Hepatitis C – cases to highlight some key points

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Western

TORONTO CENTRE FOR LIVER DISEASE

Disclosures

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- Research: Abbvie, Abbott, Gilead, Janssen, Wako/Fujifilm

- Scientific Consulting: Abbvie, Abbott, Enanta, Gilead, Janssen, Roche

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- Research Grants: Merck, Gilead, Abbvie, Intercept, Bristol Myers Squibb

- Advisory Boards and Cosulting: Merck, Gilead and Bristol Myers Squibb

Learning Objectives

By the end of this session participants should know

- HCV Treatment in 2020; do we still need to do genotype testing?
- Treatment failure; what do we need to know? And how should we retreat?
- Post HCV “CURE”; What is the long-term care and who needs it?

Case 1

- 57 yo Pakistani man
- Diagnosed with HCV in 2011 on routine screening by PCP
- Wife had terrible experience with PegIFN so he refused treatment
- New PCP convinces him to reconsider
- Feels well

- PMH: DM, HTN, BMI 31
- Meds: Metformin, ramipril, amlodipine

No ETOH, no drugs

Soc: Married, accountant

Work-up

- ALT 110 AST 125
- Bili 14 Alb 38 INR 1.1
- Cr 78
- Hb 134 WBC 7.4 Plt 110

- What else is required?

- APRI: 3.25 FIB4: 6.18
- Do you need a fibroscan?
  - Not really – clearly cirrhotic – only value is for risk stratification need for EGD
  - Done anyway – 18 KPa
  - EGD not absolutely necessary – FS<25 & Plt >110 risk of varices requiring therapy is very low (NPV 98.4%)

Additional labs

- HCV RNA 1.7 E6
- Is genotype required?
  - Yes…specifically because he turns out to have Genotype 3
- HBV: HBsAg –ve, anti-HBc +ve, anti-HBs +ve
- HIV: HIV –ve

- US needed?
  - Yes – r/o HCC (not required if not cirrhotic)

How do you want to treat him

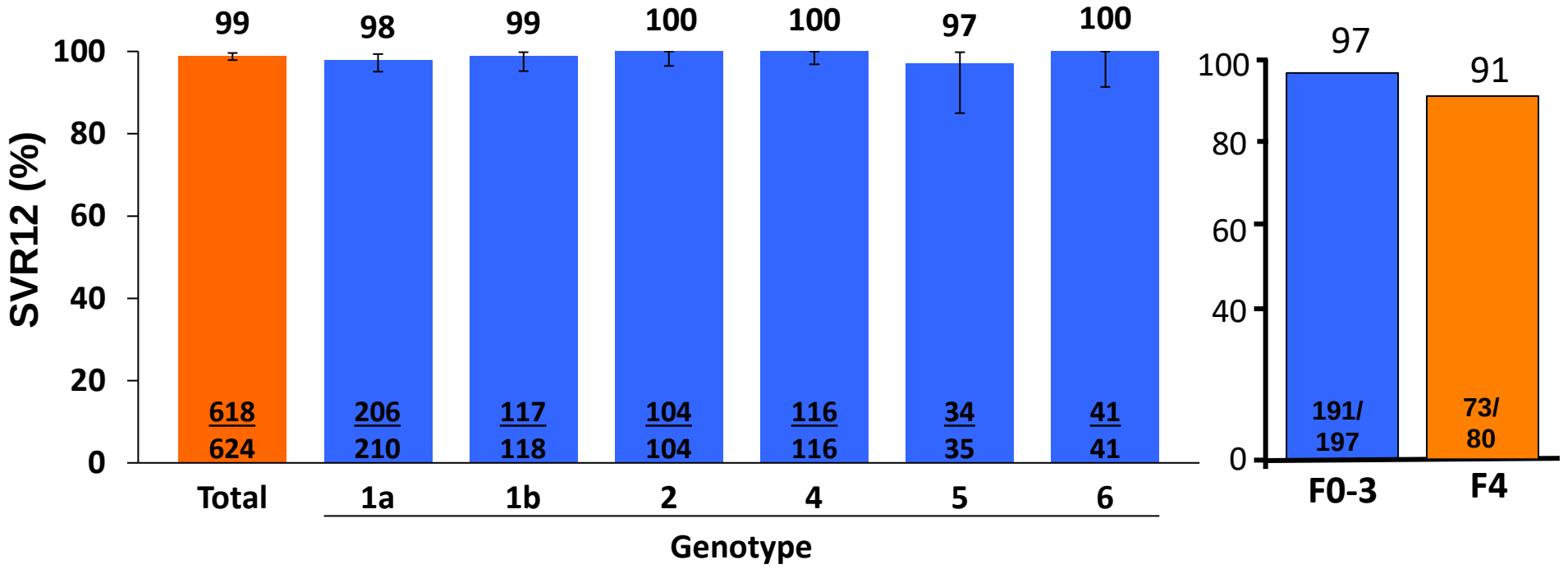
- G3, treatment-naïve, compensated cirrhosis

a. SOF/LDV (Harvoni) x 12 weeks
b. SOF/VEL (Epclusa) x 12 weeks
c. SOF/VEL (Epclusa) + RBV x 12 weeks
d. SOF/VEL (Epclusa) x 24 weeks
e. GLE/PIB (Maviret) x 12 weeks
f. GLE/PIB (Maviret) x 8 weeks
g. Need more information

Is genotyping required with pan-genotypic regimens?

