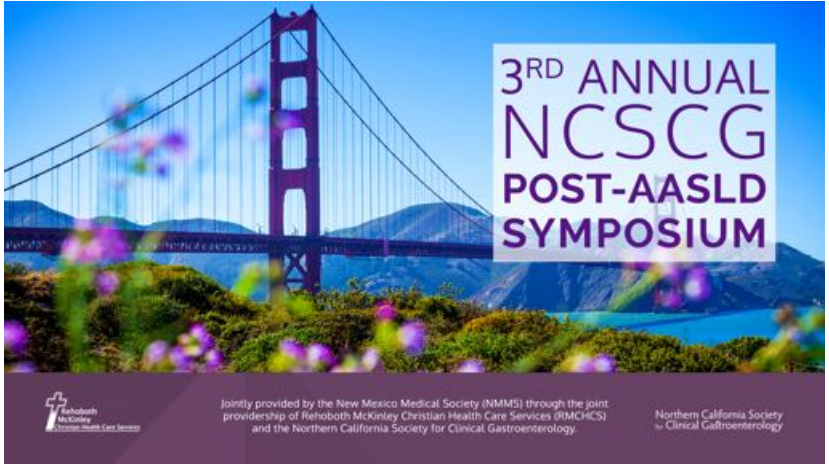

UPDATES IN VIRAL HEPATITIS

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Professor of Medicine
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San Francisco, December 2017

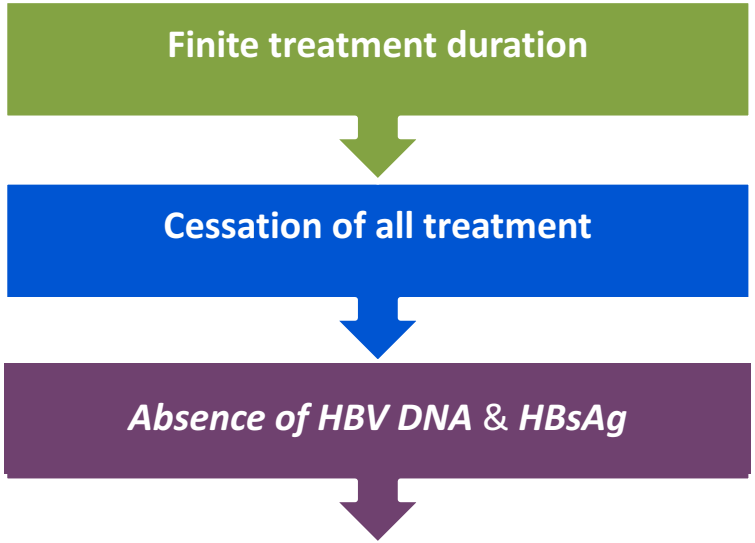
STANFORD UNIVERSITY

OUTLINE

1. **HBV updates – the "cure" frontier** and **existing Rx**
2. **HCV updates – 2017 SOC** and **SVR & HCC-2 sides of the coin?**
3. **HDV – what is new?**

HBV– “CURE” FRONTIER

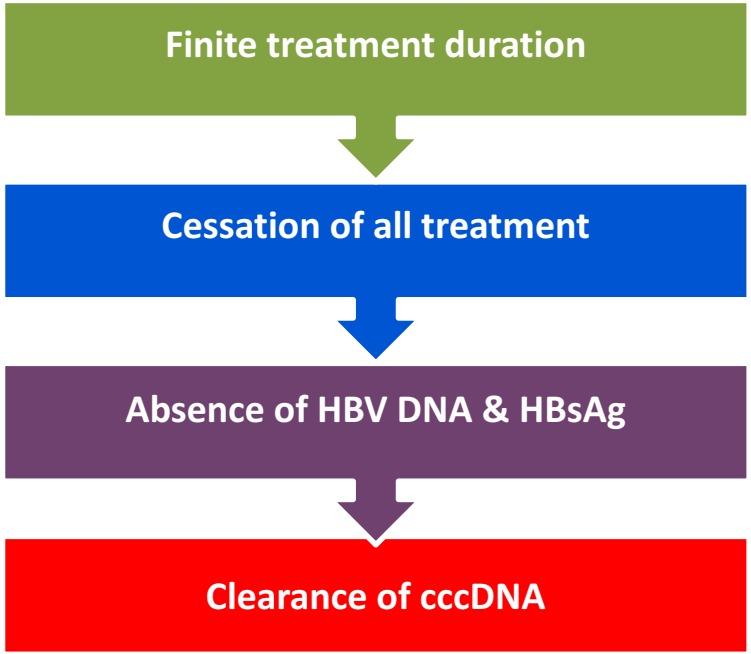
The New Goal: **Functional Cure**



Stop antiviral therapy with minimal risk of reactivation

cccDNA inactivation or control by host mechanisms

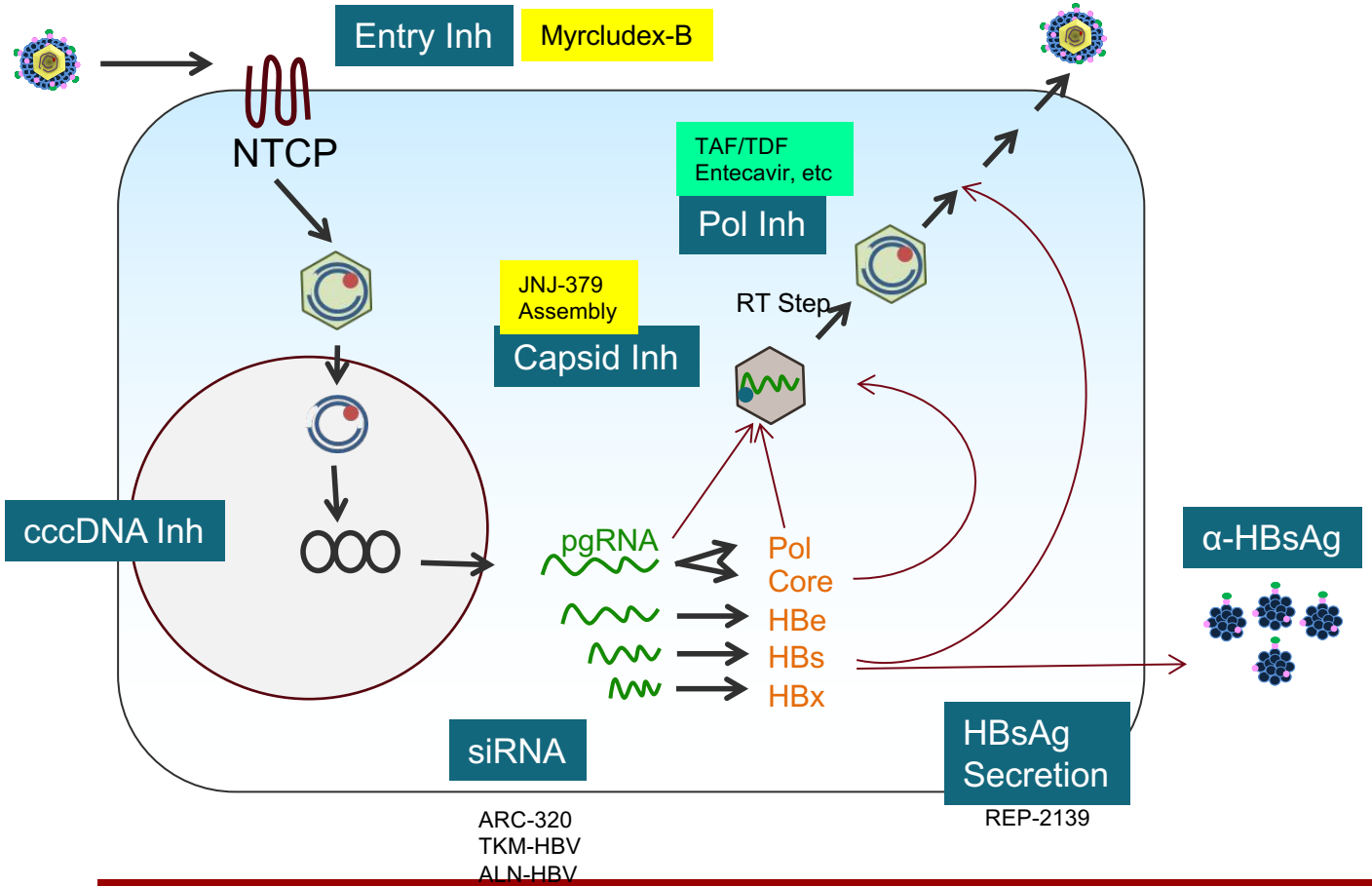
The Future Goal: **Complete Cure**



HBsAg seroconversion and cccDNA eradication
In all cases, associated with clinical benefit
Impact of integrated viral sequences to be addressed.

Zeisel, Lucifora et al, Gut 2015; Revill et al, Nature Reviews

HBV Life Cycle: offers many targets for antivirals

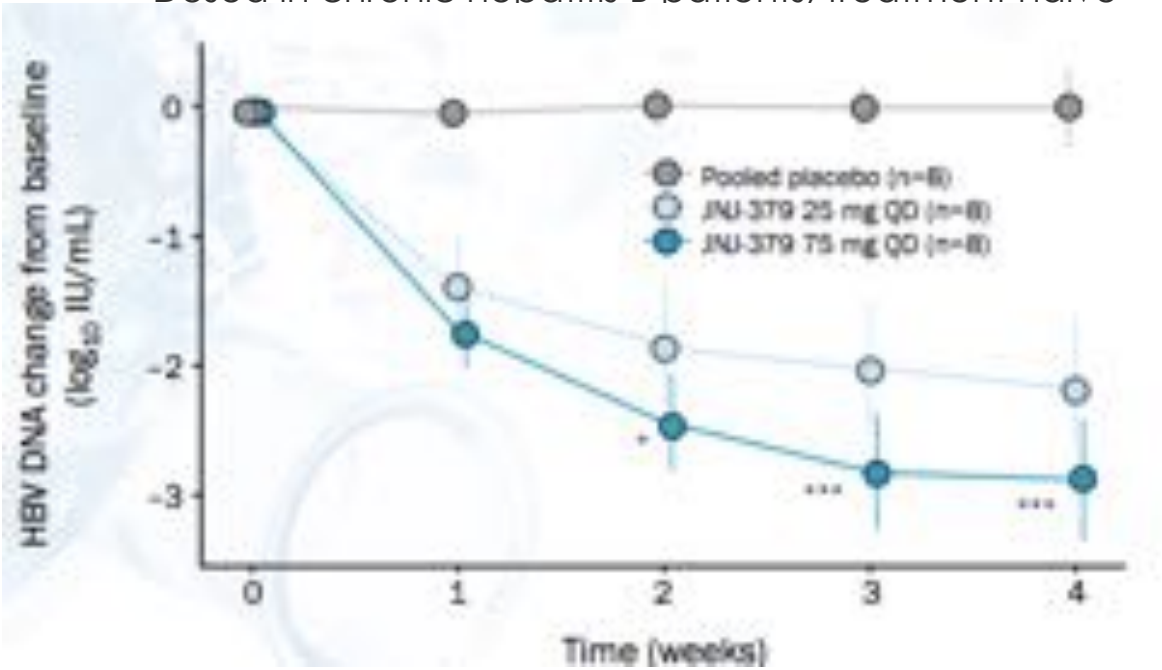


Safety, Tolerability, Pharmacokinetics and Antiviral Activity of JNJ-56136379, a Novel HBV Capsid Assembly Modulator, in Non-cirrhotic, Treatment-naïve Subjects with Chronic Hepatitis B.

JNJ-56136379 (JNJ-379): potent capsid assembly modulator (CAM)

JNJ-379 binds to the HBV core protein and interferes with the HBV capsid assembly, and prevents cccDNA formation during *de novo* infection, by interfering with capsid disassembly

Dosed in chronic hepatitis B patients, treatment naive



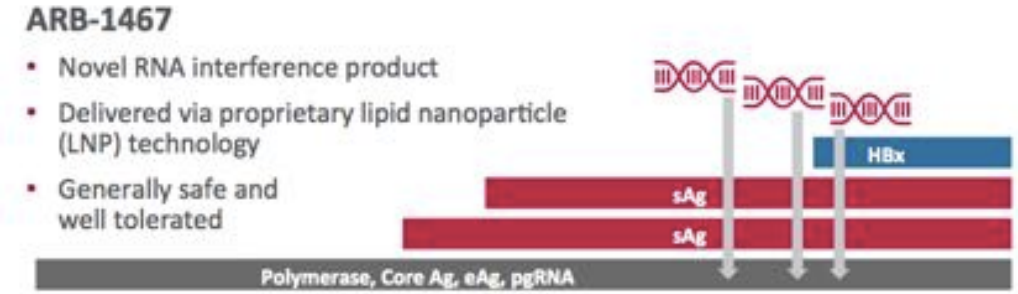
Three patients with HBV DNA <LLOQ of the HBV DNA assay.

Zoulim et alHEPATOLOGY. 2017 66(1)LB-15

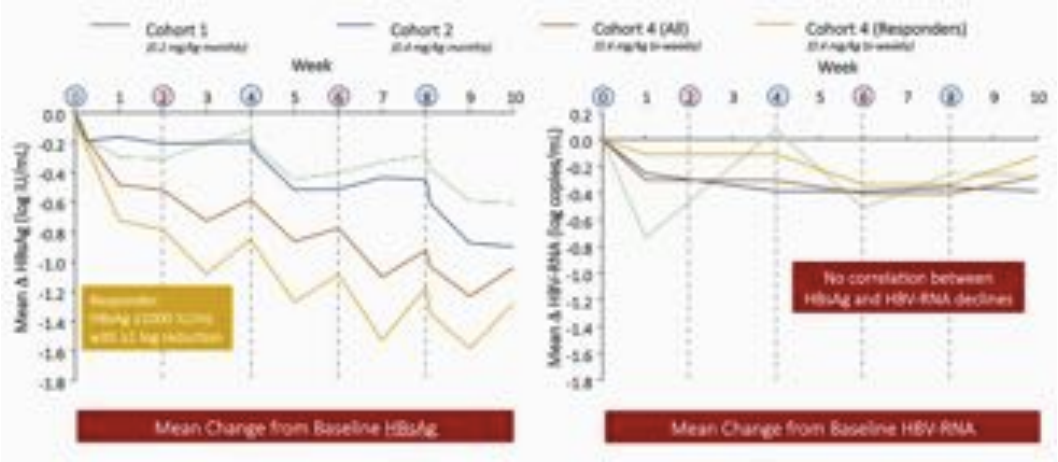
Slide courtesy Dr. P Kwo

HBcrAg, HBV-RNA Declines in A Phase 2a Study Evaluating the Multi-Dose Activity of ARB-1467 in HBeAg-Positive and Negative Virally Suppressed With Hepatitis B

Unique 3-trigger design inhibits HBV replication, reduces all HBV transcripts, and lowers all HBV antigens



- No apparent correlation was observed between declines in HBV-RNA or HBcrAg and declines in HBsAg
- Baseline HBsAg and IL28b genotype CC were significantly associated with response

