Update of Viral Hepatitis

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Annenberg Center For Health Sciences at Eisenhower
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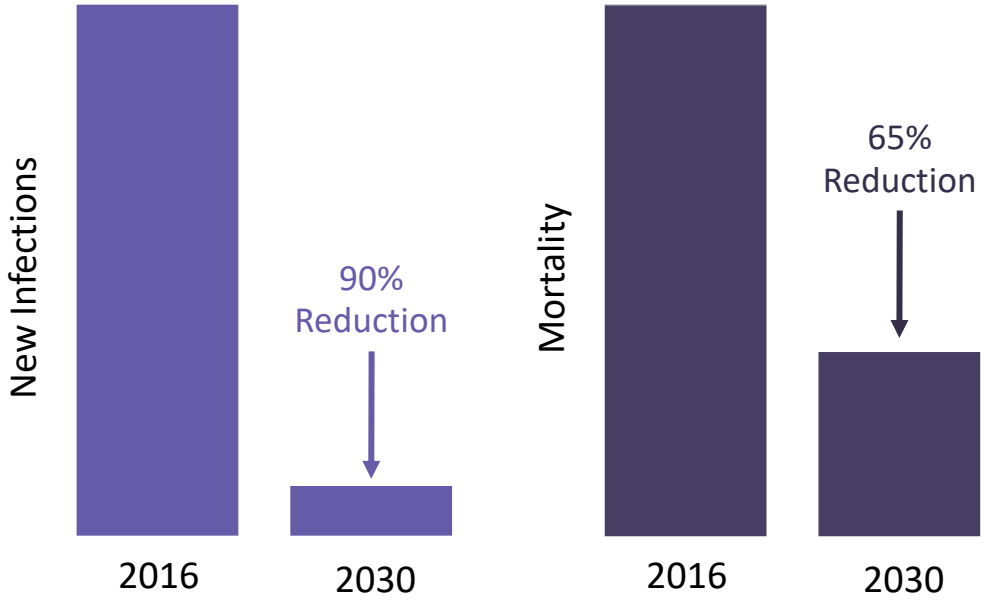
Southern California Society of Gastroenterology
SCSG

Viral Hepatitis Elimination by 2030

WHO Global Hepatitis Strategy, 2016-2021.

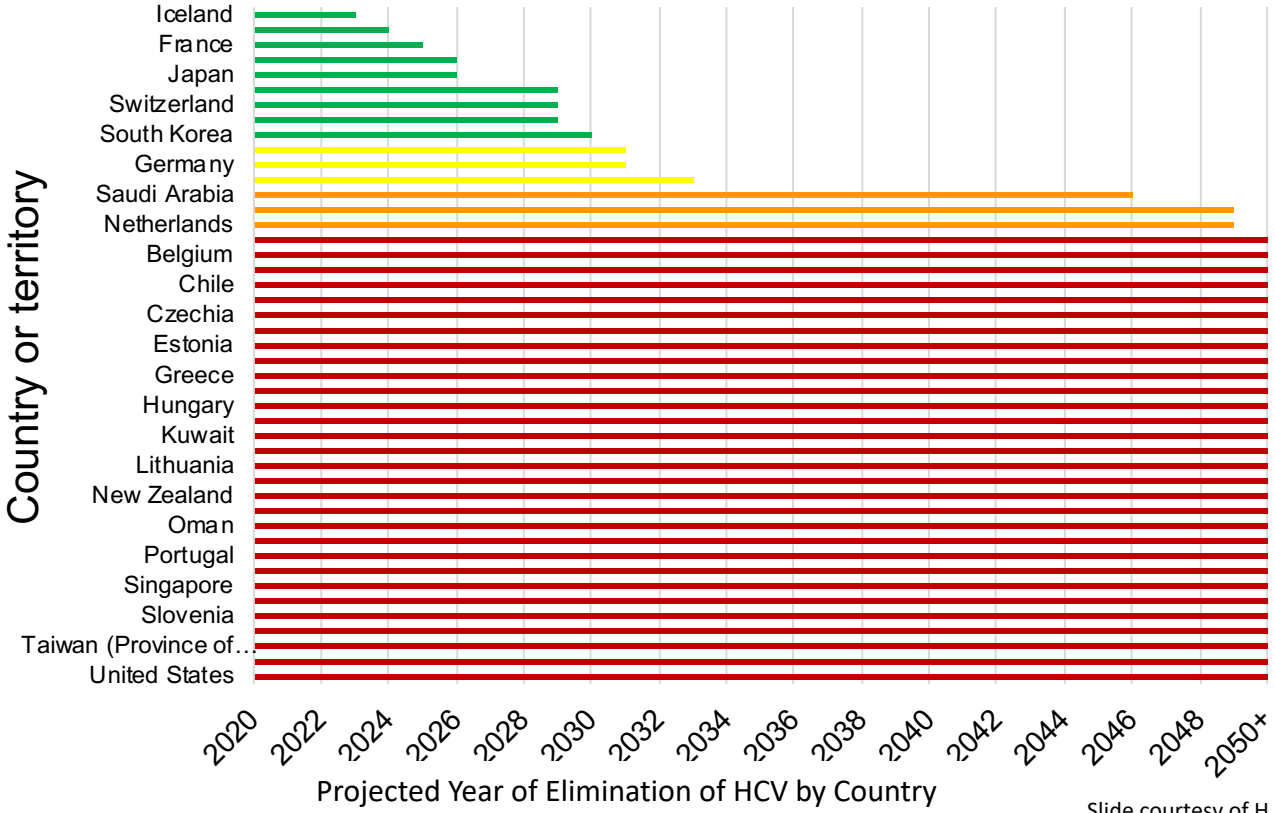


In May 2016, the World Health Assembly endorsed the *Global Health Sector Strategy (GHSS)* on viral hepatitis 2016–2021. The GHSS calls for the elimination of viral hepatitis as a public health threat by 2030

- Ambitious goals
- Recent projections for US indicates we are off track by 20+ years

H. Razavi, Presented AASLD/EASL HCV Conference, 2019

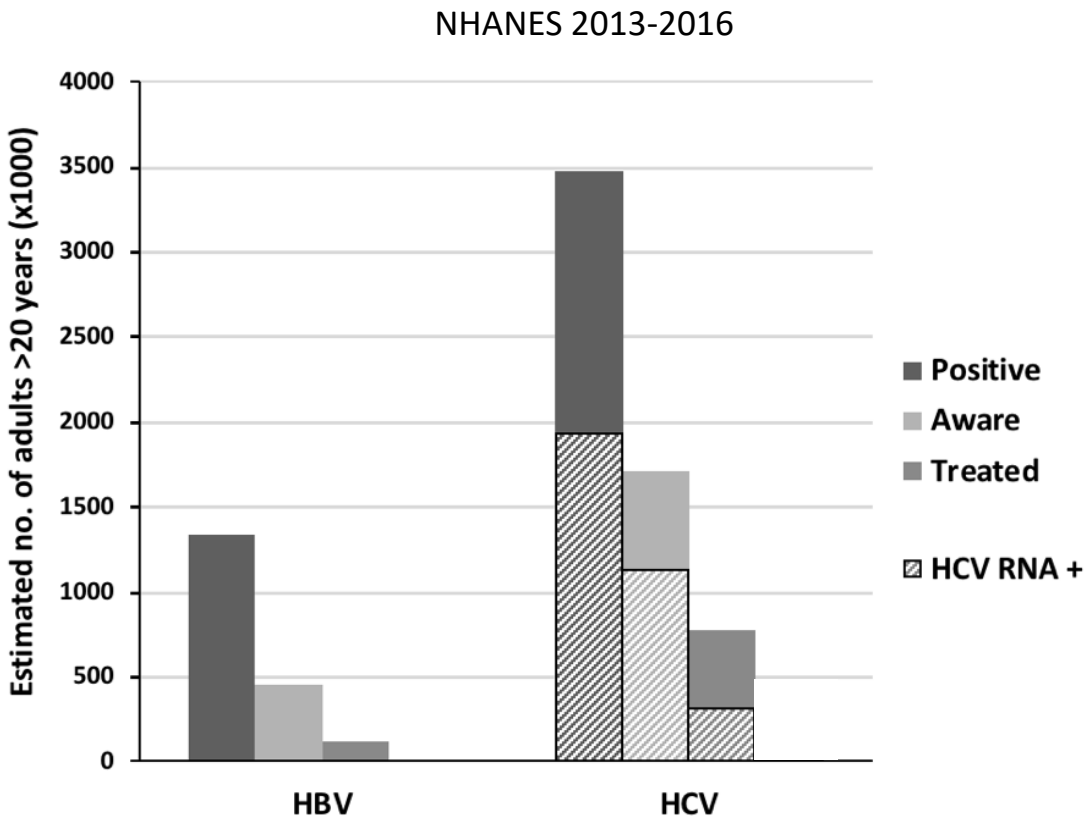
Countries on Track to Achieve Elimination Goals



Current projections indicate U.S. is NOT on track to meet the WHO's targets by at least 20 years

Slide courtesy of H. Razavi, Presented AASLD/EASL HCV Conference, 2019

Gaps in the Cascade of Care



HBV:

- 32% aware
- 28% of aware on treatment

HCV:

