Initial Treatment of the Hepatitis C Virus-Infected Patient: Key Populations

Learning Objectives

After attending this presentation, learners will be able to:

- Describe special considerations for HCV treatment for people living with HIV
- Describe special considerations for HCV treatment for people with recent history of drug use

CASE 3 – HIV/HCV coinfection

29 y.o. Hispanic M with HIV, HCV Geno 3, F2 by Fibrosure (and nl liver labs)

HCV Hx:
- Acquired 3 yrs ago, only RF unprotected sex with 2 partners
- Treatment naïve
- F2 by Fibrosure

HIV Hx: Diagnosed 8 yrs ago, CD4 475
HIV RNA not detected on TDF/FTC/EFV
Other PMH:
- Recent LGV infection
- HBV sAg- cAb+ sAb-, HBV DNA negative

ARS Question #8: You check his formulary and his insurance covers GLE/PIB x 8 wks. You need to make an adjustment for which of the following reasons?

1. 8 weeks is not appropriate for patients with HIV
2. He needs TDF switched to TAF
3. GLE/PIB should not be administered with EFV
4. GLE/PIB does not cover Genotype 3 well

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Treatment Recommendations for Patients With HIV/HCV Coinfection

RECOMMENDED	RATING
HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications (see *Initial Treatment of HCV Infection* and *Retreatment of Persons in Whom Prior Therapy Has Failed*).	I, B
Daily daclatasvir (refer to information above for dose) plus sofosbuvir (400 mg), with or without ribavirin, is a recommended regimen when antiretroviral regimen changes cannot be made to accommodate alternative HCV direct-acting antivirals. Refer to *Initial Treatment of HCV Infection* and *Retreatment of Persons in Whom Prior Therapy Has Failed* sections for treatment duration.	I, B

Regimens Not Recommended for Patients With HIV/HCV Coinfection

NOT RECOMMENDED	RATING
Ledipasvir/sofosbuvir for 8 weeks is not recommended, regardless of baseline HCV RNA level.	IIb, C

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G3 INITIAL TREAMENT RECOMMENDED REGIMENS

IDSA/AASLD/IAS-USA
www.hcvguidelines.org

NO CIRRHOSIS:
- Glecaprevir/pibrentasvir x 8 w
- Sofosbuvir/velpatasvir x 12 w

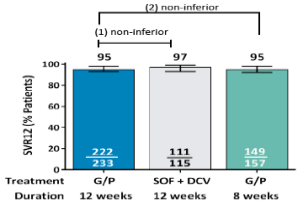
CIRRHOSIS:
- Glecaprevir/pibrentasvir x 12 w
- Sofosbuvir/velpatasvir x 12 w*

*RAV testing for Y93H and add RBV if present or consider sofosbuvir/velpatasvir/voxilaprevir

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Glecaprevir/pibrentasvir in GT3 Treatment-naïve without Cirrhosis

- Non-inferiority
  - 12W vs DAC/SOF X12W
  - 12W vs 8W
- Viral Failure 3% G/P
  - 4 in 12W (3 relapse, 1 VBT)
  - 1 in DAC/SOF
  - 6 in 8W (5 relapse, 1 VBT)
- BL Y93H: 5/5 SVR
- BL dual NS3/NS5A
  - 71-86% SVR
- Tx emergent RAS
  - 50% failures with A30K BL
  - A30K+Y93 (69-fold R

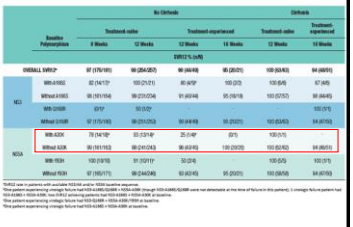


SURVEYOR-II – G3 with Cirrhosis
48 patients received G/P +/- RBV x 12 w = 100% SVR

Foster et al. EASL 2017

Glecaprevir/pibrentasvir in GT3 Treatment-naïve without Cirrhosis – A30K effect?

