Alaska ID ECHO: HCV-HIV-PrEP-STIs

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

NPAIHB
Indian Leadership for Indian Health

May 10, 2022

This program is supported by a grant from the Northwest Portland Area Indian Health Board and funding is provided from the HHS Secretary's Minority HIV/AIDS Fund.

Welcome to Alaska Infectious Disease ECHO: HCV, HIV, PrEP, STIs

Approved Provider Statements:

In support of improving patient care, Alaska Native Medical Center (ANMC) is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Contact Hours:

ANMC designates this activity for a maximum of 12 contact hours, including 3 total pharmacotherapeutics contact hours, commensurate with participation.

Financial Disclosures:

Youssef Barbour, MD & Lisa Townshend-Bulson, APRN / faculty for this educational event, are primary investigators in an ANTHC sponsored hepatitis C study funded in part by Gilead Sciences. All of the relevant financial relationships listed have been mitigated.

Requirements for Successful Completion:

To receive CE credit please make sure you have actively engaged in the entire activity, your attendance is recorded by the facilitator, and complete the course evaluation form found here: https://forms.gle/18t4EgvN2WdnM4P77

For more information contact
jlfielder@anthc.org or (907) 729-1387

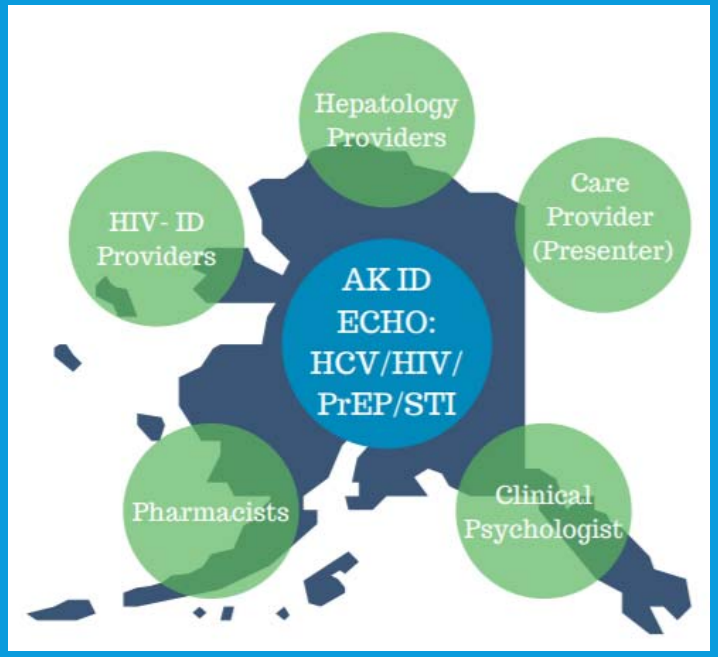
WELCOME

- Questions will be saved until the end of the didactic presentation. Feel free to put your questions in the chat for the Q&A.
- Recording - we record the didactic portion of every session and make it available on the ANTHC .org AK ID ECHO page, https://anthc.org/project-echo/hcv-hiv-prep-stis-echo

Thank you for participating!

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

AK ID ECHO: CONSULTANT TEAM



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- Leah Besh, PA-C HIV/Hepatology Provider
- Terri Bramel, PA-C HIV/STI Provider
- Rod Gordon, R.Ph. AAHIVP Pharmacist
- Jacob Gray, MD Infectious Disease Provider
- Annette Hewitt, ANP Hepatology Provider
- Brian McMahon, MD Hepatologist
- Lisa Rea, RN HIV/STI Case Manager
- Lisa Townshend, ANP Hepatology Provider

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

Drug Interactions:

Understanding the “Why” to remember the “What”

Part I: Common drug interactions for medications commonly used to treat HCV and HIV

Rod Gordon, R.Ph. AAHIVP
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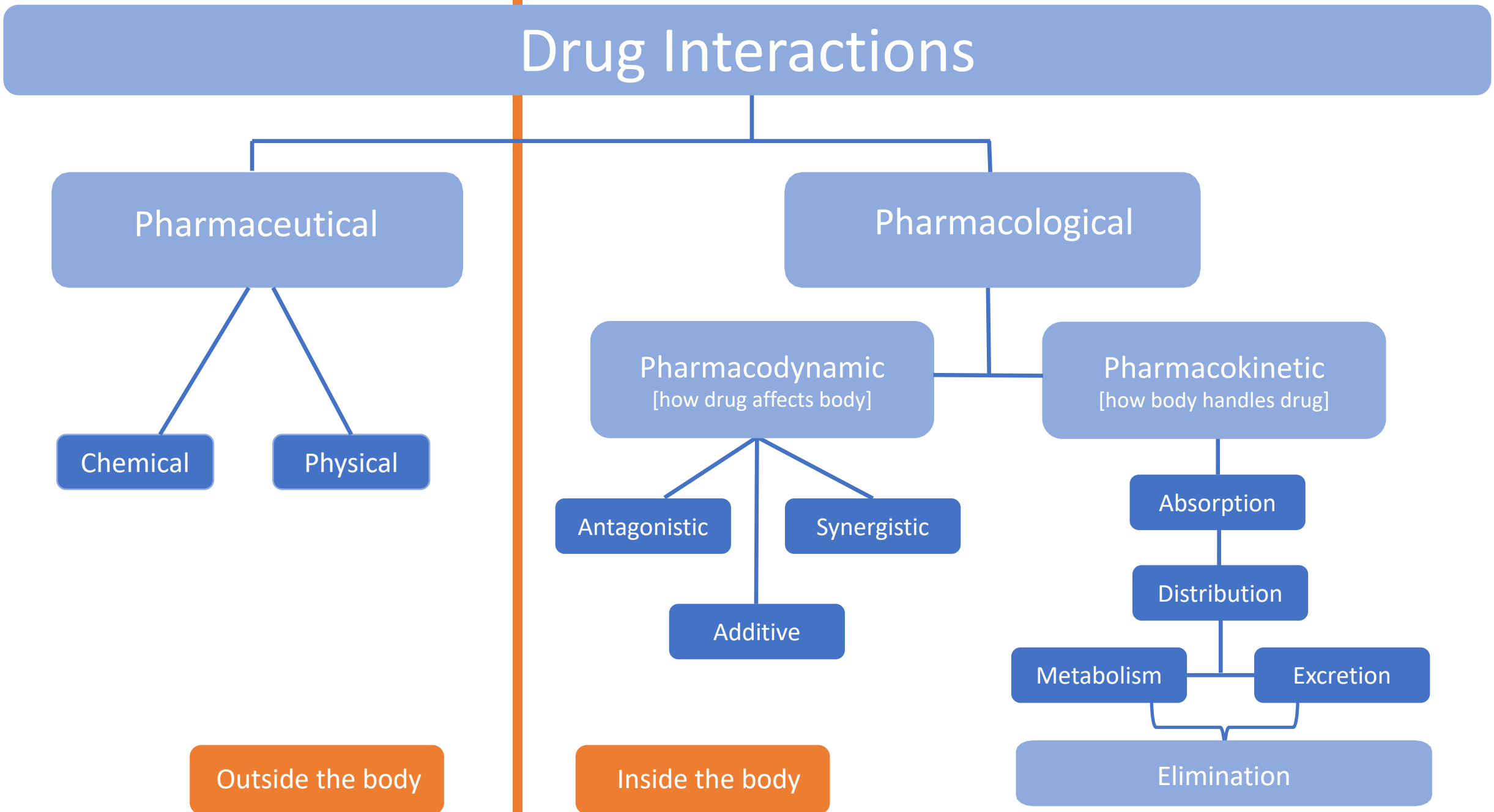
Anchorage, Alaska
May 10, 2022

It is estimated that drug-drug interactions cause 26% of all adverse drug events (ADEs), which are defined as any injuries resulting from use of a drug,[1] and cost the health care system $1.3 billion annually in hospitalizations.[2,3] It is estimated that up to 62% of ADEs are preventable.[3]

1. Veteran's Administration for Medication Safety. Adverse drug events, adverse drug reactions, and medication errors. https: //www.pbm.va.gov/PBM/vacenterformedicationsafety/tools/AdverseDrugReaction.pdf
2. Carpenter M, Berry H, Pelletier AL. Clinically relevant drug-drug interactions in primary care. *Am Fam Physician*. 2019; 99(9): 558-564.
3. Roblek T, Deticek A, Leskovar B, et al. Clinical-pharmacist intervention reduces clinically relevant drug-drug interactions in patients with heart failure: a randomized, double-blind, controlled trial. *Int J Cardiol*. 2016; 203: 647-652.


