A Practical Approach to HIV/HCV Co-infection

Focus on Drug-Drug Interactions

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Outline

- Co-infection vs. Mono-infection
- DAA Overview and efficacy in co-infection
- Approaches and tools for identifying and managing drug interactions
- Overview of mechanisms of drug interactions
- Highlights of more common drug interactions

Co-infection Burden and Progression

- 10-15% of HIV patients are co-infected with Hepatitis C (HCV) worldwide[1]
  - 25% HIV-infected patients are co-infected with hepatitis C in the US[2]
- HIV/HCV co-infection more than triples the risk for liver disease, liver failure, and liver-related death.[2]
  - HCV may also complicate the management of HIV[3]
- Highly active antiretroviral therapy (ART) slows hepatic disease progression in co-infection[4]

1. Alter MJ. J. Hepatology. 2006; 44: (suppl 1): s6-9.
2. 2. CDC HIV/AIDS and viral hepatitis. Accessed 31 Jul 2017 at www.cdc.gov.
3. Greub G, et al. Lancet 2000;356(9244):1800-5. 4. Smith C, et al. AIDS 2010;24:1537-48.

Antiretroviral Therapy Reduces Hepatic Decompensation

- Estimate the effect of ART on the rate of hepatic decompensation
- Veterans Aging Cohort Study-Virtual Cohort
  - 10,090 HCV/HIV co-infected individuals
- Median follow up: 3.1 years

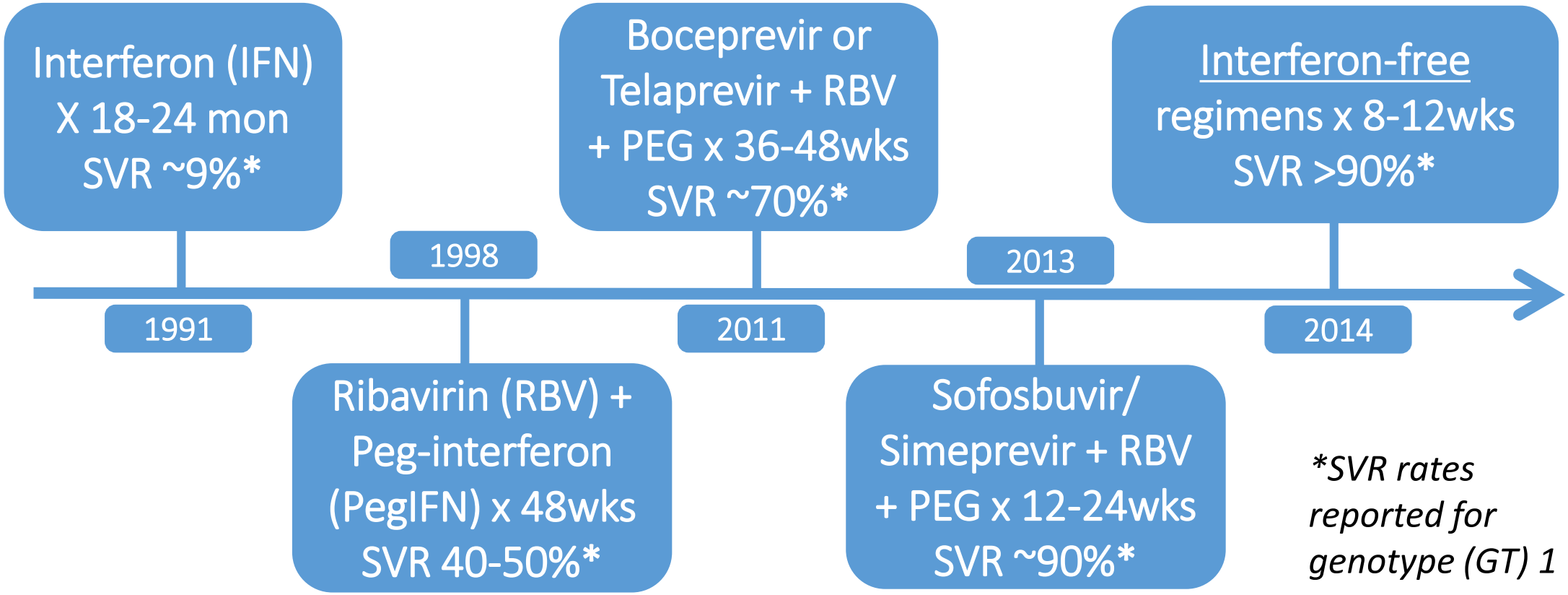
Variable	Person-years	Events	Hazard Ratio (95% CI)
No ART initiation	10,891	188	reference
ART initiation	35,553	457	0.72 (0.54-0.94)
< 2 years since initiation	10,727	154	0.75 (0.56-1.01)
2-<4 years since initiation	8560	109	0.69 (0.46-1.03)
≥ 4 years since initiation	16,266	195	0.53 (0.34-0.83)

CI: Confidence Interval

Anderson JP, et al. Clin Infect Dis 2014;58(719-27).