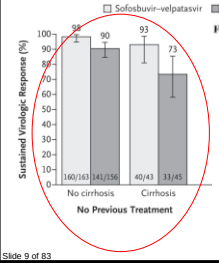
- Non-inferiority
  - 12W vs DAC/SOF X12W
  - 12W vs 8W
- Viral Failure 3% G/P
  - 4 in 12W (3 relapse, 1 VBT)
  - 1 in DAC/SOF
  - 6 in 8W (5 relapse, 1 VBT)
- Tx emergent RAS
  - 50% failures with A30K BL
    - 6% patients overall had a BL A30K

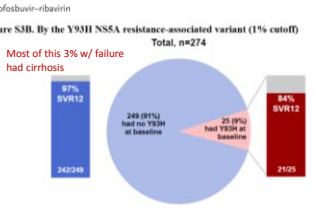


SURVEYOR-II – G3 with Cirrhosis
48 patients received G/P +/- RBV x 12 w = 100% SVR

Foster et al. EASL 2017 Krishnan et al. EASL 2017

Sofosbuvir/velpatasvir x 12 wks for G3 (ASTRAL-2)

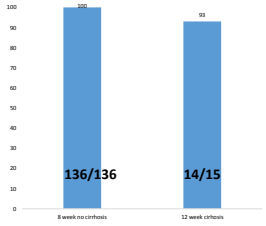




Foster, NEJM, 2015, hcvguidelines.org

Glecaprevir/pibrentasvir: HIV

- GT 1-6
- Primarily an 8 week study
- 12 weeks in 16 patients with cirrhosis
- TN or TE (19%) with IFN, P/R or SOF+P/R
- VBT on treatment – GT3 with cirrhosis



Rockstroh et al. EASL 2017

Drug Interactions Between DAAs and ARV Drugs—Recommended Regimens

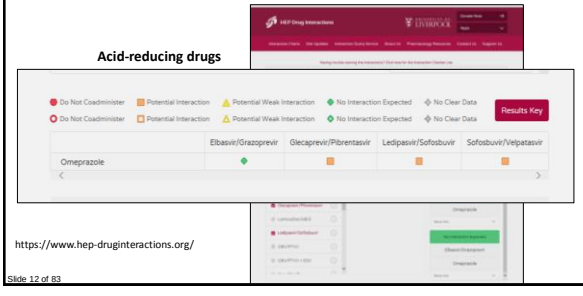
Green indicates coadministration is safe; yellow indicates dose change or additional monitoring is warranted; pink indicates combination should be avoided.

	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 (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*	▲ VEL ▲ COB*	▲ ELB ▲ GRZ ▲ COB	▲ GLE ▲ PIB ▲ COB	▲ VOX ▲ COB*
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.

Drug-Drug Interactions with DAAS

Acid-reducing drugs



https://www.hep-druginteractions.org/

Guidelines Recommendation about use of LDV or VEL with TDF

SOF/LDV + TDF

CrCl < 60 mL/min: AVOID

CrCl > 60: MONITOR

SOF/VEL + TDF

CrCl < 60 mL/min: AVOID

CrCl > 60: MONITOR

SOF/LDV + TDF + cobi- or ritonavir-boosted PI

Any CrCl: AVOID if possible, Consider TAF

SOF/VEL + TDF + cobi- or ritonavir-boosted PI

CrCl < 60 mL/min: AVOID

CrCl > 60: MONITOR or consider TAF

- **For combinations expected to increase tenofovir levels, baseline and ongoing assessment for tenofovir nephrotoxicity is recommended.**
  Rating: Class IIa, Level C

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CASE 3 – HIV/HCV coinfection (Cont)

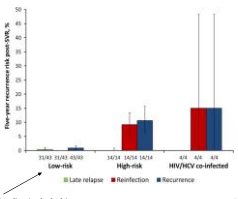
His ARVS are changed to TAF/FTC/BIC and he is tolerating well. He receives 8 weeks of GLE/PIB and achieves SVR12.

ARS Question #9: True or False: His risk of HCV reinfection is extremely low. No further follow up testing is recommended.

