Treatment discontinuation:
Asian perspective

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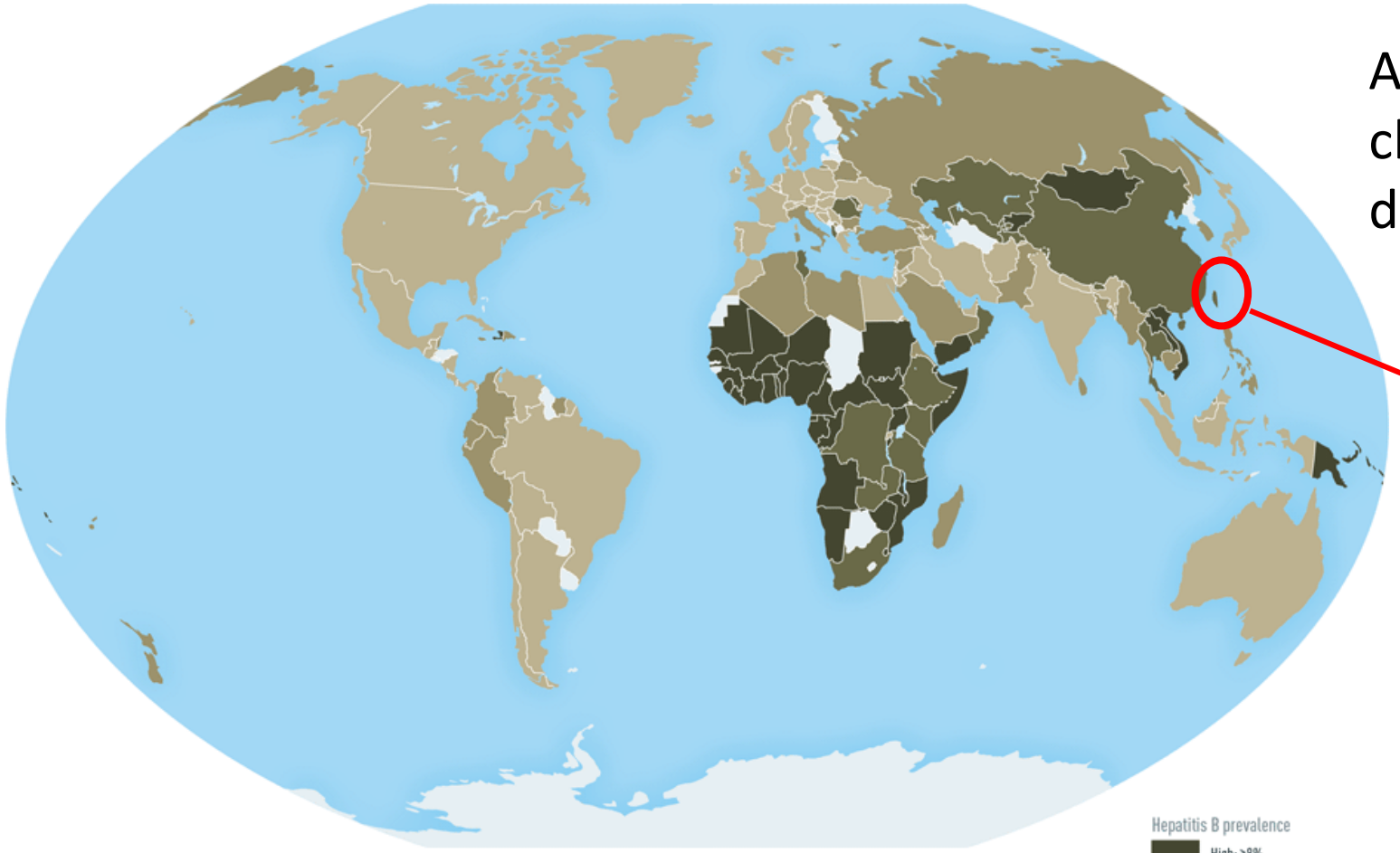
The global and regional burden of CHB



https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/hepatitis-b

An estimated 296 million subjects chronically infected and 820,000 deaths worldwide by 2019

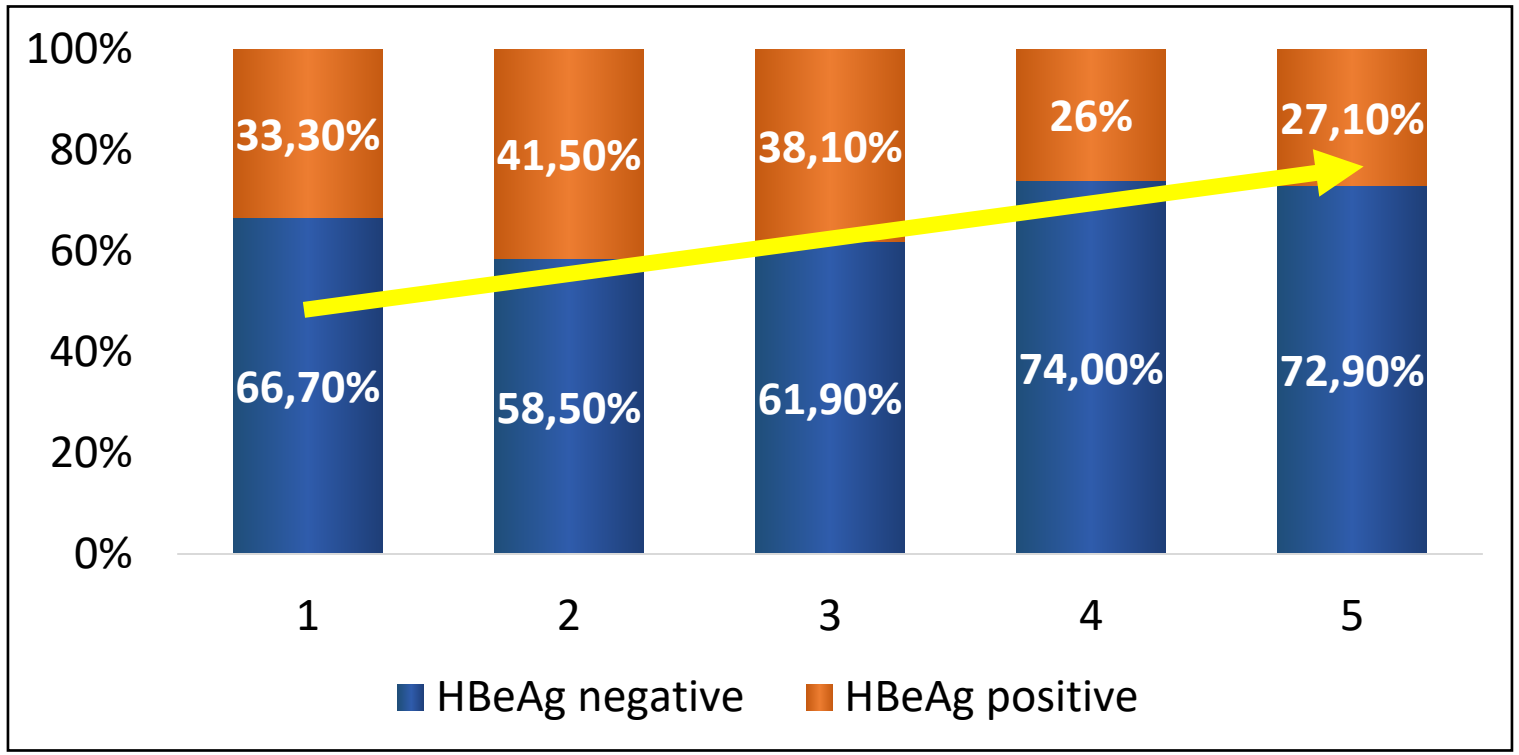
July 1st 1986 -- nation-wide neonatal HBV vaccination program:
HBV prevalence: decrease from 20% to 7%, with only 0.8% among people younger than 35.

Still, there are 1.9 million CHB patients in Taiwan

https://www.cdc.gov.tw/EpidemicTheme/Detail/HN_bvfRk6F9P3-V-G4NJxQ?archiveId=WzBAfVjRosYPV7IlB4AV3A

The changing phenotype of the CHB patients
More and more HBeAg negative CHB!

Increased HBeAg negative proportion of treatment-naïve CHB in CGMH

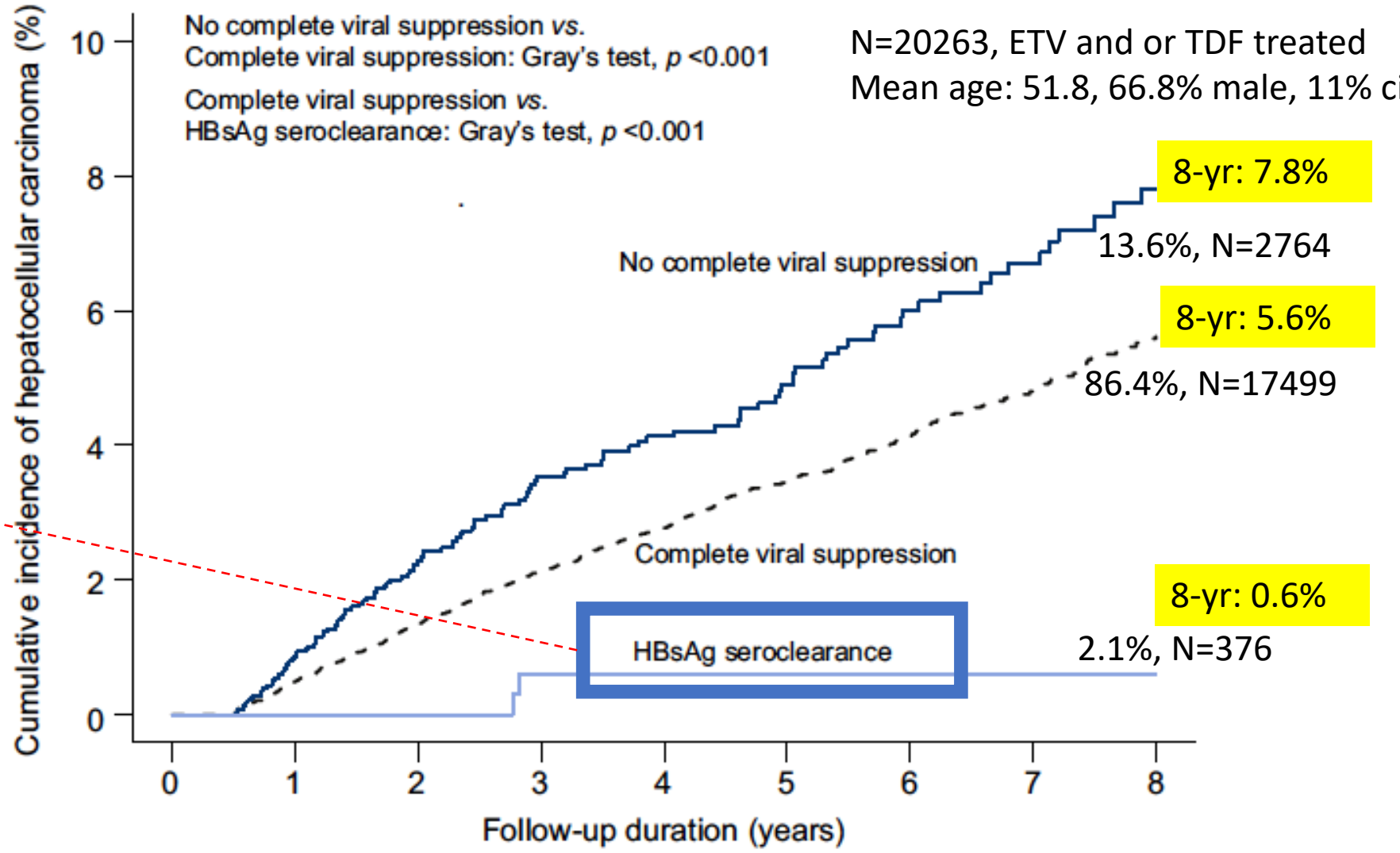


Current guideline treatment endpoint:

