National University Health System

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"When can we stop NUCs in patients with Chronic Hepatitis B?"

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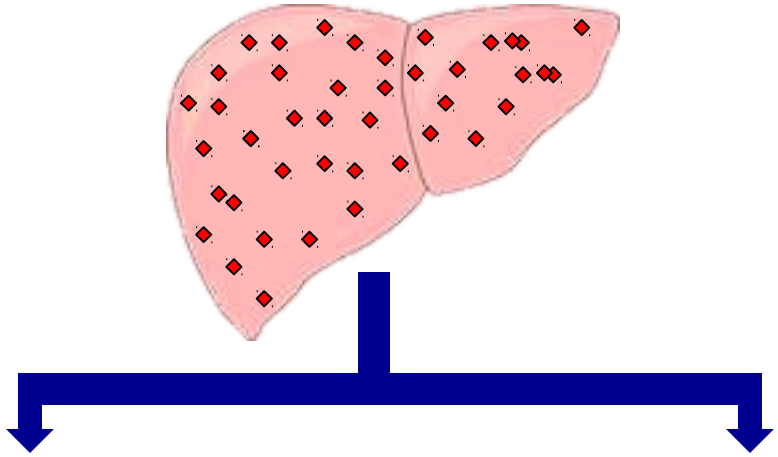
Singapore

Disclosures

- Advisory Board
  - Bristol Myer Squibb
  - MSD
  - Gilead
  - Roche
  - Abbott
  - Abbvie
- Speaker’s Bureau
  - Bristol Myer Squibb
  - MSD
  - Roche
  - Abbott
  - Abbvie
  - Gilead

Approved Treatments available



Strategy 1

Nucleos(t)ides

- Lamivudine
- Adefovir
- Telbivudine
- Entecavir*
- Tenofovir*

Strategy 2

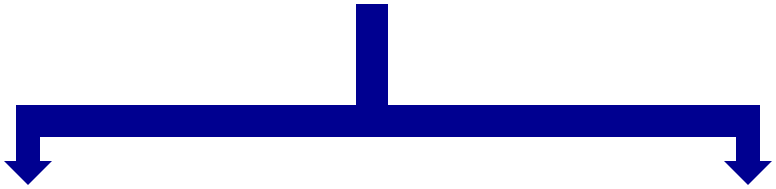
Immunomodulators

- Standard interferon
- Peg-interferon*

*Recommended by guidelines

Prescribing patterns for CHB antivirals

2614 mono-infected CHB patients from 34 hospitals in Spain, 2009



Nucleos(t)ides

- Lamivudine 34.8% (27.4–48.3%)
- Adefovir 21.0% (10.3–26.5%)
- Telbivudine 0.8% (0.0–1.5%)
- Entecavir* 25.8% (18.5–32.7%)
- Tenofovir* 16.0% (5.9–21.4%)

Immunomodulators

- Standard interferon
- Peg-interferon* 1.7% (0.3–4.4%)

Total NUCs = 98.4%

Requena, *Eur J Hosp Pharm* 2013;**20**:174-179

Long term therapy is the norm with NUCs…but can we stop therapy?

- After HBeAg seroconversion
  - Can we stop therapy and maintain remission?
- HBeAg neg CHB after viral suppression
  - Can we achieve remission if we stop NUCs?
  - When to stop?
- HBsAg seroclearance
  - Is this sufficient to stop therapy?

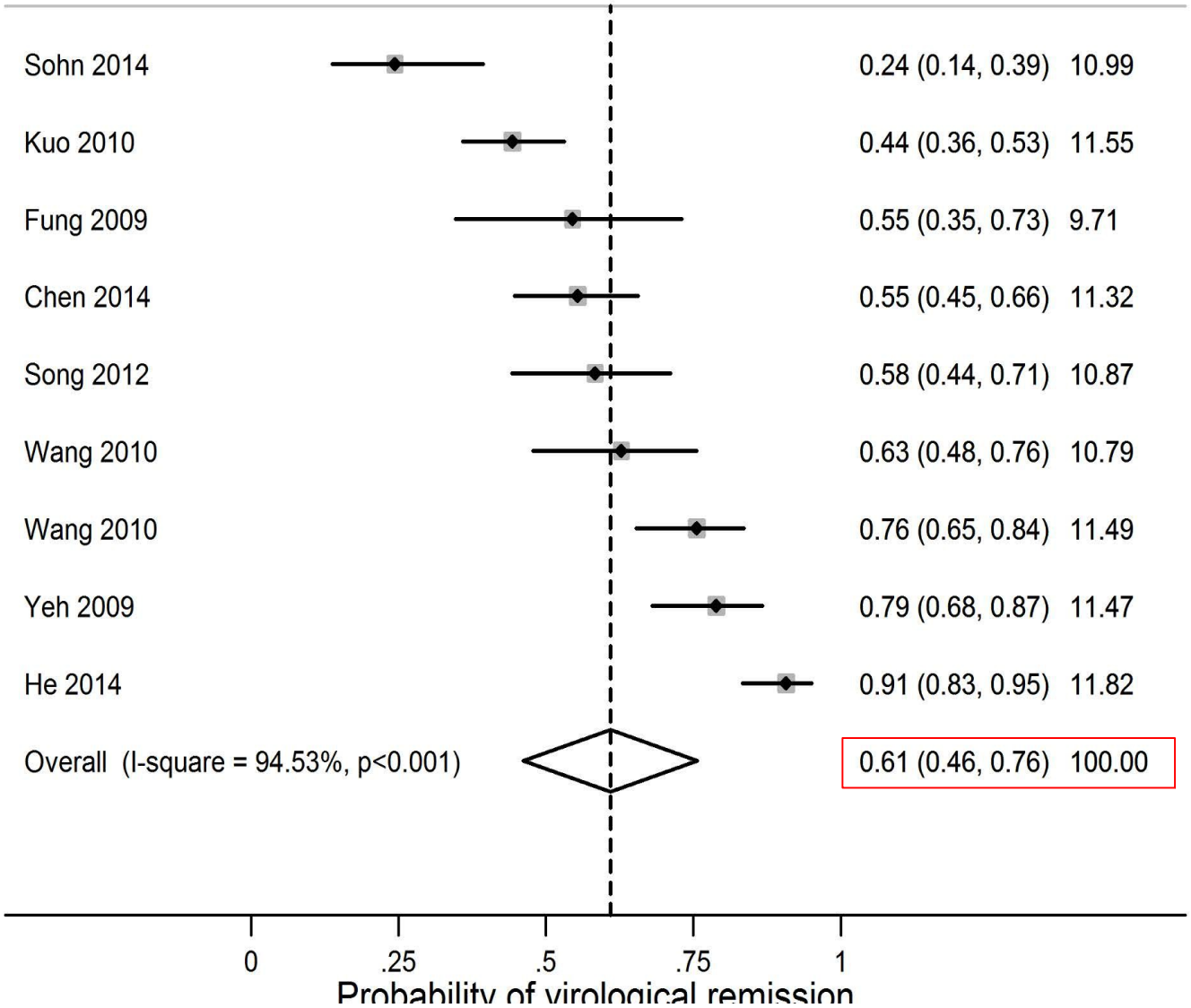
Guideline recommendations on stopping NUC therapy