SOF + Velpatasvir x 12 wks in
G1, 2, 4, 5, 6 – Naïve/Experienced +/- cirrhosis

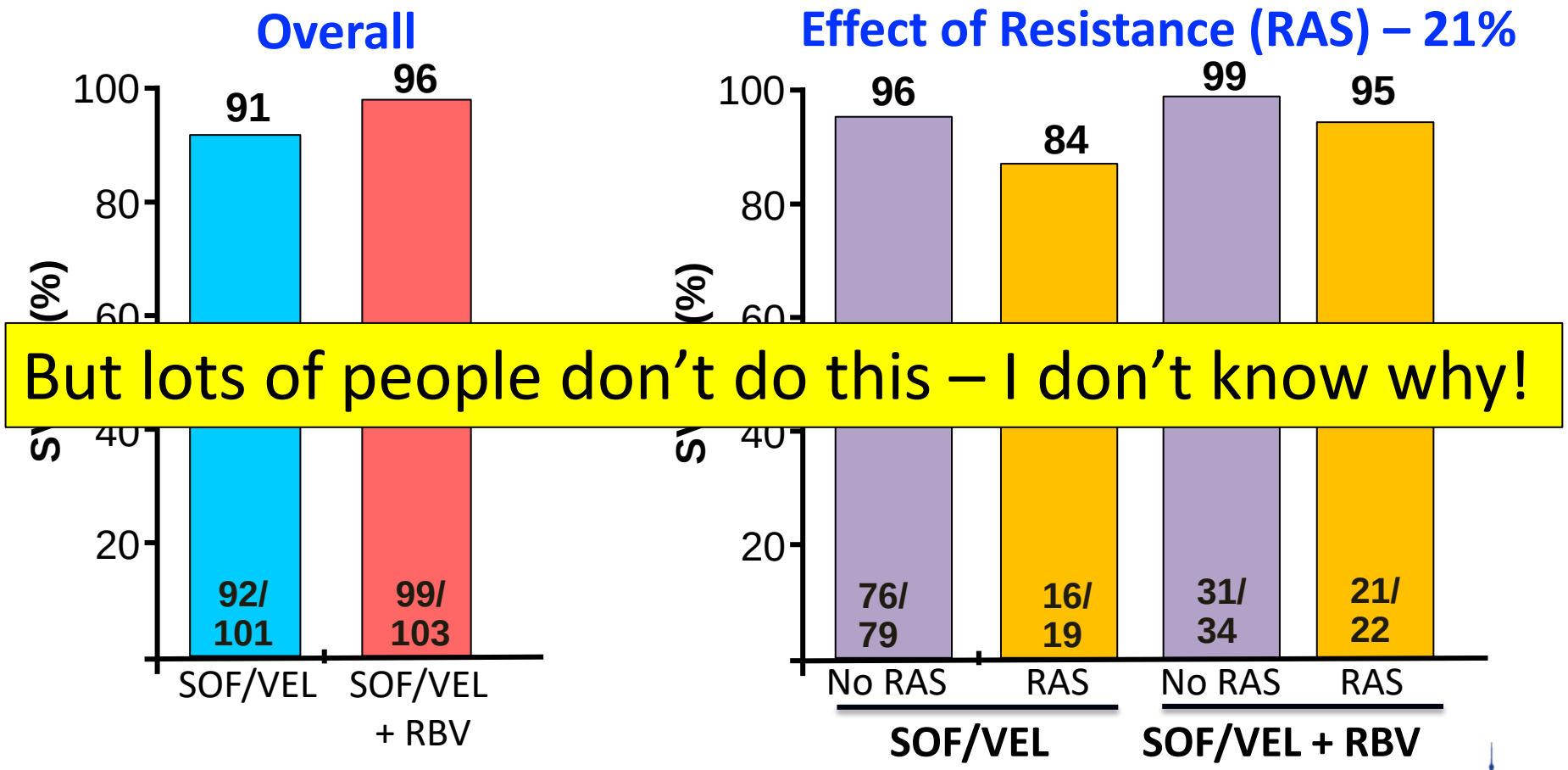
G3: SOF/RBV x 24
vs SOF/VEL x 12



Clearly not an issue without cirrhosis…what about with cirrhosis?

Why is genotyping useful with cirrhosis?

G3 cirrhosis – SOF/VEL vs SOF/VEL + RBV x 12 weeks



But lots of people don't do this – I don't know why!

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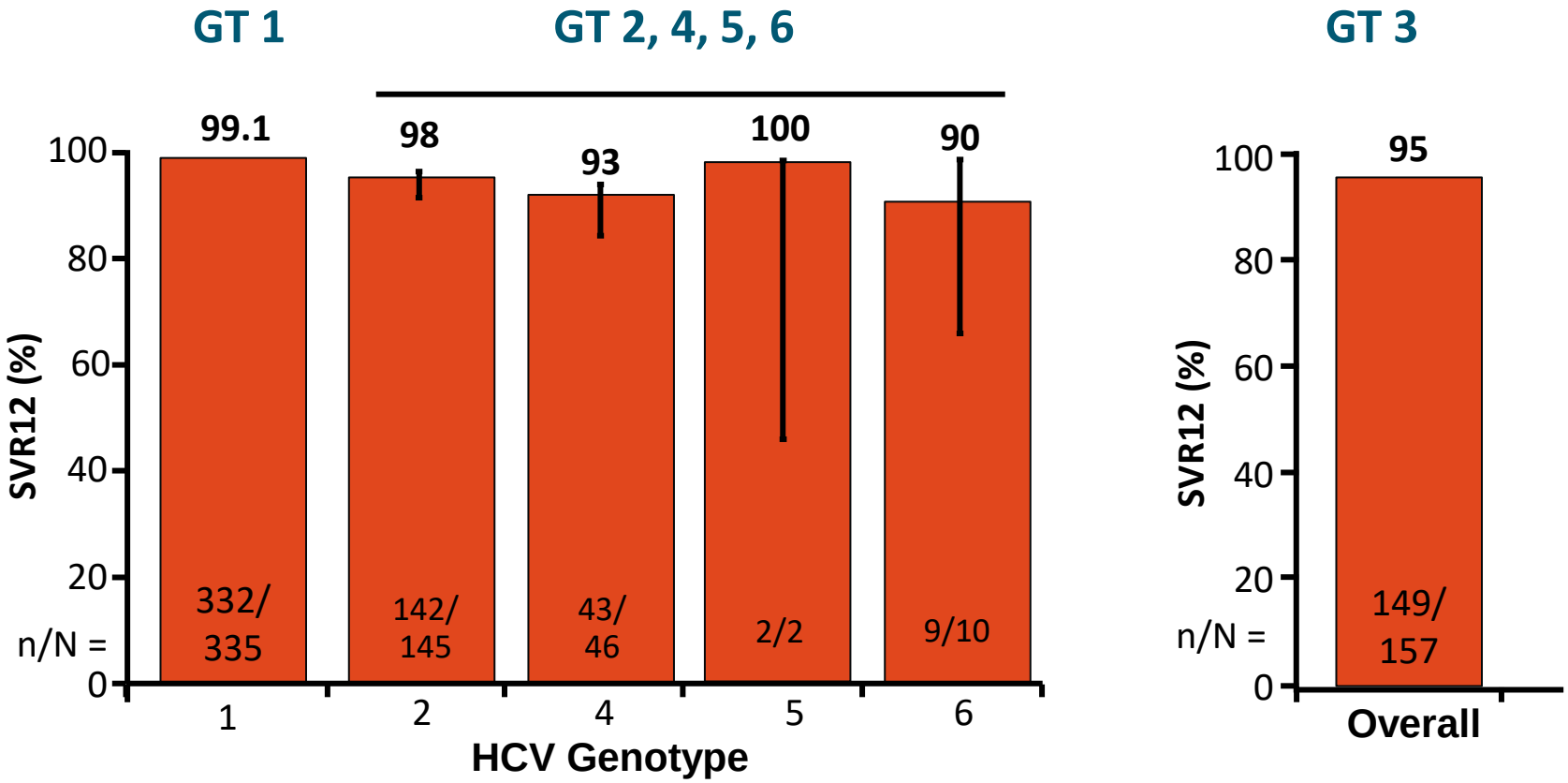
And with GLE/PIB?
8 Wks in Patients Without Cirrhosis