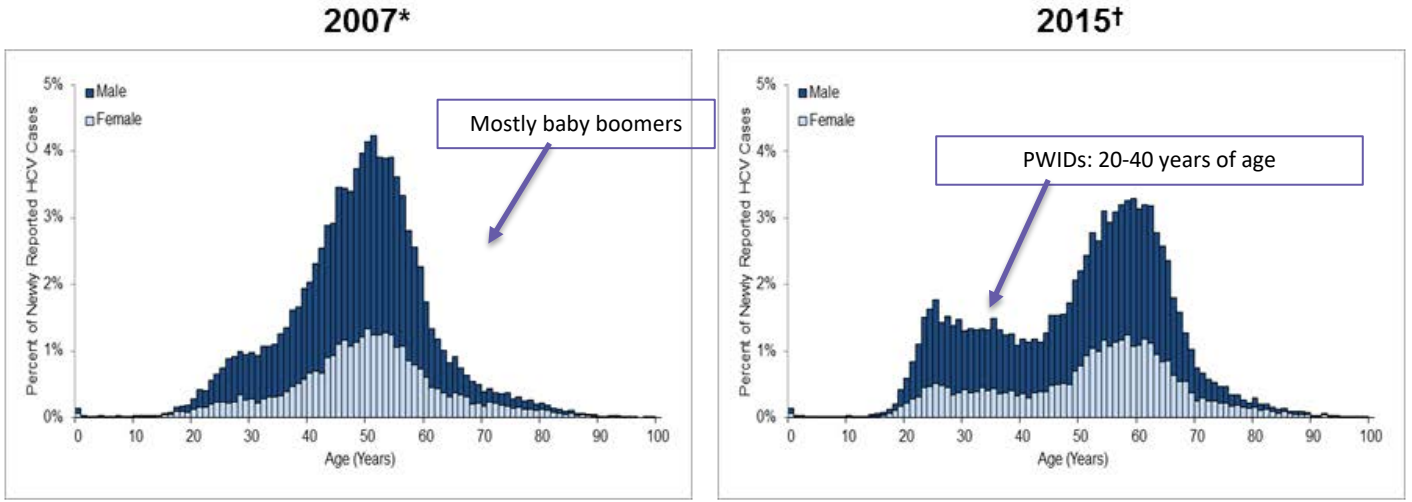
- 49% aware
- 45% of aware persons treated

Zhou K & Terrault N, CGH 2019

What's New for HCV?

- Changing epidemiology – implications for screening
- Treatment
  - Simplifying treatment algorithms
  - Real-world efficacy
  - Novel applications – transplantation

The Second Wave of HCV in the U.S.



Data from California Department of Public Health: Newly Reported Cases of Hepatitis C

~30,000 new HCV infections per year, increasing since 2006

- **Parallels the rise in opioid abuse with new consequences**
- **15-30% become HCV positive in first year; ~50% after 5 yrs**

California Department of Public Health. Chronic hepatitis C infections in California: cases newly reported through 2015. June 2017.

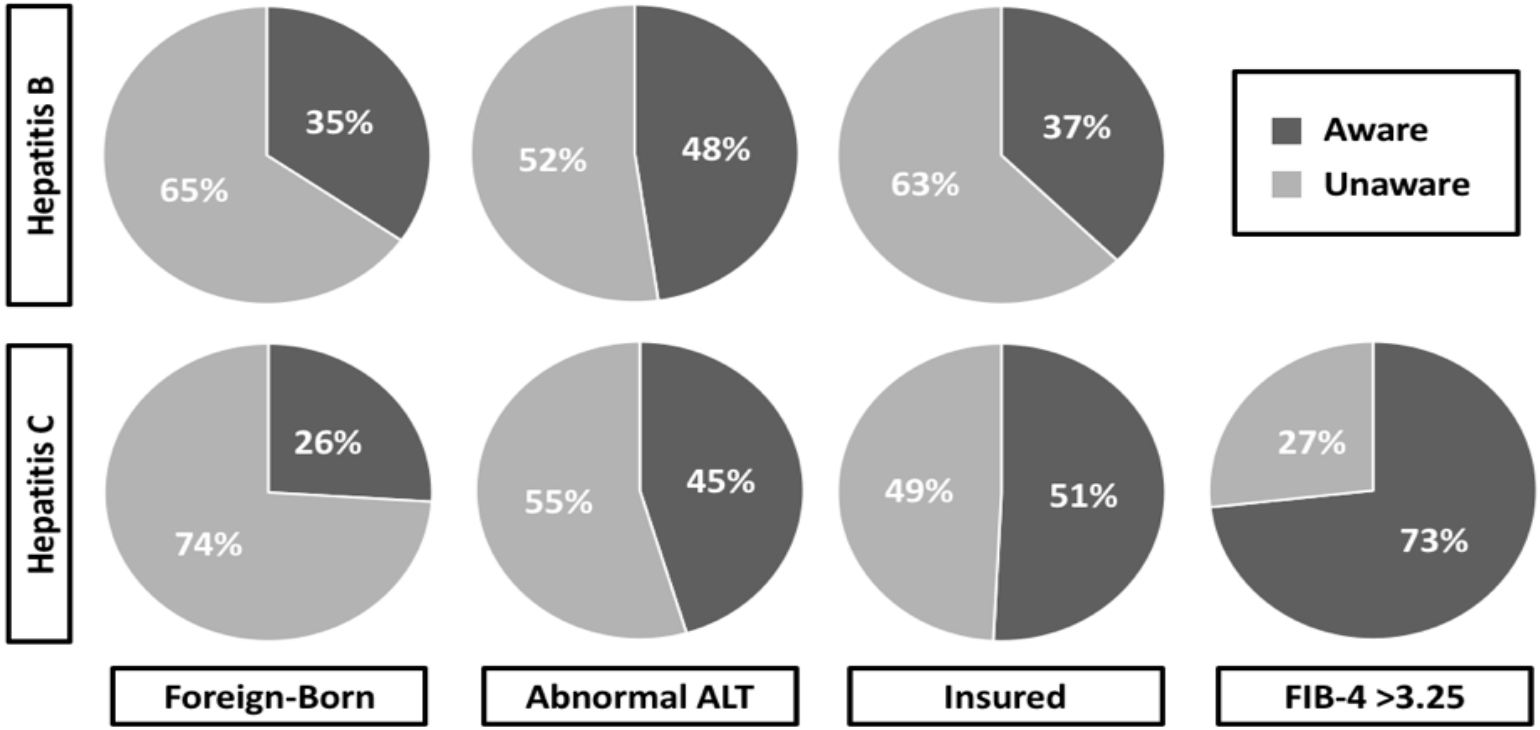
- Adults born between 1945-1965
- Risk-based:
  - IDU
  - Receipt of blood products prior to 1992 (clotting factors prior to 1987)
  - Hemodialysis
  - HIV+
  - ALT elevated
  - Recognized exposure: needlesticks, children of HCV+ moms

Foreign-born:
Medical/dental care in developing countries

AASLD — American Association for the Study of Liver Diseases
HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C
IDSA — Infectious Diseases Society of America

- **All pregnant women**
- **Opt-out screening in jails/prisons**

Gaps in Screening Remain



Zhou K & Terrault N, CGH 2019

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

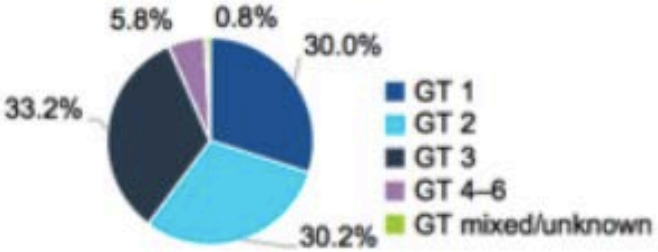
Regimen	HCV Genotype							Duration (Wks)	Pills/ Day
	1a	1b	2	3	4	5	6		
LDV/SOF	√	√			√	√	√	8-12	1
EBR/GZR		√			√			12	1
SOF/VEL	√	√	√	√	√	√	√	**12**	**1**
GLE/PIB	√	√	√	√	√	√	√	**8**	**3**

- **SVR rates ≥95% in treatment naive patients**
- **Two pangenotypic options**
- **Choice based on:**
  - **-- drug-drug interactions**
  - **-- duration**
  - **-- food requirement**
  - **-- pill burden**
  - **-- insurance preference**

AASLD/IDSA. HCV Guidance. 2018.

Real-World Experience on SOF/VEL

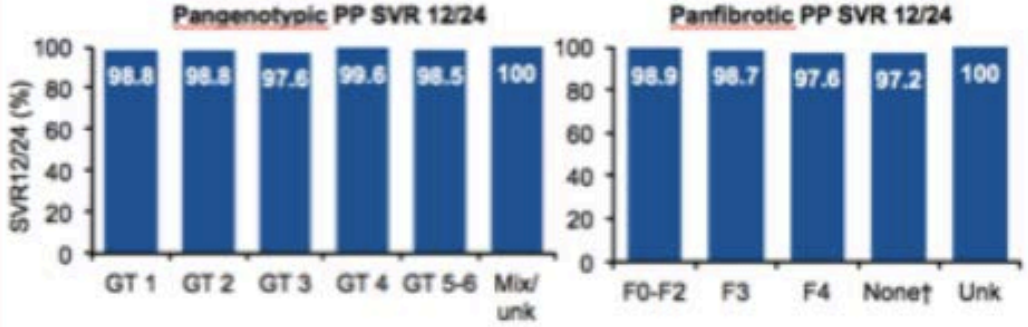
- SVR data available for 5,541 patients
  - Median age 54 years; 59.5% male
  - Genotype distribution:



  - 20.7% (1,107) patients had CC
  - 12.4% (660) patients were treatment-experienced
- 5,134 patients achieved SVR*
  - PP: 98.5%; ITT: 92.7%

*LTFU (4%) was the most common reason for not reaching SVR;
†Confirmed no cirrhosis, but fibrosis score not recorded.

