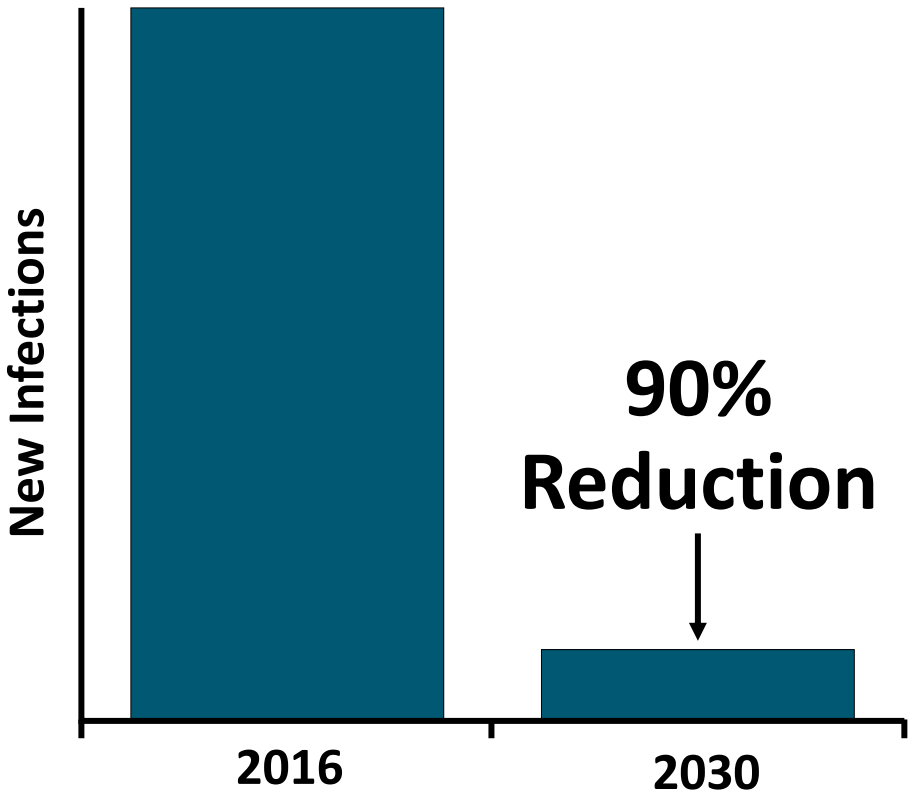
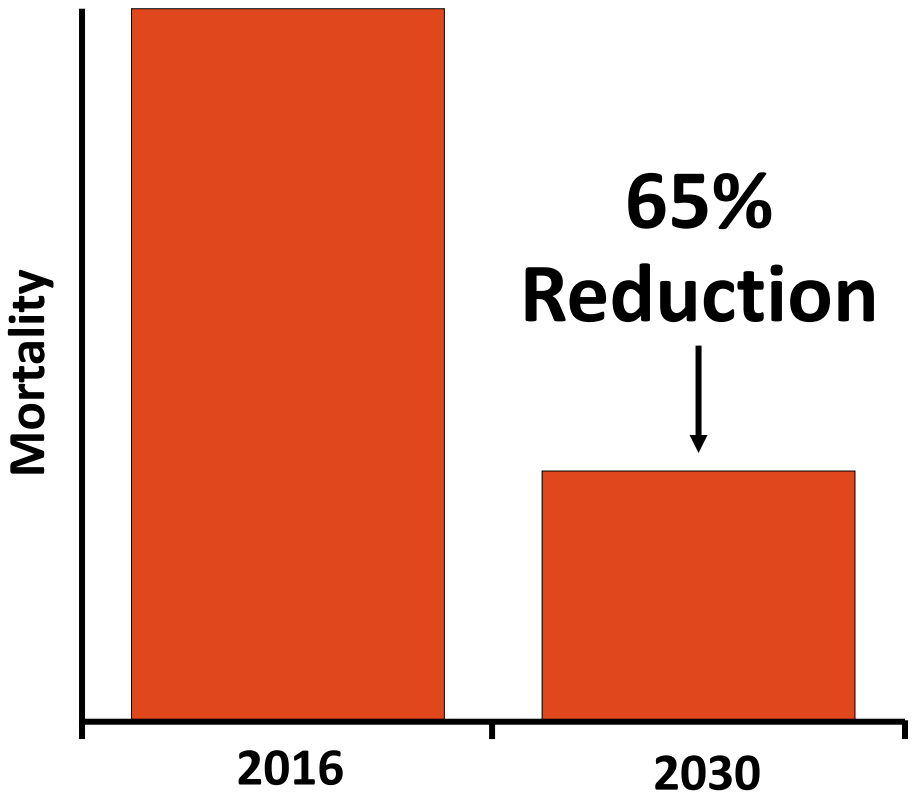
Semplificare il trattamento dei pazienti con Epatite C

Cosimo Colletta

WHO HCV Elimination Targets

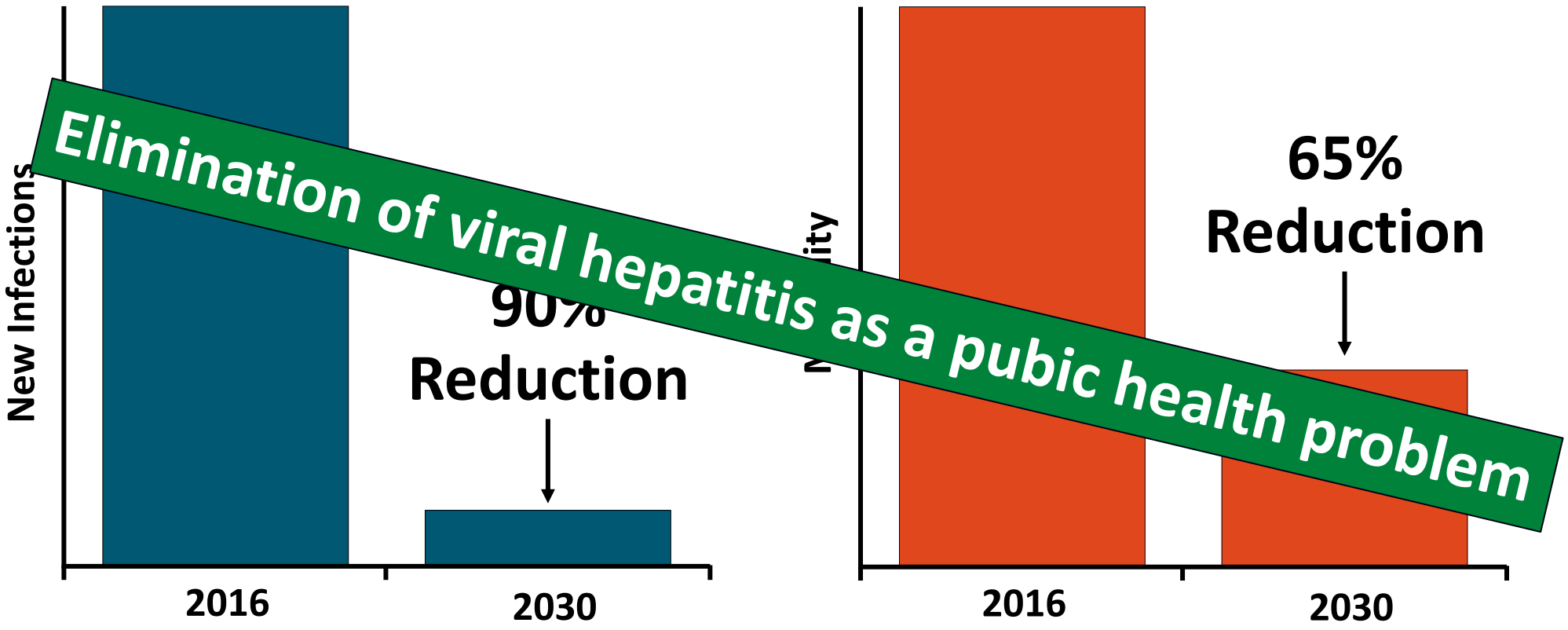




- **Ambitious goals**
- **Requires National Action Plan → good data to design policy**

WHO. Draft WHO Global Hepatitis Strategy, 2016-2021.

WHO HCV Elimination Targets



- Ambitious goals
- Requires National Action Plan → good data to design policy

WHO. Draft WHO Global Hepatitis Strategy, 2016-2021.

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.

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

Patient Case

- Patient is a 56-yr-old white man found to have chronic HCV after he switched to a new PCP who received EHR alert for HCV birth cohort screening
- Remote heroin use (last use in 1987)
- Past medical history: DM, HTN, obesity
- Medications: metformin, ramipril

Parameter	Result
HCV RNA (PCR), IU/mL	3.4×10^6
Platelets/mm^3	327,000
Albumin, g/dL	4.3
ALT/AST, IU/L	78/56
ALP, IU/L	96
Total bilirubin, mg/dL	1.0
INR	1.0
Hemoglobin, g/dL	14.3
WBC, x 10^9 cells/L	4.7
Serum creatinine, mg/dL	0.8

Checklist for Choosing a Regimen: A Few Things to Know

- **Fibrosis assessment: Essential in ALL patients!**
  - Presence of cirrhosis increases urgency of therapy and may affect regimen, duration, use of ribavirin
  - If cirrhosis:
    - Any history or signs of decompensation
    - Need for post-SVR follow up

Fibrosis Assessment: How To

- **Transient elastography**
  - > 12.5 KPa = cirrhosis
- **Serum tests**
  - FibroTest (0.75 = cirrhosis)
  - **APRI or FIB-4 – very attractive, can be done anywhere by any provider**
    - Very good **negative predictive value – rule out cirrhosis**
- **What about ultrasound – needed in all patients?**
  - **Insensitive for cirrhosis – only needed if cirrhotic to exclude HCC before treatment**
- Biopsy rarely needed

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
  - Albumin
  - INR
  - Ascites
  - Hepatic encephalopathy
- Calculate MELD – **if > 18 pay attention!**
  - Bilirubin
  - INR
  - Creatinine