Evolution of Hepatitis C Treatment

- Goal = prevent end-stage liver disease complications
  - Cure defined as sustained virologic response (SVR) 12 weeks after completion of treatment



**SVR rates reported for genotype (GT) 1*

Scheel TK. Nat Med 2013;19(7):837-49.

Ghany MG. Hepatology 2011;54(4):1433-44.

The Interferon Era

- In the interferon era SVR rates < than those in mono-infected patients
- Additional challenges:
  - Poor tolerability of interferon
  - Limitations in certain populations
    - Depression
  - Added pill burden
  - Drug interactions

- Should HIV-HCV co-infection still be considered a “special population”?[3]

1. Torriani FJ, et al. N Engl J Med. 2004; 351(5): 438-50. 2. Carrat F, et al. JAMA. 2004; 292(23): 2839-48.
3. Sulkowski MS. Liver Int. 2016; 36 (S1): 43-46.

Guideline Overview of HIV/HCV Co-infection

DHHS HIV Treatment Guidelines	• ART should be initiated in all HCV/HIV co-infected patients, regardless of CD4 count • HIV treatment-naïve patients with CD4 > 500 cells/mm^3 may defer ART treatment until HCV treatment is completed to avoid drug interactions
AASLD/IDSA Guidelines	• HIV/HCV co-infected persons should be treated/retreated the same as persons without HIV infection
EASL	• Indications for HCV treatment are the same as those with HCV mono-infection • The same IFN-Free regimens can be used in co-infection as in patients without HIV infection

DHHS Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Accessed 31 Jul 2017 at www.aidsinfo.nih.gov.
AASLD Recommendations for testing, management, and treating hepatitis C. Accessed on 31 Jul 2017 at www.hcvguidelines.org.
EASL Recommendations on Treatment of Hepatitis C in 2016. Accessed on 14 Aug 2017 at http://www.easl.eu/.

Direct-Acting Antivirals Classes

NS3/4A Protease Inhibitors *(--previr)*	NS5A Inhibitors *(--asvir)*	NS5B Polymerase Inhibitors *(--buvir)*

• Boceprevir
• Telaprevir
• Simeprevir
• Paritaprevir
• Grazoprevir
• *Voxilaprevir*
• *Glecaprevir*
	• Ledipasvir
	• Ombitasvir
	• Daclatasvir
	• Elbasvir
	• Velpatasvir
	• *Pibrentasvir*
	• *Ruzasvir*
		• Nucleoside analogs
		  • Sofosbuvir
		  • *MK-3682*
		• Non-nucleoside analogs
		  • Dasabuvir

Efficacy in Co-Infection

Regimen	Approved Genotypes	Pill burden	Efficacy in HIV co-infected	Cost $$$
ELB/GRZ x 12W	1, 4	1/day	87%[3] 96%[1]	$$
ELB/GRZ + RBV x 12W	1, 4	1/day + 6/day	97%[2]	$$
LDV/SOF x 12W	1, 4, 5, 6	1 per day	96%[3]	$$
OMB/PAR/DAS/r + RBV x 12 – 24W	1a, 1b	4/day + 6/day	94% and 91%, respectively	$$/$$$$

"ELB" = elbasvir, "GRZ" = grazoprevir, "LDV" = ledipasvir, "SOF" = sofosbuvir, "OMB" = ombitasvir, "PAR" = paritaprevir, "DAS/r" = dasabuvir/ritonavir, "RBV" = ribavirin

1) Rockstroh JK, et al. Lancet HIV. 2015; 2(8): e319-327. 3) Sulkowski MS, et al. Lancet. 2015; 385(9973): 1087-97. 2) Naggie DR, et al. N Engl J Med. 2015; 373(8): 705-13. 4) Sulkowski MS, et al. JAMA. 2015; 313(12): 1223-31.