	Endpoint for HBeAg-Neg CHB
AASLD 2018	HBsAg loss
EASL 2017	HBsAg loss, finite for selected patients (> 3-year undetectable HBV DNA)
APASL 2016	HBsAg loss or finite for patients > 2-year undetectable HBV DNA

Yeh CT et al Emerg Infect Dis. 2017 May; 23(5): 820–821; Terrault NA et al Hepatology 2018; 67(4): 1560-99; EASL J Hepatol 2017; 67(2): 370-98; Sarin SK et al, Hepatol Int 2016; 10(1): 1-98

HBsAg loss: the ultimate goal



N=20263, ETV and or TDF treated
Mean age: 51.8, 66.8% male, 11% cirrhosis

8-yr: 7.8%
13.6%, N=2764

8-yr: 5.6%
86.4%, N=17499

8-yr: 0.6%
2.1%, N=376

Functional Cure

Yip TCF et al J Hepatol 2019; 70(3):361-370

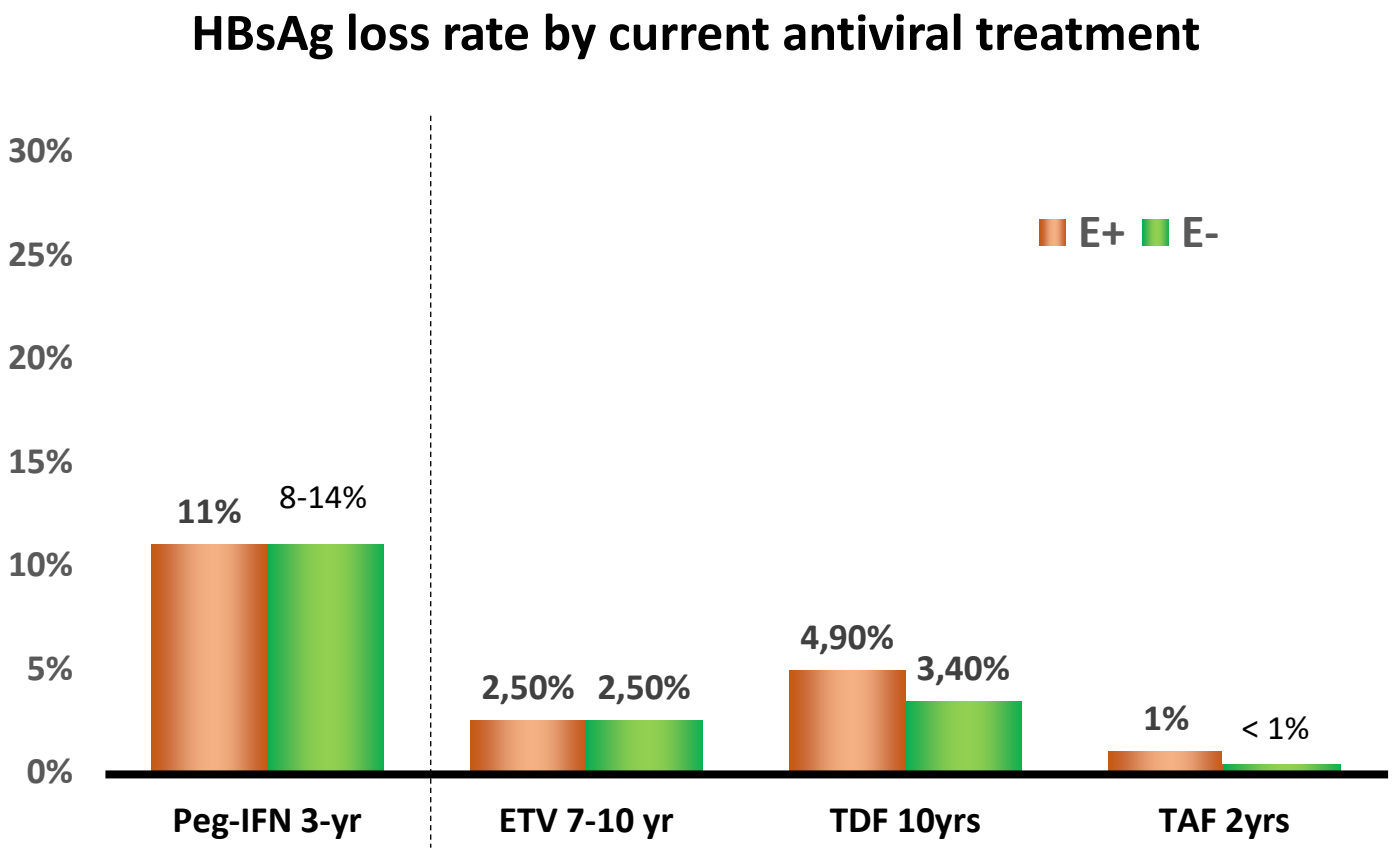
Why Finite therapy should be considered…

- Willingness/adherence/loss to follow-up in real world
- Long term drug safety > 10 years
- Low HBsAg loss rate during NA treatment
- Cost for life-long, esp. HBV endemic countries
  - (~2200 USD annually per patient, ~2,000,000 CHB patients in Taiwan*)

*estimated in 2018

1. Jeng WJ et al Hepatology 2018; 2. Kim GA et al Gut 2014; 3. Chevaliez S et al J Hepatol 2013; 58(4): 676-83; 4. Hsu YC et al J Infect Dis. 2021 Dec 1;224(11):1890-1899

Functional cure is difficult to reach



HBsAg loss rate	No.	Genotype
0.15% per year	1075	B/C[1]
0.33% per year	5409	C[2]
0.3% by 7 year	375	D[3]

An average HBsAg decline of 0.084 log_{10}IU/mL/yr, estimated time of HBsAg loss: 39-610 years![4, 5]

1. Jeng WJ et al Hepatology 2018; 68(2):425-434 2. Kim GA et al Gut 2014; 3. Buti M Dig Dis Sci 2015;; 60(5):1457-64; 4 Chevaliez S et al J Hepatol 2013; 58(4): 676-83; 5. Hsu YC et al J Infect Dis. 2021 Dec 1;224(11):1890-1899

Problem raised during long-term treatment

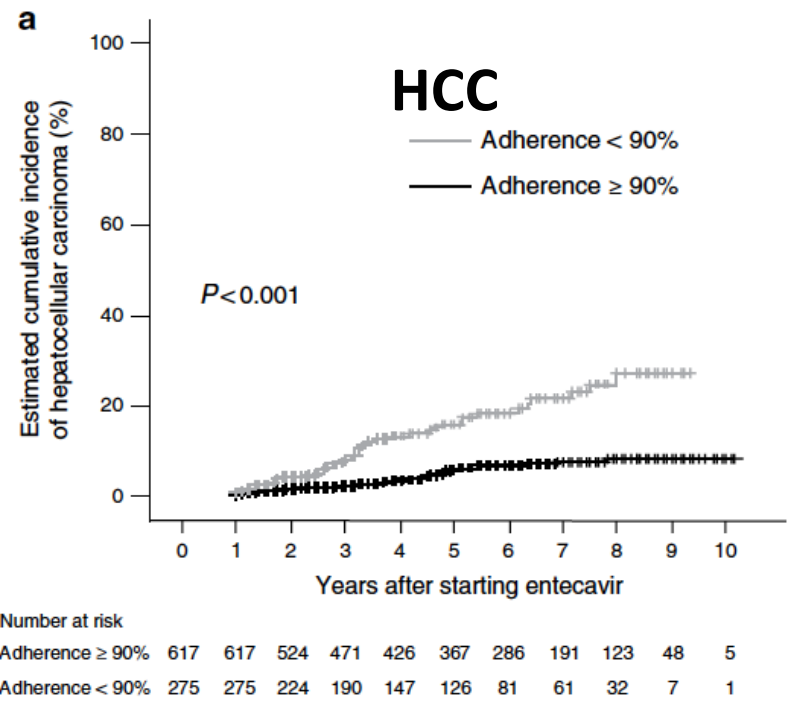
Human nature: Almost inevitable

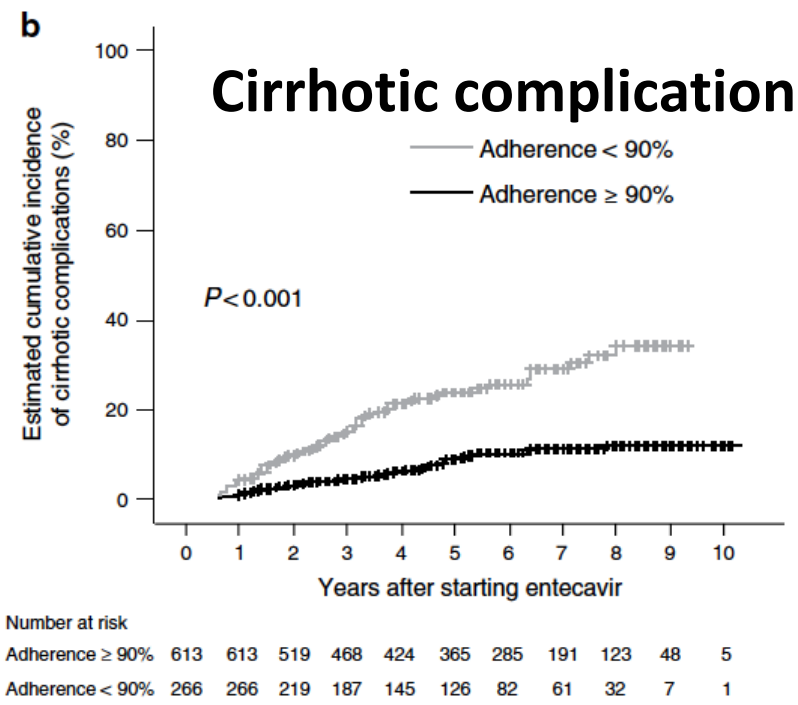
- **Adherence rate** by meta-analysis: **74.6%**[1] (Optimal: 95%)
  - Comparable between high and low income
  - Barriers: forgetting, limited understanding of the importance of adherence, change to routine
- Liver adverse events hazard ratio increase when adherence < 90%, greater in those < 70%[2] (forgot 2 times per week)
  - HR: **3.9** for HCC, **4.1** for cirrhotic complication, **22.7** for liver related mortality
- Real-world on-treatment lost follow-up cumulative rate
  - Prospective, call-back system [3] (N=147): Cumulative 1st: 3%, 3rd: 6%, 5th: 8%, 6th: 13%
  - Retrospective, cirrhotic[3] (N=1066): 1st: Cumulative 1st: 6%, 3rd: 8%, 5th :10%, 6th: 11%
- Lost to f/u without monitoring may lead to severe flare or hepatic failure[4].

