to look for acute seroconversion
  - A negative NAT and indeterminate antibody immunoassay indicates a false positive immunoassay
- However, HIV-2 is a remote possibility and the majority of cases are reported in persons born in Africa
  - It is theoretically possible that acute HIV -2 infection might produce a repeatedly reactive HIV immunoassay but negative antibody

HCV Guideline Recommendations

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Patients Genotype 1b Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks[a]	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are HIV-uninfected and whose HCV RNA level is <6 million IU/mL	8 weeks[c]	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A

[a] An 8-week regimen can be considered in those with genotype 1b infection and mild fibrosis (see text for details).

[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

[c] For HIV/HCV coinfected patients, a treatment duration of 12 weeks is recommended.

Drug Interactions – (FYI at this time)
Proton Pump Inhibitors

DAA	Resource	PPIs (Omeprazole)	H2RAs (Famotidine)
GLE/PIB - Mavyret®	Liverpool	No recommendation per product labeling	No recommendation per product labeling; AUC of GLE decreased by up to 50%
	Lexicomp	Class B	No interaction
GZR/EBR - Zepatier®	Liverpool	No interaction	
	Lexicomp		
SOF/LDV - Harvoni®	Liverpool	20mg simultaneously on empty stomach	Administer at same time or 12 hours apart; max dose: 40 mg BID
	Lexicomp		
SOF/VEL – Epclusa®	Liverpool	If medically necessary, take SOF/VEL with food 4hr prior to omeprazole 20 mg	Administer at same time or 12 hours apart; max dose: 40 mg BID
	Lexicomp	Do not coadminister	
SOF/VEL/VOX - Vosevi®	Liverpool	Max 20 mg	Administer at same time or 12 hours apart; max dose: 40 mg BID
	Lexicomp	Do not coadminister	Max dose: 40 mg BID

Recommendations

- GT1b, treatment naïve, without evidence of advanced fibrosis
- HBV co-infected
  - Needs HBV Viral Load, If high needs eAg, eAb and Rx
- HIV- likely false positive
  - Consider repeat HIV 1 NAT and try and obtain HIV-2 NAT

- <u>HCV DAA options:</u>
  - Mavyret® GLE/PIB x 8 weeks
  - Epclusa® SOF/VEL x 12 weeks
    - Zepatier® EBR/GZR 12 weeks
    - Harvoni® LED/SOF x 12 weeks

Case 216 – Dr. Deanna Cotter

Baseline Demographics					
Age: 68	**Race:** African American	**Gender: Female**		**Primary Insurance:** Medicare	
PMH/Comorbidities/Substance Use: Chronic Kidney Disease					
Pertinent Clinical Findings: None					
Weight (kg):	109	**Serum Albumin:**	3.8	**ALT:**	27
Hgb:	14.6	**Total bilirubin:**	0.6	**AST:**	27
PLT:	209	**INR:**	1.1	**SCr/CrCl:**	1.15/80mL/min

Case 216 – Dr. Deanna Cotter

HCV Evaluation					
Ultrasound: Not done	**CT:** Not done				**MRI:** Not done
Signs of Cirrhosis:	no				
Staging Modality:	**Results:**	**Interpretation:**		**APRI:**	0.32
Fibroscan/Transient Elastography:	Not done	-----		**FIB-4:**	1.69
Fibrosure:	0.34	F1-F2			
Treatment Naïve?:	Yes	**If no, previous treatment:**		**HIV Antibody:**	Negative
HCV Genotype:	**1b**	**HCV RNA:**	5,690,000	**HAV | Total Ab:**	Negative
HBV | sAb:	Negative	**HBV | sAg:**	Negative	**HBV | Total cAb:**	Non-reactive
Requested Regimen:	Epclusa x 12, Harvoni x 8 weeks, Mavyret x 8 weeks				

Case 216 – Dr. Deanna Cotter

- Medication List:
  - Atenolol daily
  - Fluticasone nasal spray
  - HCTZ 25mg daily
  - Loratadine 10mg daily prn
  - Losartan 100mg daily
  - Oxybutynin ER 5mg daily
  - Ventolin HFA prn
  - Vitamin D3 2000 units daily
  - Voltaren gel

- **Clinical considerations:**
  - **GT1b**
  - **Treatment naïve**
  - **Metavir- F1-F2**
  - **Simplified treatment regimens**
    - **Shortened course options**