Efficacy in Co-Infection (2)

Regimen	Approved Genotypes	Pill burden	Efficacy in HIV co-infected	Cost $-$$$
SOF/SIM ± RBV x 12W	1	2/day + 6/day	93%[1]	$$$
DAC/SOF x 12W	1, 4	1/day + 6/day	94-100%[2]	$$
SOF/VEL x 12W	1-6	1/day	92-100%[3]	$$
SOF/VEL/VOX x 12W	1-6	1/day	No data	$$$
GLE/PIB 8 – 12W	1-6	3/day	98 and 99%[4] respectively	$$

"SOF" = sofosbuvir, "SIM" = simeprevir, "DAC" = daclatasvir, "VEL" = velpatasvir, "VOX" voxilaprevir, "GLE" = glecaprevir, "PIB" = pibrentasvir, "RBV" = ribavirin

1. Bruno G, et al. Int J Antimicrob Agents. 2017; 49(3): 296-301. 2. Luektemeyer AF, et al. Clin Infect Dis. 2016; 62(12): 1489-96. 3. Wyles D, et al. Clin Infect Dis. 2017; 65 (1): 6-12. 4) 9th IAS Conference on HIV Science, Paris, France. July 23-26, 2017.

Real World Co-infection Data

- Retrospective, observational of HIV/HCV co-infected Veterans from 126 VA facilities
- SVR12 results available for 90.9% of cohort (905/996)

All patients: 12 weeks or less	GT1 N= 905	LDV/SOF N=685	LDV/SOF +RBV N=131	OMB/PRV/ DAS/r N=27	OMB/PRV/ DAS/r + RBV N=62
Overall SVR	90.9 (823/905)	92.1 (631/685)	86.3 (113/131)	88.9 (24/27)	88.7 (55/62)
Cirrhosis	85.9 (176/205)	87.6 (113/129)	83.9 (52/62)	100 (3/3)	100 (26/26)
No cirrhosis	92.4 (647/700)	93.2 (518/556)	88.4 (61/69)	87.5 (21/24)	80.6 (29/36)

Bhattacharya D, et al. Clin Infect Dis. 2017; 64(12): 1711-1720.

Real World Co-infection Data (2)

Patients who completed 12 weeks	GT1 N=766	LDV/SOF N=569	LDV/SOF +RBV N=119	OMB/PRV/ DAS/r N=23	OMB/PRV/ DAS/r + RBV N=55
Overall SVR	94.3 (722/766)	95.3 (542/569)	90.8 (108/119)	95.7 (22/23)	90.9 (50/55)
Cirrhosis	91.9 (159/173)	94.4 (102/108)	90.6 (48/53)	100 (2/2)	70 (7/10)
No cirrhosis	94.9 (563/593)	95.4 (440/461)	90.9 (60/66)	95.2 (20/21)	95.6 (46/45)

Bhattacharya D, et al. Clin Infect Dis. 2017; 64(12): 1711-1720.

Real World Co-infection Data (3)

- IDSA/AASLD recommends against 8 weeks LDV/SOF for co-infection
- Overall SVR in those who received 8 weeks vs. 12 wks
  - LDV/SOF x 8 weeks: 94.6% (70/74)
  - LDV/SOF x 12 weeks: 95.3% (542/569)
- Those meeting 8 week criteria and received:
  - LDV/SOF x 8: 98.1% (51/52)
  - LDV/SOF x 12: 95.7% (310/324)
- Overuse of 12 week LDV/SOF regimens has been demonstrated in clinical trials of mono-infected patients [1]
  - Excess costs