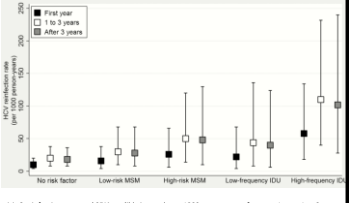
1. True
2. False

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Re-infection Rates After Treatment by Risk Group



Studies included in meta-analysis



- Hepatitis C reinfection rates and 95% credible intervals per 1000 person-years for up to 1 year, 1 to 3 years, and more than 3 years after a sustained virologic response (Canadian Co-infection Cohort, n = 257). Reference patients are those with no risk factors. Abbreviations: HCV, hepatitis C virus; IDU, injection drug use; MSM, men who have sex with men.

Clin Infect Dis. 2016;62(6):683–94

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Initial Treatment Algorithm

Algorithm

- HCV genotype/subtype & resistance
- HIV status
- Cirrhosis - yes/no - duration
  - If yes, decompensated? (e.g., ascites, encephalopathy, etc)
    - If yes, **don't use PIs**!
- Renal function
  - Avoid Sof if CrCl <30
- Medications
  - Address drug interactions
  - Ribavirin is a teratogen
- On treatment/Follow up

Our case patient

- 3, resistance testing recommended if cirrhosis and epclusa
- HIV – check drug drug interactions (efavirenz)
- Cirrhosis – no
  - 8 wk regimens
- CrCl nl, SOF ok
- Medications: efavirenz – not recommended with SOF/VEL or GLE/PIB
- need to monitor for HCV reinfection

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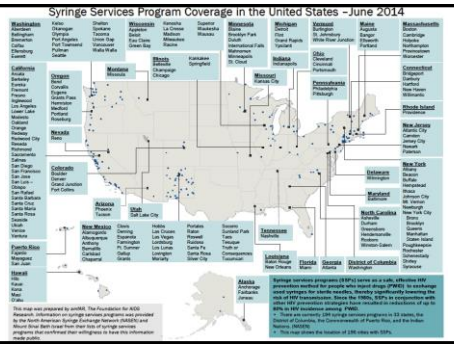
CASE 4 – HCV in PWID

19 Caucasian W recently admitted for skin and soft tissue infection. Noted to have track marks by a medical resident who sees her in ED. She confides that she has recently started injecting heroin after it became too expensive to acquire oxycodone. She has one partner who injects her. Her family is unaware of her drug addiction. She is discharged from ED with antibiotics and while she declines substance abuse treatment referral, she takes information about a harm reduction center.

PMH:
Depression –suicide attempt age, 17

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Syringe Services Program Coverage in the United States -June 2014



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CASE 4 – cont

She is seen in urgent care for a skin and soft tissue infection. She also reports some malaise. The provider asks about sharing needles and she reports that she has not. (She is injecting in a group setting and had learned it was safest to be the first one to use a syringe but does not think to mention she shared other things).

Labs reveal:
HIV 4th gen test - neg
HBV sAb+ sAg-
HCV Ab positive
AST 250
ALT 320
Bili 1.2

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CASE 4 – cont

The urgent care doctor calls her and urges her to see a primary doctor for further HCV RNA testing.

She feels fine and decides she will take care of it the next time she needs to see a doctor. She also knows someone who tried to get treated but insurance did not cover it.

But this news does prompt her to go with a friend to the harm reduction program.

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Harm Reduction Kit

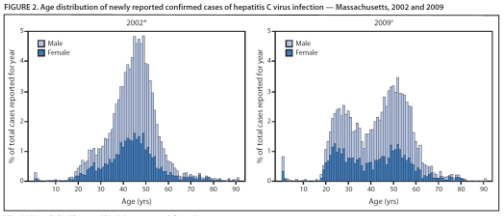


1. **Clean Bottle** for mixing water and bleach.
2. **Bleach** to disinfect used syringes when a clean one isn't available.
3. **Bandages** to help avoid infection after injecting.
4. **Sterile water** to mix the drug with.
5. **Tourniquet** to "tie off" above the injection site.
6. **Bottle cap** for mixing water with the drug before it's drawn up into the syringe (commonly called "cooker").
7. **Cotton balls** to trap dirt and debris as the drug, mixed in water, is pulled into the syringe.
8. **Syringes** don't come inside the kit but are provided at distribution sites.
9. **Step-by-step injection instructions**
10. **Alcohol swabs** to clean the injection site before insertion.

