Hepatitis C: The Easy and the Not so Easy

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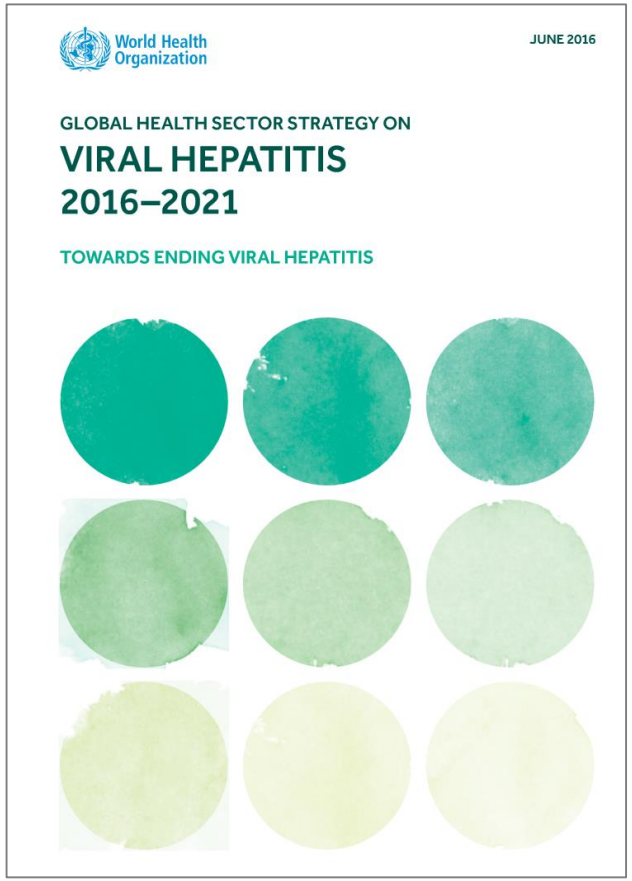
Disclosures

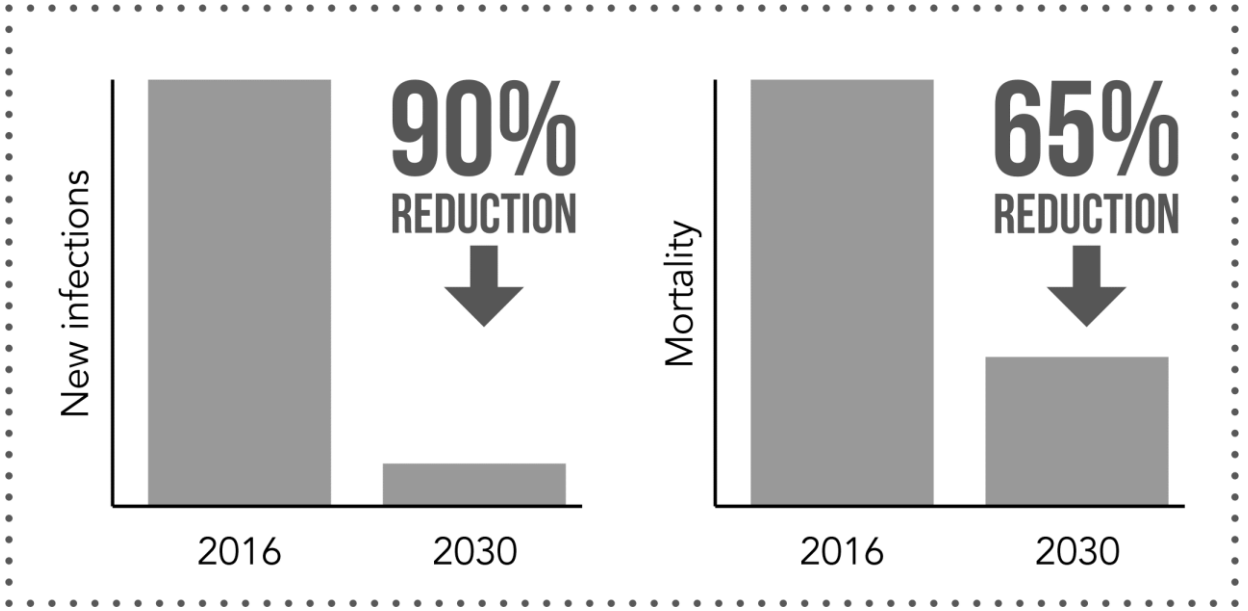
- Research: Abbvie, Abbott, Gilead, Janssen, Wako/Fujifilm

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

Eye on the prize: Viral hepatitis elimination



- Eliminate viral hepatitis as a major public health threat by 2030
- Calling on all countries to develop national action plans



What do we mean by elimination?

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Eradication

- Decrease ***global*** prevalence to 0 cases
- No ongoing surveillance or control efforts required

Likely impossible without a vaccine (among other things!)

Elimination

- Decrease in ***regional/national*** prevalence to below a threshold to ***limit impact as a public health problem***
- **Ongoing surveillance and control required**

Challenging but feasible with the right tools

To get to any of these endpoints → we need to treat a lot of people

Outline

- How easy can it be?
  - Simplified therapy
    - Pretreatment assessment and regimen selection
    - On-treatment monitoring
    - Post-treatment follow-up
- The not so easy
  - Difficult patients
    - The liver
    - The virus

Outline

- **How easy can it be?**
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Recommended Treatment Regimens

- **Genotype-specific**
  - Elbasvir/Grazoprevir: GT 1, 4
  - Ledipasvir/Sofosbuvir: GT 1, 4, 5, 6
- **Pangenotypic**
  - Sofosbuvir/Velpatasvir – GT 1-6
  - Glecaprevir/Pibrentasvir – GT 1-6
  - Sofosbuvir/Velpatasvir/Voxilaprevir – GT 1-6 (reserved for salvage therapy)

AASLD/IDSA. HCV Guidance. 2018. Shah et al CMAJ

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Lots of Options…
How Do You Choose the Right One?

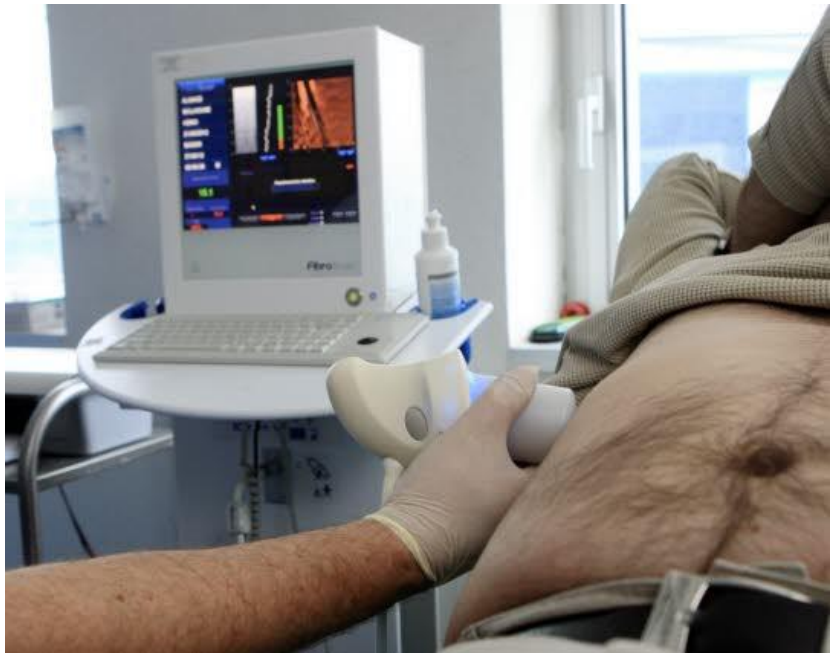
- The good news is they all work very well!
- SVR rates consistently **> 95%** in clinical trials and real-world studies
- Safety/tolerability excellent
- For most patients, any of the recommended options are fine
- ***You can make this difficult…but you need not (most of the time!)***
  - 3 pills once a day for 8 weeks
  - 1 pill once a day for 12 weeks

Checklist for Choosing a Regimen: A Few Things to Know

- **Fibrosis assessment**
  - Cirrhosis?
  - If yes – any history or signs of decompensation
- Genotype & subtype for GT 1
  - Still necessary?
- Treatment history
  - Regimen + duration
- Comorbidities
  - CKD, coinfection (HIV/HBV)
  - Drug-drug interactions
  - Ongoing risk exposures: drug use, sex, alcohol

Fibrosis Assessment is Essential

- **Don’t miss cirrhosis!!**
  - Must assess fibrosis in ALL patients
  - May affect regimen
  - **Need for post-SVR follow up**
- Fibroscan is great
  - If you have access…
  - Remember the caveats
    - **If the value is a surprise…make sure it’s a good reading and not due to inflammation, fat, big meal…**



Fibrosis Assessment

- **Serum tests**
  - **APRI or FIB-4 – very attractive, can be done anywhere by any provider**
    - Very good **negative predictive value – rule out cirrhosis**
    - Can even get this after the fact with old records…*more on this later*
    - If high – **PPV is not great…get another test to confirm** (especially if a surprise)
  - FibroTest (0.75 = cirrhosis)
- **Transient elastography**
  - > 12.5 KPa = cirrhosis
- **What about ultrasound – needed in all patients?**
  - **Insensitive for cirrhosis – only needed if cirrhotic to exclude HCC before treatment**

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!**

Checklist for Choosing a Regimen: A Few Things to Know

- Fibrosis assessment
  - Cirrhosis?
  - If yes – any history or signs of decompensation
- **Genotype & subtype for GT 1**
  - Still necessary?
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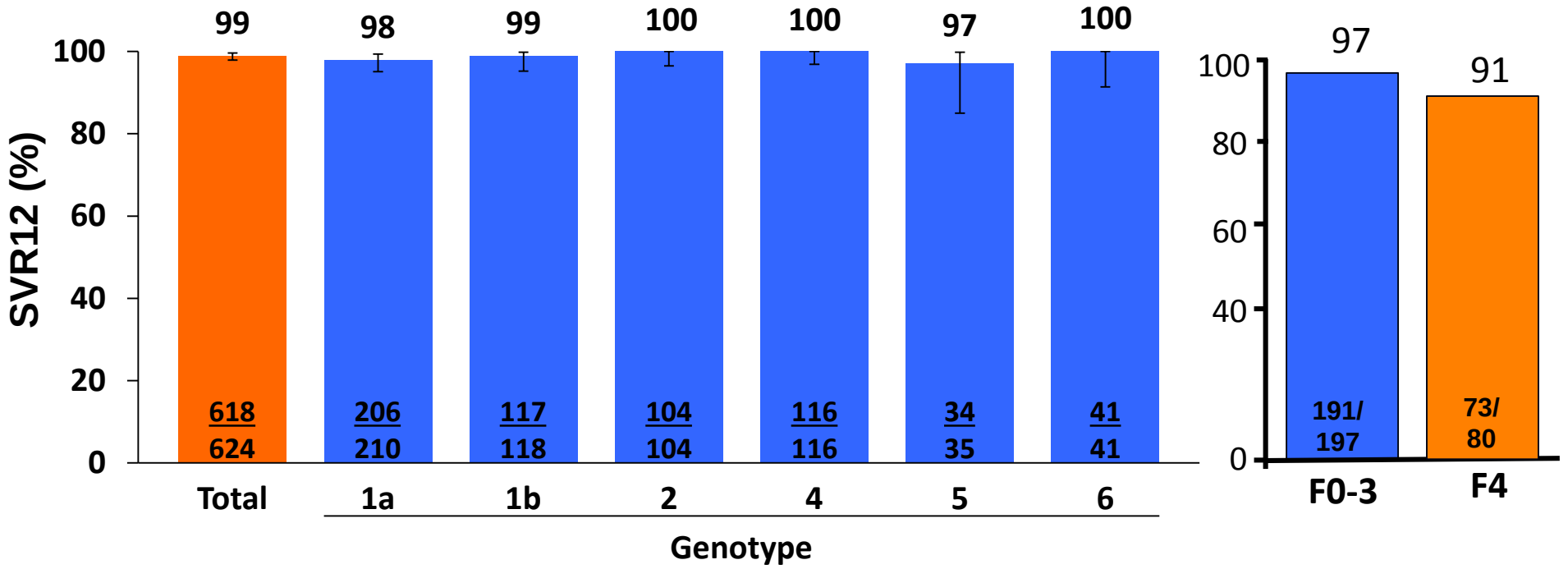
What about SOF/VEL?

SOF + Velpatasvir (NS5A) 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?

