

Approach to HCV in people living with HIV

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No disclosures or support

Goals

- Discuss the epidemiology of HCV in the US and South Africa
- Describe the initial evaluation of the patient with HCV and HIV
- Provide a strategy for the management of HCV in persons with HIV

HCV epidemiology

In US, ~70,000 cases/yr and 0.9% of adults have chronic HCV

- Majority in US are associated with prior IVDU
- HCV prevalence had been highest in those born 1945-65

Then in the early 2000s in US, acute HCV rates rose

- Fastest growing 20-40 yrs old leading to bimodal epidemic

In 2020, CDC recommended universal HCV screening

- Screening = HCV Ab test, and if (+), followed by HCV RNA

Case

- 34 yo HIV + M with CD4 656; VL UD on DTG + FTC/TAF
- HCV diagnosed 2021 (IVDU), initial genotype unk.
 - HCV tx'ed in prison in 2022 w/ direct acting antivirals (DAAs)
 - In 2023 & 2024, HCV RNA <15 IU/ml (SVR) and normal LFTs
- Today in jail clinic reports relapse to fentanyl prior to reincarceration
 - Exam – no evidence liver disease, no rash
 - AST 69, ALT 64. PLT 245K, HIV VL <20, HBsAg (-)
 - Meds: buprenorphine, ART

Mild to moderate LFT abnormalities in HIV

Common causes of mild/moderately elevated AST/ALT (~40-200 U/L) in HIV

1. Chronic viral hepatitis (HBV, HCV)
 - ✓ Test for viral hepatitis (if history of prior HCV, test for HCV RNA VL)
2. Metabolic dysfunction-assoc. steatohepatitis (MASH, prev. NASH)
 - ✓ For elevated BMI or recent weight gain, clue ALT:AST >1, obtain US
3. Alcohol use related hepatotoxicity
 - ✓ Alcohol use history, clue AST:ALT >2:1
4. Drug toxicity (e.g. isoniazid, pyrazinamide, fluconazole, PIs)
 - ✓ Review meds focus on new drugs, note Hy's law (↑ bilirubin, ↑ poor outcomes)
5. Other conditions commonly involving liver in HIV (TB, 2° syphilis, HCC)
 - ✓ Consider evaluation for TB, syphilis & HCC (imaging of liver +/- diagnostic tests)

Question

In addition to other labs and evaluation, what is the preferred next test for HCV in this patient?

1. Hepatitis C antibody
2. Hepatitis C quantitative RNA
3. Hepatitis C resistance testing
4. Liver biopsy

- 34 yo man with HIV and previously successfully treated HCV with HIV RNA UD on ART
- Relapsed to IV fentanyl before re-entering jail
- Presents with abnormal AST and ALT