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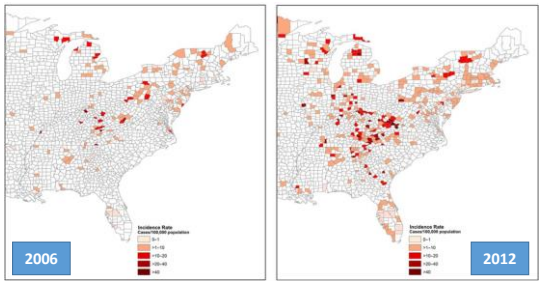
Increased injection drug use has shifted HCV demographics

FIGURE 2. Age distribution of newly reported confirmed cases of hepatitis C virus infection — Massachusetts, 2002 and 2009



* N = 6,281; excludes 35 cases with missing age or sex information.
† N = 3,904; excludes 346 cases with missing age or sex information.

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Clin Infect Dis. 2014;59(10):1411-1419.

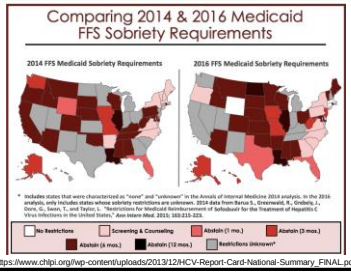
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- Estimated anti-hepatitis C virus prevalence among people who inject drugs by country
  - *The Lancet Global Health* 2017 5, e1192-e1207DOI

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Restrictions often specifically exclude PWID



https://www.chlpi.org/wp-content/uploads/2013/12/HCV-Report-Card-National-Summary_FINAL.pdf

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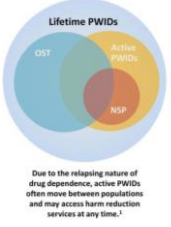
ARS Question #10: All PWID should be denied HCV treatment because…

A. No treatment data with DAAs
B. Reinfection rates are too high
C. They have low fibrosis levels so does not benefit them
D. None of the above

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What is the definition of 'PWID' (people who inject drugs?

- 'PWID' is a subjective term to any person who has ever injected drugs. (once regularly, occasionally, remotely)
- PWID populations
  - "active" or "recent" PWID – injected drugs within 1 month to 1 year (definition varies)
  - "former" PWID – ceased injecting drugs



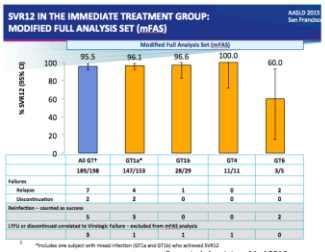
Due to the relapsing nature of drug dependence, active PWIDs often move between populations and may access harm reduction services at any time.[1]

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C-EDGE COSTAR – Clinical Trial of patients receiving opiate agonist therapy

Treatment naive PWID on opiate agonist therapy for 3 months, keeping 80% of appointments

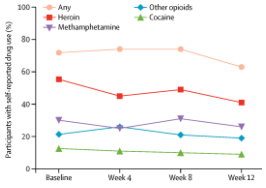
Treated with EBV/GRZ



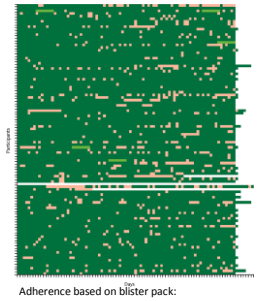
Dore et al. Ann Intern Med 2016

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Sof/vel for HCV infection in recent PWID (SIMPLIFY) SVR12 = 97/103 (94%)