Important Points in Decompensated Cirrhosis

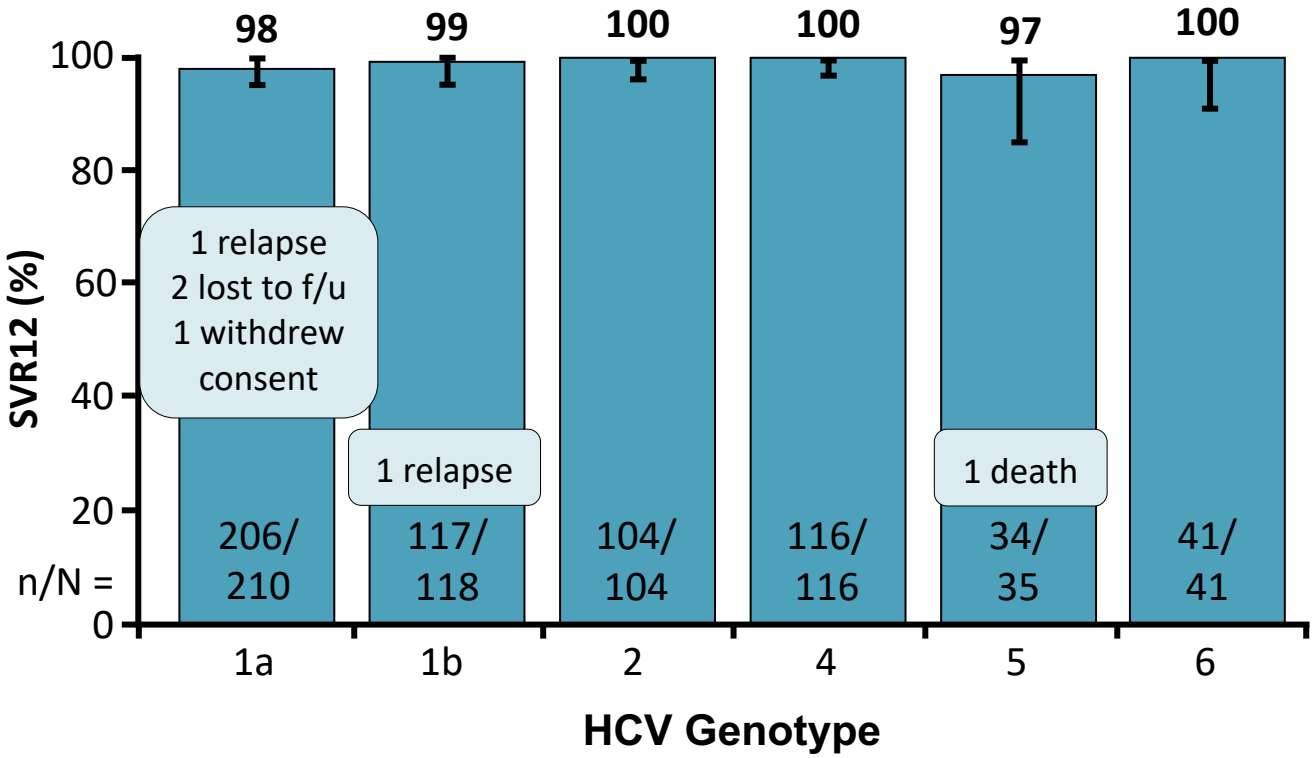
- **Be careful!!**
  - Sick patients may worsen at any time: make sure patient is aware of risks
  - Treat in experienced centers and see patient frequently
  - Drugs can be toxic
    - **ALL protease inhibitors contraindicated!**
    - Even LDV/SOL, SOF/VEL can cause liver injury in this setting
- **Add ribavirin**
  - Unclear why but seems to be helpful
- **Avoid MELD purgatory**
  - If MELD > 18 or CP-C category, risk may outweigh benefits, may consider waiting until after liver transplantation

Checklist for Choosing a Regimen: A Few Things to Know

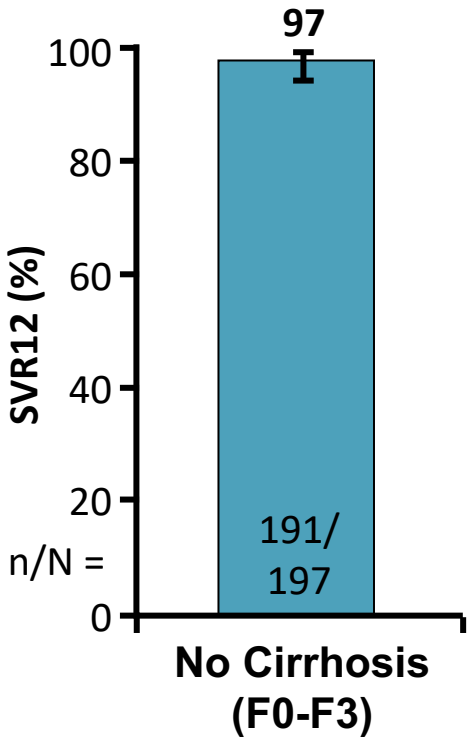
- Fibrosis assessment: Essential in ALL patients!
  - Presence of cirrhosis increases urgency of therapy and may affect regimen, duration, use of ribavirin
  - If cirrhosis:
    - Any history or signs of decompensation
    - Need for post-SVR follow up
- **Genotype & subtype for GT 1**
  - Still necessary?

Pangenotypic Regimens: SOF/VEL for 12 Wks

ASTRAL-1[1]*: SOF/VEL for 12 Wks in GT 1, 2, 4, 5, 6



ASTRAL-3†[2]: SOF/VEL for 12 Wks in GT 3

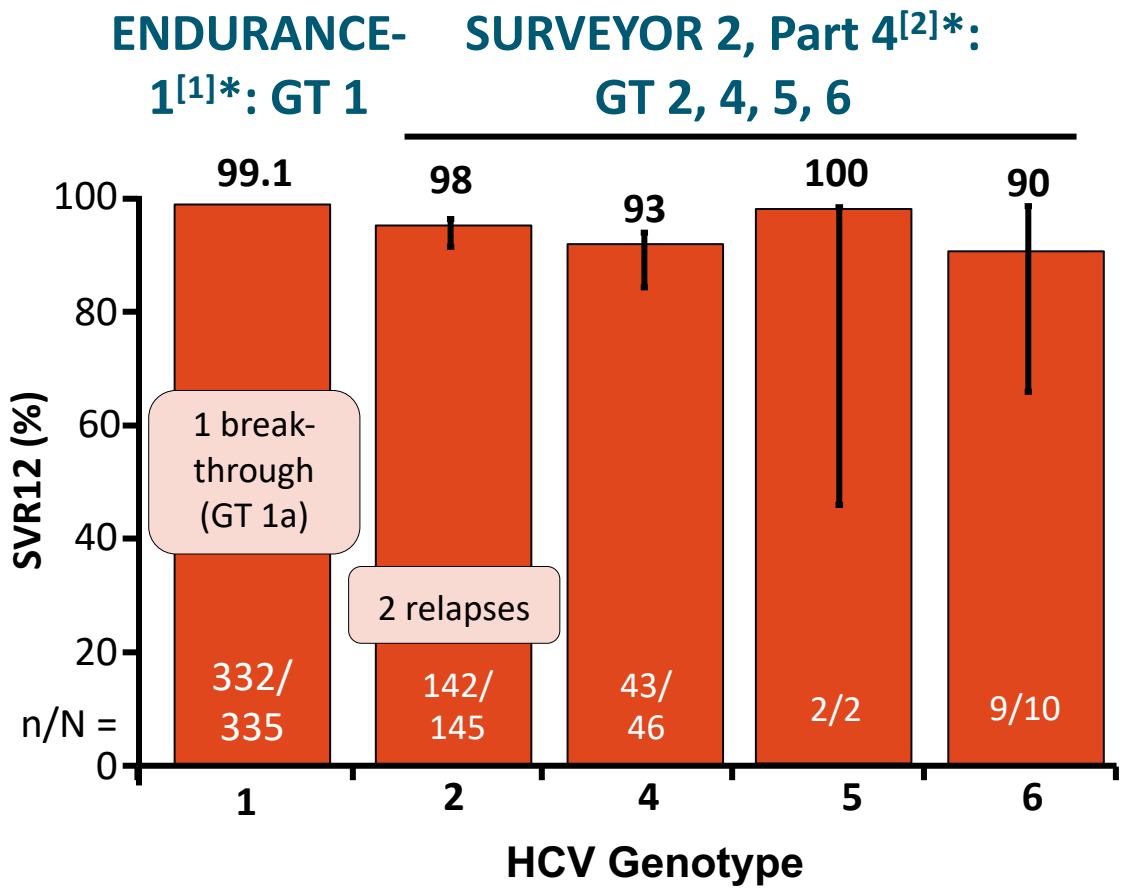


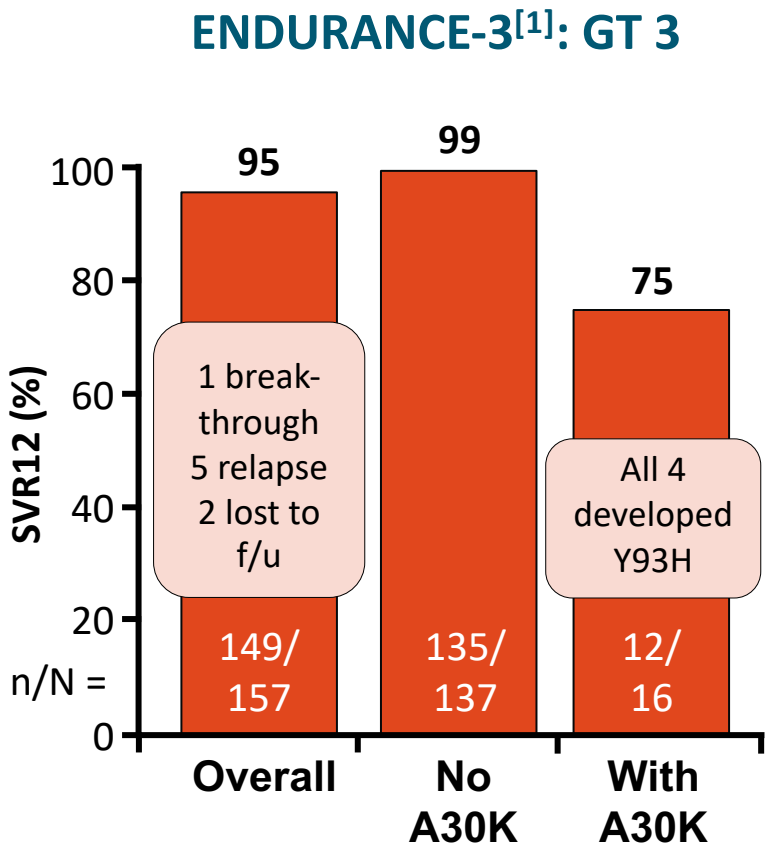
*Graph includes treatment-naive and treatment-experienced patients, with and without cirrhosis.