Case

- HCV RNA 350,000 IU/ml

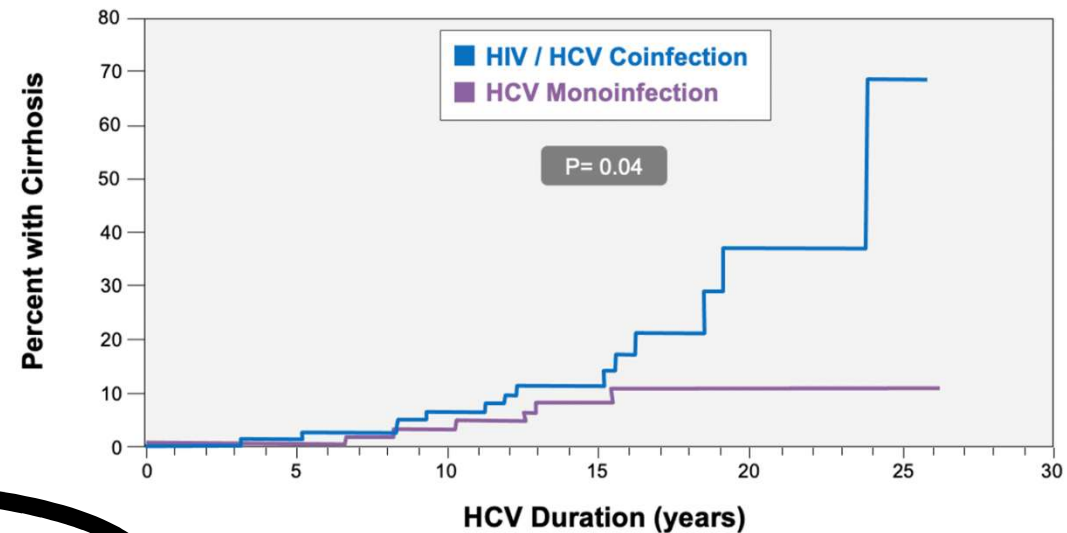
Microbiology and natural history

- HCV is a single-stranded RNA virus that does not integrate into host DNA
 - It relies on ongoing replication so cure possible with sustained suppression of replication w/ DAAs
- Substantial diversity: 6 major genotypes and >80 subtypes
- No protective immunity is generated after infection, despite a positive HCV Ab test



Microbiology and natural history

- After transmission, most go on to chronic HCV but not all develop cirrhosis & complications
- There's a markedly incr. risk of cirrhosis and accelerated timeline in HCV/HIV
- Once cirrhosis present, risk/year of:
 - Decomp. cirrhosis – 4%
 - Hepatocellular carcinoma - 2%




Morgan et al Ann Int Med 2013.
Poynard et al. Gastroenterology 2002
National HIV Curriculum 2025

Key risk factors

- History of IV drug use at any time
 - Infection risk highest in first 6 months of IDU
- Invasive medical procedures and unsafe injections
 - Worldwide has been major route: e.g. Egyptian epidemic
- Sexual transmission is related to certain practices
 - Sex with mucosa tears linked (e.g. receptive anal sex)
- Birth to a mother with HCV
 - Risk of transmission to infant 5-15% with HIV incr. risk



HCV epidemiology in S. Africa (I)

HCV Ab prevalence: 1%  HCV viraemia: 0.7%

- HCV in PWID: ~50%
- HCV in MSM: ~5%

WHO data


- Total HCV deaths in SA (2022): 2138
- Diagnosis coverage: 24%
- Treatment coverage: 1%



Estimated ~400,000 people in South Africa living with HCV

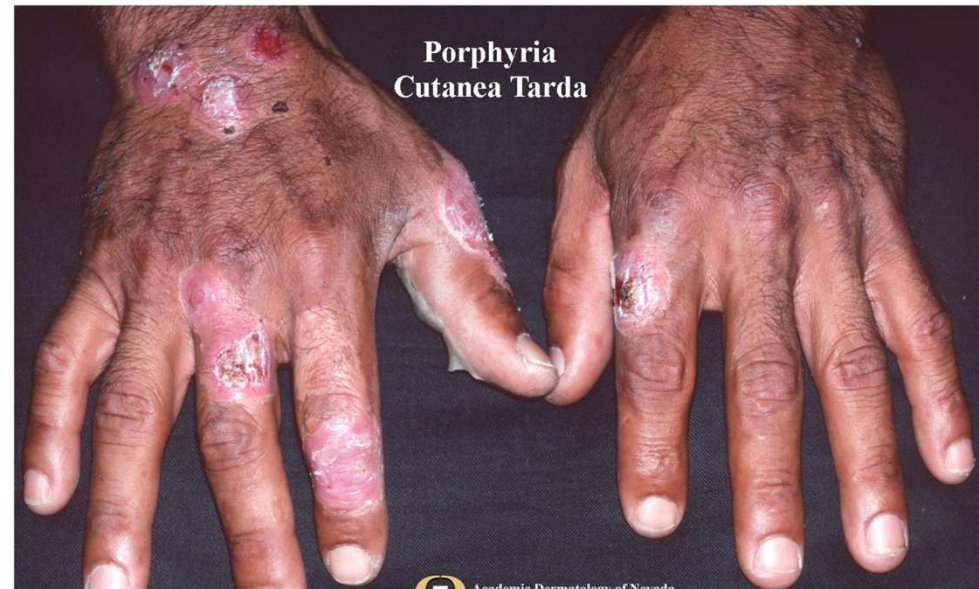
(1) Sonderup et al. The Lancet Gastroenterology – 2017 (2) WHO Global Hepatitis Report – 2024
(3) UNITAID Presentation 7C - Mohammed Majam, Ezintsha – 2025. (4) Scheibe et al BMC ID 2020