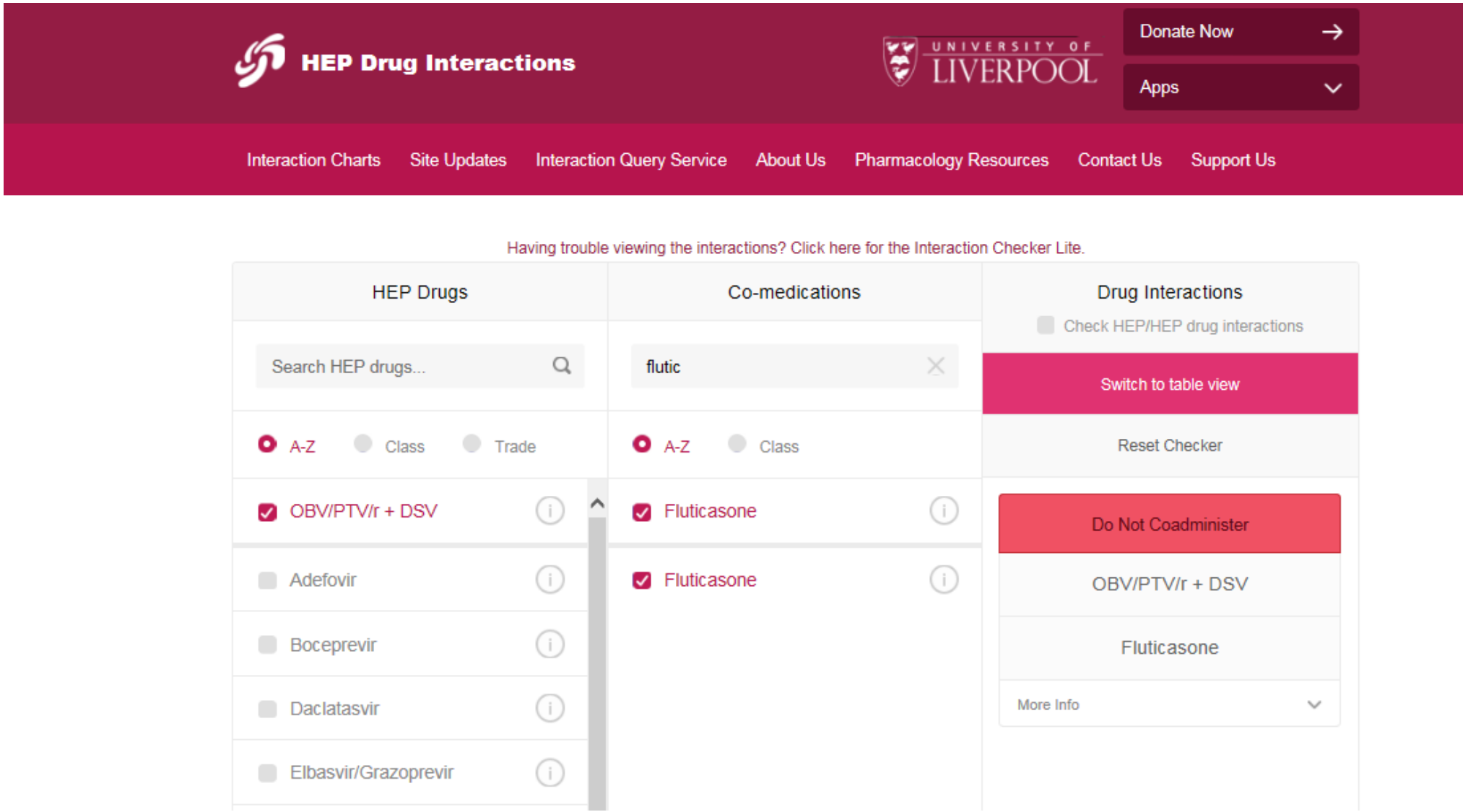
1. Terrault NA, et al. Gastroenterology. 2016; 151(6): 1131-1140.

Managing drug-drug interactions in HIV-HCV

Drug Interaction Resources

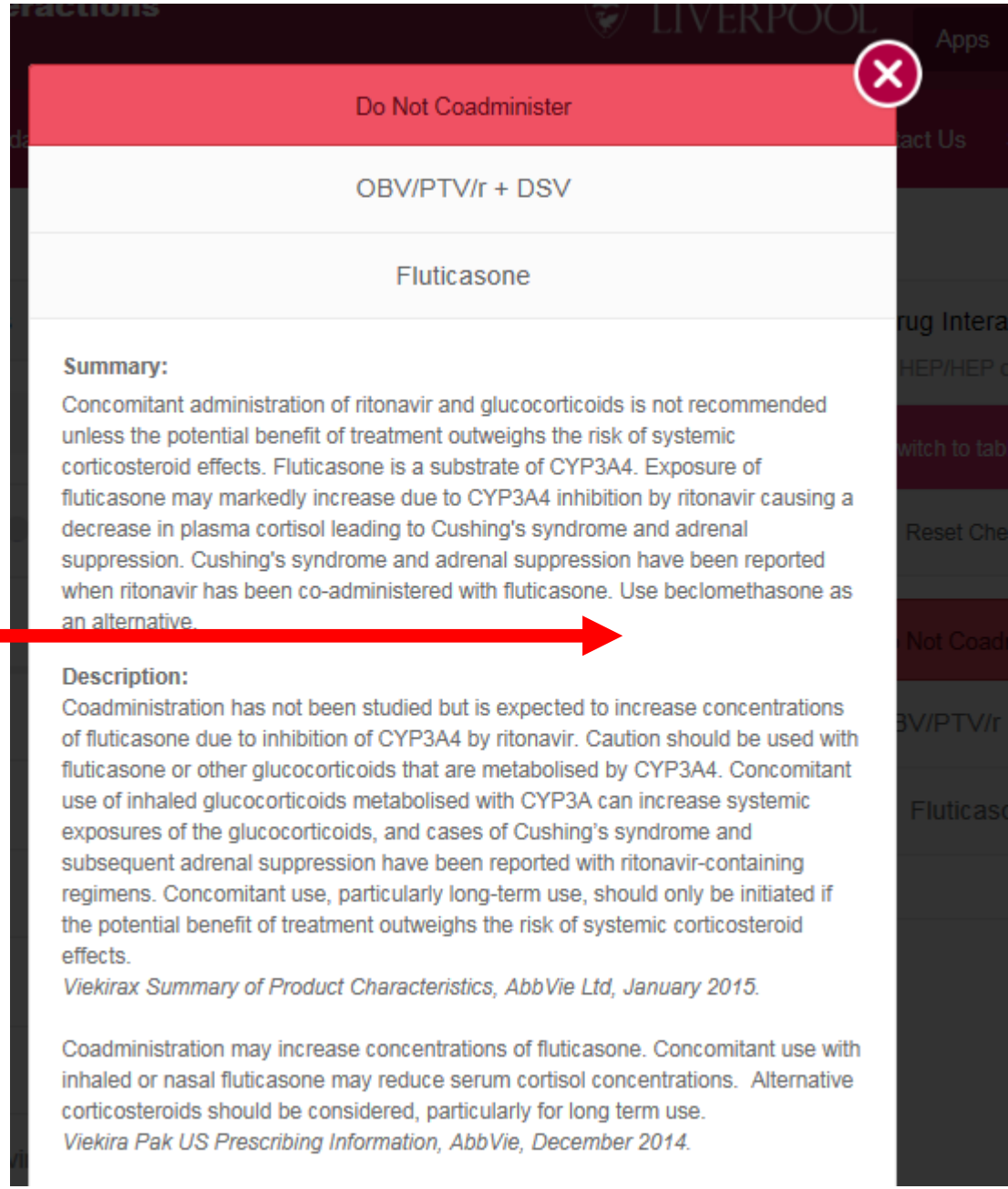
- Prescribing information
- University of Liverpool sites
  - http://www.hiv-druginteractions.org/
  - http://hep-druginteractions.org/checker
  - Mobile apps available from Google Play and the App Store
- Guidelines
  - IDSA/AALSD
  - DHHS HIV Guidelines
- Review articles by field experts
  - Jennifer Kiser, University of Colorado Denver
- Meeting abstracts
  - The Liver Meeting (AASLD)
  - CROI