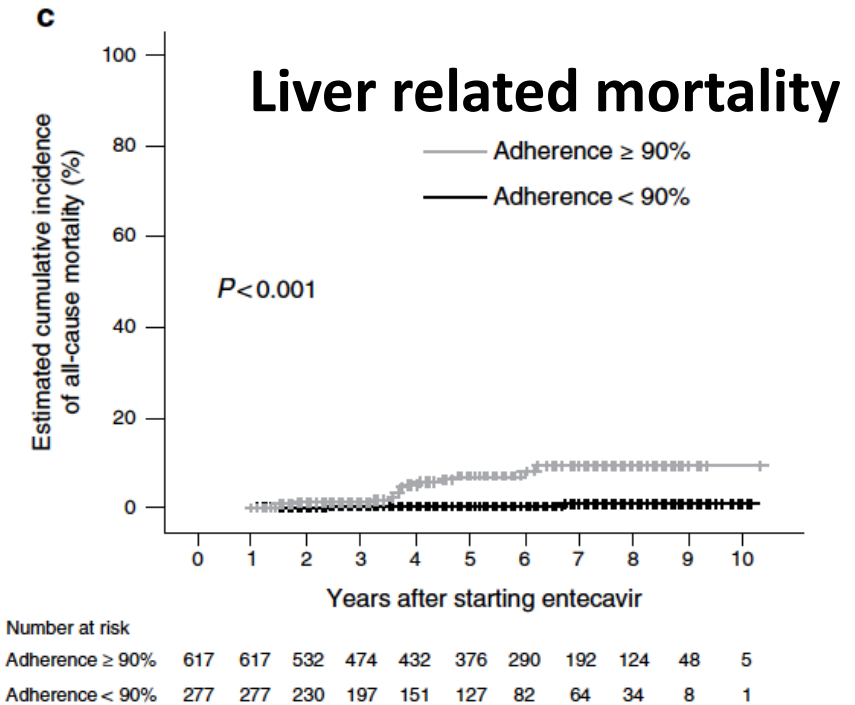
1. Ford N et al. Hepatol. Commun. 2018;2:1160–1167; 2. Shin JW et al AJG 2018; 113: 998-1008; 2. Hsu YC et al J Infect Dis. 2021 Dec 1;224(11):1890-1899; 3. Jeng WJ(unpublished); 4. Lim SG, Gut 2002 Oct;51(4):597-9

Poor adherence leads to poor outcome

894 treatment naïve CHB receiving ETV, 10-year longitudinal observational study, overall mean adherence rate: 89%[1]



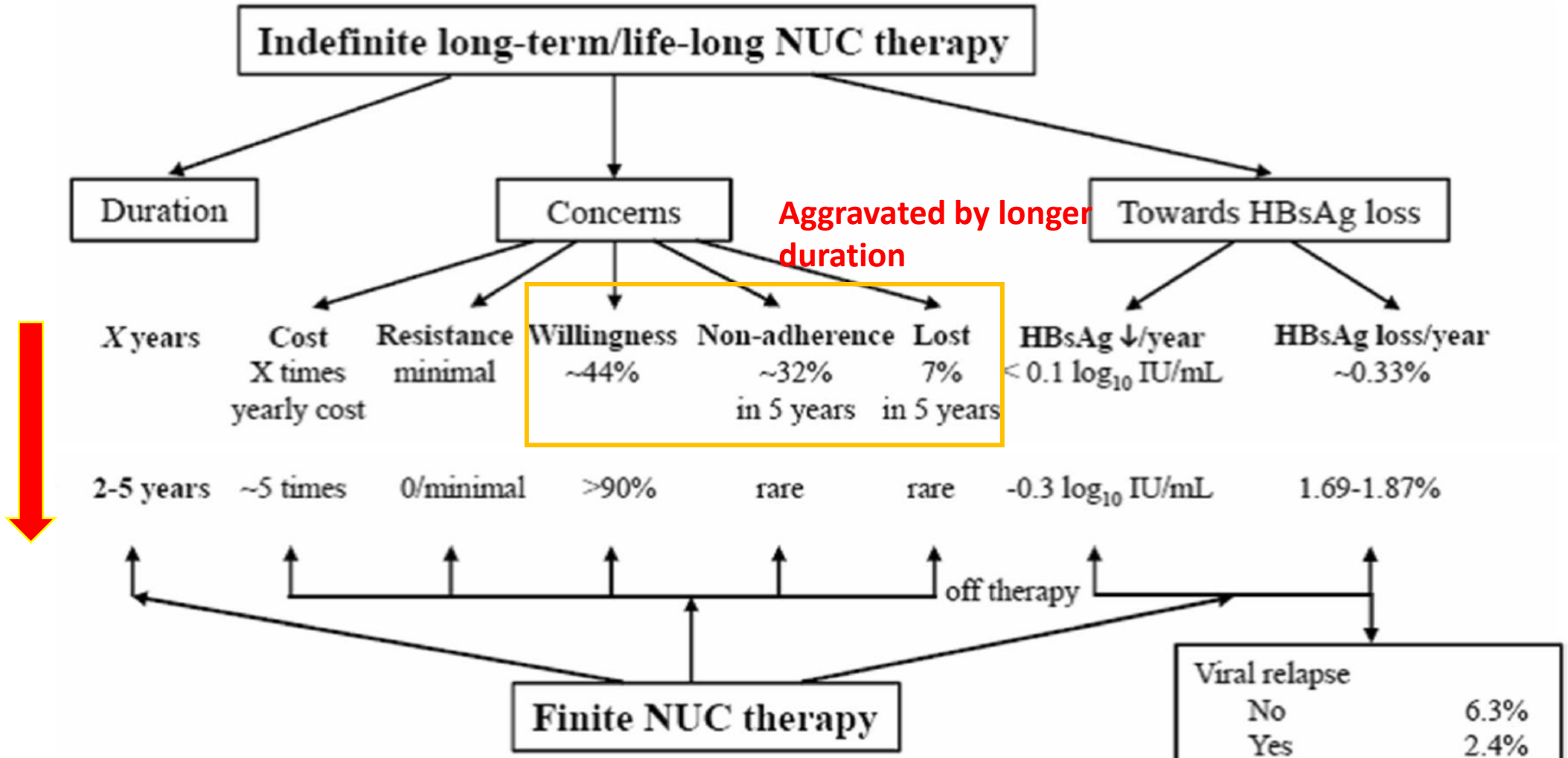




	HCC			Cirrhotic complication			Liver related mortality		
Adherence (%)	**HR**	95% CI	P value	**HR**	95% CI	P value	**HR**	95% CI	P value
≥ 90	**1**			**1**			**1**		
70-90	**2.33**	1.32-4.1	0.003	**2.04**	1.26-3.31	0.004	**7.55**	1.58-6.11	0.011
< 70	**3.9**	2.15-7.07	<0.001	**4.08**	2.56-6.53	<0.001	**22.67**	5.6-91.7	<0.0

1. Shin JW et al AJG 2018; 113: 998-1008;

A shifting paradigm for HBeAg (-) treatment endpoint

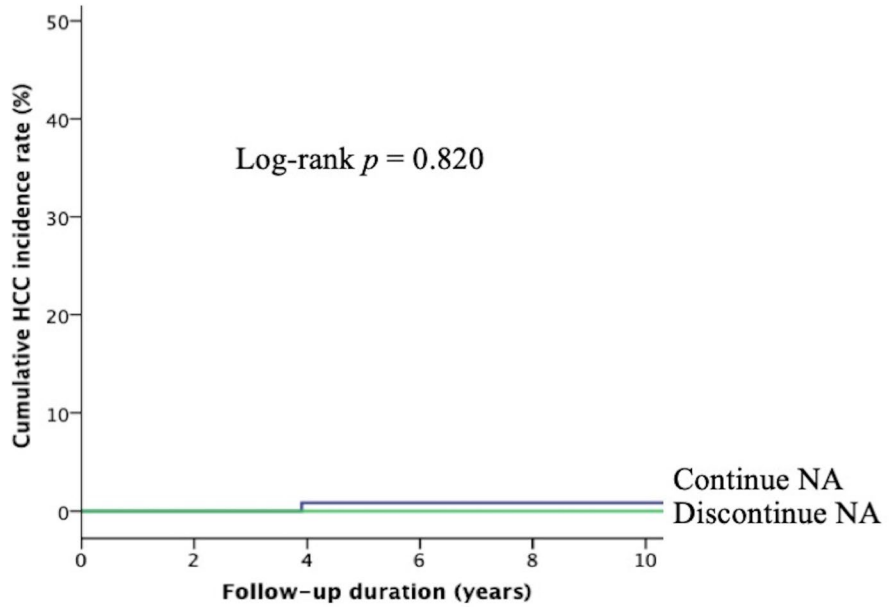


Liaw YF Hepat Int 2019; 13(6):665-673

No increase HCC events in finite therapy among HBeAg negative CHB patients

- The HCC incidence were comparable between finite arm and continued arm in both non-cirrhotic[1,2] and cirrhotic[3,4] CHB patients
  - ***Non-cirrhotic:***
  - 5-year: Finite vs. Continued[1.]:
    - Overall: 2.0% vs. 4.2%, P=0.494
    - Taiwan (NTUH): 1.3% vs. 2.2%, P=0.873
  - ***Cirrohotic:***
  - 5-year: Finite vs. Continued
    - LK-CGMH: 7.5% vs. 12.5%, P=0.182
    - KH-CGMH: Comparable, P=0.77