Feld NEJM 2015, Foster NEJM 2015

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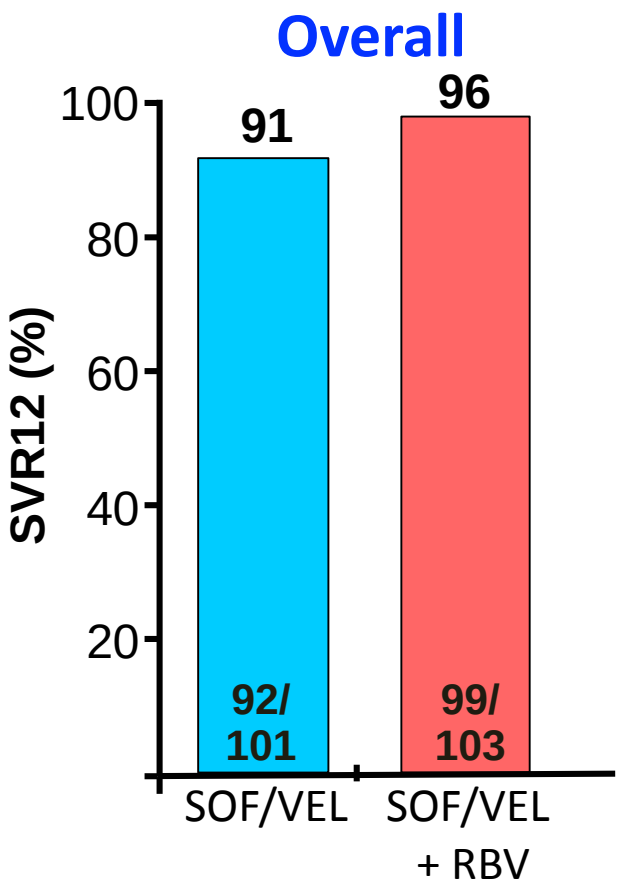
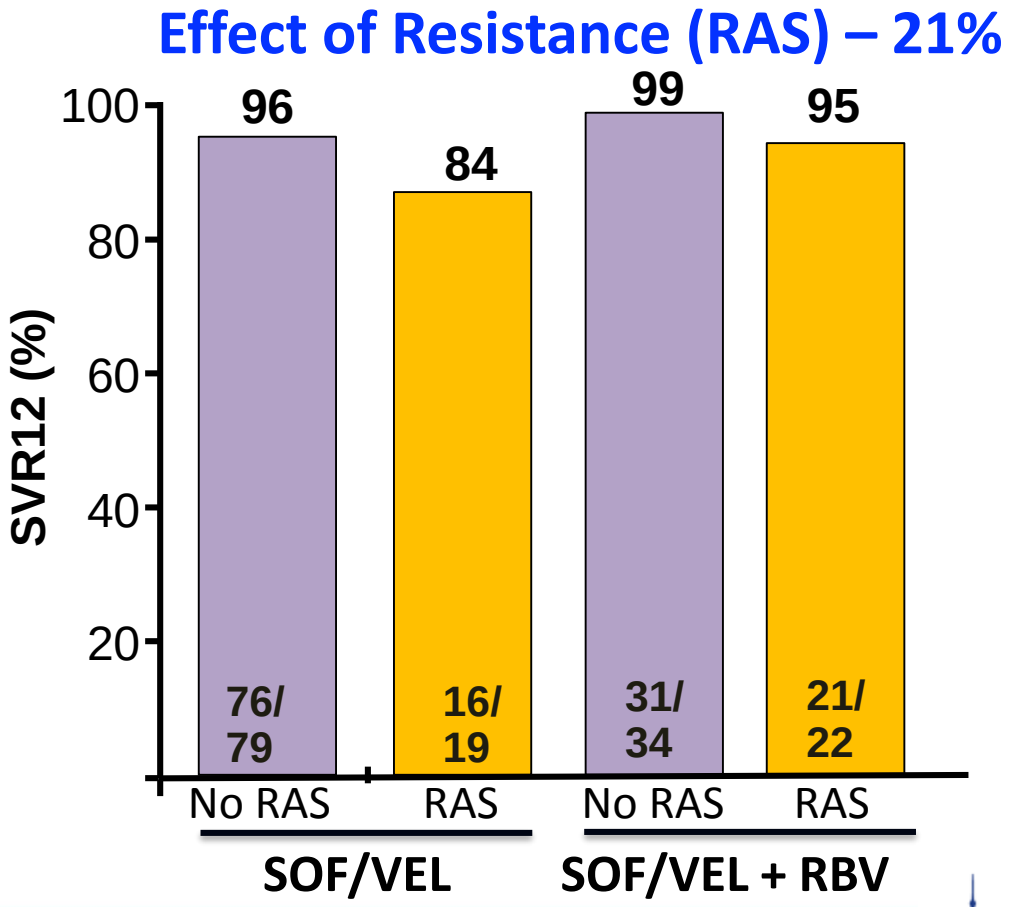
Why is genotyping useful with cirrhosis?

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





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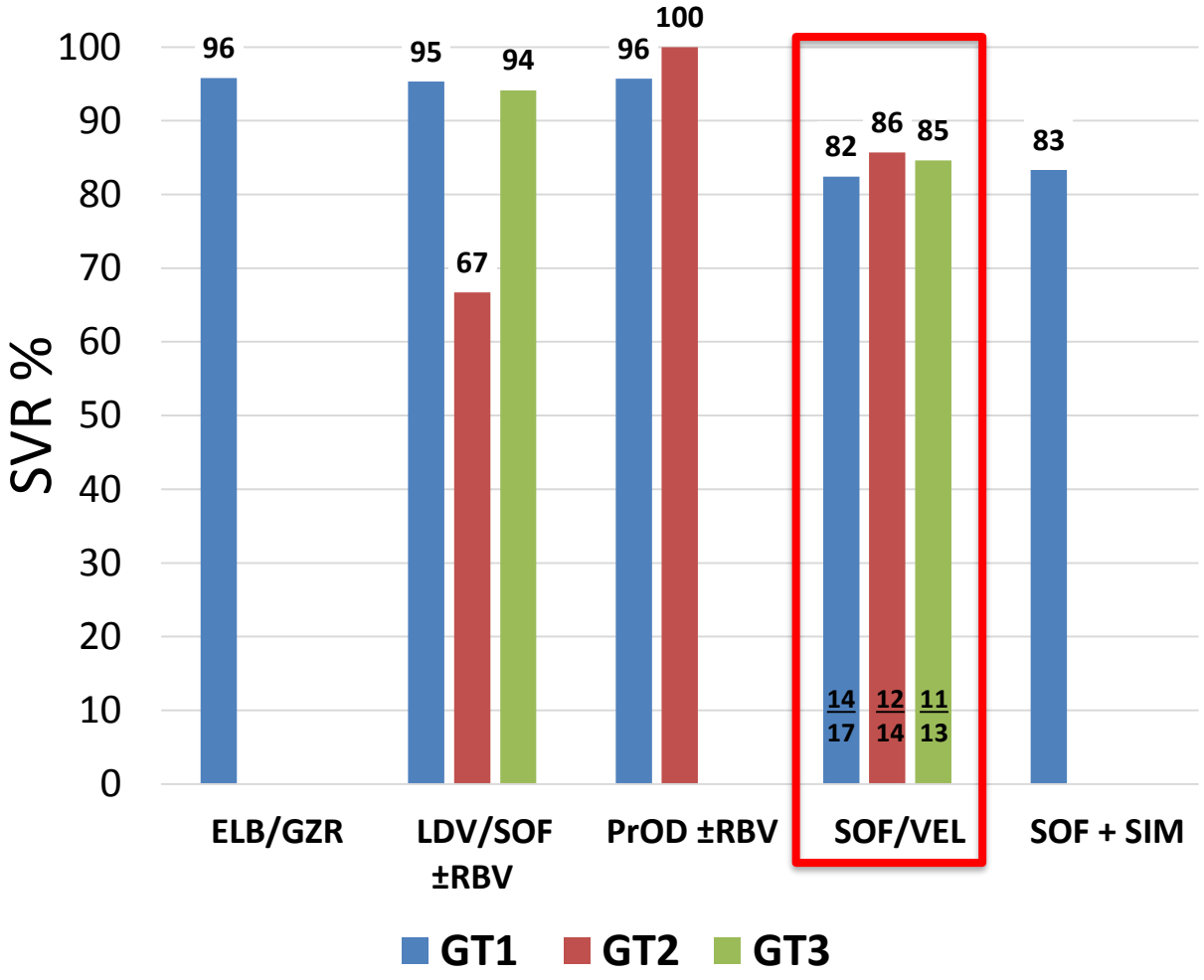
But does it really matter? Can't we just retreat?

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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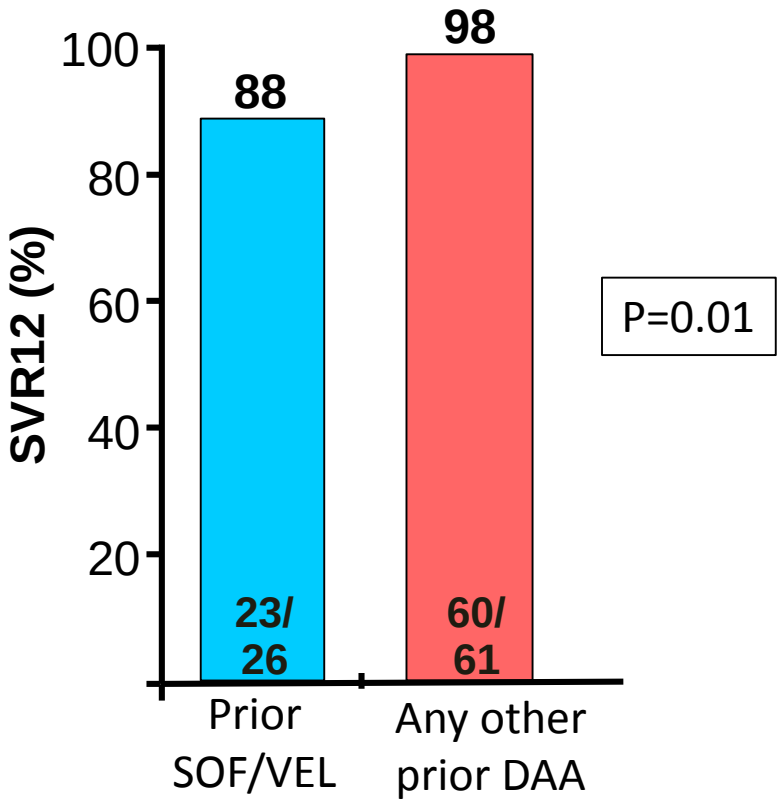
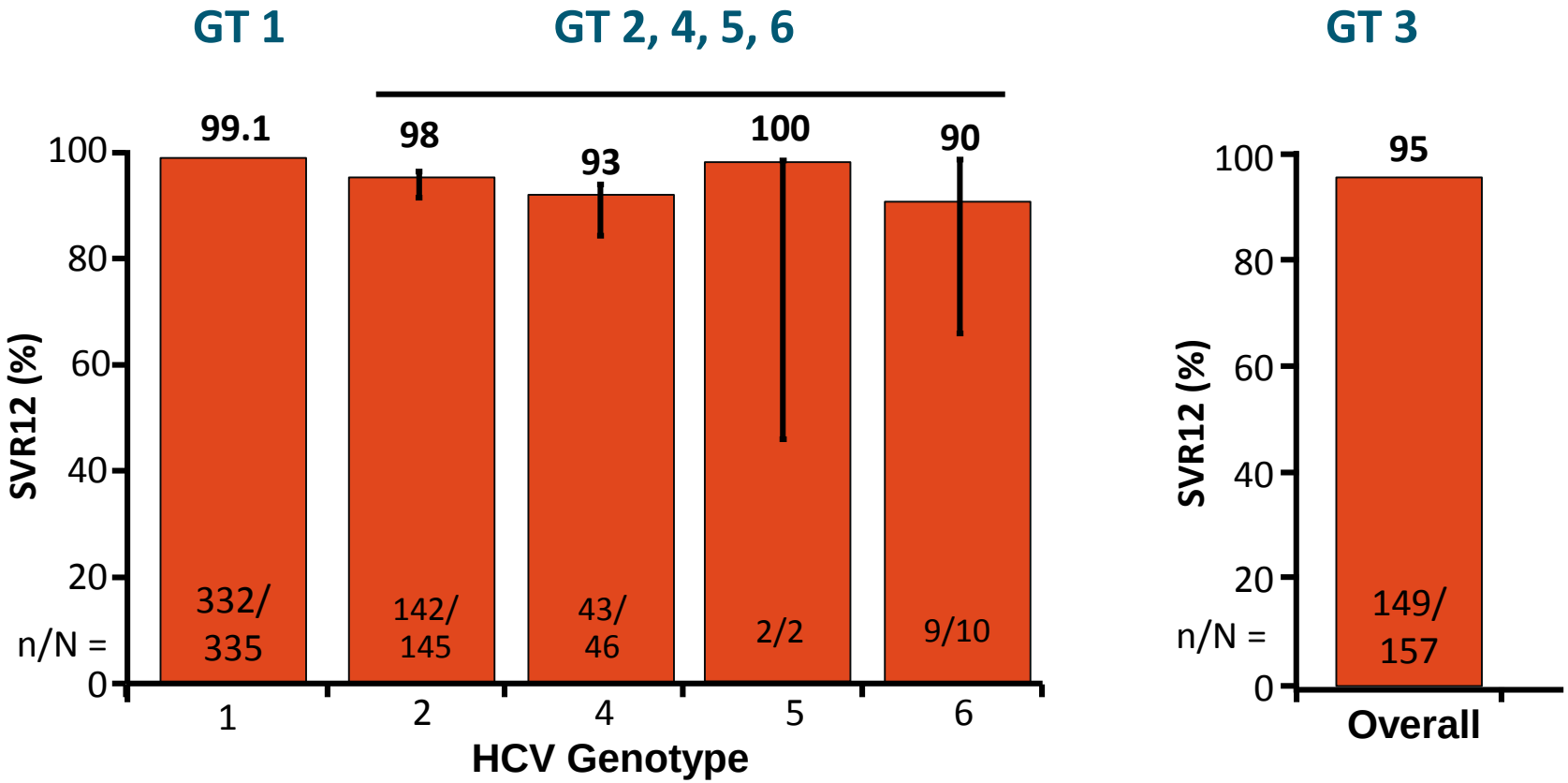
Looks similar in Canada…

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!**

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

Brown et al. AASLD 2018, LB-7

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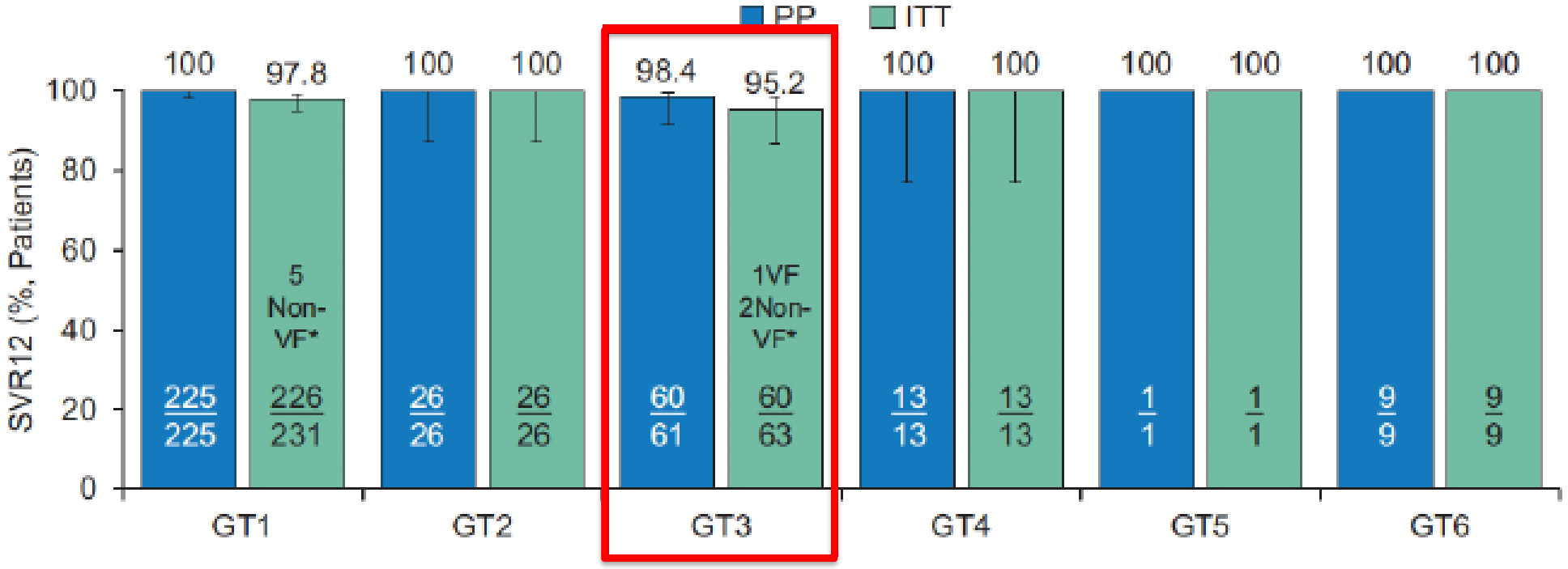
And the genotype 3 cirrhotic data?