Liverpool Site



Detailed D-D Information

- Drug interaction resources often lack specific information
  - Mechanisms
  - Actionable recommendations
  - References



Chicken or the Egg?

- Adjust ART to suit HCV regimen
  - Insurance preferences
  - Renal function
  - Treatment history
  - Liver function

- Adjust HCV regimen to suit ART regimen
  - Patient with HIV resistance and limited options

An Approach to Interactions

- Step 1: Verify is drug interaction is limited to particular HCV regimen vs all/most regimens
  - e.g. PPI with ledipasvir/sofosbuvir vs. phenytoin with all
- Step 2: Clarify indication for interacting medication
  - Is primidone for seizures or tremors?
- Step 3: Determine if interacting medication can be changed
- Step 4: Assess need for taper/washout period
- Step 5: Stop interacting medication, start substitute
- Step 6: Monitor patient closely

Mechanisms of Interactions

- pH dependent interactions
- Cytochrome P450 interactions
- Membrane transporters
  - P-Gp
  - BCRP
  - OATP1B1/3

pH Dependent Interactions

- Absorption of medications can be pH dependent
  - Ledipasvir and velpatasvir
- Data regarding SVR rates conflicting with PPIs
  - No difference in SVR rates with daily PPI/appropriately managed [1,2]
  - PPI use factor that predicted non-SVR[3]
- Management strategies vary based on acid reducer and HCV regimen
  - Ledipasvir and velpatasvir recommendations differ with regard to PPIs
    - Please refer to package labeling

1. Tapper E, et al. Hepatology. 2016; 64(6): 1893-1899. 2. Bhattacharya D, et al. Clin Infect Dis. 2017; 64(12): 1711-1720.
3. Terrault NA, et al. Gastroenterology. 2016; 151(6): 1131-1140.

pH Dependent Interactions: Management

- Example management strategies (ledipasvir):
  - PPIs: D/C if possible; max dose PPI omeprazole 20 mg QD; must be taken at the same time on an empty stomach
  - H2 antagonists: Do not exceed famotidine 40 mg BID
  - Antacids (including calcium carbonate): Space antacids by 4 hours
- Providing written instructions to patients:
  - Please reduce omeprazole to 20 mg daily (one capsule). Omeprazole must be taken at the exact same time as ledipasvir/sofosbuvir TOGETHER ON AN EMPTY STOMACH.
  - Please reduce calcium carbonate/vitamin D tablet to once daily and take this in the evening at least 4 hours before or after ledipasvir/sofosbuvir.
  - Take Maalox at nighttime to avoid the drug interaction

