

HIV-HCV Co-Infection in 2018

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AASLD/IDSA and DHHS Guidance: HIV/HCV Coinfection

- All pts with HIV should be screened for HCV^[1]
- HCV candidacy nearly universal^[2]
 - HIV coinfection creates unique considerations for pts with HCV, particularly potential drug interactions between HCV and HIV antivirals
- Even with potent HIV ARVs, pts with HIV/HCV coinfection are at increased risk for rapidly progressive liver disease^[2]

“HIV ARV therapy is not a substitute for HCV treatment”^[2]

HBV Reactivation

- HBV reactivation reported in HCV mono-infected persons not on anti-HBV treatment
- Therefore all persons with prior HBV should be on anti-HBV therapy prior to HCV treatment

Pre-Treatment Questions

- HCV genotype/ subtype
- Stage of fibrosis
 - Cirrhosis Y/N
 - Decompensated Y/N
- Method
 - Liver biopsy
 - Transient elastography
 - Fibrosure
- Prior HCV Treatment
 - Response
 - DAA usage
 - Prior side effects
- Immunization status
- HIV
- HIV drug resistance
- Medication
- Child Bearing Potential
 - Ribavirin

HCV DAAs Target Steps of HCV Life Cycle

Inhibitor Class	Suffix	Examples
Targeting HCV Protein Processing		
NS3/4A protease ^[1]	-PREVIR	▪ Glecaprevir, grazoprevir, paritaprevir, simeprevir, voxilaprevir
Targeting HCV Replication		
NS5B polymerase ^[2]	-BUVIR	▪ Nucleotide: sofosbuvir ▪ Nonnucleoside: dasabuvir
NS5A ^[3]	-ASVIR	▪ Daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, velpatasvir

1. McCauley JA, et al. Curr Opin Pharmacol. 2016;30:84-92.

2. Eltahla AA, et al. Viruses. 2015;7:5206-5224.

3. Gitto S, et al. J Viral Hepat. 2017;24:180-186.

AASLD/IDSA Recommendations for First-line HCV Treatment in HIV/HCV Coinfection

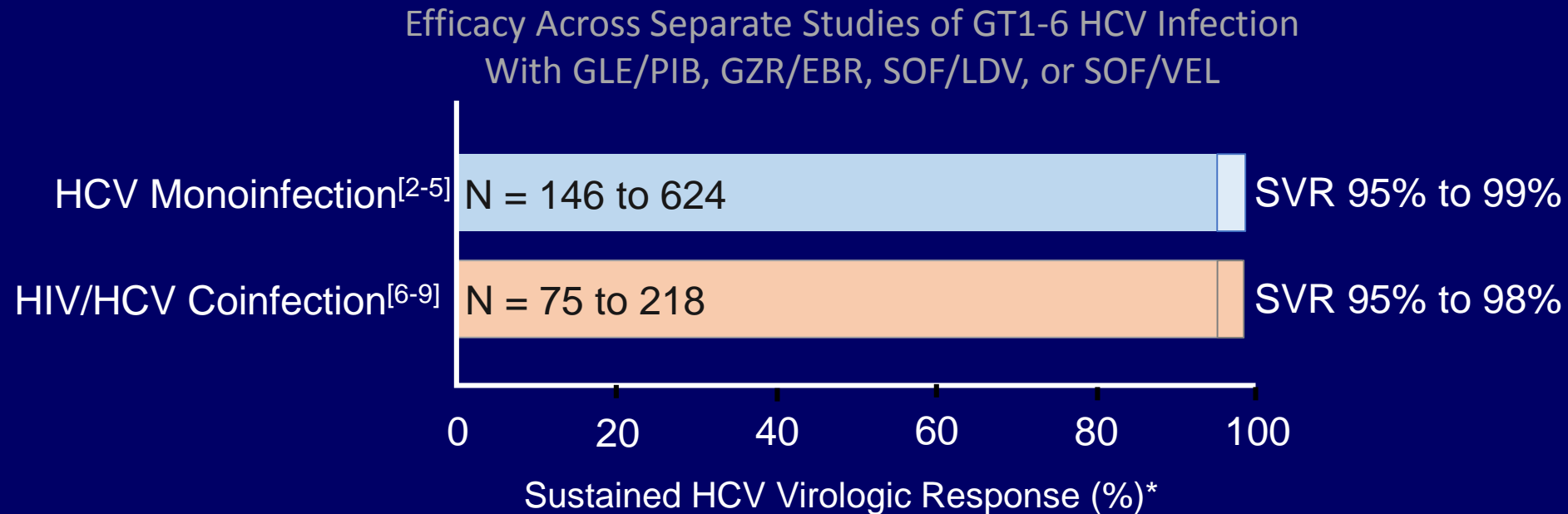
Regimen by HCV GT	Duration, Wks	No Cirrhosis	Compensated Cirrhosis [‡]	eGFR < 30 mL/min
1, 4	8	GLE/PIB	--	GLE/PIB
	12	GZR/EBR,* SOF/LDV, [†] SOF/VEL	GLE/PIB, GZR/EBR,* SOF/LDV, SOF/VEL	GZR/EBR
2, 3	8	GLE/PIB	--	GLE/PIB
	12	SOF/VEL	GLE/PIB, SOF/VEL [§]	--
5, 6	8	GLE/PIB	--	GLE/PIB
	12	SOF/LDV, SOF/VEL	GLE/PIB, SOF/LDV, SOF/VEL	--

