Cases: Management of Hepatitis C in Prior Treatment Failure

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Financial Relationships with Commercial Entities

Dr Kim has no relevant financial affiliations to disclose.
(Updated 10/19/18)

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Learning Objectives

After attending this presentation, learners will be able to:

- List treatment options for treatment-experienced patients
- Describe the relevance of resistance-associated substitutions

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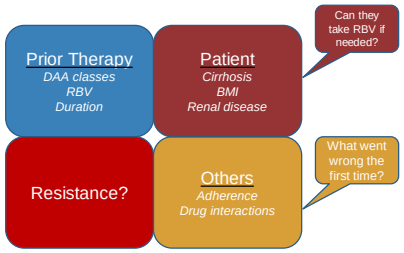
Considerations for DAA regimen failures



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Case

- 69 y/o African-American gentleman with HIV / HCV co-infection
  - HIV suppressed, CD4 568 cells/mm^3, TDF/FTC/rilpivirine
  - Plt=135K, Cirrhosis by ultrasound, no decompensation, no varices, albumin 3.6
  - BMI 33, Cr 1.1, IL-28B T-T, No prior treatment, genotype 1a
  - 12 weeks of ledipasvir/sofosbuvir, week 4 HCV RNA is target detected but not quantifiable
  - Reports good adherence, takes pills with HIV medication upon awakening, missed 2 doses (took 84 pills over 86 days). HIV RNA remains suppressed on treatment
  - HCV RNA positive at week 4 post-treatment
  - He was eating more tomatoes during the last two months of treatment that caused heartburn, was taking TUMS at night

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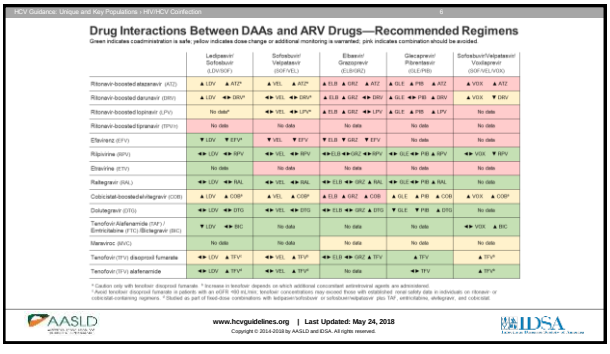

HCV Guidance: Unique and Key Populations › HIV/HCV Coinfection 6

Drug Interactions Between DAAs and ARV Drugs—Recommended Regimens

Green indicates coadministration is safe; yellow indicates dose change or additional monitoring is warranted; pink indicates combination should be avoided.