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

Can We Avoid Genotyping?

Maximizing SVR in Individual Patient

- Genotyping may be helpful
- Helpful in cirrhosis, particularly GT3
- ?add RBV to SOF/VEL
- ?Extend G/P to 12w…or not

A Reasonable Compromise

Genotype only for:

Cirrhosis

DAA-experienced

Maximize SVR in the Population

- Simplicity is key
- Genotyping adds some: cost, delay, and complexity

Other Labs?

- **Work-up for other liver diseases?**
  - Could do pretreatment or else wait for post-SVR if ALT still high
  - Iron saturation
  - Maybe nothing else **(don't need the full CLD w/u on everyone!)**
- **Renal function**
  - Still relevant although SOF/VEL shown to be safe down to GFR<30, most would still prefer to avoid
  - GLE/PIB safe in CKD including dialysis
- **HBV**
  - HBsAg is important
  - Anti-HBc not very important (but very common!)
- **HIV**
  - Important due to common risk factors and importance of diagnosis

Drug-Drug Interactions

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

(or just google Hep C drug interactions)

This is often a decider for me on which regimen to use

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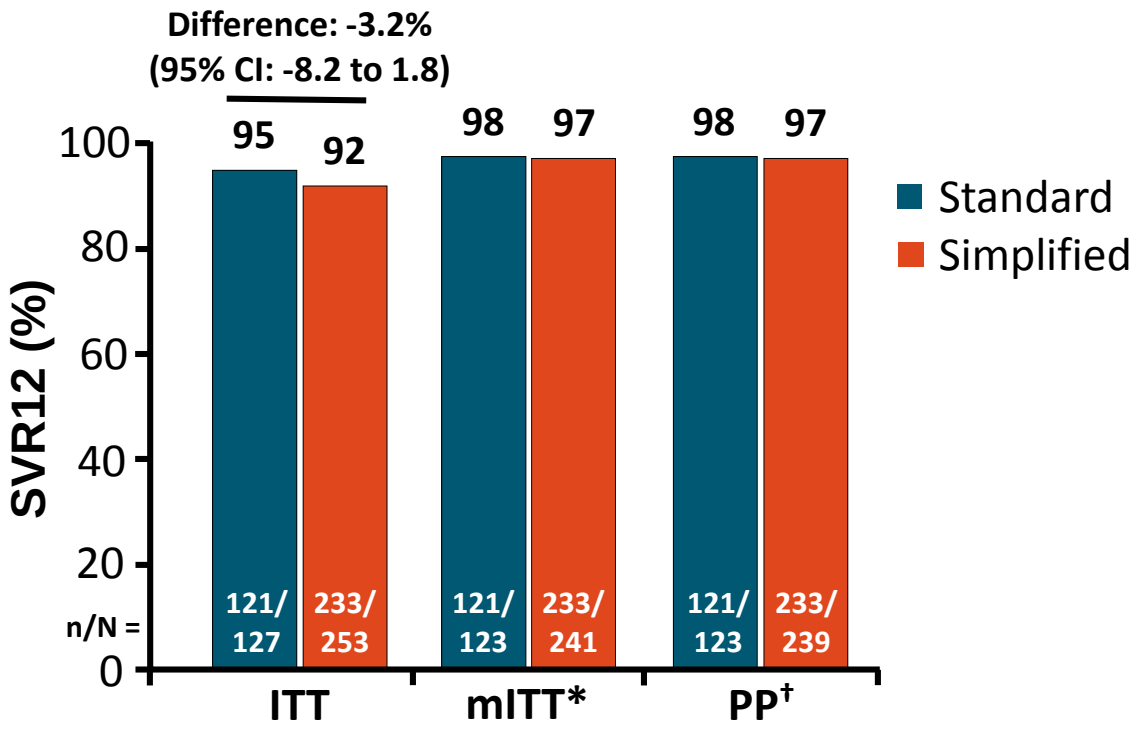
Simplifying Monitoring: Do we need visits?

Non-cirrhotic all genotypes randomized – **standard vs simplified (no visits)** monitoring



*Excludes death (n = 1), LTFU (n = 14), or missing HCV RNA (n = 1).
†Excludes discontinuation (n = 2) in addition to mITT exclusions.

Treatment-Emergent AEs, n (%)	Standard (n = 127)	Simplified (n = 253)
Unscheduled visits		
▪ On treatment	3 (2)	11 (4)
▪ Total	8 (6)	20 (8)

- VF: 2 (1.6%) standard vs 6 (2.4%) simplified
- Adherence > 95%: 98% standard vs 96% simplified

- Overall performed very well but did not quite reach noninferiority
- **Highlights need for good patient selection for this approach**

Dore J Hep *In Press*

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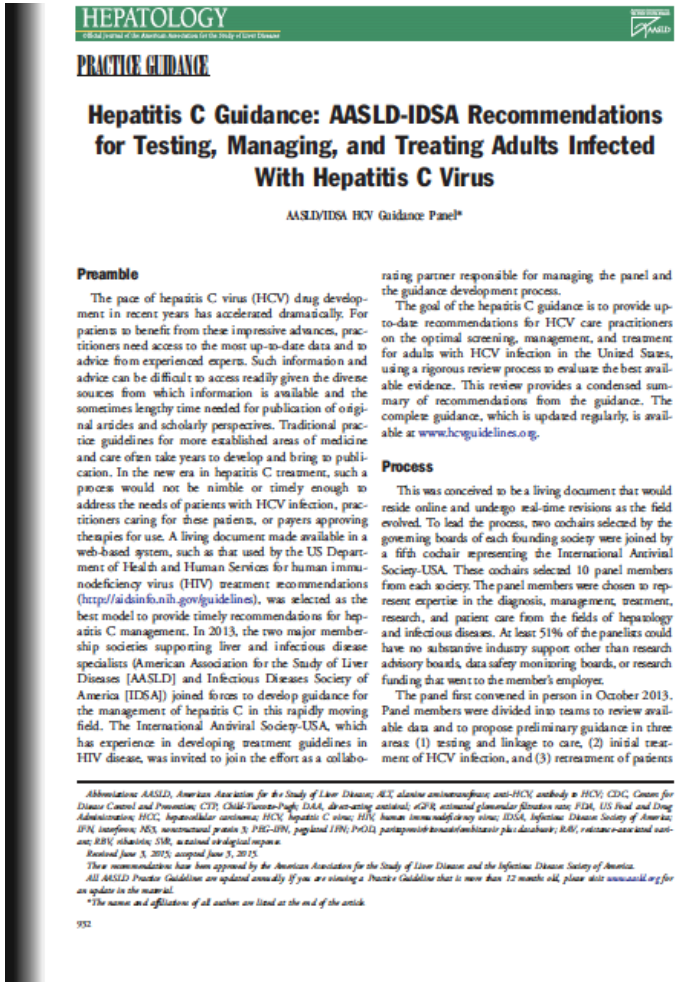
AASLD/IDSA guidance – down to 1 page!

2015 → 22 pages



HEPATOLOGY

PRACTICE GUIDANCE

Hepatitis C Guidance: AASLD-IDSA Recommendations for Testing, Managing, and Treating Adults Infected With Hepatitis C Virus

AASLD/IDSA HCV Guidance Panel*

Preamble

The pace of hepatitis C virus (HCV) drug development in recent years has accelerated dramatically. For patients to benefit from these impressive advances, practitioners need access to the most up-to-date data and to advice from experienced experts. Such information and advice can be difficult to access readily given the diverse sources from which information is available and the sometimes lengthy time needed for publication of original articles and scholarly perspectives. Traditional practice guidelines for more established areas of medicine and care often take years to develop and bring to publication. In the new era in hepatitis C treatment, such a process would not be nimble or timely enough to address the needs of patients with HCV infection, practitioners caring for these patients, or payers approving therapies for use. A living document made available in a web-based system, such as that used by the US Department of Health and Human Services for human immunodeficiency virus (HIV) treatment recommendations (http://aidsinfo.nih.gov/guidelines), was selected as the best model to provide timely recommendations for hepatitis C management. In 2013, the two major membership societies supporting liver and infectious disease specialists (American Association for the Study of Liver Diseases [AASLD] and Infectious Diseases Society of America [IDSA]) joined forces to develop guidance for the management of hepatitis C in this rapidly moving field. The International Antiviral Society-USA, which has experience in developing treatment guidelines in HIV disease, was invited to join the effort as a collaborating partner responsible for managing the panel and the guidance development process.

The goal of the hepatitis C guidance is to provide up-to-date recommendations for HCV care practitioners on the optimal screening, management, and treatment for adults with HCV infection in the United States, using a rigorous review process to evaluate the best available evidence. This review provides a condensed summary of recommendations from the guidance. The complete guidance, which is updated regularly, is available at www.hcvguidelines.org.

Process

This was conceived to be a living document that would reside online and undergo real-time revisions as the field evolved. To lead the process, two cochairs selected by the governing boards of each founding society were joined by a fifth cochair representing the International Antiviral Society-USA. These cochairs selected 10 panel members from each society. The panel members were chosen to represent expertise in the diagnosis, management, treatment, research, and patient care from the fields of hepatology and infectious diseases. At least 51% of the panelists could have no substantive industry support other than research advisory boards, data safety monitoring boards, or research funding that went to the member's employer.

The panel first convened in person in October 2013. Panel members were divided into teams to review available data and to propose preliminary guidance in three areas: (1) testing and linkage to care, (2) initial treatment of HCV infection, and (3) retreatment of patients

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; anti-HCV, antibody to HCV; CDC, Centers for Disease Control and Prevention; CTP, Child-Turcotte-Pugh; DAA, direct-acting antiviral; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDSA, Infectious Diseases Society of America; IFN, interferon; NS3, nonstructural protein 3; PEG-IFN, pegylated IFN; PrOD, paritaprevir/ritonavir/ombitasvir plus dasabuvir; RAV, resistance-associated variant; RBV, ribavirin; SVR, sustained virological response.

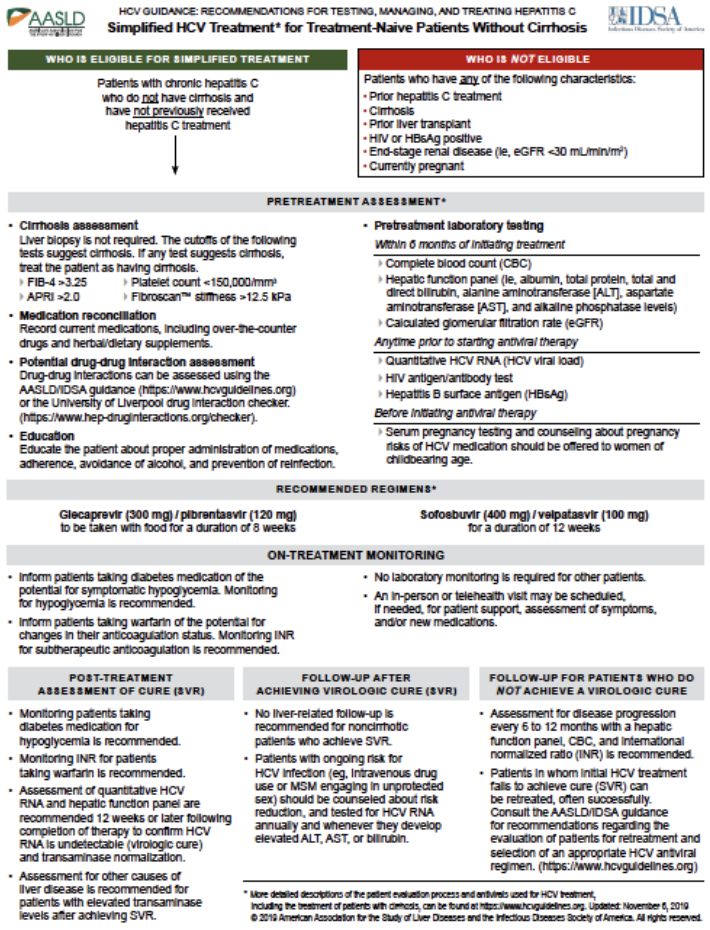
Received June 3, 2015; accepted June 5, 2015.

These recommendations have been approved by the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America.

All AASLD Practice Guidelines are updated annually. If you are viewing a Practice Guideline that is more than 12 months old, please visit www.aasld.org for an update to the material.

The names and affiliations of all authors are listed at the end of the article.

2019 → 1 page



AASLD | HCV GUIDANCE: RECOMMENDATIONS FOR TESTING, MANAGING, AND TREATING HEPATITIS C | IDSA

Simplified HCV Treatment* for Treatment-Naive Patients Without Cirrhosis

WHO IS ELIGIBLE FOR SIMPLIFIED TREATMENT

Patients with chronic hepatitis C who do not have cirrhosis and have not previously received hepatitis C treatment

WHO IS *NOT* ELIGIBLE

Patients who have any of the following characteristics:
- Prior hepatitis C treatment
- Cirrhosis
- Prior liver transplant
- HIV or HBsAg positive
- End-stage renal disease (ie, eGFR <30 mL/min/m²)
- Currently pregnant

PRETREATMENT ASSESSMENT*

- **Cirrhosis assessment**
  Liver biopsy is not required. The cutoffs of the following tests suggest cirrhosis. If any test suggests cirrhosis, treat the patient as having cirrhosis.
  - FIB-4 >3.25
  - Platelet count <150,000/mm³
  - APRI >2.0
  - Fibroscan™ stiffness >12.5 kPa
- **Medication reconciliation**
  Record current medications, including over-the-counter drugs and herbal/dietary supplements.
- **Potential drug-drug interaction assessment**
  Drug-drug interactions can be assessed using the AASLD/IDSA guidance (https://www.hcvguidelines.org) or the University of Liverpool drug interaction checker. (https://www.hep-druginteractions.org/checker).
- **Education**
  Educate the patient about proper administration of medications, adherence, avoidance of alcohol, and prevention of reinfection.
- **Pretreatment laboratory testing**

  Within 6 months of initiating treatment
  - Complete blood count (CBC)
  - Hepatic function panel (ie, albumin, total protein, total and direct bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase levels)
  - Calculated glomerular filtration rate (eGFR)

  Anytime prior to starting antiviral therapy
  - Quantitative HCV RNA (HCV viral load)
  - HIV antigen/antibody test
  - Hepatitis B surface antigen (HBsAg)

  Before initiating antiviral therapy
  - Serum pregnancy testing and counseling about pregnancy risks of HCV medication should be offered to women of childbearing age.