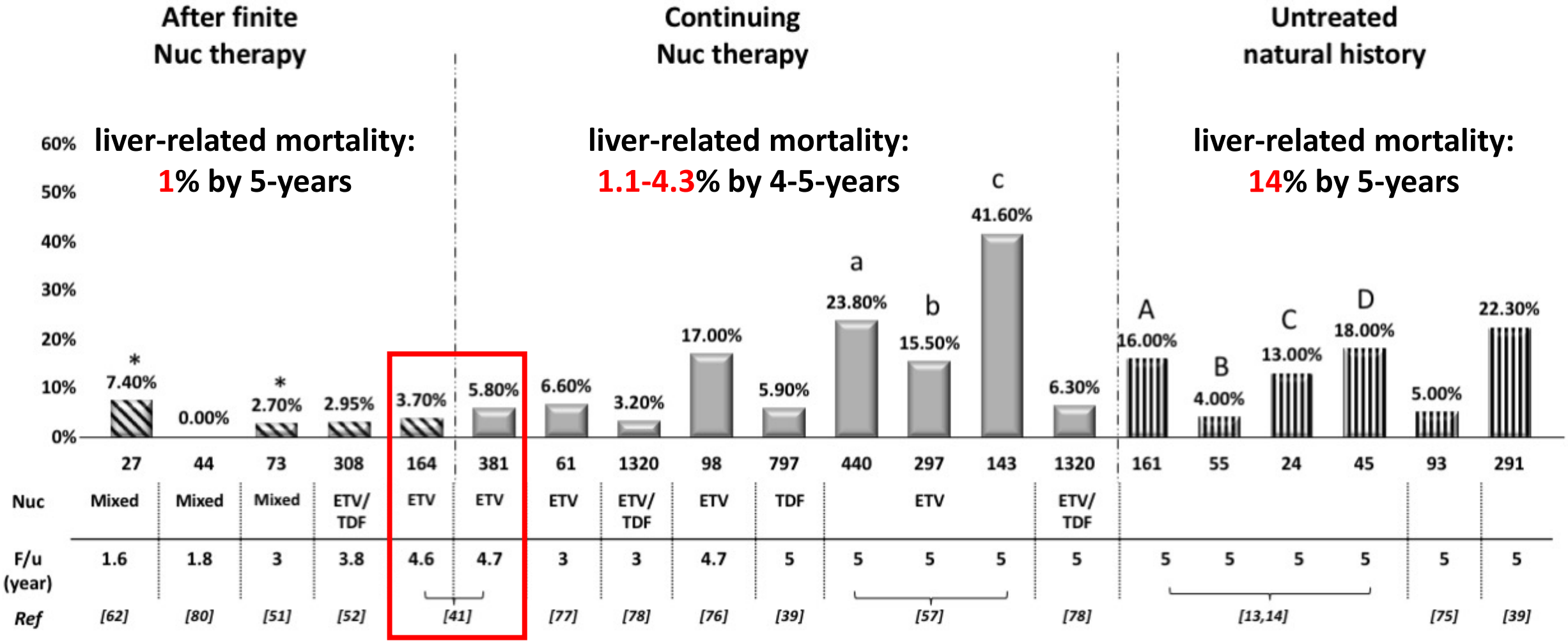
Coninue vs. disconinue NA:
3-,5-,10-years = 0%, 1%, 1% vs. 0%, 0%, 0%



Patients at risk						
Continue NA	139	127	114	91	67	47
Discontinue NA	153	152	115	107	98	88

1. Papatheodoridis M/Su TH et al Liver Int . 2022 Mar;42(3):541-550*; 2. Teng W et al.* Hepatol Int. 2021 Dec;15(6):1421-1430 (with Courtesy data from Dr. Teng).*; 3. Chen YC APT 2015 42; 1182-1191* ; 4. *Hung CH JVH 2017 24(7):599-607; 5. Jeng WJ et al Seminar in liver disease 2021; Jeng WJ et al AASLD 2021 (Left), Jeng WJ et al (submission, right); 6. Hsu YC et al CGH 2021 in press*

Hepatic decompensation in cirrhotic patients: not higher



Modified from Liaw YF. Hepatol Int. 2019 Nov;13(6):665-673; Chen CH et al Am J Cancer Res 2020;10(11):3882-95; Jeng WJ et al: Hepatology 2018; 68: 425-434; Liu K et al Aliment Pharmacol Ther 2019; 50: 1037-1048; Fattovich G et al Am J Gastroenterol 2002;97:2886 –2895.

HBsAg loss increased in patients off-Nuc

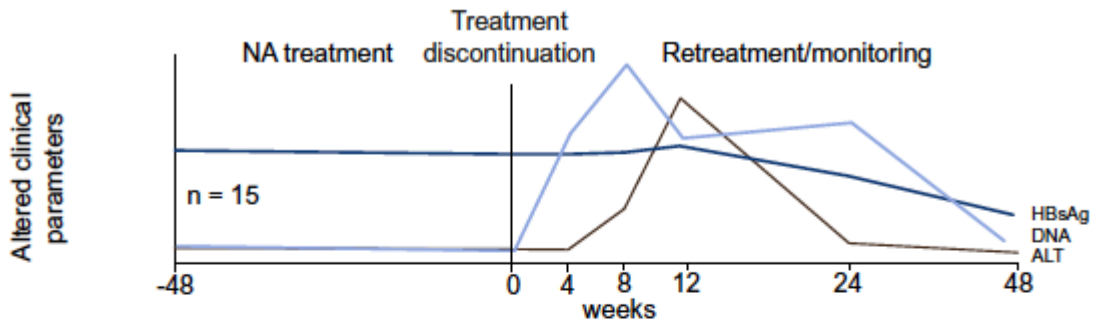
- **HBsAg loss in ETV or TDF treated Pts: 2.6-4% by 10 years**

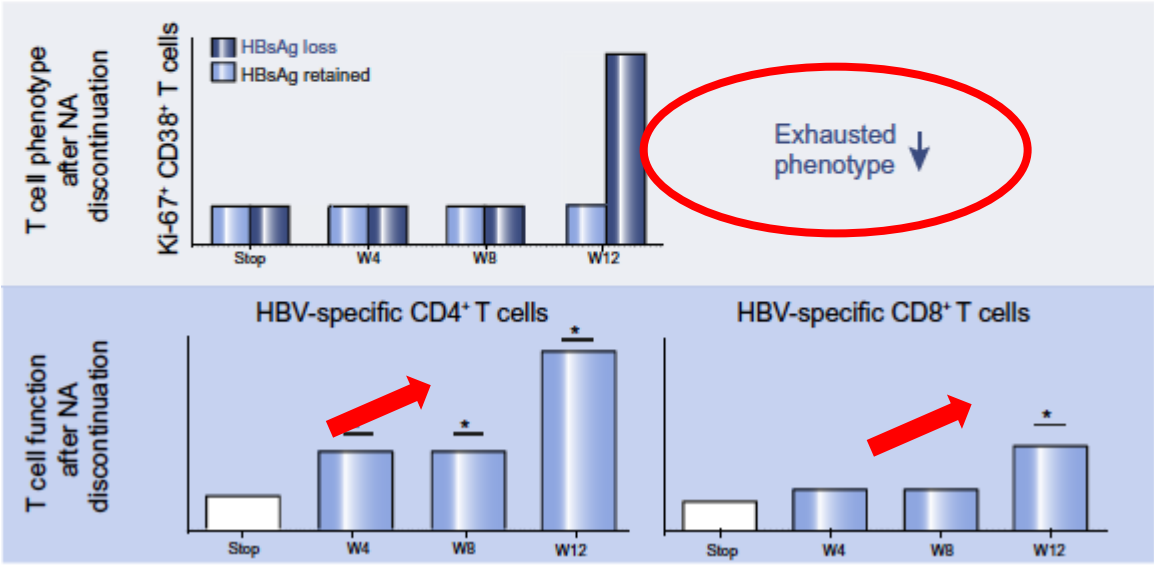
Source	Design	Ethnics	Nuc	No.	Tx (yr)	F/U (mo)	HBsAg loss
Berg	**RCT**	Caucasian (88%)	TDF	21	>4	33	30% /3 yrs
van Bommel	**RCT**	Caucasian (80%)	Mixed	79	>4	24	10.3% /2yrs
Hadziyannis	Pro/Cohort	Caucasian	ADV	33	4-5	66	39% /5 yrs
Manolakopoulos	Pro/Cohort	Caucasian	ETV/TDF	57	7.5	65	20% /3 yrs
Garcia-Lopez	Pro/Cohort	Caucasian (93%)	ETV/TDF	27	8	34	30% /3 yrs
Chan	Cohort	Asian (100%)	LAM	53	3	71	23% /5 yrs
Chi	Cohort	Asian (80%)	Mixed	59	5	19.4	14% /3 yrs
Chen	Cohort	Asian (100%)	ETV	250	3.2	>60	20.8% /6 yrs
Jeng	Cohort	Asian (100%)	ETV	671	3	36	16% /6 yrs (non-LC) 9% /6 yrs (LC)
Hirode (RETRACT)	**Global cohort**	Asian (88%) Caucasian (N=152)	Mixed	1541	3	17	14% /4 yrs (Asian: 11%, Caucasian: 1%)

Hadziyannis S et al. Gastroenterology 2012; 143: 629-36; Berg T. et al J Hepatol 2017; 67:918-924; Jeng WJ et al Hepatology 2018; 68: 425-434; Garcia-Lopez M et al J Hepatol 2020 (in press), Manolakopoulos et al, Liver Int 2021; 41:48-57; Chen CH et al Hepatol Int 2020;14:317-325; Chi H et al Aliment Pharmacol Ther. 2015 ;41(9):867-76; Chan HL et al Antivir Ther. 2011;16(8):1249-57; Hirode G et al AASLD 2020 oral presentation; van Bommel et al ILC 2020 LBO06; Marcellin P et al Liver International 2019;00:1-8; Suzuki F et al J Gastroenterol . 2019 ;54(2):182-193

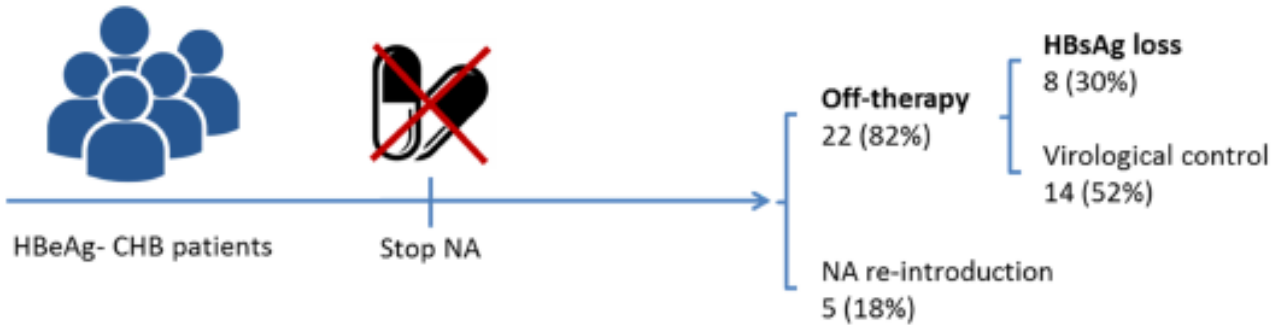
HBV specific CD8+ T cell response vs. HBsAg loss