†Graph includes treatment-naive and treatment-experienced patients.

1. Feld. NEJM. 2015;373:2599. 2. Foster. NEJM. 2015;373:2608.

Pangenotypic Regimens: GLE/PIB for 8 Wks in Patients Without Cirrhosis





*Includes treatment-naive and treatment-experienced patients.

1. Zeuzem. NEJM. 2018;378:354. 2. Asselah. Clin Gastro Hepatol. 2018;16:417.

Who Would Genotype (Treatment-naive, No Cirrhosis)? Let's Consider GLE/PIB for 8 Wks

- GT3 accounts for ~ 20% of all HCV infections in US
- A30K mutation accounts for ~ 5% to 10% of those with GT3 HCV infection
- Therefore, ≤ 2% of your patients will have GT3 with A30K
- Translation: out of 1000 patients, 200 GT3, 10-20 GT3 with A30K
- SVR rate for GT3 with A30K drops from 99% to 75% (if accurate)
- Therefore, out of 1000 patients:
  - GT3 SVR: 99% for 180-190 patients and 75% for 10-20 patients = 193-196 out of 200 will have SVR
  - Non-GT3 SVR: 99% for 800 = 792 with SVR
  - Overall number with SVR without genotyping = 985-988
  - If genotype all 1000 to achieve 99% overall SVR rate = 990 achieve SVR

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So, genotyping 1000 patients expands SVR for 2-5 additional individuals - probably not cost effective

Can We Avoid Genotyping?

- It's a delicate balancing act

Maximizing SVR in Individual Patient

- Genotyping may be helpful
- Helpful in cirrhosis, particularly GT3

Maximize SVR in the Population

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

Can We Avoid Genotyping?

- It's a delicate balancin

A Reasonable Compromise

Genotype only for:

Cirrhosis

Treatment-experienced (DAA/IFN)

Maximizing SVR in Individual Patient

- **Genotyping may be helpful**
- **Helpful in cirrhosis, particularly GT3**

Maximize SVR in the Population

- **Simplicity is key**
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Checklist for Choosing a Regimen: A Few Things to Know

- Fibrosis assessment: Essential in ALL patients!
  - Presence of cirrhosis increases urgency of therapy and may affect regimen, duration, use of ribavirin
  - If cirrhosis:
    - Any history or signs of decompensation
    - Need for post-SVR follow up
- 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

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
- HBV
  - HBsAg is important
  - Anti-HBc not very important (but very common!)
- HIV
  - Important due to common risk factors and importance of diagnosis

HBV Reactivation: What's the Risk for HBsAg-Positive Patients?

- 17 observational studies involving 1621 patients: 242 HBsAg-positive patients
- HBV reactivation common in HBsAg-positive patients: 24%
- HBV reactivation-associated hepatitis: 9%, 3 cases of liver failure
  - Risk lower if HBV DNA negative (RR: 0.17)

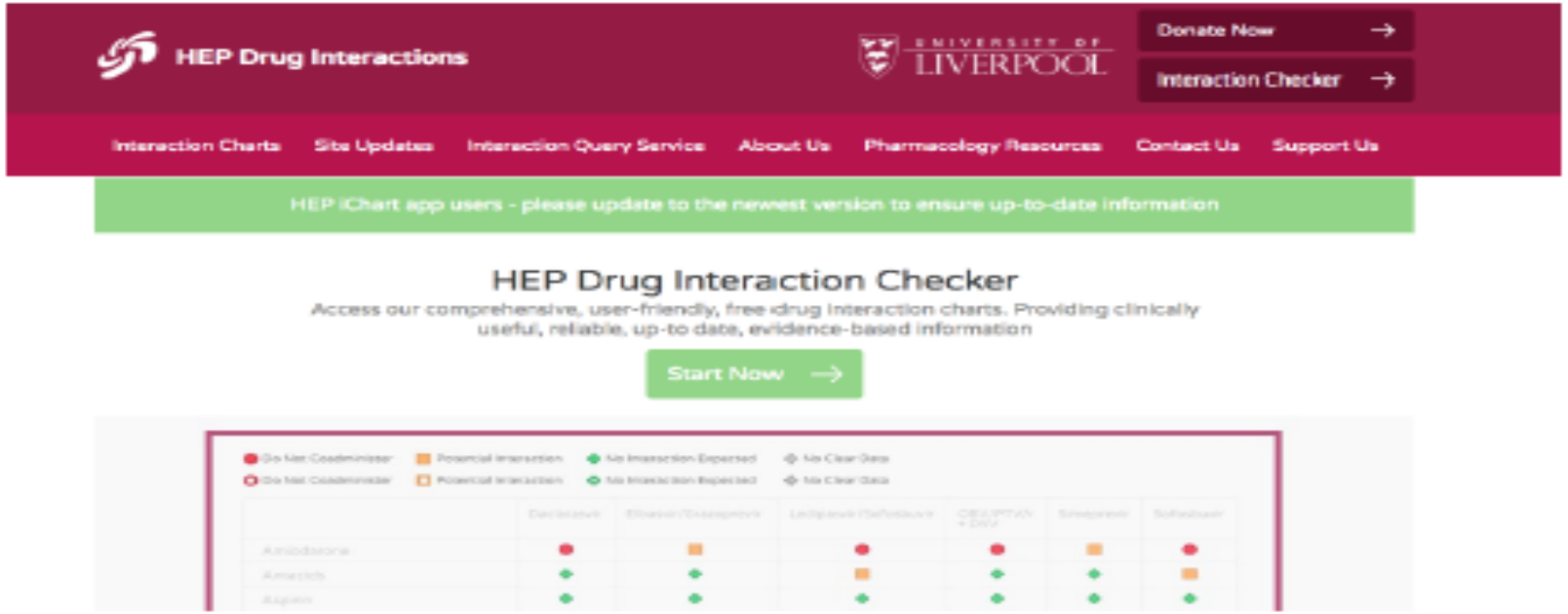
Mucke. Lancet Gastro Hepatol. 2018;3:172.

HBV Reactivation: What's the Risk for HBcAb-Positive Patients?

- 17 observational studies involving 1621 patients: 1379 HBcAb-positive only
- No cases of HBV reactivation-associated hepatitis!

Mucke. Lancet Gastro Hepatol. 2018;3:172.

Drug-Drug Interactions



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

Don’t trust your memory – look up all drugs including OTC!

Back to the Patient Case

- 56-yr-old white man with DM/HTN and
  - APRI = ?
  - FIB-4 = ?
  - If available: TE with *FibroScan* = 7.3 kPa
- Patient is HCV treatment-naive and does not have cirrhosis
- HIV negative and HBV immune

Simplified Approach to Treatment Selection in Treatment-Naive Patients Without Cirrhosis

Regimen	HCV Genotype							Duration (Wks)	Pills/ Day
	1a	1b	2	3	4	5	6		
LDV/SOF	√	√			√	√	√	8-12	1
EBR/GZR		√			√			12	1
SOF/VEL	√	√	√	√	√	√	√	12	1
GLE/PIB	√	√	√	√	√	√	√	8	3

2 once daily pangenotypic options; choice will be based on drug-drug interactions with current meds and minor considerations of pill burden, duration, food requirement

AASLD/IDSA. HCV Guidance. 2018.

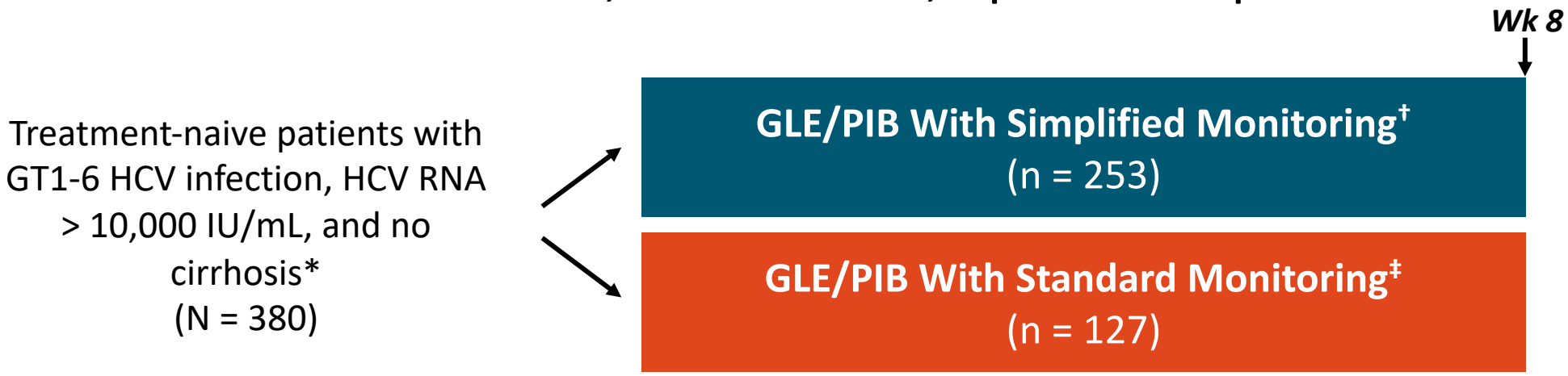
Comparison of Pangenotypic HCV Regimens for Treatment-Naive Patients Without Cirrhosis

Comparative Measure	GLE/PIB	SOF/VEL
Regimen constituents	Protease inhibitor/NS5A inhibitor	NS5B inhibitor/NS5A inhibitor
Dosing	3 pills QD	1 pill QD
Duration	8 wks	12 wks
Food requirement	Yes	No
Select DDI considerations	Anticonvulsants, statins, St John's wort, warfarin	Anticonvulsants, proton pump inhibitors, rifampin, St. John's wort, warfarin
Contraindications	▪ Severe hepatic impairment (CP C) ▪ Concurrent ATV or rifampin use	▪ Do not use with RBV in patients with RBV contraindication
Warnings/precautions	▪ HBV reactivation risk	▪ HBV reactivation risk ▪ Bradycardia with amiodarone coadministration

GLE/PIB [package insert]. SOF/VEL [package insert].