Clearly no relevance without cirrhosis – same 8 week treatment for everyone…but if cirrhotic?

EXPEDITIION 8: GP for 8 weeks with cirrhosis

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FDA NEWS RELEASE

Spoiler alert

FDA approves treatment for adults and children with all genotypes of hepatitis C and compensated cirrhosis that shortens duration of treatment to eight weeks

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Brown et al. AASLD 2018, LB-7

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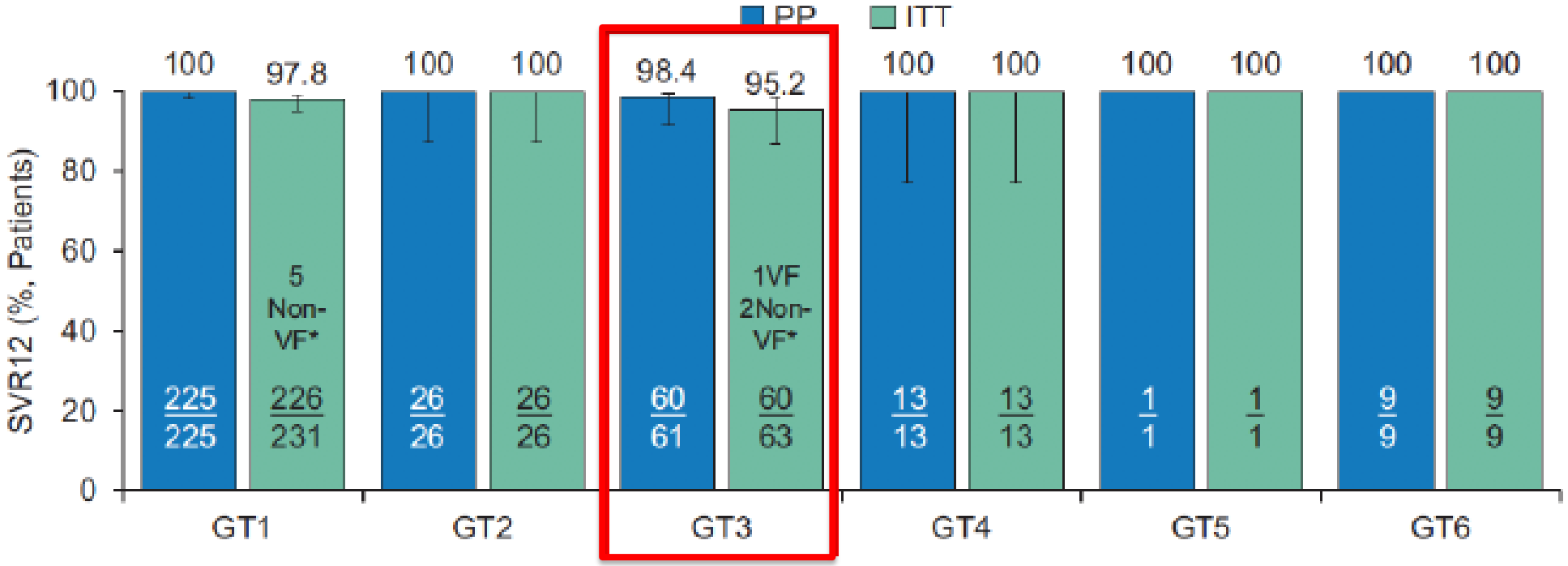
And the genotype 3 cirrhotic data?



Resistance
- 3 (5%) A30K
- 4 (6.5%) Y93H
- All SVR

- Overall GLE/PIB looks promising for 8 weeks for compensated cirrhosis in all genotypes
- ***This approach would avoid the need to genotype – 8 weeks for all with or without cirrhosis***
- But would be nice to have bigger numbers, especially with RAS for G3

How do you want to treat him

- G3, treatment-naïve, compensated cirrhosis

a. SOF/LDV (Harvoni) x 12 weeks
b. SOF/VEL (Epclusa) x 12 weeks
c. SOF/VEL (Epclusa) + RBV x 12 weeks
d. SOF/VEL (Epclusa) x 24 weeks
e. GLE/PIB (Maviret) x 12 weeks
f. GLE/PIB (Maviret) x 8 weeks
g. Need more information

} Depending on result of resistance testing

If Cirrhosis is Present

- Need to exclude **current or past decompensation**
  - Affects choice of regimen – No PIs, add RBV
  - Affects safety – warn patient & monitor closely

- Calculate Child Pugh Score – **if > 5 pay attention!**
  - **Bilirubin - Ascites**
  - **Albumin - Hepatic encephalopathy**
  - **INR**

- Calculate MELD – **if > 15 pay attention!**
  - **Bilirubin - Creatinine**
  - **INR**

Be careful…nothing very new but a good reminder

FDA warns about rare occurrence of serious liver injury with use of hepatitis C medicines Mavyret, Zepatier, and Vosevi in some patients with advanced liver disease

FDA Drug Safety Communication

- Most cases in CP-B/C (a few CP-A but A-6)
- Issues in first 4 weeks
- **If bili rising (or new ascites/HE) – stop treatment!**