*If GT1a with BL NS5A RASs for EBR, 12 wks not recommended; can increase duration to 16 wks with RBV (alternative). [†]Some data to support 8 wks in GT1, but 8 wks not recommended in HIV/HCV coinfection.

[‡]If decompensated cirrhosis, do not use HCV protease inhibitors. [§]If BL Y93H RAS present in GT3, add RBV or consider SOF/VEL/VOX. [¶]If also cirrhotic, increase duration to 12 wks.

Is HCV Treatment Different in the Setting of HIV/HCV Coinfection?

- Per AASLD/IDSA, treatment in HIV/HCV-coinfected pts should be the same as in HCV monoinfected pts, after consideration of potential drug–drug interactions between DAAs and ARVs^[1]



*Most data reported for these studies from treatment-naive pts with GT1/4 HCV infection receiving 12-wk regimens.

Case Presentation-1

- A 46y M with h/o IDU, now clean for many years
- Diagnosed in 2011
- HIV
 - On TDF/FTC and boosted atazanavir
- HCV
 - GT 1a
 - Treatment naïve
 - Was not treated till now because he was afraid of side effects

Case Presentation-1, Contd

- HIV VL < 40, CD4- 456 cells/cu mm
- HCV VL- 9 million copies/ml
- GT 1a
- HBV –ve, surface antibody +
- Creatinine- 0.9, AST-51, ALT-60, Bilirubin-1.3

HIV/HCV Drug–Drug Interactions

ARV(s)	GLE/PIB	GZR/EBR	SOF/LDV	SOF/VEL	SOF/VEL/VOX
ATV + (RTV or COBI)	X	X	✓*	✓*	X
DRV + (RTV or COBI)	X	X	✓*	✓*	✓*†
LPV + RTV	X	X	✓*	✓*	X
EFV	X	X	✓*	X	X
RPV	✓	✓	✓*	✓	✓
DTG	✓	✓	✓*	✓	✓
RAL	✓	✓	✓	✓	✓
EVG/COBI/FTC/TDF	✓*†	X	X	✓*	✓*†
EVG/COBI/FTC/TAF	✓†	X	✓	✓	✓†
3TC/ABC	✓	✓	✓	✓	✓
TAF	✓	✓	✓	✓	✓
TDF	✓	✓	✓*	✓*	✓*