Drug Interactions
Pharmaceutical
Chemical
Physical
Pharmacological
Pharmacodynamic
[how drug affects body]
Antagonistic
Synergistic
Additive
Pharmacokinetic
[how body handles drug]
Absorption
Distribution
Metabolism
Excretion
Elimination
Outside the body
Inside the body

Drug Interactions- Pharmacological

Inside the body

Pharmacodynamic
[how drug affects body]

- Antagonistic
- Synergistic
- Additive

Antagonistic: Naloxone + Opioid Analgesics
[reversing overdose]

Additive: ASA + DOAC
[APT + Anticoag potentiates risk for bleeding]

Synergistic: NS5B + NS5A Inhibitor
[potentiates HCV clearance]

Absorption: Antacid + Rilpivirine
[↑ gastric pH, ↓ absorption]

Distribution: velpatasvir + loperamide
[P-gp inhibition ↑ loperamide AUC ↑ CNS side effect]

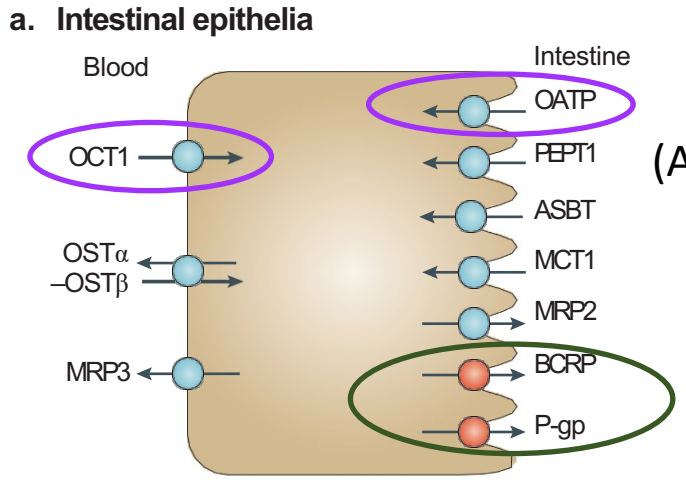
Pharmacokinetic
[how body handles drug]

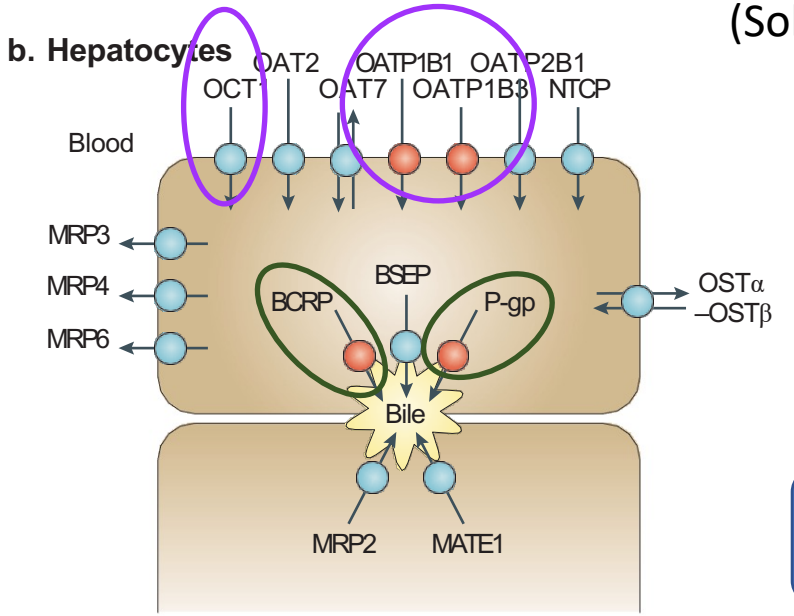
- Absorption
- Distribution
- Metabolism
- Excretion

Metabolism: grapefruit juice + simvastatin
[furanocoumarins in juice inhibit CPY3A4, ↑ statin AUC and AE]

Excretion: metformin + dolutegravir
[DTG ↓ active tubular secretion by OCT2, ↑ metformin AUC]

DDI Targets: Membrane Transporters





ABC
(ATP Binding Cassette)

Efflux

P-gp

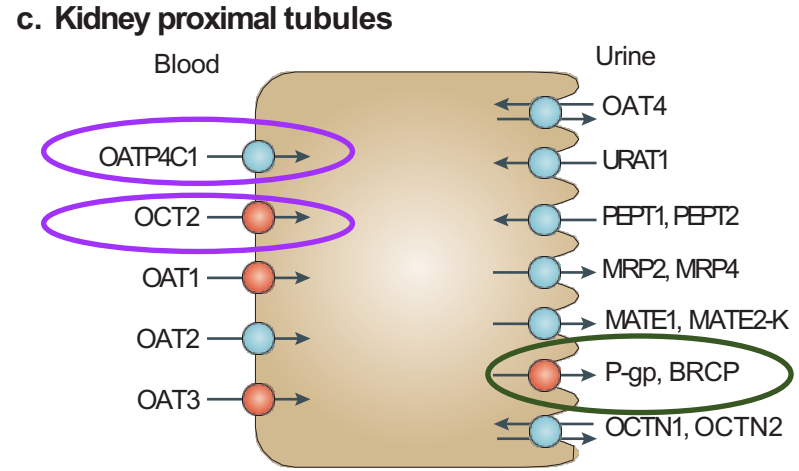
BCRP

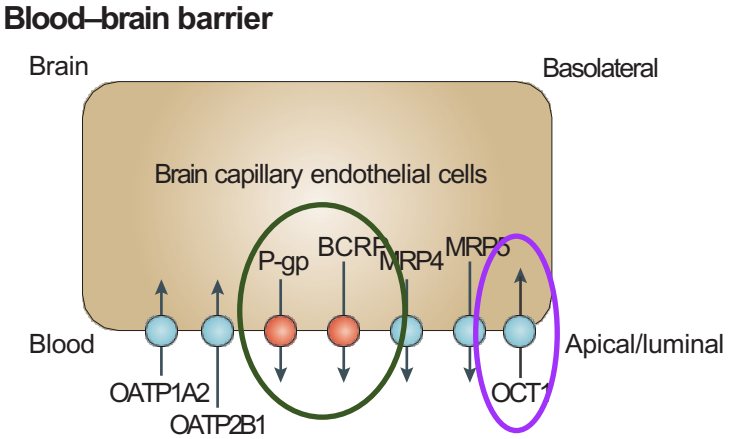
SLC
(Solute Carrier)