RECOMMENDED REGIMENS*

Glecaprevir (300 mg) / pibrentasvir (120 mg) to be taken with food for a duration of 8 weeks

Sofosbuvir (400 mg) / velpatasvir (100 mg) for a duration of 12 weeks

ON-TREATMENT MONITORING

- Inform patients taking diabetes medication of the potential for symptomatic hypoglycemia. Monitoring for hypoglycemia is recommended.
- Inform patients taking warfarin of the potential for changes in their anticoagulation status. Monitoring INR for subtherapeutic anticoagulation is recommended.
- No laboratory monitoring is required for other patients.
- An in-person or telehealth visit may be scheduled, if needed, for patient support, assessment of symptoms, and/or new medications.

POST-TREATMENT ASSESSMENT OF CURE (SVR)

- Monitoring patients taking diabetes medication for hypoglycemia is recommended.
- Monitoring INR for patients taking warfarin is recommended.
- Assessment of quantitative HCV RNA and hepatic function panel are recommended 12 weeks or later following completion of therapy to confirm HCV RNA is undetectable (virologic cure) and transaminase normalization.
- Assessment for other causes of liver disease is recommended for patients with elevated transaminase levels after achieving SVR.

FOLLOW-UP AFTER ACHIEVING VIROLOGIC CURE (SVR)

- No liver-related follow-up is recommended for noncirrhotic patients who achieve SVR.
- Patients with ongoing risk for HCV infection (eg, intravenous drug use or MSM engaging in unprotected sex) should be counseled about risk reduction, and tested for HCV RNA annually and whenever they develop elevated ALT, AST, or bilirubin.

FOLLOW-UP FOR PATIENTS WHO DO *NOT* ACHIEVE A VIROLOGIC CURE

- Assessment for disease progression every 6 to 12 months with a hepatic function panel, CBC, and international normalized ratio (INR) is recommended.
- Patients in whom initial HCV treatment fails to achieve cure (SVR) can be retreated, often successfully. Consult the AASLD/IDSA guidance for recommendations regarding the evaluation of patients for retreatment and selection of an appropriate HCV antiviral regimen. (https://www.hcvguidelines.org)

* More detailed descriptions of the patient evaluation process and antivirals used for HCV treatment, including the treatment of patients with cirrhosis, can be found at https://www.hcvguidelines.org. Updated: November 6, 2019

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What is on the 1 page?

Eligible for simplified assessment – No cirrhosis, no prior DAAs, no HIV/HBV

Pretreatment Assessment

- **Exclude cirrhosis** – any of the following suggests cirrhosis
  - FIB4>3.25
  - Fibroscan>12.5 KPa
  - APRI>2.0
  - Plt< 150,000
- **Other labs**
  - Liver panel – ALT/AST, INR, Bili, Albumin + Creatinine
  - HCV RNA
  - HIV, HBsAg
  - Pregnancy test
- **Drug interactions → look them up**

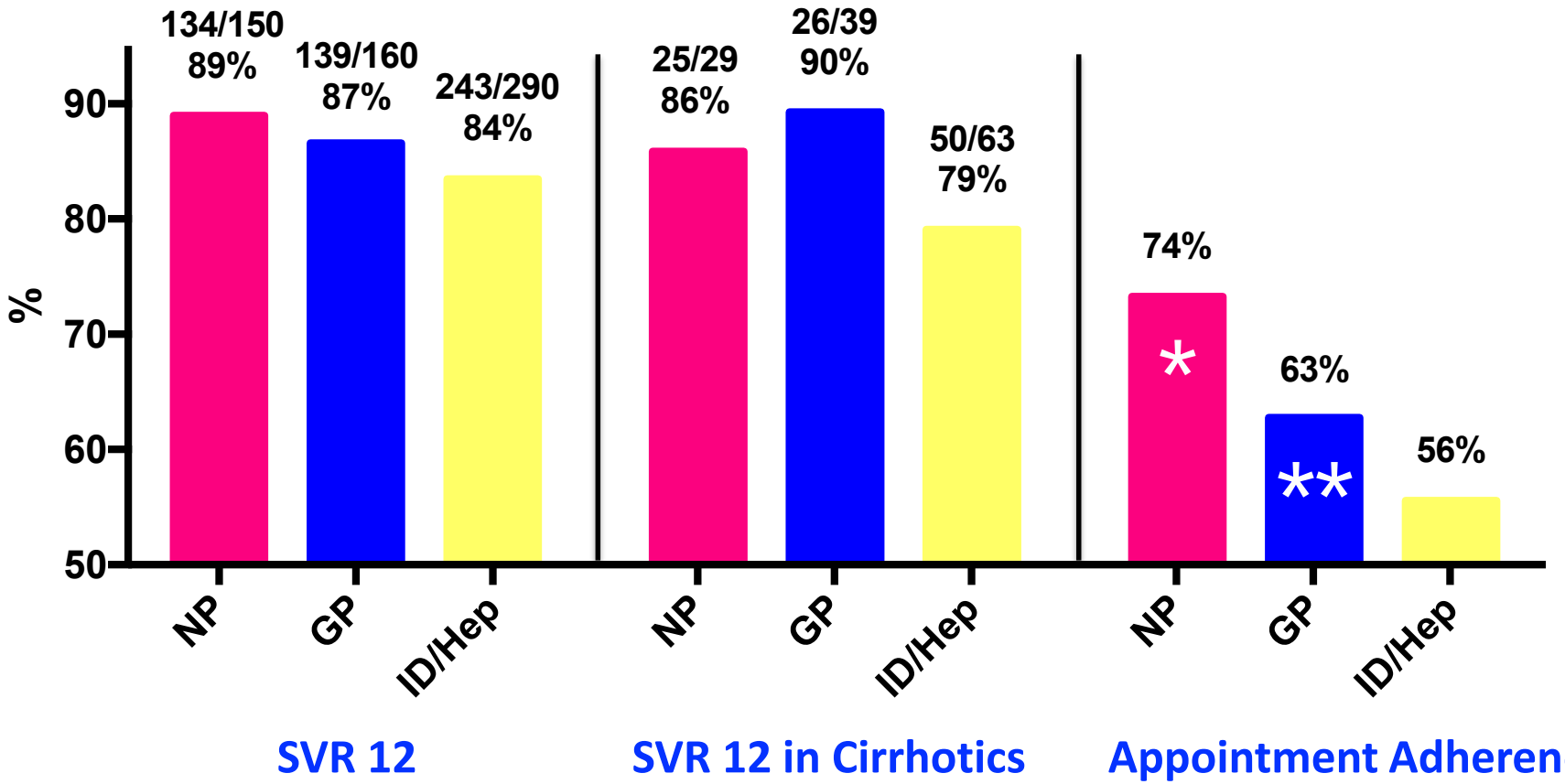
Treatment

- **GLE/PIB x 8 weeks or SOF/VEL x 12 weeks (no genotyping required)**
- No monitoring required (Blood sugar if DM, INR if on warfarin)

Post–treatment follow-up

- SVR12 HCV RNA – if no SVR, retreat
- HCV RNA serially if ongoing risk exposures

Time to give up some turf: Treatment should move out of specialty clinics



So my how many years of training and research are reduced to 3 hours???

Kattakhuzy Annals Int Med 2017

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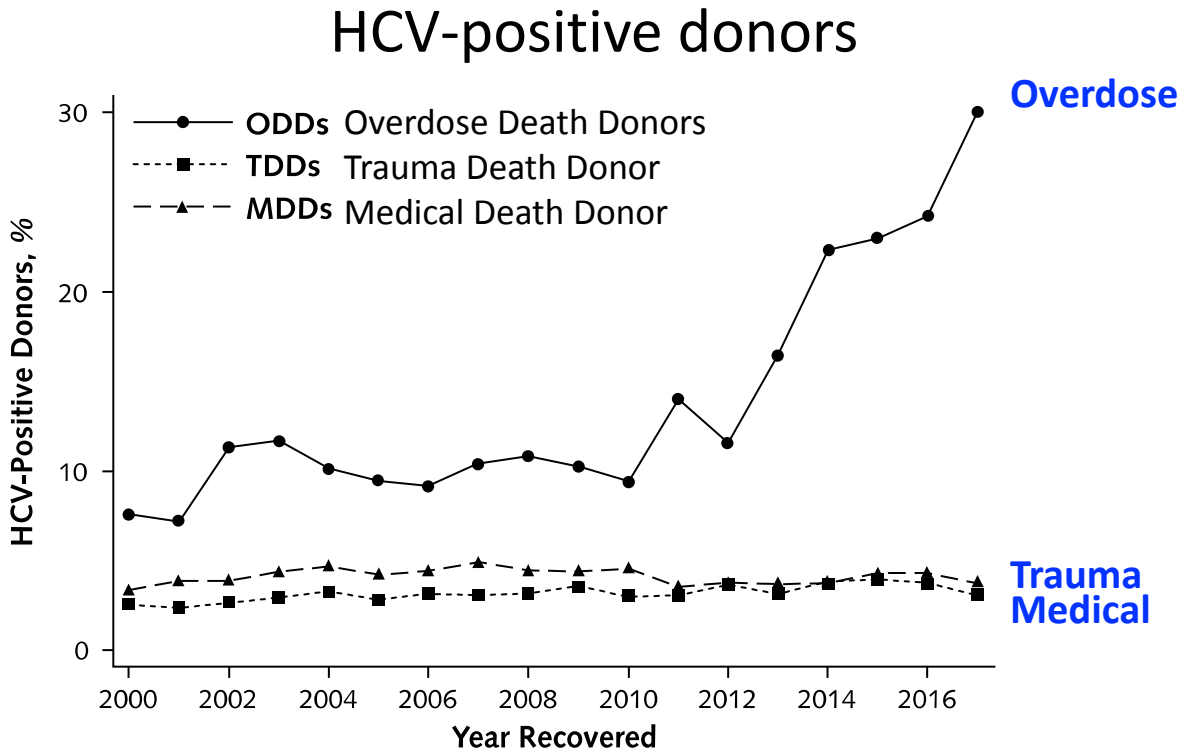
If it’s so easy to treat…maybe we can give it to people on purpose…

Increasing HCV-infected donors



Most are young and often otherwise healthy donors

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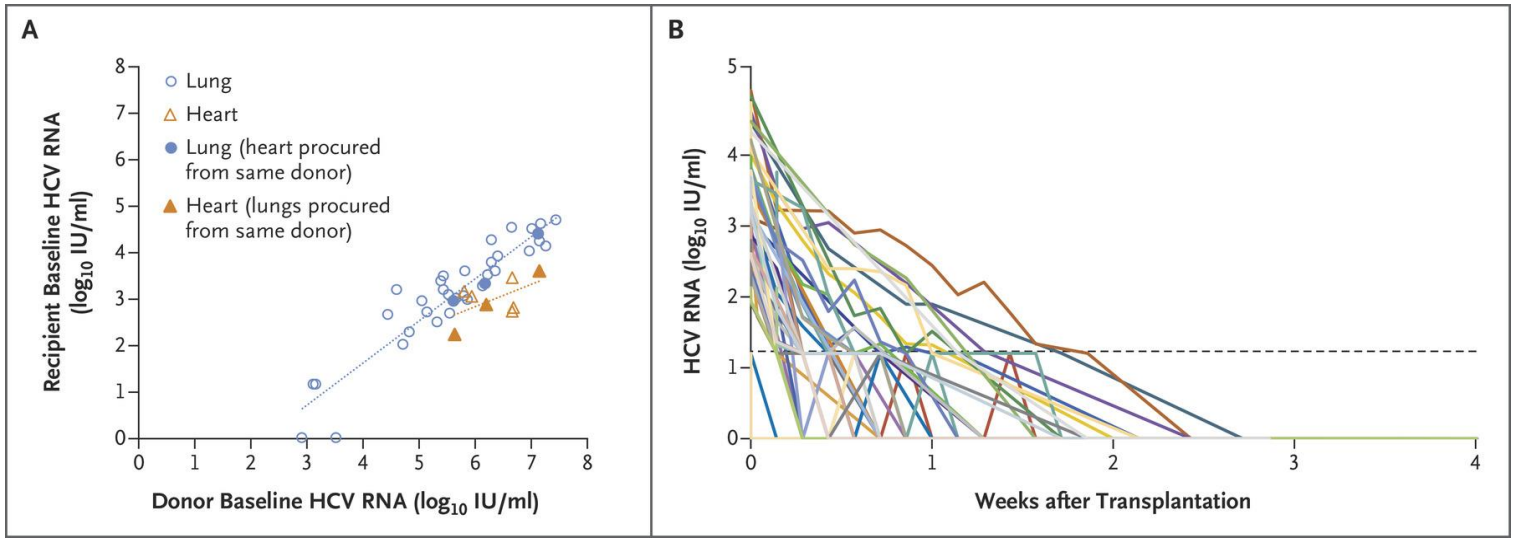
Using HCV+ donors in HCV- recipients

- 36 lung + 8 heart transplants from HCV NAT+ donors
- SOF/VEL first dose given a few hours post-transplant then x 4w

- **Viremia**
  - 42 of 44 recipients
  - **Median VL 3.26 (0 to 4.6 log IU/mL)** correlated with donor VL
  - Rapidly cleared – negative by week 2
- **Genotype**
  - G1 61%
  - G2 17%
  - G3 17%
  - Indet 5%