PP SVR12/24 according to patient status



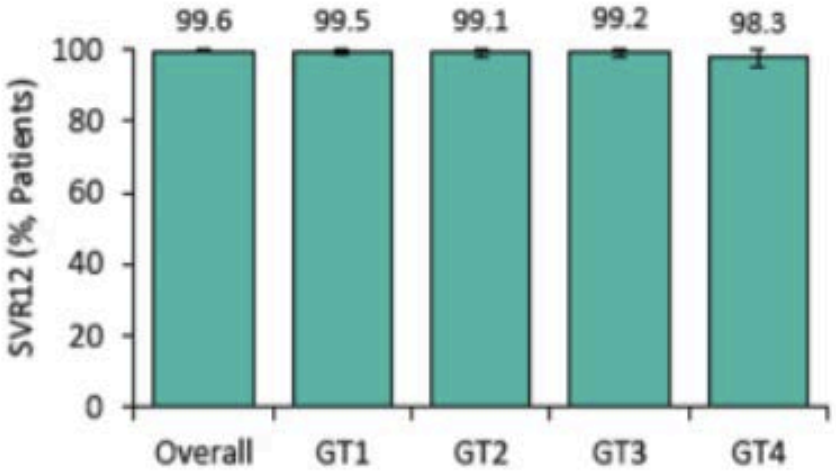
SOF/VEL for 12 weeks is a simple, highly effective regimen that cures HCV patients, irrespective of genotype, cirrhosis status or treatment history, with a manageable drug interaction profile and broad clinical utility, which will help simplify the care pathway and will contribute to the WHO 2030 targets for HCV elimination

Mangia A, EASL 2019,GS-03 L

Real-World Experience with GLE/PIB

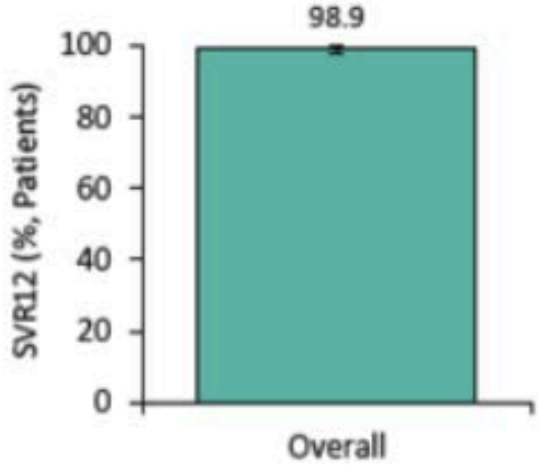
16 unique cohorts

Treatment-Naïve Patients Without Cirrhosis Who Underwent 8 Weeks of Treatment



	Overall	GT1	GT2	GT3	GT4
Total patients in subgroups, N	3280	807	230	320	55
Cohort, N	8	5	5	4	2

Treatment-Naïve Patients With Cirrhosis Who Underwent 12 Weeks of Treatment†



	Overall
Total patients in subgroups, N	298
Cohort, N	7

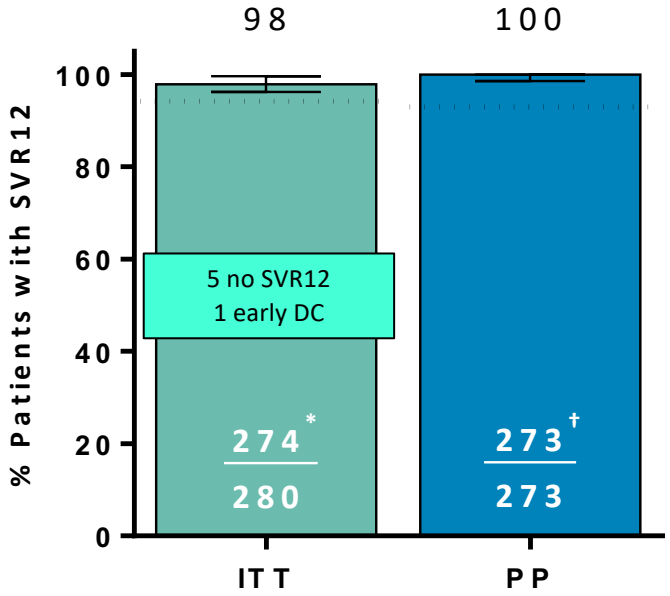
mITT analysis: excludes those who failed for non-virologic reasons

Cornberg M, EASL 2019

GLE/PIB for 8 weeks in Treatment-Naive Patients with Compensated Cirrhosis

EXPEDITION 8

Characteristic	N=302 (%)
Genotype 1a/1b 2 4/5/6	 34/ 49% 9% 5/ <1/ 3%
CPT Score 5 6	 90% 9%
BL NS5A polymorphisms	36%



- **No virologic failures**
- **No safety concerns**

- *Extension to include genotype 3 with compensated cirrhosis ongoing*

Brown et al. AASLD 2018, LB-7

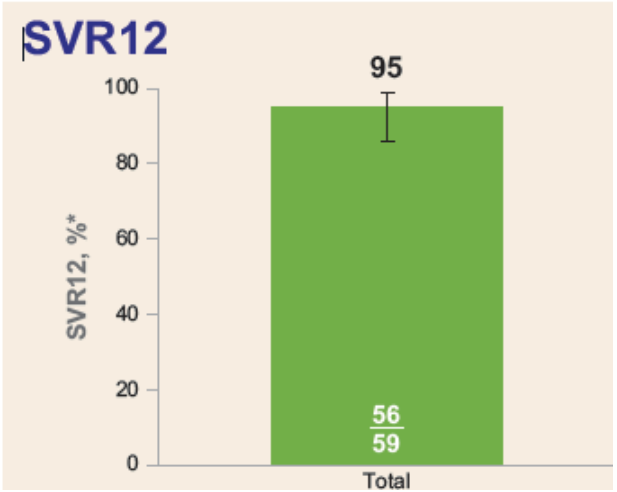
SOF/VEL in Patients on Dialysis

Open label phase 2 study, N=59

SOF/VEL once daily for 12 wks

Key eligibility criteria:

- Undergoing hemodialysis or peritoneal dialysis
- Any HCV genotype
- Treatment naïve or experienced
- With or without compensated cirrhosis



3 patients did not achieve SVR12

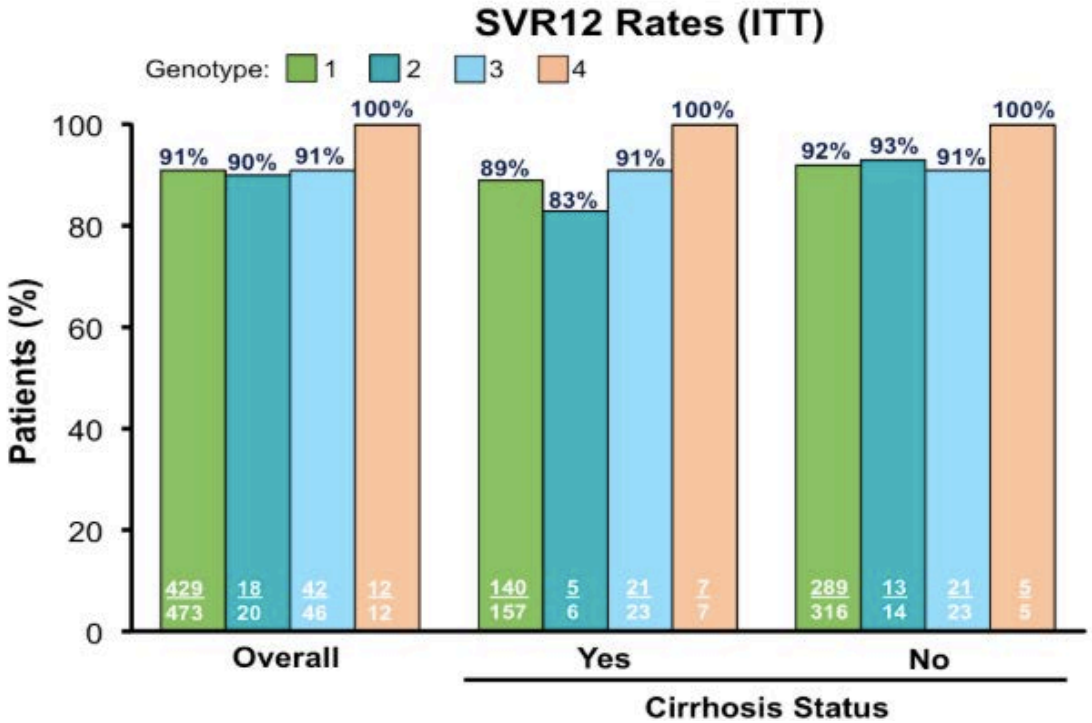
- N=1, HCV GT 3 and cirrhosis relapsed
- N=1 with noncompliance relapsed
- 1 died of suicide after treatment end (SVR4)