Uptake

OATP

OCT

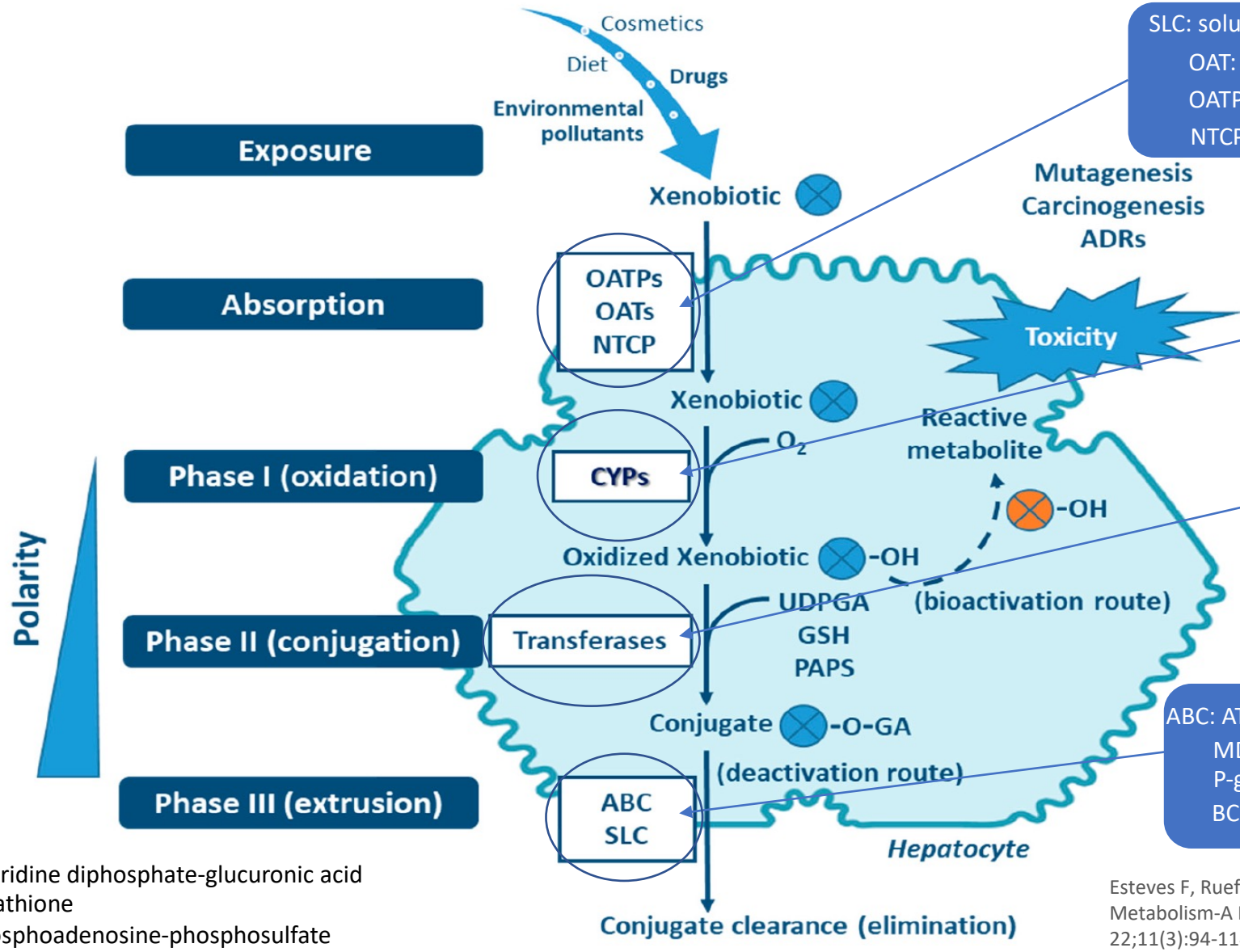




Membrane transport proteins play a crucial role in the pharmacokinetic pathways of drug absorption, distribution, metabolism, and excretion, and help set systemic drug levels that drive either therapeutic or adverse drug effects. Transporters are a major targets for DDIs

International Transporter Consortium, Giacomini KM, et. al. Membrane transporters in drug development. Nat Rev Drug Discovery. 2010 Mar; 9(3):215-36. doi: 10.1038/nrd3028. PMID: 20190787; PMCID: PMC3326076.

Other DDI Targets: CYPs and Transferases



SLC: solute carrier transporter proteins—Uptake Processes
- OAT: organic anion transporters;
- OATP: organic anion transporting polypeptides;
- NTCP: sodium taurocholate cotransporting polypeptide;

Biotransformation Step 1

Biotransformation Step 2

ABC: ATP binding cassette transporter proteins –Efflux processes
- MDR: multidrug resistance transporters
- P-gp: P-glycoprotein transporter
- BCRP: breast cancer resistance protein

UDPGA: uridine diphosphate-glucuronic acid
GSH: glutathione
PAPS: phosphoadenosine-phosphosulfate

Esteves F, Rueff J, Kranendonk M. The Central Role of Cytochrome P450 in Xenobiotic Metabolism-A Brief Review on a Fascinating Enzyme Family. J Xenobiot. 2021 Jun 22;11(3):94-114. doi: 10.3390/jox11030007. PMID: 34206277; PMCID: PMC8293344.

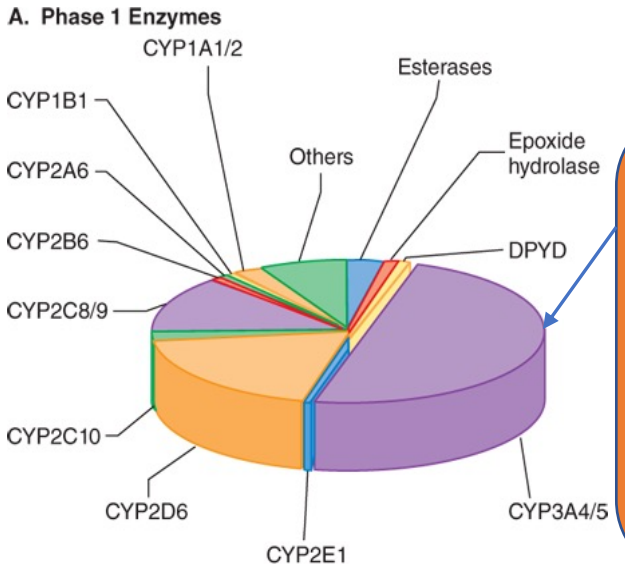
DDI Targets: Phase I and Phase II Enzymes

Types of Phase I Biotransformation

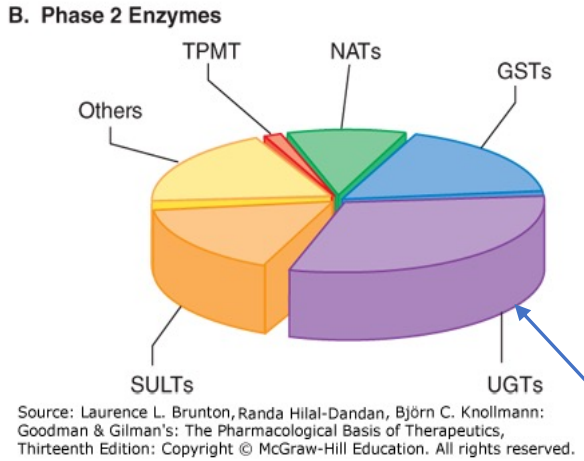
CYP mediated:
epoxidation, dealkylation, oxygenation, dehydrogenation, dehalogenation

Non-CYP Mediated:
Flavin-containing monooxygenases (FMOs), NAD(P)H:quinone oxidoreductases (NQOs), amine oxidases, alcohol dehydrogenases, esterases and peroxidases

12 CYPs (CYP1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, and 3A5) are important for metabolism of 70-80% of drugs in clinical sue



CYP3A4, the most abundantly expressed CYP in the liver, is involved in the metabolism of over 50% of clinically used drugs



Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Thirteenth Edition: Copyright © McGraw-Hill Education. All rights reserved.

UGTs represent the highest percentage of Phase 2 reactions

Types of Phase II Biotransformation

UDP glucuronsyltransferase (UGTs)..to add glucuronic acid
Sulfotransferases (SULT) ……..to add sulfate
Glutathione S-transferases (GSTs)…..to add glutathione
N-acetyltransferase (NATs)……..to add acetyl group
Methyl transferases (MTs)……..to add methyl group

Citation: Chapter 6 Drug Metabolism, Brunton LL, Hilal-Dandan R, Knollmann BC. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e;* 2017. Available at: https://accesspharmacy.mhmedical.com/ViewLarge.aspx?figid=194542687&gbosContainerID=0&gbosid=0&groupID=0&sectionId=167889421&multimediaId=undefined
Accessed: April 22, 2022

Basic DDI Concepts

"Substrate": a drug that interacts with or is modified by an enzyme or membrane transporter.