Guideline	HBeAg positive	HBeAg negative	Cirrhosis
AASLD 20161	• HBeAg seroconversion with ≥12m consolidation therapy and normal ALT with undetectable HBV DNA • HBsAg loss	• HBsAg loss	• Not recommended
EASL 20122	• HBeAg seroconversion with 12 months consolidation therapy	• No recommendation	• Not recommended
APASL 20153	• HBeAg seroconversion with undetectable HBV DNA > 12 months, preferably 3 years	• HBsAg loss with annti HBs seroconversion, OR • HBsAg loss after 12 months consolidation therapy OR • 2 years undetectable HBV DNA , 3 separate occasions 6 months apart	• Can consider in compensated cirrhosis with careful monitoring plan

1 Terrault NA et al. Hepatology. 2016;63:261–283; 2 EASL, J Hepatol. 2012;57:167–185; 3 Sarin et al, Hepatol Int.2016;10:1–98.

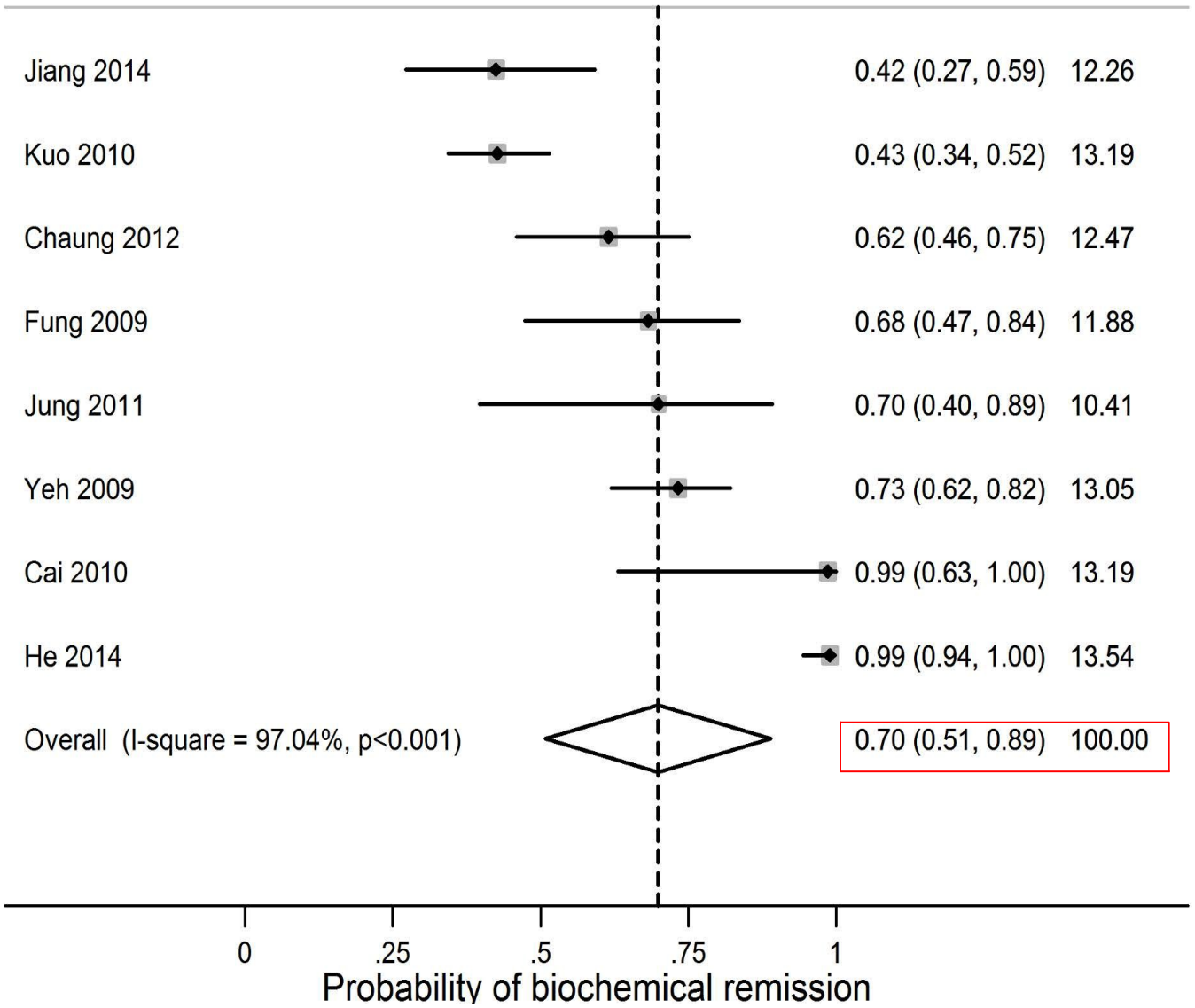
HBeAg seroconversion

Meta-analysis - HBeAg positive: Virological Remission



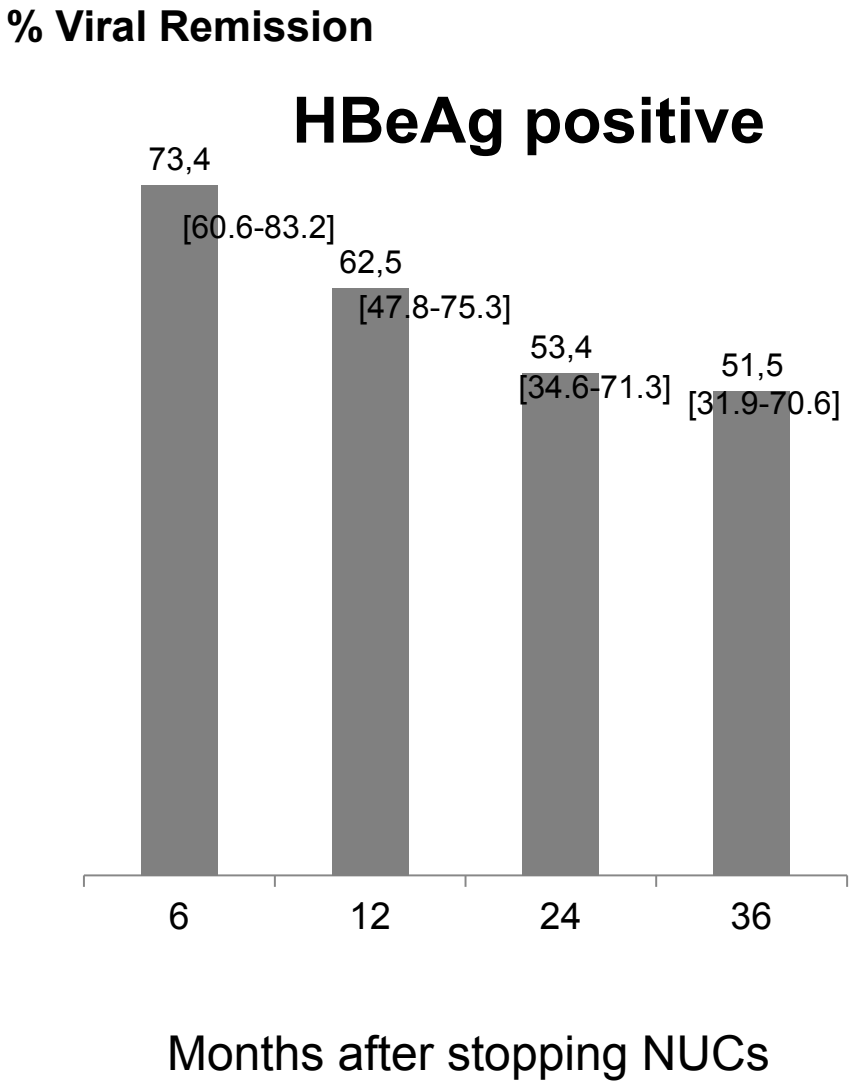
Papatheodoridis G et al, Hepatology 2016; 63(5): 1481-92