	Ledipasvir/ Sofosbuvir (LDV/SOF)	Sofosbuvir/ Velpatasvir (SOF/VEL)	Elbasvir/ Grazoprevir (EBR/GRZ)	Glecaprevir/ Pibrentasvir (GLE/PIB)	Sofosbuvir/Velpatasvir/ Voxilaprevir (SOF/VEL/VOX)
Ritonavir-boosted atazanavir (ATZ)	▲ LDV ▲ ATZ*	▲ VEL ▲ ATZ*	▲ ELB ▲ GRZ ▲ ATZ	▲ GLE ▲ PIB ▲ ATZ	▲ VOX ▲ ATZ
Ritonavir-boosted darunavir (DRV)	▲ LDV ◀▶ DRV*	◀▶ VEL ◀▶ DRV*	▲ ELB ▲ GRZ ◀▶ DRV	▲ GLE ◀▶ PIB ▲ DRV	▲ VOX ▼ DRV
Ritonavir-boosted lopinavir (LPV)	No data*	◀▶ VEL ◀▶ LPV*	▲ ELB ▲ GRZ ◀▶ LPV	▲ GLE ▲ PIB ▲ LPV	No data
Ritonavir-boosted tipranavir (TPV/r)	No data	No data	No data	No data	No data
Efavirenz (EFV)	▼ LDV ▼ EFV*	▼ VEL ▼ EFV	▼ ELB ▼ GRZ ▼ EFV	No data	No data
Rilpivirine (RPV)	◀▶ LDV ◀▶ RPV	◀▶ VEL ◀▶ RPV	◀▶ ELB ◀▶ GRZ ◀▶ RPV	◀▶ GLE ◀▶ PIB ▲ RPV	◀▶ VOX ▼ RPV
Etravirine (ETR)	No data	No data	No data	No data	No data
Raltegravir (RAL)	◀▶ LDV ◀▶ RAL	◀▶ VEL ◀▶ RAL	◀▶ ELB ◀▶ GRZ ▲ RAL	◀▶ GLE ◀▶ PIB ▲ RAL	No data
Cobicistat-boosted elvitegravir (COB)	▲ LDV ▲ COBP	▲ VEL ▲ COBP	▲ ELB ▲ GRZ ▲ COB	▲ GLE ▲ PIB ▲ COB	▲ VOX ▲ COBP
Dolutegravir (DTG)	◀▶ LDV ◀▶ DTG	◀▶ VEL ◀▶ DTG	◀▶ ELB ◀▶ GRZ ▲ DTG	▼ GLE ▼ PIB ▲ DTG	No data
Tenofovir Alafenamide (TAF) / Emtricitabine (FTC) /Bictegravir (BIC)	▼ LDV ◀▶ BIC	No data	No data	No data	◀▶ VOX ▲ BIC
Maraviroc (MVC)	No data	No data	No data	No data	No data
Tenofovir (TFV) disoproxil fumarate	◀▶ LDV ▲ TFV*	◀▶ VEL ▲ TFV*	◀▶ ELB ◀▶ GRZ ▲ TFV	▲ TFV	▲ TFV*
Tenofovir (TFV) alafenamide	◀▶ LDV ▲ TFV*	◀▶ VEL ▲ TFV*	No data	◀▶ TFV	▲ TFV*

* Caution only with tenofovir disoproxil fumarate. ^ Increase in tenofovir depends on which additional concomitant antiretroviral agents are administered.
‡ Avoid tenofovir disoproxil fumarate in patients with an eGFR <60 mL/min; tenofovir concentrations may exceed those with established renal safety data in individuals on ritonavir- or cobicistat-containing regimens. # Studied as part of fixed-dose combinations with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir plus TAF, emtricitabine, elvitegravir, and cobicistat.

AASLD | www.hcvguidelines.org | Last Updated: May 24, 2018 | IDSA

	Simeprevir	Sofosbuvir	Ledipasvir	Daclatasvir	P/r/O + D
DDI	**Substrate of CYP3A4, OATP1B1/3**	**Substrate of P-gp and BCRP**	**Inhibitor/ Substrate of P-gp and BCRP**	**Inhibitor of OATP1B1/3, BCRP, Substrate of P-gp and CYP3A4**	**Inhibit/Sub of UGT1A1,OATP1B1/3 , BCRP, CYP3A4, CYP2C8, P-gp**
ATV/r	No data	No data	LDV ↑; ATV ↑	DCV ↑*	ATV ↑; PAR ↑
DRV/r	SIM ↑; DRV ↔	SOF ↑; DRV ↔	LDV ↑; DRV ↔	ALLY-2 ↔	DRV ↓; PAR ↓
LPV/r	No data	No data	No data	ALLY-2 ↔	LPV ↔; PAR ↑
TPV/r	No data	No data	No data	No data	No data
EFV	SIM ↓; EFV ↔	SOF ↔; EFV ↔	ION-4 ↔	DCV ↓*	No PK data**
RPV	SIM ↔; RPV ↔	SOF ↔; RPV ↔	LDV ↔; RPV ↔	ALLY-2 ↔	PAR ↑; RPV ↑
ETV	No data	No data	No data	No data*	No data
RAL	SIM ↔; RAL ↔	SOF ↔; RAL ↔	LDV ↔; RAL ↔	ALLY-2 ↔	PrOD ↔; ↑ RAL
ELV/ cobi	No data	Cobi ↑; SOF ↑	LDV ↑; SOF ↑	No data	No data
DLG	No data	No data	LDV ↔; DOL ↔	ALLY-2 ↔	PAR ↓; DOL ↑
MVC	No data	No data	No data	No data	No data
TDF	SIM ↔; TFV ↔	SOF ↔; TFV ↔	LDV ↔; ↑TFV	DCV ↔; TFV ↔	PrOD ↔; TFV ↔

Slide courtesy of Jennifer Kiser

ARS Question 1: What type of HCV resistance testing would you perform at this time?