No treatment-related adverse events

Borgia SM, AASLD LB-15

SOF/VEL/VOX in Prior DAA Failures
Real World VA Experience

VA study: SOF/VEL/VOX in N=573 after DAA failure



High overall efficacy:

GT 1: 95.1% (409/430)

GT-2: 89.5% (13/15)

GT-3: 93.3% (42/45)

GT-4: 100% (12/12)

Lower SVR rates if prior SOF/VEL failure:

GT-1: 78.9% (15/19)

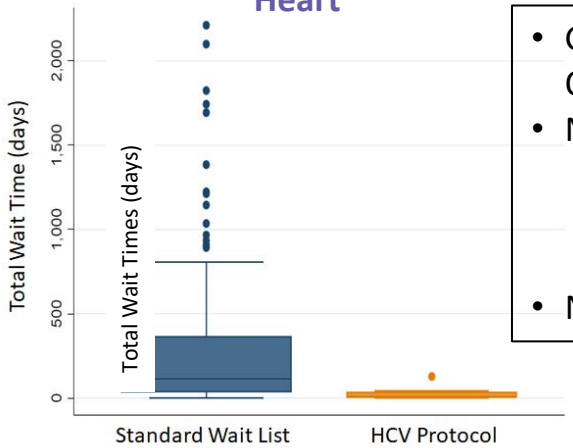
GT-2: 86.7% (13/15)

GT-3: 84.6% (11/13)

Belperio et al J Viral Hepatitis, 2019

HCV+ donors to HCV- recipients

Heart



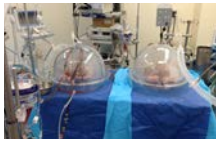
- GLE/PIB x 8w on call to OR
- N=25
  - SVR12 – 12
  - SVR4 – 5
  - Others undetectable
- NAT-/Ab+ → no viremia

Cardiac: Reduced wait times

Lung

HCV+ Donor

Ex Vivo Lung Perfusion x 6 h (reduce HCV RNA)



HCV- Recipient (n=20)

SOF/VEL x 12w – median 21d post-OLTx
2 of 8 relapse
High level resistance
1 early FCH

- **Non-liver transplants using organs from HCV+ recipients reduce wait times**
- **Treatment failures associated with high level viral resistance**
- **Promising but needs planning and guaranteed access to DAA therapies**

Bethea et al. AASLD 2018, Abstract 0007, Feld et al, Abstract 0223, O'Dell Abstract 0225

Summary of HCV Management 2019

- Undiagnosed still an issue – broadening of screening needed
  - Foreign-born, pregnant women
- Treatment is simplified with 2 pangenotypic regimens available
  - Very high rates of SVR
  - Staging of fibrosis still important: HCC risk after cure
- Few “difficult to cure” patient groups left
  - DAA failures: SOF/VEL/VOX is highly effective but responses lower if prior SOF/VEL treatment
- HCV+ donors increased → opportunity for increased use in transplant recipients

What's New for HBV?

- Treatment algorithms
  - Who to treat
  - What to treat with: ETV versus TDF/TAF
  - When to stop
- New treatment goal → functional cure
  - New HBV drugs

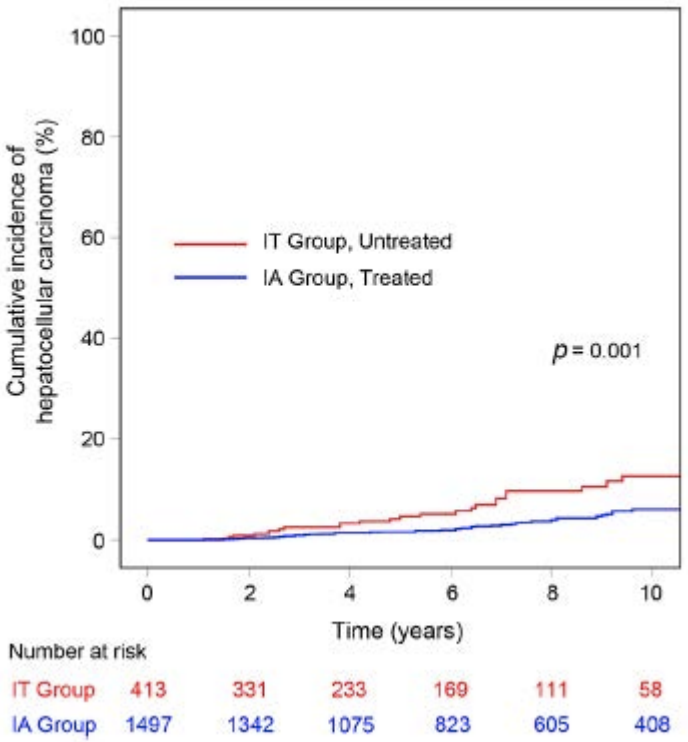
Controversies on When to Start Treatment

- **Immune active:** ALT> ULN and HBV DNA >2000 (HBeAg-) or 20,000 (HBeAg+) IU/mL
- **Immune tolerant phase (or non-inflammatory replicative phase)**
  - Very high levels of viremia (>10^7 IU/mL) but normal ALT
  - Normal liver stiffness and/or histology
  - Young age

	Treatment	Except if:
AASLD	No	>40 years and evidence of histologic disease
EASL	No	>30 years, regardless of histologic disease
APASL	No	>30 years and evidence of liver disease or family history of HCC or cirrhosis

AASLD HBV Treatment Guideline 2016
EASL HBV Treatment Guideline 2017
APASL HBV Treatment Guideline 2015

Higher Risk of HCC in Untreated Immune Tolerant than Treated Immune Active CHB



Model	HR (95% CI)	p Value
Hepatocellular carcinoma		
Unadjusted	2.23 (1.38 to 3.61)	0.001
Multivariable Cox regression	2.54 (1.54 to 4.18)	<0.001
IPTW analysis	2.69 (1.63 to 4.45)	<0.001
PS-matched analysis	2.43 (1.23 to 4.78)	0.01
Competing risks analysis	2.09 (1.08 to 4.05)	0.03

Conclusions Untreated IT-phase patients with CHB had higher risks of HCC and death/transplantation than treated IA-phase patients. Unnecessary deaths could be prevented through earlier antiviral intervention in select IT-phase patients.

Kim GA, Gut 2018;67:945-952

Higher Risk of HCC in Untreated OLDER Immune Tolerant: Unrecognized Immune Active Disease?

Table 1 Baseline characteristics of the study patients

Characteristic	IT phase group	IA phase group	p Value
n	413	1497	
Age, mean±SD, years	38±11	40±11	0.04
Male sex	276 (66.8%)	973 (65.0%)	0.49
HBV DNA, median (IQR), log_{10} IU/mL	8.0 (7.0–8.4)	7.7 (6.9–8.3)	0.20
4.00–6.99	108 (26.2%)	428 (28.6%)	
7.00–7.99	105 (25.4%)	516 (34.5%)	
≥8.00	200 (48.4%)	553 (36.9%)	
ALT, median (IQR), IU/mL	19 (16–25)	156 (95–308)	<0.001
AST, median (IQR), IU/mL	25 (21–31)	113 (69–216)	<0.001
Albumin, median (IQR), g/dL	4.0 (3.8–4.3)	3.9 (3.7–4.1)	<0.001
Total bilirubin, median (IQR), mg/dL			
Platelets, n			
Diabetes m			
Hypertensi			
Duration of follow-up period, median (IQR), years			

Take home message:

Age is important additional factor to consider in IT patients

Kim GA, Gut 2018;67:945-952

What to Treat With?

If no comorbidities (for most pts) → Monotherapy with ETV, TDF, or TAF

If risk of or preexisting bone or renal disease, prioritize ETV or TAF

- Age > 60 yrs
- Bone disease
  - Chronic steroids or other meds that affect bone
  - History of fragility fracture
  - Osteoporosis
- Renal abnormalities
  - eGFR < 60 min/mL/1.73 m^2
  - Albuminuria > 30 mg or moderate proteinuria
  - Low phosphate (< 2.5 mg/dL)
  - Hemodialysis

When to prioritize TAF over ETV

- Previous nucleoside exposure[2]
  - Lamivudine with or without adefovir resistance
- HIV/HBV coinfection
- No dose adjustment for CrCl ≥ 15 mL/min

When to prioritize ETV over TAF

- If less expensive (generic available)
- No prior nucleoside exposure and HIV uninfected
- CrCl < 15 mL/min (with dose adjustment)

Adapted from: clinicaloptions.com

Terrault N, Hepatology 2018
. EASL. J Hepatol. 2017;67:370-398.