A possible approach

1. Fibrosis assessment & pre-treatment labs
2. Cirrhosis present
   - No? **Treat with G/P x 8 wks or SOF/VEL x 12 wks (no need for genotype)**
   - Yes?
     - G/P eligible (No decompensation or drug interactions)?
       - Yes → **G/P 12 weeks (maybe 8 weeks in the future – no need for gt)**
       - No → **Genotype & if G3, resistance testing before SOF/VEL re: RBV**

What happened

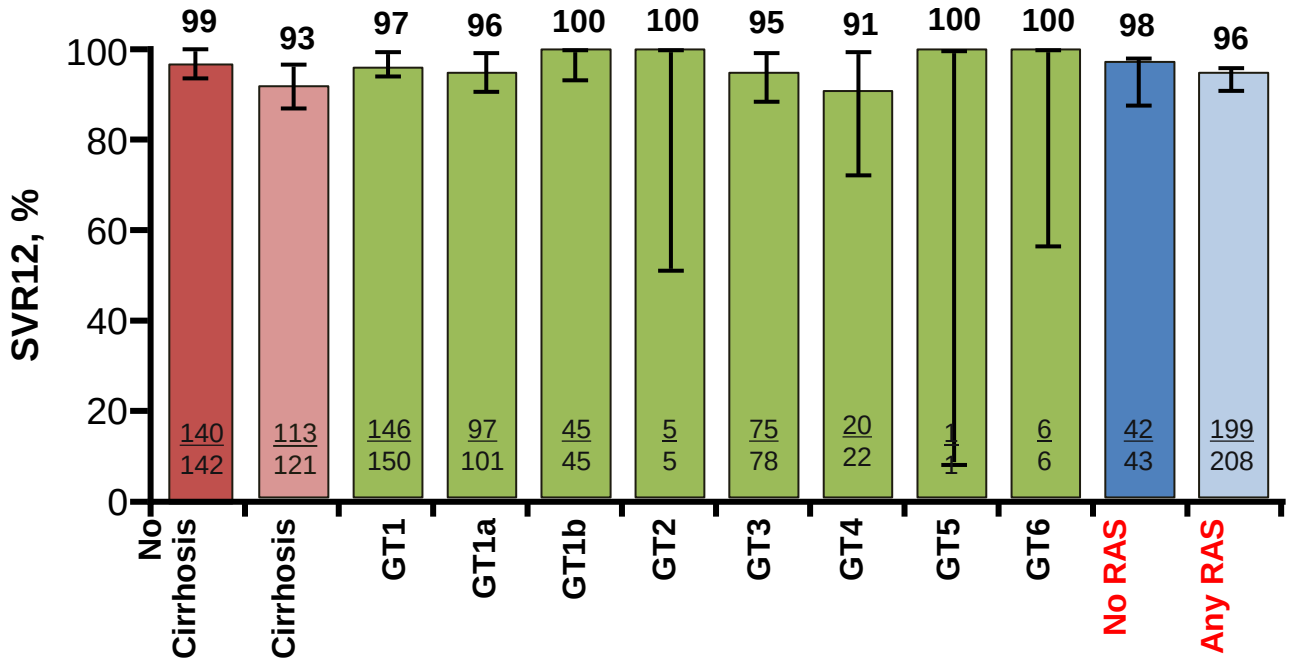
- Given SOF/VEL x 12 weeks
- Resistance testing not done, no ribavirin given

- Suppressed nicely on therapy…but relapsed
  - HCV RNA 3.8E5, ALT 78 at SVR12 timepoint

- Now what?
  - No big deal, we can just retreat right?

POLARIS 1 - Prior NS5A Failures

SOF/VEL + **VOX (PI)** x 12 weeks → G1-6 prior NS5A, 41% cirrhosis



- 7 virologic failures
  - 6 relapse
  - 1 breakthrough
- All cirrhotic – **G1a or 3 (1 GT4)**
- No treatment emergent RAS!

- Looks pretty good so we can just give him SOF/VEL/VOX right?

Bourliere NEJM 2017

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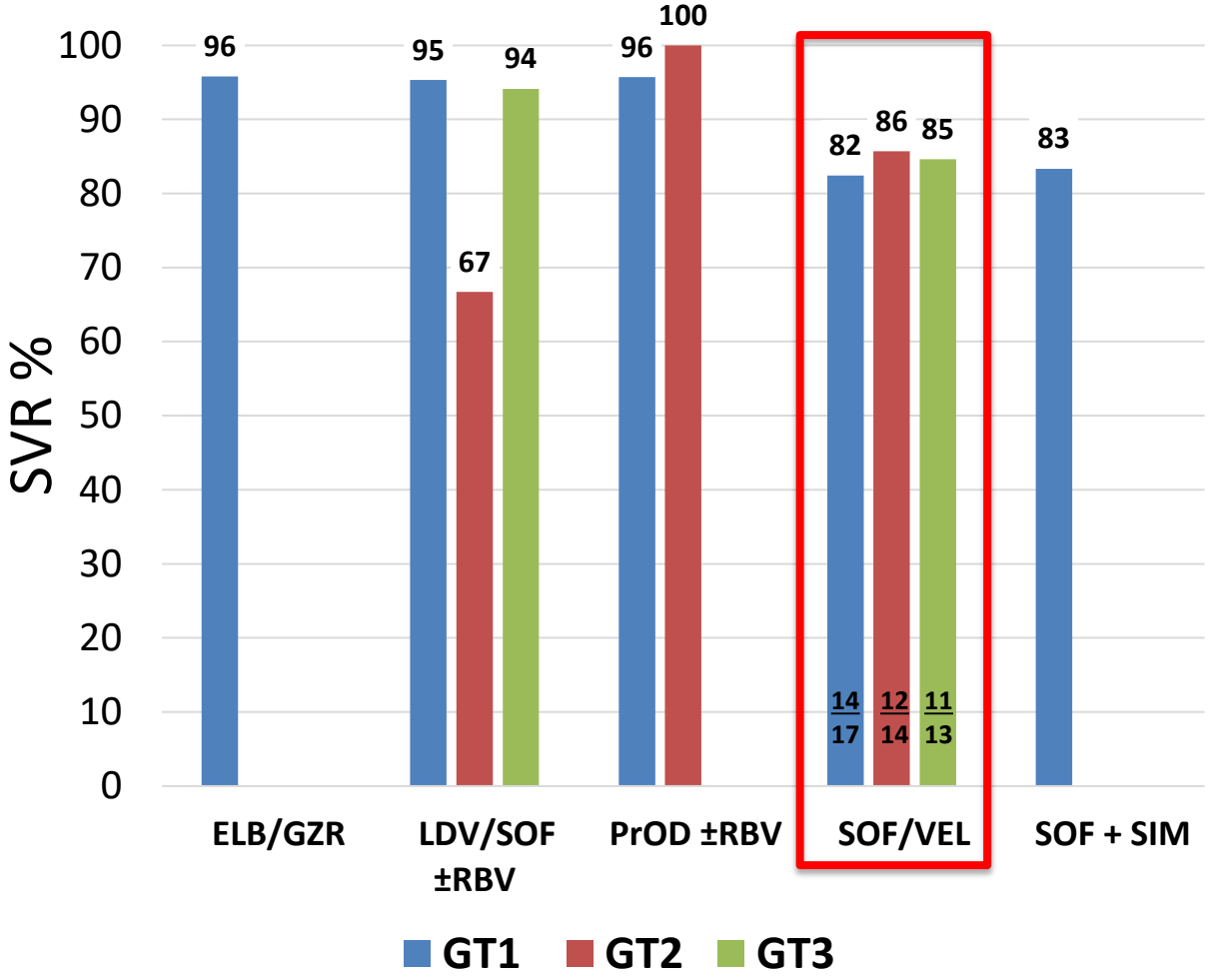
But does it really matter? Can't we just retreat?