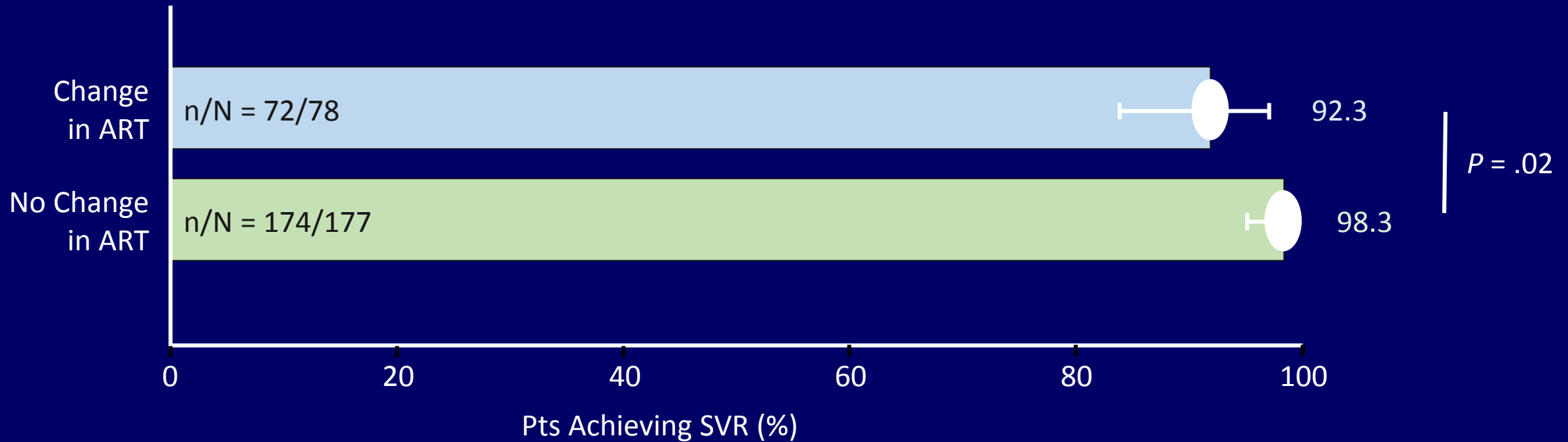
*Monitor for tenofovir toxicity if used with TDF. †No clinically significant drug interaction per prescribing information; AASLD/IDSA and DHHS guideline recommend monitoring liver enzymes owing to lack of clinical safety data.

Principles of Regimen Switching in Virologically Suppressed Pts

- Review ART history for prior intolerance or HIV virologic failure
- Review HIV resistance test results
- If prior HIV resistance uncertain, consider switch only if new regimen likely to maintain suppression of resistant virus
- In pts with HIV/HBV coinfection, continue ARVs active against HBV (even if not needed for HIV suppression)
 - (TAF or TDF) plus (3TC or FTC)
- Switches usually maintain HIV suppression if no resistance to drugs in new regimen
- Check HIV-1 RNA during first 3 mos after switch to ensure suppression
- Boosted PI or INSTI monotherapy not recommended

Does Switching ART Affect Likelihood of HCV Cure?

- Real-world, single-center, cohort study of HIV/HCV-coinfected pts treated with DAAs (N = 255)



Case-1 Continued

- Option #1
- Pick HCV that does not interact with ARV
 - LDV/SOF
 - SOF/VEL
- Option #2
- Switch ARV
 - RAL
 - RPV
 - DTG
- Wait 4 wks to ensure pt is tolerating new ART and HIV-1 RNA remains suppressed prior to starting HCV treatment

Case-2

- A 28 y F with well controlled HIV
- TDF/FTC/RPV
- Was treated with 12 weeks of SOF/LDV
- GT1a
- HCV VL rebounds at 4 weeks post treatment
- CD4- 574, GT 1a,
- HCV resistance
 - NS3: wild type
 - NS5a: Y93H

AASLD/IDSA Recommendations for HCV Treatment of DAA-Experienced Pts

HCV GT	Duration, Wks	NS3 + PegIFN/RBV Experience	Non-NS5A, SOF-Containing Experience	NS5A Experience
1	12	GLE/PIB, SOF/LDV,* SOF/VEL	GLE/PIB, SOF/VEL, [†] SOF/VEL/VOX [‡]	SOF/VEL/VOX
2	12		GLE/PIB, SOF/VEL	
3	12	SOF/VEL/VOX [§]	SOF/VEL/VOX [§]	SOF/VEL/VOX [§]
4-6	12	SOF/VEL/VOX	SOF/VEL/VOX	SOF/VEL/VOX

*Not recommended if also cirrhotic. [†]For genotype 1b only. [‡]For genotype 1a only. [§]If also cirrhotic with prior NS5A failure, add RBV.