Simplifying Treatment Monitoring: Can We Avoid Clinic Visits?

- SMART-C: Multicenter, randomized, open-label phase IIIb study

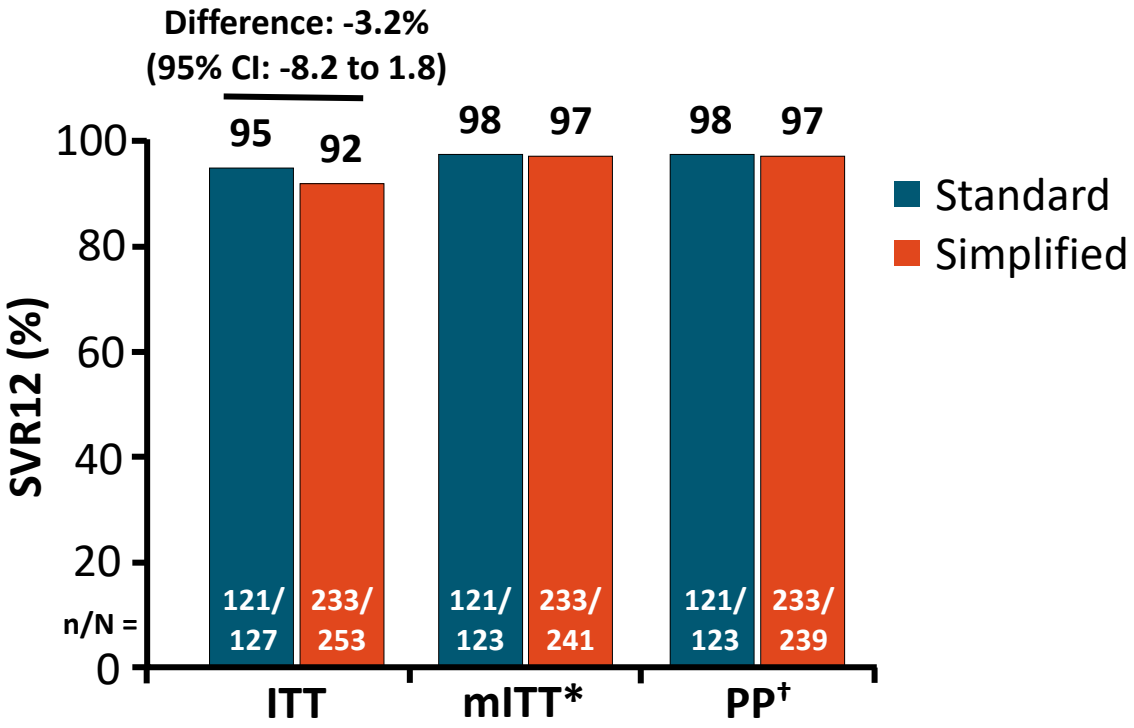


AEs and adherence assessed by study nurse via phone contact at Wks 4 and 8 in all patients.
*Exclusion criteria: anticipated poor adherence, IDU within past 6 mos, positive urine drug screen.
†Medication dispensed at BL; no on-treatment clinic visits.
‡Medication dispensed at BL and Wk 4; clinic visits involving physician, study nurse, and pathology at Wks 4 and 8.

- Primary endpoint: SVR12 in ITT population (6% noninferiority margin)

Dore. EASL 2019. Abstr PS-178.

SMART-C: Efficacy and Safety



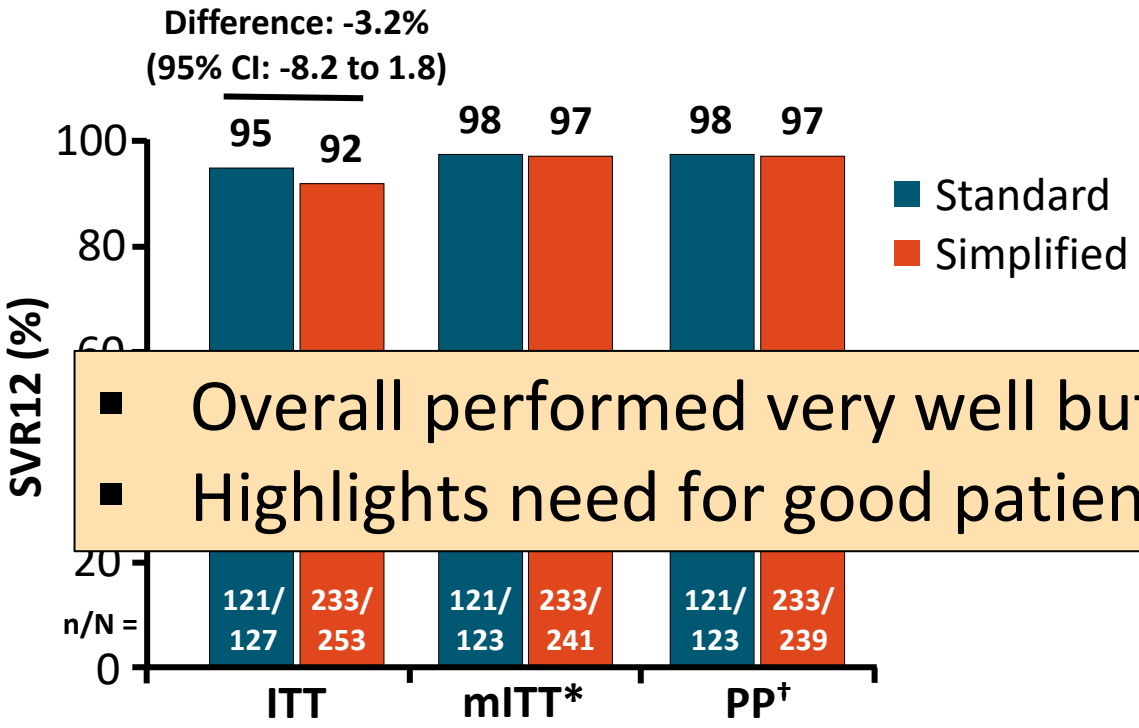
*Excludes death (n = 1), LTFU (n = 14), or missing HCV RNA (n = 1).
†Excludes discontinuation (n = 2) in addition to mITT exclusions.

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

Treatment-Emergent AEs, n (%)	Standard (n = 127)	Simplified (n = 253)
AEs	70 (55)	133 (53)
▪ Grade 1/2	69 (54)	131 (52)
▪ Grade 3	1 (0.8)	2 (0.8)
▪ Grade 4	0	0
Common AEs (> 5%)		
▪ Fatigue	30 (14)	52 (15)
▪ Headache	26 (12)	43 (13)
▪ Nausea	25 (12)	17 (5)
Serious AEs	0	3 (1.2)
Unscheduled visits		
▪ On treatment	3 (2)	11 (4)
▪ Total	8 (6)	20 (8)

Dore. EASL 2019. Abstr PS-178.

SMART-C: Efficacy and Safety



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- 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

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Dore. EASL 2019. Abstr PS-178.

Issues After Treatment

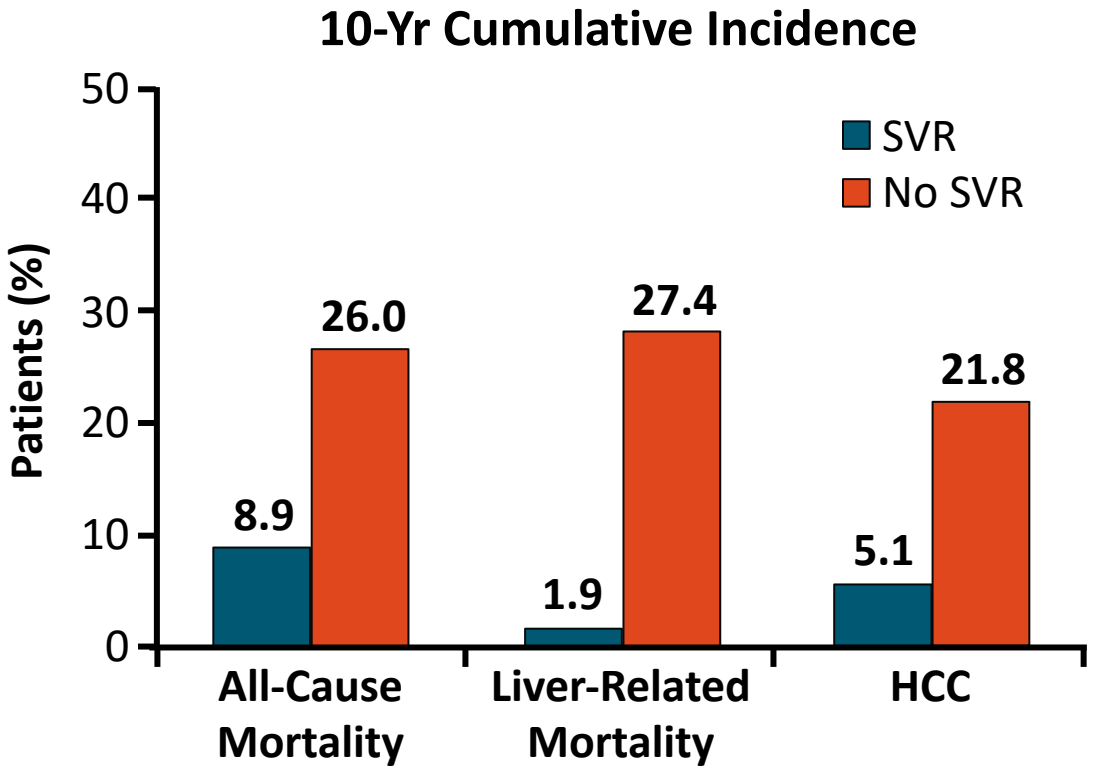
- Consequences of liver disease
  - Only an issue with cirrhosis (fibrosis assessment pretreatment!)
  - HCC risk
  - Liver function – MELD purgatory
- Reinfection risk
  - Ongoing exposures – HCV RNA testing every 6-12 mos
  - No ongoing exposures – annual ALT, promote liver health (diet & alcohol), and nothing else!