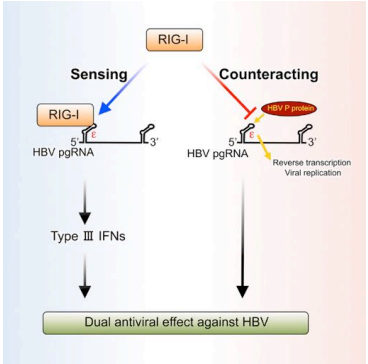


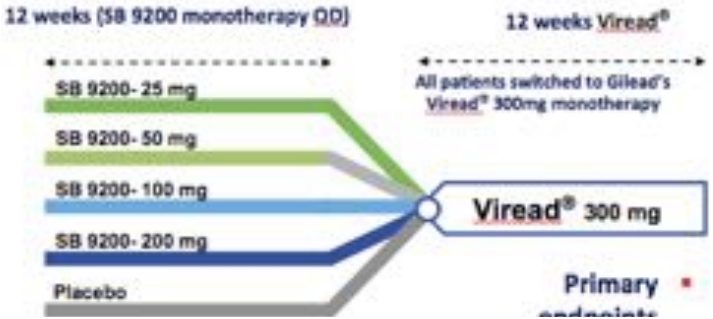
Slide courtesy Dr. P Kwo

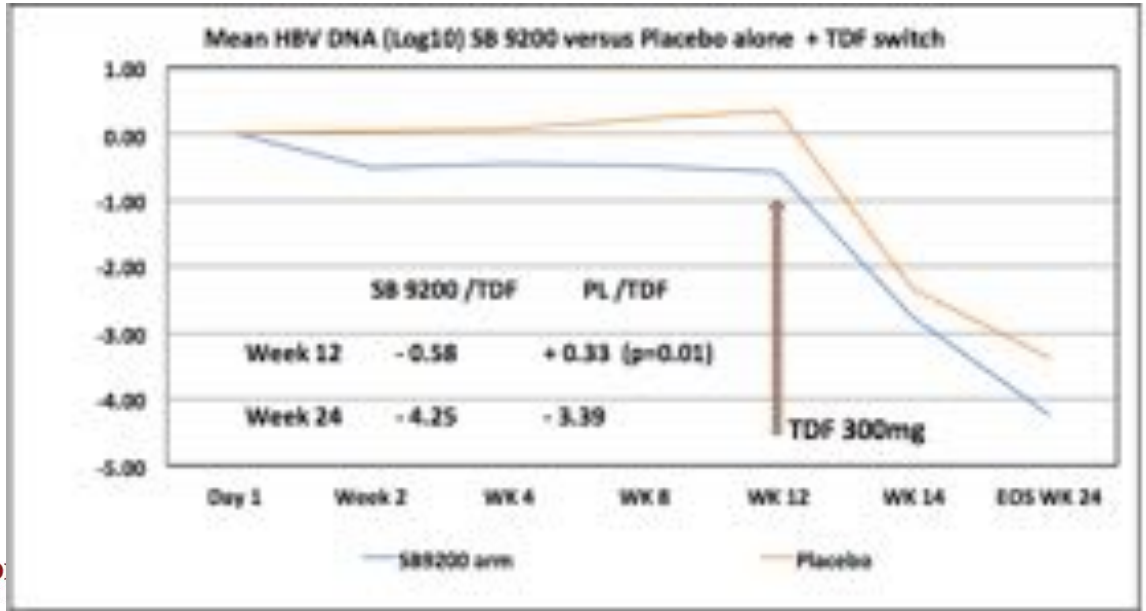
Agarwal et al HEPATOLOGY. 2017 66(1). #40, LB-17

SB 9200 (Inarigivir), an oral selective immunomodulator is safe and efficacious in treatment-naïve, non-cirrhotic HBV patients: RIG-1 Activator

- RIG-I counteracts the interaction of HBV polymerase with pgRNA to suppress viral replication
- Induction of type I and III IFNs







Anti-viral efficacy on HBV DNA, HBsAg and HBV RNA at 12 weeks - more prominent in HBeAg –ve patients

Yuen et alHEPATOLOGY. 2017 66(1)39

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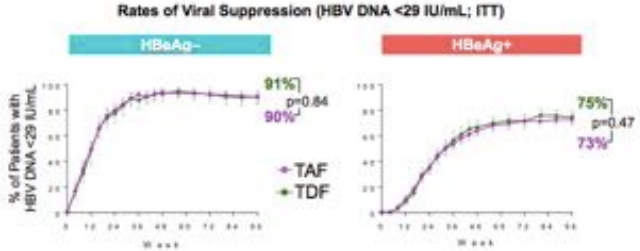
HBV– EXISTING THERAPIES

Tenofovir Alafenamide (TAF)

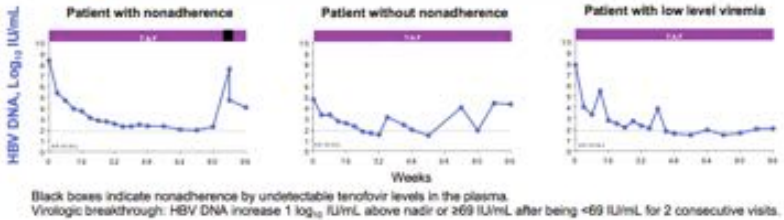
Similar efficacy as TDF, no resistance

Week 96



- The majority of patients (23/36, 64%) with virologic breakthrough had either evidence of nonadherence by plasma tenofovir levels, or residual low level viremia near 69 IU/mL

	TAF n=23	TDF n=13
Nonadherence	5	6
No evidence of nonadherence	9	4
Fluctuating low level viremia	9	3

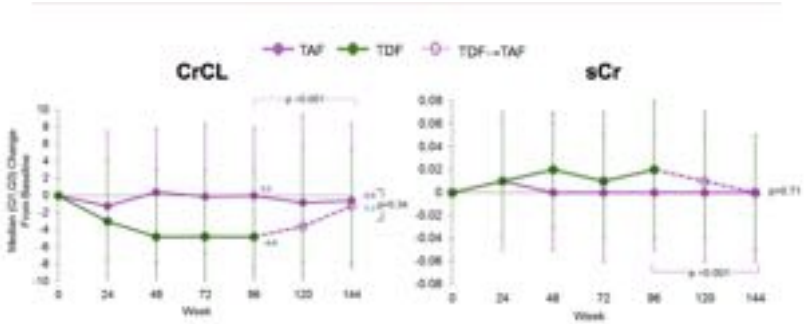


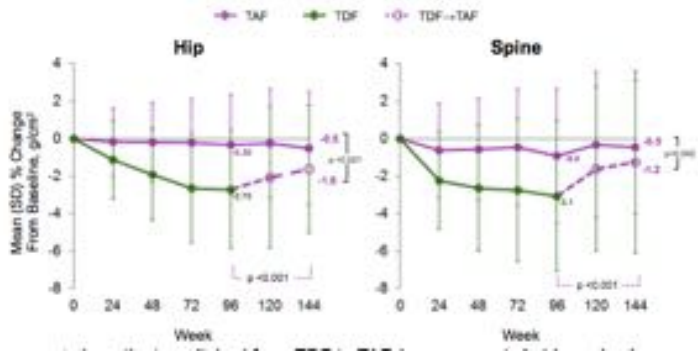
Black boxes indicate nonadherence by undetectable tenofovir levels in the plasma.
Virologic breakthrough: HBV DNA increase 1 $\log_{10}$ IU/mL above nadir or ≥69 IU/mL after being <69 IU/mL for 2 consecutive visits.

Chan et al, HEPATOLOGY. 2017 66(1)26

Improved bone and renal parameters

Week 144





Pan et al, HEPATOLOGY. 2017 66(1)904

REAL-B - Real-world Effectiveness from the Asia Pacific Rim Liver Consortium for HBV

A Risk Score for the Prediction of Hepatocellular Carcinoma (HCC) in Chronic Hepatitis (CHB) Patients Treated with Oral Anti-HBV

6 U.S. and 11 Asia-Pacific Centers

US
- Stanford University Medical Center, Palo Alto, CA
- San Jose Gastroenterology, San Jose, CA
- Palo Alto Medical Foundation, Mountain View, CA
- Chinese Hospital, San Francisco, CA
- Christopher Wong Clinic, Sutter Health, San Francisco, CA
- Clifford Wong Clinic, Sutter Health, San Francisco, CA

China
- Beijing Ditan Hospital, Beijing

Hong Kong
- Chinese University of Hong Kong
- Hong Kong University

Japan
- Kyushu University, Fukuoka
- Osaka City University, Osaka
- Yamagata University, Yamagata

New Zealand
- Auckland City Hospital, Auckland

Taiwan
- National Taiwan University, Taipei
- China Medical University, Taichung
- Chang Gung Medical Center, Kaohsiung
- Kaohsiung University, Kaohsiung

Total cohort: 9,106 patients

HCC at baseline: 396
<1 year of follow-up/HCC diagnosed within 1 year of baseline: 1,070
History of antiviral therapy prior to study entry: 286

Patients including in study analyses: 7,354 patients

Random assignment

Derivation group: 4,902 patients, 368 HCC cases

Validation group: 2,452 patients, 173 HCC cases

Nguyen MH et al, Hepatology 2017(suppl), Parallel Session

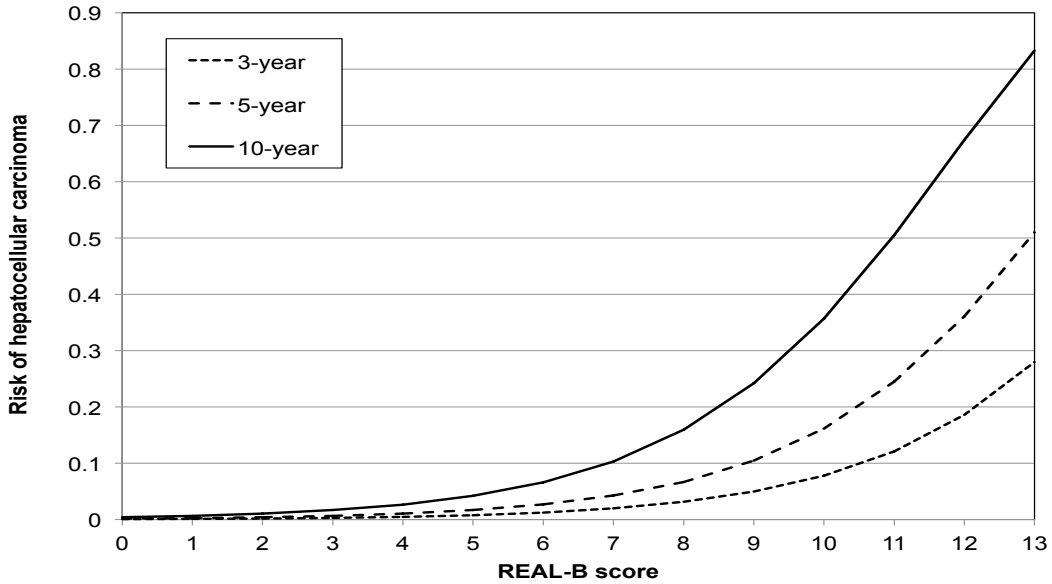
Results: Cox regression analysis for prediction of HCC in the Derivation cohort

	Regression Coefficient	Multivariate-adjusted hazard ratio (95% CI)	*P*-value	Score
Male sex	0.53548	1.71 (1.31-2.23)	<.0001	1
Age (per 10 year intervals)	0.46641	1.59 (1.44-1.76)	<.0001	1
Cirrhosis at baseline	0.95322	2.59 (2.00-3.36)	<.0001	2
Diabetes	0.53524	1.71 (1.30-2.25)	0.0001	1
Baseline platelet (ref: ≥200)				
100-200	0.33825	1.40 (1.02-1.93)	0.0391	1
<100	0.80498	2.24 (1.54-3.25)	<.0001	2
Baseline AFP >20	0.46080	1.59 (1.22-2.06)	0.0005	1

- Twelve significant variables (sex, age, alcohol drinking, cirrhosis, diebetes, HBeAg, ALT, platelet, ALB, TB, AFP, Cr) in the univariate analysis with less than 700 missing values were included in the multivariate analysis
- Only significant variables in multivariate analysis were kept in the final model

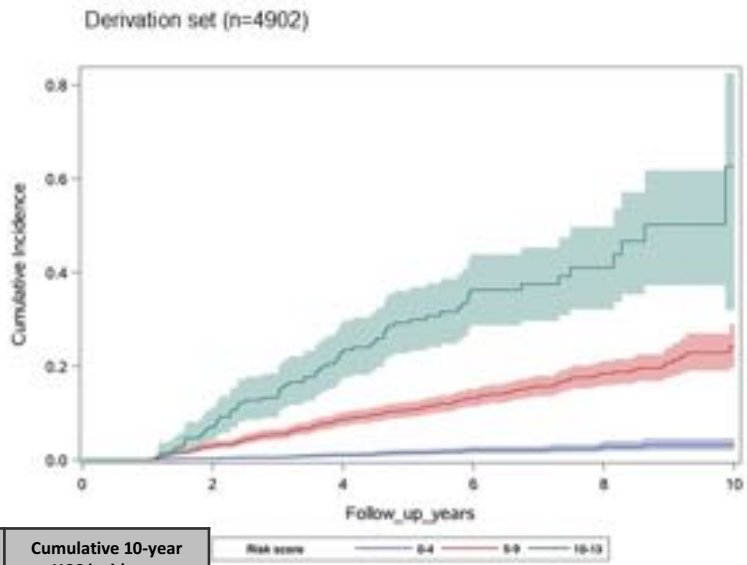
REAL-B scoring system derived from Cox regression analysis

Sex	Age	Cirrhosis at baseline	Diabetes	Platelet count	AFP
Female: 0	15-29: 0	No: 0	No: 0	≥200: 0	≤20: 0
Male: 1	30-39: 1	Yes: 2	Yes: 1	100-200: 1	>20: 1
	40-49: 2			<100: 2	
	50-59: 3				
	60-69: 4				
	70-79: 5				
	≥80: 6				



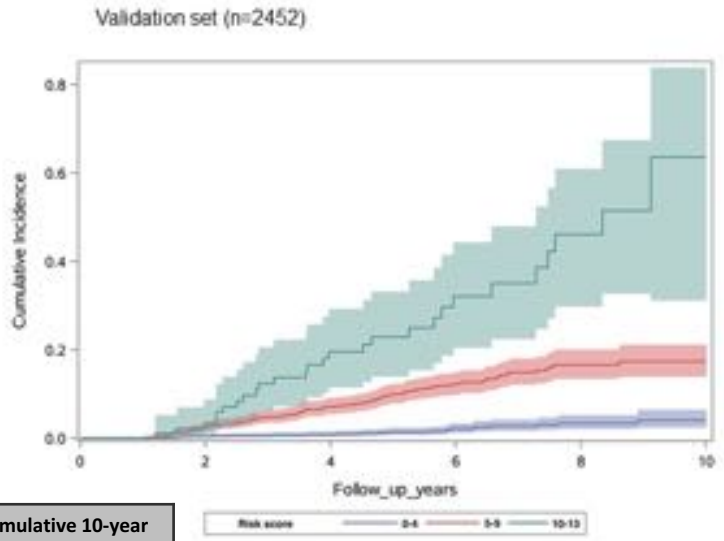
Cumulative Incidence of HCC according to REAL-B Risk Score Groups

Derivation Cohort



Risk score group	Cumulative 10-year HCC incidence
0 - 4	3.1%
5 - 9	24.2%
10 - 13	62.7%

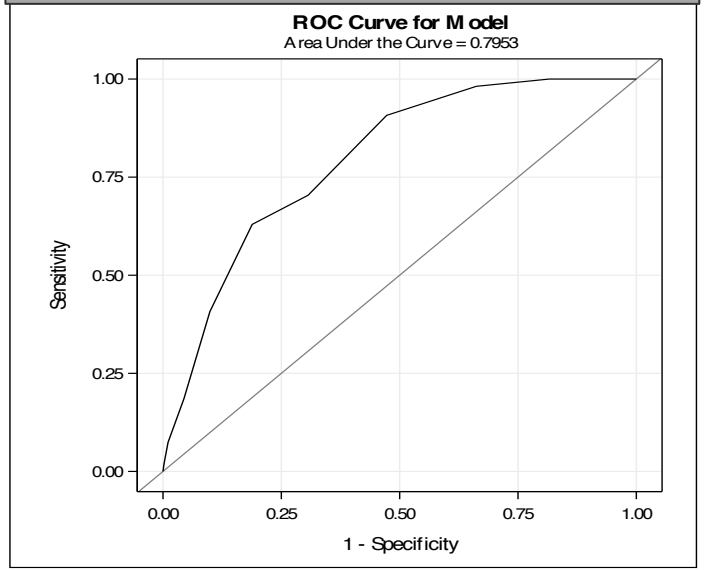
Validation Cohort



Risk score group	Cumulative 10-year HCC incidence
0 - 4	4.1%
5 - 9	17.4%
10 - 13	63.6%

