Cases: Initial Treatment of Hepatitis C

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Learning Objectives

After attending this presentation, learners will be able to:

- Determine the necessary baseline laboratory tests to obtain for a patient initiating HCV therapy
- Discuss the considerations in selecting HCV therapy for a treatment naïve patient
- Recognize therapeutic classes of medications with the potential to interact with HCV therapies

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Patient Case

- 54 yo African American male HCV+ genotype 1b
- Weight 72.6 kg, height 188 cm
- HCV treatment naïve, HCV RNA 2,189,351 IU/mL
- AST 339 U/L, ALT 306 U/L, tbili 0.7 mg/dL, Alb 4.0 g/dL, platelets 150 10^9/L, Hgb 16.4 g/dL

What additional information would you obtain to guide treatment decisions?

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AASLD/IDSA HCV Guidance

www.hcvguidelines.org

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What additional laboratory tests would you like?

- Transient elastography 7kPa (IQR 0.7, IRQ/med 10%)
- SCr 0.72 mg/dL, eGFR 138 mL/min/1.73 m^2
- HBsAg (-), anti-HBc (-), anti-HBs (+)
- Vaccinated against HAV

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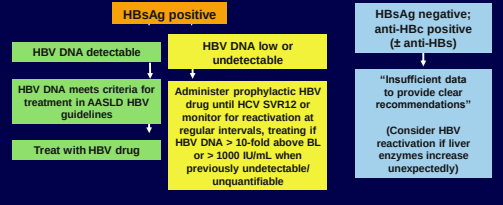
HBV Testing/Monitoring During HCV DAA Therapy

- Test all pts initiating HCV therapy for HBsAg, anti-HBc, and anti-HBs
  - Vaccinate if no HBV markers; follow flow chart below if HBV markers present



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AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

Recommended DAA Regimens

blue = NS5B (nucs), green = NS5A, red = NS3 (protease)

1. Sofosbuvir/ledipasvir 
2. Sofosbuvir/velpatasvir 
3. Elbasvir/grazoprevir 
4. Glecaprevir/pibrentasvir 

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Factors to consider in choosing between the recommended regimens for a treatment-naïve patient

1. HCV Genotype (1-6)
2. Resistance Associated Variants
3. Severity of Liver Disease
4. Renal Function
5. Drug Interactions

Table: Clinically Significant NS5A Resistance-Associated Variants (RAVs)

Wild-type Amino Acid (sensitive)	Position	Variant Amino Acid (reduced EBR activity)
M	28	A/G/T
Q	30	D/E/H/G/K/L/R
L	31	F/M/V
Y	93	C/H/N/S

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ARS Question 1: In which patient population(s) should RAS testing be performed?

1. GT1a, non-cirrhotic with LDV/SOF
2. GT3, cirrhotic with GP
3. GT1a, non-cirrhotic with ELB/GZR
4. GT3, cirrhotic with SOF/VEL
5. 1 and 2
6. 3 and 4
7. All of the above

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Genotype 1 treatment naïve

Recommended and Alternative

Treatment Naïve		EBR/GZR	GLE/PIB	LDV/SOF	SOF/VEL
1a	Non-cirrhotic	12WKS* RASs: 16WKS+R	8WKS	8$-12WKS	12WKS
	Cirrhotic	12WKS* RASs: 16WKS+R	12WKS	12WKS	12WKS
1b	Non-cirrhotic	12WKS	8WKS	8$-12WKS	12WKS
	Cirrhotic	12WKS	12WKS	12WKS	12WKS

$- additional criteria apply – only for non-black, HIV-uninfected, and whose HCV RNA level is <6 M IU/mL
R=weight-based Ribavirin
*RAS testing recommended-RASs= EBR specific NS5A RAVs (28, 30, 31, 93)

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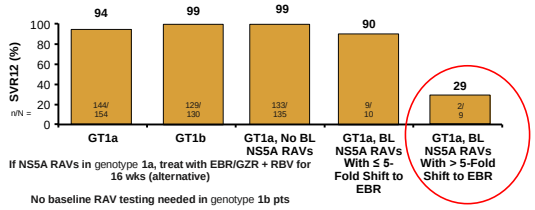
Impact of Baseline NS5A RAVs:

SVR12 With 12 Wks of Grazoprevir/Elbasvir for initial treatment



If NS5A RAVs in genotype **1a, treat with EBR/GZR + RBV for 16 wks (alternative)**

No baseline RAV testing needed in genotype **1b pts**

Slide credit clinicaloptions.com

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Zeuzem S, et al. Ann Intern Med. 2015;163:1-13.