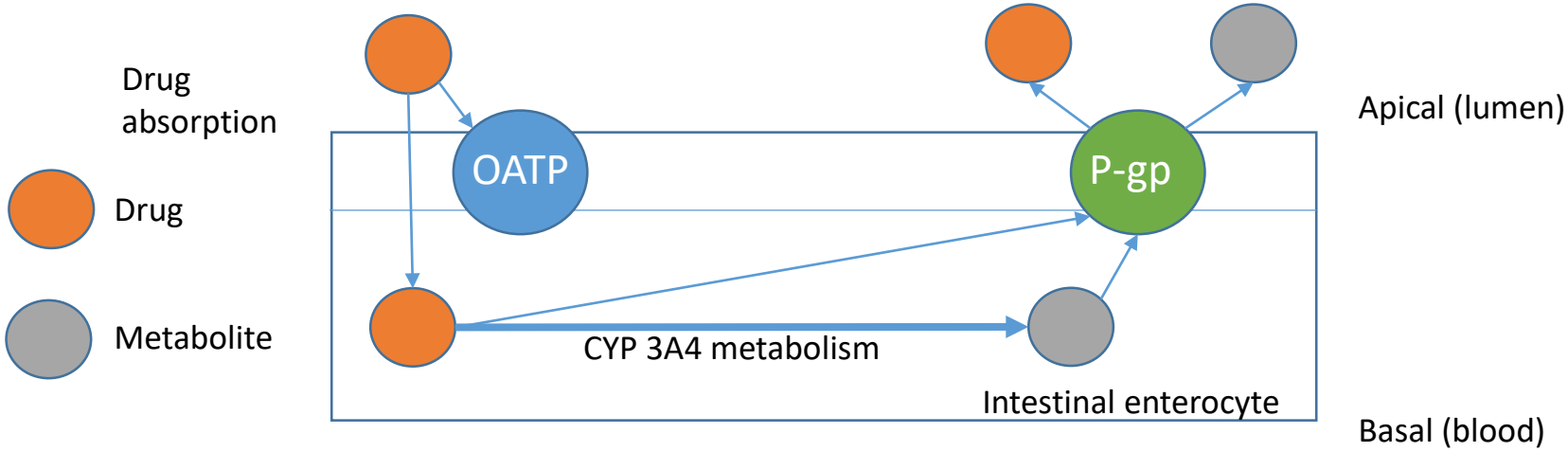
Cytochrome P450 (3A4)

- CYP450 isoenzyme system: Responsible for breakdown of many medications
  - Substrate: What is acted on by inducers/inhibitors
  - Inducer: Reduces concentrations of substrates
  - Inhibitor: Increases concentrations of substrates

- Common CYP450 interactions:
  - Statins and protease inhibitors
  - Rifampin and many antiretrovirals

Drug Transporters

- Transporter proteins in the liver, kidney, or intestines
- Move medications from one compartment to the next through efflux or uptake
- P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)
- Inhibition or induction of these transporter can lead to increased or decreased medication concentrations in the blood



DAA Enzymatic and Drug Transporter Interactions

	Substrate	Inhibition	Induction	Transporter Inhibition
Simeprevir	**3A4,** P-gp	1A2		P-gp
Paritaprevir	**3A4**, P-gp	2C8, UGT1A1		P-gp, OATP1B1, BCRP
Grazoprevir	**3A4**, OATP1B1, P-gp	3A4		BCRP
Ledipasvir	P-gp			P-gp, BCRP, OAT1B1/3
Ombitasvir	**3A4**, P-gp	2C8, UGT1A1		
Daclatasvir	**3A4**, P-gp			P-gp, OAT1B1/3, BCRP
Elbasvir	**3A4**, P-gp		3A4 (weak)	P-gp, BCRP
Velpatasvir	**3A4,** 2C8, 2B6, P-gp			P-gp, BCRP, OAT1B1/3
Sofosbuvir	P-gp, BCRP			
Dasabuvir	**3A4**, 2C8, 2D6, P-gp	UGT1A1		BCRP, OCT1
Ribavirin				

OATP: Organic anion-transporting polypeptide
UGT1A1: UDP-glucuronosyltransferase 1A1

P-gp: P-glycoprotein
BCRP: breast cancer resistance protein

AASLD Recommendations for testing, management, and treating hepatitis C. Accessed on 31 Jul 2017 at www.hcvguidelines.org.
Top Antivir Med 2016;24(3):106-10.