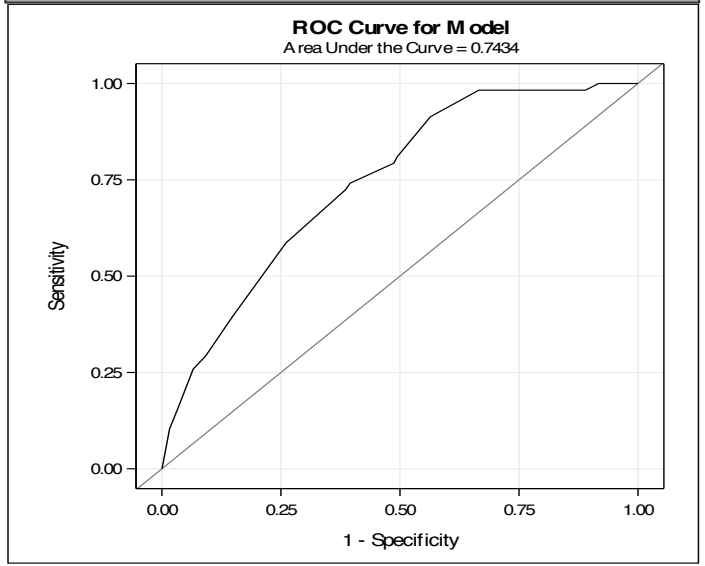
Predicting 3-year HCC Risk in the Validation Cohort

REAL-B



AUROC: 0.80 (0.75 – 0.85)

PAGE-B



AUROC: 0.74 (0.69 – 0.80)

***P*-value for comparison of AUROCs*: 0.011**

* Nonparametric approach by DeLong ER et al. Biometrics 1988;44:837-45

Increasing age and comorbidity in CHB pts in the Bay area

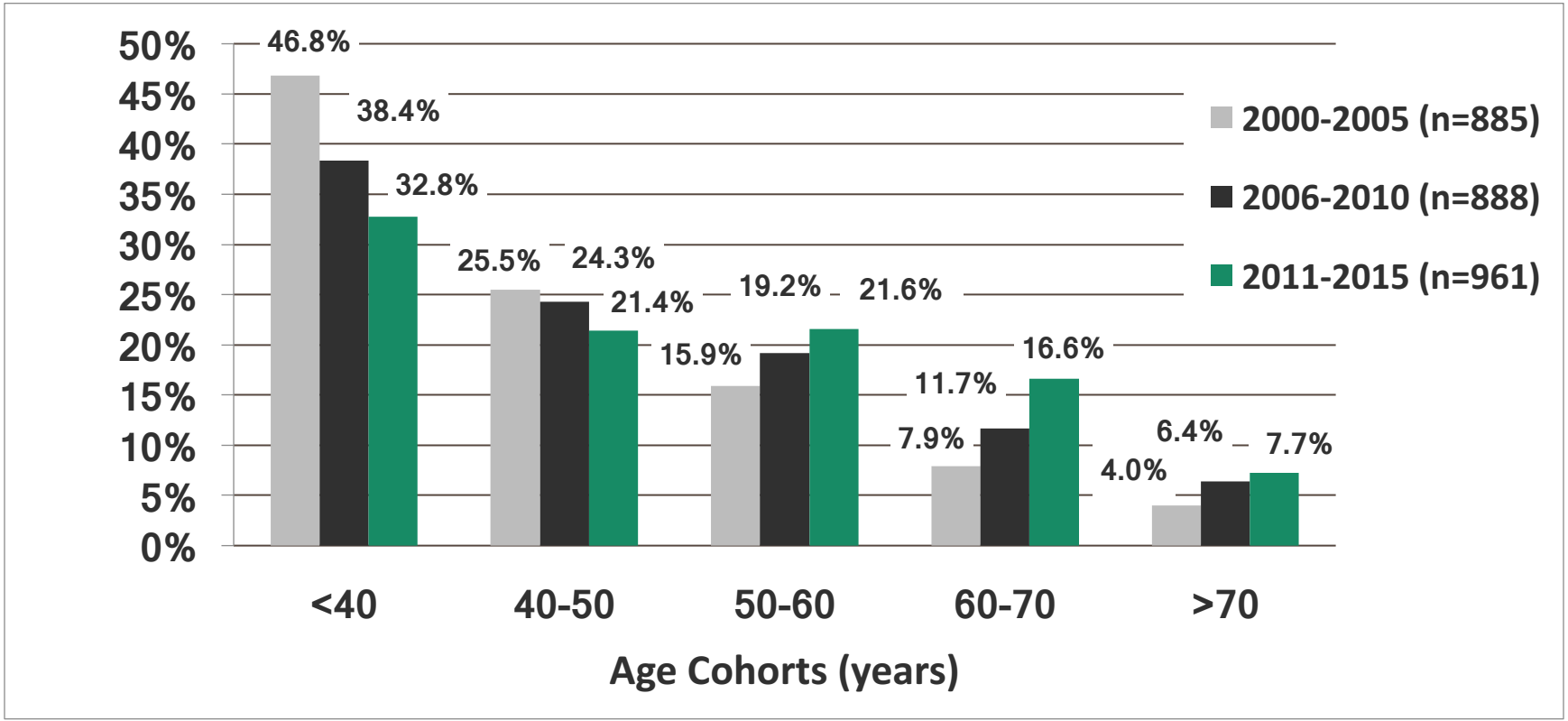
N=2734

Stanford
Wong Clinics, SF
Chinese Hospital Clinicas, SF and Daly City

	2000-2005 (n = 885)	2006-2010 (n = 888)	2011-2015 (n = 961)	*p*-value
Age mean ± SD	43.3 ± 13.4	46.6 ± 14.4	49.1 ± 14.4	<0.001
Male	58.3%	56.2%	59.0%	0.451
Body Mass Index mean ± SD	24.2 ± 3.6	24.2 ± 4.7	24.8 ± 5.1	0.033
Tobacco Use	22.9%	24.3%	24.6%	0.762
Alcohol Use	24.7%	26.5%	29.8%	0.069
HBeAg+	26.4%	20.9%	15.8%	<0.001
AST mean (range)	31 (23 - 48)	27 (22 - 38)	28 (21 - 44)	0.64
ALT mean (range)	39.5 (27 - 69)	40 (28 - 60)	40 (28 - 60)	0.59
Total Bilirubin mean ± SD	0.97 ± 0.88	0.94 ± 1.4	1.3 ± 6.2	0.11
Albumin mean ± SD	4.7 ± 5.4	4.4 ± 3.9	4.3 ± 4.2	0.22
Platelets mean (range)	216 (161.5 - 264)	209 (169 - 257)	199 (153 - 246)	0.16
HBV DNA (log10 IU/mL) Mean ± SD	4.2 ± 2.6	3.7 ± 2.4	3.3 ± 2.3	<0.001
Treated	46.1%	41.6%	47.0%	0.057

Liu A/Nguyen MH. AASLD 2017

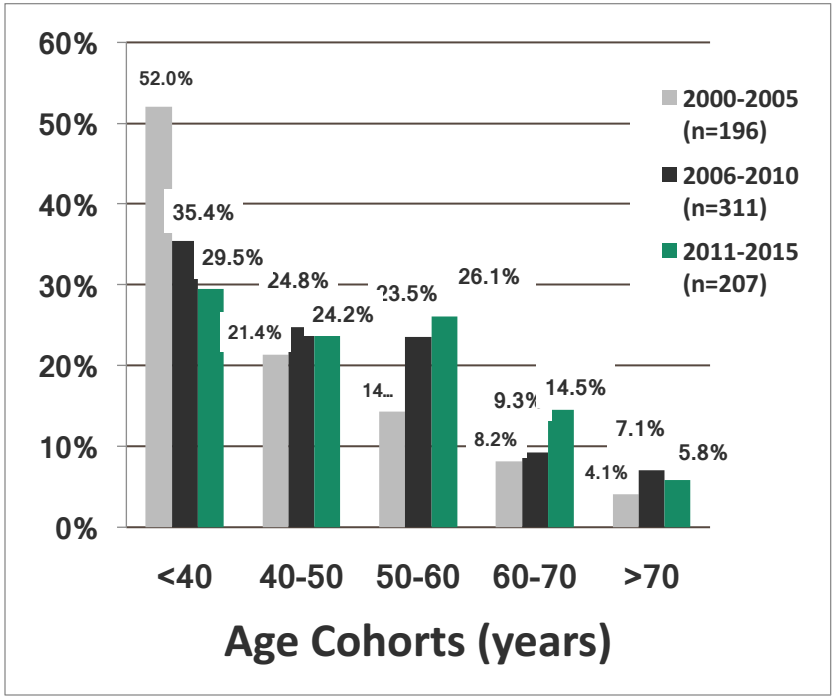
Mean age increased significantly from 43.3± 13.4 years during 2000-2005 to 49.1± 14.4 during 2011-2015 (p<0.001).



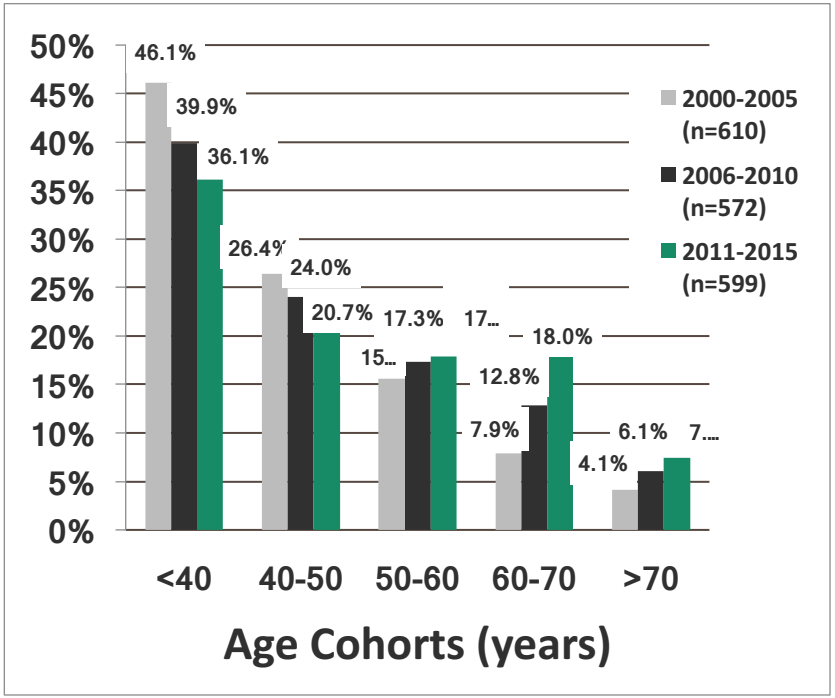
Liu A/Nguyen MH. AASLD 2017

Similar aging trend in primary care and specialty clinic settings:

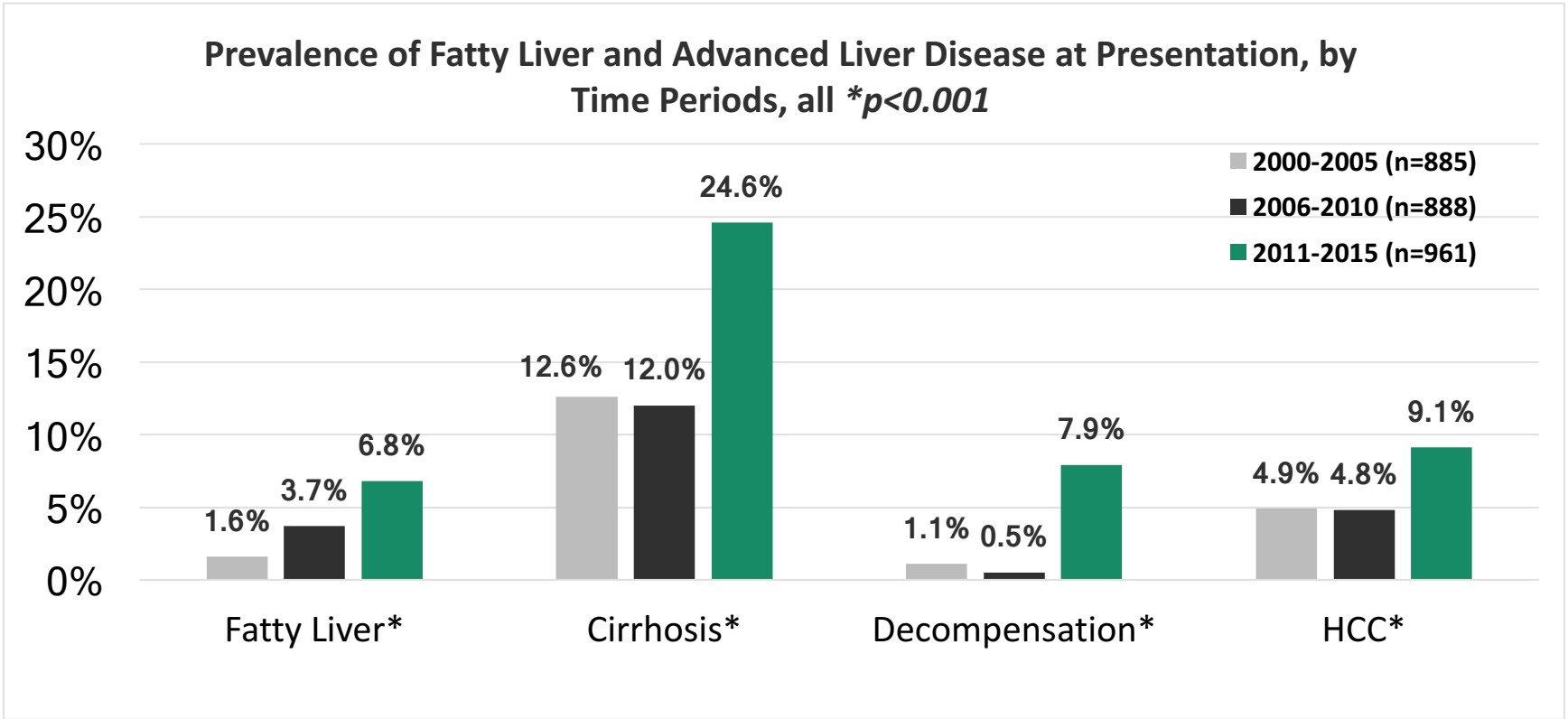
Primary care clinics (p<0.001)



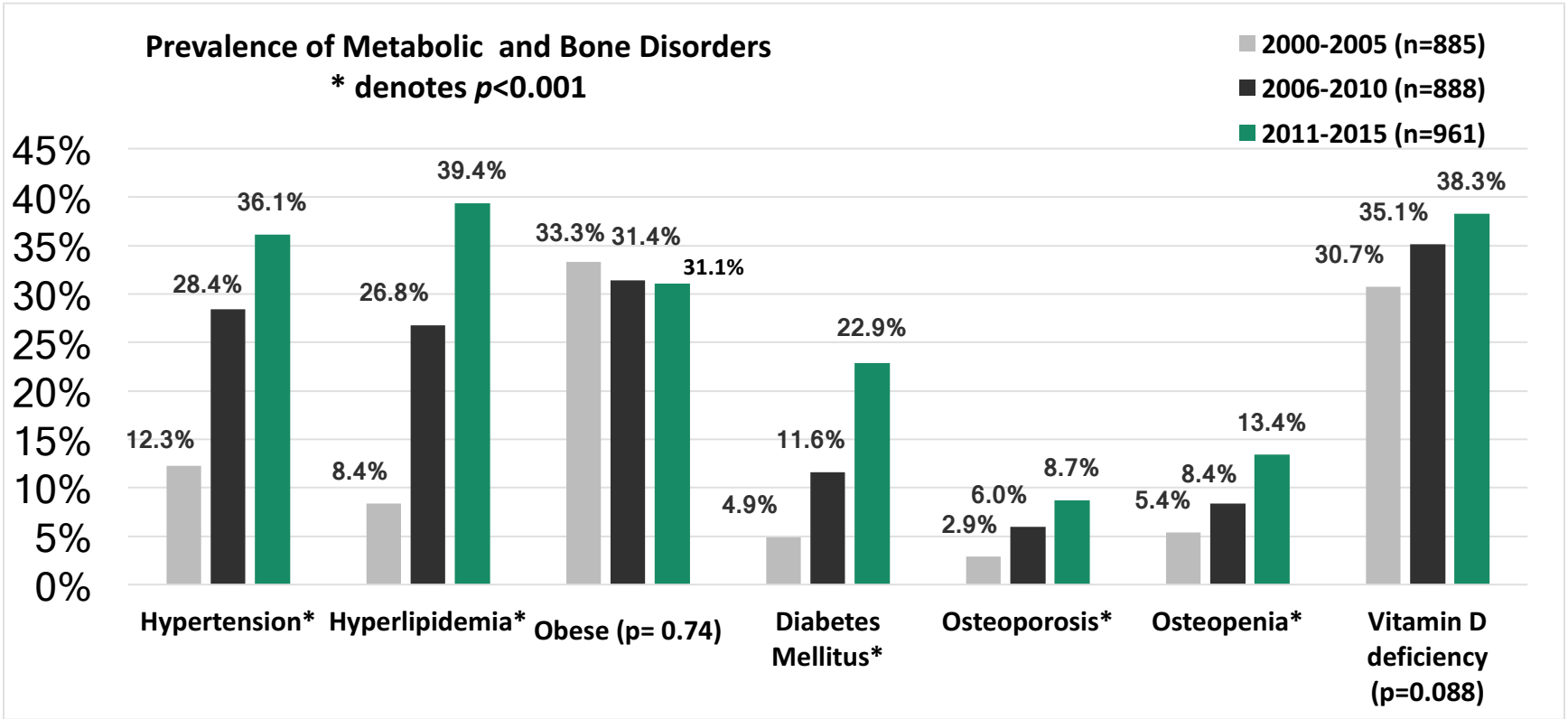
Liver clinics (p<0.001)