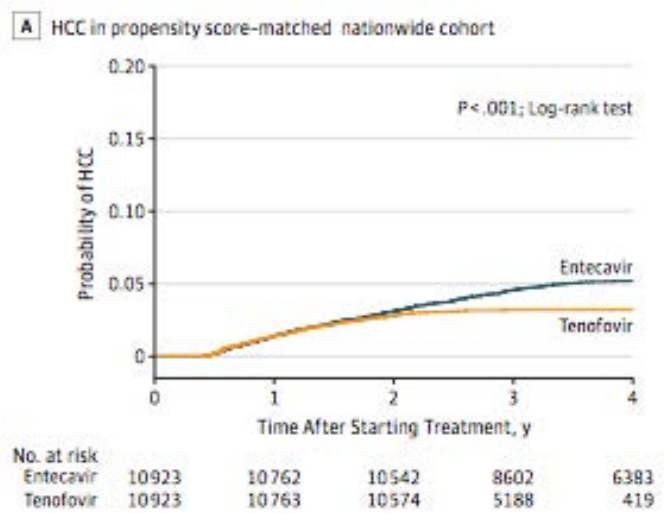
The Study that Started the Controversy

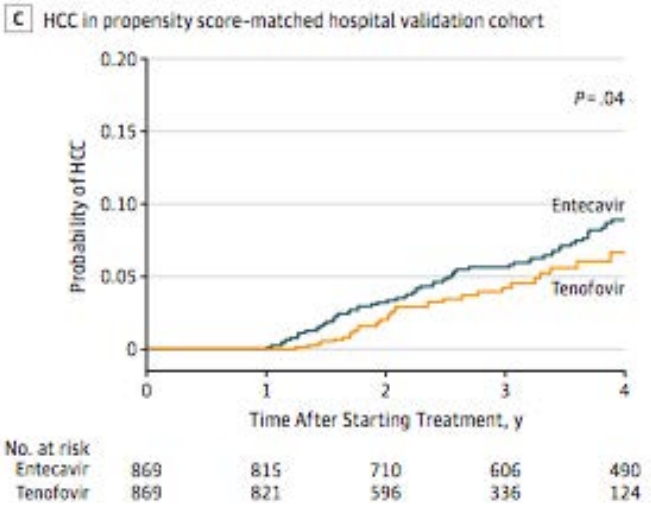
JAMA Oncology | Original Investigation

Risk of Hepatocellular Carcinoma in Patients Treated With Entecavir vs Tenofovir for Chronic Hepatitis B
A Korean Nationwide Cohort Study

Jonggi Choi, MD; Hyo Jeong Kim, MPH; Jayoun Lee, PhD; Songhee Cho, MPH; Min Jung Ko, PhD; Young-Suk Lim, MD, PhD

TDF(vs ETV) associated with ~30% reduction in HCC risk



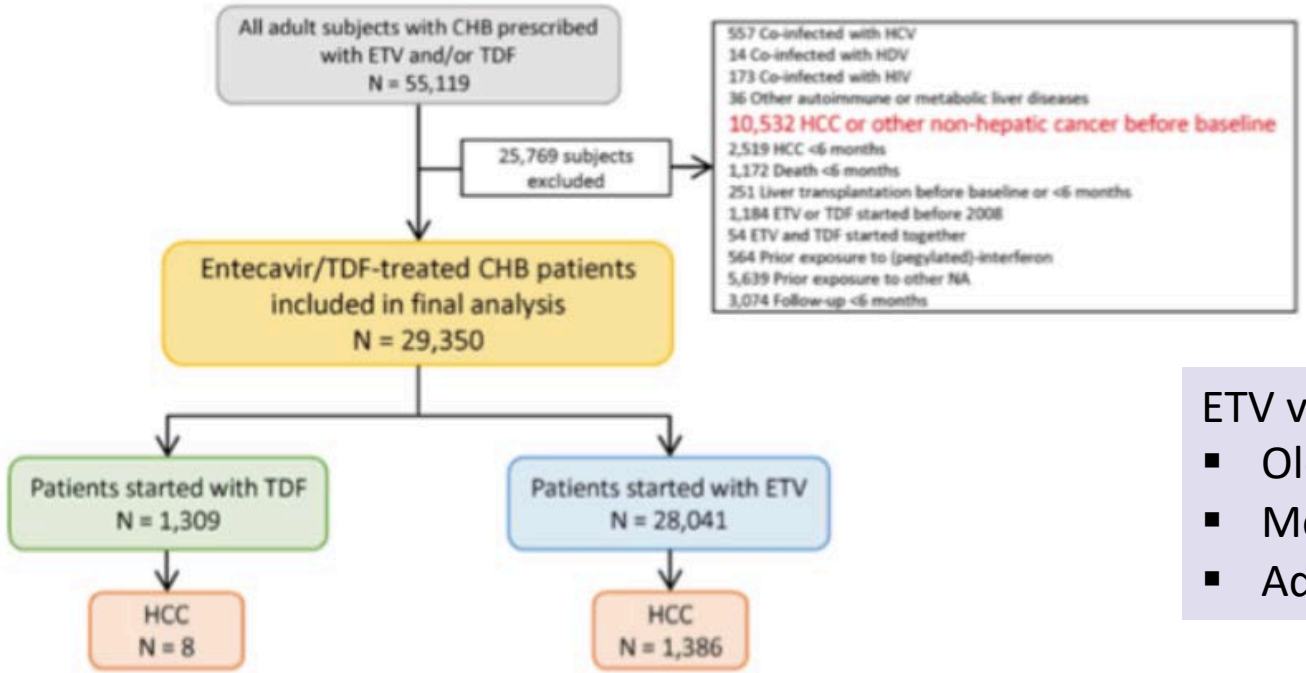


JAMA Oncol. 2019;5(1):30-36. doi:10.1001/jamaoncol.2018.4070
Published online September 27, 2018. ***Retracted and replaced on April 25, 2019.***

Entecavir vs Tenofovir and Risk of HCC

Hong Kong Cohort

29,350 patients were included in the analysis



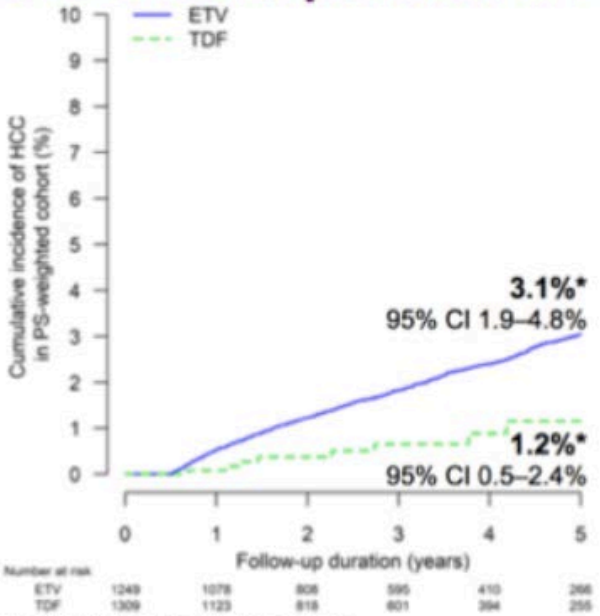
ETV vs TDF patients

- Older
- More males
- Advanced fibrosis

Yip T, EASL 2019, Vienna

Propensity-Matched HCC Risk

TDF-treated patients have a lower risk of HCC than ETV-treated patients in PS weighting analysis



*Result from a single imputation data set.
Cumulative incidence estimated by Kaplan-Meier method in the PS-weighted cohort.
SHR = subdistribution hazard ratio

In cohort after PS weighting

Parameters	Propensity score weighting analysis		
	SHR	95% CI	*P* value
TDF *vs.* ETV	0.36	0.16–0.80	0.013

In cohort before PS weighting

Parameters	Multivariable analysis		
	SHR	95% CI	*P* value
TDF *vs.* ETV	0.32	0.16–0.65	0.002

Yip T, EASL 2019, Vienna

When to Stop Treatment

Cirrhosis	HBeAg-positive CHB	HBeAg-negative CHB
▪ **Indefinite therapy**	▪ **Until HBeAg seroconversion plus ≥1 year consolidation**	▪ **HBsAg loss (indefinite therapy)**