HCV rural investigation – S. Africa, 2021

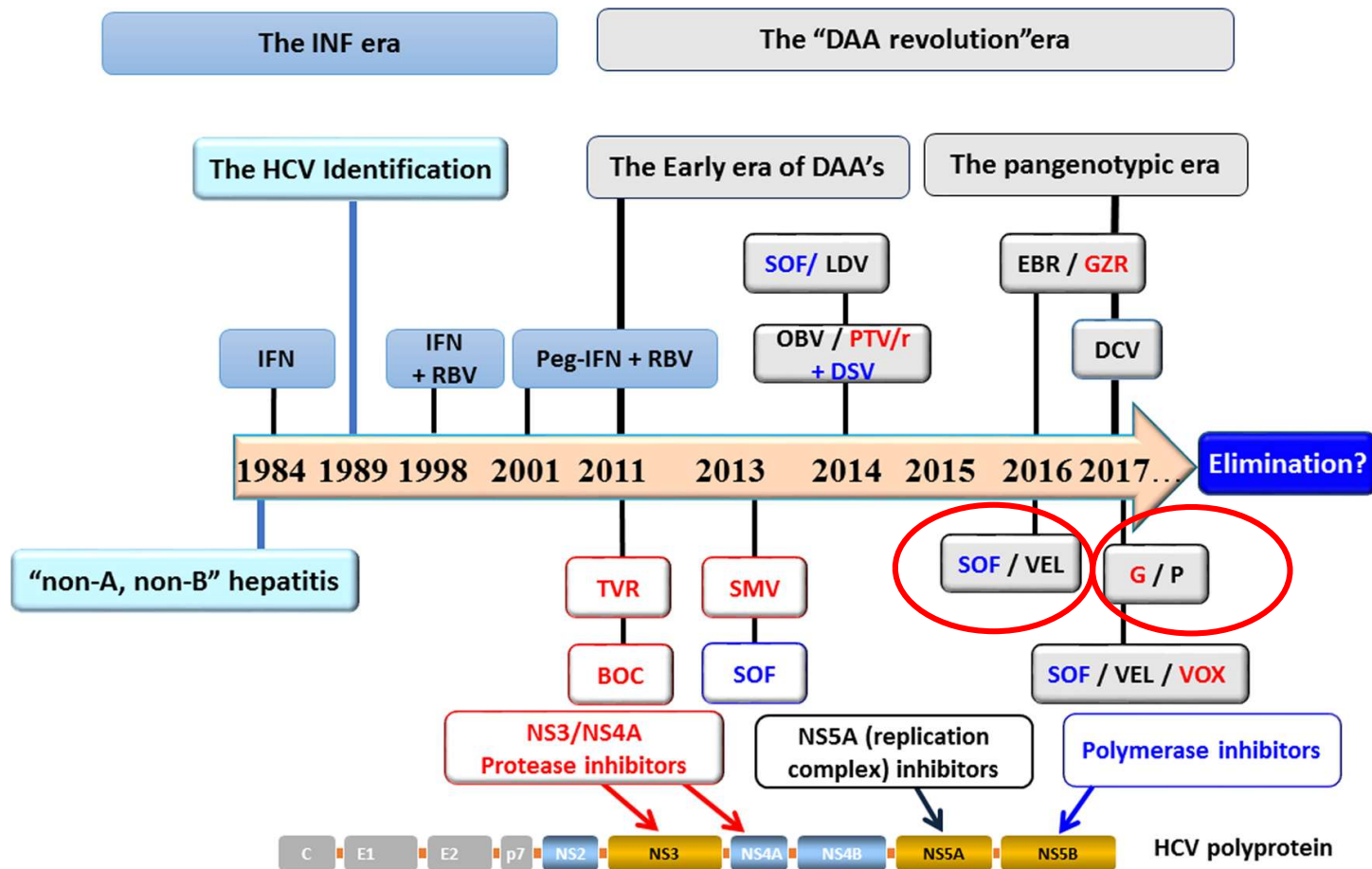
- HCV highly transmissible via needlestick: 3% transmission risk vs HIV risk 0.3% —N=21 (24% w/ HIV), ~age 64
 - Unusual number of patients with HCV reported from rural town near PE  —Med. ALT 51, AST 54
 - 42% adv. fibrosis / cirrhosis
 - 2 genetic clusters = common source events
 - 95% reported prior injections at the local clinic
- Conclusions:
- There was likely nosocomial HCV transmission at least a decade earlier
 - People with HCV in SA may not have “classic” risk factors like prior IVDU. Modest LFTs do not rule out adv. fibrosis / cirrhosis.