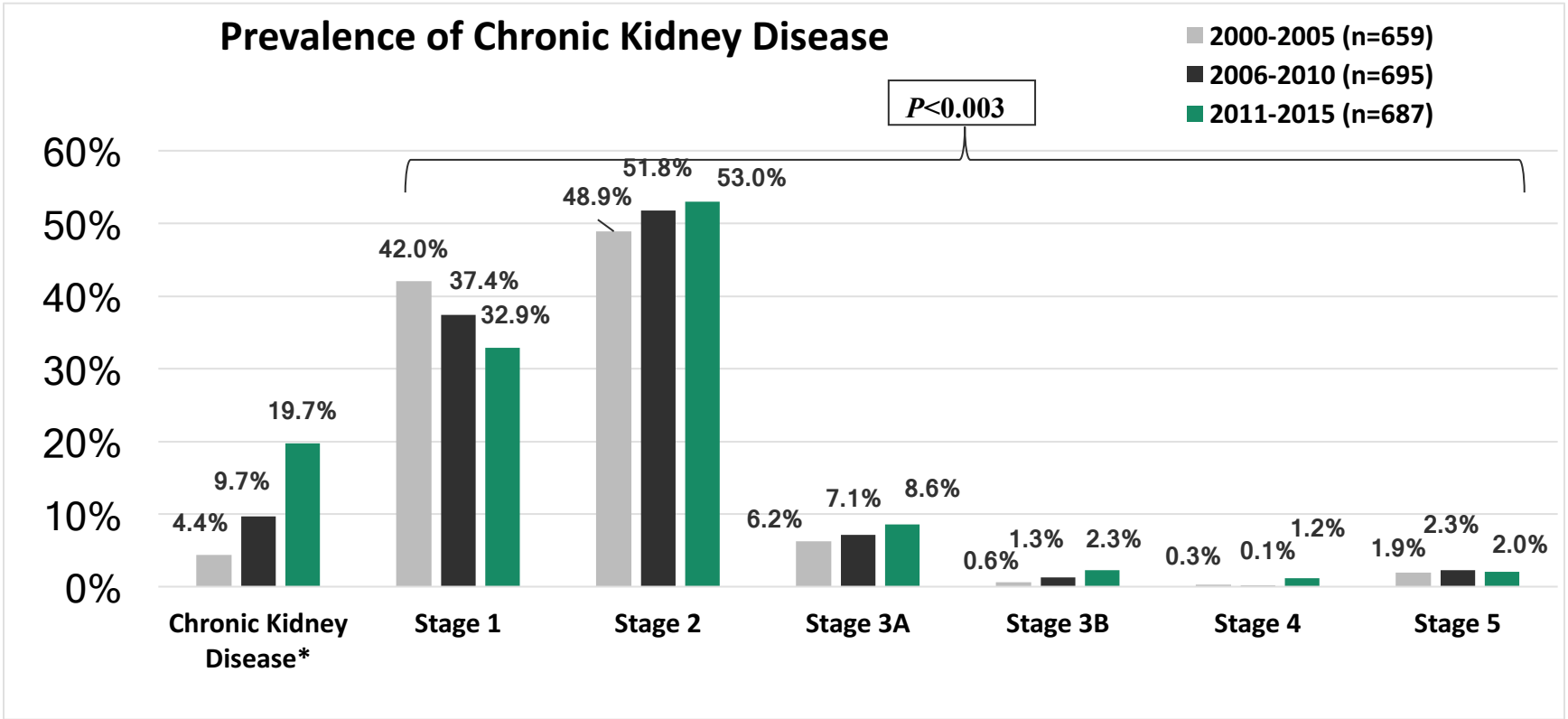
Liver morbidities



Non-liver comorbidities



Non-liver comorbidities



Similar findings in a nationwide claim database study

Data source: de-identified U.S. administrative healthcare claims from

- **Truven Health MarketScan® Commercial (41 million)**
- **Medicare (4 million)**
- **Multi-State Medicaid (8 million)**

Study design: retrospective observational study between 07/01/2004 – 06/30/2015 with continuous enrollment for at least one full calendar year during 2006-2015 and at least ≥ 6 months of continuous medical and prescription coverage before and after index date (date of first non-rule-out claim for CHB)

Study cases: Age ≥ 18 years patients with CHB (070.22. 070.23, 070.32, 070.33, 070.30 or 070.31) without concurrent HDV coinfection (ICD-9 CM diagnosis codes: 070.23, 070.33, or 070.31)

Matched controls: *Non-CHB patients matched to each CHB cases and up to 3 controls per case* (by calendar year of diagnosis date, payer type, year, age, gender, and for a subset of patients with available data -geographic region and race)

Nguyen MH et al, EASL 2017

Increasing age over time, by insurance types

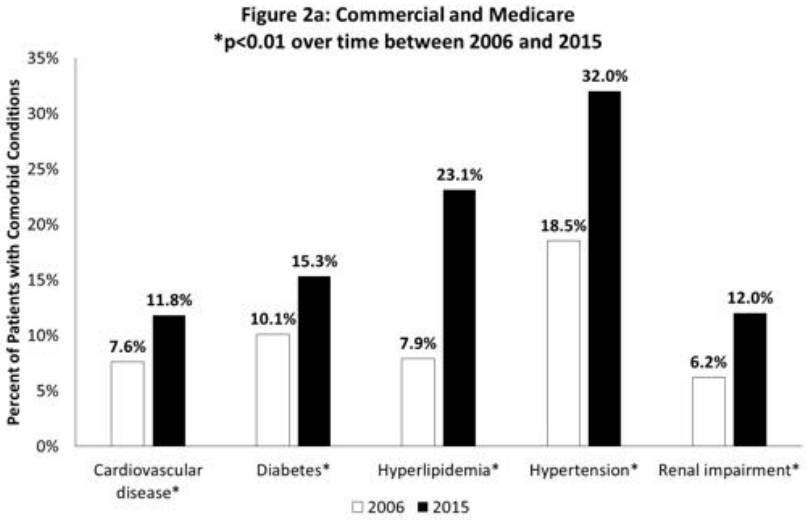
Demographic Characteristics	Commercial and Medicare			Medicaid		
	CHB (2006)	CHB (2015)	P-value	CHB (2006)	CHB (2015)	P-value
	N=3,819	N=9,094		N=1,425	N=2,278	
Age (years), Mean (SD)	48.1 (11.9)	51.8 (12.4)	<0.001	44.1 (11.1)	50.2 (10.2)	<0.001
Median	48.0	52.0		45.0	52.0	
Age group (N, %)						
18-34	531 (13.9%)	764 (8.4%)	<0.001	310 (21.8%)	235 (10.3%)	<0.001
35-44	975 (25.5%)	1,922 (21.1%)		364 (25.5%)	342 (15.0%)	
45-54	1,147 (30.0%)	2,541 (27.9%)		491 (34.5%)	774 (34.0%)	
55-64	893 (23.4%)	2,775 (30.5%)		247 (17.3%)	883 (38.8%)	
65+	273 (7.2%)	1,092 (12.0%)		13 (0.9%)	44 (1.9%)	
Gender (N, %)						
Male	2,296 (60.1%)	5,091 (56.0%)	<0.001	647 (45.4%)	1,040 (45.7%)	0.88
Female	1,523 (39.9%)	4,003 (44.0%)		778 (54.6%)	1,238 (54.3%)	

Higher comorbidities in CHB vs. non-CHB controls

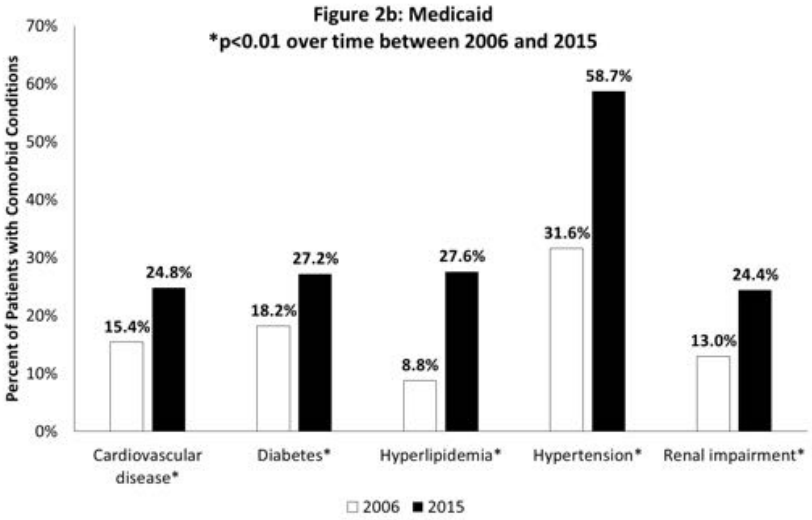
Clinical characteristics	Commercial and Medicare			Medicaid		
	CHB	No CHB	P-value	CHB	No CHB	P-value
	N=9,094	N=26,337		N=2,278	N=5,773	
Mean Deyo-Charlson comorbidity index (SD)	1.1 (2.2)	0.5 (1.2)	<0.001	2.6 (3.0)	1.2 (1.8)	<0.001
Mean Deyo-Charlson comorbidity index without liver disease (SD)	1.0 (2.1)	0.5 (1.2)	<0.001	2.4 (2.9)	1.2 (1.8)	<0.001
Comorbidities (N, %)						
Alcoholism	154 (1.7%)	236 (0.9%)	<0.001	426 (18.7)%	422 (7.3%)	<0.001
Carcinoma, malignancy (any)	569 (7.3%)	1,592 (6.0)%	<0.001	153 (6.7%)	254 (4.4%)	<0.001
Cardiovascular disease	1,076 (11.8)%	2,506 (9.5%)	<0.001	564 (24.8%)	1,135 (19.7%)	<0.001
Diabetes	1,392 (15.3%)	3,257 (12.4%)	<0.001	620 (27.2%)	1,604 (27.8%)	0.608
Hepatitis C virus	395 (4.3%)	49 (0.2%)	<0.001	589 (25.9)%	188 (3.3%)	<0.001
Human Immunodeficiency virus	371 (4.1%)	46 (0.2%)	<0.001	369 (16.2)%	109 (1.9%)	<0.001
Hyperlipidemia	2,103 (23.1%)	6,528 (24.8%)	0.001	629 (27.6%)	1,955 (33.9%)	0.002
Hypertension	2,910 (32.0%)	8,326 (31.6%)	0.495	1,337 (58.7%)	3,167 (54.9%)	<0.001
Osteoporosis	197 (2.2)%	410 (0.9%)	<0.001	43 (1.9%)	91 (1.6%)	0.325
Overweight, obesity, morbid obesity	982 (10.8%)	3,271 (12.4%)	<0.001	451 (19.8%)	1,125 (19.5%)	0.752
Renal Impairment	1,091 (12.0%)	1,307 (5.0%)	<0.001	556 (24.4%)	707 (12.3%)	<0.001
Smoking	584 (8.4%)	1,318 (5.0%)	<0.001	1,192 (52.3%)	1,818 (31.5%)	<0.001
Concomitant medication use (N, %)						
Corticosteroids	1,224 (13.5%)	3,759 (14.3%)	0.054	610 (26.8%)	1,307 (22.6%)	<0.001
Osteoporosis medications	233 (2.6%)	432 (1.6%)	<0.001	44 (1.9%)	112 (1.9%)	0.980
Hormone suppression therapy	137 (1.5%)	235 (0.9%)	<0.001	35 (1.5%)	90 (1.6%)	0.941
Biologics/Targeted/Immunotherapies	221 (2.4%)	450 (1.7%)	<0.001	247 (10.8%)	383 (6.6%)	<0.001
Cardiovascular medications	3,076 (33.8%)	9,964 (37.8%)	<0.001	1,149 (50.4%)	2,974 (51.5%)	0.384
Antidiabetes medications	1,060 (11.7%)	2,728 (10.4%)	0.001	446 (19.6%)	1,292 (22.4%)	0.006

Comorbidities in chronic hepatitis B patients over time (2006 vs. 2015), by insurance type

Commercial and Medicare insurance population (2006 N=3,819; 2015 N=9,094)

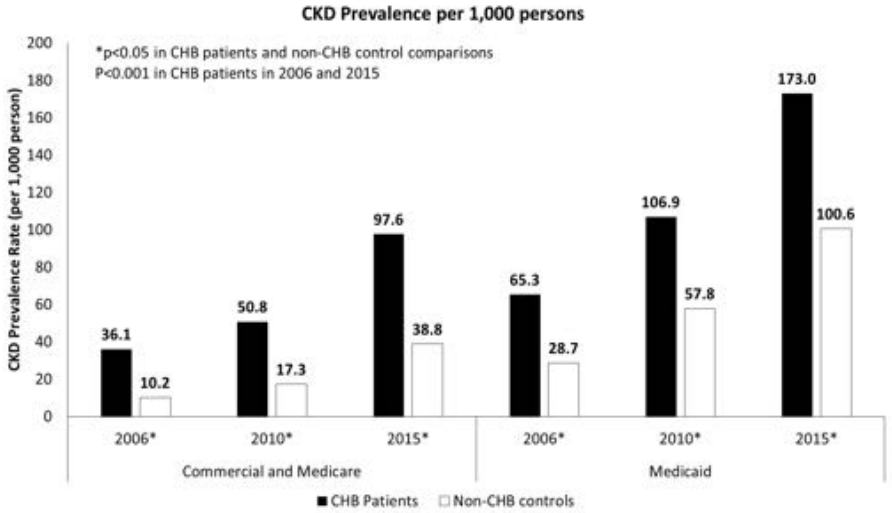


Medicaid insurance population (2006 N=1,425; 2015 N=2,278)