Meta-analysis - HBeAg positive: Biochemical Remission



Papatheodoridis G et al, Hepatology 2016; 63(5): 1481-92

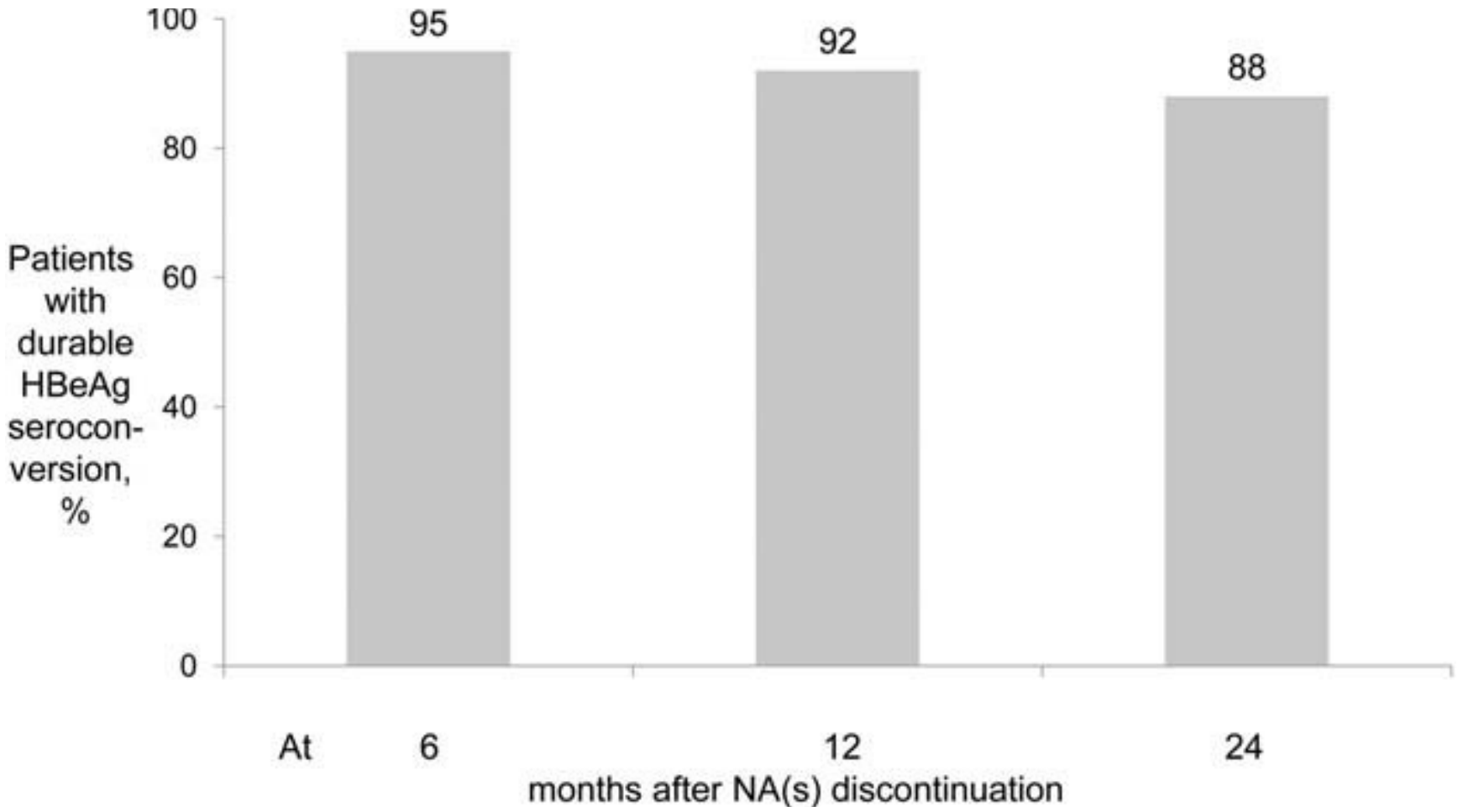
Meta-analysis - Durable viral remission after stopping NUCs in HBeAg positive CHB



- Viral Remission:
  - HBV DNA ≤ 2 x 104 IU/ml
- Biochemical Remission
  - ALT< ULN (14 studies)
  - ALT<1.25xULN (1 study)