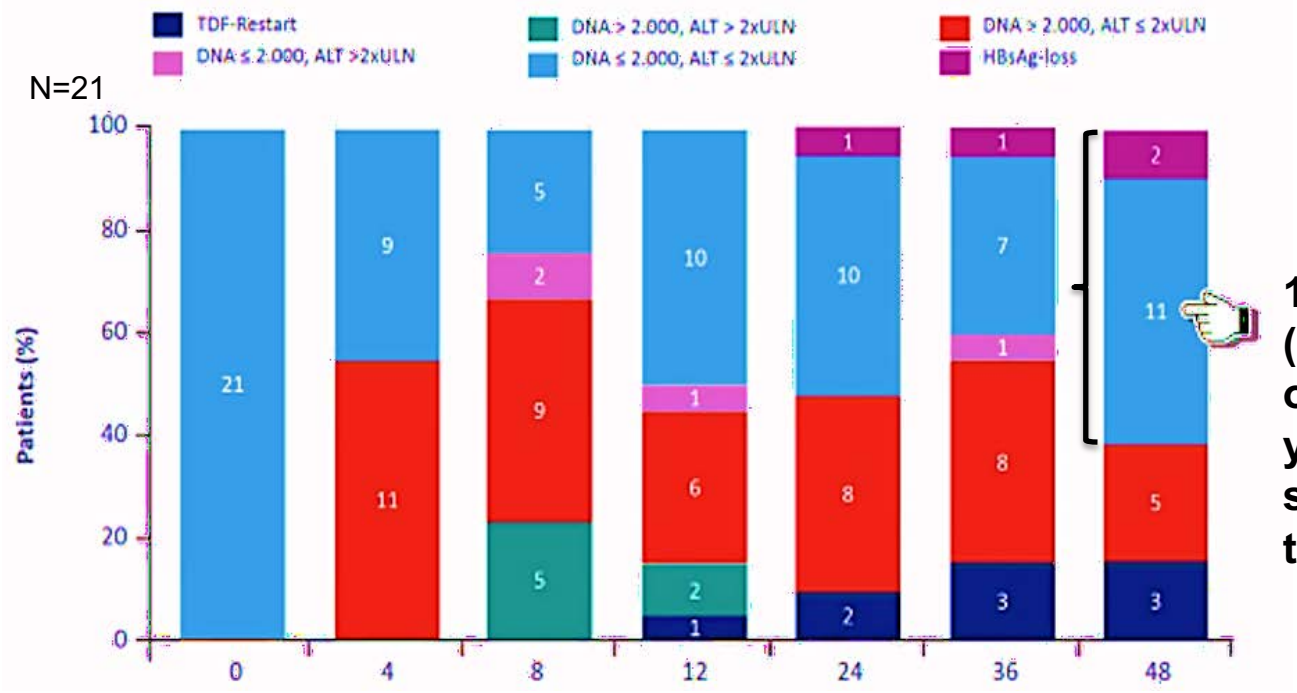
For HBeAg-negative CHB: other guidance recommendations differ:

EASL: if no cirrhosis, can stop after >3 year of normal ALT and HBV DNA undetectable
APASL: if no cirrhosis, stop after ≥4 years of normal ALT and HBV DNA undetectable

AASLD HBV Treatment Guidelines 2018

Outcomes in HBeAg-Negative CHB TDF Stopped After 4 Years

Berg T, J Hepatol 2017;67:918-92



13/21 (62%) remain off TDF at 4 years after stopping treatment

4/21 (19%) achieved HBsAg loss at 3 years post-cessation

Prospective Canadian Trial of NA Withdrawal

Inclusion

HBeAg-neg with DNA neg:

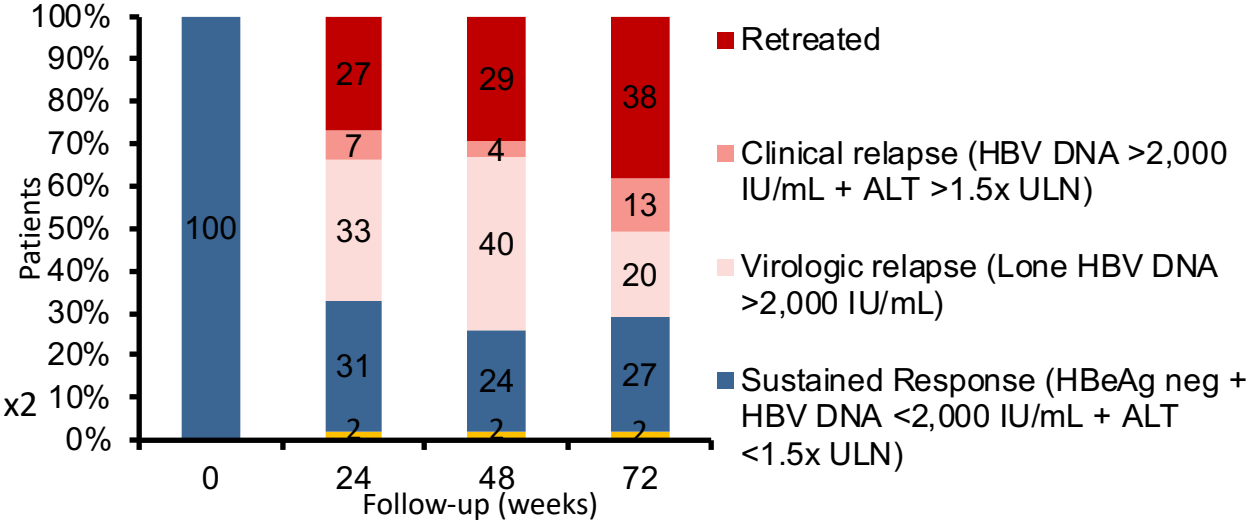
- > 3 yrs (start HBeAg-neg)
- >1 yr post HBeAg loss (start HBeAg+)

Intervention

- Randomized 2:1 stop vs continue NA
- F/u x 72 weeks

Retreatment criteria

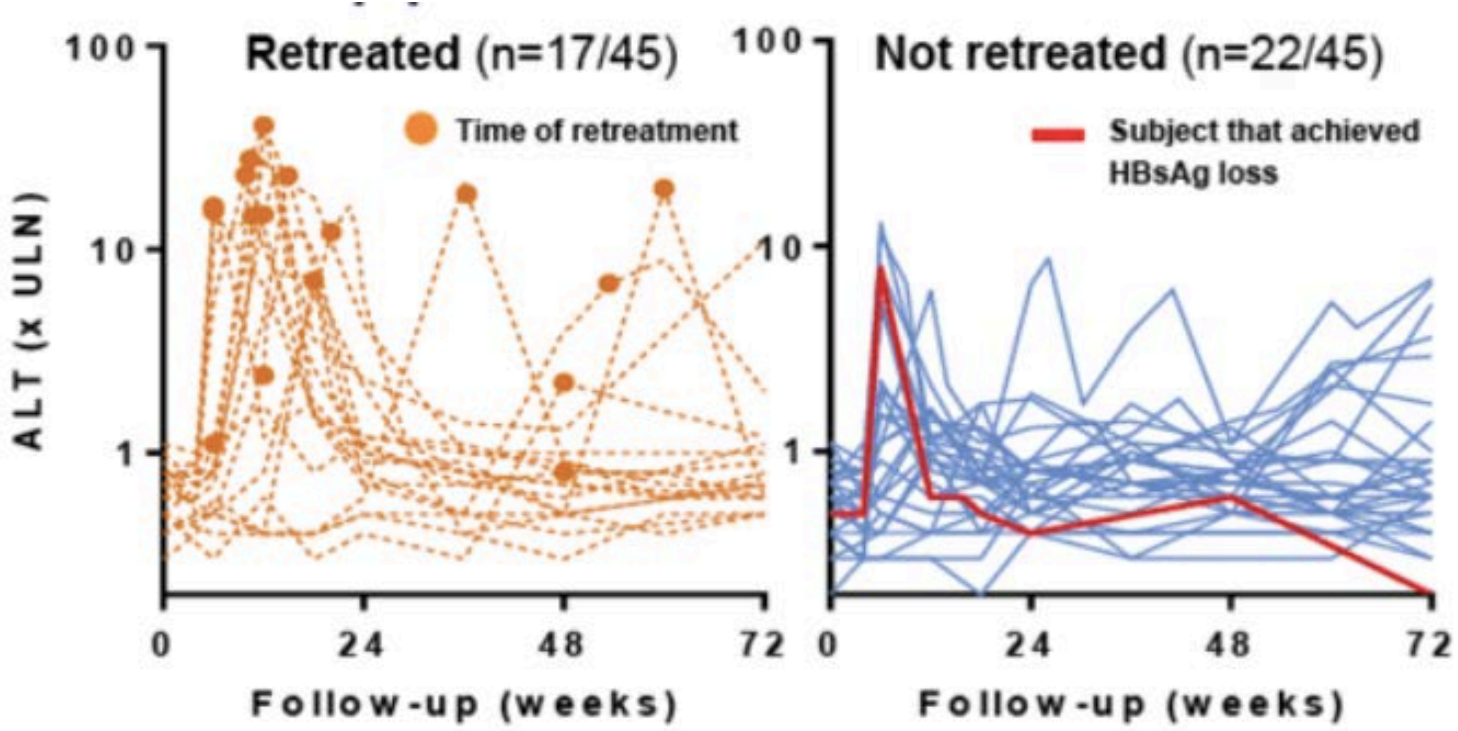
1. HBeAg seroreversion
2. HBV DNA>2000 IU/mL + ALT>5xULN x2 or ALT >15xULN x 1
3. HBV DNA >20,000 x 2



- Clinical relapse or retreatment in >50% and only ~30% with sustained off-treatment response
- Very low rate of HBsAg loss -- ? related to predominance of Asians in study population