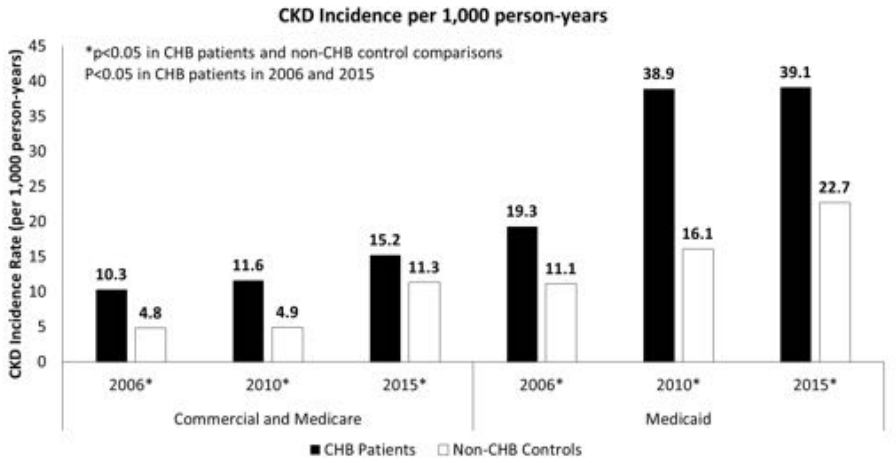


Chronic kidney disease in CHB patients vs. non-CHB controls

Prevalence over time

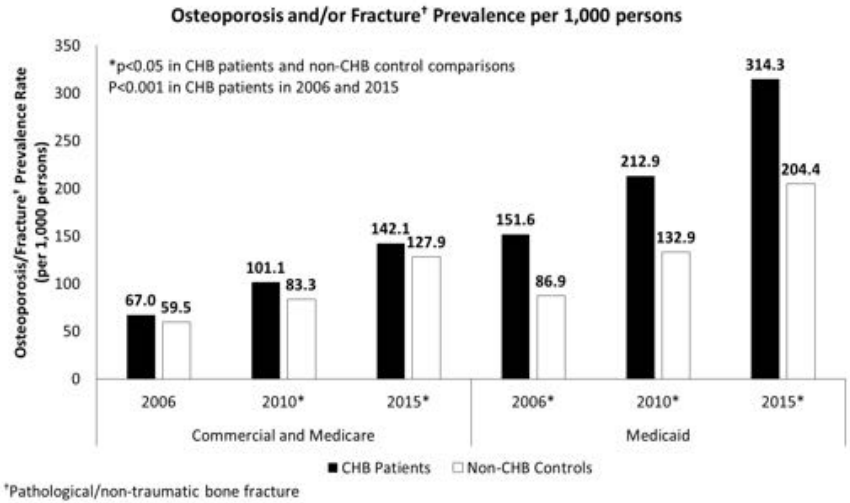


Incidence over time



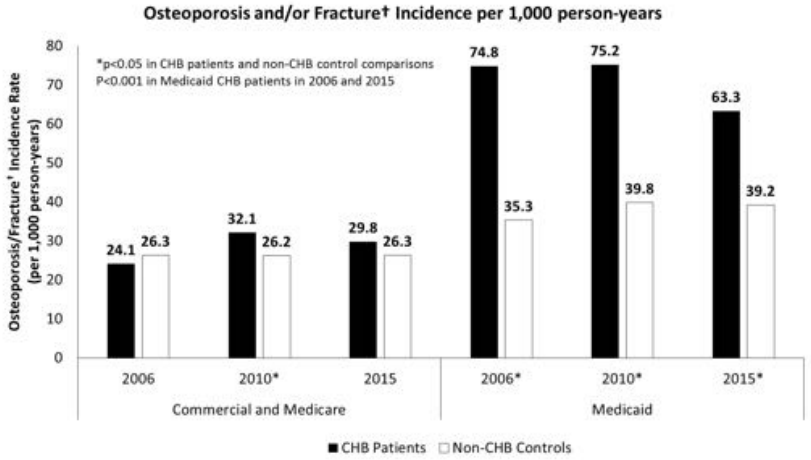
Osteoporosis and/or nontraumatic bone fractures in CHB patients vs. non-CHB controls

Prevalence over time



†Pathological/non-traumatic bone fracture

Incidence over time

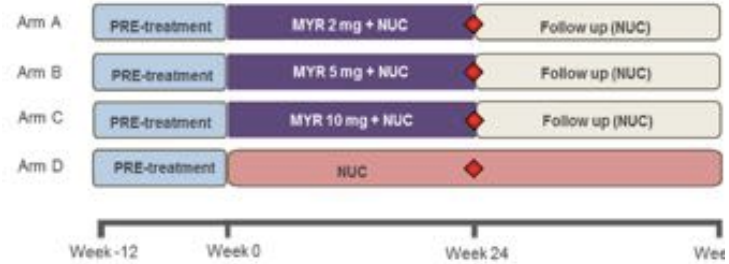


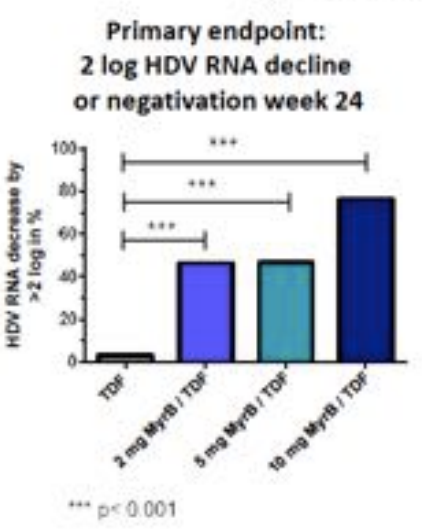
†Pathological/non-traumatic bone fracture

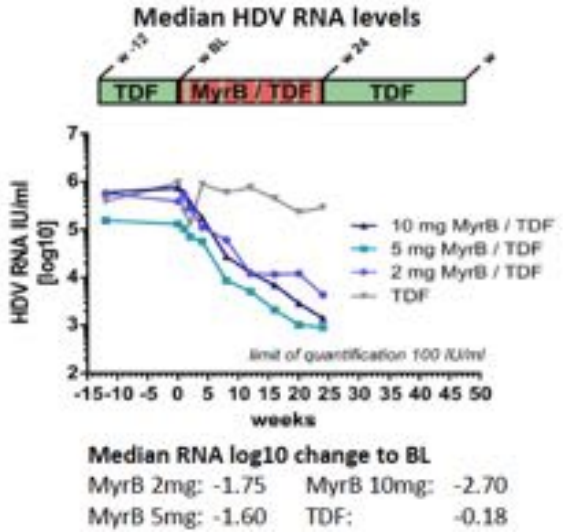
HDV – anything new?

Interim results of a multicenter, open-label phase 2b clinical trial to assess safety and efficacy of Myrcludex B in combination with Tenofovir in patients with chronic HBV/HDV co-infection

first-in-class entry inhibitor exerting its antiviral function by blocking the jointly used HBV/HDV receptor sodium taurocholate co-transporter NTCP







- ALT levels improve
- HBsAg does not change
- Bile acids increase without pruritus

Wedemeyer et al HEPATOLOGY. 2017 66(1)# 37.

Slide courtesy Dr. P Kwo

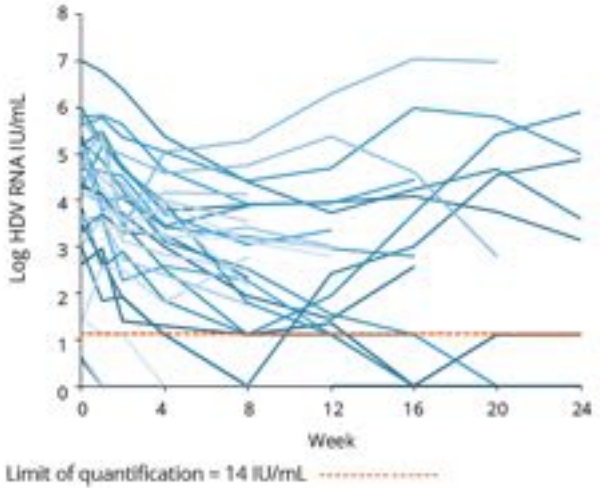
A Phase 2 Randomized Clinical Trial to Evaluate the Safety and Efficacy of Pegylated Interferon Lambda Monotherapy in Patients with Chronic Hepatitis Delta Virus Infection. Interim Results From the LIMT HDV Study

A novel first in class Type III interferon

Binds to a unique receptor versus Type I interferons

− Highly expressed on hepatocytes

− Limited expression on hematopoietic cells and CNS cells



Week	N	≥ 2 log decline	PCR-negative
4	33	7 (21.2%)	3 (9.1%)
8	32	12 (36.4%)	5 (15.6%)
12	23	9 (39.1%)	4 (17.4%)
24	10	6 (60.0%)	4 (40.0%)

Hamid et alHEPATOLOGY. 2017 66(1)927

Slide courtesy Dr. P Kwo

HBV Summary

1. Multiple emerging therapies for HBV cure and HDV
2. Good existing options for long-term suppressive Rx for HBV – TAF in addition to ETV and TDF
3. CHB are presenting older and with more comorbidity→ improved linkage to care is needed
4. HCC still occurs in HBV patients with NUCs

New approval:

Daily fixed-dose combination of SOF (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)*

Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)**

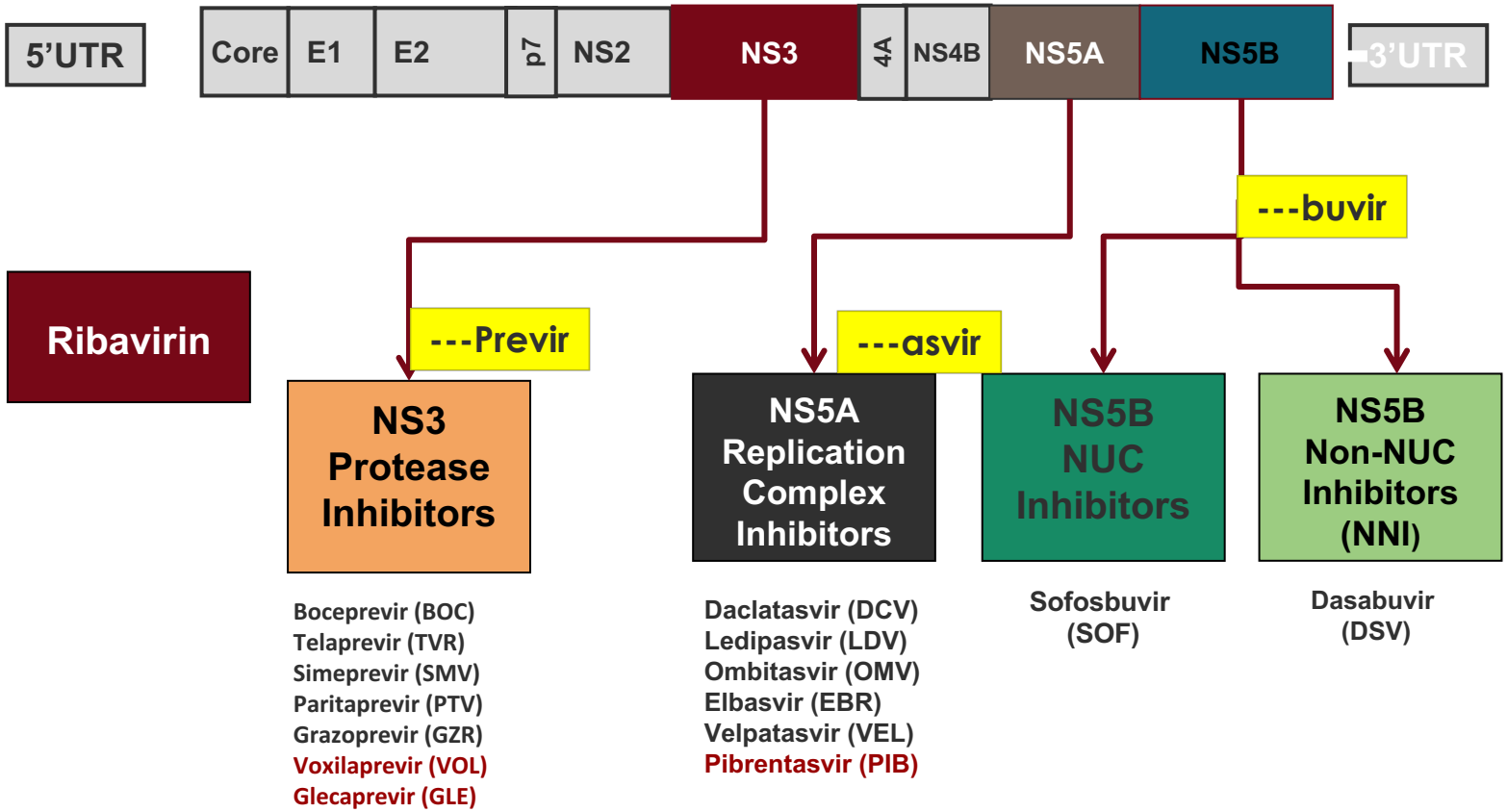
****Largely recommended for DAA-experienced cases (12 wks)***

*****Duration range 8 weeks → 12 wks except for Rx-experienced cirrhotic GT3 (16 wks)***

-----Both are pangenotypic

HCV: 2017 STANDARD OF CARE

DAA Classes


5'UTR
Core
E1
E2
p7
NS2
NS3
4A
NS4B
NS5A
NS5B
3'UTR
Ribavirin
---Previr
---asvir
---buvir
NS3 Protease Inhibitors
NS5A Replication Complex Inhibitors
NS5B NUC Inhibitors
NS5B Non-NUC Inhibitors (NNI)
Boceprevir (BOC)
Telaprevir (TVR)
Simeprevir (SMV)
Paritaprevir (PTV)
Grazoprevir (GZR)
Voxilaprevir (VOL)
Glecaprevir (GLE)
Daclatasvir (DCV)
Ledipasvir (LDV)
Ombitasvir (OMV)
Elbasvir (EBR)
Velpatasvir (VEL)
Pibrentasvir (PIB)
Sofosbuvir (SOF)
Dasabuvir (DSV)

HCV: Genotypes 1A and 1B
Treatment-Naive, Non-Cirrhotic

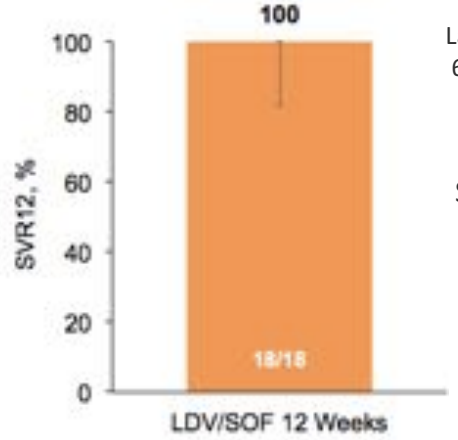
Regimen	Weeks	Study	SVR12	
Sofosbuvir + ledipasvir*				
(HCV RNA <6 M IU/mL)	**8**	ION-3	**119/123 (97%)**	
(HCV RNA >6 M IU/mL)	**12**		**206/216 (95%)**	
Elbasvir/Grazoprevir (1b)*				
(-) -NS5A RAVs (1a)	**12**	C-EDGE	**133/135 (99%)**	
			129/131 (99%)	
Glecaprevir + pibrentasvir*	**8**	Endurance	**333/336 (99%)**	12 wks if Rx-exp (non-DAA)+cirrhos
PrOD (1b)	**12**	PEARL III	**207/209 (99.5%)**	
PrOD +/- ribavirin (1a)	**12**	PEARL IV	**97/100 (97%)**	
		SAPPHIRE-I	**307/322 (95%)**	
Simeprevir + sofosbuvir	**12**	OPTIMIST-1	**112/115 (97%)**	
Daclatasvir + sofosbuvir	**12**	ALLY-2 (HIV Co-infected)	**70/72 (97%)**	
Sofosbuvir+ velpatasvir)*	**12**	ASTRAL-1	**251/257 (98)%**	Also OK for DAA-experienced

SVIR12, sustained virologic response rate at 12 weeks; PrOD, paritaprevir/ritonavir/ombitasvir + dasabuvir.

AASLD/IDSA HCV Guidance Panel (2015). *Hepatology*. 2015;62(3):932-954. Initial treatment of HCV infection. http://www.hcvguidelines.org/treatment-naive/gt1. Last updated April 12, 2017. Accessed December 8, 2017.