  - ALT<2xULN (6 studies)

Papatheodoridis G et al, Hepatology 2016; 63(5): 1481-92

Meta-analysis - Durability of HBeAg seroconversion



Papatheodoridis G et al, Hepatology 2016; 63(5): 1481-92

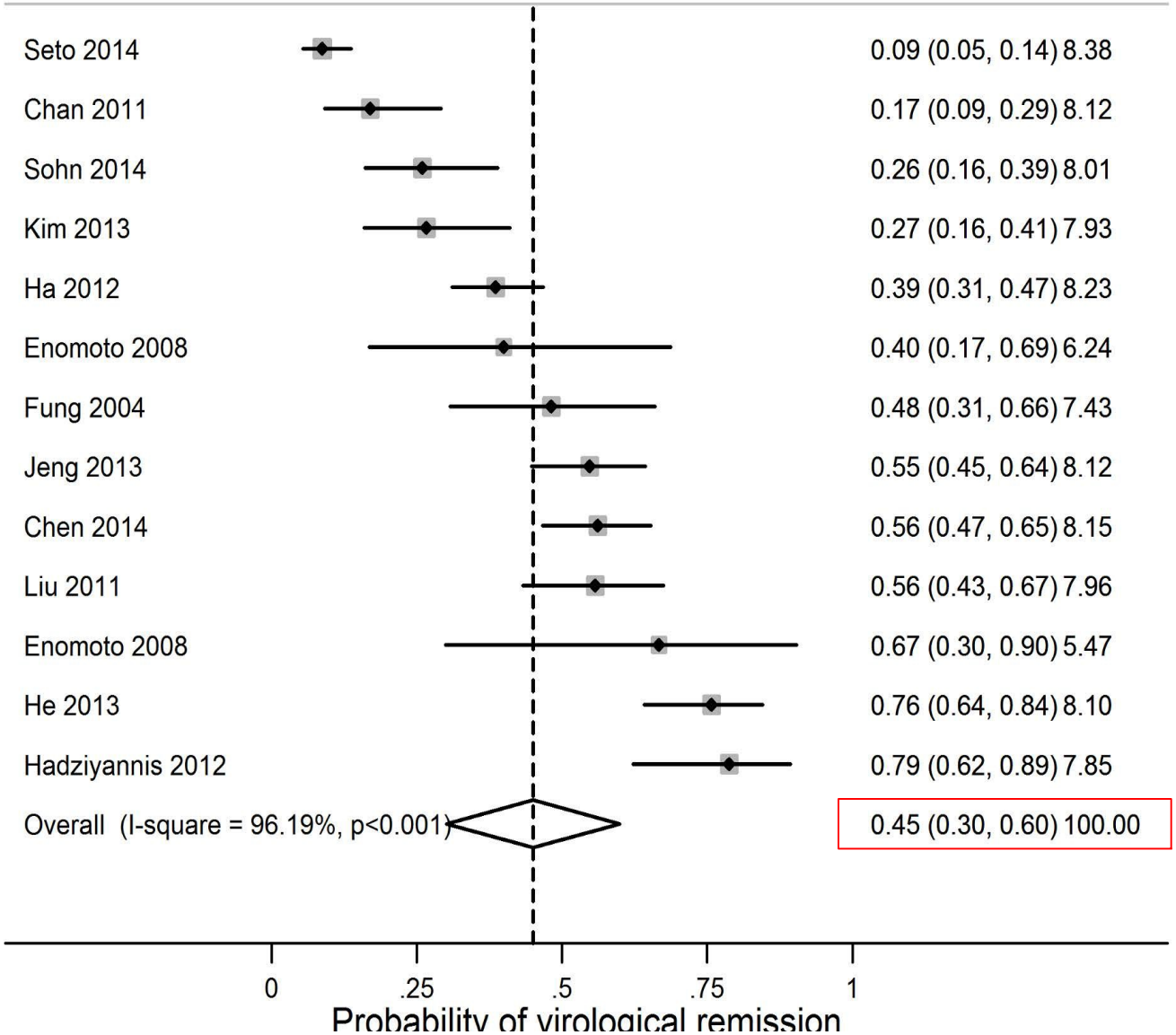
Meta-analysis - Factors associated with durable VR at 12 Months After stopping NUCs: HBeAg positive CHB