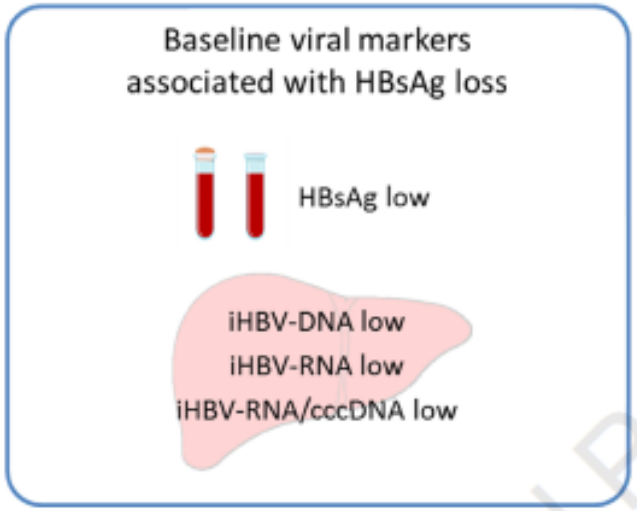
Increase along with follow-up

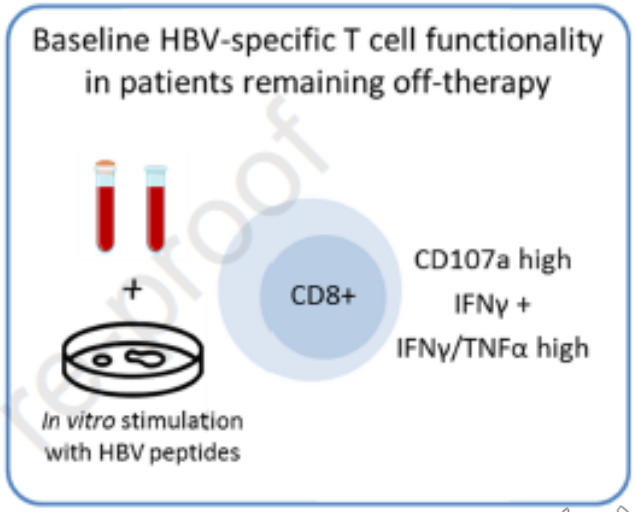




No increase along with follow-up

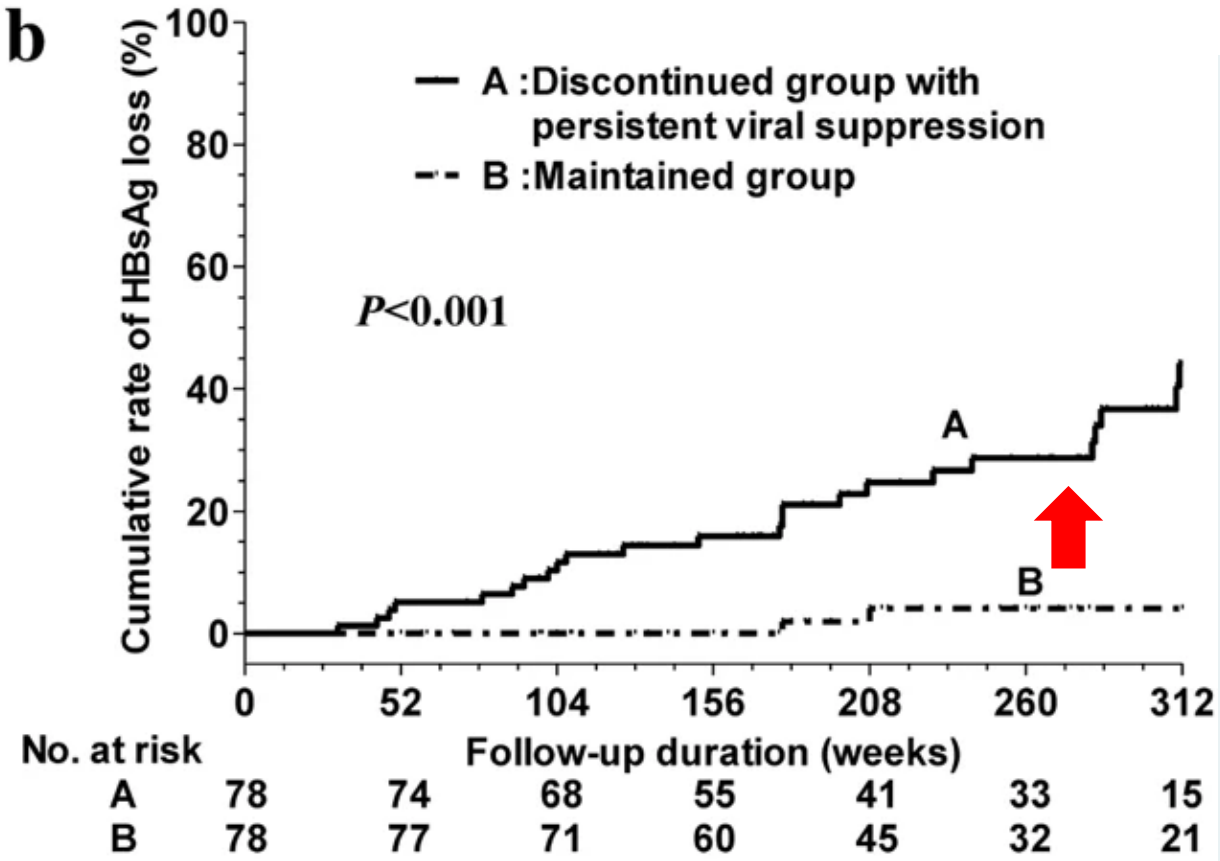




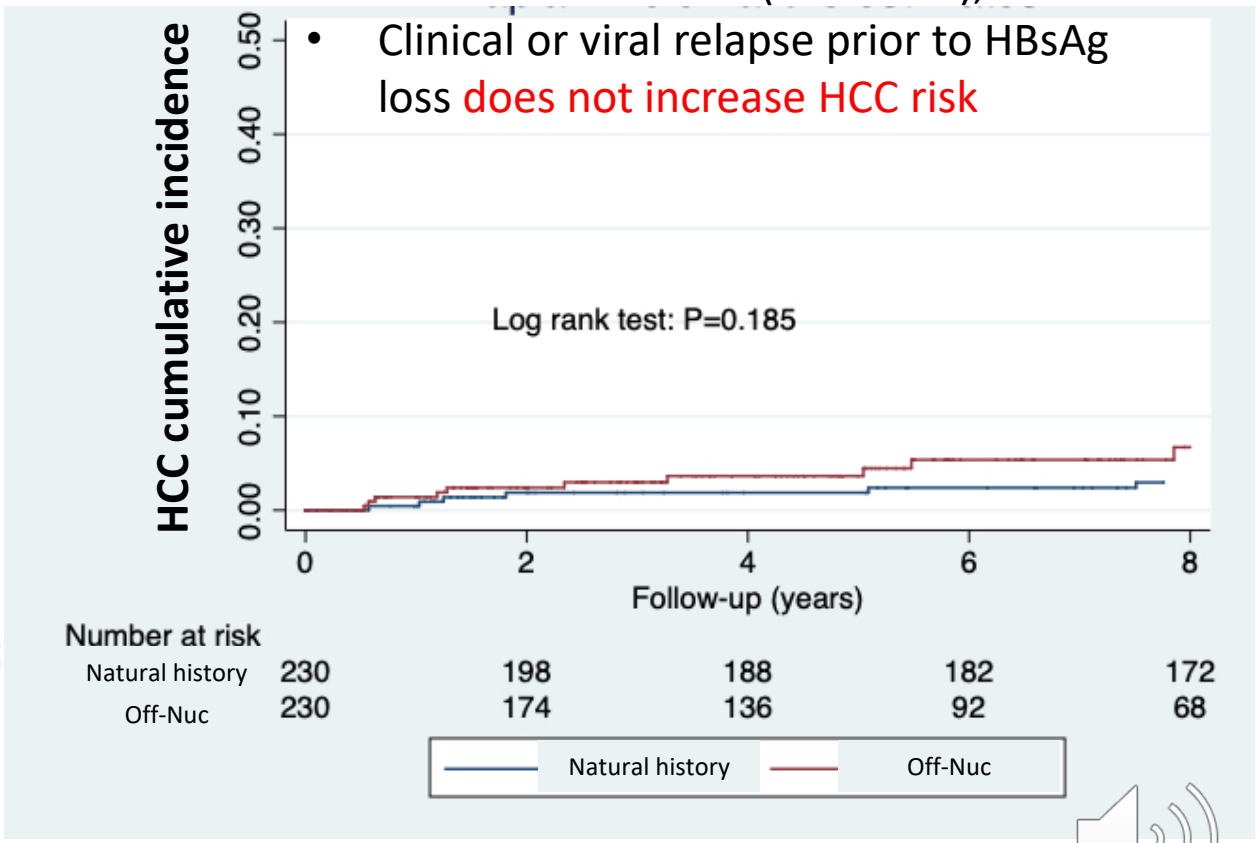


Rinker F et al JH 2018 ; García-López M et al J Hepatol 2020

Much increased HBsAg loss rate in finite therapy, with comparable excellent prognosis as spontaneous HBsAg loss patients