Wooley NEJM 2019

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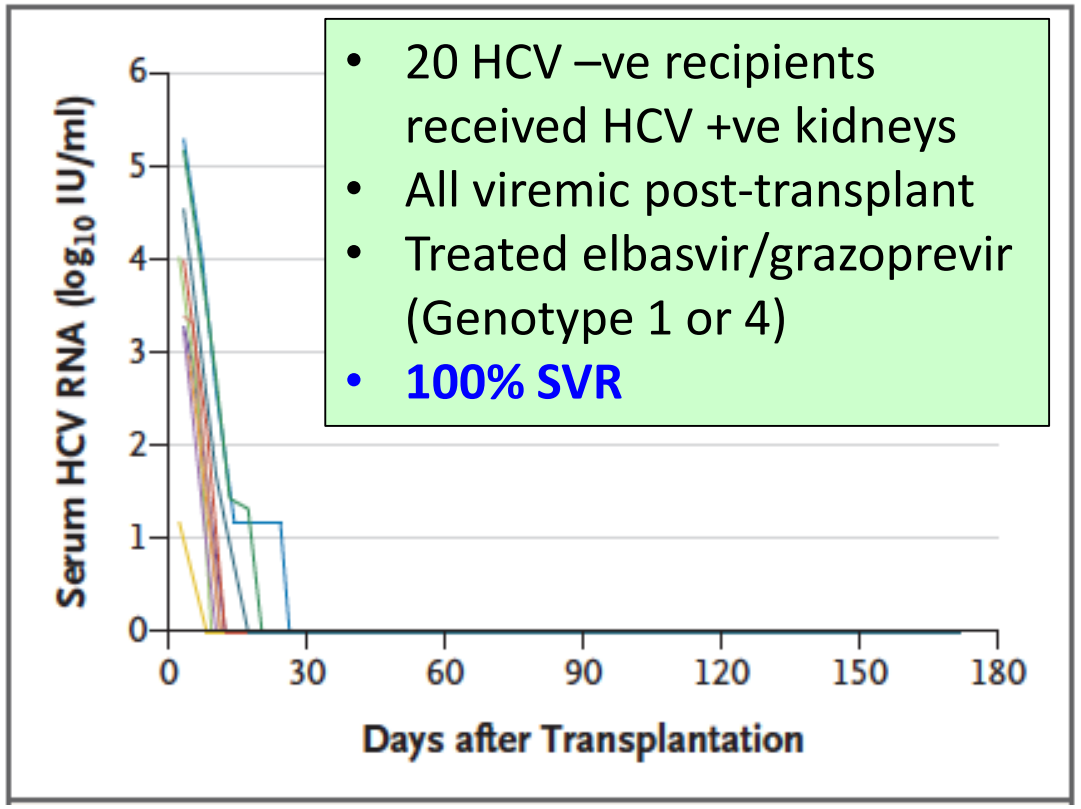
Using HCV+ donors in HCV- recipients

The NEW ENGLAND JOURNAL of MEDICINE

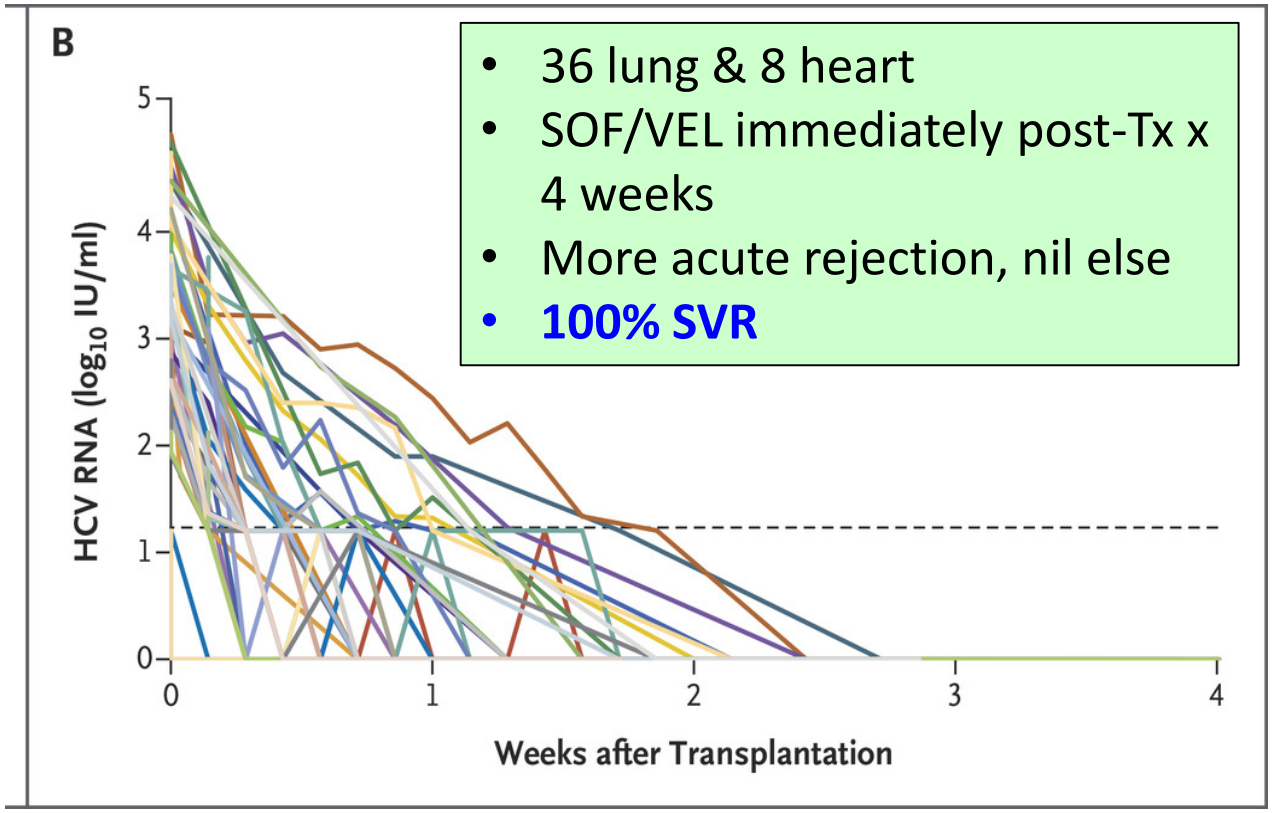
Trial of Transplantation of HCV-Infected Kidneys into Uninfected Recipients



- 20 HCV –ve recipients received HCV +ve kidneys
- All viremic post-transplant
- Treated elbasvir/grazoprevir (Genotype 1 or 4)
- **100% SVR**

The NEW ENGLAND JOURNAL of MEDICINE

Heart and Lung Transplants from HCV-Infected Donors to Uninfected Recipients



- 36 lung & 8 heart
- SOF/VEL immediately post-Tx x 4 weeks
- More acute rejection, nil else
- **100% SVR**

Goldberg NEJM 2017, Woolley NEJM 2019

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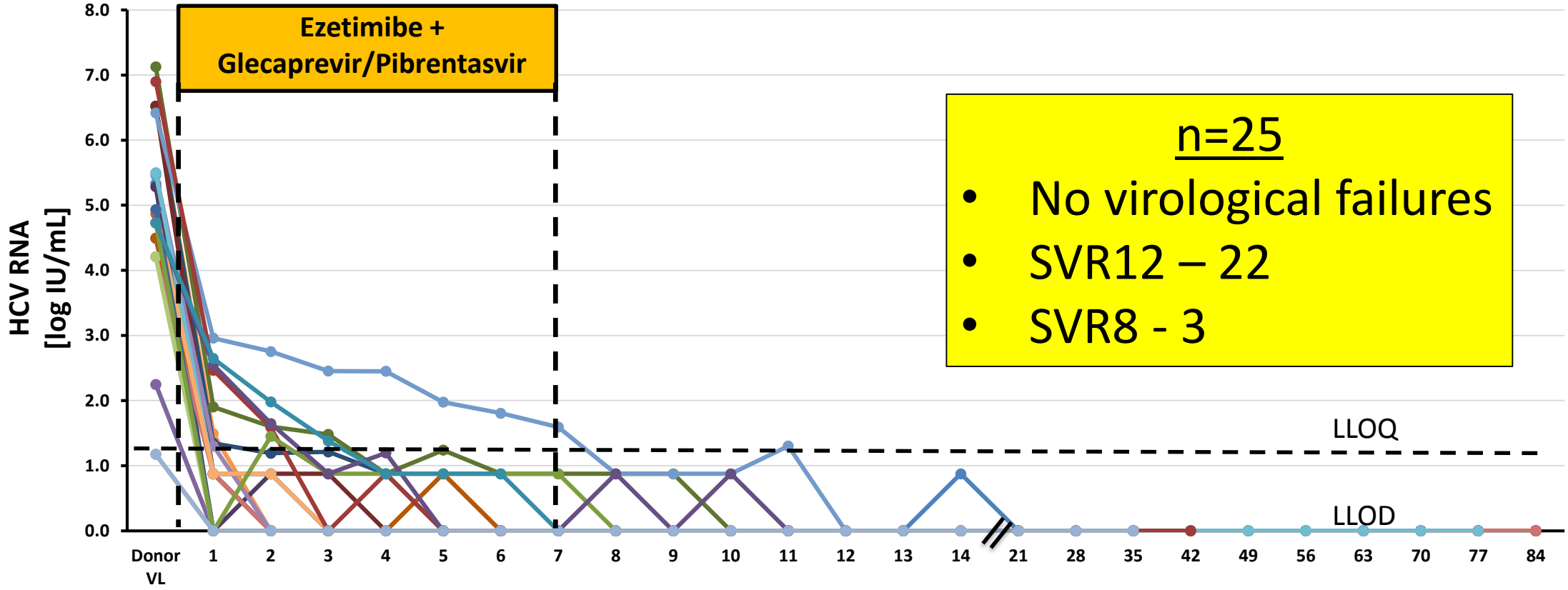
Prevention is better than treatment

25 recipients from 14 donors → **GLE/PIB + Ezetimibe before and x 7 days after transplant**



n=25

- No virological failures
- SVR12 – 22
- SVR8 - 3

It can't get much easier…

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Issues after treatment

1. Consequences of liver disease

- Only an issue with cirrhosis (fibrosis assessment **pre-treatment!**)
- HCC risk
- Liver function – MELD purgatory (later to come)

2. Reinfection risk

- Ongoing exposures – HCV RNA testing q6-12 m
- No ongoing exposures – annual ALT, promote liver health (diet & ETOH) and *nothing else!*

- Communicate information well - people don't know what SVR means
- Templated notes with key features
  e.g. anti-HCV Ab remains positive → don't check it!

What About Post-SVR HCC Surveillance?

- AASLD/IDSA and EASL guideline recommendation: US surveillance every 6 mos after SVR in patients with "advanced fibrosis" or cirrhosis (ie, F3/F4)[1,2]

Characteristic	HCC Incidence per 100 Person-Yrs[3]	ICER for Surveillance (Ultrasound Every 6 Mos) vs No Surveillance, per QALY[4]
SVR		
▪ Without	3.45	--
▪ With	0.90	--
Cirrhosis status		
▪ **With**	**1.82**	**$40,803**
▪ Without	0.34	$187,000
FIB-4		
▪ **> 3.25**	**2.16**	**$32,016**
▪ 1.45-3.25	0.45	$133,977
▪ < 1.45	0.30	

Can we limit surveillance post-SVR to those with **cirrhosis or FIB-4 > 3.25?**

Zangneh Clin Gastro Hep2019;

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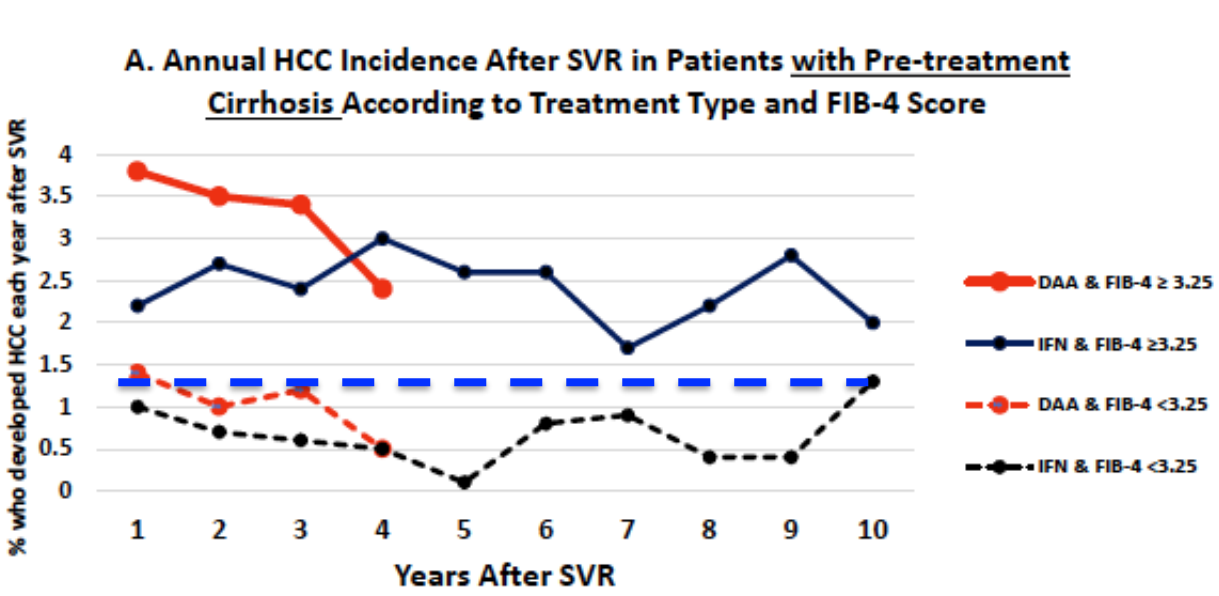
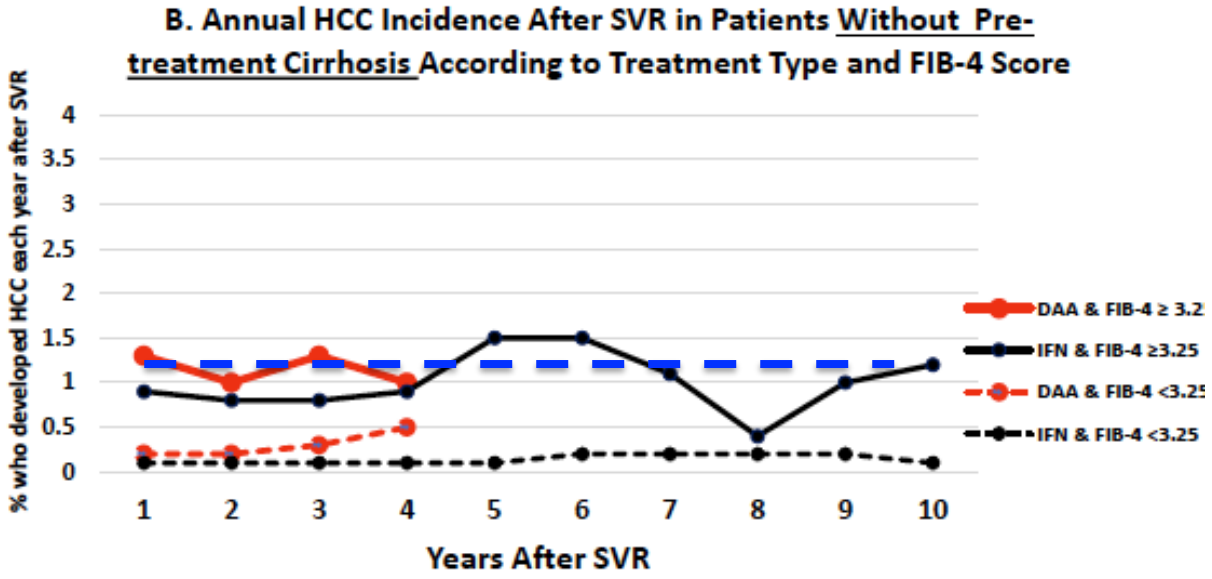
Using FIB4 to guide post-SVR HCC surveillance