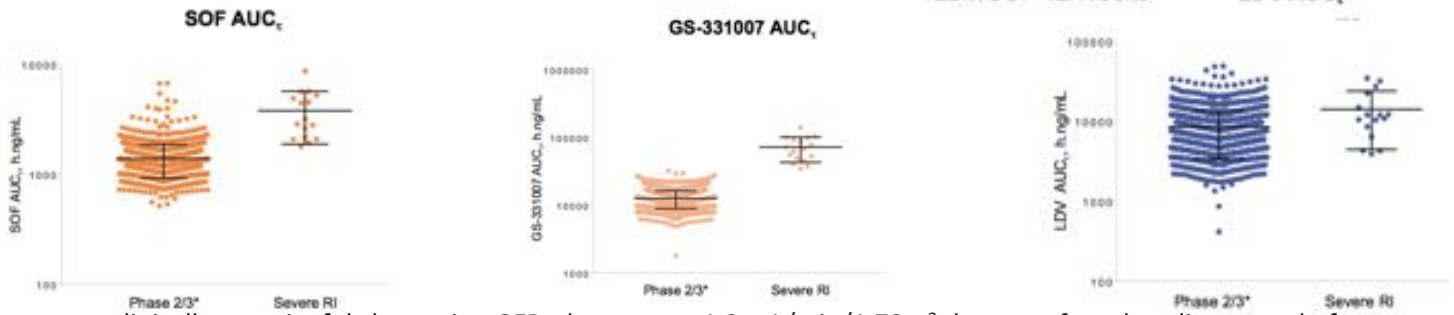
Safety and Efficacy of Treatment With Once-Daily Ledipasvir/Sofosbuvir (90/400 mg) for 12 Weeks in Genotype 1 HCV-Infected Patients With Severe Renal Impairment

	LDV/SOF 12 Weeks n=18
Mean age, y (range)	57 (32–66)
Male, n (%)	12 (67)
White, n (%)	8 (44)
Black, n (%)	10 (56)
Mean BMI, kg/m² (range)	30 (21–39)
Mean eGFR, mL/min/1.73 m² (range)	24.9 (9.0–39.6)
Cirrhosis, n (%)	2 (11)
HCV GT 1 (total), n (%)	18 (100)
1a	14 (78)
1b	4 (22)
IL28B non-CC, n (%)	17 (94)
Mean HCV RNA, $\log_{10}$ IU/mL (range)	6.2 (5.0–7.1)



Lawitz et al HEPATOLOGY. 2017 66(1). #1587

Slide courtesy Dr. P Kwo



There was no clinically meaningful change in eGFR: there was a 1.2-mL/min/1.73m² decrease from baseline to end of treatment

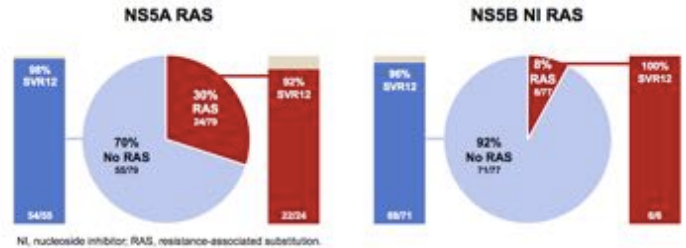
Similar results **#1180:** Sofosbuvir with NS5A Inhibitors in Hepatitis C Virus Infected Patients with Severe Renal Insufficiency

Sofosbuvir/Velpatasvir for 12 Weeks in Genotype 1–4 HCV-Infected Liver Transplant Recipients

Agarwal et al HEPATOLOGY. 2017 66(1). #1069

Slide courtesy Dr. P Kwo

	Total	GT 1	GT 1a	GT 1b	GT 2	GT 3	GT 4
	96	95	93	96	100	97	100
	78/79	35/37	14/15	21/22	3/3	34/35	4/4
Relapse	2	1	1	0	0	1	0
On-treatment VF	0	0	0	0	0	0	0
Other	1	1	0	1	0	0	0



- 2 virologic relapses occurred in patients with baseline NS5A RASs
  - GT 3b–infected patient with A30K+L31M at baseline
  - GT 1a–infected patient with K24R at baseline
- 4 patients with baseline Y93H RASs (3 GT 3 and 1 GT 1b) all achieved SVR12

No changes in immunosuppression were needed for rejection or suspected drug-drug interactions

HCV: Genotypes 2
Treatment-Naive, Non-Cirrhotic

Regimen	Weeks	Study	SVR12
Velpatasvir + sofosbuvir	**12**	ASTRAL-1	**99%**
Glecaprevir + pibrentasvir*	**8**	SURVEYOR-II	**99%**

12 wks if cirrhotic + Rx-experienced including SOF-experienced

NOT HEAD-TO-HEAD TRIALS.

AASLD/IDSA HCV Guidance Panel (2015). Hepatology. 2015;62(3):932-954. http://www.hcvguidelines. org/full-report/when-and-whom-initiate-hcv-therapy. Last updated April 12, 2017. Accessed December 8, 2017.

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HCV: Genotypes 3
Treatment-Naive, Non-Cirrhotic

Regimen	Weeks	Study	SVR12
Velpatasvir + sofosbuvir**	**12**	ASTRAL-3	**98%**
Daclatasvir + sofosbuvir	**12**	ALLY-3	**97%**
Glecaprevir + pibrentasvir*	**8**	Endurance 3	**95%**

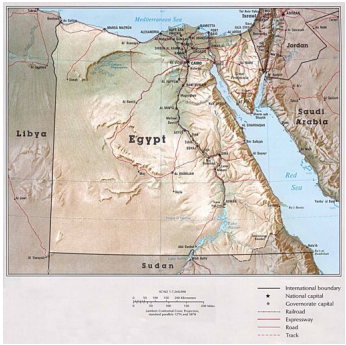
12 wks if cirrhotic, 16wks if treatment experienced (but non-DAA) and/or cirrhotic

****Can be used for DAA-experienced cirrhotic (12 wks)***

NOT HEAD-TO-HEAD TRIALS.

AASLD/IDSA HCV Guidance Panel (2015). Hepatology. 2015;62(3):932-954. http://www.hcvguidelines. org/full-report/when-and-whom-initiate-hcv-therapy. Last updated April 12, 2017. Accessed December 8, 2017.

HCV: Genotype 4
Treatment-Naive, Non-Cirrhotic



Regimen	Weeks	Study	SVR12
Velpatasvir + sofosbuvir	**12**	ASTRAL-1	100%
Sofosbuvir + ledipasvir	**12**	Synergy	95%
Elbasvir/Grazoprevir	**12**	C-Edge	97%
Paritaprevir/Ombitasvir/RBV	**12**	PEARL-1	100%
Glecaprevir + pibrentasvir*	**8**	Endurance 4	99%

*12 wks if Rx-exp (non-DAA) plus cirrhosis

RBV, ritonavir.

NOT HEAD-TO-HEAD TRIALS.

AASLD/IDSA HCV Guidance Panel (2015). Hepatology. 2015;62(3):932-954. http://www.hcvguidelines. org/full-report/when-and-whom-initiate-hcv-therapy. Last updated April 12, 2017. Accessed December 8, 2017.

HCV: Genotypes 5
Treatment-Naive, Non-Cirrhotic

Regimen	Geno-type	Weeks	Study	SVR12
Velpatasvir + sofosbuvir	5	**12**	ASTRAL-1	**96%**
Sofosbuvir + ledipasvir	5	**12**		**95%**
Glecaprevir + pibrentasvir	5	**8**	Endurance 4	**100%**

NOT HEAD-TO-HEAD TRIALS.

AASLD/IDSA HCV Guidance Panel (2015). Hepatology. 2015;62(3):932-954. http://www.hcvguidelines. org/full-report/when-and-whom-initiate-hcv-therapy. Last updated April 12, 2017. Accessed December 8, 2017.

HCV: Genotypes 6
Treatment-Naive, Non-Cirrhotic

Regimen	Geno-type	Weeks	Study	SVR12
Velpatasvir + sofosbuvir	5	**12**	ASTRAL-1	**96%**
Sofosbuvir + ledipasvir	5	**12**		**95%**
Glecaprevir + pibrentasvir*	5	**8**	Endurance 4	**100%**

*12 wks if Rx-exp (non-DAA) plus cirrhosis

LED/SOF 8 weeks – 94% SVR12 for noncirrhotic, Rx-naïve
Nguyen MH et al, Am J Gastroenterol 2017. Epub ahead of print

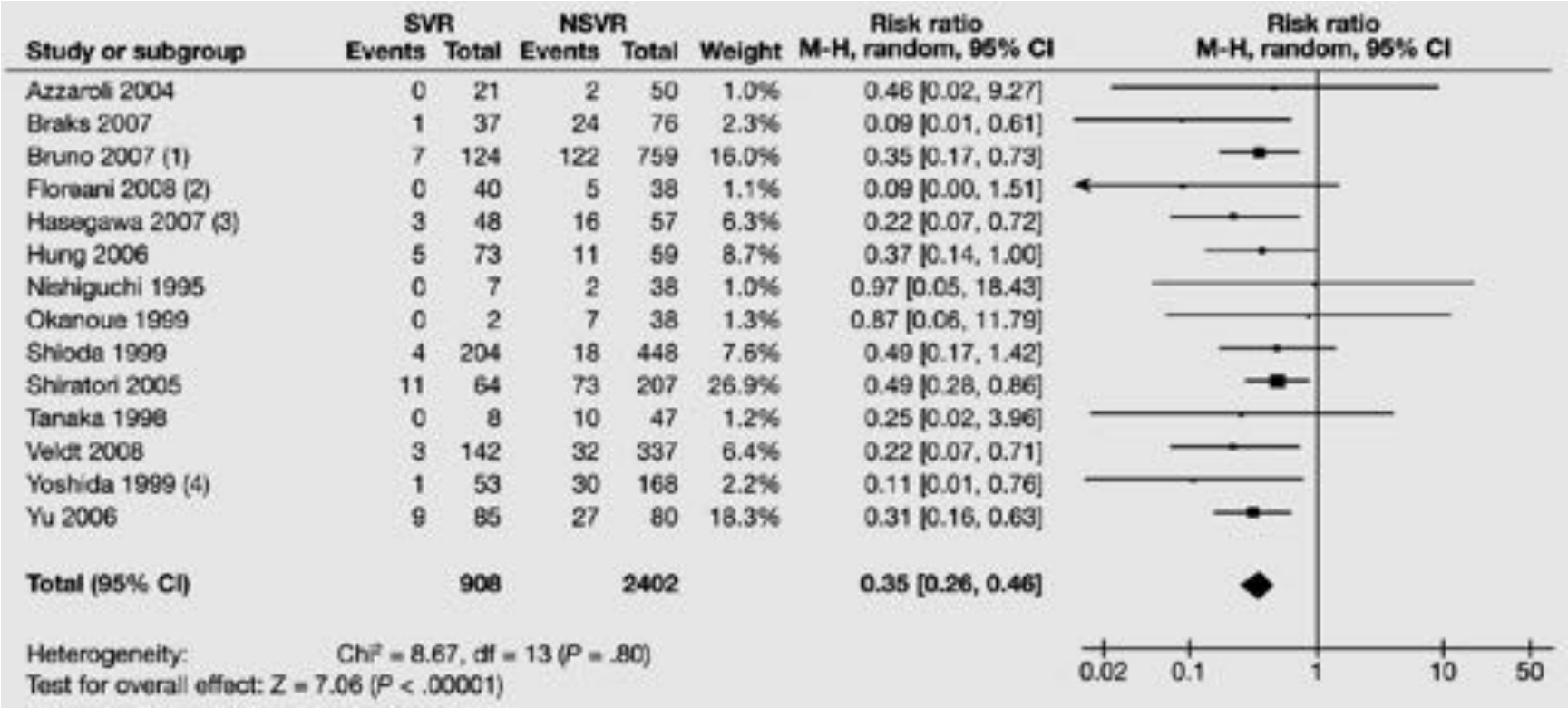
NOT HEAD-TO-HEAD TRIALS.

AASLD/IDSA HCV Guidance Panel (2015). Hepatology. 2015;62(3):932-954. http://www.hcvguidelines. org/full-report/when-and-whom-initiate-hcv-therapy. Last updated April 12, 2017. Accessed December 8, 2017.

HCV– DAA and HCC Prevention

SVR lowers HCC risk by 65% - IFN/PEG IFN data

14 studies (3310 pts with cirrhosis)
RR = 0.35 (0.26-0.46, 95% CI)



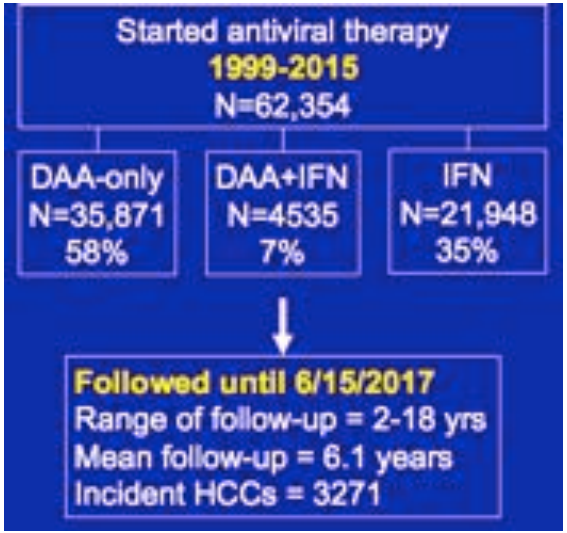
Study or subgroup	SVR Events	SVR Total	NSVR Events	NSVR Total	Weight	Risk ratio M-H, random, 95% CI
Azzaroli 2004	0	21	2	50	1.0%	0.46 [0.02, 9.27]
Braks 2007	1	37	24	76	2.3%	0.09 [0.01, 0.61]
Bruno 2007 (1)	7	124	122	759	16.0%	0.35 [0.17, 0.73]
Floreani 2008 (2)	0	40	5	38	1.1%	0.09 [0.00, 1.51]
Hasegawa 2007 (3)	3	48	16	57	6.3%	0.22 [0.07, 0.72]
Hung 2006	5	73	11	59	8.7%	0.37 [0.14, 1.00]
Nishiguchi 1995	0	7	2	38	1.0%	0.97 [0.05, 18.43]
Okanoue 1999	0	2	7	38	1.3%	0.87 [0.06, 11.79]
Shioda 1999	4	204	18	448	7.6%	0.49 [0.17, 1.42]
Shiratori 2005	11	64	73	207	26.9%	0.49 [0.28, 0.86]
Tanaka 1998	0	8	10	47	1.2%	0.25 [0.02, 3.96]
Veldt 2008	3	142	32	337	6.4%	0.22 [0.07, 0.71]
Yoshida 1999 (4)	1	53	30	168	2.2%	0.11 [0.01, 0.76]
Yu 2006	9	85	27	80	18.3%	0.31 [0.16, 0.63]
Total (95% CI)		**908**		**2402**		**0.35 [0.26, 0.46]**

Heterogeneity: $Chi^2 = 8.67$, $df = 13$ ($P = .80$)
Test for overall effect: $Z = 7.06$ ($P < .00001$)

Singal et al. Clin Gastro Hep 2010;8:192-99

What about DAA and HCC occurrence (new cases) and recurrence?