Is Resistance Testing Needed When Retreating Pts Who Failed DAA-Containing Regimens?

Regimen	AASLD/IDSA RAS Testing Recommendations for Treatment-Experienced Pts
GLE/PIB	<ul style="list-style-type: none">▪ RAS testing not recommended
SOF/LDV	<ul style="list-style-type: none">▪ Consider for pts with GT1a HCV; if significant resistance present, add RBV (and extend duration, if cirrhotic) or select a different regimen
SOF/VEL	<ul style="list-style-type: none">▪ Recommended for pts with GT3 HCV; if Y93H mutation present, add RBV
SOF/VEL/VOX	<ul style="list-style-type: none">▪ RAS testing not recommended

HIV/HCV Drug–Drug Interactions

ARV(s)	SOF/VEL/VOX
ATV + (RTV or COBI)	X
DRV + (RTV or COBI)	✓*†
LPV + RTV	X
EFV	X
RPV	✓
DTG	✓
RAL	✓
EVG/COBI/FTC/TDF	✓*†
EVG/COBI/FTC/TAF	✓†
3TC/ABC	✓
TAF	✓
TDF	✓*

← No significant DDI

*Monitor for tenofovir toxicity if used with TDF. †No clinically significant drug interaction per prescribing information; AASLD/IDSA and DHHS guideline recommend monitoring liver enzymes owing to lack of clinical safety data.

AASLD/IDSA Recommendations for LDV or VEL With Tenofovir

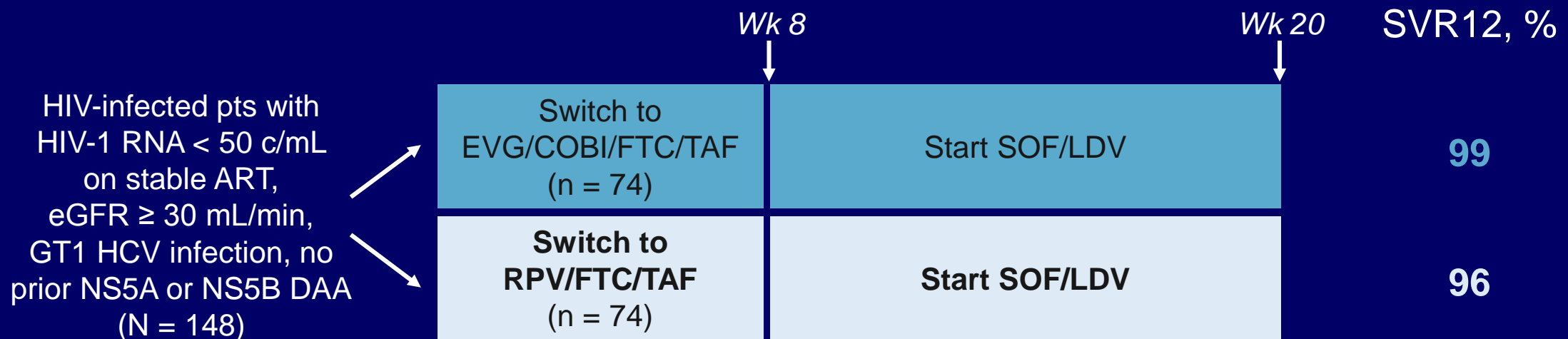
Regimen	Guidance for Coadministration With TDF ^{[1]*}	
	Without COBI or RTV	With COBI or RTV
SOF/LDV	Monitor ^[2]	Monitor; consider TAF or ART switch
SOF/VEL	Monitor	Monitor; consider TAF
SOF/VEL/VOX	Monitor	Monitor (My approach: consider TAF)
Guidance for Coadministration With TAF ^[1]		
SOF/LDV, SOF/VEL, SOF/VEL/VOX	No significant interaction	

*If eGFR < 60 mL/min, avoid TDF coadministration with SOF/LDV, SOF/VEL, or SOF/VEL/VOX.