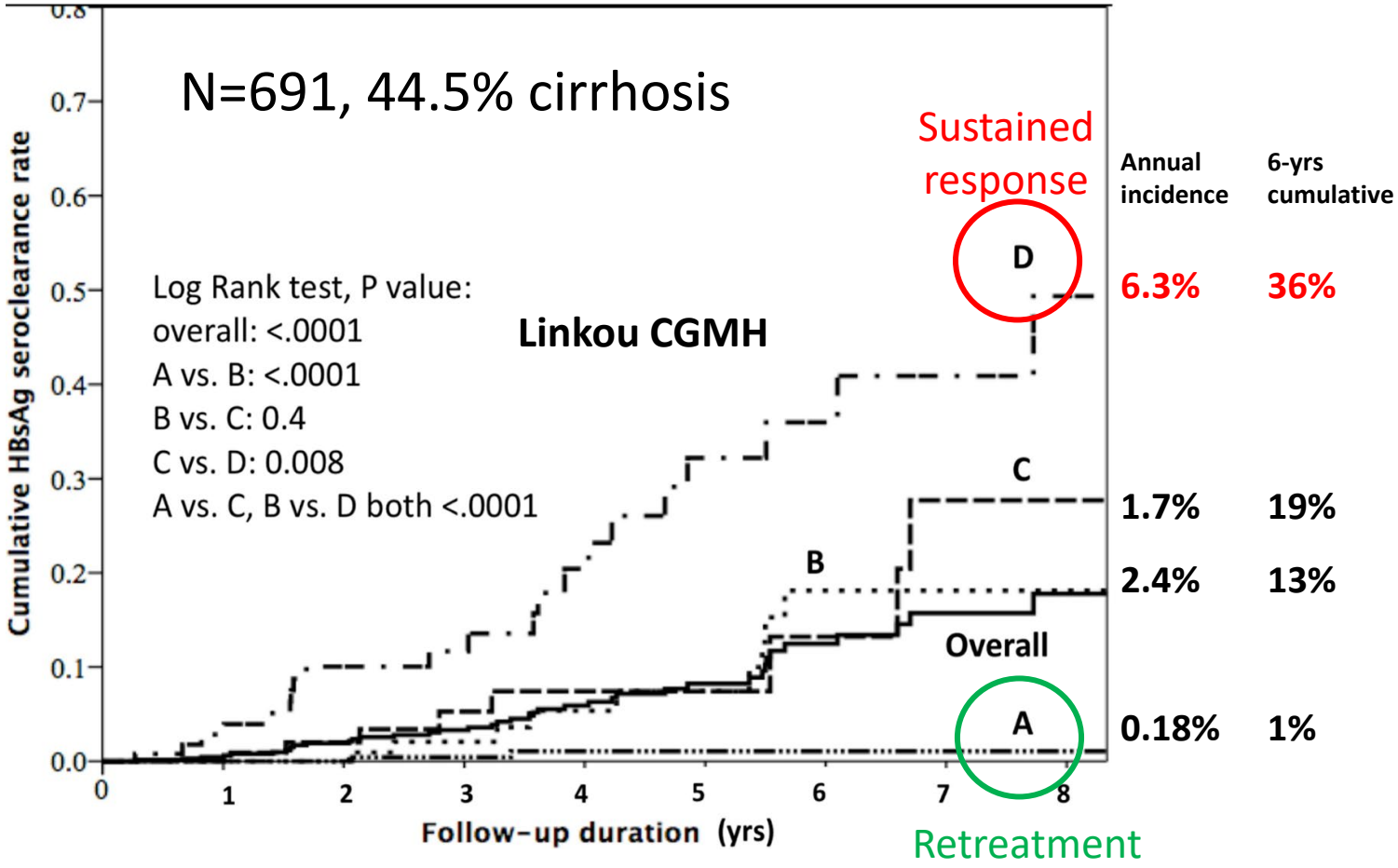
- Cirrhosis is the only independent factor for HCC : aHR: 8.86 (1.86-42.1), P<0.01
- Clinical or viral relapse prior to HBsAg loss does not increase HCC risk

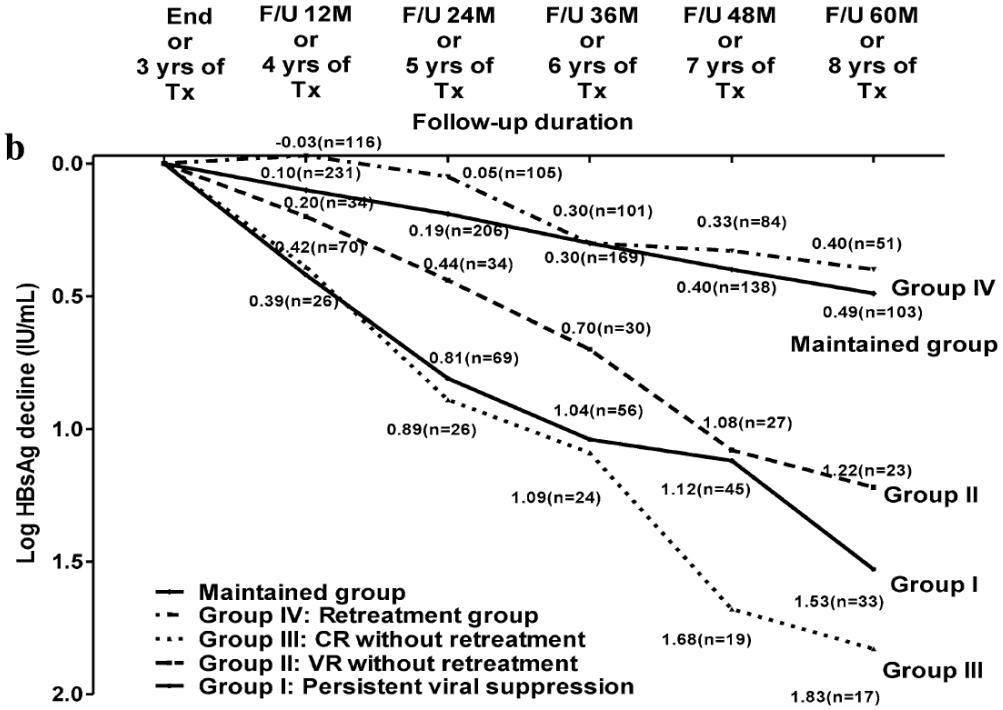


Chen CH et al JID 2019 219(10):1624-1633 ; Jeng WJ et al AASLD 2021 (Left), Jeng WJ et al (submission, right)

The cumulative HBsAg seroclearance rate was highest in patients with sustained response and lowest in those retreated

SR > CR untreated > CR treated in two independent cohort





Jeng WJ et al, Hepatology 2018, Chen CH et al JID 2019 219(10):1624-1633; Chen CH et al Hepatol Int. 2020 May;14(3):317-325

Retreatment decision is crucial: Not too late for safety, not too early to halt HBsAg clearance

Decompensation is rare, mostly reported in cirrhotic patients[1]
5-year: 2.95% in cirrhosis and 0% in non-cirrhosis [HBeAg: (-)][4]

Source	NA	Tx (yrs)	F/U (mos)	HBsAg loss		aOR or aHR, P value
				CR (retx)	No retx	
Hadziyannis[2]	ADV	4-5	66	1/15 (6%)	13/18 **(72.2%)**	0.027 (retx vs. no retx), P=0.002
Berg[3]	TDF	> 4	36	0/8 (0%)	4/13 **(30.7%)**	
Jeng[4]	ETV/TDF	3	36	2/269 (0.7%)	40/410 **(9.8%)**	7.34 (CR+/no-retx vs. CR+/retx), P=0.0124
Garcia-Lopez[5]	ETV/TDF	8	34	0/5 (0%)	8/22 **(36.4)**	
Manolakopoulos[6]	ETV/TDF	7.5	65	0/28 (0%)	8/29 **(27.5%)**	

Among 267 no-Rx HBeAg-Neg CHB with 6-year f/u : HBsAg loss in **SR: 52.9%, VR: 21.2%, CR: 41.4%**
CGMH-LK cohort: 10-year HBsAg loss: **no-CR: 51%, CR: 27%, Rx: 5%**

1. Hall S. et al Gut 2021; 0:1-13; Hadziyannis S et al. Gastroenterology 2012; 143: 629-36; Berg T. et al J Hepatol 2017; 67:918-924; Jeng WJ et al Hepatology 2018; 68: 425-434; Garcia-Lopez M et al J Hepatol 2020 (in press), Manolakopoulos S et al, Liver Int 2021; 41:48-57; Chen CH et al TDDW 2022 Oral; Jeng WJ et al unpublished data

Current known risk factors for off-Nuc clinical relapse

Host

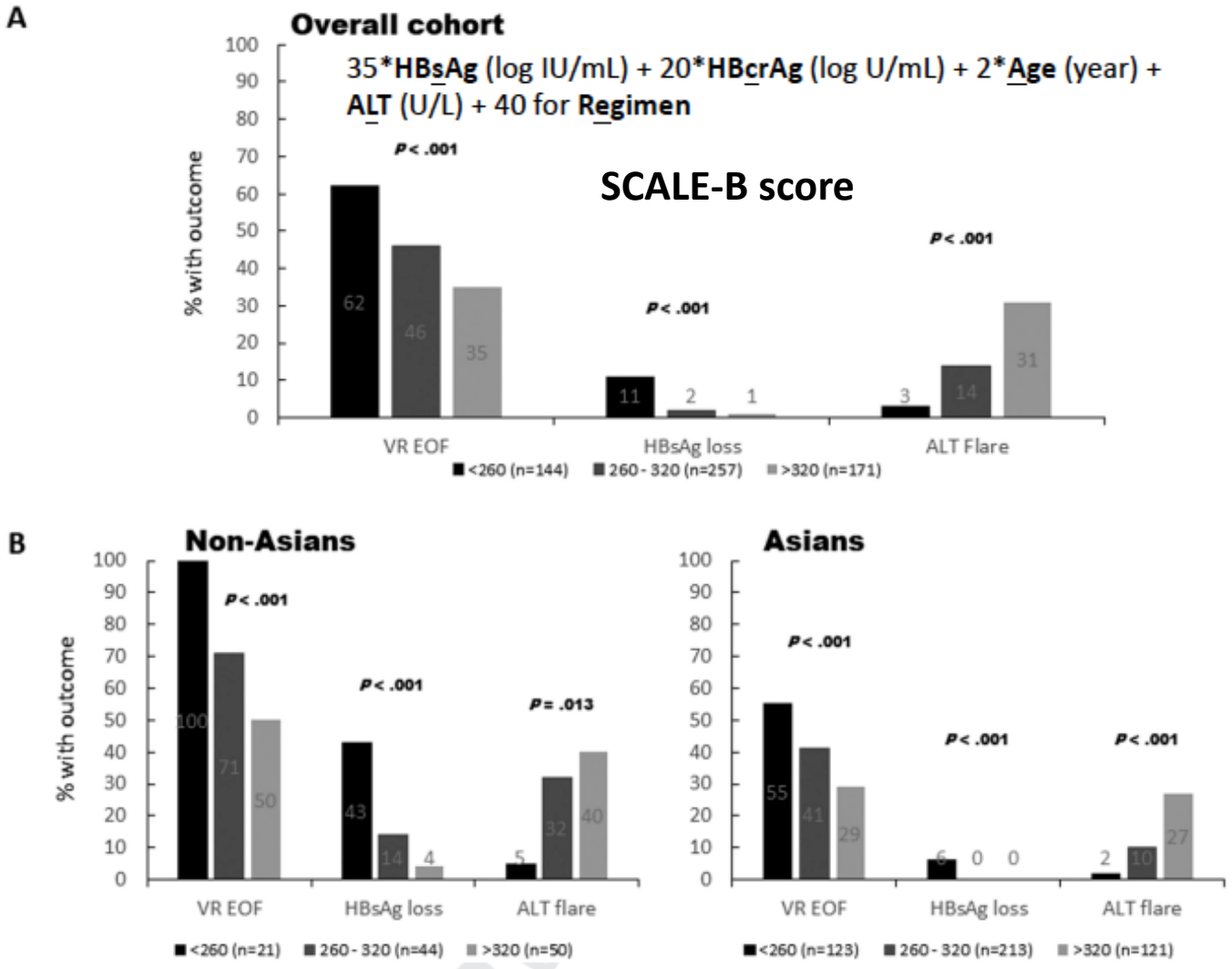
Older age

Host genetic factc

CTLA4 (rs231775); rs3077 [1]