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

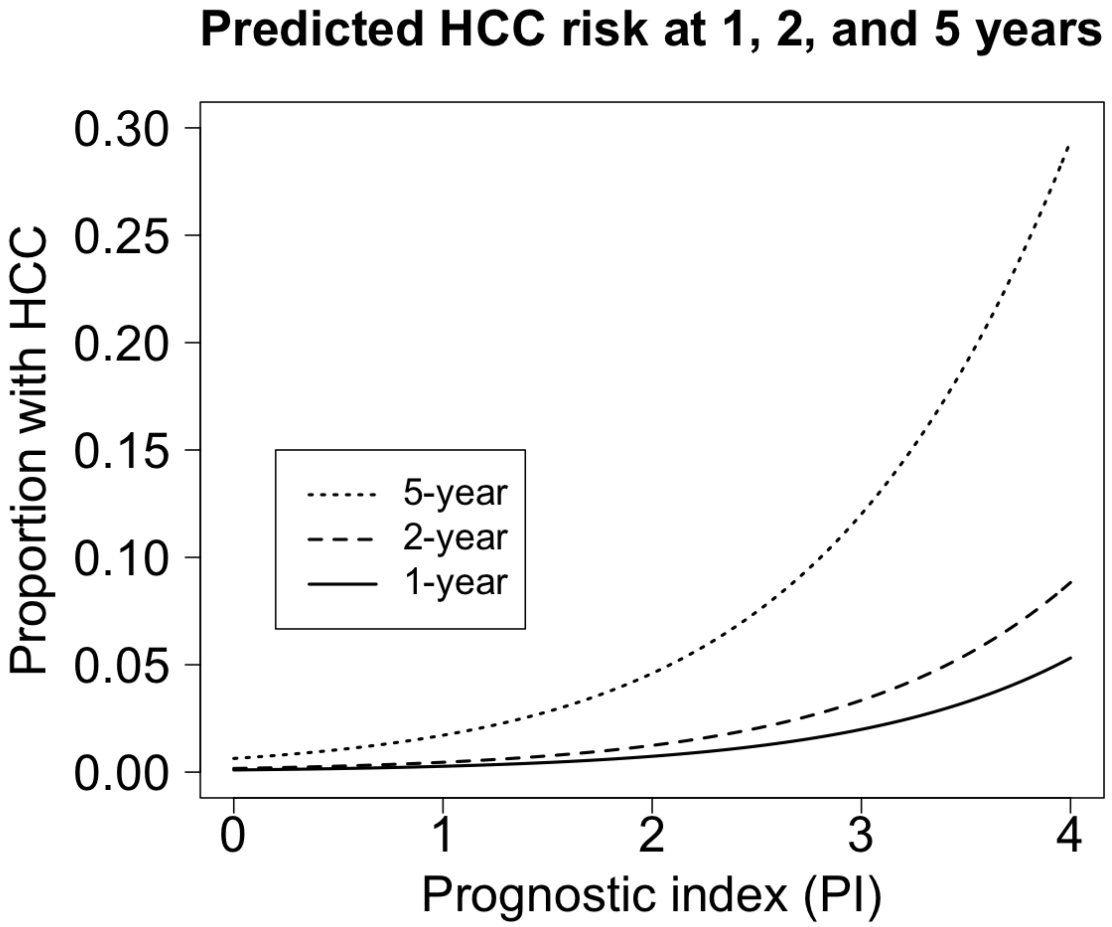
TORONTO CENTRE FOR LIVER DISEASE

Can we improve on FIB4?

1,131 F3/F4 patients followed after SVR → 50 HCCs & validated in 2 Scottish cohorts n=1,176

Model developed using
- Age
- Sex
- Platelets
- Albumin

C-index
- **FIB4 – 0.66**
- **ASPA - 0.80**



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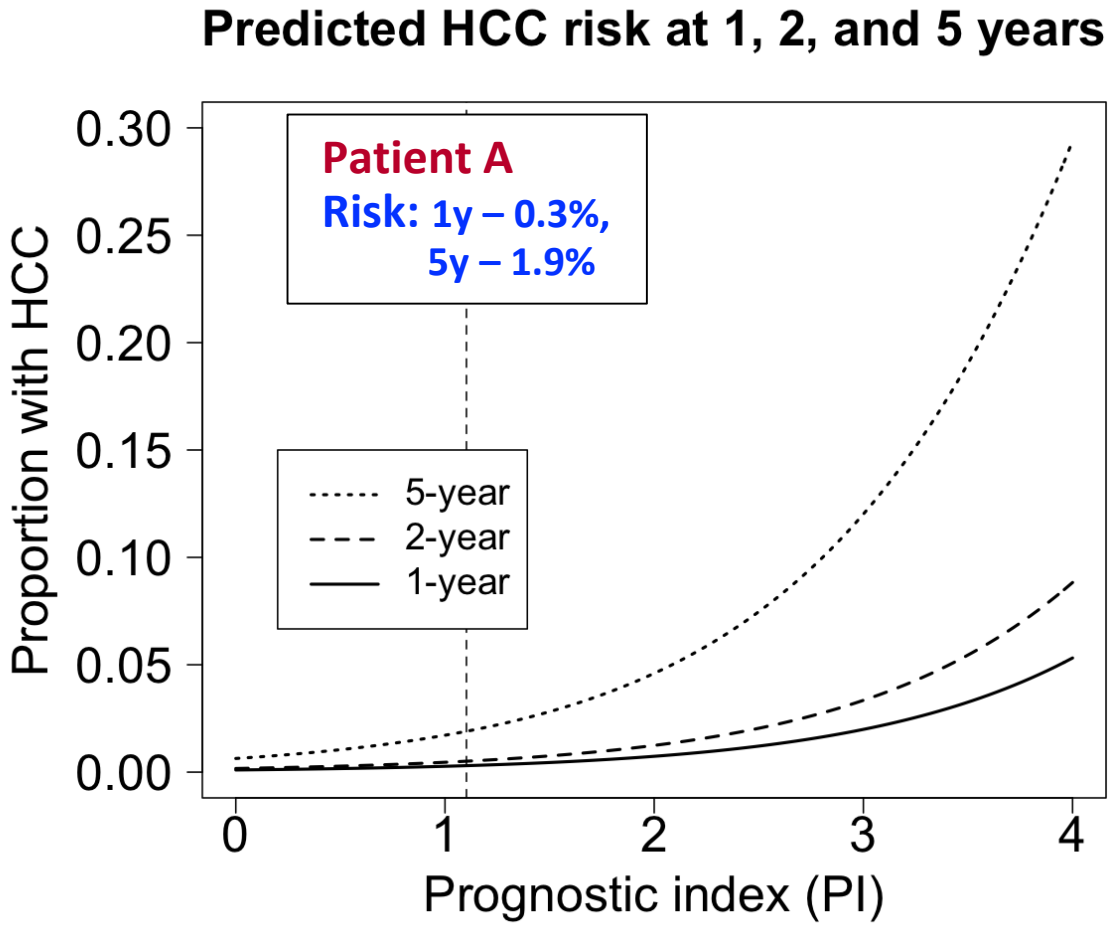
A. Age = 50, female, albumin = 40, platelets = 150; **PI = 1.10**



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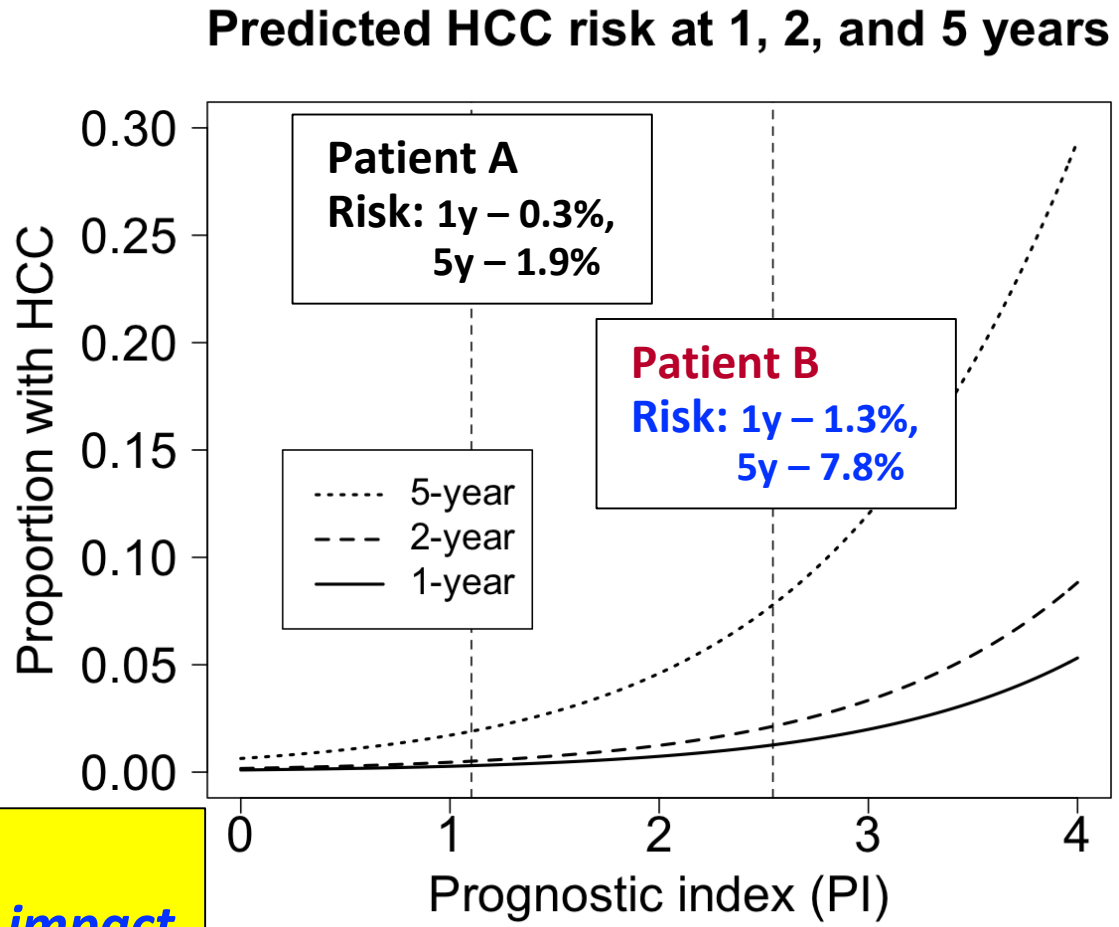
- **ASPA - 0.80**

A. Age = 50, female, albumin = 40, platelets = 150; **PI = 1.10**

B. Age = 60, male, albumin = 40, platelets = 150; **PI = 2.54**



- Improved prediction over FIB4
- Surprisingly – ***post-treatment variables of minimal impact***

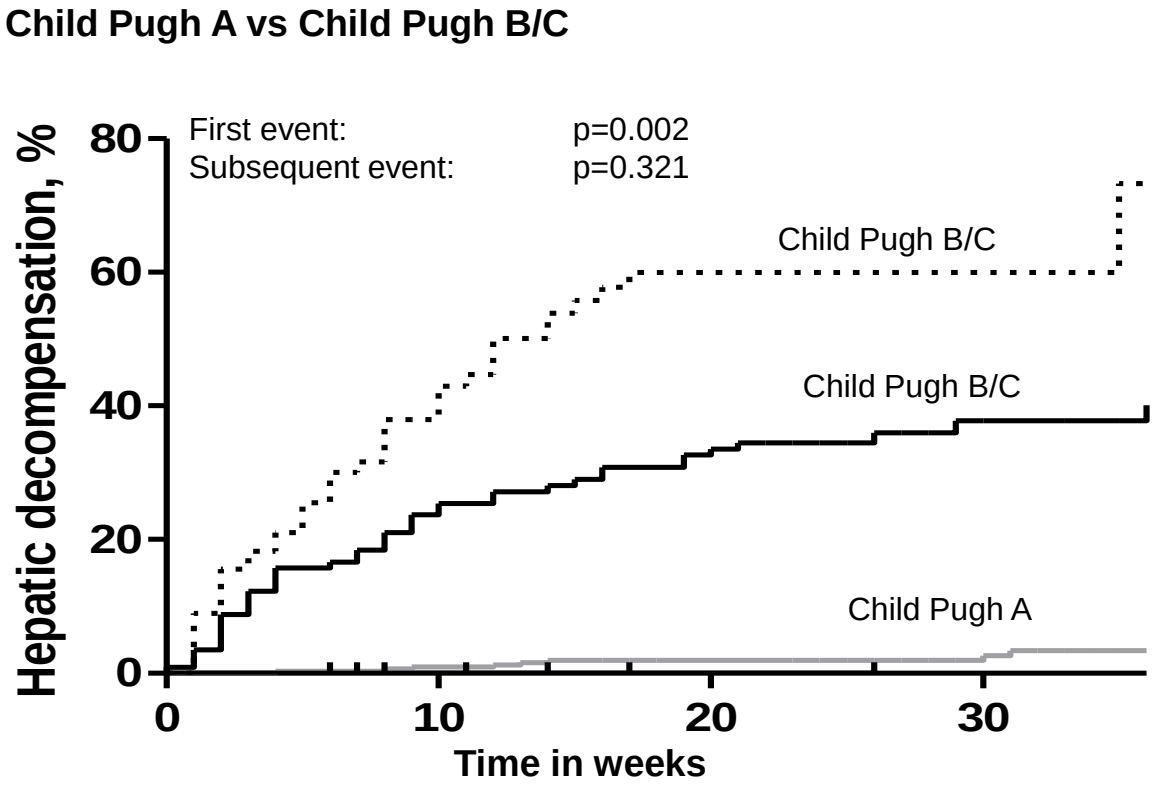
TORONTO CENTRE FOR LIVER DISEASE

Outline

- How easy can it be?
  - Simplified therapy
    - Pretreatment assessment and regimen selection
    - On-treatment monitoring
    - Post-treatment follow-up
- **The not so easy**
  - **Difficult patients**
    - **The liver**
    - The virus