“For combinations expected to increase tenofovir levels, baseline and ongoing assessment for tenofovir nephrotoxicity is recommended”

GS-1992: SOF/LDF in HIV/HCV Coinfection After Switch to TAF-Based Regimens

- Randomized, open-label phase IIIb trial



- Switch to TAF-based regimen maintained HIV-1 RNA < 50 copies/mL in 95% of pts
 - D/c before Wk 8 for lack of efficacy (n = 1), no resistance to ART

Case-3

- A 48 y M with HCV, compensated cirrhosis
- HCV treatment naive
- HIV infection well controlled with single-tablet regimen of EFV/FTC/TDF
 - HLA-B*5701 negative
- Past history of HBV infection with documented anti-HBs seroconversion ~ 9 yrs ago

Consider Potential for HBV Reactivation

- Test all pts initiating HCV DAA therapy for HBsAg, anti-HBc, and anti-HBs^[1]
- HIV-infected pts with active HBV infection (HBsAg positive) should receive NRTIs with anti-HBV activity^[2]
 - (TAF or TDF) plus (3TC or FTC), or entecavir if TAF or TDF not feasible
 - Initiate ART prior to DAA therapy owing to risk of HBV reactivation with DAAs
- In pts positive for anti-HBc ± anti-HBs,^[1] no consensus
 - Risk of HBV reactivation is very low,^[3] but consider monitoring transaminases at Wks 4 and 8
 - Insufficient data to inform HBV DNA monitoring

AASLD/IDSA Recommendations for Treatment-Naive GT3 HCV Without Cirrhosis

Regimen	Duration
Recommended	
▪ GLE/PIB	8
▪ SOF/VEL*	12
Alternative	
▪ DCV + SOF	12

AASLD/IDSA Recommendations for Treatment-Naive GT3 HCV With Compensated Cirrhosis

Regimen	Duration, Wks
Recommended	
▪ GLE/PIB	12
▪ SOF/VEL*	12
Alternative	
▪ SOF/VEL/VOX	12
▪ DCV + SOF ± weight-based RBV	24

*If Y93H, add RBV or use SOF/VEL/VOX as alternative.

HIV/HCV Drug–Drug Interactions

ARV(s)	GLE/PIB	SOF/VEL	SOF/VEL/VOX	SOF + DCV
ATV + (RTV or COBI)	X	✓*	X	Decrease DCV dose
DRV + (RTV or COBI)	X	✓*	✓*†	✓
LPV + RTV	X	✓*	X	✓
EFV	X	X	X	Increase DCV dose
RPV	✓	✓	✓	✓
DTG	✓	✓	✓	✓
RAL	✓	✓	✓	✓
EVG/COBI/FTC/TDF	✓*†	✓*	✓*†	Decrease DCV dose
EVG/COBI/FTC/TAF	✓†	✓	✓†	Decrease DCV dose
3TC/ABC	✓	✓	✓	✓
TAF	✓	✓	✓	✓
TDF	✓	✓*	✓*	✓

*Monitor for tenofovir toxicity if used with TDF. †No clinically significant drug interaction per prescribing information; AASLD/IDSA and DHHS guideline recommend monitoring liver enzymes owing to lack of clinical safety data.