Characteristic	Prob of durable response	Odds Ratio	P value
HBeAg-positive patients			
VR defined by HBV DNA			0.289
<200 IU/mL	42.0 (16.6-72.4)	1	
<2000 IU/mL	71.2 (52.2-84.8)	3.41 (0.74-15.71)	
<20,000 IU/mL	63.1 (32.8-85.7)	2.37 (0.39-14.33)	
Duration of on-NA VR			0.544
<12 months	53.2 (27.4-77.4)	1	
12-24 months	72.0 (49.2-87.2)	2.26 (0.52-9.84)	
>24 months	60.3 (27.1-86.1)	1.33 (0.22-7.98)	
Duration of consolidation therapy after HBeAg seroconversion			0.928
<12 months	62.6 (38.5-81.8)	1	
≥12 months	64.1 (42.2-81.3)	1.06 (0.28-4.02)	

Papatheodoridis G et al, Hepatology 2016; 63(5): 1481-92

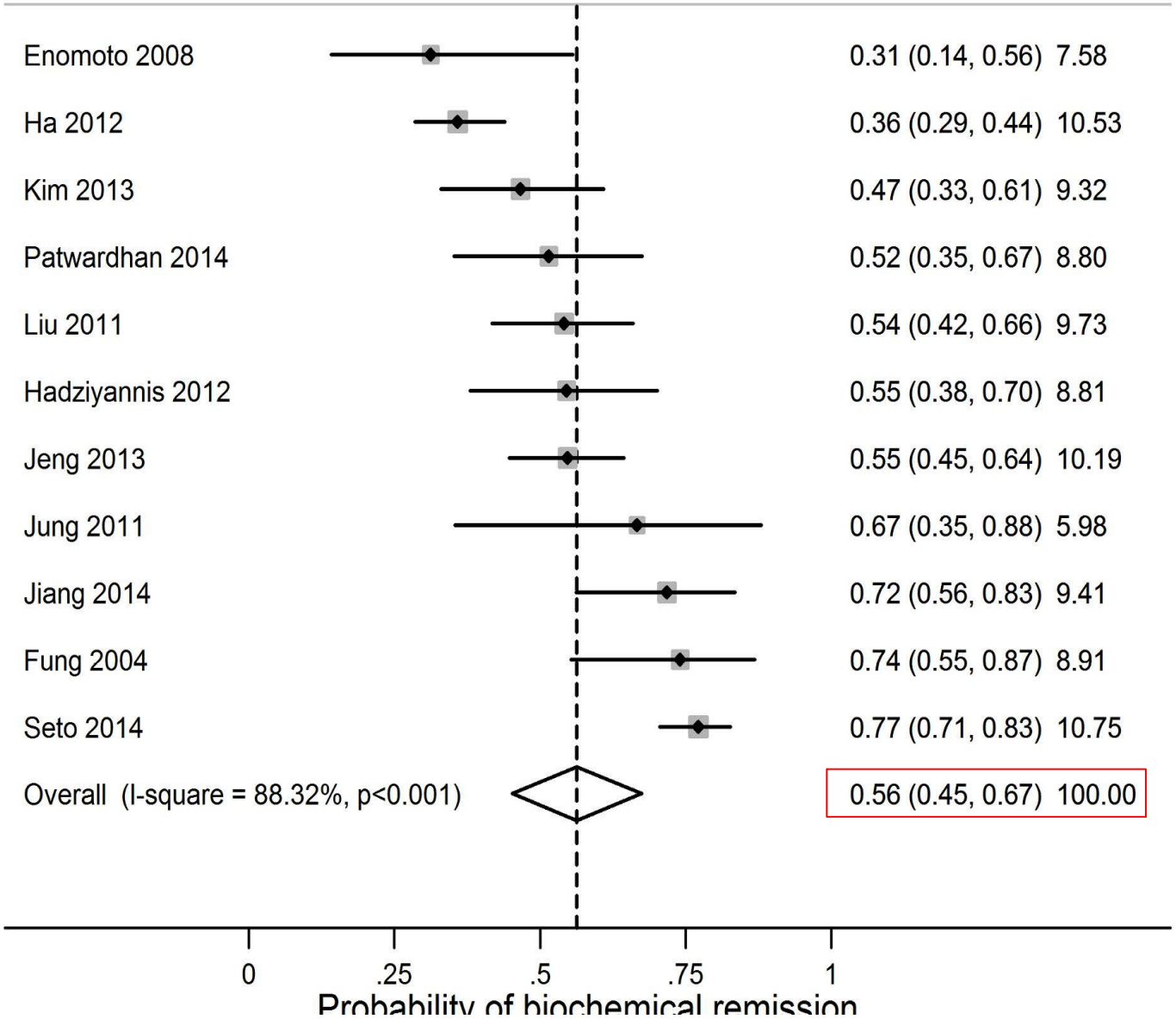
HBeAg negative CHB

Meta-analysis - HBeAg negative: Virological Remission



Papatheodoridis G et al, Hepatology 2016; 63(5): 1481-92

Meta-analysis - HBeAg negative: Biochemical Remission



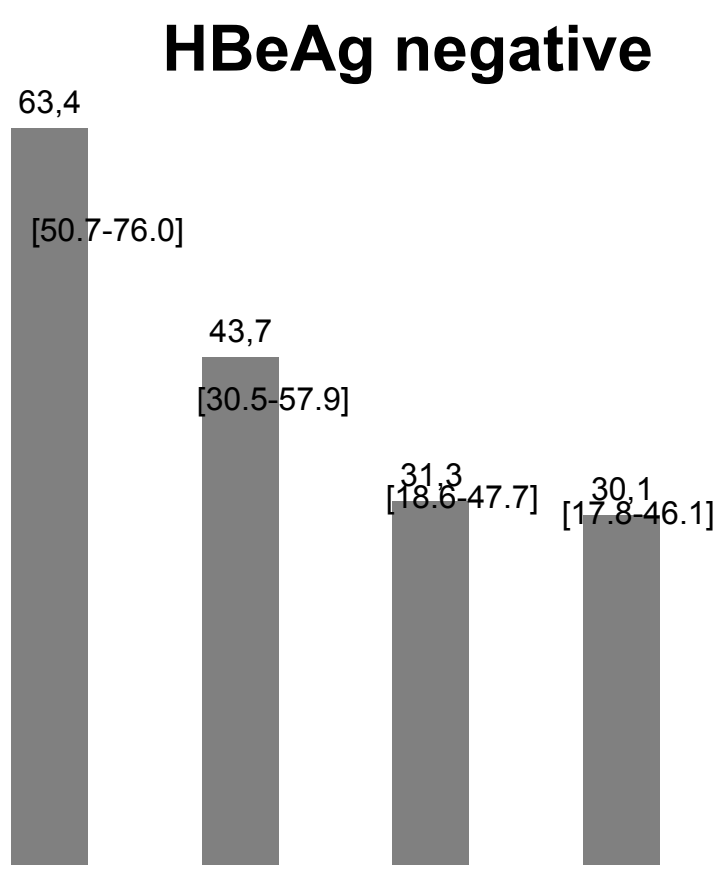
Papatheodoridis G et al, Hepatology 2016; 63(5): 1481-92

Meta-analysis - Factors associated with durable VR at 12 Months After stopping NUCs: HBeAg neg CHB

Characteristic	Prob of durable response	Odds Ratio	P value
HBeAg-negative patients			
VR defined by HBV DNA			0.513
<200 IU/mL	29.3 (10.8-58.7)	1	
<2000 IU/mL	48.0 (30.6-65.9)	2.24 (0.53-9.41)	
Duration of on-NUC VR			0.005
<24 months	35.6% (24.6-48.2)	1	
>24 months	75.0% (51.1-89.6)	5.45 (1.68-17.70)	

Papatheodoridis G et al, Hepatology 2016; 63(5): 1481-92

Meta-analysis - Durable viral remission after stopping NUCs in HBeAg negative CHB



- Viral Remission:
  - HBV DNA ≤ 2 x 104 IU/ml
- Biochemical Remission