SOF/VEL/VOX in 573 Veteran's after DAA failure



High overall efficacy

- G1-4 >93% SVR

- **Lower SVR with SOF/VEL/VOX after SOF/VEL** → small numbers but important to clarify if this is an issue

Belperio et al AASLD 2018, Abstract 227

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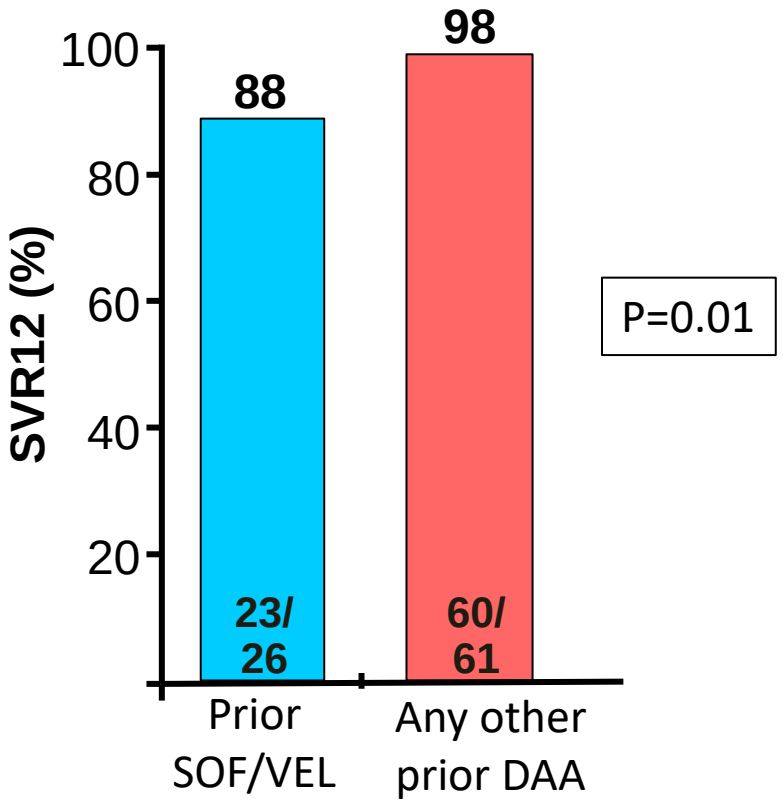
Looks similar in Canada…

Patients retreated with SOF/VEL/VOX after DAA failure in the CANUHC cohort



- Small numbers but SOF/VEL/VOX may not be as effective for retreatment after SOF/VEL failure
- **Message: Get it right the first time!**

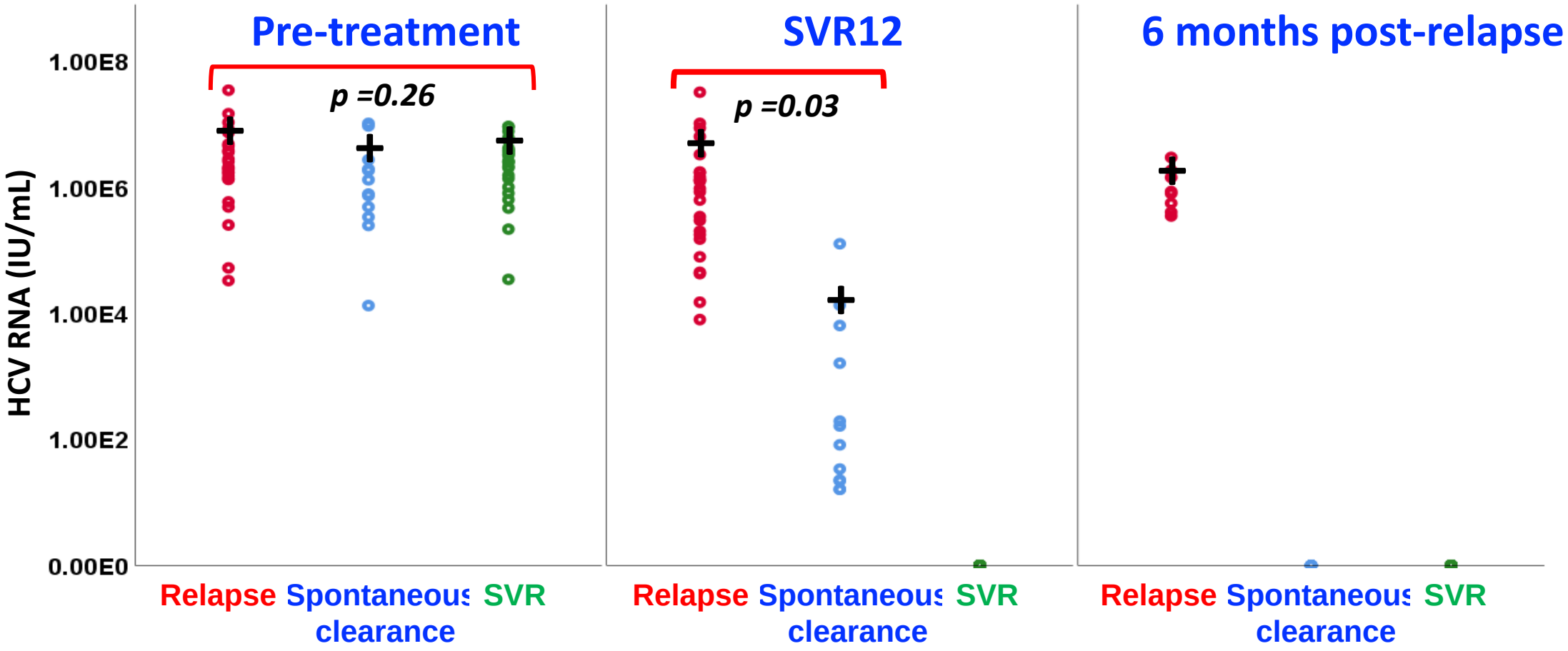
So what to do now?