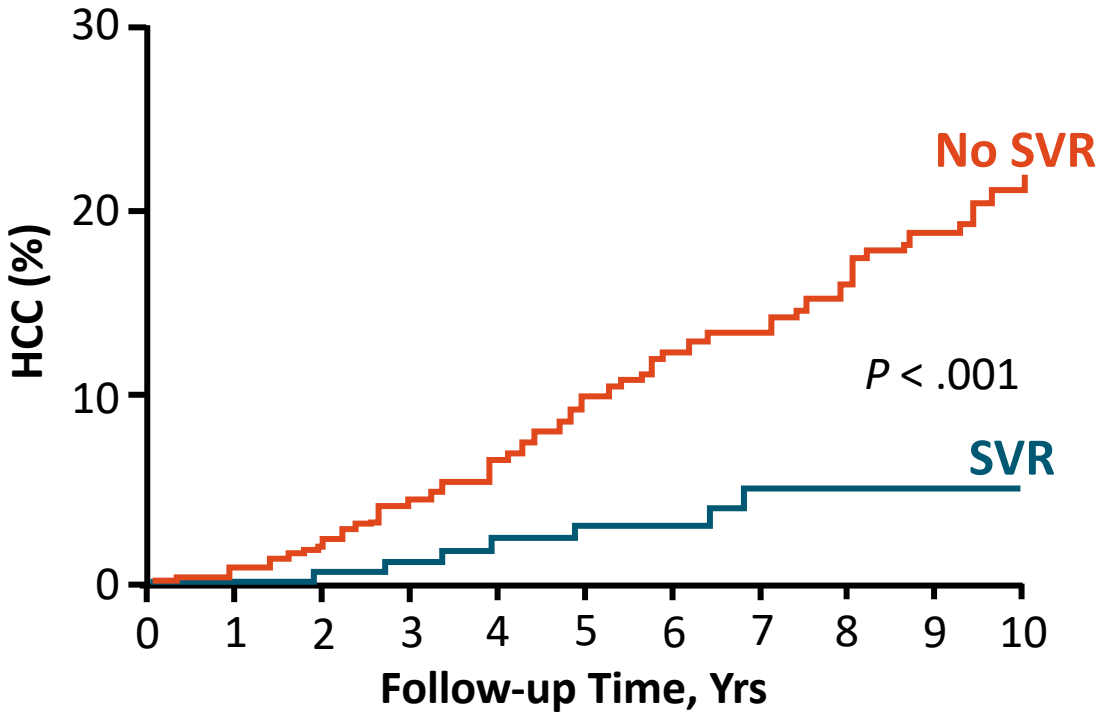
Issues After Treatment

- Consequences of liver disease
  - Only an issue with cirrhosis (fibrosis assessment pretreatment!)
  - HCC risk
- Communicate information well - people don't know what SVR means
- Templated notes with key features
  - Eg, anti-HCV Ab remains positive → don't check it!
  - No ongoing exposures – annual ALT, promote liver health (diet & ETOH), and nothing else!

Hepatocellular Carcinoma (HCC) After Interferon-Based Treatment

- Long-term follow-up of 530 patients with F3/F4, treated for HCV





van der Meer. JAMA. 2012;308:2584.

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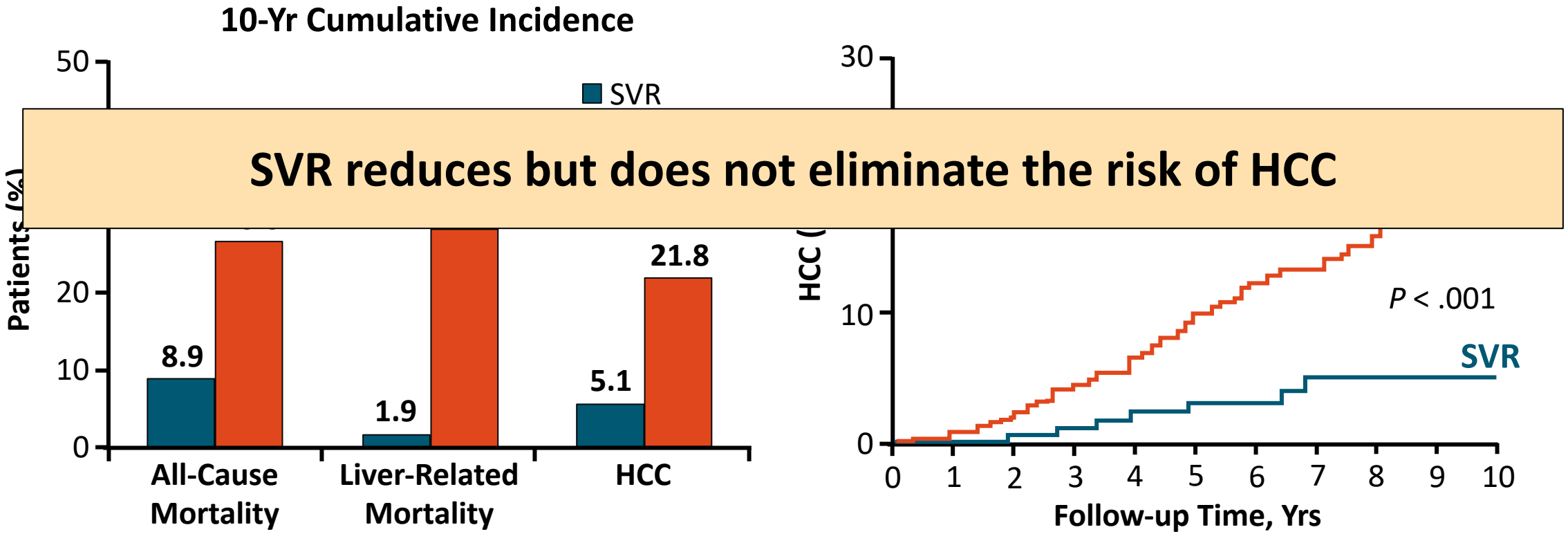

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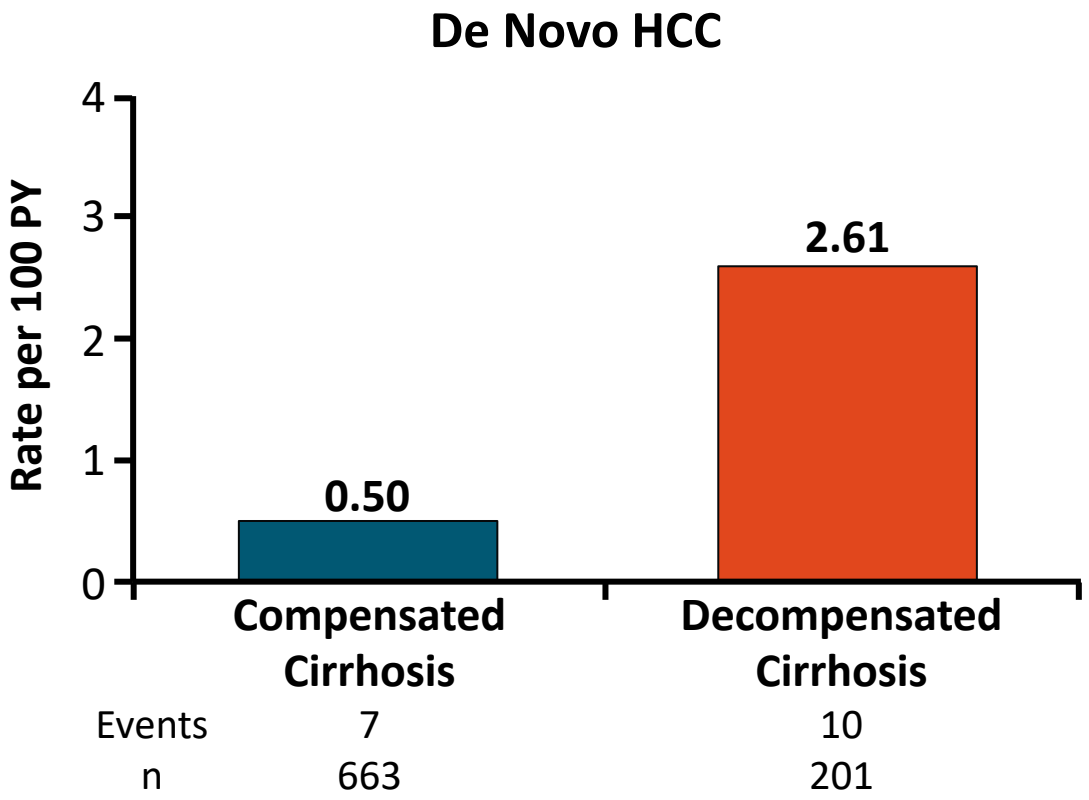
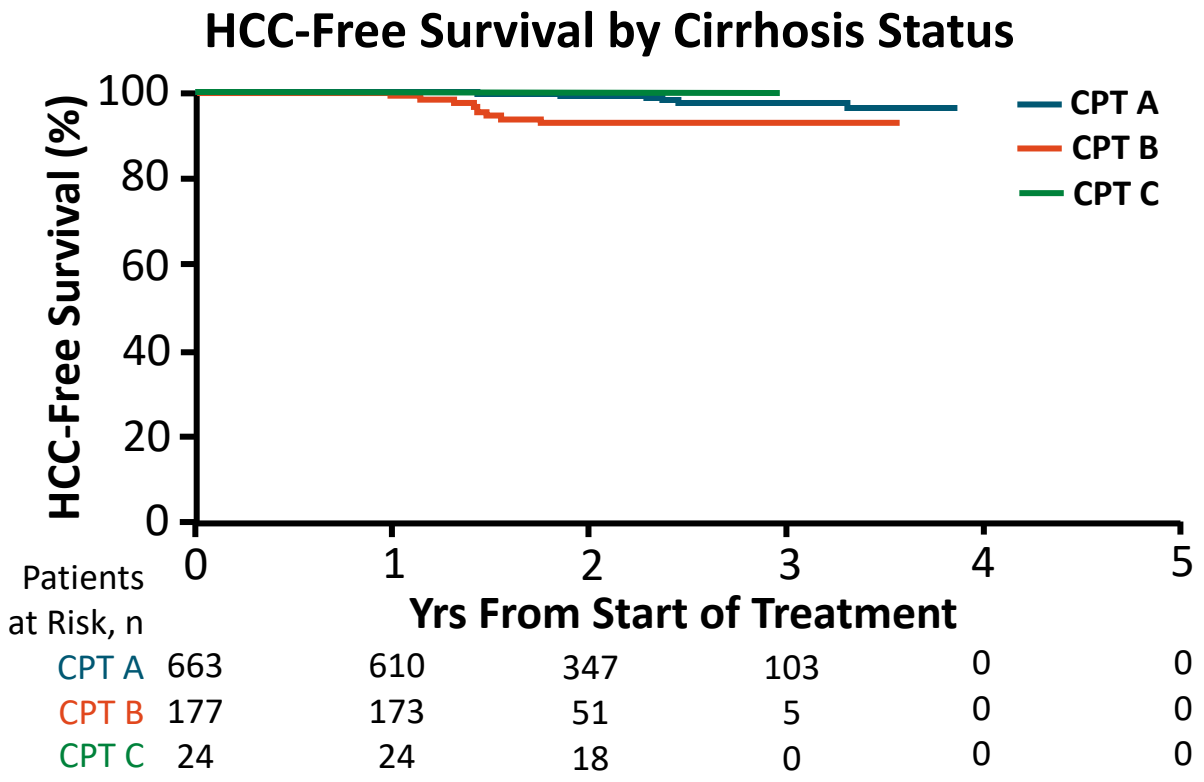
And With DAAs?