1. NS3
2. NS5A
3. NS5B
4. Both NS3 and NS5A testing
5. None

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Case part 2

- NS5A resistance testing:
  - Mutation: Q30R

Agent	Result
Daclatasvir	Resistance Probable
Ledipasvir	Resistance Probable
Ombitasvir	Resistance Probable
Elbasvir	Resistance Probable

- NS3/4A resistance (2 years earlier):
  - Mutation: I37V

Agent	Result
Boceprevir	Sensitive
Simeprevir	Sensitive
Telaprevir	Sensitive

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Key principles of HCV resistance-associated substitutions (RASs)

- **Viruses with RASs may exhibit variable "fitness" compared to wildtype**
  - Higher fitness last longer (e.g.NS5A), lower fitness may be transient (e.g. NS5B)
- **RAS are present at baseline in the absence of drug exposure, but may or may not be detected. RASs that are selected during treatment tend to confer more resistance.**
  - The longer on treatment the more likely to have RASs at time of virologic failure.
- **RASs may impact treatment responses in select situations**
  - Situation is often worse in presence of other treatment characteristics
- **Resistance is NOT futile**
  - May be overcome by longer durations, addition of ribavirin, or later-generation agents
- **For newly approved regimens detection of RASs is most often NOT necessary**

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Resistance Testing Assays

- Traditional approach is population sequencing, newer assays use "ultra-deep sequencing (next-generation sequencing, or NGS)
- Available:
  - HCV NS5A drug resistance assay (LabCorp / Monogram Biosciences)
    - NGS - 10% threshold for reporting
  - HCV NS3 and NS5 HCV RNA genotype + resistance (Quest)
    - RT-PCR with DNA sequencing
  - For GT1 and GT3
    - GT1 assays are subtype specific

Adapted from David Wyles

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Differences in the barrier to resistance by drug class

- RAVs to one drug are generally cross resistant to other drugs within a class (but not always)
- Viral fitness of RAVs effects their persistence after discontinuation of therapy

	NS3/4A Protease Inhibitors	NS5B Nucleos(t)ide Polymerase Inhibitors	NS5B Nonnucleoside Polymerase Inhibitors	NS5A Inhibitors
Drugs in Class	**Simeprevir Paritaprevir Grazoprevir Voxilaprevir Glecaprevir**	**Sofosbuvir**	**Dasabuvir**	**Ledipasvir Ombitasvir Daclatasvir Elbasvir Pibrentasvir**
Barrier to resistance	Variable (1a lower barrier than 1b)	Extremely High (1a=1b)	Very low (1a lower barrier than 1b)	Variable (1a lower barrier than 1b)
Comments	2nd and 3rd generation Pts have higher barrier, pangenotypic	Single target Active site	Allosteric Many targets	Multiple antiviral Mechanism of Action

Modified from Schaefer EA, et al. Gastroenterology. 201

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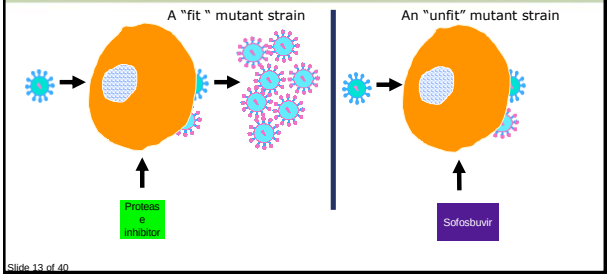
What do we mean by barrier to resistance? Mutations may produce strains of varying fitness to replicate



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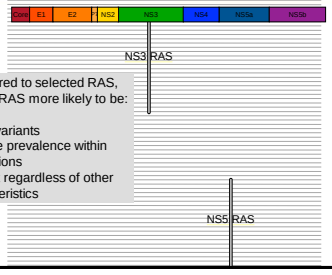
Baseline RAS versus selected



Compared to selected RAS, baseline RAS more likely to be:

1. Single variants
2. Variable prevalence within populations
3. Present regardless of other characteristics

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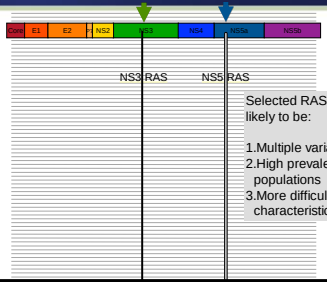
Baseline RAS versus selected



Selected RAS more likely to be:

1. Multiple variants
2. High prevalence within populations
3. More difficult to treat characteristics

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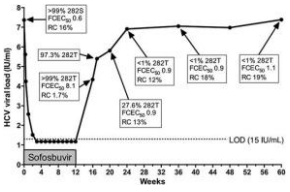
Viruses with RASs exhibit variable "fitness" compared to wildtype

Significant sofosbuvir RASs are rare / super low frequency at baseline

S282T rarely detected Disappears quickly



Svarovskaia, et al. Clin Infect Dis 2014: 59(12), 1666–1674

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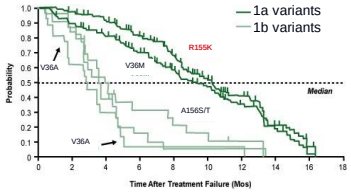
Viruses with RASs exhibit variable "fitness" compared to wildtype

Variable at baseline (R155K ~1%)

Fitness varies by mutation and subtype



Sullivan, et al. EASL. 2011

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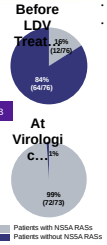
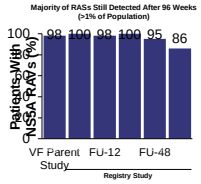
Viruses with RASs exhibit variable "fitness" compared to wildtype

Variable at baseline

Higher fitness



- NS5A RASs in patients who failed LDV treatment without SOF
- Positions 24, 28, 30, 31, 32, 58, 93 that confer >2.5-fold reduced susceptibility to LDV *in vitro* were included



Wyles, et al. Abstract O059, EASL 2015.

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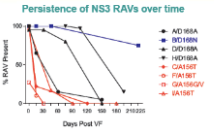
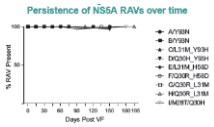
Ability of RASs to persist is dependent on class

Variable at baseline (R155K ~1%)

NS3 | NS5A | NS5B

Fitness varies by class





Black et al. EASL 2017

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ARS Question #2: How would you treat a patient with SOF/LDV experience and documented NS5A resistance?

1. SOF/VEL + RBV x 24 weeks
2. SOF + PrOD + RBV x 12 weeks
3. Glecaprevir/pibrentasvir x 16 weeks
4. SOF/VEL/VOX x 12 weeks
5. SOF/VEL/VOX + RBV x 12 weeks

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Examples of salvage regimens before the newest approvals

Off label:

sofosbuvir + simeprevir + RBV x 24 weeks

paritaprevir/ritonavir/ombitasvir/dasabuvir + sofosbuvir +/- RBV

elbasvir/grazoprevir + sofosbuvir +/- RBV

simeprevir + daclatasvir + sofosbuvir +/- RBV

"The kitchen sink"

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$19,377

- Taken from http://hcvguidelines.org April 17, 2017

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Broad Cross-resistance With "Early Generation" NS5As

Fold-change	1a				1b	
	M28T	Q30R	L31M/V	Y93H/N	L31V	Y93H/N
Ledipasvir	20x	>100x	>100x/ >100x	>1,000x/ >10,000		>100x/--
Ombitasvir	>1000x	>100x	<3x >100x	>10,000x/ >10,000x	<10x	20x/50x
Daclatasvir	>100x	>1000x	>100x/ >1000x	>1,000x/ >10,000x	<10x	20x/50x
Elbasvir	20x	>100x	>10x >100x	>1,000x/ >1,000x	<10x	>100x/--
Velpatasvir	<10x	<3x	20x/50x	>100x/ >1000x		<3x/--
ACH-3102	30x	20x	<10x	>100x/>100x		<3x/<3x
Pibrentasvir	<3x	<3x	<3x	<10x/<10x	<3x	<3x/<3x
MK-8408	<10x	<10x	<10x	<10x	<10x	<10x

Wang C. AAC 2012. Cheng G. #1172. EASL 2012; Zhao Y. #AB45 EASL 2012. Yang G. EASL 2013; Ng T. #639 CROI 2014. Asante-Appiah E. AASLD 2014.