Lancet Gastroenterol Hepatol 2018; 3: 153–61



Adherence based on blister pack: Median adherence 94%

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DAA treatment for hepatitis C among people who use or inject drugs: a systematic review and meta-analysis

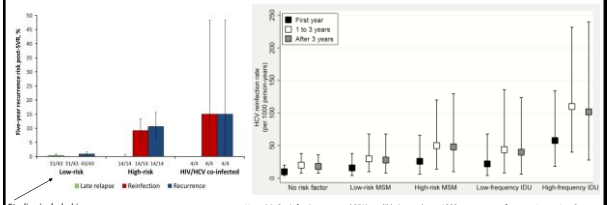
	Number of studies or substudies	Number of participants	Treatment completion (95% CI)	P	ITT SVR (95% CI)	P	mITT SVR (95% CI)	P	Loss to follow-up (95% CI)	P
Exclusive study population/subpopulation										
Recent IDU, with or without OST	8	670	96·9% (95·6–98·2)	0·0%	87·4% (82·0–92·8)	80·8%	91·7% (87·9–95·4)	66·1%	2·8% (0·5–5·7)	74·8%
OST, with or without recent IDU/non-IDU	25	2331	97·5% (96·5–98·5)	49·9%	92·6% (90·2–94·9)	79·5%	95·3% (93·6–97·0)	72·5%	3·0% (1·7–4·3)	65·5%
Other	10	633	96·5% (94·5–98·5)	45·7%	86·7% (80·2–93·2)	87·0%	93·8% (90·3–97·2)	76·3%	7·3% (2·6–11·9)	88·1%
Study design										
Observational	28	2483	96·9% (95·9–98·0)	51·6%	88·8% (85·8–91·9)	82·1%	93·4% (91·3–95·5)	80·2%	4·6% (2·9–6·3)	84·1%
Clinical trial	10	1151	98·2% (97·4–99·0)	0·0%	93·9% (92·5–95·3)	7·2%	96·2% (94·6–97·8)	52·4%	2·5% (1·2–3·8)	53·1%

IDU=injecting drug use. ITT=intention to treat. mITT=modified intention to treat. non-IDU=non-injecting drug use. OST=opioid substitution therapy. SVR=sustained virological response.

Table 3: Pooled estimates of treatment completion, SVR and loss to follow-up, by study population and study design

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Additional Treatment Considerations: Re-infection

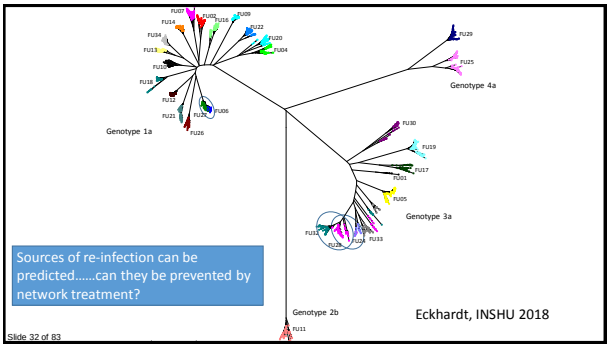


Studies included in meta-analysis

- Hepatitis C reinfection rates and 95% credible intervals per 1000 person-years for up to 1 year, 1 to 3 years, and more than 3 years after a sustained virologic response (Canadian Co-infection Cohort, n = 257). Reference patients are those with no risk factors. Abbreviations: HCV, hepatitis C virus; IDU, injection drug use; MSM, men who have sex with men.

Clin Infect Dis. 2016;62(6):683–94

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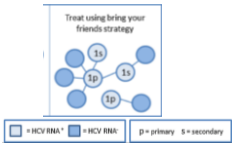


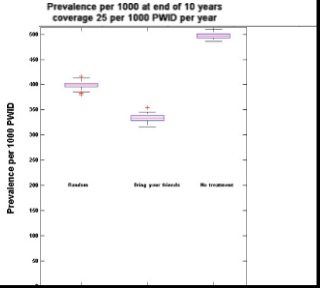
Sources of re-infection can be predicted……can they be prevented by network treatment?