Genotypes 2 and 3 treatment naïve

Recommended

Treatment Naïve		GLE/PIB	SOF/VEL
2 and 3	Non-cirrhotic	8WKS	12WKS
	Cirrhotic	12WKS	12WKS*

*Only if no baseline Y93H for genotype 3. If Y93H present for genotype 3, add RBV or choose alternative regimen (consider SOF/VEL/VOX).

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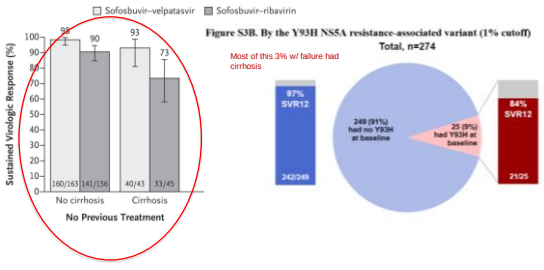
Sofosbuvir/velpatasvir x 12 wks for G3 (ASTRAL-3)



Foster, NEJM, 2015, hcvguidelines.org

ARS Question 1: In which patient population(s) should RAS testing be performed?

1. GT1a, non-cirrhotic with LDV/SOF
2. GT3, cirrhotic with GP
3. GT1a, non-cirrhotic with ELB/GZR
4. GT3, cirrhotic with SOF/VEL
5. 1 and 2
6. **3 and 4**
7. All of the above

Genotypes 4, 5 and 6 treatment naïve

Recommended

Treatment Naïve		EBR/GZR	GLE/PIB	LDV/SOF	SOF/VEL
4	Non-cirrhotic	12WKS	8WKS	12WKS	12WKS
	Cirrhotic	12WKS	12WKS	12WKS	12WKS
5 and 6	Non-cirrhotic	Not recommended	8WKS	12WKS	12WKS
	Cirrhotic	Not recommended	12WKS	12WKS	12WKS

3. Severity of Liver Disease

- Cirrhotic patients are harder to cure
  - They may require longer treatment or the addition of ribavirin
- Protease inhibitors not safe in decompensated cirrhosis
  - concentrations are higher in liver impairment, potential for increased risk of hepatotoxicity

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4. Renal Function

- SOF levels significantly increased in renal impairment, do not use in CrCl < 30 mL/min
- Glecaprevir/pibrentasvir drug of choice in renal impairment
  - Elbasvir/grazoprevir also an option but not used as often

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5. Drug Interactions

- Concomitant Medication Use is Frequent Among Persons with HCV
- Retrospective review of 20M enrollees across 100 US insurers identified 53,461 HCV+ individuals, average of 10 prescriptions per person (not including HCV treatment)

Therapeutic Classes Most Commonly Prescribed
Analgesics/antipyretrics and opiate agonists
Antidepressants
Gastrointestinal drugs
Benzodiazepines
Beta blockers
ACE Inhibitors
Calcium channel blockers
Anxiolytics/sedative hypnotics

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Lauffenberger J, et al. Eur J Gastro & Hepatol 2014;26:1073

Patient Case Continued…

ARS Question 2: He's coinfected with HIV, suppressed on TAF/FTC/DRV/cobi, which regimens are compatible?

1. ELB/GZR
2. GP
3. LDV/SOF
4. SOF/VEL
5. 1 and 2
6. 3 and 4
7. 1, 2, 3, and 4

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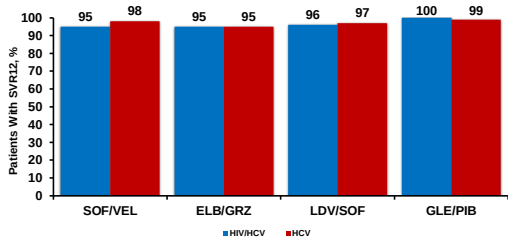
Treatment of HCV in HIV/HCV Coinfection - Same Regimens, Same Efficacy



Composite slide adapted from Naggie S, Duke University. 1. Wyles D, et al. *Clin Infect Dis.* 2017;65(1):6-12; 2. Rockstroh JK, et al. *Lancet HIV.* 2015;2(8):e319-327; 3. Naggie S, et al. *N Engl J Med.* 2015;373(8):705-713; 4. Rockstroh JK, et al. European Association for the Study of the Liver (EASL) – The International Liver Congress™ 2017. April 19–23, 2017; Amsterdam, the Netherlands. Abstract LB-522.