"Inhibitor": a drug that exerts a direct effect to block the activity of an enzyme or membrane transporter through a competitive, reversible process or a mechanistic based, irreversible process.

"Inducer": a drug that exerts an indirect effect to activate the transcription and induce the nuclear expression of genes that encode for drug-metabolizing enzymes or membrane transporters

Comparison of Drug Interactions Caused by Metabolic Inhibition or Induction

	Inhibition	Induction
Mechanism	Direct effect on enzyme	Indirect effect by increased protein expression
Onset of effect	Rapid	Slow
Offset of effect	Rapid	Slow
Effect on substrate clearance	Reduced	Increased
Effect on substrate AUC	Increased	Decreased
Potential clinical consequence	Enhanced effect, or toxicity	Reduced effect, or ineffectiveness

Greenblatt DJ. Mechanisms and Consequences of Drug-Drug Interactions. Clin Pharmacol Drug Dev. 2017 Mar;6(2):118-124. doi: 10.1002/cpdd.339. PMID: 28263467.

Basic DDI Concepts

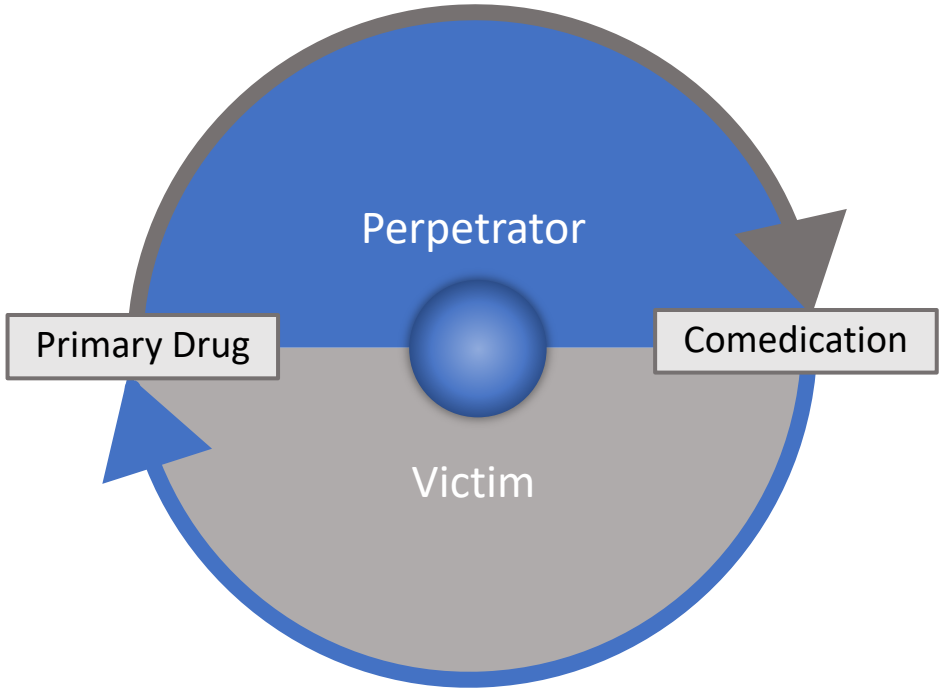
Questions to consider:

Is the drug a substrate of Phase 1 or Phase 2 enzymes?

Does it interact with membrane transporters?

Is it likely to be a victim or perpetrator of interactions? [Does it inhibit or induce enzymes or transporters?]

All drugs have the potential to be a “victim” or a “perpetrator” of DDIs.



Greenblatt DJ. Mechanisms and Consequences of Drug-Drug Interactions. Clin Pharmacol Drug Dev. 2017 Mar;6(2):118-124. doi: 10.1002/cpdd.339. PMID: 28263467.

Specific DDIs: HIV & HCV Co-infection

AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org.

Tables like this answer “What” but not ”Why”

Avoid | **Use Caution** | Safe

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 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.

For antiretroviral agents not included in the table above, please refer to the US Department of Health and Human Services HIV treatment guidelines (https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines) and/or the University of Liverpool drug interactions website (www.hep-druginteractions.org).

https://www.hcvguidelines.org/unique-populations/hiv-hcv

		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	
	Cabotegravir	ND	ND	ND	ND	ND
	Cobicistat-boosted elvitegravir	C	C			C
	Dolutegravir					ND
	Raltegravir					ND
Entry Inhibitors	Fostemsavir	ND	ND	ND	ND	ND
	Ibalizumab-uiyk	ND	ND	ND	ND	ND
	Maraviroc	ND	ND	ND	ND	ND
NRTIs	Abacavir		ND	ND		ND
	Emtricitabine					
	Lamivudine		ND	ND		ND
	Tenofovir disoproxil fumarate	B, C	B, C			C
	Tenofovir alafenamide	D	D	ND		D

Antiretroviral and Directly Acting Antiviral Drug Metabolism and Transporter Characteristics (Summary)

	Substrate	CYP450 and UGT		Transporters	
		Inhibitor	Inducer	Inhibitor	Inducer
DIRECT ACTING ANTIVIRALS					
Mavyret®					
glecaprevir (ABT-493) (NS3/4A PI) + pibrentasvir (ABT-530) (NS5A inhibitor)	P-gp and/or BCRP. OATP1B1/3 (glecaprevir). Minimal metabolism and primary biliary excretion, negligible renal excretion (<1%).	CYP1A2, 3A4 and UGT1A1 (weak); do not inhibit CYP2D6, 2C19, 2C9. Significant interactions with substrates of these enzymes are not expected.[41]		P-gp, BCRP, OATP1B1/3.	
Epclusa®					
sofosbuvir (NS5B inhibitor)	P-gp, BCRP, GS-331007 (primary systemic nucleoside metabolite, accounts for >90% of systemic drug exposure): not a P-gp substrate	No Inhibiting or inducing effects on P450 and UGT1A1.	No inhibiting or inducing effects on P450 and UGT1A1	No inhibiting or inducing effects on P-gp, BCRP, OATP1B1, OATP1B3, OCT1, BSEP.	No inhibiting or inducing effects on P-gp, BCRP, OATP1B1, OATP1B3, OCT1, BSEP.
Velpatasvir (NS5A inhibitor)	CYP3A4, 2C8, 2B6; OATP1B1, OATP1B3, P-gp, BCRP.	No inhibiting or inducing effects on P450.	No inhibiting or inducing effects on P450.	P-gp, OATP1B1, OATP1B3, OATP2B1, BCRP (limited to intestinal efflux and hepatic uptake – clinically relevant interactions in systemic circulation not expected).	