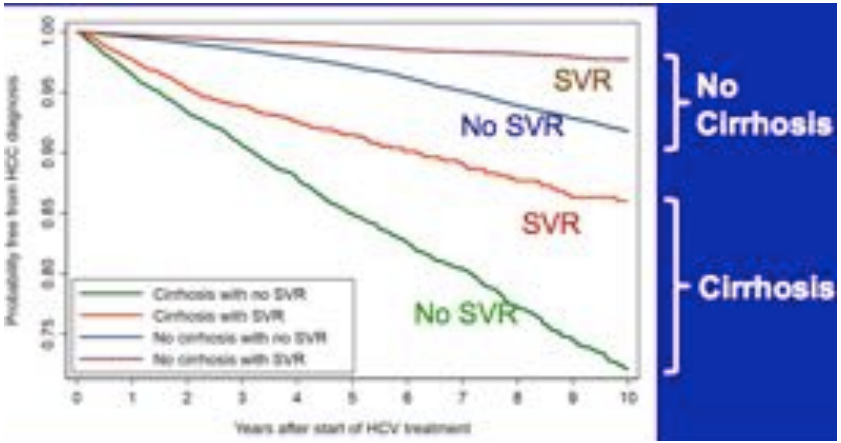
Eradication of HCV induced by DAAs is associated with a 71% reduction in HCC risk VA Retrospective Cohort study



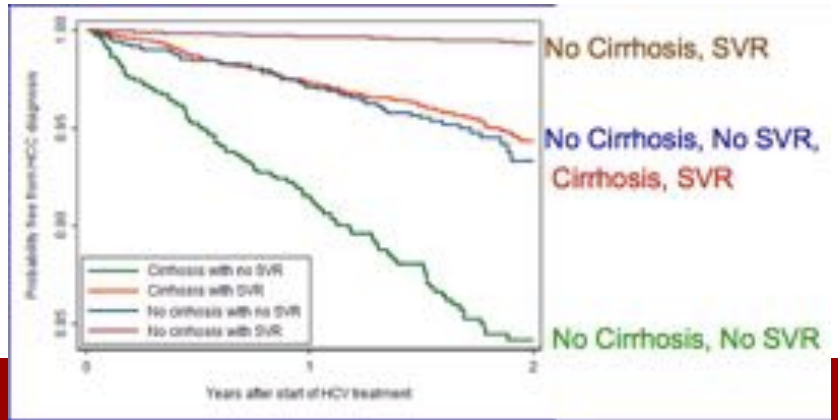
- Receipt of DAAs is not associated with increased HCC risk compared to receipt of IFN

Ioannou et al HEPATOLOGY. 2017 66(1). #142

Patients with SVR had lower HCC incidence



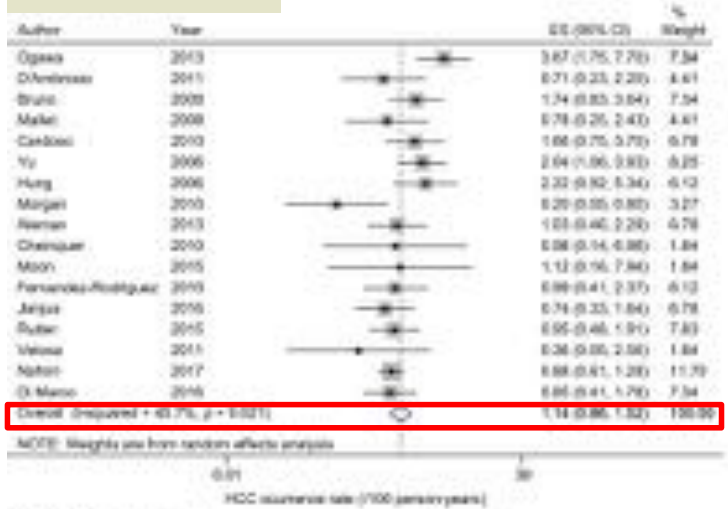
DAA-induced SVR and reduction in HCC incidence



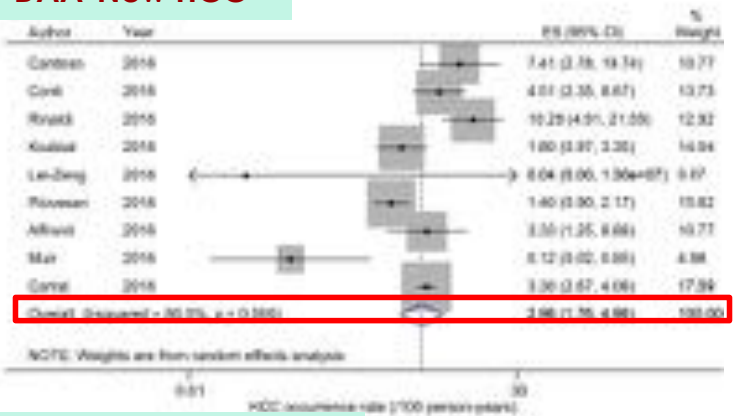
Incidence of new and recurrent HCC with IFN and DAA

Warizy R et al
J Hep 2017

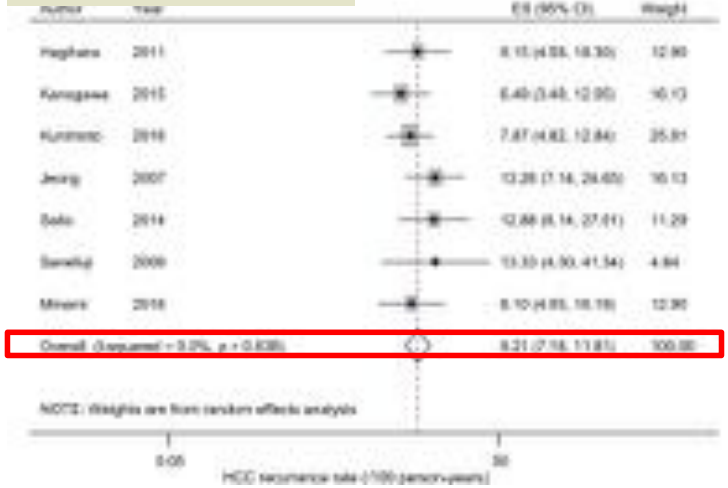
IFN-New HCC



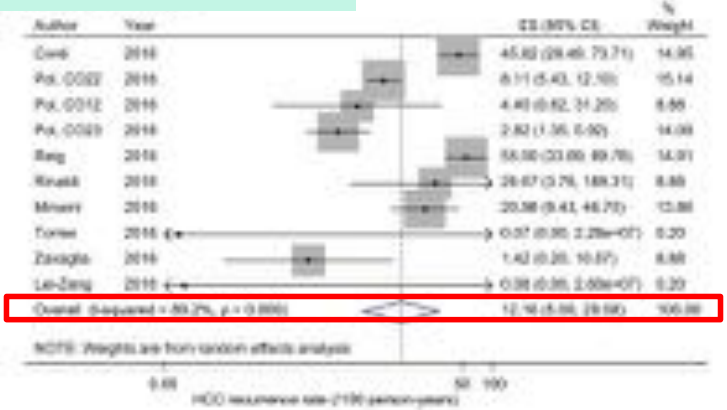
DAA-New HCC



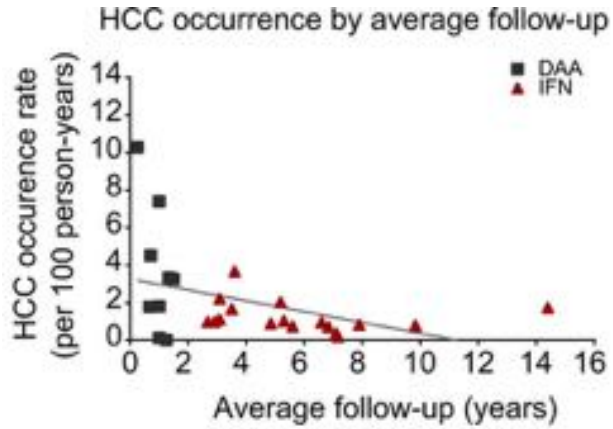
IFN-Recurrent HCC

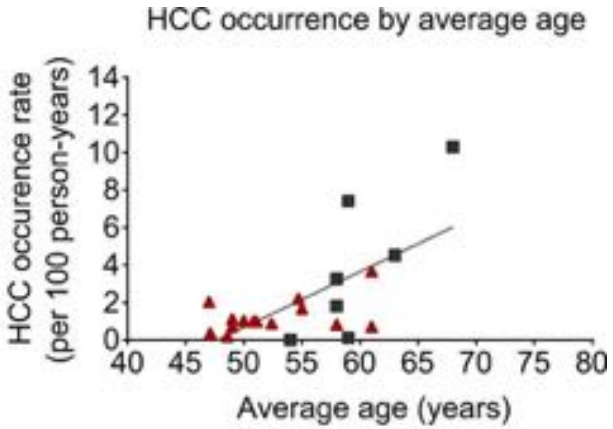


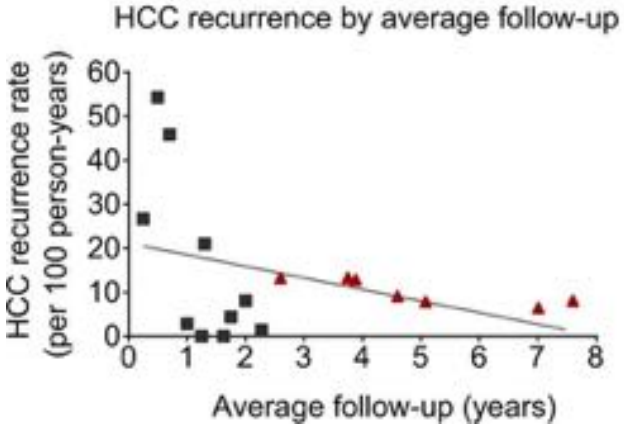
DAA-Recurrent HCC

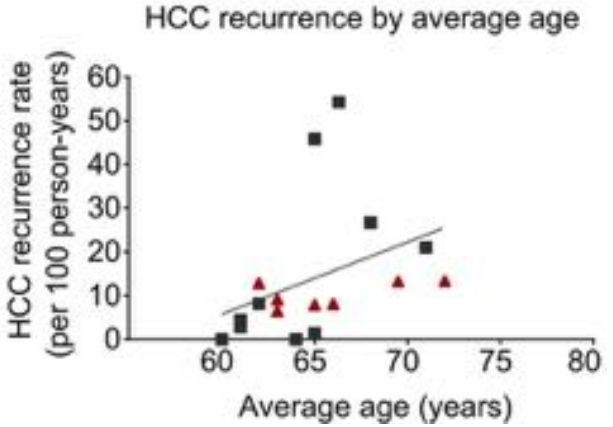


DAA studies have much shorter follow-up and older patients









New and recurrent HCC: no significant difference between IFN and DAA after adjustment for follow-up duration, age and genotype

Table 3. Meta-regression analysis of factors associated with occurrence of hepatocellular carcinoma following HCV cure (Observations = 26).

Variable	Univariate analysis			Multivariate analysis[1]		
	RR	95% CI	p value	aRR	95% CI	p value
Treatment						
IFN	1.00	–	–	1.00	–	–
DAA	2.77	1.46–5.25	<0.01	0.68	0.18–2.55	0.56
Average follow-up, years	0.88	0.80–0.97	0.01	0.75	0.56–0.99	0.04
Average age	1.11	1.03–1.18	<0.01	1.06	0.99–1.14	0.12
Genotype 1	1.01	0.99–1.03	0.14	–	–	–

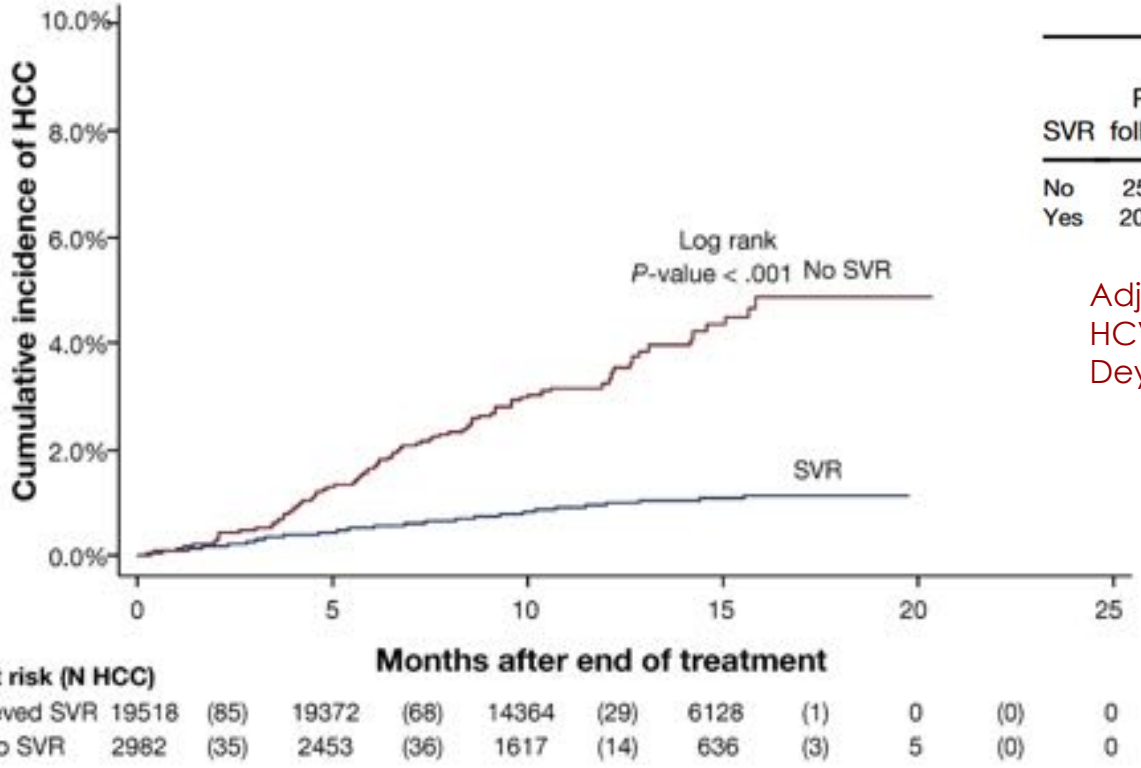
All numbers were rounded to two decimal places.
aRR, adjusted rate ratio; CI, confidence interval; DAA, direct-acting antiviral; IFN, interferon; RR, Rate Ratio.
[1] Five studies were excluded from the adjusted analysis due to incomplete data on age.

Table 4. Meta-regression analysis of factors associated with recurrence of hepatocellular carcinoma following HCV cure (Observations = 17).

Variable	Univariate analysis			Multivariate analysis		
	RR	95% CI	p value	aRR	95% CI	p value
Treatment						
IFN	1.00	–	–	1.00	–	–
DAA	1.36	0.49–3.76	0.53	0.62	0.11–3.45	0.56
Average follow-up, years	0.86	0.70–1.05	0.15	0.79	0.55–1.15	0.19
Average age	1.11	0.96–1.28	0.12	1.11	0.96–1.27	0.14
Genotype 1	1.01	0.97–1.05	0.49	–	–	–

All numbers were rounded to two decimal places.
aRR, adjusted rate ratio; CI, confidence interval; DAA, direct-acting antiviral; IFN, interferon; RR, Rate Ratio.

SVR by DAA is also associated with lower HCC risk
US population-based study (veterans)



SVR	PY of follow-up	HCC N	Incidence rate (per 100 PY, 95% CI)	Adjusted hazard ratio[a] (95% CI)	P value
No	2547.34	88	3.45 (2.73–4.18)	1	
Yes	20,415.3	183	0.90 (0.77–1.03)	0.28[b] (0.22–0.36)	<.0001

Adjusted for age, gender, race, cirrhosis, HCV genotype, DM, HIV, alcohol, drug use, Deyo index, visits in year prior to DAA

Kanwal F, Gastroenterology 2017

What about SVR rate in HCC patients!