- He still feels well
- No decompensation (past or current) – very important
- Why did he fail?
  - Possibly baseline resistance
  - Consider other things

What do we need to know?

- Adherence
  - Says he took all the pills (may have missed 1)
- AEs
  - Mild headache
- DDIs
  - Turns out he was taking high dose pantoprazole 40 BID for bad GERD
  - Affects absorption of velpatasvir (Epclusa) and ledipasvir (Harvoni)
  - Most important early when viral load high
  - Best to avoid if possible but otherwise minimize dose and dose together
- Other things?

Confirm relapse before retreatment



13% of relapsers clear without retreatment → especially if normal ALT and VL<4 logs

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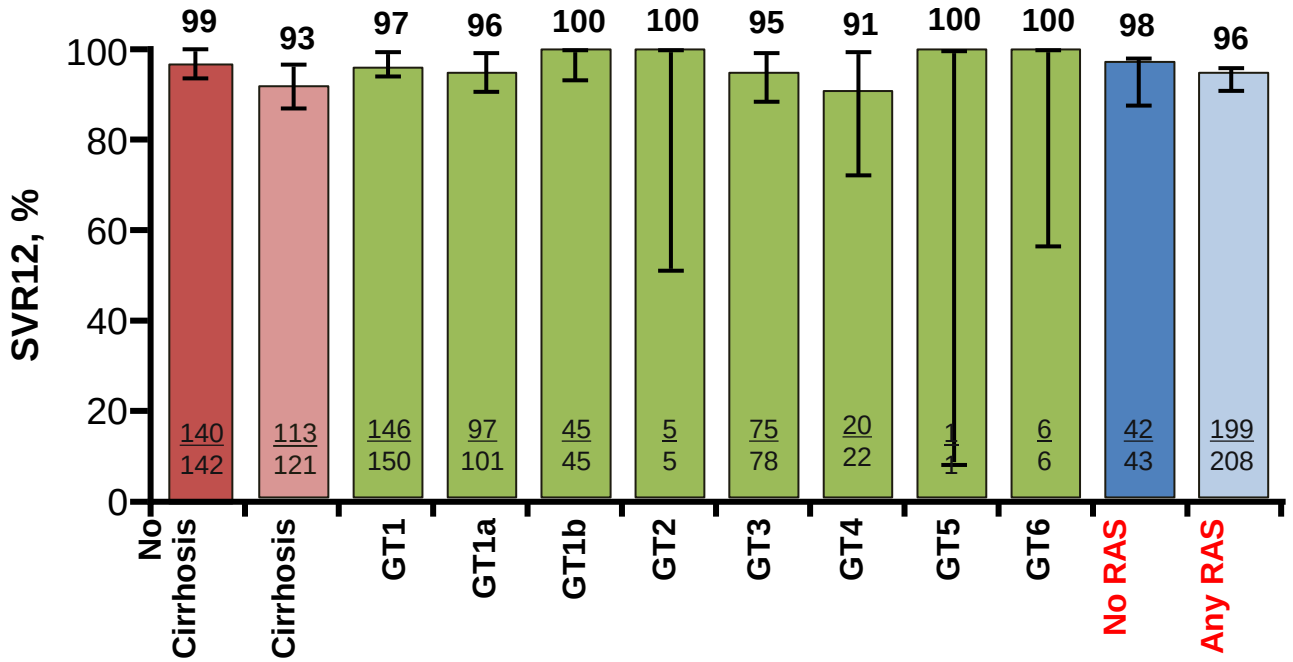
Do we need to do resistance testing before retreatment?

SOF/VEL + **VOX (PI)** x 12 weeks → G1-6 prior NS5A, 41% cirrhosis



- 7 virologic failures
  - 6 relapse
  - 1 breakthrough
- All cirrhotic – **G1a or 3 (1 GT4)**
- No treatment emergent RAS!

- Based on this…no reason to do resistance testing…right?
- ***But we won't know unless we test…***
- With enough data, almost certainly relevant…