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DAA & ARV DDI

Boosted PIs are a challenge with DAAs

EFV and ETV incompatible with DAAs

Integrases compatible with DAAs except ELV/cobi

NRTIs compatible with DAAs caution with TDF + boosters

		Ledipasvir/ Sofosbuvir (LDV/SOF)	Sofosbuvir/ Velpatasvir (SOF/VEL)	Elbasvir/ Grazoprevir (ELB/GRZ)	Glecaprevir/ Pibrentasvir (GLE/PIB)	Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VOX)
Protease inhibitors	Boosted Atazanavir	A	A			
	Boosted Darunavir	A	A			
	Boosted Lopinavir	ND, A	A			ND
NNRTIs	Doravirine		ND		ND	ND
	Efavirenz				ND	ND
	Rilpivirine					
	Etravirine	ND	ND	ND	ND	ND
Integrase inhibitors	Bictegravir		ND	ND	ND	
	Cobicistat-boosted elvitegravir	A	A			A
	Dolutegravir					ND
	Raltegravir					ND
	Maraviroc	ND	ND	ND	ND	ND
NRTIs	Abacavir		ND	ND		ND
	Emtricitabine					
	Lamivudine		ND	ND		ND
	Tenofovir disoproxil fumarate	C, D	C, D			C
	Tenofovir alafenamide	E	E	ND		C

Green indicates coadministration is safe; yellow indicates a dose change or additional monitoring is warranted; and red indicates the combination should be avoided.
ND, No data
[A] Caution with tenofovir disoproxil fumarate
[B] Caution with ritonavir, but not cobicistat
[C] Caution when tenofovir DF is boosted by additional concomitant antiretroviral agents are administered.
[D] 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.
[E] Studied as part of fixed-dose combinations with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir plus TAF, emtricitabine, elvitegravir, and cobicistat.

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Patient Case Continued…

ARS Question 2: He's coinfected with HIV, suppressed on TAF/FTC/DRV/cobi, which regimens are compatible?

1. ELB/GZR
2. GP
3. LDV/SOF
4. SOF/VEL
5. 1 and 2
6. **3 and 4**
7. 1, 2, 3, and 4

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Patient Case Continued…

He takes several other drugs: gabapentin 300mg BID for peripheral neuropathy, albuterol prn, HCTZ 25mg po QD, omeprazole 20mg po QD, risperidone 0.5mg po QD

Are you concerned about any of his concomitant medications?

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ARS Question 3: All of the following therapies may interact with SOF/VEL EXCEPT…

1. Statins
2. Proton Pump Inhibitors
3. DOACs
4. Antiepileptics
5. Hormonal Therapies
6. All of the above

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ARS Question 4: All of the following therapies may interact with GP EXCEPT…

1. Statins
2. Proton Pump Inhibitors
3. DOACs
4. Antiepileptics
5. Hormonal therapies
6. All of the above

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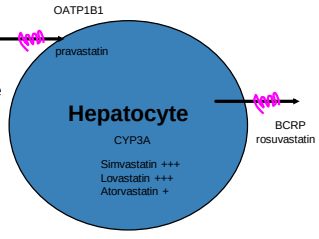
Statins – Always check for interactions with DAAs

Both CYP and transporter mediated interactions to consider with statins

DAAs that inhibit the uptake transporter OATP1B1, the efflux transporter BCRP, and/or CYP3A result in ↑ plasma concentrations of statin



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Statin / DAA interactions, recommendations

	EBR/GZR	LDV/SOF	SOF/VEL	GP	SOF/VEL/ VOX
Atorvastatin	↑ 94%, NTE 20mg QD	Consider dose reduction	Consider dose reduction	Not recommended	Use lowest dose
Fluvastatin	Use lowest dose	Consider dose reduction	Use lowest dose	Use lowest dose	Use lowest dose
Lovastatin	Use lowest dose	Use lowest dose	Consider dose reduction	Not recommended	Use lowest dose
Pitavastatin	√	Consider dose reduction	Consider dose reduction	Use lowest dose	Not recommended
Pravastatin	√	Consider dose reduction	√	Reduce dose by 50%	NTE 40mg QD
Rosuvastatin	↑ 126%, NTE 10mg QD	NTE 10mg*	↑ 170%, NTE 10mg QD	NTE 10mg QD	Not recommended
Simvastatin	Use lowest dose	Use lowest dose	Use lowest dose	Not recommended	Use lowest dose