AASLD: New Simplified HCV Treatment Approach

GT1b, tx naïve, non-cirrhotic (concordant results)

- Assess cirrhosis (liver biopsy not required)
  - Treat as though cirrhotic if any of the following suggest cirrhosis
  - FIB-4 > 3.25, platelet count < 150,000/mm^3, APRI > 2.0, *FibroScan* > 12.5 kPa
- Record medications and supplements, assess DDIs
- Conduct recommended baseline labs
- Provide patient education

APRI	0.32
FIB-4	1.69
Fibrosure	F1-F2

Treatment Options:
GLE/PIB 3 pills/day for 8 wks (with food) or SOF/VEL 1 pill/day for 12 wks

Commonly used Liver staging modalities

APRI
FIB-4

- **APRI**
- AST to PLT ratio index
  - *<0.5-low likelihood of fibrosis*
  - *>1.5: High likelihood of cirrhosis*
- **FIB-4**
  - Age, AST, ALT, PLTs.
  - *<1.45: Low likelihood of fibrosis*
  - *>3.25: High likelihood of cirrhosis*

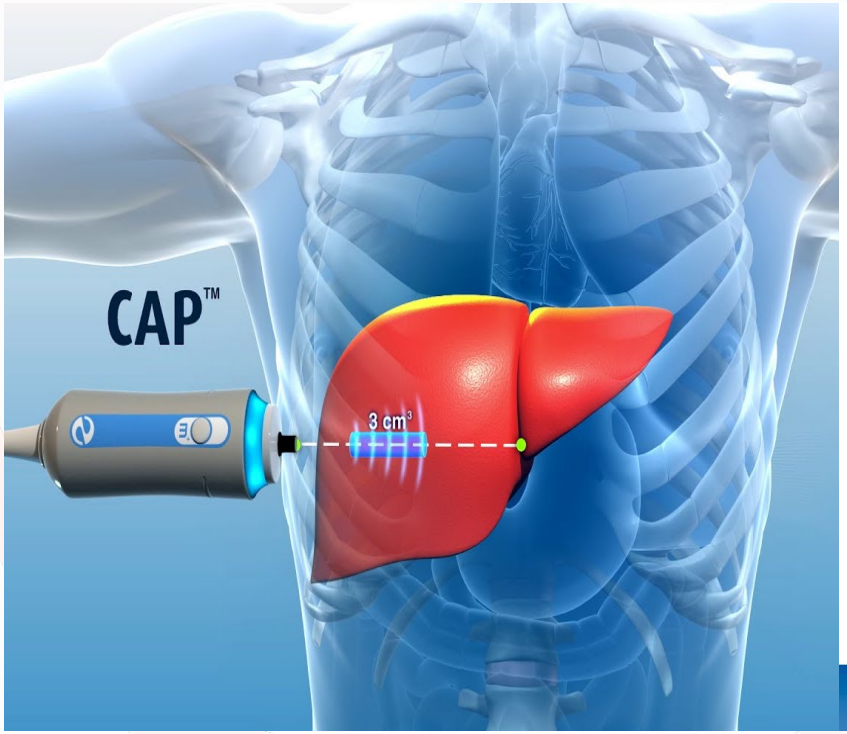
Fibrosure

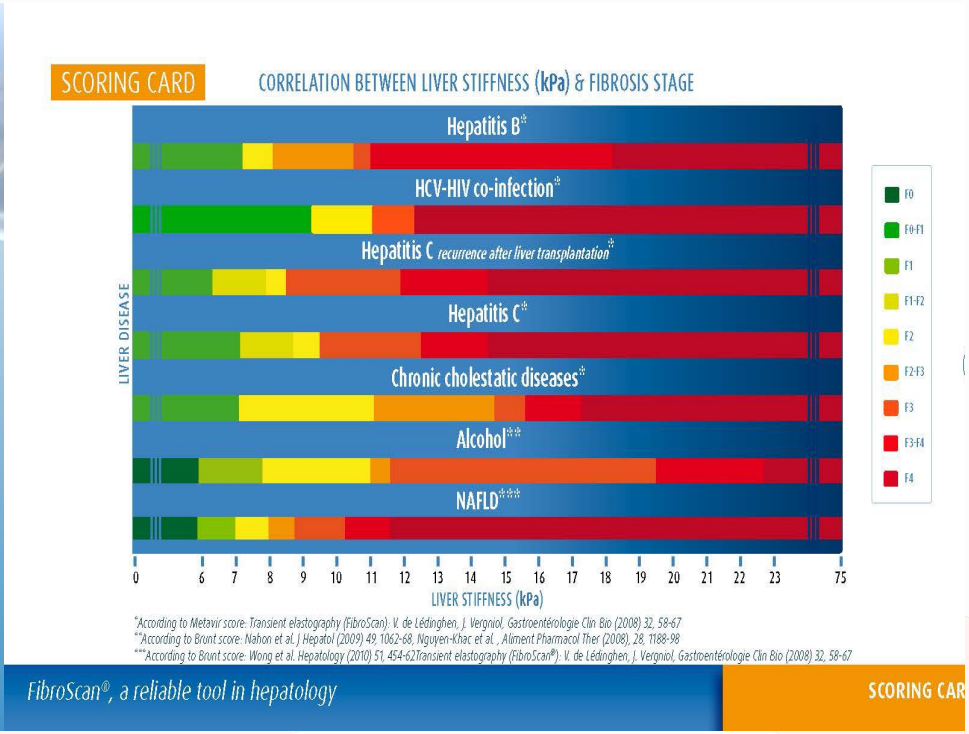
- **Patented Blood test**
- Measures-
  - alpha-2 macroglobulin, haptoglobin, GGT, ALT, and apolipoprotein A1
  - Gives a fibrosis score and inflammation score
  - *>0.75 consistent with cirrhosis*

Fibroscan

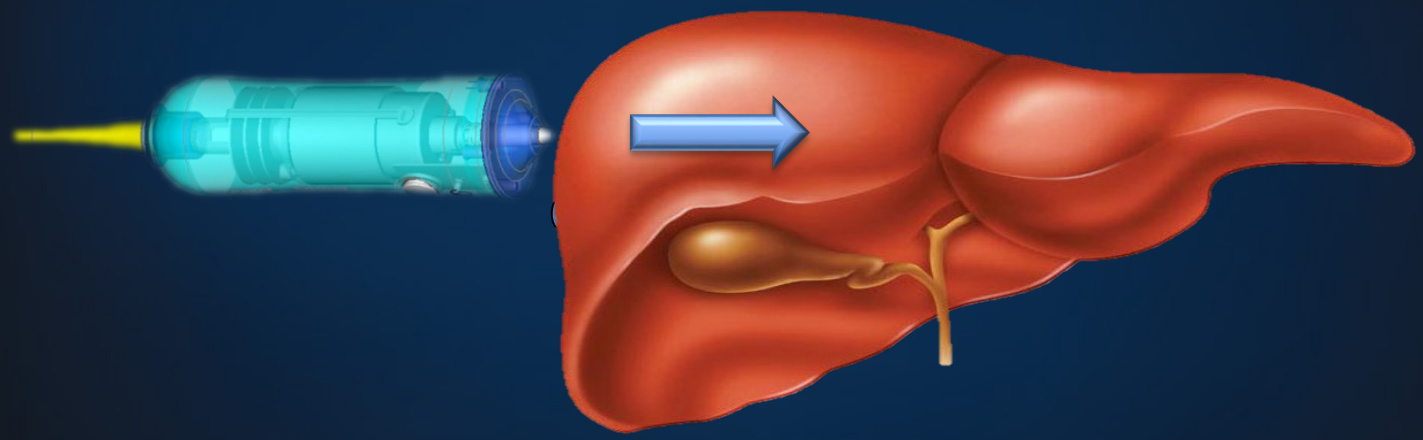
- **Ultrasound Transient elastography**
  - Non invasive
  - Equally accurate in measuring degree of liver inflammation and fibrosis as biopsy
  - > 9.5 is considered Metavir F3
  - > 12.5 (>14 in some studies) is consistent with cirrhosis (F4)