  - ALT< ULN (14 studies)
  - ALT<1.25xULN (1 study)
  - ALT<2xULN (6 studies)

Papatheodoridis G et al, Hepatology 2016; 63(5): 1481-92

Studies evaluating APASL stopping rules for NUCs in HBeAg neg CHB

- 2 years undetectable HBV DNA , 3 separate occasions 6 months apart

Study	Number	Viral Relapse	Clinical Relapse
Ha et al 48	145	95 (65.5%)	93 (64.1%)
Jeng et al 24	95	55 (57.9%)	43 (45.3%)
kim et al 49	45	33 (73.3%)	24 (53.3%)
Chen et al 22	169	108 (64.3%)	87 (51.6%)
Jiang et al 50	39	25 (64.1%)	19 (48.7%)
Lee et al 51	64	50 (77.7%)	26 (41.9%)
Seto et al 31	184	168 (91.4%)	42 (22.8%)
Jung et al 52	68	37 (54.4%)	19 (28.9%)
Overall (total)	809	571	353
Overall (%)		**70.5%**	**43.6%**

- **Viral relapse Serum HBV DNA≥2000 IU/ml after stopping treatment in patients with virological response**
- **Clinical relapse Viral relapse along with ALT ≥ 2x ULN**

HBsAg level to predict relapse

study	n	qHBsAg cutoff	Sensitivity	Specificity	AUROC
Chen1	105	≥205.5	97%	73.7%	0.861
Ge2	204	≥1443	88.2%	30.2%	0.603
Liang3	73	>1000	NA	NA	0.68

1Chen, J Hepatol 2014; 61(3): 515-22
2Ge, World J Gastroenterol 2015; 21(28): 8653-9
3Liang, Aliment Pharmacol Ther 2011; 34(3): 344-52

Safety of stopping NUCs in cirrhosis

Clinical Event	Risk
Decompensation	0.8% (2/243)
jaundice	2.5% (6/243)
Death	0.4% (1/243)

Meta-analysis

Papatheodoridis G et al, Hepatology 2016; 63(5): 1481-92

APASL stopping rule for HBeAg neg cirrhosis

Clinical Event	Risk
Severe flares	16.2% (15/94)
Decompensation	8.2% (8/94)
Death	1.1% (1/94)

Chang, Clin Gastroenterol Hepatol 2015; 13(5): 979-86.