Liver cirrhosis

Prior Tx history



-treatment

alization (lower risk

s for TDF)

(e.g. TDF) vs. ETV

ation duration? (Tx

d consolidation ≥

r risk for TDF pts)

Jeng WJ et al Hepatology. 2013 Dec;58(6):1888-96, Chen CH et al Clinical Gastroenterology and Hepatology 2015;13:1984–1992, Su TH 2018, *Chen CH et al CMI 2018 24(9): 997-1*[illegible] *Chang ML et al. Kou MT et al APT 2019; Kou MT et al Hepatol Int. 2021 Mar 4.; Tseng TN et al Clin Gastroenterol Hepatol. 2020 Nov;18(12):2803-2812; Fan R et al J Infect Dis. 2020 Jul 23;222(4):611-618; Hsu YC et al Aliment Pharmacol Ther. 2019 Jan;49(1):107-115; Sonnoveld MJ et al CGH 2021 in press*

EOT HBsAg level is not the absolute factor for finite therapy decision

Among 691 HBeAg (-) finite therapy, only 16.5% EOT HBsAg <100 IU/mL

- No correlation between EOT HBsAg level and time to relapse
- No correlation between EOT HBsAg level and flare severity
  - Using EOT HBsAg 100IU/mL for prediction of CR or flare: AUROC: 0.66, 0.6, respectively[1]
- Sustained responder by 2-year f/u

EOT HBsAg, IU/mL	ETV	TDF
<100	71%	47%
100-999	42%	29%
>=1000	35%	23%

1. Liu YC/Jeng WJ et al Liver International 2022; Liu YC et al EASL 2021 Oral presentation, submission

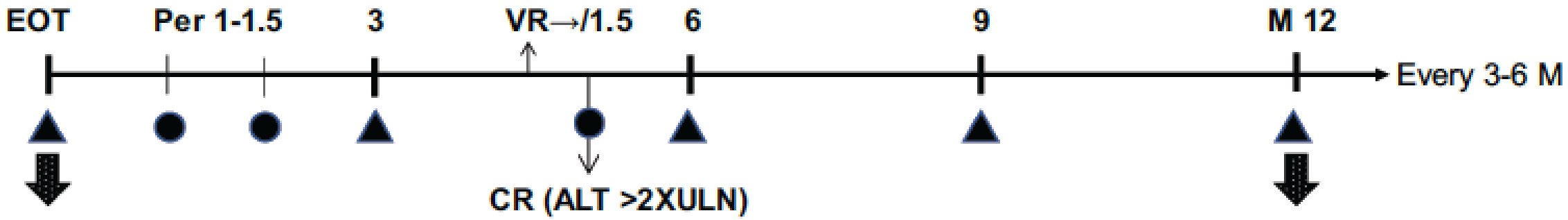
Biochemical marker(s) for retreatment

Source	Fu	Criteria to retreat
• Berg T 2017 J Hepatol 2017	2-weekly x 3mo 4-weekly ~	ALT>10X > 2 visit* or 5-10X ≥ 4wk* Bil ↑ >1.5 mg or INR ↑ > 0.5
• Papatheodoridis GV Hepatology 2018	monthly x 3mo 3-monthly~	ALT x 10X# ALT x 5X + Bil >2 mg ALT >3X + DNA >10^5 IU/mL#
• Liem KS Gut 2019	wk 4 and 6 then/6-8 wk	ALT >15X ULN (40)# ALT >5X >2 visit* ALT 200-600 for 6-8 wks*
•Garcia-Lopez J Hepatol 2020	monthly x 6 mo then/3 or 4 monthly~24mo	ALT >10X ULN x 2 visits* ALT >5-10X ULN + DNA>2000IU/mL ≥ 4wk ALT >2-5X ULN + DNA>2000IU/mL ≥ 6 mos

* follow-up >4-weekly: may be too late

 # data at one time point may be too early

Off-Nuc follow-up strategy: APASL guideline *(modified)*

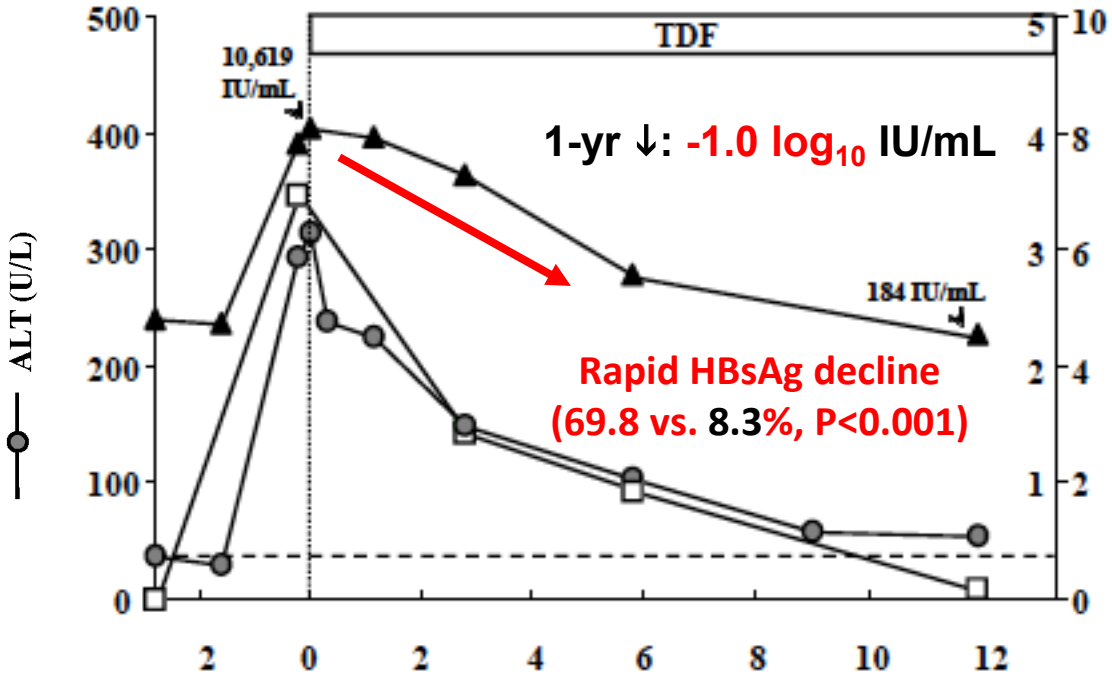


- **Monitoring is mandatory !**
  - *Off-NUC:* ALT/m x 3m; ALT+HBV DNA/3m for 1yr; then ALT/HBV per 3-6m
  - *Once virological relapse (HBV DNA>2000IU/mL)* → ***q1-1.5m ALT*** *check up*
  - **If ALT increasing or > 5X ULN: ALT, bilirubin, INR/1-2 wk for retreatment decision**

APASL guideline, Hepatol Int (2016) 10:1–98 ; Liaw YF et al Hepatology. 2021 Feb;73(2):843-852.

Retreatment in patients with host-dominating flare halts the decline of HBsAg

Virus dominating flare (Ineffective flare)

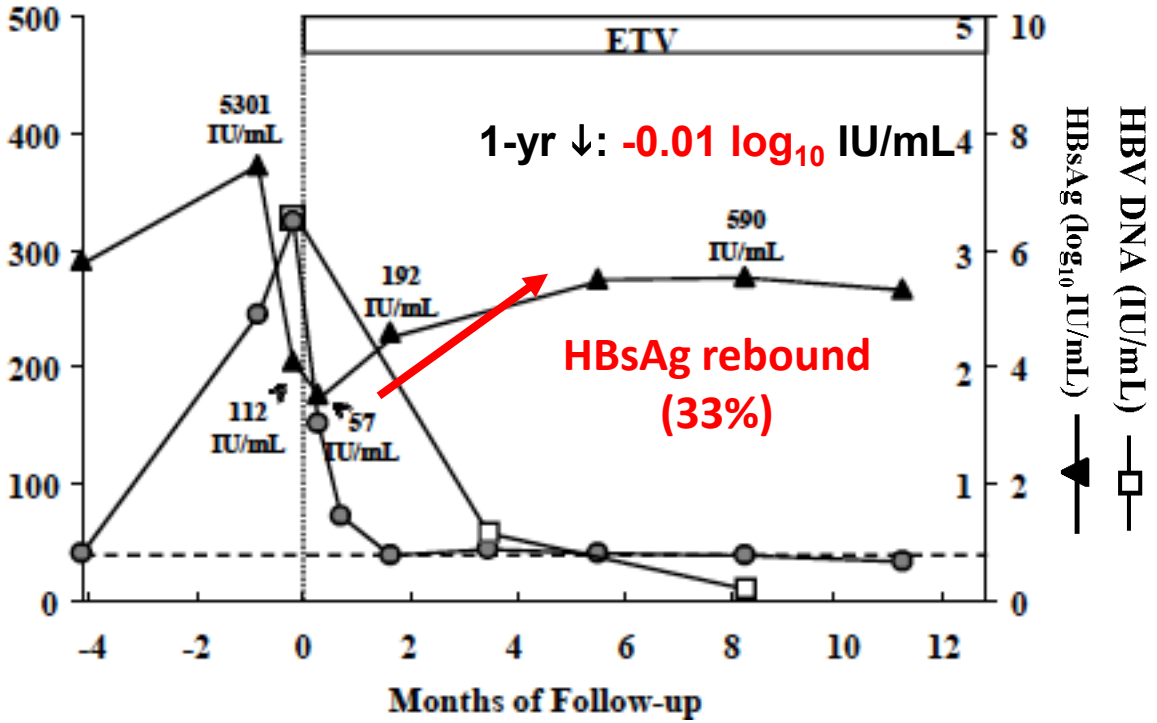


Rapid HBsAg decline: >0.5 log/6m or >1 log/1yr

HBsAg < 100 IU/mL and HBsAg loss by 3 year:

- **No retx: 20% and 6%**
- **Retx: 32% and 2%**

Host dominating flare (Effective flare)



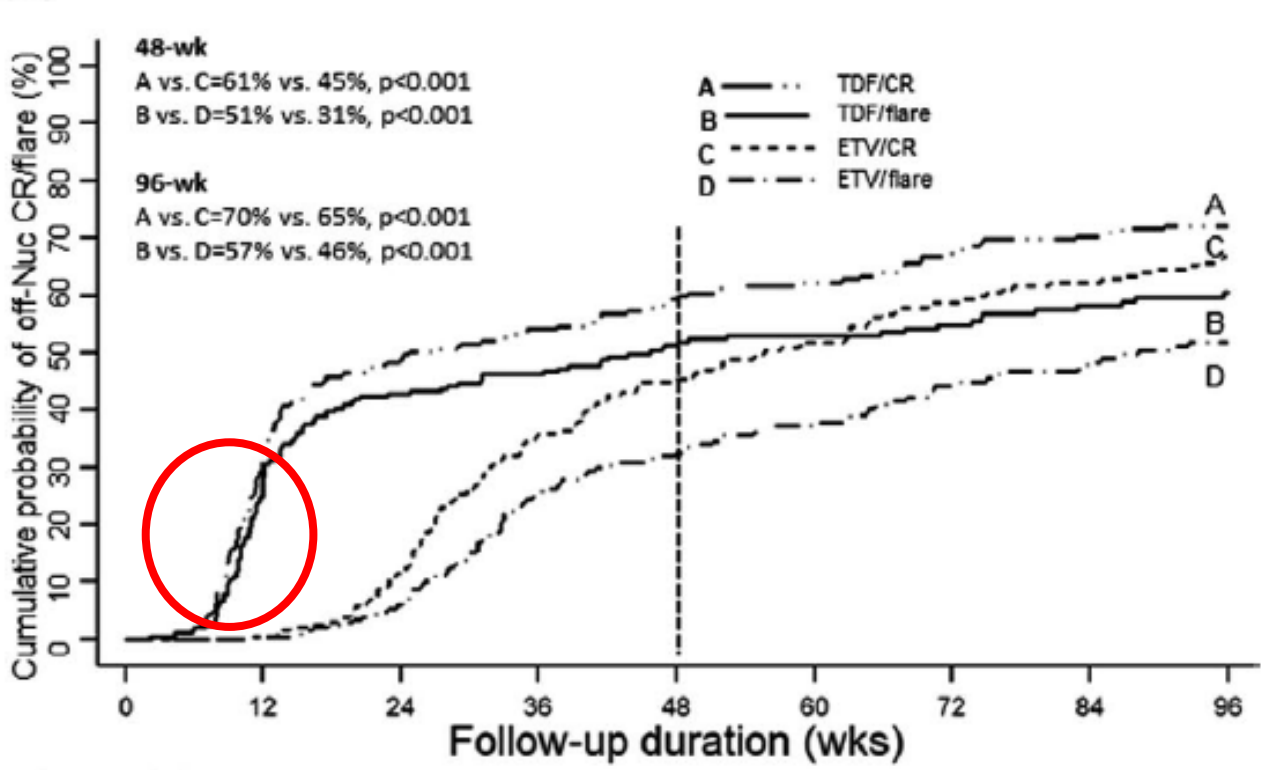
HBsAg < 100 IU/mL and HBsAg loss by 3 year:

- **No retx: 25% and 21%**
- **Retx: 12% and 0%**

Jeng WJ /Liaw YF et al J Antimicrob Chemother. 2021 Dec 24;77(1):205-212

Distinct different relapse pattern between ETV and TDF Valid in all subgroups

Off-therapy relapse and flare occurs simultaneously in off-TDF patients



Number at risk

ETV/CR	209	208	185	135	114	94	74	66	57
ETV/flare	209	148	108	96	85	71	56	49	45
TDF/CR	209	208	193	147	131	107	85	74	66
TDF/flare	209	156	118	105	94	81	68	60	51

Factors for off-therapy flare	aHR (95%CI)	P value
Age >=55	1.37 (1.14-1.64)	<0.001
Cirrhosis	1.49 (1.24-1.79)	<0.001
Prior Tx	1.37 (1.14-1.64)	<0.001
HBV Genotype C vs. B	0.69 (0.53-0.88)	0.004
PreTx HBV DNA >6 $\log_{10}$IU/mL	1.28 (1.05-1.57)	0.001
PreTx HBsAg >3 6 $\log_{10}$IU/mL	1.45 (1.12-1.81)	<0.001
TDF vs. ETV	2.35 (1.91-2.89)	<0.001
EOT HBsAg<100	0.49 (0.35-0.67)	<0.001

Liu YC/Jeng WJ et al Liver Int . 2022 Mar;42(3):551-560

Although severe flare or hepatic decompensation is rare in non-cirrhotic patients, it happens.

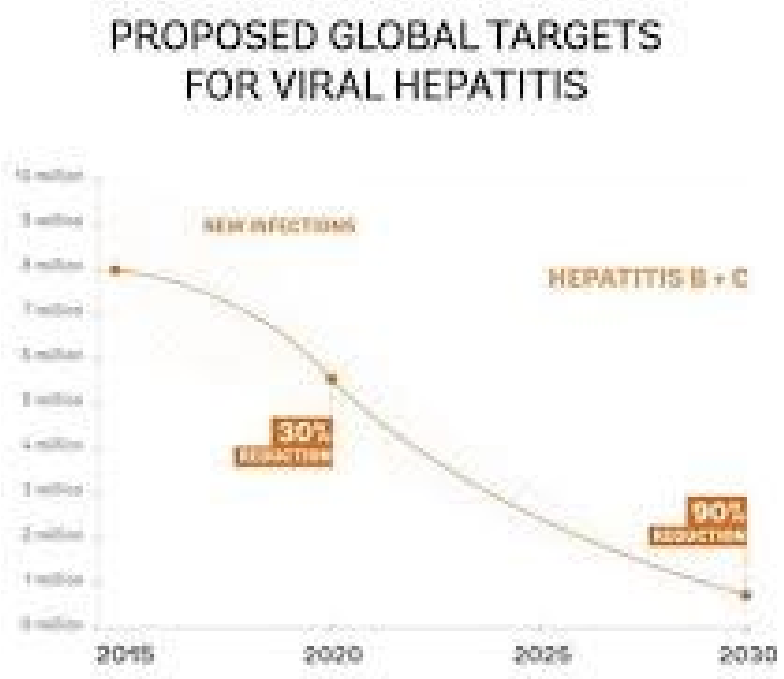
- During 1999-2020, 13 of the 1234 patients (1%) encountered hepatic decompensation after stopping Nuc [12/495 (2.4%): cirrhosis, 1/739 (0.1%): non-cirrhosis→ the non-LC Pt successfully recovered] [1]
  - 7 of 13 not adhered to follow-up protocol
  - Off-Nuc hepatic decompensation risk factor: **Cirrhosis** [aHR: 20.5 (2.65-159.37), P=0.004], **Off-TDF** [vs. ETV, aHR: 5.53 (1.73-17.69), P=0.004]
- 5 of 411 (1.2%) non-LC hepatic decompensation, 8-year: 3%[2]
  - LAM or ETV, 3/148 (2%) HBe+ -> one mortality, 2/263 HBe- (0.76%)
- 4 of 375 (1%) HBeAg Neg non-LC hepatic decompensation (T.Bil>2 or INR prolonged 3 sec)
  - 2 ETV, 2TDF

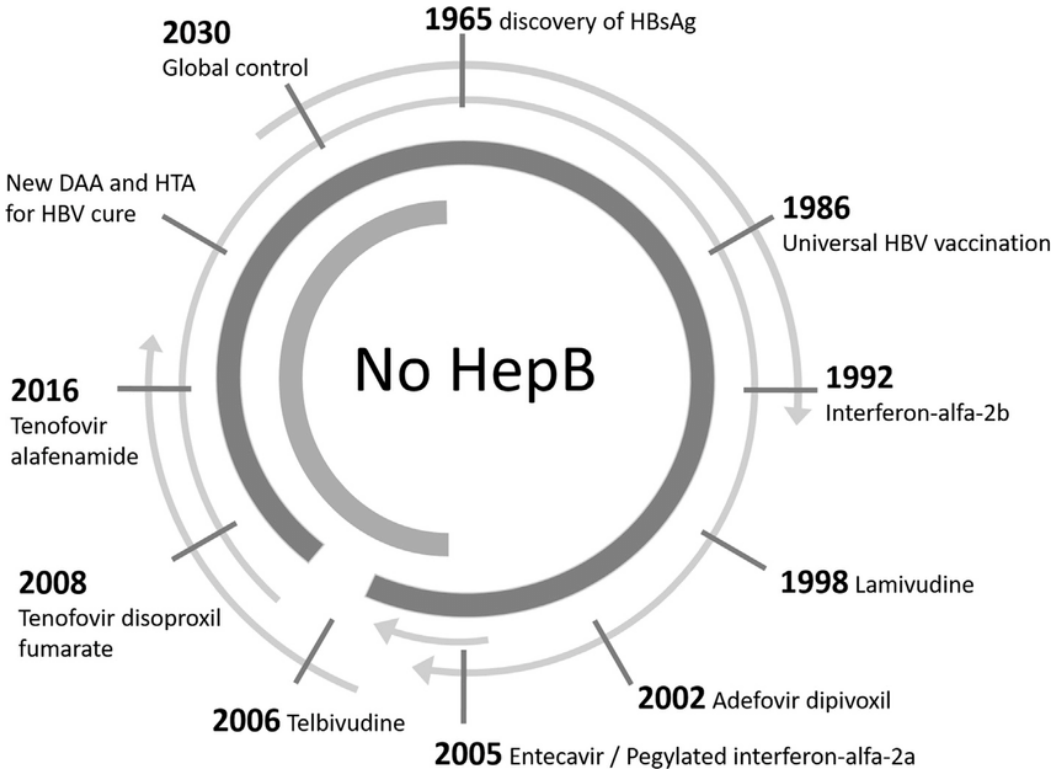
Same site

1. Liu YC/Jeng WJ et al Liver Int . 2022 Mar;42(3):551-560; 2. Chen CH et al, Clin Microbiol Infect . 2018 Sep;24(9):997-1003. 3. Ma TL et al, PLoS One . 2019 Oct 4;14(10):e0222221

Summary

- Finite therapy in HBeAg negative non-cirrhotic patients is considerable if stringent follow-up being provided and with well mutual communication between physicians and patients, about the risk and benefit.
- Retreatment criteria is still await to be explored: how to be safe but not too early to halt the chance toward functional cure





Thank you for your attention!