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Management of Patients on Statins

- Avoid statins “contraindicated” or “not recommended” per product label
  - Except perhaps LDV/SOF and rosuvastatin
- High ASCVD risk patients
  - Maintain current statin dose if compatible, dose reduce if indicated, or change to equivalent dose of statin without interaction potential
- Low risk ASCVD patients
  - Reduce statin dose vs. hold

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DAAs and PPIs

	Interaction in Healthy Volunteers (Formal DDI study)	Recommendation
LDV/SOF	• OME 20mg QD simultaneous ↔ LDV AUC • OME 20mg 2 hr before LDV/SOF ↓ LDV AUC 42%	NTE OME 20mg equivalent LDV/SOF in **fasted** state simultaneous with OME 20mg equivalent
SOF/VEL	• OME 20mg QD food ↓ VEL AUC 26-38% • OME 20mg QD fasted ↓ VEL AUC 37-56% • OME 40mg QD ↓ VEL AUC 53%	Not recommended, if medically necessary NTE OME 20mg equivalent SOF/VEL in the **fed** state 4 hours before OME 20mg equivalent
SOF/VEL/VOX	• OME 20mg 2 hr before SOF/VEL/VOX ↓ VEL AUC 54% • OME 20mg 4hr after SOF/VEL/VOX ↓ VEL AUC 51%	Not recommended, if medically necessary NTE OME 20mg No specifications around timing
GP	• OME 20mg QD ↓ GLE AUC 29% • OME 40mg QD 1 hr before GP + breakfast ↓ GLE AUC 51% • OME 40mg QD in evening ↓ GLE AUC 49%	No warnings/recommendations/dose adjustments with PPI in product label

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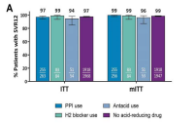
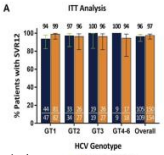
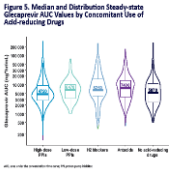
SVR Rates with GP in Patients on Gastric Acid Modifiers

SVR rates not lower with gastric acid modifiers



No signal of lower SVR in those on higher PPI doses





- Data are reassuring that SVR not compromised
- No data with omeprazole equivalents > 40mg once daily

Overall glecaprevir AUC not different, but was 41% lower in 24 participants that had samples obtained while taking a high dose PPI vs. no PPI

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Flamm S, et al. ACG 2017, P1435, Flamm S, et al. Clin Gastroenter & Hepatol In press

PPI Options

- For most patients, unlikely to compromise SVR with use of 20mg OME with LDV/SOF and SOF/VEL or 40mg OME with GP.
- There may be clinical scenarios where a 50% reduction in GLE exposures or VEL exposures is risky.
  - Cirrhotic patients?
  - All patients received SOF/VEL/VOX?
- No effect of PPIs on grazoprevir/elbasvir exposures.

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Direct Oral Anticoagulants (DOACs)

▪Used for prevention and treatment of arterial and venous thromboembolism.
▪For primary prevention or treatment DOAC typically used for 3-6 months, but for Afib or secondary prevention, chronic administration may be used.
▪Dabigatran direct thrombin inhibitor and others factor Xa inhibitors

	ELB/GZR	GP	LDV/SOF	SOF/VEL	SOF/VEL/VOX
Dabigatran	Monitor	X	Monitor	Monitor	X
Apixaban	Monitor	Monitor	Monitor	Monitor	Monitor
Edoxaban	Monitor	Monitor	Monitor	Monitor	X
Rivaroxaban	Monitor	Monitor	Monitor	Monitor	Monitor