- Patients with cirrhosis followed after SOF-based SVR; median follow-up: 85 wks





Muir. AASLD 2016. Abstr 880.

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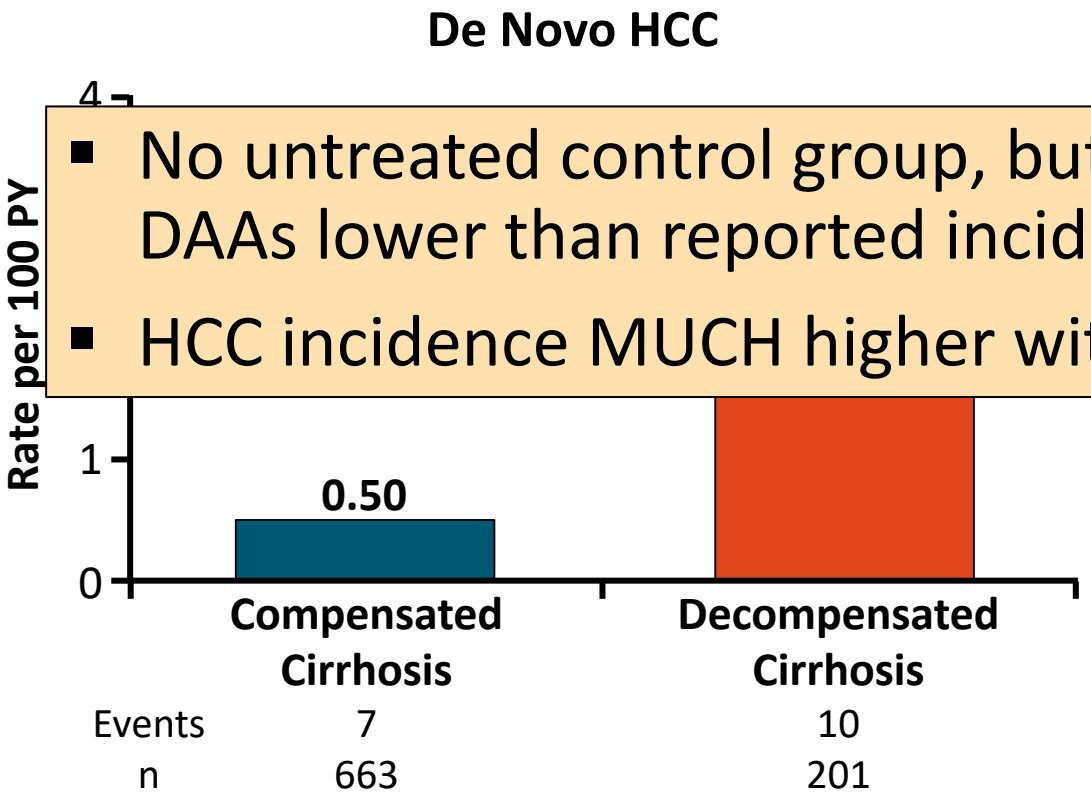
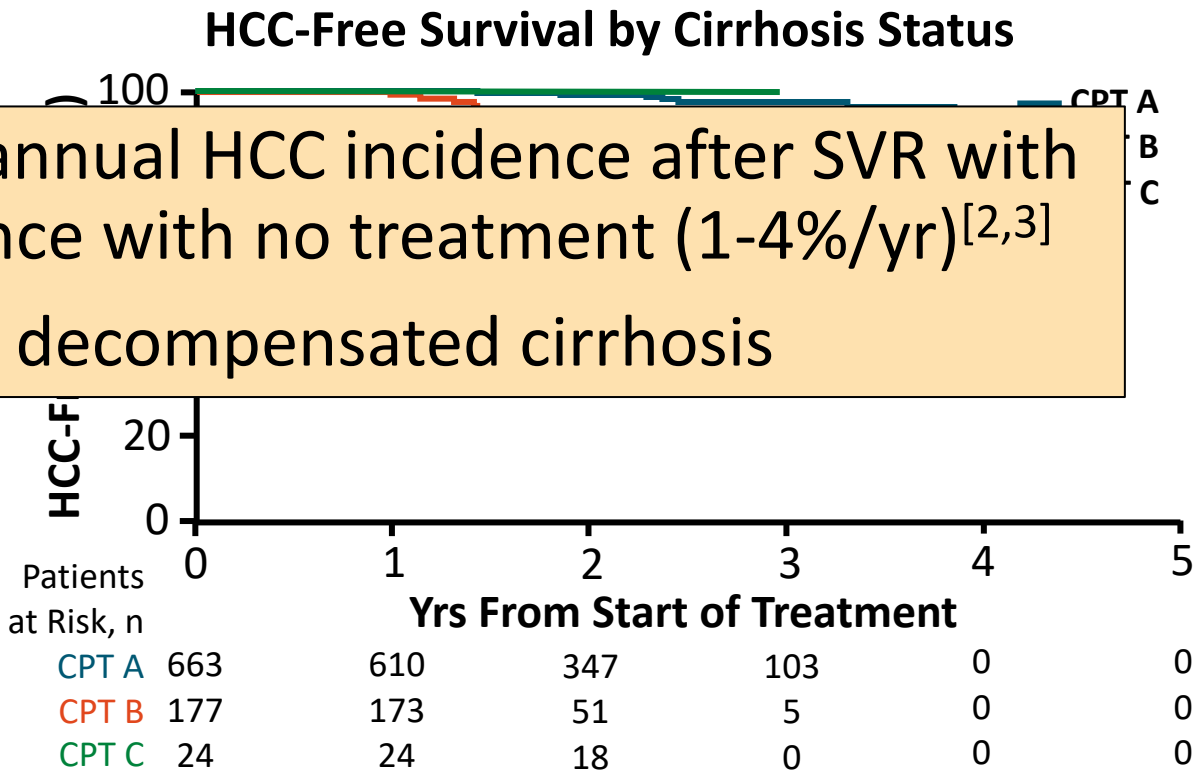
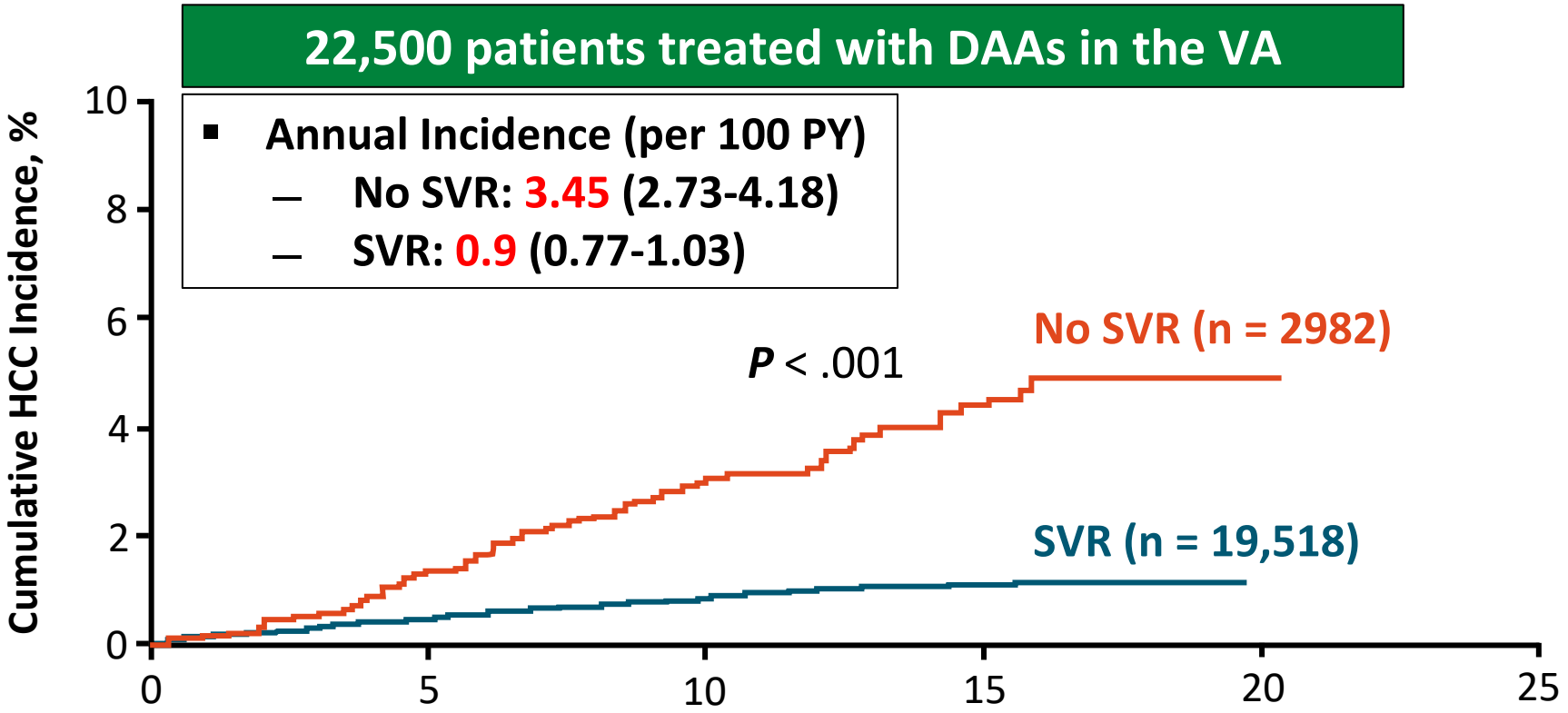