Common Antiretroviral Enzymatic and Drug Transporter Interactions

	Substrate	Inhibition	Induction	Transporter Inhibition
Efavirenz	**3A4, 2B6**	2C8, 2C9	3A4, 2B6, 2C19	
Etravirine	**3A4, 2C9, 2C19**	2C9, 2C19	3A4	
Rilpivirine	**3A4**			
Atazanavir	**3A4**	**3A4,** 2C8, 2C9		BRCP
Darunavir	**3A4,** P-gp	**3A4,** 2D6		
Ritonavir	**3A4**, 1A2, 2B6, 2D6, P-gp	**2C8, 3A4** 2C9, 2E1	1A2, 2B6, 2C9, 2C19	**P-gp, BRCP**
Cobicistat	**3A4**	**3A4,** 2D6		BCRP, OATP1B1, OATP1B3
Raltegravir	UGT1A1			
Elvitegravir	**3A4**, UGT1A1/3		2C9	
Dolutegravir	3A4, P-gp, UGT1A1/3/9			OCT2

OATP: Organic anion-transporting polypeptide
UGT1A1: UDP-glucuronosyltransferase 1A1

P-gp: P-glycoprotein
BCRP: breast cancer resistance protein

Accessed from LexiComp at wwww.crlonline.com on 15 Aug 2017.

Tenofovir and DAA Interactions

- Ledipasvir and velpatasvir increase tenofovir concentrations
- Summary of tenofovir recommendations based on creatinine clearance and concurrent ART agents

Creatinine Clearance and Concurrent ART	Velpatasvir/sofosbuvir	Ledipasvir/sofosbuvir
CrCl ≥ 60 mL/min	Monitor for TDF side effects	Monitor for TDF side effects
CrCl < 60 mL/min	Avoid TDF use	Avoid TDF use
CrCl ≥ 60 mL/min + ritonavir or cobicistat	Monitor for TDF side effects	Avoid TDF use
CrCl < 60 mL/min + ritonavir or cobicistat	Avoid TDF use	Avoid TDF use

- Tenofovir alafenamide (TAF) can be considered as an alternative to tenofovir disoproxil fumerate (TDF)
- No changes in renal function noted with TDF use in real world data[2]

1. AASLD Recommendations for testing, management, and treating hepatitis C. Accessed on 31 Jul 2017 at www.hcvguidelines.org.2. 2. Bhattacharya D, et al. Clin Infect Dis. 2017; 64(12): 1711-1720.

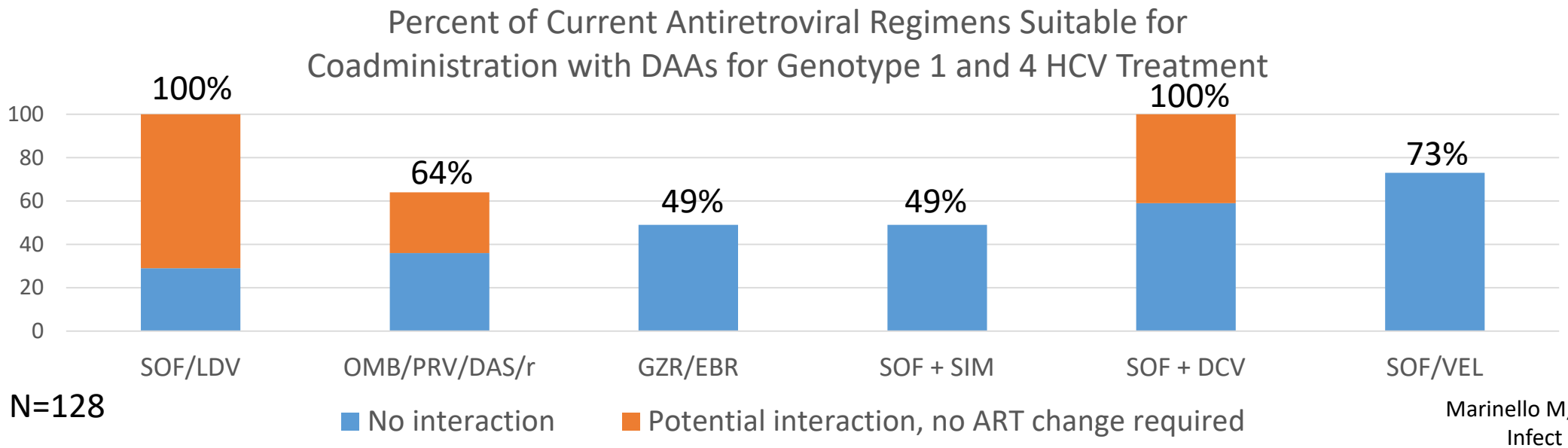
Ribavirin and NRTI Interactions

- *In vitro,* ribavirin reduces phosphorylation of zidovudine, stavudine, lamivudine
  - In vivo analysis does not show an impact on NRTI concentrations
- Concerns for exacerbations of anemia with co-administration of zidovudine and ribavirin
  - Consider discontinuation of zidovudine
- Hepatic decompensation risk with zidovudine and interferon-alfa +/- ribavirin

Gries JM, et al. 11th CROI, San Francisco, February 2004, abstract 136LB.
www.HIV-druginteractions.org Access on 31 Jul 2017.