Glecaprevir & pibrentasvir are both substrates of P-gp and BCRP Glecaprevir is also a substrate of OATP1B1/3

Glecaprevir & pibrentasvir are both inhibitors of P-gp, BCRP and OATP1B1/3 (Weak inhibitors of CYP1A2, 3A4, and UGT1A1)

Sofosbuvir (NS5B inhibitor) is a substrate of P-gp and BCRP

Sofosbuvir does not induce or inhibit CYPs, UGTs or transporters

Velpatasvir (NS5A inhibitor) is a substrate of P-gp, BCRP, CYP3A4, 2C8, 2B6, and OATP1B1/3

Velpatasvir is an inhibitor of P-gp, BCRP OATP1B1/3 and OATP2B1

https://hivclinic.ca/wp-content/uploads/2020/09/ARV-and-DAA-pharmacokinetic-characteristics-summary-table.pdf Product Package Inserts

Antiretroviral and Directly Acting Antiviral Drug Metabolism and Transporter Characteristics (Summary)

	Substrate	CYP450 and UGT		Transporters	
		Inhibitor	Inducer	Inhibitor	Inducer
ANTIRETROVIRALS					
HIV INSTIs					
bictegravir (GS-9883)[27, 28]	UGT1A1, CYP3A4 (similar contribution)	Does not inhibit CYP including CYP3A4 or UGT1A1.	Does not induce CYP3A4 or UGT1A1.	OCT2 (less than dolutegravir), MATE1. Does not inhibit OATP1B1/3, OCT1, BSEP, OAT1/3.	
cabotegravir[29]	UGT1A1, UGT1A9 (minor). Substrate of P-gp, BCRP (high intrinsic membrane permeability limits impact of these transporters on intestinal absorption).	Does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19 or 2D6. Weakly inhibits CYP3A4 and inhibits UGT1A3 (not clinically relevant).	Does not induce CYP1A2, 2B6 or 3A4.	OAT1/3. Does not inhibit P-gp, BCRP, BSEP, MRP2, OACT1, OATP1B1, OATP1B3.	
dolutegravir[30]	UGT1A1, CYP3A4 (10-15%); also a substrate of UGT1A3, UGT1A9, P-gp and BCRP in vitro. Not a substrate of OATP1B1, OATP1B3, or OCT1.		Does not induce CYP1A2, CYP2B6, or CYP3A4 in vitro.	OCT2, MATE1; also MATE2 but low potential to affect transport of MATE2 substrates.	
elvitegravir[31]	CYP3A4		CYP2C9 (modest)		
raltegravir[32]	UGT1A1	Raltegravir has no inhibitory or inductive potential in vitro.	Raltegravir has no inhibitory or inductive potential in vitro.		

Bictegravir- equally metabolized by UGT1A1 and CYP3A4,

Dolutegravir- primarily metabolized by UGT1A1, but 10-15% by CYP3A4

OCT2 inhibition by bictegravir in proximal renal tubule> ↑ metformin AUC 39% and ↑ Sr Cr 0.1mg/dL

OCT2 inhibition by dolutegravir in proximal renal tubule> ↑ metformin AUC 79% and ↑ Sr Cr 0.15mg/dL

Elvitegravir completely metabolized by CYP3A4

Raltegravir completely metabolized by UGT1A1

INSTIs do not induce or inhibit, i.e., they do not perpetrate DDIs but are often victims of DDIs by induction of UGT, and CYP3A4

https://hivclinic.ca/wp-content/uploads/2020/09/ARV-and-DAA-pharmacokinetic-characteristics-summary-table.pdf Product Package Inserts

Atazanavir and darunavir- both substrates of CYP3A & P-gp; makes them targets of PK boosters- good example of a therapeutic PK DDI

Ritonavir is both an inhibitor and an inducer of multiple CYP enzymes-makes DDIs sometimes difficult to predict

Antiretroviral and Directly Acting Antiviral Drug Metabolism and Transporter Characteristics (Summary)

	Substrate	CYP450 and UGT		Transporters	
		Inhibitor	Inducer	Inhibitor	Inducer
HIV Protease Inhibitors					
atazanavir[2]	Mainly CYP3A P-gp, MRP1	3A4, UGT1A1 >>2C8 (weak)		P-gp, MRP1, OATP1B1, OATP1B3, BCRP	
darunavir[3]	Mainly CYP3A, P-gp	CYP3A4		BCRP, OATP1B1[4]	
PK Boosters					
ritonavir[13]	CYP3A4, P-gp, MRP1	CYP3A4 (potent)> >2D6* >2C9 >2C19 >2A6 >1A2>2E1. *negligible effect at boosting doses[7]	UGT, CYP1A2, CYP2C9/19, 2B6 (inhibits in vitro,[14] but induces in vivo[15])	P-gp, OATP1B1, OATP1B3, BCRP, OATP2B1, OCT2, MATE1[16]	
cobicistat[17]	CYP3A, 2D6 (minor)	CYP3A, CYP2D6		P-gp, BCRP, OATP1B1 and OATP1B3, MATE1[16, 18]	

Ritonavir and Cobicistat are both strong inhibitors of multiple CYP enzymes, primarily CYP3A4 and CYP2D6

Ritonavir and Cobicistat both inhibit P-gp, BCRP and multiple transporters

Atazanavir and darunavir- both inhibit CYP3A4 and multiple membrane transporters;

https://hivclinic.ca/wp-content/uploads/2020/09/ARV-and-DAA-pharmacokinetic-characteristics-summary-table.pdf

HIV & HCV Co-infection

Hep C Drug	Mechanism	DDI	Perpetrator	Victim	Comments
Glecaprevir/Pibrentasvir (Mavyret)	Inhibition of OATP1B1/3 by PK boosted HIV regimen	HIV PK Boosted PI inhibits OATP 1B1, 1B3	Any of the ritonavir or cobicistat boosted PI regimens [Elvitegravir boosted regimen OK]	↑ Glecaprevir AUC ↑ risk for toxicity	Avoid Combination
Sofosbuvir/Velpatasvir (Epclusa)	Inhibition P-gp, BCRP, by velpatasvir	Velpatasvir inhibits P-gp and BCRP	Sofosbuvir/Velpatasvir	Any TDF containing HIV regimen, in a Cobi or ritonavir boosted regimen, ↑ TFV-DP AUC 40-80% ↑ risk for renal toxicity	Use Caution, especially with boosted regimen; CrCL must be > 60mL/min

Mavyret + Boosted PI HIV regimens
Avoid Combination

Epclusa + Any TDF containing HIV regimens
Use caution and monitor renal function

https://www.hcvguidelines.org/unique-populations/hiv-hcv https://www.hiv-druginteractions.org/checker https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AA_Tables.pdf https://www.hep-druginteractions.org/checker

HIV and HCV Drug Interactions: Quick Guides for Clinicians

Publish date: *November 02, 2019*

AETC Source: Northeast/Caribbean AETC

A collection of clinical guides regarding drug interactions of hepatitis C virus (HCV) direct-acting antivirals (DAAs) with other common primary care medications and HIV antiretrovirals.

https://aidsetc.org/resource/hiv-and-hcv-drug-interactions-quick-guides-clinicians

AETC AIDS Education & Training Center Program Northeast/Caribbean

Glecaprevir/Pibrentasvir (Mavyret™) Drug Interactions
A Quick Guide for Clinicians – November 2019