- No untreated control group, but annual HCC incidence after SVR with DAAs lower than reported incidence with no treatment (1-4%/yr)[2,3]
- HCC incidence MUCH higher with decompensated cirrhosis

1. Muir A. AASLD 2016. Abstr 880. 2. El-Serag. Hepatology. 2016;64:130. 3. Axley. J Clin Transl Hepatol. 2018;6:79.

Big Numbers…the VA is Helpful



Patients at Risk, n (N HCC)											
Achieved SVR	19,518	(85)	19,372	(68)	14,364	(29)	6128	(1)	0	(0)	0
No SVR	2982	(35)	2453	(36)	1617	(14)	636	(3)	5	(0)	0

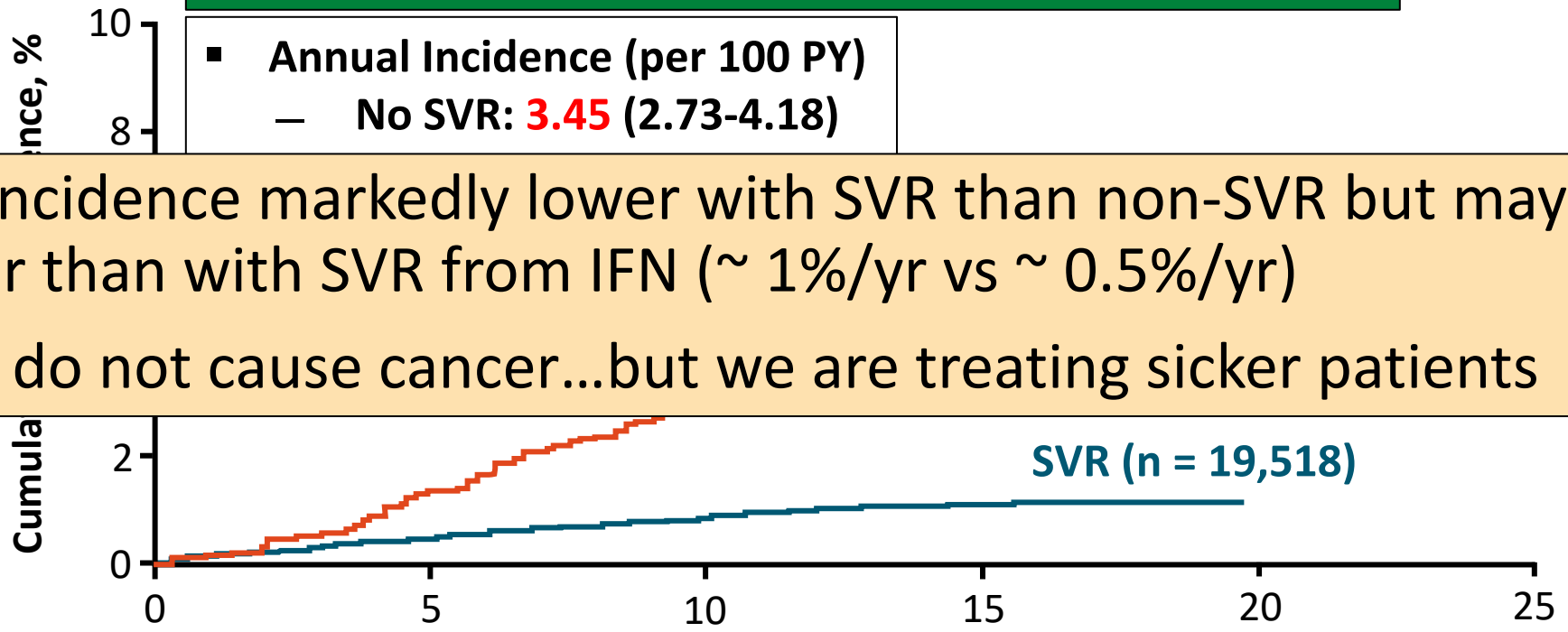
Kanwal. Gastroenterol. 2017;153:996.

Big Numbers…the VA is Helpful

22,500 patients treated with DAAs in the VA

- **Annual Incidence (per 100 PY)**
  - **No SVR: 3.45 (2.73-4.18)**

- HCC incidence markedly lower with SVR than non-SVR but may be higher than with SVR from IFN (~ 1%/yr vs ~ 0.5%/yr)
- DAAs do not cause cancer…but we are treating sicker patients



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Benefit of SVR on HCC Incidence is Similar With DAAs vs IFN

HCV Treatment	SVR	Patients	HCC	HCC per 100 Patient-Yrs	Crude HR	Adjusted* HR	Risk Reduction
IFN only[1]	No	23,883	2348	1.07	1	1	
	Yes	11,988	303	0.28	0.25	0.32	68%
DAA + IFN[1]	No	1772	116	1.73	1	1	
	Yes	2763	59	0.6	0.34	0.48	52%
DAA only[1]	No	2039	165	5.19	1	1	
	Yes	19,909	280	0.92	0.18	0.29	71%

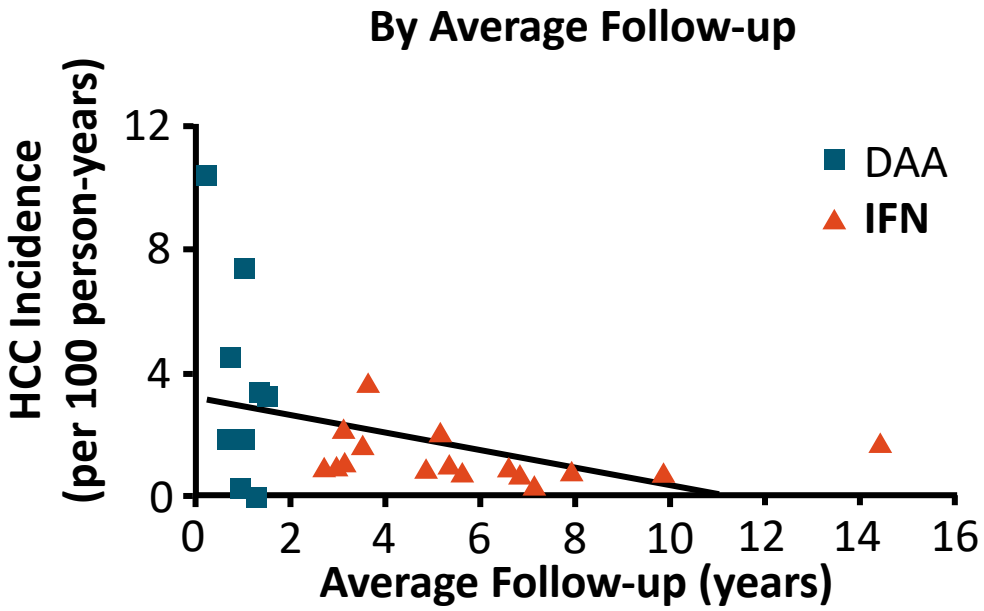
*Adjusted for cirrhosis, decompensated cirrhosis, age, sex, race/ethnicity, body mass index, HCV genotype, HCV viral load, HIV coinfection, HBV coinfection, type 2 diabetes mellitus, alcohol use disorders, substance use disorder, platelet count, serum bilirubin, serum creatinine, serum albumin, serum AST/ALT ratio, blood INR, blood hemoglobin levels.