Safety first

433 patients with cirrhosis treated with DAAs at 4 centers

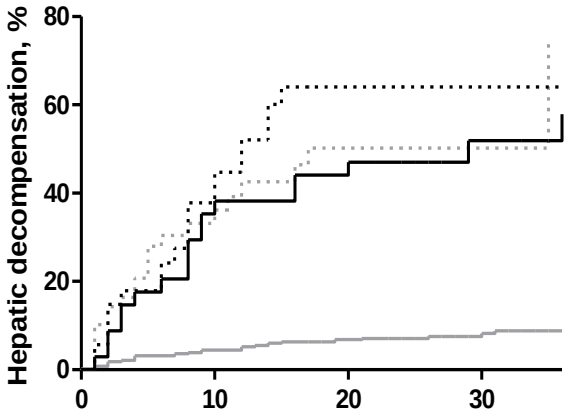


Treatment very safe in CP-A

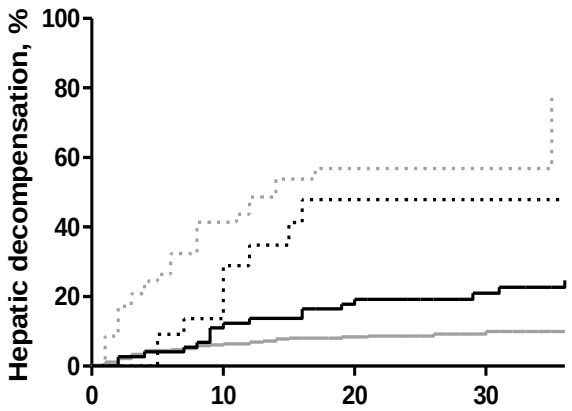
If CP-B or C…who is at risk?

Factors associated with decompensation during treatment

MELD <15 vs ≥15

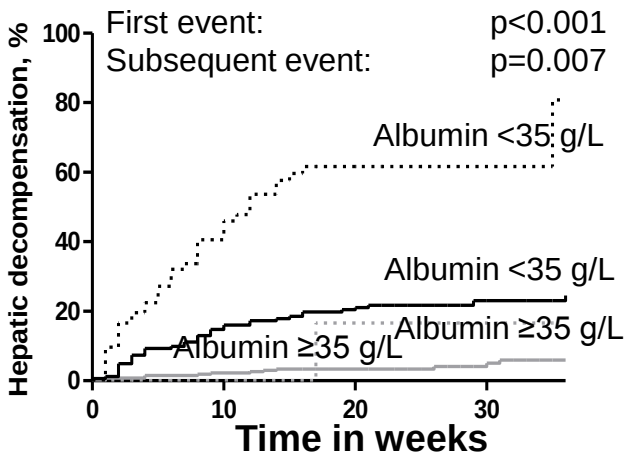


G3 vs non-G3



3

Albumin<3.5 vs >3.5



But even if you cure them…do they get better?

Same, same…but different

Case 1

- 54 yo Pakistani F G4 cirrhosis, NR to Peg/RBV
- Complications:
  - Variceal bleed x 2 - banded
  - Mild encephalopathy
  - Diuretic controlled ascites
  - MELD – 18-20
- Treated SOF/SIM + RBV x 24w
- SVR in July 2015

Case 2

- 72 yo Caucasian M G1b
- Past treatment Peg/RBV x 2, P/R + TVR → NR
- Complications:
  - Encephalopathy – lactulose
  - Ascites – Furos 120, Spir 300
  - MELD 18-22
- Treated SOF/SIM + RBV x 24w
- SVR in Nov 2015

Who will do better?

Same, same...but different

Case 1 – 54F G4

- Post SVR course
  - Persistent ascites
  - Persistent encephalopathy (lactulose/rifaximin)
  - Umbilical hernia repair (2 mild incarcerations)
  - MELD 16-18
- June 2018 – listed for transplant
- Apr 2019 – finally transplanted (took a long time due to low MELD)

Case 2 – 72M G1b

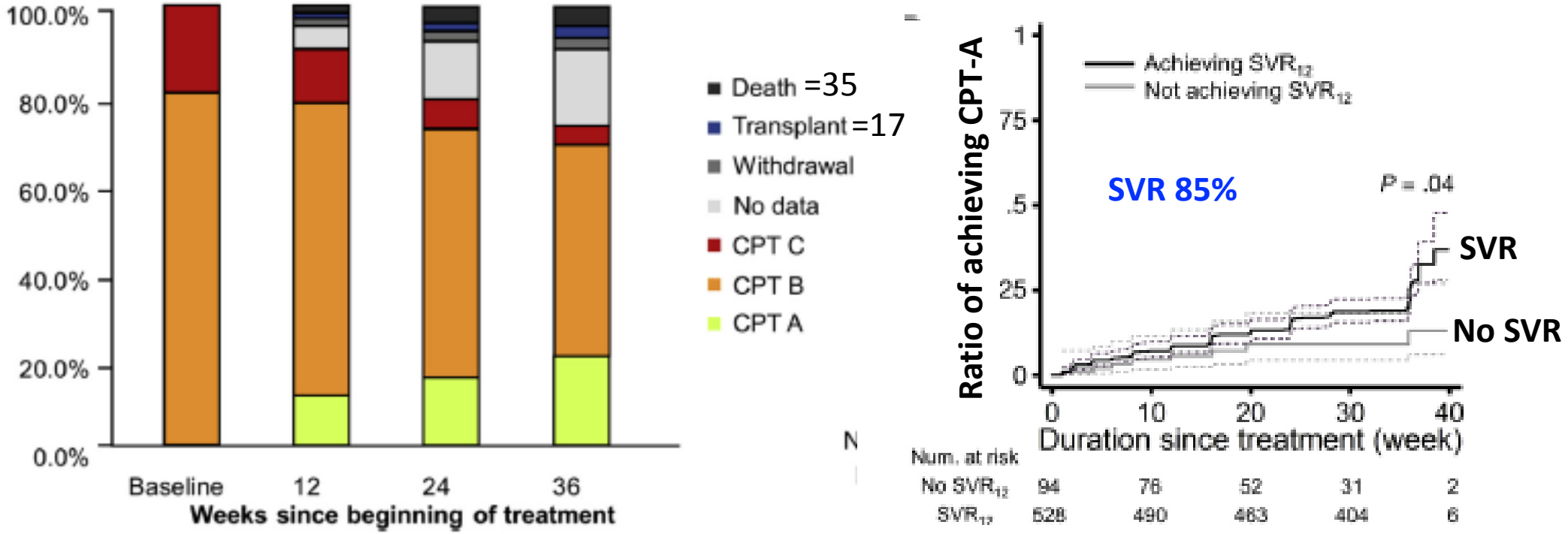
- Post SVR course
  - Resolution of ascites – off diuretics since mid-2016
  - Resolution of encephalopathy
  - No other complications
  - MELD 6-8
- Sep 2019 – highly functional 76 yo man

How do we avoid MELD purgatory?

Jaundiced with ascites (and mildly encephalopathic) with no prospect of a transplant….

Can we predict MELD purgatory?

Follow-up SOF trials for decompensated cirrhosis (CP-B n=502, CP-C n=120) chance of improvement to CP-A or **MELD purgatory = CPT-B/C with MELD<15**



- Improvement in some but definitely not all (or even most)
- SVR associated with improvement but short-term follow-up (36w)

El-Sherif, Jiang Gastro 2018

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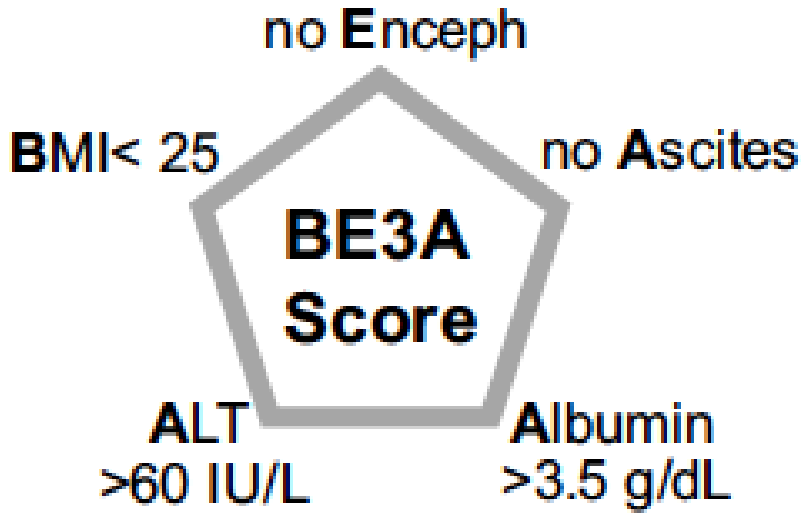
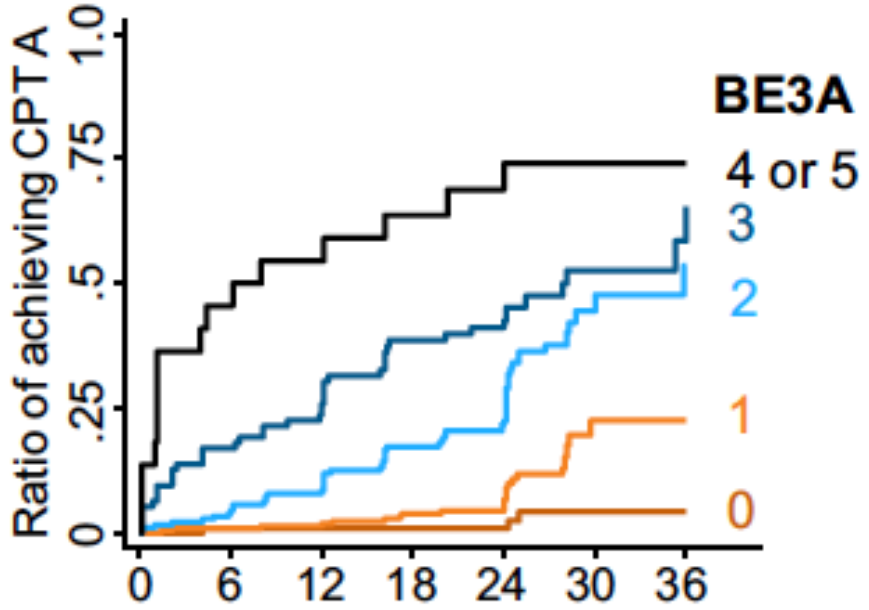
A simple pre-treatment score

Assign 1 point to each of the following





BE3A 0	106	99	89	19	52%
BE3A 1	219	206	181	25	
BE3A 2	180	161	131	17	44%
BE3A 3	95	70	49	14	
BE3A 4-5	22	10	7	1	3.5%

El-Sherif, Jiang Gastro 2018

TORONTO CENTRE FOR LIVER DISEASE

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BE3A score = 2

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  - Encephalopathy – lactulose
  - Ascites – Furos 120, Spir 300
  - MELD 18-22
- Treated SOF/SIM + RBV x 24w
- SVR in Nov 2015

BE3A score = 2

So where are we with treating decompensated patients?

- Fortunately there are fewer…but not none - late diagnosis still an issue
  - 28% of those of those with decompensation/HCC diagnosed within 6 m of complication!!
- Don't miss it
- If low BE3A score (0/1) – transplant first…(<25% chance of improving to CP-A with SVR)
- If not low…
  - Careful discussion with patients about pros and cons to treatment
  - Careful discussion with transplant program about pros and cons to treatment
- **If you treat – be careful**

Important Points in Decompensated Cirrhosis

- **Be careful!!**
  - Sick patients may worsen at any time: make sure patient is aware of risks
  - Treat in experienced centers and see patient frequently
  - Drugs can be toxic
    - **ALL protease inhibitors contraindicated!**
    - Even LDV/SOL, SOF/VEL can cause liver injury in this setting
- **Add ribavirin**
  - Unclear why but seems to be helpful

Outline

- How easy can it be?
  - Simplified therapy
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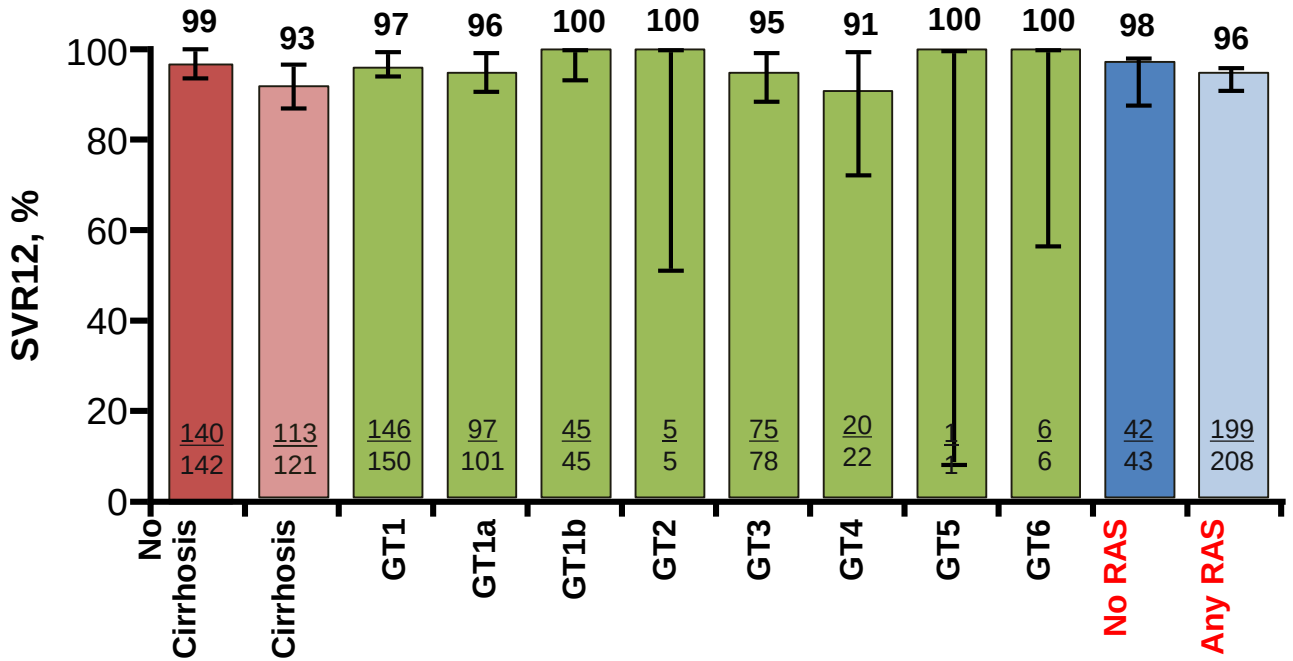
- **The not so easy**
  - Difficult patients
    - The liver
    - **The virus**

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!