John J Faragon, PharmD, BCPS, AAHIVP

G/P inhibits P-gp

G/P inhibits CYP1A2

G/P substrates of P-gp, BCRP
G minor substrate of CYP3A

PD interaction between
G/P and Ethinyl Estradiol

G/P inhibits OATP1B1/3,
P-gp, BRCP, & CYPs

G/P inhibits OATP1B1/3

G/P caution with PPIs
(↓AUC of G but not P)
Omeprazole max 20mg/day

Medication and or Class	Recommendation and Clinical Comments
Antiarrhythmic – Digoxin (P-gp substrate)	• Increased digoxin levels expected. Measure serum digoxin level prior to initiating therapy with glecaprevir/pibrentasvir; reduce digoxin dosage 50%.
Anticoagulant – Dabigitran, Warfarin (P-gp substrate) (CYP1A2 substrate)	• Refer to dabigatran package insert and follow dosage recommendations for patients receiving concurrent P-gp inhibitors. • Monitor INR closely in patients receiving warfarin.
Anticonvulsants – carbamazepine (Induces CYP3A, P-gp)	• Significant decrease in glecaprevir/pibrentasvir levels expected. Co-administration not recommended.
Antimycobacterials – rifampin (Induces CYP3A, P-gp)	• Significant decrease in glecaprevir/pibrentasvir levels expected. Co-administration not recommended.
Ethinyl Estradiol (PD interaction)	• Potential increased risk of ALT elevations when glecaprevir/pibrentasvir is combined with ethinyl estradiol. Co-administration not recommended.
Herbal products – St. John's Wort (Induces CYP3A, P-gp)	• Significant decrease in glecaprevir/pibrentasvir levels expected. Co-administration not recommended.
HMG-CoA Reductase Inhibitors – atorvastatin, lovastatin, simvastatin (OATP1B1/3, P-gp, BCRP subs)	• Significant increase in statin levels when combined with glecaprevir/pibrentasvir. Co-administration not recommended.
HMG-CoA Reductase Inhibitors – fluvastatin, pitavastatin, pravastatin, rosuvastatin (OATP1B1/3 substrates)	• Fluvastatin, pitavastatin – Increase statin levels likely when used with glecaprevir/pibrentasvir; Use lowest dose and monitor closely for statin toxicity, including myopathy. • Pravastatin – Increased statin levels likely when used with glecaprevir/pibrentasvir. Reduce pravastatin dosage 50% prior to adding glecaprevir/pibrentasvir. • Rosuvastatin – Increased statin levels likely when used with glecaprevir/pibrentasvir. Do not exceed rosuvastatin 10mg when combined.
Immunosuppressants – cyclosporine (OATP1B1/3 substrate)	• Increased levels of cyclosporine expected when combined with glecaprevir/pibrentasvir. Co-administration not recommended in patients requiring cyclosporine doses greater than 100mg daily.

Sofosbuvir/Velpatasvir (Epclusa®) Drug Interactions
A Quick Guide for Clinicians – November 2019

John J Faragon, PharmD, BCPS, AAHIVP

AETC AIDS Education & Training Center Program Northeast/Caribbean

Vel requires an acidic gastric pH for solubility and absorption

Avoid PPI if possible Omeprazole 20mg/day max, take 4 hours later

Sof-PD interaction

Vel inhibits P-gp

PD interaction

Vel inhibits P-gp, BCRP

Sof/Vel are Subs P-gp, BCRP
Vel minor substrate of CYP2B6, 2C8, 3A4

Vel inhibits P-gp, BCRP, OATP1B1

Medication and or Class	Recommendation and Clinical Comment
Antacids H2-receptor antagonists (See specific administration Guidance)	• Separate antacids and sofosbuvir/velpatasvir administration by 4 hours. • Administer simultaneously with or 12 hours apart from sofosbuvir/velpatasvir. Do not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors (Avoid is possible; if not able to avoid, max dose of omeprazole 20mg once daily, taken 4 hours after Sof/Vel. Take Sof/Vel with food)	• Co-administration not recommended. If medically necessary, sofosbuvir/velpatasvir should be administered with food and taken 4 hours before omeprazole 20mg. Use with other proton pump inhibitors has not been studied.
Antiarrhythmic – Amiodarone (PD interaction- due to Sof/Amiodarone>> bradycardia)	• Significant bradycardia expected with concurrent use. Co-administration not recommended. If concurrent use required, cardiac monitoring is recommended, see package insert for additional information.
Antiarrhythmic – Digoxin (P-gp substrate)	• Increase in digoxin levels possible. Monitor digoxin levels.
Anticoagulant – Warfarin (PD interaction- due to improved LF>> changes in INR)	• Frequent INR monitoring during co-administration and after stopping therapy recommended.
Anticancer – topotecan (oral only--P-gp, BCRP substrate)	• Coadministration not recommended.
Anticonvulsants – carbamazepine, oxcarbazepine, phenobarbital, phenytoin (Induce CYP2B6, 2C8, 3A4, P-gp)	• Significant decrease in sofosbuvir/velpatasvir levels expected. Co-administration not recommended.
Antimycobacterials – rifampin, rifabutin, rifapentine (Induce CYP2B6, 2C8, 3A4, P-gp)	• Significant decrease in sofosbuvir/velpatasvir levels expected. Co-administration not recommended.
Herbal products – St. John's Wort (Induces CYP3A, P-gp)	• Significant decrease in sofosbuvir/velpatasvir levels expected. Co-administration not recommended.
HMG Co-A Reductase Inhibitors: Atorvastatin, Rosuvastatin (Atorvastatin: P-gp, BCRP, OATP1B1/3 substrate) (Rosuvastatin: BCRP, OATP1B1 substrate; max dose 10mg)	• Increase in atorvastatin likely with sofosbuvir/velpatasvir; monitor for signs of myopathy and rhabdomyolysis. • Significant increase in rosuvastatin levels when used with sofosbuvir/velpatasvir leading to increased risk of myopathy, including rhabdomyolysis. Rosuvastatin may be used at a dose that does not exceed 10mg.

https://hivclinic.ca/drug-information/drug-interaction-tables/

Drug Interaction Tables

Our Interactive HIV/HCV Drug Therapy web application is now live!

This website application incorporates HIV and HCV pharmacology and drug interaction information in an easy-to-use, searchable and interactive format.

Drug Interaction Summary Tables

Immunodeficiency Clinic

HOME | CLINIC | PATIENT | DRUG INFORMATION | RESEARCH | RESIDENCY | PHARMACY ORG

Drug Interaction Summary Tables

Concise, colour-coded quick reference charts for use in conjunction with our drug interaction application. These summary charts will be replacing the previous pdf tables which are no longer being updated. These tables are also available in a consolidated handbook in English and French. For more detailed drug interaction information, please visit our app.

Drug Name/Class	English	French
Acid suppressing Agents	pdf	pdf
Analgesics: opioids, opioid substitution, non-narcotics	pdf	pdf
Anticonvulsants	pdf	pdf
Anti-infectives: azoles and macrolides	pdf	pdf
Anti-infectives: TB drugs	pdf	pdf
Hepatitis C drugs	pdf	pdf
Cardiovascular drugs: antihypertensives, digoxin	pdf	pdf
Cardiovascular drugs: antiplatelets, anticoagulants	pdf	pdf
Cardiovascular drugs: lipid-lowering agents	pdf	pdf
Corticosteroids	pdf	pdf
Chemotherapy regimens	pdf	pdf
Diabetes medications	pdf	pdf
Genitourinary drugs: erectile dysfunction, pulmonary arterial hypertension	pdf	pdf
Genitourinary drugs: BPH, LUTS	pdf	pdf
Hormonal therapy: gender affirming	pdf	pdf
Hormonal therapy: contraceptives, hormone replacement therapy	pdf	pdf
Osteoporosis medications	pdf	pdf
Psychotropics	pdf	pdf
Transplant drugs	pdf	pdf
Recreational drugs	pdf	pdf
Vitamins, herbals, body-building supplements	pdf	pdf
Miscellaneous: ergot alkaloids, colchicine	pdf	pdf

Additional Resources:

- Antiretroviral Treatment Options for Patients on DAAs – Summary
- Drug Metabolism and Transporter Characteristics of Antiretrovirals and Hepatitis C Directly Acting Antivirals

https://hivclinic.ca/drug-information/drug-interaction-tables/

ACID SUPPRESSING DRUGS:
ANTACIDS, H2-RECEPTOR ANTAGONISTS, PROTON PUMP INHIBITORS

HIV AGENTS

	INSTIs		NNRTIs		PIs
	• BICTEGRAVIR *(Biktarvy)* • DOLUTEGRAVIR *(Tivicay, Triumeq, Juluca)* • ELVITEGRAVIR/ COBICISTAT *(Stribild, Genvoya)* • RALTEGRAVIR *(Isentress)*	• RILPIVIRINE *(Edurant, Complera, Odefsey, Juluca)*	• DORAVIRINE *(Pifeltro, Delstrigo)* • EFAVIRENZ *(Sustiva, Atripla)* • ETRAVIRINE *(Intelence)* • NEVIRAPINE *(Viramune)*	Boosted with ritonavir (Norvir) or cobicistat • ATAZANAVIR *(Reyataz, Evotaz)*	Boosted with ritonavir (Norvir) or cobicistat • DARUNAVIR *(Prezista, Prezcobix, Symtuza)* • LOPINAVIR *(Kaletra)*
ANTACIDS CONTAINING MAGNESIUM, ALUMINUM OR CALCIUM					
• Antacids *(Tums, Maalox, Mylanta, Gaviscon)*	↓ INSTI Raltegravir 600 mg HD tablets Raltegravir 400 mg OK with calcium	↓ rilpivirine		↓ atazanavir	
H2 RECEPTOR ANTAGONISTS					
• Famotidine *(Pepcid)*, nizatidine *(Axid)*, ranitidine *(Zantac)*		↓ rilpivirine		↓ atazanavir	
PROTON PUMP INHIBITORS (PPIs)					
• Esomeprazole *(Nexium)*, lansoprazole *(Prevacid)*, omeprazole *(Losec)*, pantoprazole *(Pantoloc)*, rabeprazole *(Pariet)*		↓ rilpivirine		↓ atazanavir with low dose PPI ↓↓ atazanavir with high dose PPI	