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www.hep-druginteraction

DOAC Pharmacology

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Available Formulations	75mg, 110mg, 150mg capsules	10mg, 15mg, 20mg tablets	2.5mg and 5mg tablets	15mg, 30mg, 60mg tablets	40mg, 80mg capsules
Prodrug?	Yes (CES)	No	No	No	No
Bioavailability (%)	3-7	90 (with food)	50	62	34 (with fatty food)
Protein Binding (%)	35	92.7	93.2	55	60
Renal excretion of unchanged drug (%)	~80	~33	~27*	~50	~19
Metabolism (%)	~4 (UGT2B15)	~67 (CYP3A4, CYP2J2)	~25 (CYP3A4, SULT1A1)	<10 (CES, CYP3A4, UGT)	<1
Transporter involvement	P-gp (dabigatran etexilate only)	P-gp, BCRP	P-gp, BCRP	P-gp	P-gp
Dose Adjustment for P-gp inhibitors	Don't use CrCl < 50 mL/min	Don't use with strong P-gp and CYP3A4 inhibitors	Don't use with strong P-gp and CYP3A4 inhibitors	Dose adjustment may be required based on indication	AUC 2-3 fold higher, use 40mg daily
Mild eGFR ≥60 - < 90	1.5-fold	1.5-fold	1.2-fold	1.4-fold	1.89-fold
Moderate eGFR ≥30 - < 60	3.2-fold	1.7-fold	1.3-fold	1.8-fold, reduce dose <50 mL/min	2.27-fold
Severe (≥15 - < 30)	6.3-fold	1.8-fold	1.4-fold	1.9-fold	2.63-fold
Decompensated Cirrhosis	No dose adjustment needed for CPB, do not use CPC	AUC ↑ 127% CPB; no data CPC	Not recommended	Not recommended	No data

Pharmacology of DOACs, Adapted from Padrini R. Eur J Drug Metab and Pharmacokinetics Epub Aug 30 2018

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DOAC Considerations with DAAs

- Duration of DOAC- 3/6 months- can you wait? Lifelong?
- Renal function
- Hepatic function
- Low molecular weight heparins no interaction
- Monitor vs. Reduce Dose
- Monitoring options:
  - Anti-Xa levels?
  - DOAC concentrations?
- Anti-Xa reversal agent now (Andexxa®), but only available at major stroke centers

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High dose daclatasvir plus anticonvulsants

- Six patients (4/6 treatment naïve), used DAC 60mg BID or 60mg TID
- All 6 patients achieved SVR, despite ~66% lower DAC exposures in those on carbamazepine vs. historical data
- SOF/007 levels pending
- Suggests potential for successful use of anticonvulsants with DAAs
- Additional data needed to reassure

	Anti-epileptic drug and daily dose	Daclatasvir dose	C_{trough} (mg/L)	C_{max} (mg/L)	$AUC_{0\text{-}24}$ (h*mg/L)*
Reference[2]	N/A	60 mg QD	0.232	1.534	14.12
Patient #1	Carbamazepine 400 mg	60 mg BID	0.083	0.460	7.08
Patient #2	Carbamazepine 1000 mg	60 mg BID	0.028	0.149	1.48
Patient #2	Carbamazepine 1000 mg	60 mg TID	0.093	0.374	4.41
Patient #3	Carbamazepine 1200 mg	60 mg TID	0.101	0.320	3.90
Patient #4	Carbamazepine 1200 mg	60 mg TID	0.054	0.323	3.07
Patient #5	Phenytoin 225 mg	60 mg TID	0.561	1.094	17.54
Patient #6	Phenobarbital 100 mg	60 mg TID	1.293	2.717	41.24
Median for TID patients (IQR)	N/A		0.101 (0.093-0.561)	0.37 (0.32-1.09)	4.41 (3.90-17.54)

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Van Seven M, EASL 2018

Possible Anticonvulsant Strategies – Data needed to support

- Use higher dose of DAC
  - Van Seven M, EASL 2018
- Attempt double dose of other fixed-dose combination products
  - Collect plasma samples to measure DAAs
- Add ribavirin to protect against reduced DAA exposures – most likely needs to be done with an increased DAA dose
  - Smolders E, J Antimicrob Agents 2016:48:342
- For DAAs that are substrates for CYP3A, use a booster (e.g., ritonavir or cobicistat) to attempt to protect against reduced DAA exposures
  - Burger DM, J Antimicrob Agents 2014;44:81 (with ↑ telaprevir dose and ATV/r)

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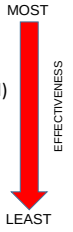
Hormonal Therapies