Liem et al AASLD 2018, Abstract 268; EASL 2019

Flares are Frequent and Need Active Management



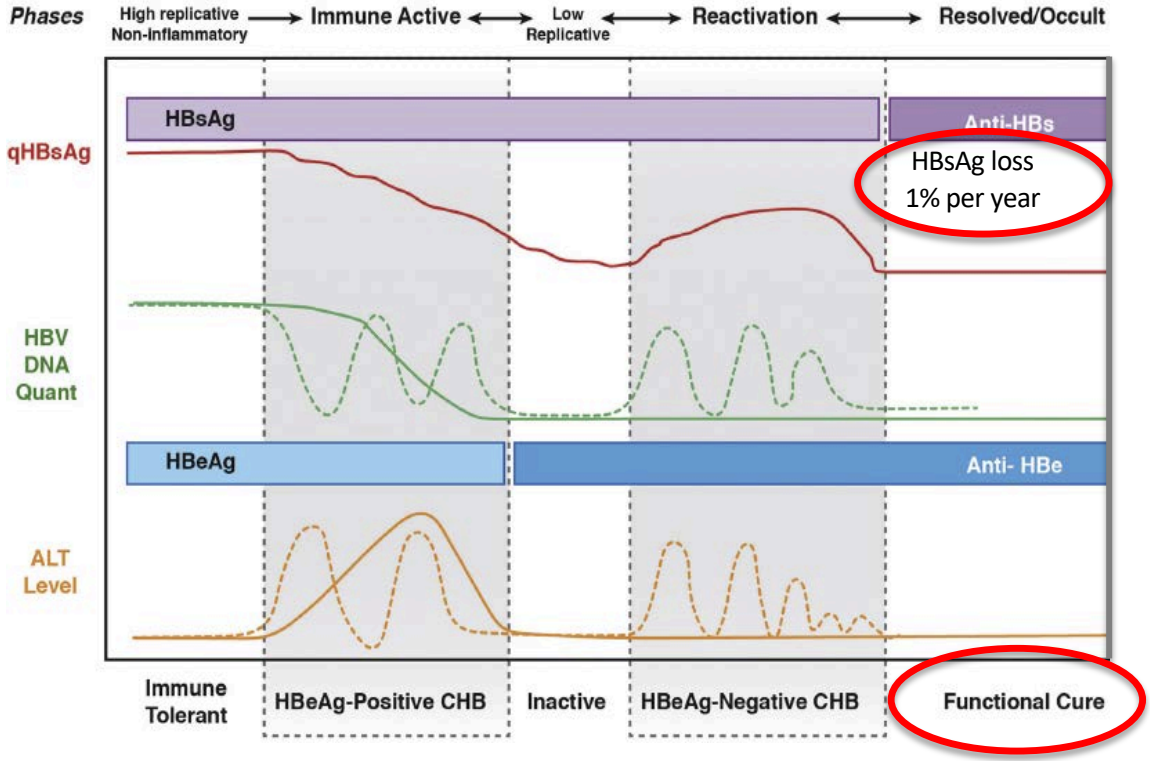
Liem et al EASL 2019, Vienna

Issues with Interpreting Studies of NA Withdrawal

- **Heterogeneous patient populations**
- **Different NA therapy and different durations of suppression**
- **“Rules” for restarting NA therapy are highly variable across studies**
- **Flares appear important but lack ability to distinguish good versus bad flares**
- **Duration of time needed to establish benefit (maximum HBsAg loss)**
- **Lack of well-established predictors of who achieve HBsAg loss off treatment**

Bottom-line: not ready for prime time

Goals of Therapy Shifting from HBV DNA Suppression to HBsAg Loss



- Partial Cure: HBsAg positive but HBV DNA persistently undetectable off treatment
  - = what we achieve now
- Functional Cure: HBsAg loss and HBV DNA undetectable ± anti-HBs
  - = what new therapies what to achieve
- Complete sterilizing cure: Absence of cccDNA and integrated HBV DNA
  - = unclear if achievable

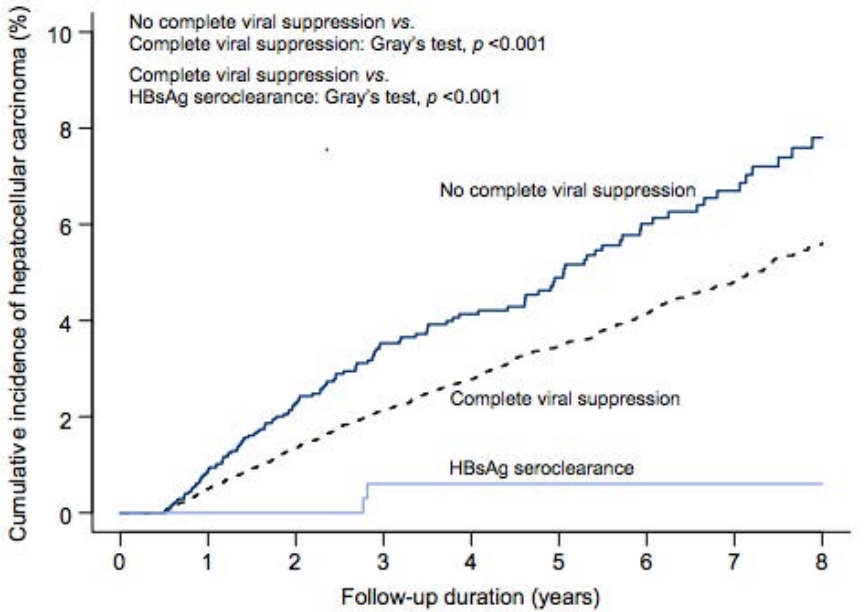
EASL-AASLD Hepatitis B Treatment Endpoints Workshop 2019

Suppression Good, HBsAg Clearance Better

Hong-Kong Cohort:

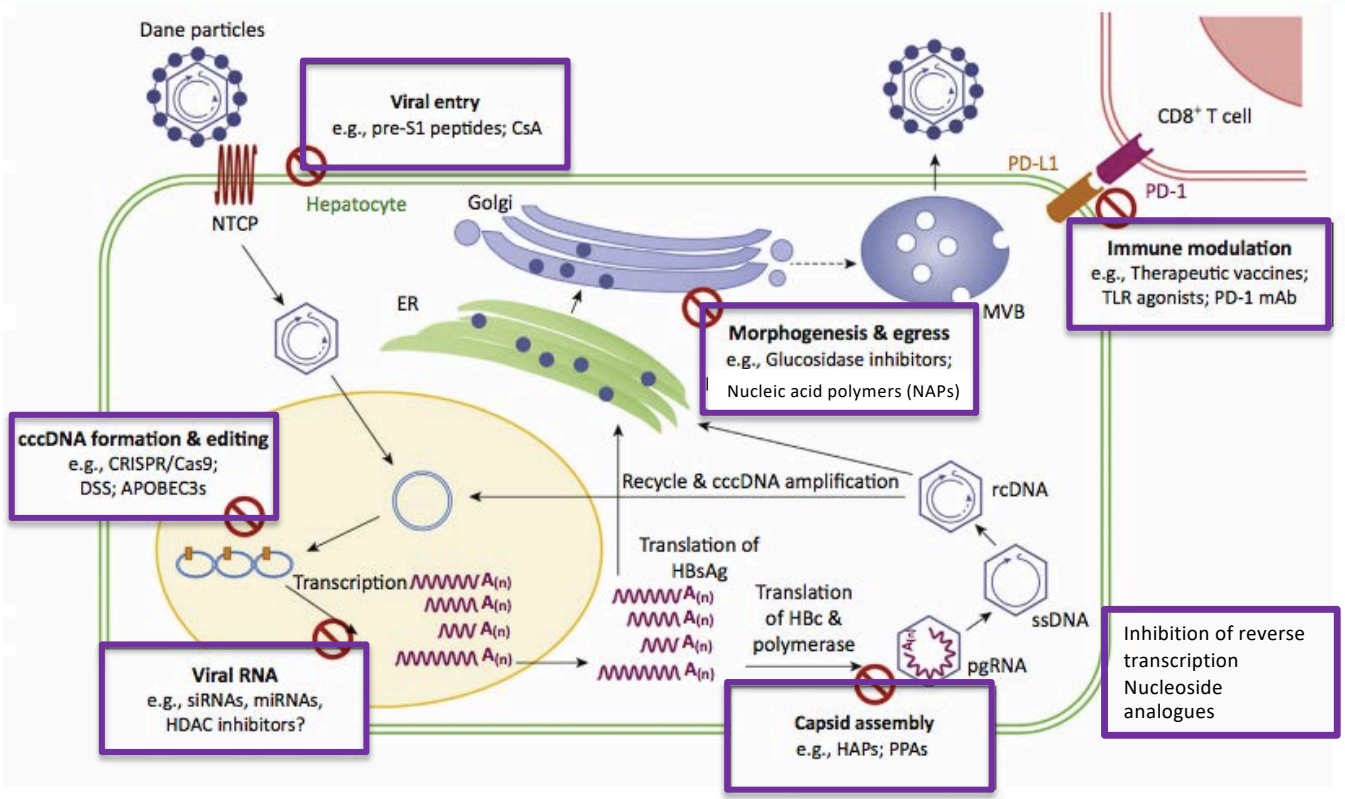
- **20,263 nucleos(t)ide analogue (NA)-treated patients with chronic hepatitis B**
- **17,499 (86.4%) patients had complete viral suppression (HBV DNA <20 IU/mL)**
- **376 (2.1%) achieved HBsAg seroclearance.**
- **Median follow-up 4.8 (IQR: 2.8–7.0) yrs**