INSTIs adversely affected by cation chelation but not acid suppression

Only two HIV meds adversely affected by acid suppression

Avoid PPIs with rilpivirine

https://hivclinic.ca/drug-information/drug-interaction-tables/

Mechanism of Drug Interactions, Management and Monitoring

Acid Suppressing Drugs	Mechanism of Interaction	Management
Antacids	**Integrase Inhibitors:** chelation leading to poor absorption	**Bictegravir:** Take bictegravir 2 hours before or after medications or supplements containing polyvalent cations. If given with food, may be taken at same time as calcium and iron supplements. **Dolutegravir**: Administer 2 hours before or 6 hours after medications containing polyvalent cations (Mg, Al, Fe or Ca) including antacids or laxatives, sucralfate, oral iron or calcium supplements and buffered medications. If given with food, may be taken at same time as calcium and iron supplements. **Elvitegravir:** Separate by at least 2 hours from antacids containing Al, Mg or Ca. **Raltegravir:** Do not coadminister with Mg or Al containing antacids. Calcium-containing antacids may be coadministered with raltegravir 400 mg tablets, but not 600 mg HD tablets.
	Atazanavir: increase in gastric pH leads to poor absorption	**Atazanavir:** administer 2 hours before or 1 hour after antacids.
	Rilpivirine: increase in gastric pH leads to poor absorption	**Rilpivirine:** Administer antacids at least 2 hours before or 4 hours after rilpivirine.
H_2RAs	**Atazanavir:** increase in gastric pH leads to poor absorption	**Atazanavir:** Give simultaneously with or 10 hours after H_2RA. If also on tenofovir-containing regimen increase to atazanavir 400 mg and ritonavir 100 mg in experienced patients.
	Rilpivirine: increase in gastric pH leads to poor absorption	**Rilpivirine:** Give rilpivirine 4 hours before or 12 hours after H_2RA.
Proton Pump Inhibitors	**Atazanavir, rilpivirine:** increase in gastric pH leads to poor absorption	**Atazanavir:** Coadministration with omeprazole 40 mg (or equivalent) is contraindicated. If unavoidable, increase atazanavir dose to 400 mg with 100 mg of ritonavir and do not exceed doses of omeprazole 20mg or comparable. **Rilpivirine:** contraindicated with PPIs.

Legend:

- No dose adjustment required.
- Use combination with caution. Adjustment in drug dose or frequency or additional/more frequent monitoring may be required. May wish to consult with a pharmacist knowledgeable in HIV drug interactions.
- Contraindicated/avoid combination.

https://hivclinic.ca/drug-information/drug-interaction-tables/

CARDIOVASCULAR DRUGS:
STATINS AND LIPID LOWERING AGENTS

HIV AGENTS

	INSTIs		NNRTIs		PIs
	• BICTEGRAVIR *(Biktarvy)* • DOLUTEGRAVIR *(Tivicay, Triumeq, Juluca, Dovato)* • RALTEGRAVIR *(Isentress)*	• ELVITEGRAVIR/ COBICISTAT *(Stribild, Genvoya)*	• DORAVIRINE *(Pifeltro, Delstrigo)* • RILPIVIRINE *(Edurant, Complera, Odefsey, Juluca)*	• EFAVIRENZ *(Sustiva, Atripla)* • ETRAVIRINE *(Intelence)* • NEVIRAPINE *(Viramune)*	Boosted with ritonavir (Norvir) or cobicistat • ATAZANAVIR *(Reyataz, Evotaz)* • DARUNAVIR *(Prezista, Prezcobix, Symtuza)* • LOPINAVIR *(Kaletra)*
STATINS					
• Atorvastatin *(Lipitor)*		Potential for ↑ statin		Potential for ↓ statin	Potential for ↑ statin. Use lowest statin dose possible (maximum 20 mg atorvastatin daily).
• Rosuvastatin *(Crestor)*		Potential for ↑ statin			Potential for ↑ statin. Use lowest statin dose possible (maximum 10 mg rosuvastatin daily).
• Pitavastatin *(Livalo)*					
• Pravastatin *(Pravachol)*		Potential for ↑ statin			Potential for ↑ statin
• Lovastatin *(Mevacor)*, simvastatin *(Zocor)*		Potential for ↑ statin and toxicity		Potential for ↓ statin	Potential for ↑ statin and toxicity

The more CYP3A4 dependent statins pose a greater risk for accumulation and myopathy when co-administered with a cobicistat or ritonavir boosted HIV regimen. Note dosing limits for atorvastatin and rosuvastatin; Avoid simvastatin and lovastatin.

https://hivclinic.ca/drug-information/drug-interaction-tables/

CORTICOSTEROIDS:
INHALED, INTRANASAL, INJECTABLE, ORAL

HIV AGENTS

	INSTIs		NNRTIs		PIs
	• BICTEGRAVIR *(Biktarvy)* • DOLUTEGRAVIR *(Tivicay, Triumeq, Juluca)* • RALTEGRAVIR *(Isentress)*	• ELVITEGRAVIR/ COBICISTAT *(Stribild, Genvoya)*	• DORAVIRINE *(Pifeltro, Delstrigo)* • RILPIVIRINE *(Edurant, Complera, Odefsey, Juluca)*	• EFAVIRENZ *(Sustiva, Atripla)* • ETRAVIRINE *(Intelence)* • NEVIRAPINE *(Viramune)*	Boosted with ritonavir (Norvir) or cobicistat • ATAZANAVIR *(Reyataz, Evotaz)* • DARUNAVIR *(Prezista, Prezcobix, Symtuza)* • LOPINAVIR *(Kaletra)*
INTRANASAL OR ORAL INHALATION					
• Beclomethasone *(Qvar, Beconase)*					
• Budesonide *(Pulmicort, Symbicort, Rhinocort)* • Ciclesonide *(Alvesco)* • Mometasone *(Asmanex, Zenhale, Nasonex)*		Potential ↑ systemic corticosteroid and risk of Cushing's syndrome and adrenal failure.			Potential ↑ systemic corticosteroid and risk of Cushing's syndrome and adrenal failure.
• Fluticasone *(Flovent, Advair, Flonase, Avamys)*		Potential ↑ systemic corticosteroid and risk of Cushing's syndrome and adrenal failure. Avoid combination.			Potential ↑ systemic corticosteroid and risk of Cushing's syndrome and adrenal failure. Avoid combination.