- Many hormonal contraceptive options
  - ~~Intrauterine devices (IUD)~~ – DDI not as relevant, local hormone delivery
  - Progestin-containing subdermal implants (etonogestrel)
  - Transdermal patch (ethinyl estradiol/norelgestromin)
  - Vaginal ring (ethinyl estradiol/etonogestrel)
  - Injectables (medroxyprogesterone acetate)
  - Oral contraceptives (estrogen and progestin or progestin-only)



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Effects of DAAs on Contraceptive Hormones

	Ethinyl estradiol	Levo-norgestrel	Norgestimate, norelgestromin or norgestrel	Norethindrone	Comments
Route of Hormone Metabolism[1]	3A4 (61%), 2C9 (23%), minor (<20% total): 1A2, 2C19, 3A5	3A4	3A4	3A4	
EBR/GZR	↔	↔			√
LDV/SOF	↑ 20%		↔		√
SOF/VEL	↔		↔		√
PrOD[2]	↔ or ↑ 22%; but 5/21 patients had grade 3-4 LFT elevations		↑2.6-fold	↔	• No patch, no ring, no estrogen-containing pills. • The progestin-only contraceptives can be used. • Can restart estrogen-containing contraceptives 2 weeks after completing.
GP	↑ 28%-40%, ALT elevations observed	↑68%	↑ 44%-63%		
SOF/VEL/VOX	↔	↔	↔		European SmC has contraindication, US prescribing info "no interaction"

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Hormonal Contraceptives and GP

- Asymptomatic LFT elevations observed with ethinyl estradiol-containing oral contraceptives
  - No LFT elevations observed with norethindrone-only
  - Mechanism unknown
- 35 mcg ethinyl estradiol and 250 mcg norgestimate
  - 2 out of 12 healthy women discontinued study due to LFT elevations
    - One was grade 3 ALT elevation (>5-20xULN) occurring 7 days after discontinuing GP (participant also had a breast abscess), grade 2 AST
    - One was grade 2 (3-5xULN) ALT elevation (grade 1 AST) occurring after 6 days of the combination
- 20 mcg ethinyl estradiol and 100 mcg of levonogestrel
  - 3 of 14 had grade 1 LFT (< 3xULN)

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ARS Question 3: All of the following therapies may interact with SOF/VEL EXCEPT…

1. Statins
2. Proton Pump Inhibitors
3. DOACs
4. Antiepileptics
5. **Hormonal Therapies**
6. All of the above

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ARS Question 4: All of the following therapies may interact with GP EXCEPT…

1. Statins
2. Proton Pump Inhibitors
3. DOACs
4. Antiepileptics
5. Hormonal therapies
6. **All of the above**

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Resources for Interactions

- University of Liverpool www.hep-druginteractions.org
- Toronto General Hospital Immunodeficiency Clinic http://app.hivclinic.ca/
- AASLD/IDSA and EASL guidelines
- Specific to Antiretroviral Agents
  - DHHS Guidelines Drug Interaction Tables
  - www.aidsinfo.nih.gov/guidelines

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Patient Case Continued…

- Treated with 12 weeks of LDV/SOF
- Adherence to LDV/SOF was 83% according to wireless pillbox
- No reported IV drug use, patient heavy daily EtOH, marijuana, and crack cocaine user
- HCV RNA undetectable at week 12, but 12 weeks after completing treatment, HCV RNA was detectable

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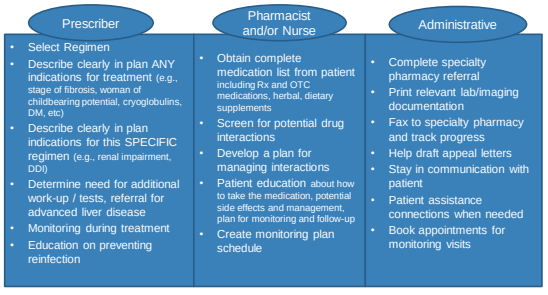
Possible Team Approach to HCV Treatment



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Adapted with permission from Kristen Marks, MD

Summary

- Tremendous advances in HCV treatment in past several years
- Multiple well-tolerated, simple treatment options
- SVR > 95% in almost all patient populations, including HIV coinfected individuals, with 8-12 weeks of treatment
- Drug interactions are an important consideration
- Successful treatment does not prevent reinfection

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Question-and-Answer
Remember to raise your hand and wait until you have the microphone before you ask your question—we are recording!
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