Case-3, Contd

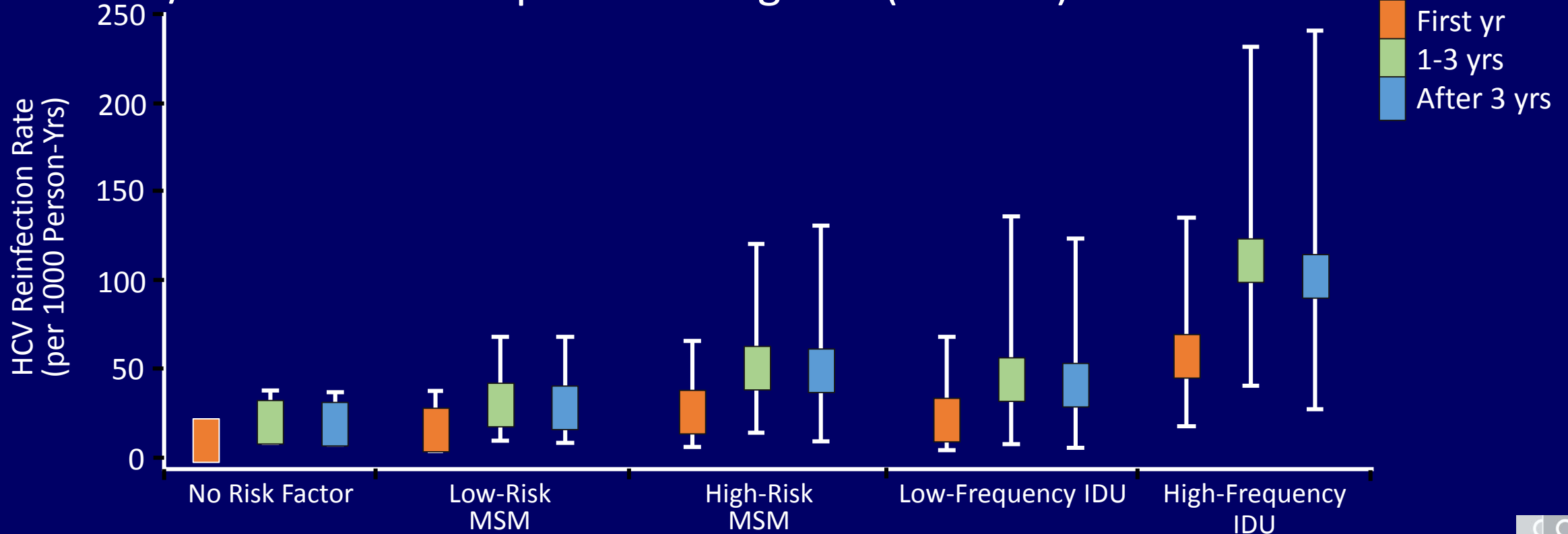
- ARV switched to DTG+ TDF/FTC
- Regimen change tolerated
- Pt started HCV treatment with GLE/PIB for 12 weeks
- Achieved cure/SVR

Case-4

- A 39y M with h/o IDU on EFV/TDF/FTC
- HIV VL < 50, CD4- 744 cells
- Had h/o HCV previously treated with IFN/RBV treated successfully
- Was incarcerated for 2 years
- Now back into care
- Labs show ALT of 57
- HCV PCR- 6 million

HCV Reinfection Risk After SVR in HIV/HCV-Coinfected Pts

- Prospective cohort study of risk factors for HCV reinfection in HIV/HCV-coinfected pts achieving SVR (N = 257)



Case-5

- A56 y male with HIV
- Abacavir, Lamivudine and Dolutegravir
- HIV VL < 20, CD4-357
- HCV treatment naive
- GT 1a, HCV VL 6.5 million copies
- Never treated because his creatinine is 3.5

HCV Recommendations for CKD stage^a 1,2,3

- Recommended
 - Daclatasvir (60 mg)^b
 - Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)
 - Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)^c
 - Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)
 - Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)
 - Simeprevir (150 mg)
 - Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)
 - Sofosbuvir (400 mg)

^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 Refer to the prescribing information and the section on [HIV/HCV coinfection](#) for patients on antiretroviral therapy.

^c This is a 3-tablet coformulation. Please refer to the prescribing information.

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

Recommended	Genotype	Duration
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	1a, 1b, 4	12 weeks
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b	1, 2, 3, 4, 5, 6	8 to 16 weeks ^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)