FYI: Liverpool HIV DDI recommends avoiding budesonide and mometasone and to use caution with ciclesonide

Oral Inhaled or Nasal Steroids: CYP3A inhibition by ritonavir or cobicistat boosted HIV regimens ↑ steroid AUC and ↑ risk for adrenal suppression and cushing syndrome. Beclomethasone recommended alternative for oral inhalation or nasal administration.

https://hivclinic.ca/drug-information/drug-interaction-tables/

CORTICOSTEROIDS:
INHALED, INTRANASAL, INJECTABLE, ORAL

HIV AGENTS

	INSTIs		NNRTIs		PIs
	• BICTEGRAVIR *(Biktarvy)* • DOLUTEGRAVIR *(Tivicay, Triumeq, Juluca)* • RALTEGRAVIR *(Isentress)*	• ELVITEGRAVIR/ COBICISTAT *(Stribild, Genvoya)*	• DORAVIRINE *(Pifeltro, Delstrigo)* • RILPIVIRINE *(Edurant, Complera, Odefsey, Juluca)*	• EFAVIRENZ *(Sustiva, Atripla)* • ETRAVIRINE *(Intelence)* • NEVIRAPINE *(Viramune)*	Boosted with ritonavir (Norvir) or cobicistat • ATAZANAVIR *(Reyataz, Evotaz)* • DARUNAVIR *(Prezista, Prezcobix, Symtuza)* • LOPINAVIR *(Kaletra)*
INJECTABLE					
• Triamcinolone		Potential ↑ systemic corticosteroid and risk of Cushing's syndrome and adrenal failure.			Potential ↑ systemic corticosteroid and risk of Cushing's syndrome and adrenal failure.
ORAL					
• Dexamethasone	Potential for ↓ bictegravir with chronic dexamethasone; intermittent dexamethasone is OK Dolutegravir, raltegravir	Potential for ↑ dexamethasone and ↓ INSTI with chronic dexamethasone; intermittent dexamethasone is OK	Potential for ↓ NNRTI with chronic dexamethasone; intermittent dexamethasone is OK More than single dose of dexamethasone is contraindicated with rilpivirine	Potential for ↓ dexamethasone and ↓ NNRTI with chronic dexamethasone; intermittent dexamethasone is OK	Potential for ↑ dexamethasone and ↓ PI with chronic dexamethasone; intermittent dexamethasone is OK

Injectable triamcinolone also boosted by cobicistat or ritonavir

Dexamethasone interactions are more complex. Cobicistat and ritonavir boosted HIV regimens increase dexamethasone AUC by CYP3A4 inhibition; Dexamethasone also induces CYP3A4 when used chronically, lowering the AUC of multiple CYP3A4 substrates.

https://hivclinic.ca/drug-information/drug-interaction-tables/

HORMONAL AGENTS:
CONTRACEPTIVES AND HORMONE REPLACEMENT THERAPY

Oral contraceptives and hormone replacement therapy: check Liverpool and other references carefully with any cobicistat or ritonavir boosted HIV regimen. Especially difficult to predict with ritonavir.

	INSTIs		NNRTIs		PIs
HIV AGENTS	• BICTEGRAVIR *(Biktarvy)* • DOLUTEGRAVIR *(Tivicay, Triumeq, Juluca)* • RALTEGRAVIR *(Isentress)*	• ELVITEGRAVIR/ COBICISTAT *(Stribild, Genvoya)*	• DORAVIRINE *(Pifeltro, Delstrigo)* • RILPIVIRINE *(Edurant, Complera, Odefsey, Juluca)*	• EFAVIRENZ *(Sustiva, Atripla)* • ETRAVIRINE *(Intelence)* • NEVIRAPINE *(Viramune)*	Boosted with ritonavir (Norvir) or cobicistat • ATAZANAVIR *(Reyataz, Evotaz)* • DARUNAVIR *(Prezista, Prezcobix, Symtuza)* • LOPINAVIR *(Kaletra)*
CONTRACEPTIVES					
• Combined oral contraceptives • Transdermal contraceptives • Plan B • Nuva-Ring		Potential for ↓ ethinyl estradiol and ↑ progestin (combined oral, transdermal, vaginal ring)		Potential for ↓ ethinyl estradiol and ↓ progestin (combined oral, transdermal, vaginal ring)	Atazanavir/ritonavir: Use OC with <u>minimum</u> 30 mcg ethinyl estradiol Darunavir, lopinavir/r: potential for ↓ ethinyl estradiol and ↑/↓ norethindrone
• DMPA *(Depo-Provera)*					
HORMONE REPLACEMENT THERAPY					
• Estrogens, 17-beta estradiol, conjugated estrogens		Potential for ↑ estradiol		Potential for ↓ estradiol	Cobicistat-boosted PIs: potential for ↑ estradiol Ritonavir-boosted PIs: potential for ↓ estradiol
• Progestins, medroxy-progesterone		Potential for ↑ progestin		Potential for ↓ progestin	Potential for ↑ progestin, especially with cobicistat

https://hivclinic.ca/drug-information/drug-interaction-tables/

HIV & HCV Drug Interaction Resources

Liverpool Hep Drug Interactions: https://www.hep-druginteractions.org/checker

Liverpool HIV Drug Interactions: https://www.hiv-druginteractions.org/checker

*Clinical Pharmacology: https://www.clinicalkey.com/pharmacology/login

*Lexicomp/Facts & Comparisons: https://www.wolterskluwer.com/en/solutions/lexicomp/login-create-account

*Micromedex: https://www.micromedexsolutions.com/home/dispatch

Credible Meds [QT Prolongation]: https://crediblemeds.org/

Immunodeficiency Clinic-Drug Interaction Tables: https://hivclinic.ca/drug-information/drug-interaction-tables/

NE/Caribbean AETC- HIV and HCV Drug Interactions-Quick Guide for Clinicians: https://aidsetc.org/resource/hiv-and-hcv-drug-interactions-quick-guides-clinicians

*Requires subscription/fee

HIV & HCV Drug Interactions

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AK ID ECHO DIDACTIC TOPICS FOR 2022

- June 14: Common drug interactions part 2: now adding COVID Tx meds into the mix
- Upcoming topics
  - Public health reporting – requirements/laws
  - Hepatitis B screening and lab interpretation
  - STI EPI Update to include HIV, C, G, w/ treatment update pearls
  - HCV Reinfection vs Treatment Failure

What topics would you like to learn about?

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

HCV SIMPLIFIED TREATMENT TRAINING

Receive the most current updates in patient care for screening and treatment of HCV.

This training will cover topics of HCV EPI, screening, confirmation of HCV, assessment of patient before treatment, HCV treatment, medication coverage, follow up and harm reduction.

- Presented by: Brian McMahon, MD, Leah Besh, PA-C, Lisa Townshend-Bulson, APRN, FNP-C and Annette Hewitt, APRN, FNP-C
- Continuing education credits will be available and the live training will be recorded and available for enduring access credits.
- To register, https://echo.zoom.us/meeting/register/tZIqdeqrrjMuG9N3Git-BRF30DBPBP1A9qiC
- *Contact Marla at mjwehrli@anthc.org*

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

ADDITIONAL LEARNING OPPORTUNITIES

ANTHC Liver Disease ECHO

- Third Thursday of every month from 12:00-1:00 PM AKST
- May 19: Hepatitis B and Other Vaccine Updates

anthc.org/project-echo/alaska-liver-disease-echo

ANTHC LiverConnect

- Second Tuesday of every month 8:00-9:00 AM AKST
- June 14: Workup of Alkaline Phosphatase Elevations with Case Slides Included

anthc.org/what-we-do/clinical-and-research-services/hep/liverconnect

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

ADDITIONAL LEARNING OPPORTUNITIES

Addiction Medicine ECHO

- Second and fourth Thursday of every month from 12:00-1:oo PM
- May 12: Screening Tools

anthc.org/project-echo/addiction-medicine-echo

Indian Country ECHO Programs

- Harm Reduction, Infectious Disease, and more!
  www.indiancountryecho.org/teleecho-programs
- Ending the Epidemics Training Program: 4-part series in May, the second Tuesday each week from 10:30 a.m. – 12:00 p.m.

  Register: https://www.surveymonkey.com/r/EndingtheEpidemicsinIndianCountry

  Questions: jrienstra@npaihb.org

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ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

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NPAIHB
Indian Leadership for Indian Health

Thank you!

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