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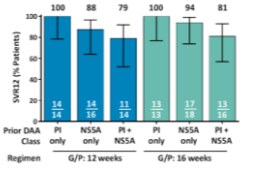
Glecaprevir / pibrentasvir for re-treatment of NS5A failures - MAGELLAN 1

GLE
PIB

- 12 versus 16 weeks, GT1,4-6
- 34% / 26% cirrhosis per grou
- Baseline RAS
  - NS5A only: 55% / 52%
  - NS3+NS5A: 11% / 9%
- Overall SVR 89% vs 91%
- 12wks higher relapse w/ NS RAS
- Dual NS3/NS5A - 55% relap

SVR12 by DAA Class in Prior Therapy



Poordad et al. EASL 2017

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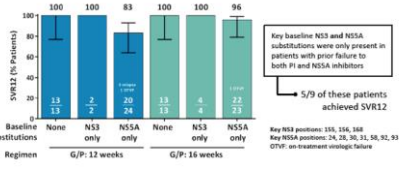
Glecaprevir / pibrentasvir for re-treatment of NS5A failures - MAGELLAN 1

GLE
PIB

SVR12 by Key NS3 and NS5A Baseline Substitutions



Y93H/N at baseline: 100% (13/13) SVR12 in patients with NS5A inhibitor experience (PI-naïve)

Poordad et al. EASL 2017

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Glecaprevir / pibrentasvir for re-treatment of NS5A failures - MAGELLAN 1

GLE
PIB

Adverse Events (AE) and Laboratory Abnormalities

Event, n (%)	G/P 12 weeks N = 44	G/P 16 weeks N = 47
Any AE	33 (75)	32 (68)
Serious AE	1 (2)	2 (4)
Serious AE potentially related to DAA	0	0
AE leading to study drug d/c	0	0
AEs occurring in ≥10% of patients		
Headache	6 (14)	11 (23)
Post-baseline laboratory abnormalities		
Alanine aminotransferase*, Grade ≥3 (>5 × ULN)	0	0
Total bilirubin, Grade ≥3 (>3 × ULN)	0	0
Hemoglobin, Grade ≥3 (<8 g/dL)	0	0

Serious AEs: gastrointestinal viral infection, back pain, and wound infection
*Post-rash increase in grade to Grade ≥3

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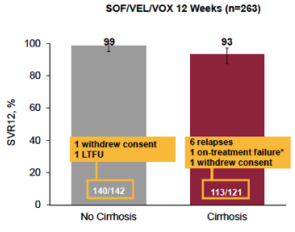
Poordad et al. EASL 2017

SOF/VEL/VOX for re-treatment of NS5A failures

VOX
VEL
SOF

- POLARIS 1
  - GT 1-6 (30% GT3)
- 12 weeks of therapy
  - vs placebo
- Including compensated cirrhosis (46%)
- 2.2% relapse
- 4 GT 3 relapse – all 3a and ¾ had BL NS5A RAS
- No treatment emergent RAS
- all VF had cirrhosis (6 R, 1 VBT)



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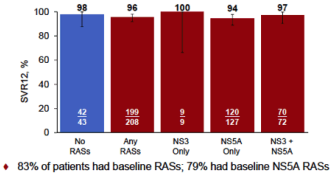
Bourliere et al. NEJM 2017

POLARIS-1



- 83% of patients had baseline RASs; 79% had baseline NS5A RASs
- Two patients had S282T at baseline, both achieved SVR12
- None of the patients who relapsed had treatment-emergent RASs

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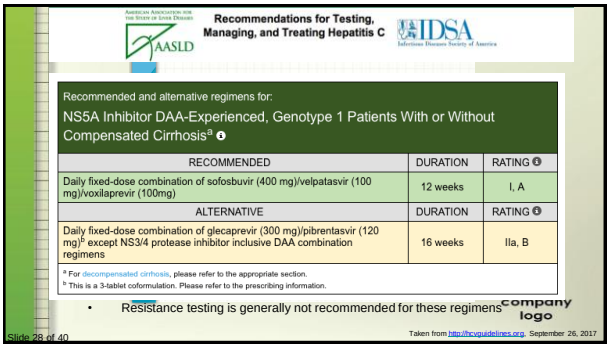