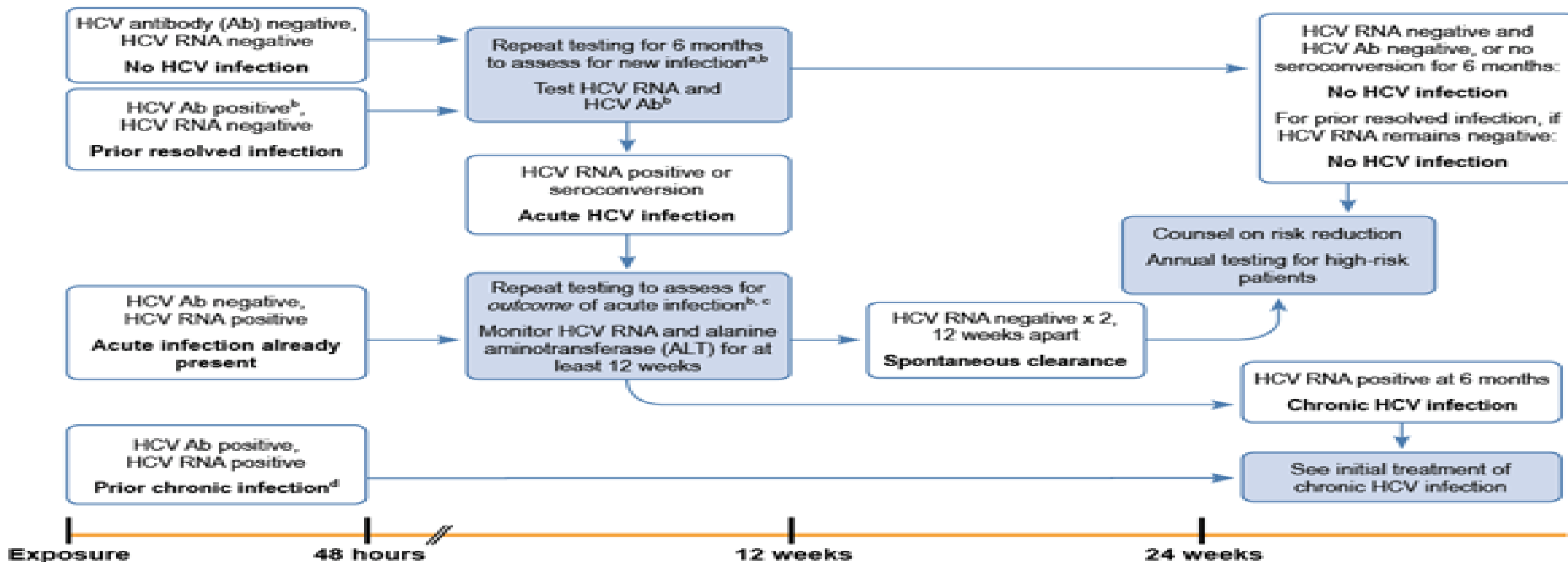
^b This is a 3-tablet coformulation. Please refer to the prescribing information.

^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.

Case-6

- A 24 y Man with HIV for 2 years doing well on TDF/FTC/EVG/c
- HIV VL < 20, CD4-645 cells/ cu mm
- On routine monitoring found to have elevated LFTs and now has HCV Ab positive
- Last HCV negative was negative 6 months ago

Figure. Testing Algorithm for Discrete Recognized Hepatitis C Virus (HCV) Exposure^a