Incidence of HCC highest in those without complete VR; lowest if HBsAg loss



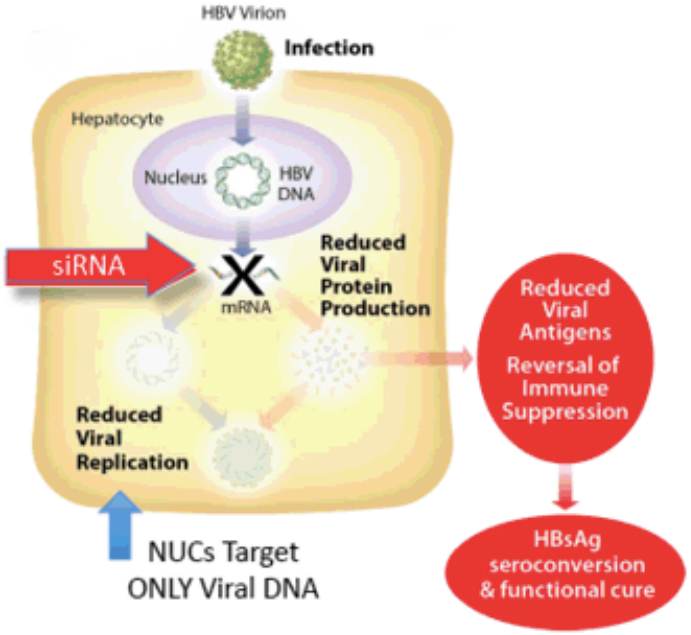
Yip TCK, J Hepatology 2019;70:361-370

The Many New Targets Aiming at HBV Cure



Shih C, Trends in Microbiology 2016

RNA Interference

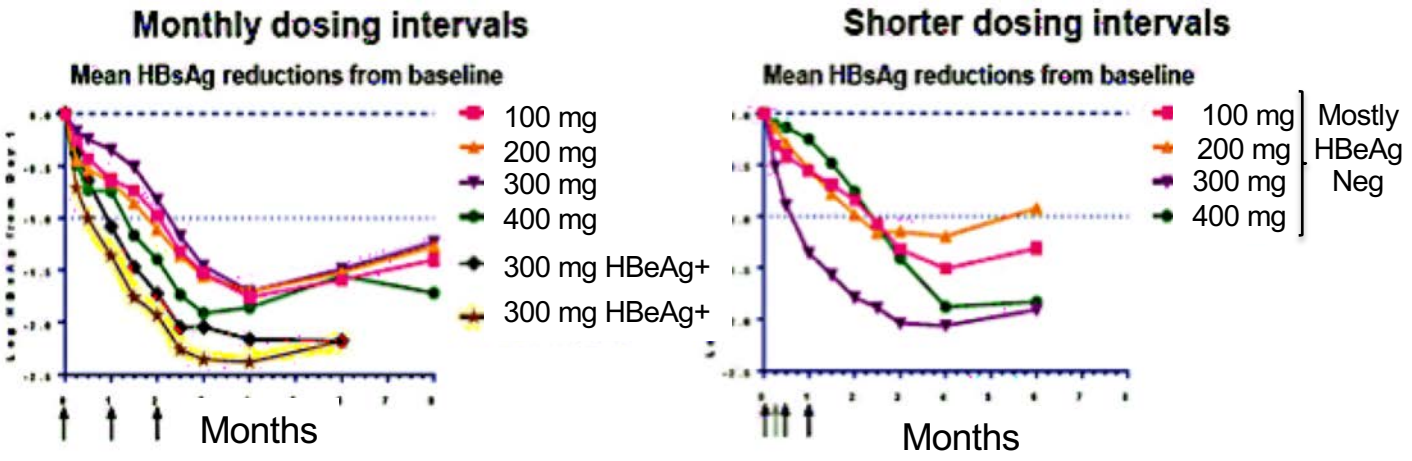


RNAi	Phase of Development
JNJ-3989 (Janssen) *formerly ARO-HBV-1001 (Arrowhead)*	**Phase 1/2**
AB-729 (Arbutus)	Preclinical
ALN-HBV (Alnylam)	Preclinical

JNJ-3989: Short Duration RNAi

Phase 2

- **JNJ-3989 targets entire HBV transcriptome**
- **3 SC doses weekly to monthly (100, 200, 300, 400 mg) in HBeAg+/neg CHB on suppressive therapy with ETV or TDF**
- **No SAE, including ALT elevations; 10% mild injection site rejections**

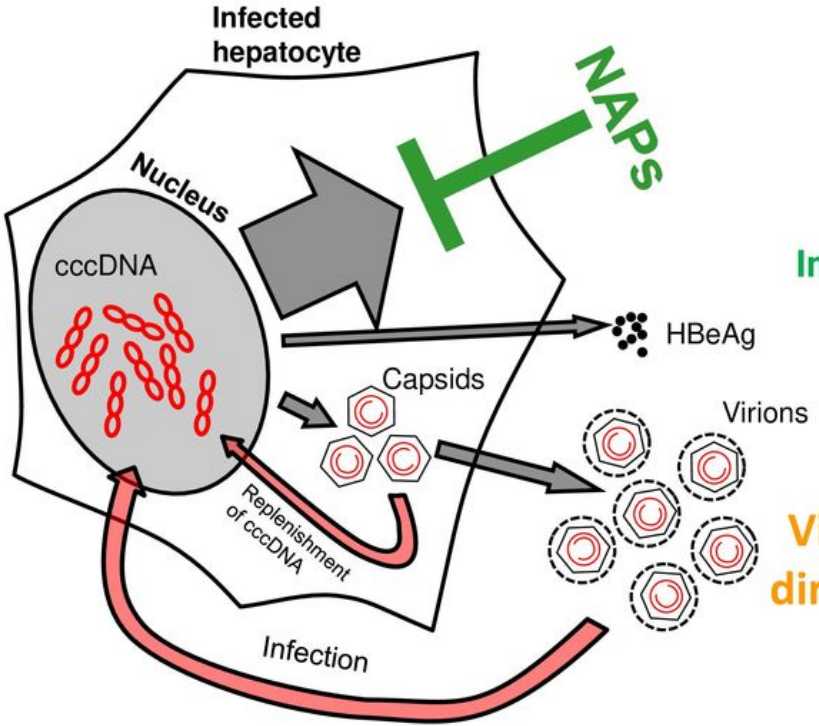


- **Nadir in HBsAg decline at ~4 months**
- **100% had ≥1-log reduction in qHBsAg**
- **Response regardless of HBeAg status or type of NA**

Yuen MF, EASL Vienna, 2019

Blocking Viral Release

NAPs= nucleic acid polymers



HBsAg mediated immunosuppression removed

↓

Permissive immunological environment restored

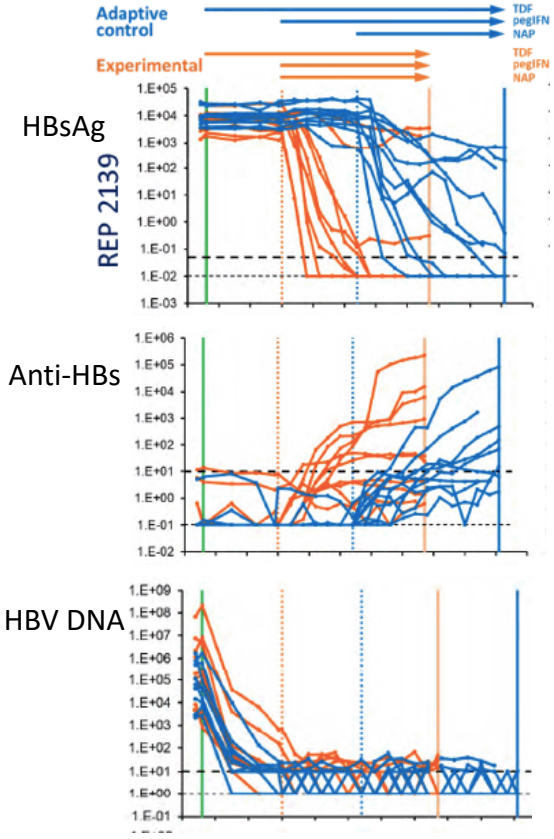
↓

Improved effect of immunotherapy (and potentially other antiviral agents)

Virions are not directly targeted by NAPs

Vaillant, 2016 Antiviral Res: 133: 32-40

NAPs (REP-2139/REP-2165) in Combination with TDF and Peg-IFN



Phase 2

REP 2139/2165 + TDF + peg-IFN (48 wks combination) HBeAg neg treatment naive	HBsAg response at end of treatment	N=40
	>1 log from baseline	36
	<1 IU/mL	27
	<0.05 IU/mL	23 (57.5%)

- ALT/AST elevations common during treatment
- No associated with bilirubin elevations
- May be associated with functional remission

Valliant A, EASL 2019 Abstract 343 and AASLD Industry Colloquium 2018

Summary: Hepatitis B

- TDF, TAF, entecavir are preferred drugs; **ETV or TAF best for older patients with renal or bone risks**
  - HCC data interesting but preliminary
- **Stopping rules** only applicable to non-cirrhotic patients
  - In HBeAg-positive CHB → consolidation therapy for ≥1 year (more if >40 years?)
  - In HBeAg-negative CHB → best to await studies that provide better predictors of who benefits
- **Functional cure (HBsAg loss)** is infrequently with current therapies
  - Many new HBV drugs in pipeline