- 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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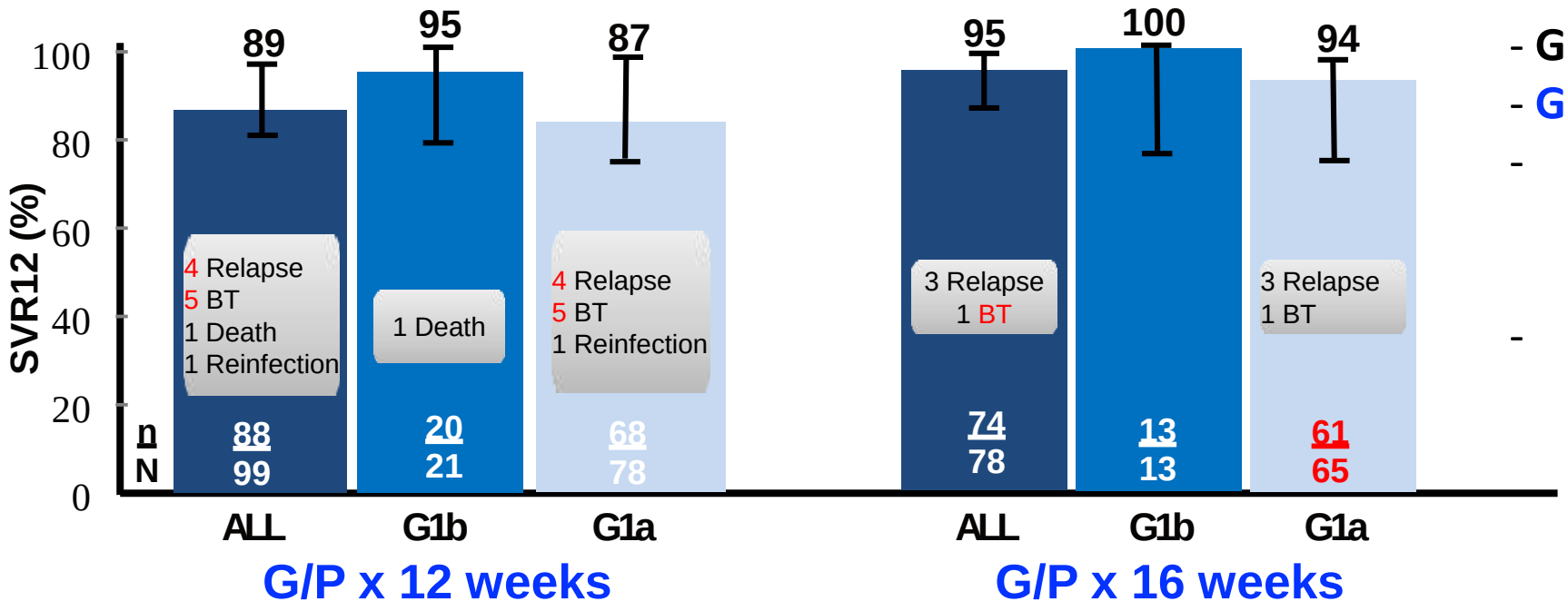
Retreatment with GLE/PIB

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

Sulkowski et al. AASLD 2018, Abstract 226

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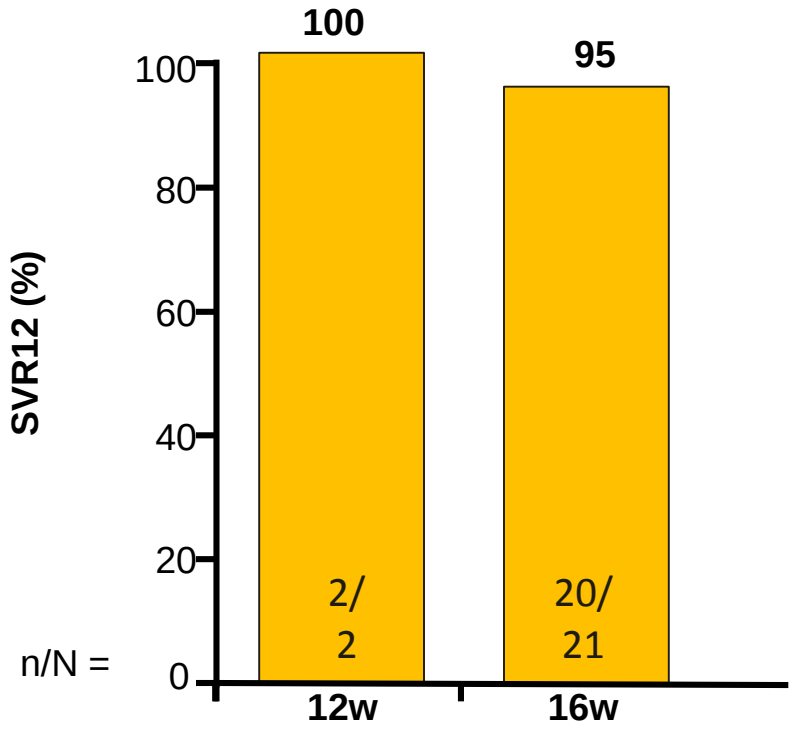
And after G/P (and likely SVV) failure?

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

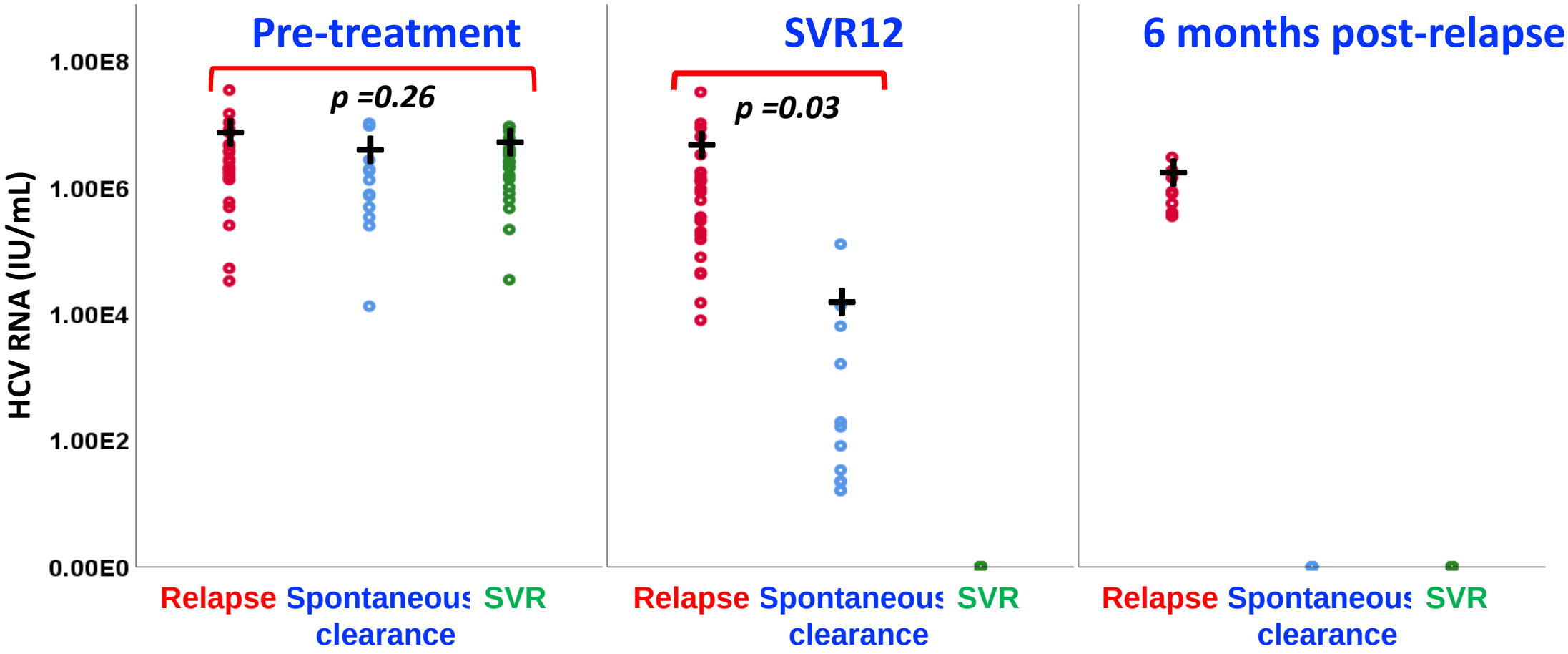


- 1 relapse G1a – prior SOF/LDV then G/P before G/P + RBV
- Overall reassuring
- Unclear if RBV is necessary
- Duration unclear
- Need more data with SOF + G/P

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)

Confirm relapse before retreatment



TORONTO CENTRE FOR LIVER DISEASE

Bottom line on retreatment

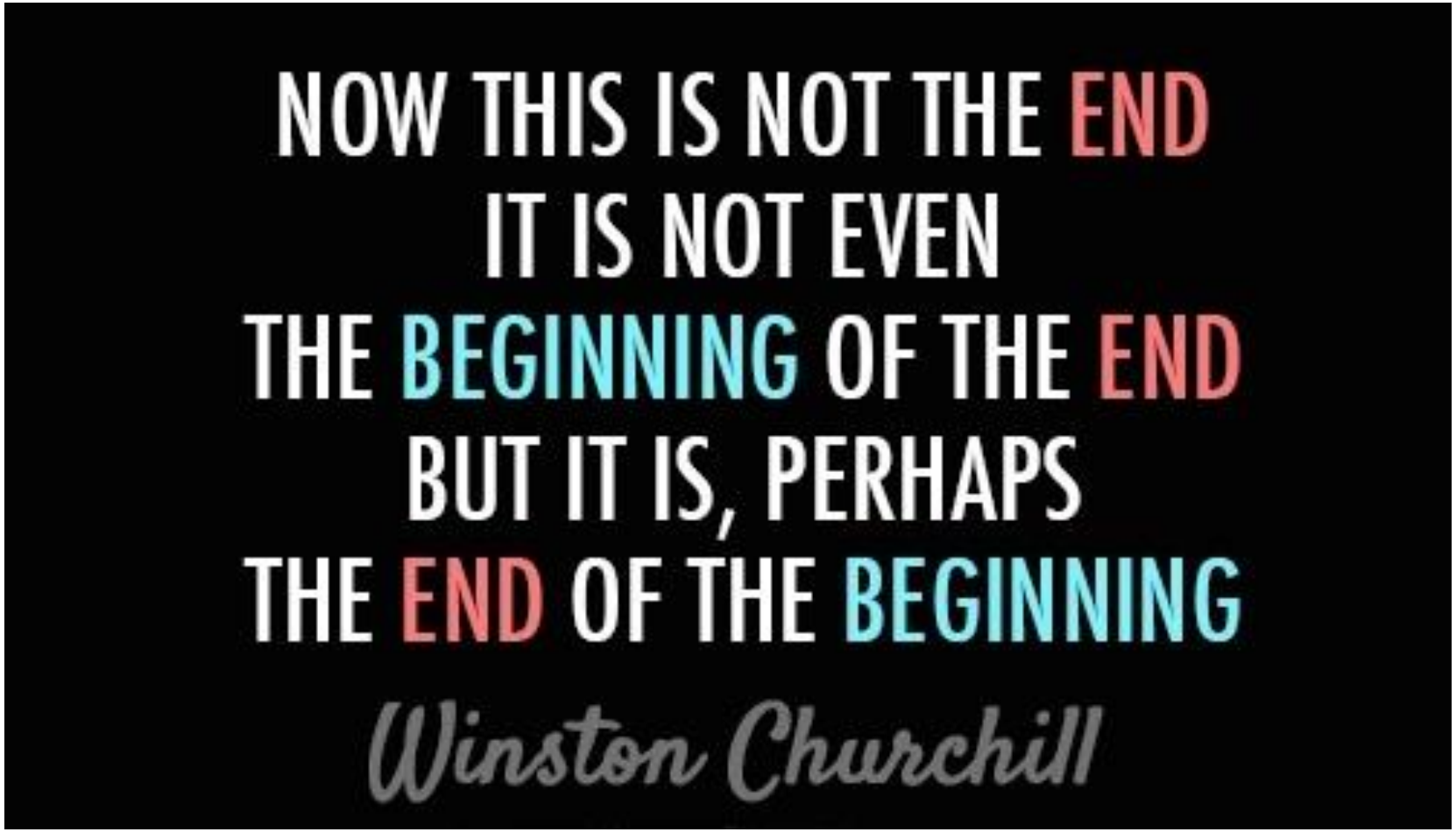
- Fortunately a rare event
- Check a few things:
  1. **Adherence**
  2. **DDIs**
  3. **Spontaneous clearance after relapse** (~15%, especially if low VL)
  4. **Reinfection** – discuss with everyone
- **Do resistance testing – even if it does not change your plan…it may one day!**

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**

Summary

- Most HCV treatment is now VERY easy
- Fibrosis assessment still important
- Post-SVR surveillance for cirrhotics only → FIB4 or ASPA useful guide
- Decompensated cirrhosis still challenging – don't be afraid to transplant first
- Retreatment after DAA failure usually easy…but please do resistance testing to help the few cases that are not!
- Our biggest challenge is still finding and engaging the undiagnosed & untreated…we still have lots of work to do!



Was he talking about HCV in the era of DAAs?