Eckhardt, INSHU 2018

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Modeling studies of Network Treatment





Int J Drug Policy. 2015;26(10):958–62.

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HCV treatments are compatible with opioids and medication-assisted therapies

Opioid / Opioid Substitutes	LDV/SOF	SOF/VEL	PrOD	GZR/EBR	GP	SOF/VEL/ VOX
Hydromorphone	√	√	Monitor*	√	√	√
Fentanyl	√	√	Monitor*	√	Monitor*	√
Hydrocodone	√	√	Monitor*	√	Monitor*	√
Morphine	√	√	Monitor*	√	√	√
Oxycodone	Monitor*	√	Monitor*	Monitor*	Monitor*	√
Codeine	√	√	√	√	√	√
Methadone	√	√	√	√	√	√
Buprenorphine	Monitor*	√	Monitor*	√	√	√

www.hep-druginteractions.org

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HCV treatments are compatible with other drugs of abuse

	LDV/SOF	SOF/VEL	PrOD	GZR/EBR	GP	SOF/VEL/ VOX
Cannabis	√	√	√	√	√	√
Cocaine	√	√	Monitor*	√	√	√
Diamorphine	√	√	Monitor*	√	√	√
Gamma-hydroxybutyrate	√	√	Monitor*	√	Monitor*	√
Ketamine	√	√	Monitor*	√	√	√
MDMA (Ecstasy)	√	√	Monitor*	√	√	√
Methamphetamines	√	√	Monitor*	√	√	√
Phencyclidine	√	√	Use lowest dose	√	√	√

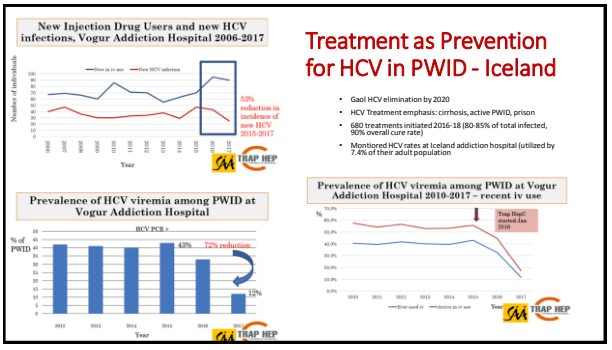
Slide courtesy of David Back (with modification), University of Liverpool, www.hep-druginteractions.org

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Models of Treatment Delivery for PWID

- The shift from INF-based therapy to DAA has allowed for increased decentralization of care
- Treatment environments that can provide multi-disciplinary services around addiction, social support, mental health, and re-infection prevention will be essential
- Examples of models being evaluated include:
  - integrated primary care facilities
  - methadone clinics
  - prison

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CONCLUSIONS CASE 4

- DAA therapy is **safe and effective** among PWID
- HCV **reinfection will occur** when treating HCV in PWID
- Testing, diagnosis, and **linkage to care** remain a significant barrier that must be addressed
- **Simplification of models** of care will be essential to achieve HCV elimination in PWID

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Resources

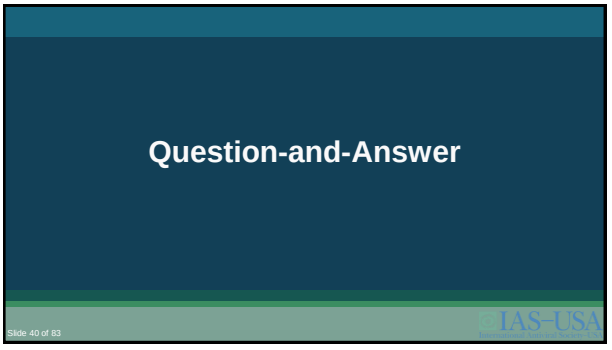
- HCVguidelines.org
- nynjaetc.org
- http://www.hep-druginteractions.org

THANK YOU

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Question-and-Answer
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