Clinical Event	Risk with stopping ETV	Risk with stopping TDF
Clinical relapse	43.6% (17/39)	47.4% (18/34)
jaundice	NA	14.7% (5/34)
Decompensation	2.6% (1/39)	5.9% (2/34)

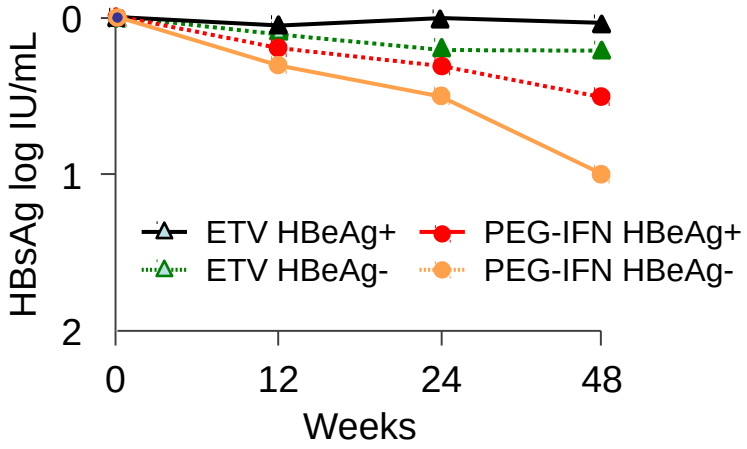
Jeng, Hepatology 2013;58:1888-1896
Jeng, Clin Gastroenterol Hepatol 2016;14(12):1813-1820

Benefits of stopping NUCs

- Relatively safe (esp non-cirrhosis)
- Avoid long term therapy
- Convert from active CHB to viral/clinical remission
- Cost savings
- HBsAg seroclearance?

HBsAg decline with NAs

- Slower on-treatment HBsAg decline with NUCs than with PEG-IFN1
- Modelling predicts 36-39y of NUCs to achieve HBsAg loss3



- HBsAg reduction during NA therapy is most pronounced in Year 1 and then remains stable2
- The mechanism of HBsAg decline during NA therapy is unclear, but HBsAg reduction may reflect a better degree of host immune control against the virus2

1. Adapted from Reijnders R, et al. J Hepatol 2011;54:449–54;
2. Tseng T-C, et al. J Gastroenterol 2013;48:13–21.
3. Zoutendijk R, et al. J Infect Dis 2012;206:974–80

ETV: entecavir; HBeAg: hepatitis B ‘e’ antigen;
PEG-IFN: pegylated interferon

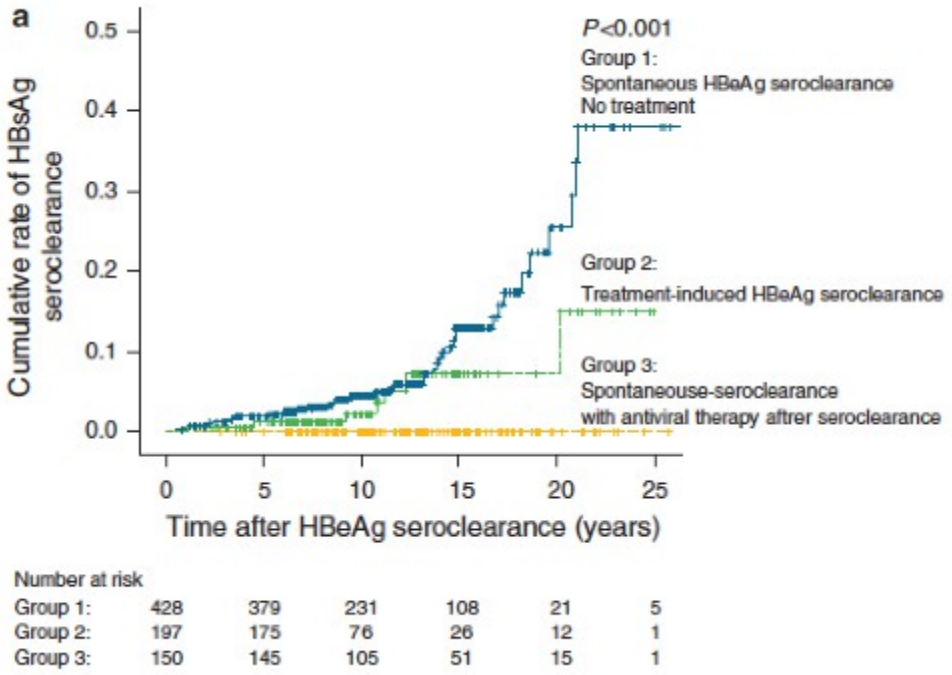
Poor HBsAg clearance rate in Asian HBV patients on NUC treatment

Study	n	Median FU	Treatment	HBsAg clearance
Seto et al, JGH 2014	222	5y	ETV	0.45%
Kim et al, Gut 2013	5409	6y	LAM or ETV	2%