Case 2

- A 55 year old woman with GT 3 HCV has failed SOF + DCV x 12
- She is HIV pos on elvitegravir, cobi, FTC, TAF
- Other Meds: HCTZ 25mg; Vit D
- Exam: normal
- HCV 6.2 log IU/ml; alb 3.6; TB 1.2; creat 1.1; INR 1; AST 62 U/L; ALT 47; PLTs 120K; FibroSure 0.8; elastography 15.6 kPa; Fib-4 4.14

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ARS Question 3: What is the next step?

1. Test for resistance
2. SOF/VEL/VOX x 12 wks
3. SOF/VEL/VOX + RBV x 12 wks
4. GP x 16 wks
5. SOF/DCV/RBV x 24

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Retreatment of GT 3 failure with cirrhosis

Recommended regimen for:

DAA-Experienced (Including NS5A Inhibitors), Genotype 3 Patients With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/ voxilaprevir (100 mg)	12 weeks	I, A
For patients with prior NS5A inhibitor failure and cirrhosis, weight-based ribavirin is recommended.	12 weeks	IIa, C

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

No alternative recommendation for this situation

Bourliere M NEJM 2017

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ARS Question #4: What is the next step before that step?

1. No changes needed
2. Switch ART

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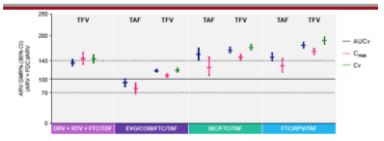
Sofosbuvir/velpatasvir/voxilaprevir: ARV DDI

- Healthy volunteer study included
  - DRV/r + TDF/FTC, EVG/cobi/TAF/FTC, BIC/TAF/FTC, RPV/TAF/FTC
  - Remember no EFV/ETR allowed due to VEL

Effect of SOF/VEL/VOX on HIV ARV PK



Garrison et al. Clin Pharm 2017

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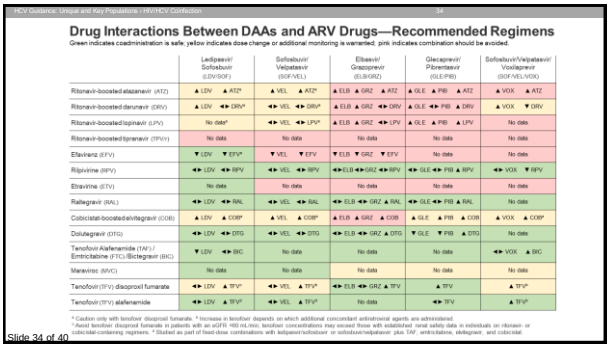

Drug Interactions Between DAAs and ARV Drugs—Recommended Regimens

Green indicates coadministration is safe; yellow indicates dose change or additional monitoring is warranted; pink indicates combination should be avoided.