Transient Elastography





Mechanical Shear Wave Induction



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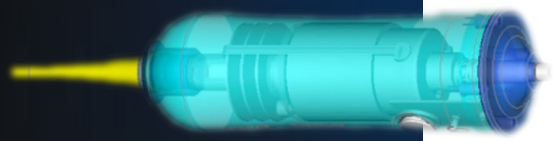
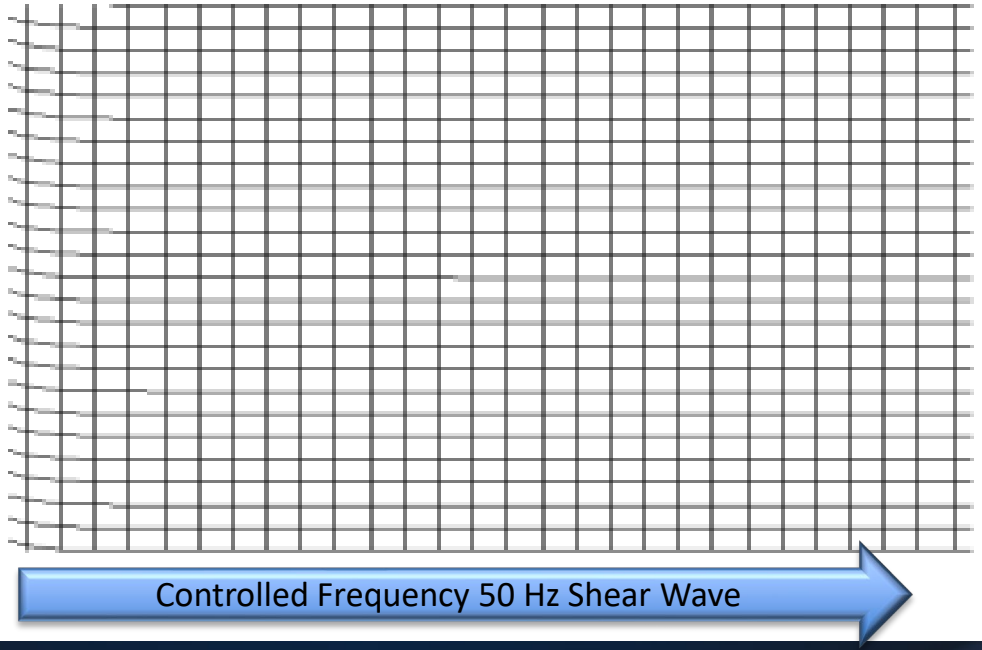
Shear Wave Movement





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Treatment Plan

- **Requested Regimens:**
- Epclusa x 12, *Harvoni x 8 weeks,* Mavyret x 8 weeks

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Patients Genotype 1b Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks[a]	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are HIV-uninfected and whose HCV RNA level is <6 million IU/mL	8 weeks[c]	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A

[a] An 8-week regimen can be considered in those with genotype 1b infection and mild fibrosis (see text for details).

[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

[c] For HIV/HCV coinfected patients, a treatment duration of 12 weeks is recommended.

Pretreatment Assessment: Shortened-course Harvoni®

- Shortened course Harvoni (Ledipasvir/Sofosbuvir) for **African Americans** without cirrhosis has been evaluated in real-world cohorts

Marcus, 2018: 436 African American patients	SVR12 rates were 95.6% for 8-week therapy and 95.8% for 12-week therapy
Tang, 2018: 503 African American veterans	Primarily genotype 1 patients; SVR12 rates were 93.7% for 8-week therapy and 91.4% for 12-week therapy

1. Marcus JL, Hurley LB, Chamberland S. Clin Gastroenterol Hepatol. 2018;16(6):927-935.
2. Tang L, Parker A, Flores Y, et al. J Viral Hepat. 2018;25(2):205-208.

Recommendations

- GT1b, treatment naïve, without evidence of advanced fibrosis & HBV/HIV negative
  - HAV/HBV Vaccination needed

- <u>DAA options:</u>
  - Zepatier® EBR/GZR x 8 or12 weeks
    - STREAGER trial (GT1b, with low fibrosis defined as a TE score <9.5 or a Fibrotest® score <0.59 [F0 to F2], found an SVR rate of 98% (87/89)) while using 8 weeks of therapy
  - Harvoni® LED/SOF x 8 weeks
  - Mavyret® GLE/PIB x 8 weeks
  - Epclusa® SOF/VEL x 12 weeks

Case 217 – Dr. Andre

Baseline Demographics					
Age: 35	**Race:** White	**Gender:** Female		**Primary Insurance:** Private	
PMH/Comorbidities/Substance Use: diabetes, depression, s/p C section Feb 2020					
Pertinent Clinical Findings: None					
Weight (kg):	143	**Serum Albumin:**	3.5	**ALT:**	189
Hgb:	11.9	**Total bilirubin:**	0.6	**AST:**	187
PLT:	309	**INR:**	1.0	**SCr/CrCl:**	0.82/216.4