Bourliere NEJM 2017

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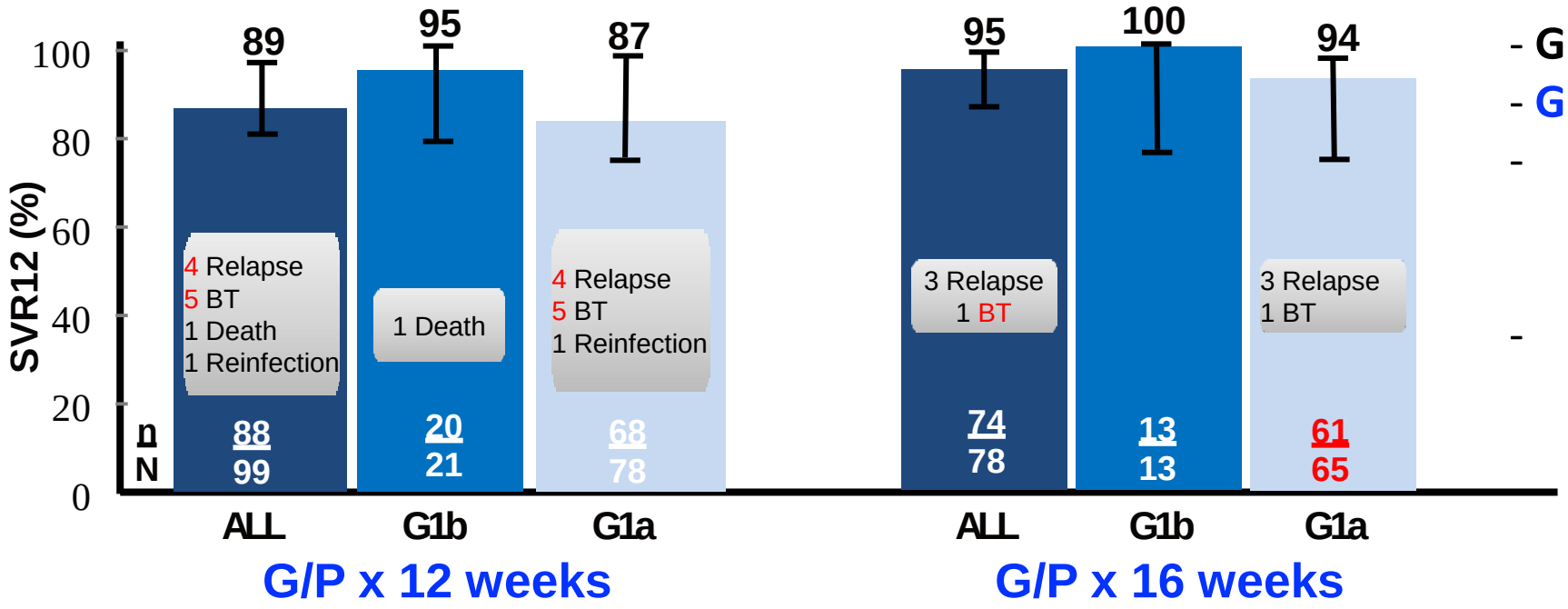
Can you use GLE/PIB?

G1 with past failure with NS5A + SOF → **No cirrhosis 12w vs 16 w, compensated cirrhosis 12w + RBV vs 16w**



- **G1b** (n=34) – no virological failures
- **G1a failures**
- **Breakthrough (n=6)**
  - Complicated NS5A RAS at BL
  - Emergent NS3 & NS5A RAS
- **Relapse (n=7)**
  - NS5A RAS at BL
  - Emergent (4/7) & NS5A RAS

- **Effective for G1b (12 or 16w)**
- G1a requires 16w with no benefit from RBV but failures may be challenging
- Not for G3 or other genotypes

Sulkowski et al. AASLD 2018, Abstract 226

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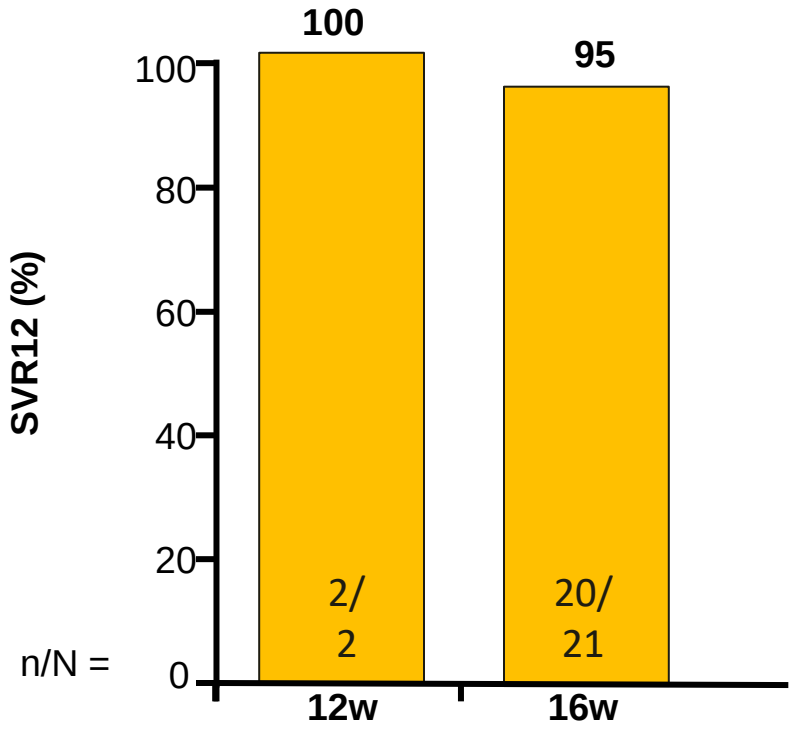
Back to the patient

- Repeat HCV RNA 3.7 E5 (no spontaneous clearance)
- Resistance testing done
  - NS3: A168V
  - NS5A: Y93H, A30K, L31M
  - NS5B: N262S
- Willing to stop PPI

- What regimen?
  - No right answer here…
  - He was given SOF/VEL/VOX + RBV x 12 weeks – **relapse again**

And after G/P (and likely SVV) failure?

SOF + glecaprevir/pibrentasvir + RBV x 12 vs 16w after G/P failure (8, 12 or 16w)



- 1 relapse G1a – prior SOF/LDV then G/P before G/P + RBV
- Overall reassuring
- Unclear if RBV is necessary
- Duration unclear
- Need more data with SOF + G/P

And now what?