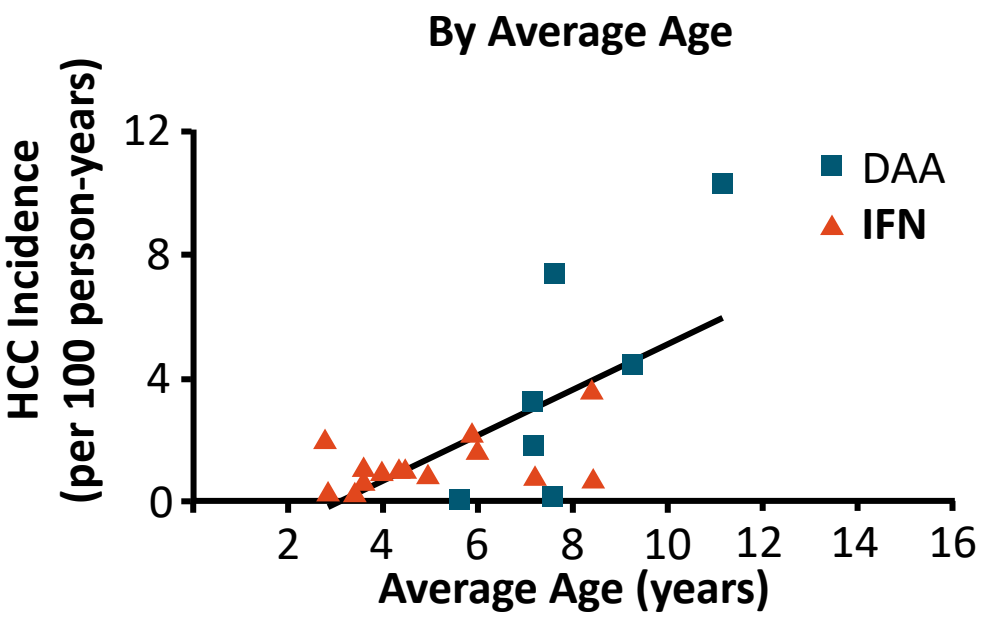
- **More HCCs after DAAs – sicker patients**
- **Benefit of SVR equivalent with DAA vs IFN**
- **Similar results from ERCHIVES cohort**[2]

1. Ioannou. J Hepatol. 2018;68:25. 2. Li. Hepatology. 2018;67:2244.

Putting the Data Together

- Systematic review and meta-regression of 26 studies on HCC occurrence after SVR in IFN- vs DAA-treated patients





- **DAA studies: shorter follow-up and older patients with more severe liver disease than in IFN studies**
- **"Controlling for follow-up" and age: similar HCC risk in DAA and IFN studies**

Waziry. J Hepatol. 2017;67:1204.

What About Post-SVR HCC Surveillance? Cirrhosis is the Key Risk Factor for HCC Post-SVR

- 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	

1. AASLD/IDSA HCV guidance. 2018. 2. EASL Guidelines. 2018. 3. Kanwal. Gastroenterol. 2017;153:996.
4. Zangneh. Clin Gastroenterol Hepatol. 2018;[Epub].

What About Post-SVR HCC Surveillance? Cirrhosis is the Key Risk Factor for HCC Post-SVR

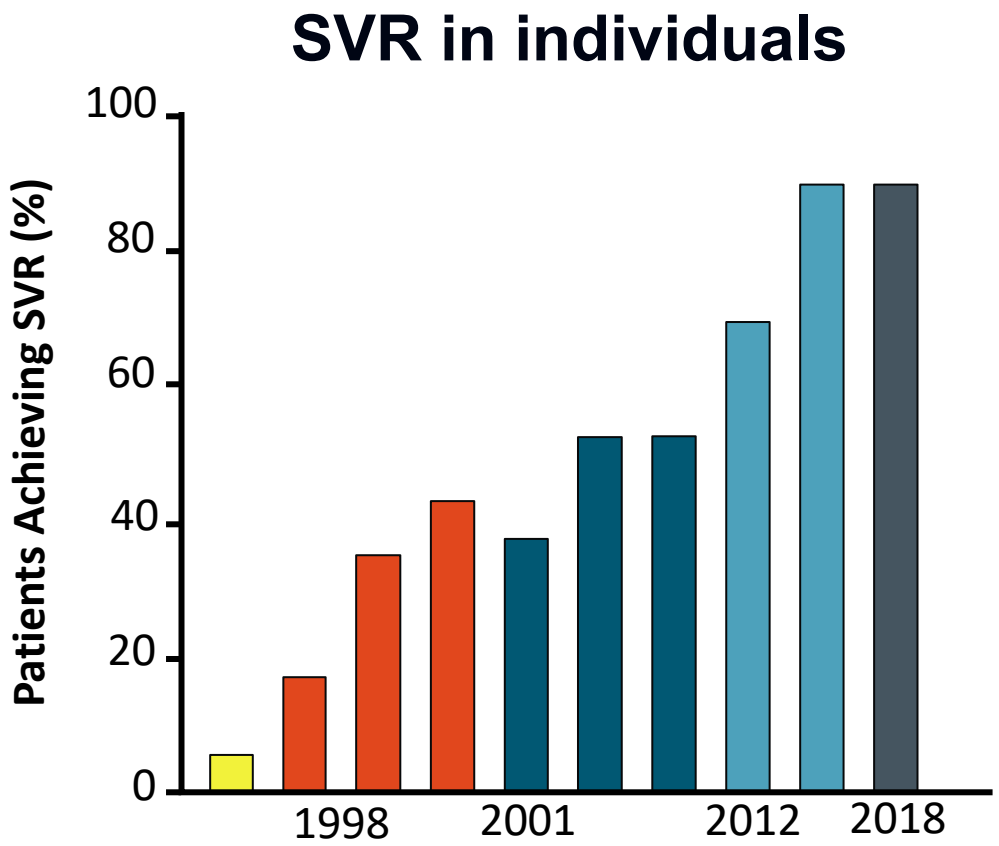
- AASLD/IDSA and EASL guideline recommendation: US surveillance every 6 mos after SVR in patients with "advanced fibrosis" or cirrhosis (ie, F3/F4)[1,2]

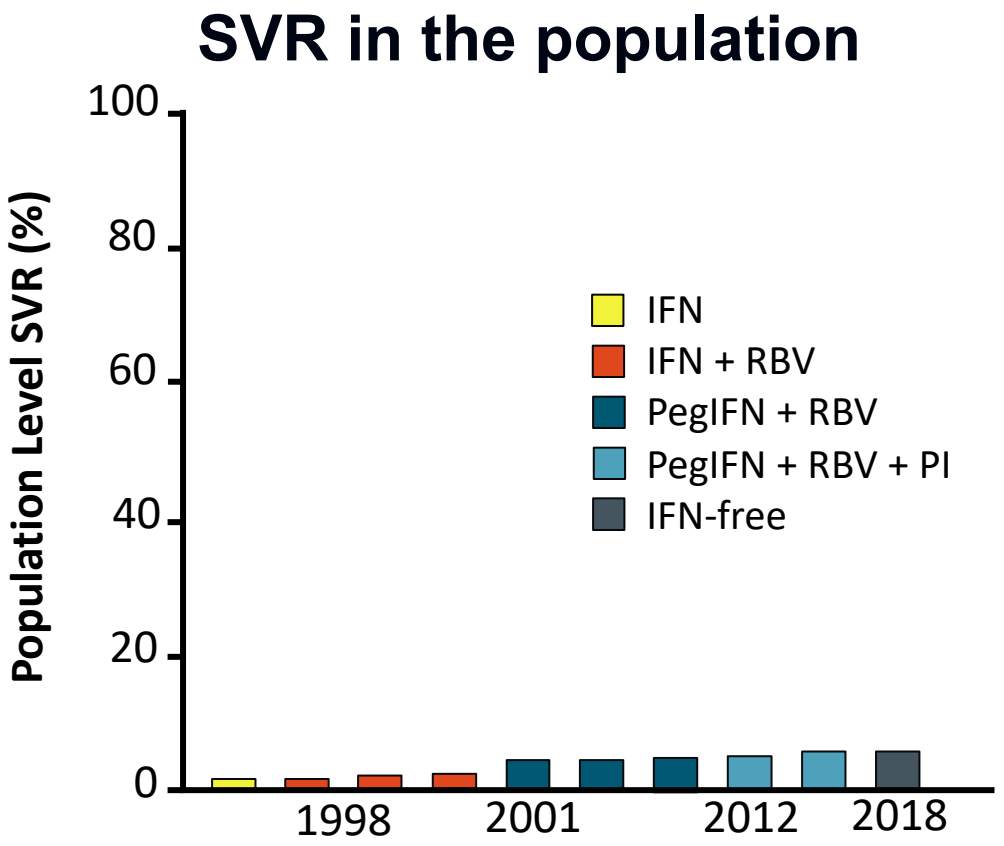
Characteristic	HCC Incidence per 100 Person-Yrs[3]	ICER for Surveillance (Ultrasound Every 6 Mos) vs No Surveillance, per QALY[4]
With	0.90	
Cirrhosis status		
With	**1.82**	**$40,803**
Without	0.34	$187,000
FIB-4		
> 3.25	**2.16**	**$32,016**
1.45-3.25	0.45	**$133,977**
< 1.45	0.30	

My approach: Probably should limit surveillance post-SVR to those with cirrhosis or FIB-4 > 3.25

1. AASLD/IDSA HCV guidance. 2018. 2. EASL Guidelines. 2018. 3. Kanwal. Gastroenterol. 2017;153:996.
4. Zangneh. Clin Gastroenterol Hepatol. 2018;[Epub].

HCV Elimination Requires More Than Good Drugs





Grebley. JID. 2013;207(S1):S19.

Greatest Remaining Challenge: HCV Cascade of Care

- Diagnosis
  - Rates remain low
- After diagnosis – many may never be treated
  - Access to providers
  - Access to therapy – cost, restrictions (fibrosis, sobriety)
  - Competing concerns – opioid epidemic, substance use risks

Novel innovations (POC testing) and models of care (task shifting) are required to overcome current barriers

Summary

- HCV assessment and treatment are now simple
- Assessment can be limited to fibrosis staging (still required in all patients before treatment!), HBV and HIV testing, and drug-drug interaction review
- Genotyping limited to treatment-experienced patients and those with cirrhosis
- Pangenotypic regimens for most if not all settings
- On-treatment monitoring limited to those with adherence concerns
- Post-SVR follow-up limited to HCC surveillance for those with cirrhosis and HCV RNA for those with ongoing risk exposures