Case 217 – Dr. Andre

HCV Evaluation					
Ultrasound: Not done	**CT:** Not done				**MRI:** Not done
Signs of Cirrhosis:	None				
Staging Modality:	**Results:**	**Interpretation:**		**APRI:**	1.51
Fibroscan/Transient Elastography:	Not done	-----		**FIB-4:**	1.54
Fibrosure:	0.48	F2, severe necroinflammatory activity (0.81)			
Treatment Naïve?:	Yes	**If no, previous treatment:** N/A		**HIV Antibody:**	Negative
HCV Genotype:	**1a**	**HCV RNA:**	2,024,274	**HAV | Total Ab:**	Negative
HBV | sAb:	Negative	**HBV | sAg:**	Negative	**HBV | Total cAb:**	Non-reactive
Requested Regimen:	Epclusa x 12 weeks				

Case 217 – Dr. Andre

- **Medication List:**
  - Aspirin 81 mg daily
  - Sprintec daily
  - Ferrous sulfate 325 mg daily
  - Novolin 70/30 24 units BID
  - Synthroid 100 mcg daily
  - PNV daily

- **Clinical considerations:**
  - GT1a
  - Treatment naïve
  - Cirrhosis assessment
    - APRI 1.51
    - FibroSURE- F2
  - Simplified vs. comprehensive approach
  - Drug interactions
  - Needs vaccination

AASLD: New Simplified HCV Treatment Approach

GT1a, tx naïve

- Assess cirrhosis (liver biopsy not required)
  - Treat as though cirrhotic if any of the following suggest cirrhosis
  - FIB-4 > 3.25, platelet count < 150,000/mm^3, APRI > 2.0, *FibroScan* > 12.5 kPa
- Record medications and supplements, assess DDIs
- Conduct recommended baseline labs
- Provide patient education

APRI	1.51
FIB-4	1.54
Fibrosure	F2

Treatment Options:
GLE/PIB 3 pills/day for 8 wks (with food) or SOF/VEL 1 pill/day for 12 wks

AASLD Guidance. November 2019.

SIMPLIFIED vs. STANDARD

Cirrhosis Assessment

- FIB-4 >3.25 OR
- *Previously documented*: FibroScan, FibroSure, clinical evidence of cirrhosis, biopsy
- If cirrhosis: CTP score and genotype testing

Coinfection Assessment

- HIV antigen/antibody
- Hepatitis B surface antigen

Cirrhosis Assessment

- Serologic: FIB-4, APRI, FibroSURE
- Non-invasive: FibroScan
- Genotype testing

Coinfection Assessment

- HIV antigen/antibody
- HBV surface antigen, surface antibody, core antibody

Recommendations

GENOTYPE 1A

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1a Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs for elbasvir[a]	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are HIV-uninfected and whose HCV RNA level is <6 million IU/mL	8 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A

[a] Includes genotype 1a resistance-associated substitutions (RASs) at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance. If 1 or more RASs are present, another recommended regimen should be used.

[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

APRI	1.51
FIB-4	1.54
Fibrosure	F2

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[b] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[c]	8 weeks	I, B

[a] For decompensated cirrhosis, please refer to the appropriate section.

[b] Includes genotype 1a RASs at amino acid position 28, 30, 31, or 93 known to confer antiviral resistance. If 1 or more RASs are present, another recommended regimen should be used.

[c] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information. For patients with HIV/HCV coinfection, a treatment duration of 12 weeks is recommended.

Drug-Drug Interactions

	Ethinyl Estradiol (for example)
Route of Hormone Metabolism	3A4 (61%), 2C9 (23%), minor (<20% total): 1A2, 2C19, 3A5
EBR/GZR	↔
LDV/SOF	↑ 20%
SOF/VEL	↔
GP	↑ 28%-40%, ALT elevations observed
SOF/VEL/VOX	↔

Recommendations

- HCV GT1a, tx naïve, non-cirrhotic
  - Epclusa (SOF/VEL) x 12 weeks (also appropriate regimen for advanced fibrosis)
    - GLE/PIB & LDV/SOF: more pronounced LFT elevations with EE
    - EBV/GZR- need resistance testing
- Needs vaccination (HAV/HBV)

Case 218 – Dr. Adebajo

Baseline Demographics					
Age: 64	**Race:** Black	**Gender:** Female		**Primary Insurance:** Medicaid	
PMH/Comorbidities/Substance Use: None					
Pertinent Clinical Findings: None					
Weight (kg):	Not provided	**Serum Albumin:**	Not provided	**ALT:**	145
Hgb:	14.9	**Total bilirubin:**	0.4	**AST:**	92
PLT:	112	**INR:**	1.1	**SCr/CrCl:**	0.84/----