Clinical syndromes

- Most patients have no syndrome at the time of acute infection
 - ~20% with jaundice
- During chronic HCV most people also have no symptoms or signs
 - Majority of HCV detected via HCV screening or in evaluation of LFTs
 - Rarely extra-hepatic disease: PCT, B-cell NHL, glomerulonephritis
 - HCV incr. risk for DM2, stroke and CV disease



The HCV treatment revolution is (still) here



Pretreatment evaluation

- Assess for cirrhosis
 - Ask about prior treatment
 - History and exam typically will reveal if decompensated cirrhosis present
 - Non-invasive tests (e.g. **FIB-4** uses age, PLT, AST, ALT) to estimate likelihood of cirrhosis often sufficient
- Lab evaluation
 - CBC, liver function tests, creatinine, PT
 - HCV RNA
 - HCV genotype, if cirrhosis present or risk for a genotype/subtype with ↓ cure rate
 - HAV and HBV serologic testing / vaccination
- Review other medications, alcohol use and potential drug-drug interactions

Slide courtesy of Maria Corcorran, MD, University of Washington

FIB-4

1. Calculate FIB-4 using the ALT, AST, platelets, age (www.hepatitis.uw.edu/clinical-calculators/fib-4)
 - If FIB4 <1.45, cirrhosis is very unlikely
 - If FIB4 >3.25 cirrhosis is likely
2. If FIB-4 or history or exam suggest cirrhosis, imaging with U/S is a good next step
 - Otherwise, typically, no need to delay with U/S

Why U/S ?

- People with cirrhosis from HCV should be screened for HCC
- HCV management changes in decomp. cirrhosis (Child B,C)
 - Consider GI/liver specialty referral

Case

- 34 yo HIV + M with CD4 656; VL UD on DTG + FTC/TAF
- Today in jail clinic reports relapse to fentanyl prior to incarceration
 - Exam – no evidence liver disease.
 - AST 69, ALT 64. PLT 245K, CD4 360 and HIV VL <20 c/ml



FIB4 = 1.15

- Cirrhosis is very unlikely.

No further liver staging required

If FIB4 <1.45, cirrhosis very unlikely

If FIB4 >3.25 cirrhosis is likely

Treatment and natural history

- Successful treatment of HCV resolves inflammation, improves fibrosis and reduces mortality
 - Severity of fibrosis declines in most; in 1/2 of those with cirrhosis cured of HCV, cirrhosis resolves
 - HCC risk ↓ 70% but occasionally HCC can occur after HCV cure
 - In cirrhosis, even after cure, I obtain US every 6-12 months
 - Risk for subsequent DM, stroke, CAD also decreases

HCV treatment in people with HIV

SVR Rates with GT 1 HCV-HIV Coinfection and HCV Monoinfection

Regimen (12 weeks)	Genotype 1			
	HCV-HIV Coinfection		HCV Monoinfection	
	Study	SVR	Study	SVR
Elbasvir-Grazoprevir	C-EDGE Coinfection	95%	C-EDGE TN	95%
Glecaprevir-Pibrentasvir	EXPEDITION-2	98%	ENDURANCE-1	99%
Ledipasvir-Sofosbuvir	ION-4	96%	ION-1	99%
* Sofosbuvir-Velpatasvir	ASTRAL-5	95%	ASTRAL-1	98%

Slide courtesy of Maria Corcoran, MD, University of Washington

Sofosbuvir/velpatasvir (Epclusa)

Dose:

1 tablet daily for 12 weeks*

- Well-tolerated: adverse events uncommon; 2% discontinuation
- Not adjustment needed for ↓GFR
 - Consider monitoring Cr if CKD and on TDF
- No food requirement

* In decompensated cirrhosis, 24 weeks

Epclusa SAHPRA File, 2022

Sofosbuvir:

A pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase
(other ex. dasabuvir)

Velpatasvir:

An inhibitor targeting the HCV NS5A protein, essential for RNA replication & assembly of virions
(other ex. ledipasvir, elbasvir)

ASTRAL-5 trial of patients with HIV-HCV

Design: Single-arm open label study of sof/vel once daily for 12 weeks

Setting: 17 sites in US

Eligibility:

- Adults with HIV and HCV (G1-6), with HCV RNA >10,000 IU/ml
- HIV RNA <50 cpm and CD4 >100 on ARVs
- ARVs permitted: integrase or boosted PI-based ART + TDF, ABC, 3TC/FTC
- Compensated cirrhosis allowed, CrCl >60 ml/min
- Treatment w/ older HCV drugs allowed if no prior NS5A or NS5B inhibitor

Primary endpoint: SVR12

ASTRAL-5 trial of HIV-HCV (n=106)

Characteristics

Male sex	91 (86)
Race	
White	54 (51)
Black	48 (45)
Asian	3 (3)
Other	1 (1)
BMI, kg/m ² , mean (range)	27.2 (18.6–43.4)
Baseline HCV RNA, log ₁₀ IU/mL, mean (range)	6.3 (5.0–7.4)
ALT, U/L, mean (range)	70 (15–326)
HCV genotype	
1a	66 (62)
1b	12 (11)
2	11 (10)
3	12 (11)
4	5 (5)
Median CD4	598 cells/ul

Outcomes by genotype

Genotype	N	SVR12
1a/b	75	95%
2	11	100%
3	11	93%
4	5	100%
Overall SVR 12		95% [85-99%]
Cirrhosis	19	100%

Wyles et al. CID 2017

ASTRAL-5 trial of patients with HIV-HCV

Adverse events: Most common were fatigue (25%) and headache (13%)

Serious adverse events: 2 patients (2%)

Treatment discontinuation: 2 patients (2%)

Limitations:

- Fewer patients with Genotype 2,3 and 4 and none w/ Genotype 5,6
- Only 20% had cirrhosis

Monitoring patients with HCV during treatment

- Implementation research subsequently showed close monitoring not needed, including in HCV/HIV, during treatment w/ sof/vel
- In MINMON study :
 - Participants received entire 12 wk course
 - There was no lab monitoring
 - There was remote contact at weeks 4 and 22
- In MINMON, SVR achieved in 389 (95%) of 399