	Ledipasvir/ Sofosbuvir (LDV/SOF)	Sofosbuvir/ Velpatasvir (SOF/VEL)	Elbasvir/ Grazoprevir (ELB/GRZ)	Glecaprevir/ Pibrentasvir (GLE/PIB)	Sofosbuvir/Velpatasvir/ Voxilaprevir (SOF-VEL/VOX)
Ritonavir-boosted atazanavir (ATZ)	▲ LDV ▲ ATZ[a]	▲ VEL ▲ ATZ[a]	▲ ELB ▲ GRZ ▲ ATZ	▲ GLE ▲ PIB ▲ ATZ	▲ VOX ▲ ATZ
Ritonavir-boosted darunavir (DRV)	▲ LDV ◄► DRV[a]	◄► VEL ◄► DRV[a]	▲ ELB ▲ GRZ ◄► DRV	▲ GLE ◄► PIB ▲ DRV	▲ VOX ▼ DRV
Ritonavir-boosted lopinavir (LPV)	No data[a]	◄► VEL ◄► LPV[a]	▲ ELB ▲ GRZ ◄► LPV	▲ GLE ▲ PIB ▲ LPV	No data
Ritonavir-boosted tipranavir (TPV/r)	No data	No data	No data	No data	No data
Efavirenz (EFV)	▼ LDV ▼ EFV[a]	▼ VEL ▼ EFV	▼ ELB ▼ GRZ ▼ EFV	No data	No data
Rilpivirine (RPV)	◄► LDV ◄► RPV	◄► VEL ◄► RPV	◄►ELB ◄►GRZ ◄► RPV	◄► GLE ◄► PIB ▲ RPV	◄► VOX ▼ RPV
Etravirine (ETV)	No data	No data	No data	No data	No data
Raltegravir (RAL)	◄► LDV ◄► RAL	◄► VEL ◄► RAL	◄► ELB ◄► GRZ ▲ RAL	◄► GLE ◄► PIB ▲ RAL	No data
Cobicistat-boosted elvitegravir (COB)	▲ LDV ▲ COB[a]	▲ VEL ▲ COB[a]	▲ ELB ▲ GRZ ▲ COB	▲ GLE ▲ PIB ▲ COB	▲ VOX ▲ COB[a]
Dolutegravir (DTG)	◄► LDV ◄► DTG	◄► VEL ◄► DTG	◄► ELB ◄► GRZ ▲ DTG	▼ GLE ▼ PIB ▲ DTG	No data
Tenofovir Alafenamide (TAF) / Emtricitabine (FTC) /Bictegravir (BIC)	▼ LDV ◄► BIC	No data	No data	No data	◄► VOX ▲ BIC
Maraviroc (MVC)	No data	No data	No data	No data	No data
Tenofovir (TFV) disoproxil fumarate	◄► LDV ▲ TFV[a]	◄► VEL ▲ TFV[a]	◄► ELB ◄► GRZ ▲ TFV	▲ TFV	▲ TFV[a]
Tenofovir (TFV) alafenamide	◄► LDV ▲ TFV[a]	◄► VEL ▲ TFV[a]	No data	◄► TFV	▲ TFV[a]

[a] Caution only with tenofovir disoproxil fumarate. [b] Increase in tenofovir depends on which additional concomitant antiretroviral agents are administered. [c] Avoid tenofovir disoproxil fumarate in patients with an eGFR <60 mL/min; tenofovir concentrations may exceed those with established renal safety data in individuals on ritonavir- or cobicistat-containing regimens. [d] Studied as part of fixed-dose combinations with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir plus TAF, emtricitabine, elvitegravir, and cobicistat.

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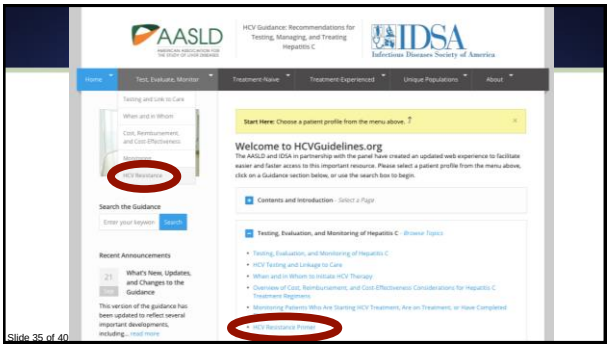

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Regimen-Specific Recommendations for Use of RAS Testing in Clinical Practice

When should one test for RASs?

RECOMMENDED	RATING
Elbasvir/grazoprevir NS5A RAS testing is recommended for genotype 1a-infected, treatment-naive or -experienced patients being considered for elbasvir/grazoprevir. If present, a different regimen should be considered.	I, A
Ledipasvir/sofosbuvir NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients without cirrhosis being considered for ledipasvir/sofosbuvir. If clinically important[a] resistance is present, a different recommended therapy should be used. NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients with cirrhosis being considered for ledipasvir/sofosbuvir. If clinically important[a] resistance is present, a different recommended therapy should be used.	I, A
Sofosbuvir/velpatasvir NS5A RAS testing is recommended for genotype 3-infected, treatment-naive patients with cirrhosis and treatment-experienced patients (with or without cirrhosis) being considered for 12 weeks of sofosbuvir/velpatasvir. If Y93H is present, weight-based ribavirin should be added or sofosbuvir/velpatasvir/voxilaprevir should be used.	I, A
Daclatasvir plus sofosbuvir NS5A RAS testing is recommended for genotype 3-infected, treatment-experienced patients without cirrhosis being considered for 12 weeks of daclatasvir plus sofosbuvir. If Y93H is present, weight-based ribavirin should be added. NS5A RAS testing is recommended for genotype 3-infected, treatment-naive patients with cirrhosis being considered for 24 weeks of daclatasvir plus sofosbuvir. If Y93H is present, treatment should include weight-based ribavirin, or a different recommended therapy used.	I, B