- 1 additional NS5A and NS5B substitution – very complex profile

- Kitchen sink regimen

- SOF/GLE/PIB + RBV x 24 weeks → SVR
- (EASL guidelines helpful for getting it funded)

Bottom line on retreatment

- Fortunately a rare event
- Check a few things:
  1. **Adherence**
  2. **DDIs**
  3. **Spontaneous clearance after relapse** (~15%, especially if low VL)

Bottom line on retreatment

- Fortunately a rare event
- Check a few things:
  1. **Adherence**
  2. **DDIs**
  3. **Spontaneous clearance after relapse** (~15%, especially if low VL)
  4. **Reinfection** – discuss with everyone
- **Do resistance testing – even if it does not change your plan…it may one day!**

EASL

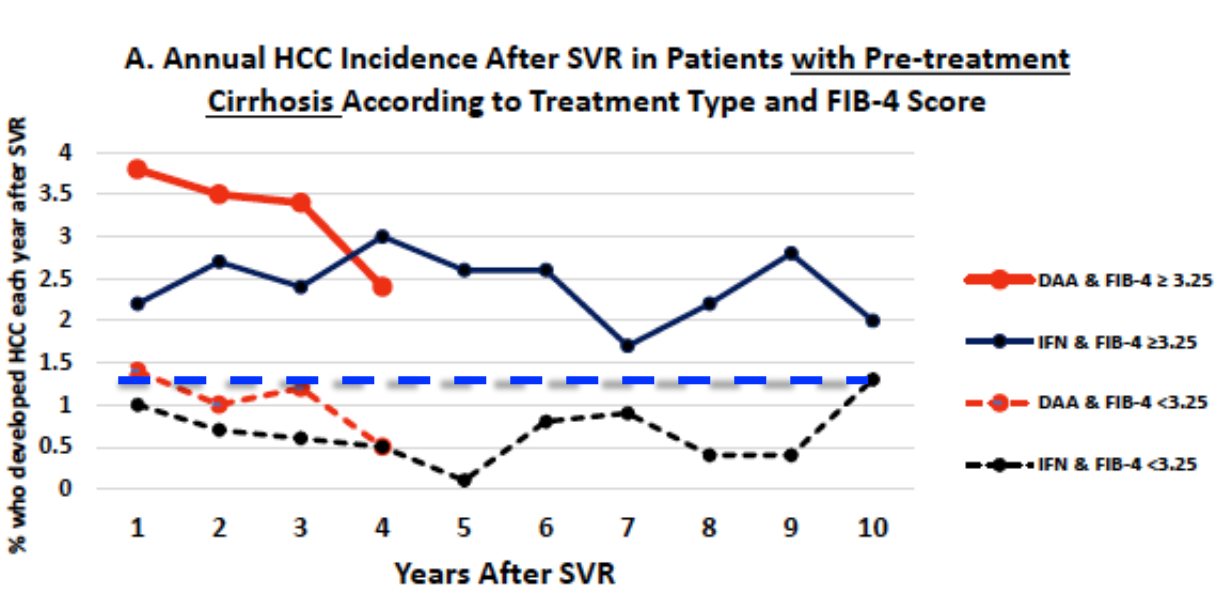
Scenario	Previous Experience IFN-free DAA Combo
Genotype 1-6	**SOF/VEL/VOX**
High risk for failure (Cirrhosis, complex RAS, multiple courses)	Consider **SOF + G/P x 12w**
Very difficult-to-cure (NS5A RAS and >1 failure)	Consider **SOF/VEL/VOX** or **SOF + G/P + RBV x 12-24w**

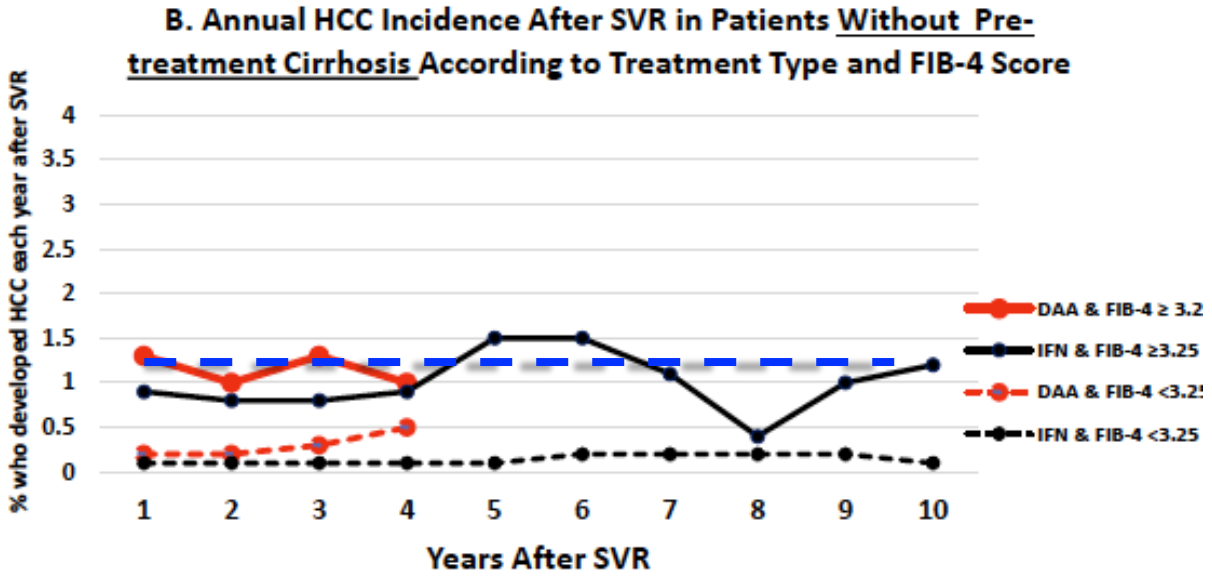
Ongoing care

- Does he need HCC surveillance?
- YES!!
- 2 years later…
  - ALT 12, AST 16
  - BILI, ALB, INR normal, Cr normal
  - Plt 162
  - Fibroscan 6.4 (F1)
  - And now?

Using FIB4 to guide post-SVR HCC surveillance

HCC incidence during follow-up after SVR in 9,784 with cirrhosis and 38,351 without cirrhosis





- HCC risk remains stable out to 10 years…**cannot stop surveillance**
- Surveillance cost-effective if **FIB4>3.25 and probably in all with cirrhosis**

Ioannou Gastro 2019, Zangneh Clin Gastro Hep 2019

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Summary

- Genotype required for patients with cirrhosis
- If G3
  - If using SOF/VEL → don't forget RAS testing and RBV
  - If using GLE/PIB → still 12 weeks (for now) and make sure no past/present decompensation
- Treatment failure
  - Confirm relapse
  - Adherence, DDIs, AEs
  - Resistance testing still useful
- HCC surveillance
  - If cirrhosis by any means or FIB4>3.25 → indefinite surveillance