*MINMON Study did not include those w/ Childs B,C or serious adherence barriers

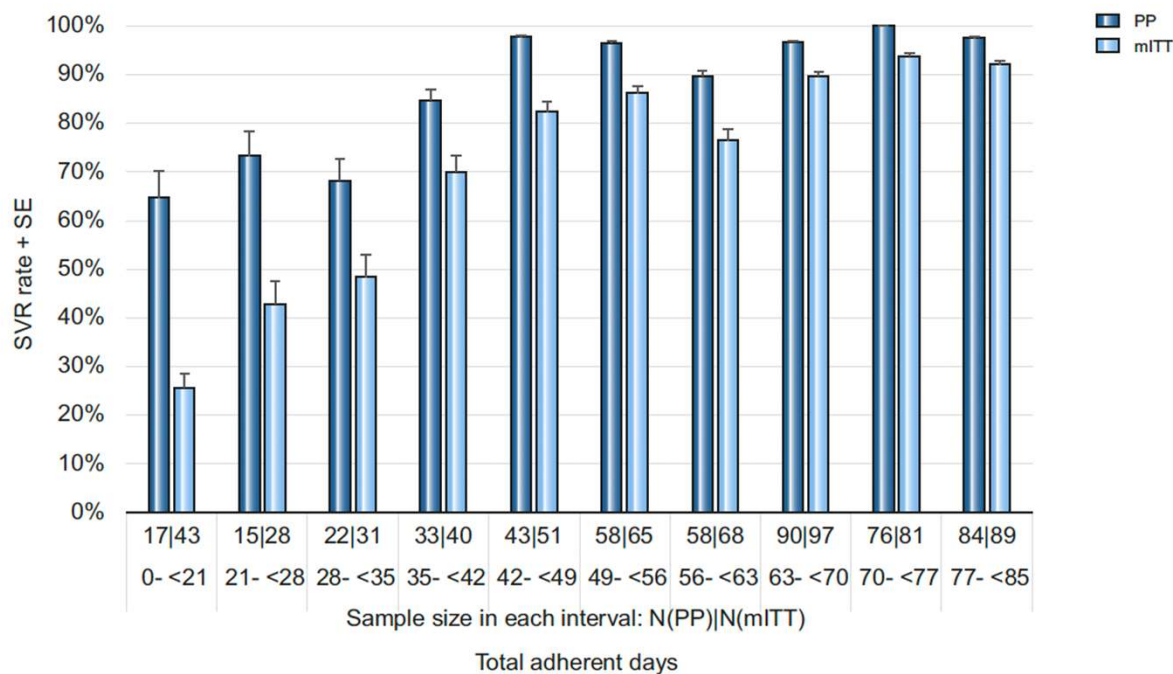
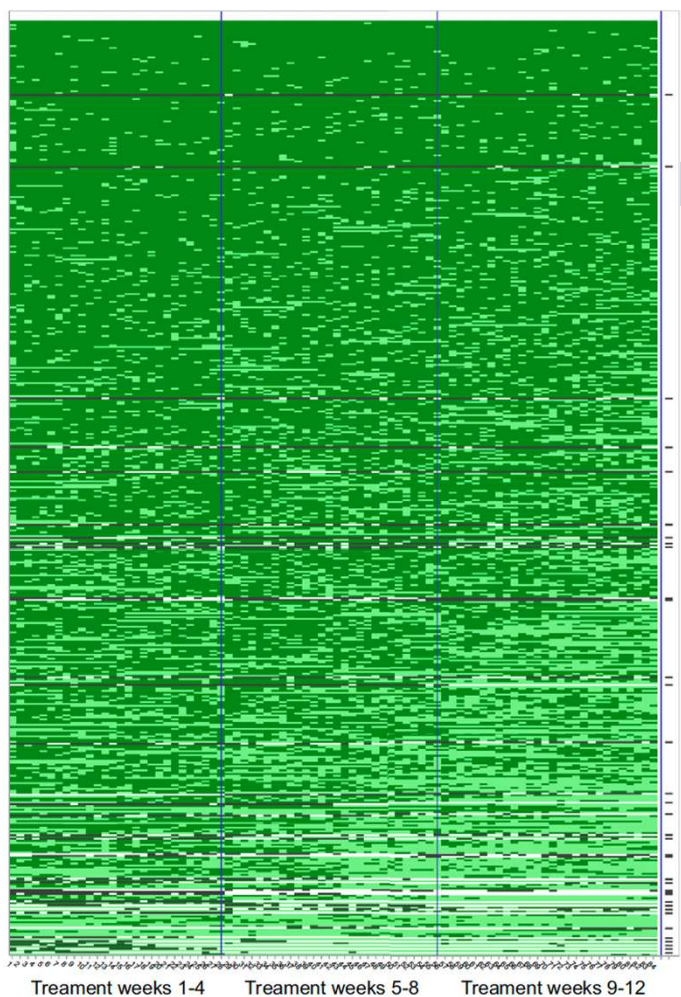
Sof/vel has a few DDIs: Typically no ART change needed

- Avoid with NNRTIs: efavirenz, nevirapine
 - Sof/vel compatible with dolutegravir-based ART (TLD) and boosted PIs
- Avoid with rifamycins, including rifampicin & rifabutin
- Avoid with acid suppression (PPIs + H2 blockers) if possible
 - It reduces velpatasvir conc. If acid suppression essential, separate the dosing

If uncertainty or patient receiving multiple medications:

✓ the Liverpool HEP Drug Interactions: [hep-druginteractions.org](https://www.hep-druginteractions.org)

Treatment outcome by adherence to sof/vel in PWID



- In the per protocol analysis (excluding those with unk. SVR status) median adherence 70% & overall SVR 93%.
- Significantly lower SVR found if discontinuation in 1st month or if >14 d of consecutive missed doses
- Perfect adherence with sof/vel not required for cure but cure rates increased at higher adherence levels

Adherence: Additional thoughts

“Imperfect” candidates for treatment can be good candidates:

- Consider HCV therapy even in patients who may be expected to have less than ideal adherence
 - Many with HCV have substance use disorders, mental illness and/or experience extreme poverty

Responding to missed doses at follow-up:

- Given robustness of sof/vel, usually best to continue rather than stop
 - For gaps ≤ 14 days - if past 1st month of treatment - restarting without \checkmark HCV RNA likely preferable
 - Instead continue to support adherence & add missed days to the end
 - If there is significant gap in 1st month, I obtain HCV VL and resistance test

Distinguishing treatment failure from reinfection

- Treatment failure occurs in 5-10%
 - Generally do not achieve (or missing) SVR12
 - Most common cause: insufficient adherence
 - Consider referring for second-line treatment
- Reinfection with HCV occurs in ~10%
 - Risk factor: most commonly ongoing IVDU
 - Those with reinfection are typically managed as treatment-naïve.
 - *Substance use disorder is a relapsing disease*

HCV Guidelines Accessed 14 July 2025.