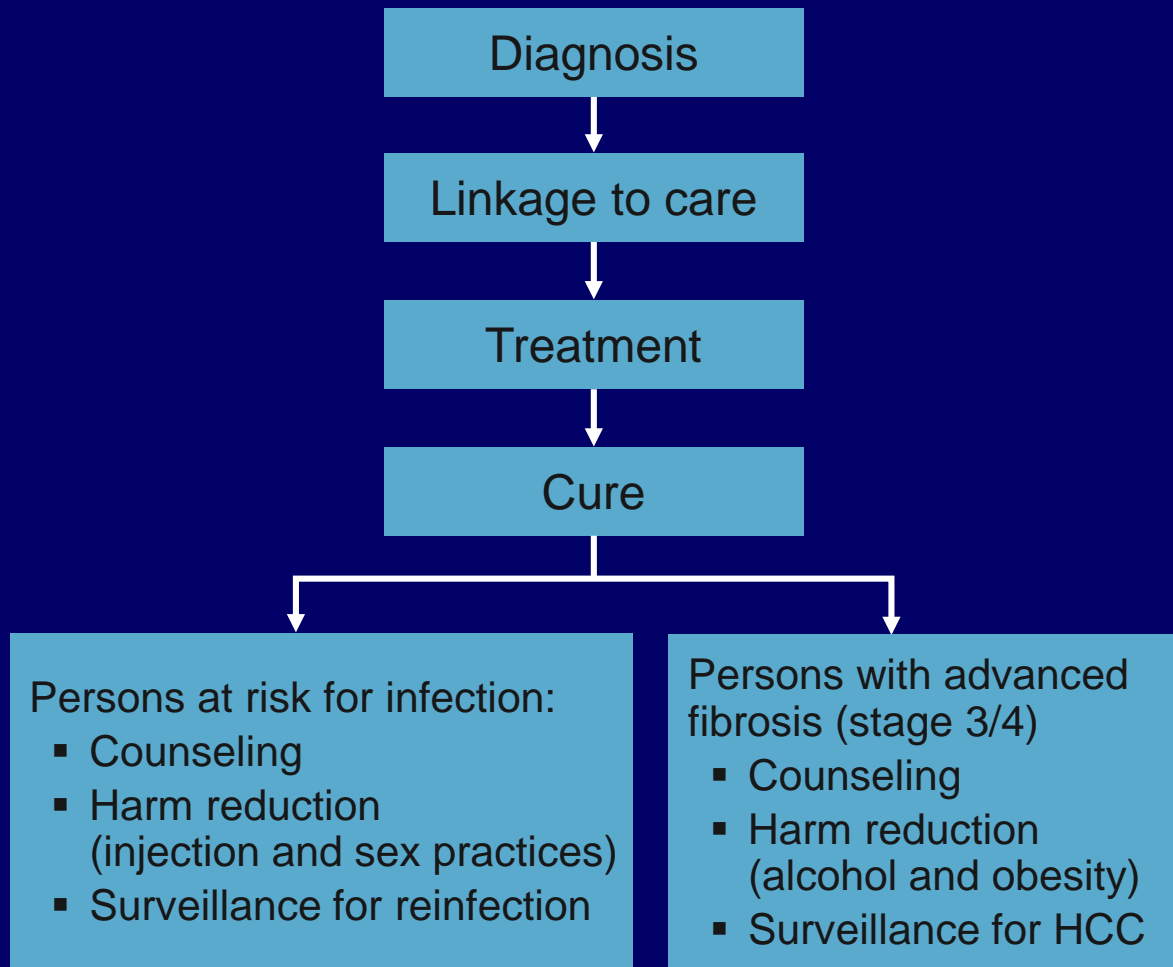
Baseline testing within 48 hours of exposure^a

- ^a Often there is no discrete exposure or the entry to health care occurs with jaundice or elevated liver enzymes. In those instances, baseline testing cannot be done and the diagnosis of acute infection is more challenging (see text).
- ^b Repeat HCV Ab is not needed if it is positive at baseline. Frequency of testing can be tailored based on management objectives (eg, monthly testing to identify and treat acute infection).
- ^c Some would treat after waiting 8 weeks to 12 weeks for spontaneous clearance (see text). Benefits of HCV antiviral therapy or IFN-based (alternative) within 12 weeks of acute infection are that this may decrease transmission risk to others (eg, among injection drug users or surgeons), prevent severe complications (eg, underlying cirrhosis superinfected with acute HCV infection), and minimize chance of being lost to follow-up.
- ^d If there were additional exposures in the preceding 6 months, a patient with a new diagnosis who is HCV RNA and HCV Ab positive may still be in the acute infection phase. Symptoms, high ALT level, or viral fluctuations may help distinguish acute from chronic HCV.
- ^e Baseline testing should be done within 48 hours of exposure to determine existing infection status: HCV RNA, HCV Ab, and ALT.

Treatment of Acute HCV

- Monitor for 6-12 months for possible spontaneous clearance
- Risk reduction counseling: alcohol, hepatotoxic medications etc
- Can start treatment sooner if clinician deems it necessary

HCV Care Continues Past Achievement of SVR



Characteristic	Follow-up After SVR
No advanced fibrosis (Metavir stage F0-F2), no or low risk of HCV reinfection	<ul style="list-style-type: none"> ▪ Standard medical care, as in someone without HCV
Advanced fibrosis (Metavir stage F3 or F4)	<ul style="list-style-type: none"> ▪ Ultrasound surveillance for HCC every 6 mos ± AFP
Moderate to high risk of HCV reinfection	<ul style="list-style-type: none"> ▪ Harm reduction ▪ HCV RNA every 12 mos

Key Points

- Treatment regimens similar to HCV mono-infected
- Monitor for DDI
- Except for 1 exception treatment duration generally 12 weeks
- ART interruption for HCV treatment never allowed
- If significant DDI and ART cannot be changed
 - Daclatasvir plus Sofosbuvir +/- Ribavirin acceptable