Case 218 – Dr. Adebajo

HCV Evaluation					
Ultrasound: Pending	**CT:** Not done				**MRI:** Not done
Signs of Cirrhosis:	None				
Staging Modality:	**Results:**	**Interpretation:**		**APRI:**	2.05
Fibroscan/Transient Elastography:	Pending	-----		**FIB-4:**	4.37
Fibrosure:	0.73	F3-F4, severe necroinflammatory activity (0.87)			
Treatment Naïve?:	Yes	**If no, previous treatment:** N/A		**HIV Antibody:**	Negative
HCV Genotype:	**1a**	**HCV RNA:**	18,800,000	**HAV | Total Ab:**	Negative
HBV | sAb:	Positive	**HBV | sAg:**	Negative	**HBV | Total cAb:**	Non-reactive
Requested Regimen:	Epclusa x 12, Mavyret x 8 weeks				

Case 218 – Dr. Adebajo

- **Medication List:**
  - Amlodipine 2.5 mg daily
  - Flonase as needed

- **Clinical considerations:**
  - GT1a, tx naïve, with compensated cirrhosis
  - Platelets 112
  - HBV sAb positive – immune
  - Received 1st dose of HepA vaccine (Havrix® or Vaqta®) – needs 2nd dose 6 months after first dose

Liver Staging Modalities

APRI:	2.05
FIB-4:	4.37

Fibrosure:	0.73	F3-F4, severe necroinflammatory activity (0.87)

APRI; FIB-4

- APRI
  - **<0.5/0.7 Low likelihood of fibrosis**
  - **>1.5 High likelihood of cirrhosis**
- FIB-4
  - **<1.45 Low likelihood of fibrosis**
  - **>3.25 High likelihood of cirrhosis**

FibroSURE™

- Measurement of:
  - Alpha-2 macroglobulin, haptoglobin, GGT, ALT, apolipoprotein A1
  - Fibrosis score and inflammation score
  - **0.72-0.74 consistent with F3-F4**

FibroScan®

- Ultrasound Transient elastography
- Non-invasive
- As accurate in measuring degree of liver inflammation and fibrosis as biopsy
- **>9.5 is considered F3**
- **>12.5 is consistent with cirrhosis (F4)**

Brown et al. *J Hepatol*. 2019;S0168-8278(19)30647-6.

Additional Pretreatment Assessment: Child-Turcotte-Pugh

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	Points		
	1	2	3
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Ascites	None	Diuretic Responsive	Diuretic Refractory
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin Time Seconds Prolonged or INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3

Albumin not provided

Class A = 5-6 points
Class B = 7-9 points
Class C = 10-15 points

Cirrhosis with CTP Class B and C is considered decompensated

Pugh RN et al. Br J Surg. 1973;60:646-9.

HBV Evaluation

- Ensure adequate treatment of HBV as necessary prior to initiating HCV therapy

Marker	Interpretation	Acute Infection	Window Period	Chronic Infection	Remote Infection	Immuni-zation	Inactive Chronic Carrier
HBcAb	Exposure	+	+	+	+	–	+
HBsAg	Infection	+	–	+	–	–	–
HBsAb	Immunity	–	–	–	+	+	–

AASLD/IDSA HCV Guidelines. 2019.

Recommendations

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[b] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[c]	8 weeks	I, B

[a] For decompensated cirrhosis, please refer to the appropriate section.

[b] Includes genotype 1a RASs at amino acid position 28, 30, 31, or 93 known to confer antiviral resistance. If 1 or more RASs are present, another recommended regimen should be used.

[c] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information. For patients with HIV/HCV coinfection, a treatment duration of 12 weeks is recommended.

- **GT1a, tx naïve, with compensated cirrhosis**
- *All of the above are valid options*
  - Different payers have different requirements & agents of choice

Recommendations

- GT1a, treatment naïve, compensated cirrhotic
  - Epclusa® (SOF/VEL) x 12 weeks
  - Mayvret ® (GLE/PIB) x 8 weeks
  - Harvoni ® (LDV/SOF) x 12 weeks
  - Zepatier ® (EBV/GZR)- need resistance testing since GT1a
- HAV vaccination series in process