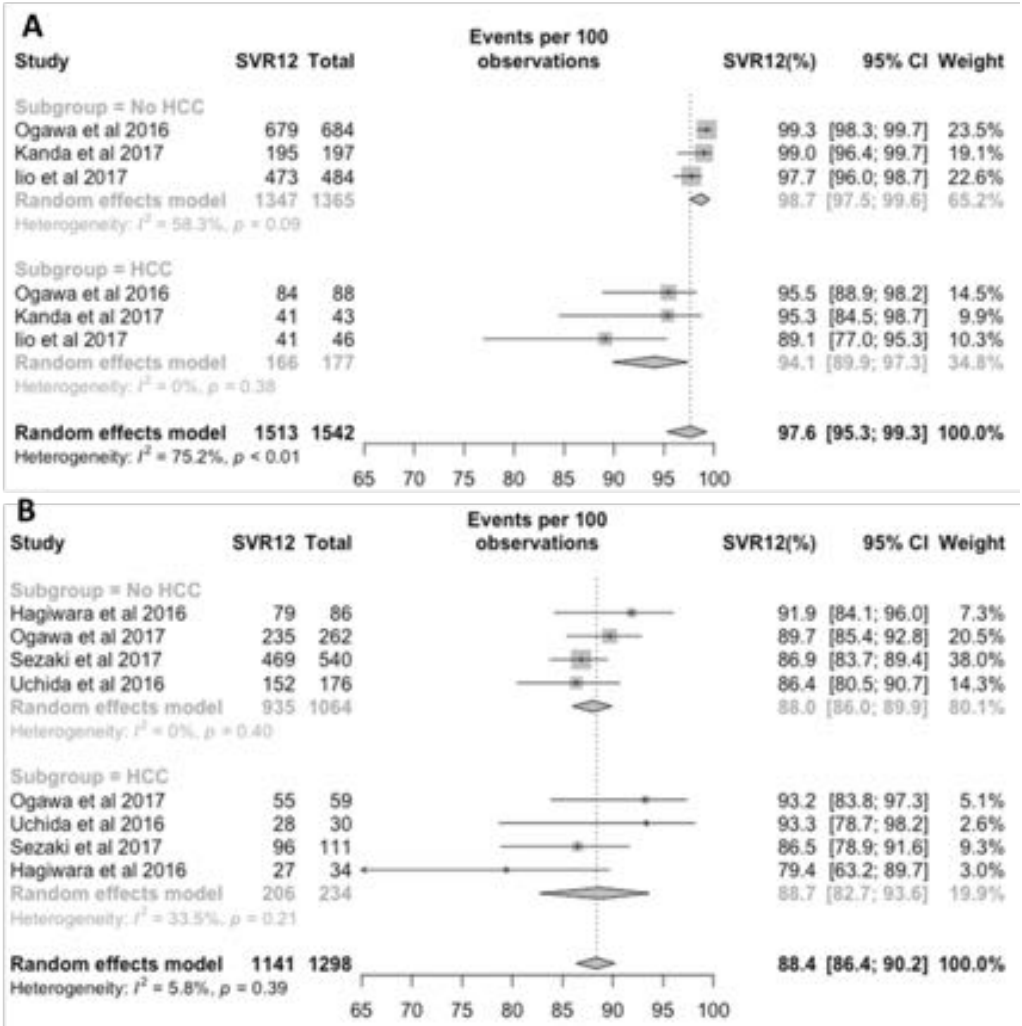
Real-World Asia Studies

Limited data

Lower SVR in HCC vs. non-HCC patients treated with ledipasvir/sofosbuvir:
94.1% vs. 98.7%

Similar SVR in HCC vs. non-HCC patients treated with dalclastavir/asunaprevir:
88.7% vs. 88.0%

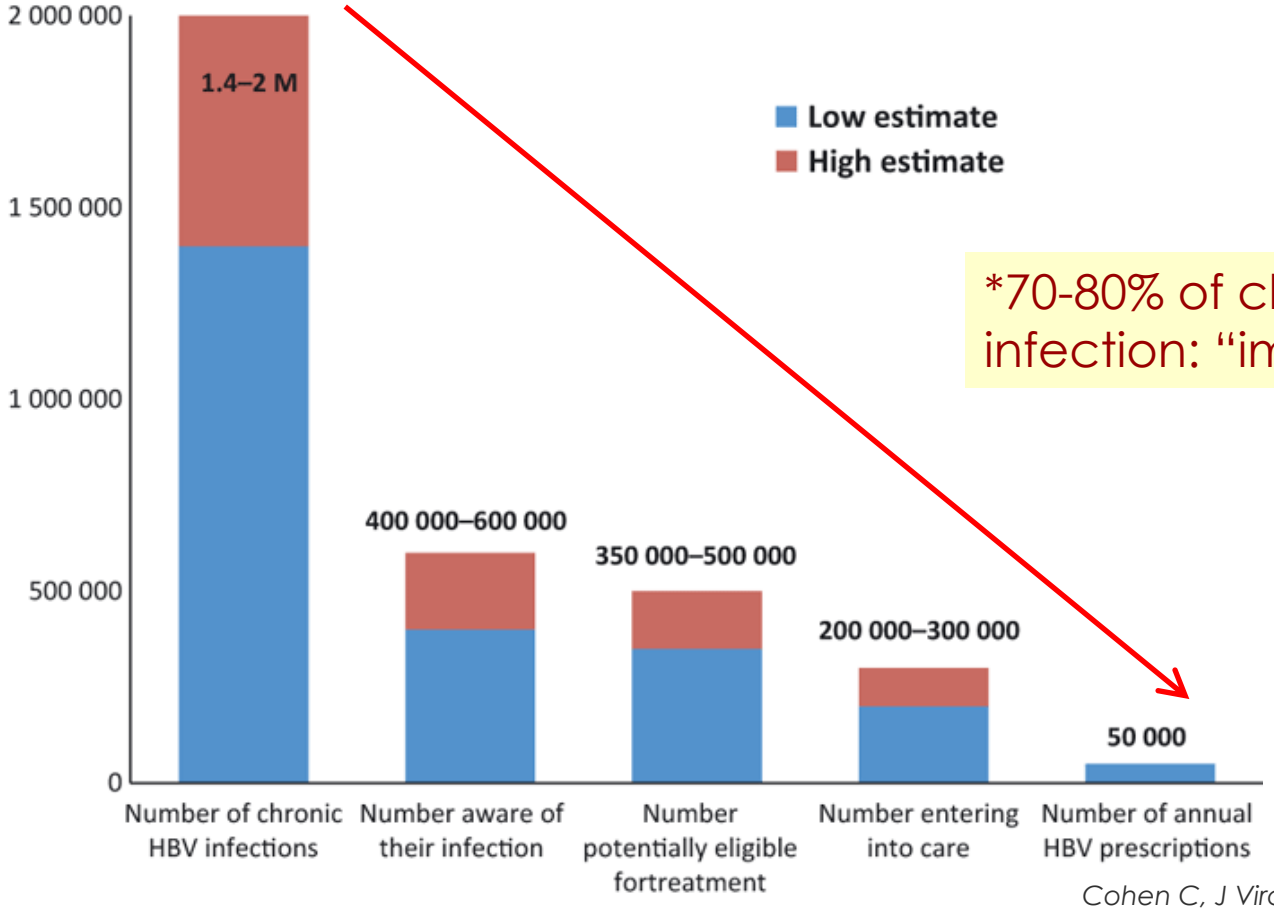
Fanpu Ji/Nguyen MH, Hepatology 2017 (in press)



Summary

1. HCC still occurs in patients on oral antiviral therapies though at lower rate. These patients need continued HCC surveillance.
2. HBV cure effort continues to make progress
3. Many good options for IFN/RBV-free options for all HCV genotypes
4. Oral DAA can decrease risk of HCC
5. Oral DAA unlikely cause more rapid progression of HCC in patients who already have HCC
6. HCC patients may have lower SVR compared to non-HCC patients
7. However, additional real-world data is needed to evaluate the effect of HCC on SVR and the long-term effect of DAA on HCC development and progression

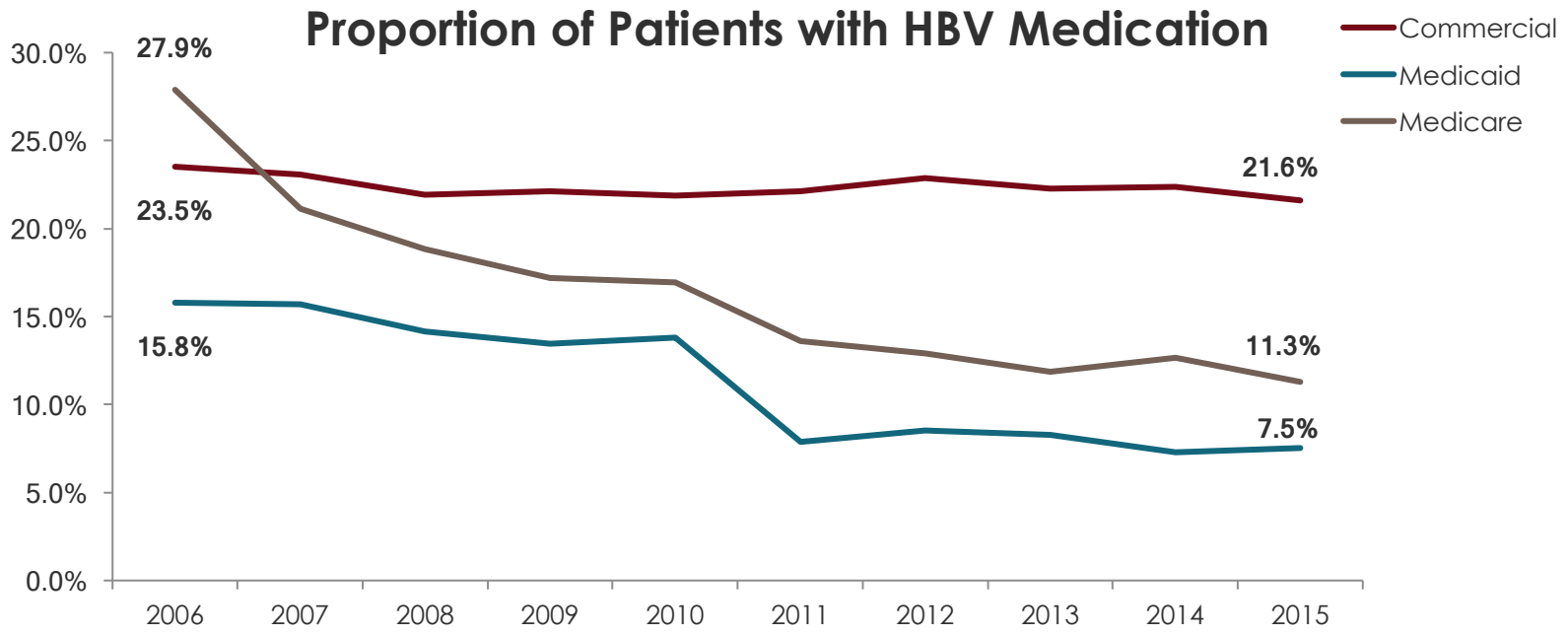
Care Cascade of Hepatitis B in the US



*70-80% of chronic HBV infection: "imported"

Cohen C, J Viral Hepat 2010; 18: 377

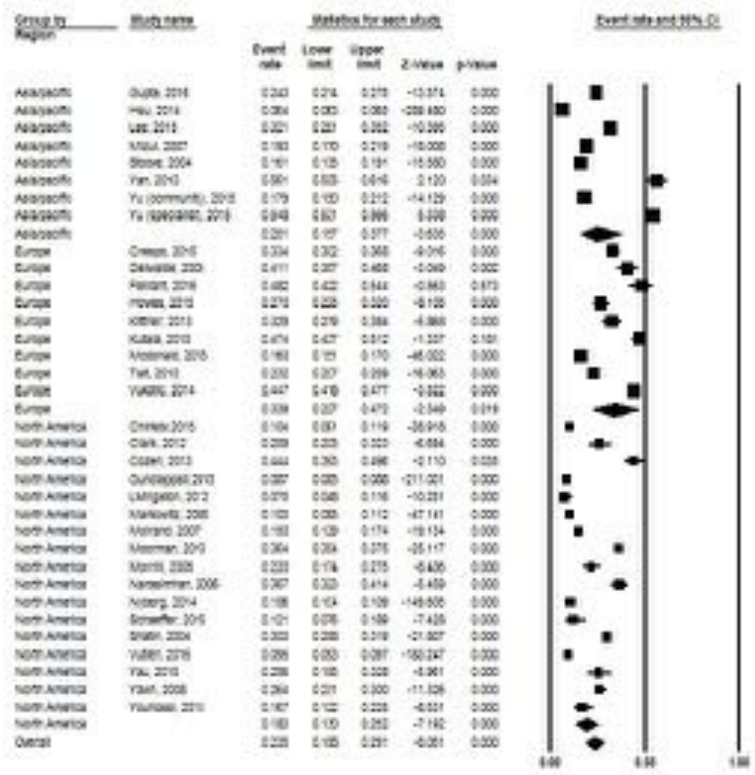
	CHB Patients with HBV Medication (N)									
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Commercial	839	1,074	1,284	1,790	2,027	2,397	2,842	2,696	2,365	1,775
Medicaid	225	241	255	300	285	145	169	213	231	171
Medicare	70	71	81	100	118	133	150	151	150	99

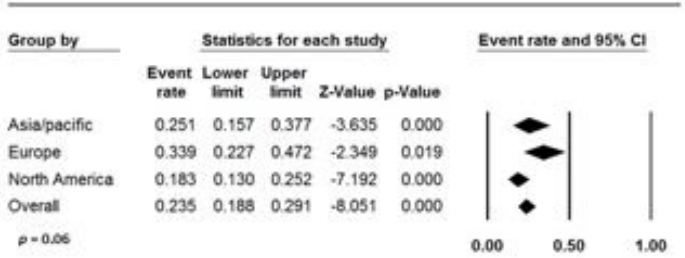


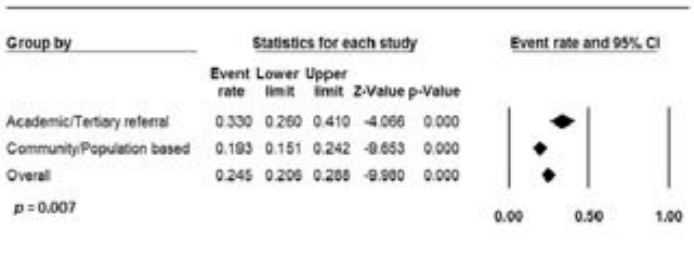
Truven Marketscan® Database, unpublished data (2017)

Treatment Rate in Pre-DAA Era – ~18%

Vutien P/Nguyen MH, Plos ONE 2017

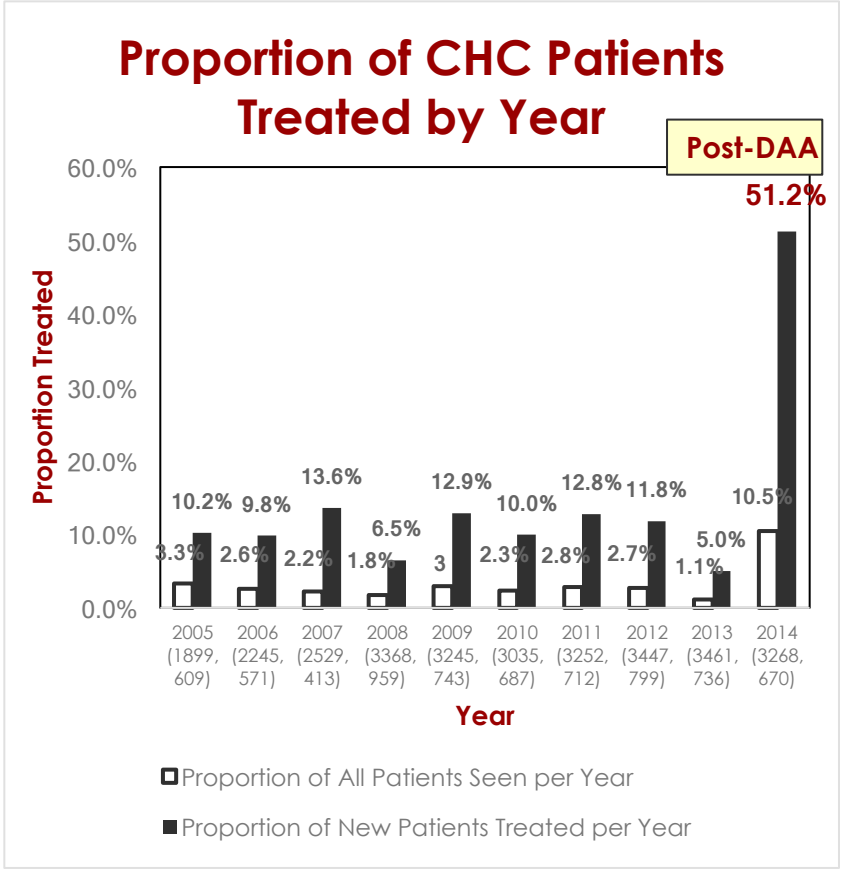






Treatment Rate in Post-DAA Era

- 9360 consecutive confirmed HCV patients at Stanford University Medical Center
- Seen in 1999-2014
- Overall treatment rate - stable time trend until 2014 (pre-DAA)



Vutien P/Nguyen MH. BMJ Open Gastro 2017.

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THANK YOU