[a] Clinically important = greater than 100-fold resistance

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NOT RECOMMENDED	RATING
Elbasvir/grazoprevir RAS testing is not recommended for any genotype 1b-infected patients being considered for elbasvir/grazoprevir therapy.	I, A
Glecaprevir/pibrentasvir RAS testing is not recommended for patients with genotype 1, 2, 3, 4, 5, or 6 infection being considered for glecaprevir/pibrentasvir for 8, 12, or 16 weeks.	I, A
Ledipasvir/sofosbuvir NS5A RAS testing is not recommended for any genotype 1b-infected patients being considered for ledipasvir/sofosbuvir therapy.	I, A
NS5A RAS testing is not recommended for genotype 1a-infected, treatment-naive patients being considered for ledipasvir/sofosbuvir therapy.	I, A
NS5A RAS testing is not recommended for genotype 1a- or 1b-infected, treatment-naive patients without cirrhosis and with a viral load <6 million IU/mL being considered for an 8-week course of ledipasvir/sofosbuvir therapy.	I, A
Paritaprevir/ritonavir/ombitasvir with dasabuvir ± weight-based ribavirin, or paritaprevir/ritonavir/ombitasvir + weight-based ribavirin RAS testing is not recommended for genotype 1- or 4-infected, treatment-naive or -experienced patients being considered for therapy with paritaprevir/ritonavir/ombitasvir with dasabuvir ± weight-based ribavirin or paritaprevir/ritonavir/ombitasvir + weight-based ribavirin, respectively.	I, A
Sofosbuvir/velpatasvir RAS testing is not recommended for patients with genotype 1, 2, 4, 5, or 6 infection being considered for 12 weeks of sofosbuvir/velpatasvir therapy.	I, A
Sofosbuvir/velpatasvir/voxilaprevir RAS testing is not recommended for patients with genotype 1, 2, 3, 4, 5, or 6 infection being considered for 12 weeks of sofosbuvir/velpatasvir/voxilaprevir therapy.	I, A

When should one NOT test for RASs?

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Key principles of HCV resistance-associated substitutions (RASs)

- **Viruses with RASs may exhibit variable "fitness" compared to wildtype**
  - Higher fitness last longer, lower fitness may be transient
- **RAS are present at baseline in the absence of drug exposure, but may or may not be detected**
  - Possibility of transmission
- **RASs may impact treatment responses in select situations**
  - Situation is often worse in presence of other treatment characteristics
- **Resistance is NOT futile**
  - May be overcome by longer durations, addition of ribavirin, or later-generation agents
- **For newly approved regimens detection of RASs is most often NOT necessary**

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Take home points

- The most important factor in deciding upon re-treatment regimens is the prior DAA failure
- Resistance-associated substitutions are NOT futile
  - May impact select situations
  - Certain mutations may require longer treatment courses, ribavirin
- Ribavirin-free regimens are newly available approved for many re-treatment considerations

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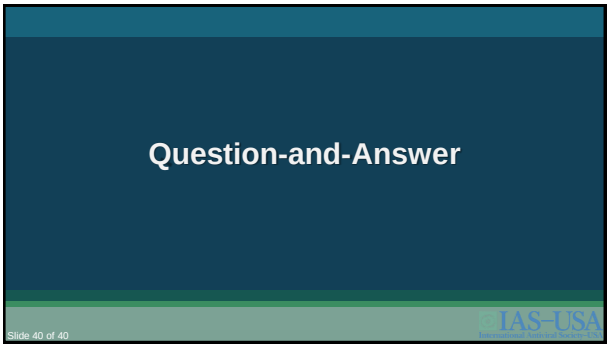
Question-and-Answer
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