How to distinguish failure from reinfection?
In both cases HCV RNA ↑

Likely treatment failure

- SVR12 not achieved or documented
- Treatment adherence was poor

Likely reinfection

- SVR12 achieved
- New genotype present
- Ongoing behaviors linked w/ transmission

Case

- HCV RNA 350,000 IU/ml

- 34 yo man with HIV and previously treated HCV, HIV RNA UD on ART
- Previously treated for HCV and had SVR12 but relapsed to fentanyl
- Presents with abnormal AST and ALT and elevated HCV RNA

Question

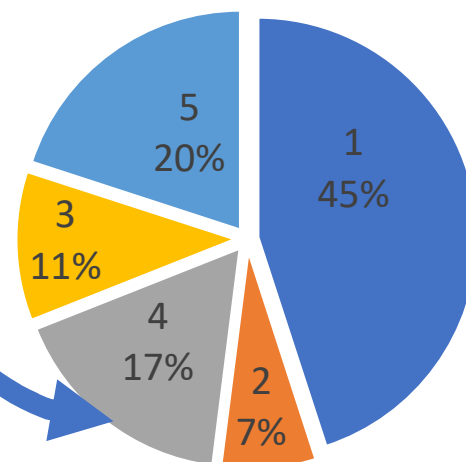
What does this elevated HCV RNA result most likely represent?

1. Late HCV treatment failure, refer to specialist
2. HCV reinfection, consider retreatment with sof/vel
3. A false positive HCV RNA, repeat testing recommended

HCV epidemiology in S. Africa (II)

- HCV genotypes in SA are diverse
 - G1 & G5 dominated Cape Town study
 - Of note, G4 represents 17%
 - Why important? In G4 fewer cured ~86%
 - Certain “rare” G4 subtypes and non a/b G1 subtypes have lower cure rate with sof/vel
 - Ex. G4r, G4w, G4v, G1k, G1l, G1m
 - More common in patients from outside SA: Rwanda, DRC, Cameroon, Malawi

HCV Genotypes in South Africa



When to consider referral to specialist?

- Decompensated cirrhosis (Child B,C) or HCC
- Prior unsuccessful treatment with HCV DAAs
- Patients with less common genotypes linked with lower cure rate using sof/vel
 - Consider in patients with HCV from other regions of Africa



Rapid fire

- **Decompensated cirrhosis** (Child B,C): 24 wks of sof/vel 86% cure
 - ↓ complex, ↑ accessible than alternative: sof/vel + RBV
- **Acute HCV**: Sof/vel for 12 wks results in 91% cured
- For **pregnant people** with HCV, DAAs have not been rigorously evaluated beyond small series with non-pangenotypic regimens
- In **HBV/HCV** – particularly if HBV surface Ag (+) – HBV suppression recommended during HCV treatment
 - To avoid HBV reactivation, TDF is active & usually already part of ART

Case follow-up

- As a re-infection he was treated with sof/vel for 12 wks
- SVR checked 12 wks after treatment completion
 - He achieved undetectable HCV RNA and is in treatment for substance use disorder & on buprenorphine
- Initially no cirrhosis was thought present (based on FIB4) so he will not be monitored for HCC
 - Yearly testing for HCV RNA until stable in recovery for OUD

Thank You

- LA County Jail HCV/HIV Task Force

- Stephen Judge
- Naira Ghazaryan
- Sulma Herrera

- LA General Medical Center HCV Clinic

- Devin Clark
- Rachel Baden

- AWACC organizers and participants

HCV: Epidemiology in South Africa

Genotypes

- UCT / Groote Schuur Hosp. Liver Clinic (2020)

HCV GT, n (%)	#	Proportion
1a	58	28%
1b	36	17%
2	16	7%
3	22	11%
4	36	17%
5	42	20%



GT-4 (N=36)	
4a	3 (8)
4b	2 (6)
4c	1 (3)
4d	5 (14)
4c/d	2 (6)
4k	7 (19)
4q	1 (3)
4r	8 (22)
4v	3 (8)
4 (no subtype)	4 (11)