Frequency of Antiretroviral and DAA Interactions

- HIV/HCV coinfected patients (n=249) enrolled July 2014 to Dec 2015
- ART regimens consisted of:
  - NRTI (96%): TDF 65%, FTC 63%, ABC 27%, 3TC 30%
  - NNRTI (37%): efavirenz 15%, rilpivirine 11%, nevirapine 6%, etravirine 4%
  - PI (29%): atazanavir 12%, darunavir 12%, lopinavir 6%
  - INSTI (48%): dolutegravir 22%, raltegravir 20% , elvitegravir/cobicistat 6%
- Sofosbuvir/ledipasvir and sofosbuvir/daclatasvir had least potential for interactions with ART



N=128

Marinello M, et al. Open Forum Infect Dise 2016;3(2):1-8.

ART for Co-infected, HIV Treatment Naïve

- Consider selecting ART in anticipation of HCV treatment
- If all recommended treatment naïve antiretroviral regimens are options, consider one with less potential interactions with DAAs
  - Examples: dolutegravir based or raltegravir based (recommended regimens), rilpivirine based (alternative regimen)
  - Ritonavir, cobicistat, or TDF regimens tend to have more interactions

ART for Co-Infected, HIV Treatment Experienced

- ART with higher potential for interactions with DAAs
  - Ritonavir or cobicistat-boosted protease inhibitors
    - Can increase DAA concentrations
  - Efavirenz and etravirine
    - CYP enzyme inducers can decrease DAA concentrations
- If a switch in ART is needed in a virologically suppressed patient
  - Review past regimens and resistance testing
  - Within class switches should maintain virologic control if no viral resistance
  - Close viral load monitoring within the first three months after switch
  - Goal: maintain HIV viral suppression

DHHS Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Accessed 31 Jul 2017 at www.aidsinfo.nih.gov.
AASLD Recommendations for testing, management, and treating hepatitis C. Accessed on 31 Jul 2017 at www.hcvguidelines.org.

Primary Care: Common DAA Drug Interactions

- Check your drug-drug interaction resource
- Important to consider the entire medication list, including over the counter medications and herbal supplements
- Clarify indication and dosing for concurrent medication
  - Example: cardiovascular risk category for statin therapy or confirming anticonvulsants for epilepsy
- Determine if alternatives to concurrent medication exist
- Consult with prescribing physician and/or pharmacist

DAA and Cardiovascular Medication Interactions

- Amiodarone: contraindicated with all current DAA regimens
  - Serious symptomatic bradycardia
  - Consultation with cardiology is advised
- Anti-hypertensives:
  - Amlodipine, diltiazem, verapamil: caution with CYP 3A4 inhibitors
- Statins are P-gp and BCRP substrates
  - Pravastatin has the least potential for interactions
  - Patients with high cardiovascular risk: consider switching to high dose pravastatin for duration of DAA treatment
  - Patients with low cardiovascular risk: consider holding statin
  - Consider consultation with cardiologist

DAAs and Mental Health and Neurology Medication Interactions

- Anti-convulsants:
  - Carbamazepine, oxcarbazepine, phenytoin, phenobarbital, primidone
  - P-gp and CYP enzyme inducers
  - Lead to decreased DAA concentrations
  - Consult with neurology regarding alternatives such as levetiracetam
- Antidepressants:
  - For many DAA regimens, no adjustments are needed
  - DAA CYP enzyme inhibitors – watch for increased antidepressant concentrations and side effects

DAAs and Miscellaneous Agent Interactions

- Alpha-blockers
  - Caution with CYP inhibitors, monitor blood pressure
- Contraceptive agents
  - Ethinylestradiol containing product + OMB/PAR/DAS/r can lead to hepatoxicity and increased liver function tests
  - Progestin containing products are recommended during treatment
  - Can restart ethinylestradiol products 2 weeks after completing therapy

Viekira Pak Package Insert. AbbVie Inc; North Chicago, IL. 2016.

Takeaway Points

- Hepatitis C treatment has similar efficacy in co-infected patients compared to mono-infected patients

- HIV-HCV co-infection--- Still a special population?
  - Drug-drug interactions
    - Important to utilize your resources to identify and manage drug-drug interaction
  - Faster progression
  - Short course therapies?

- What to do for special subpopulations
  - Co-infected patients with DAA treatment experience
  - Patients with drug interactions and renal failure

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