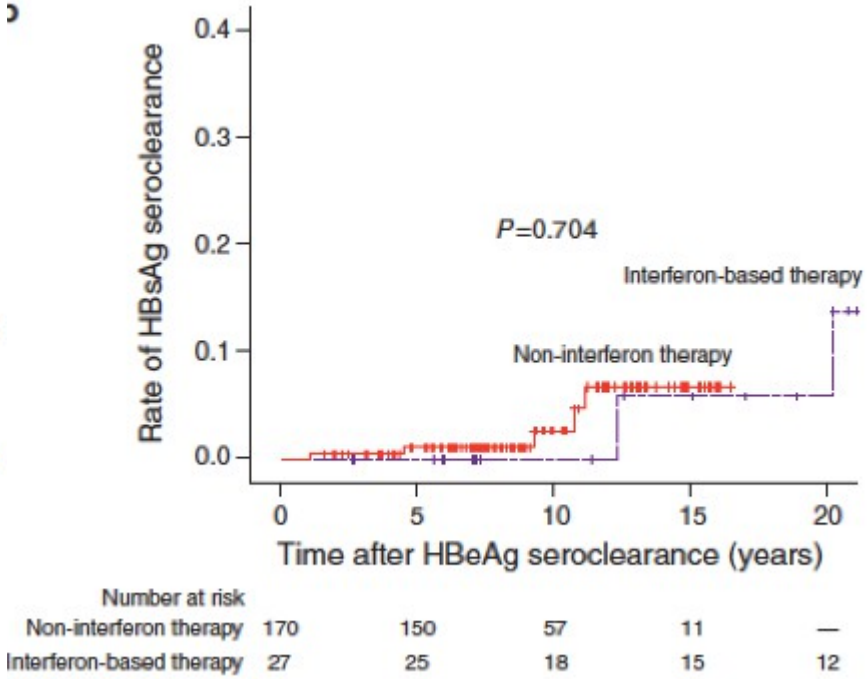
Seto, J Gastro Hep 2014;29:1028–1034
Kim, Gut. 2013 Oct 25. doi: 10.1136/gutjnl-2013-305517

Possibility of HBsAg seroclearance after HBeAg seroconversion

Spontaneous vs treatment induced HBsAg seroclearance



IFN vs NUC induced HBsAg seroclearance



Fung, Am J Gastro Sept 2014;109:1764–1770

Durability of HBsAg seroclearance

- Multivariate analysis of 5409 CHB patients show HBsAg seroconversion is a significant protector against HBsAg seroreversion [HR=0.21 (95% CI 0.02 to 0.89), p= 0.03]
- A sustained response, which was defined as HBsAg negativity combined with undetectable HBV DNA, was observed in more than 90% of the patients at most of the time points during follow-up:

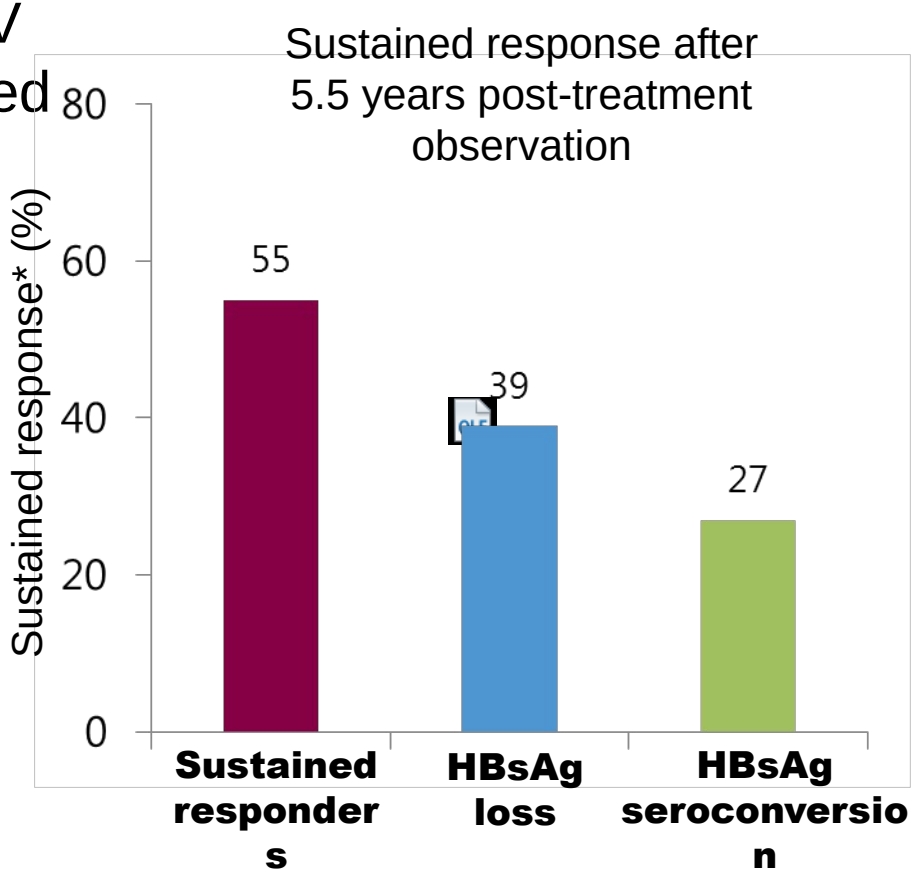
1y	**2y**	**3y**
66/73	51/55	31/33
90.4%	92.7%	93.9%

Kim G-A, et al. Gut 2013;**0**:1–8.

qHBsAg as a predictor of HBsAg seroclearance during NUC therapy

Durability of response to ADV in HBeAg-negative patients from Greece

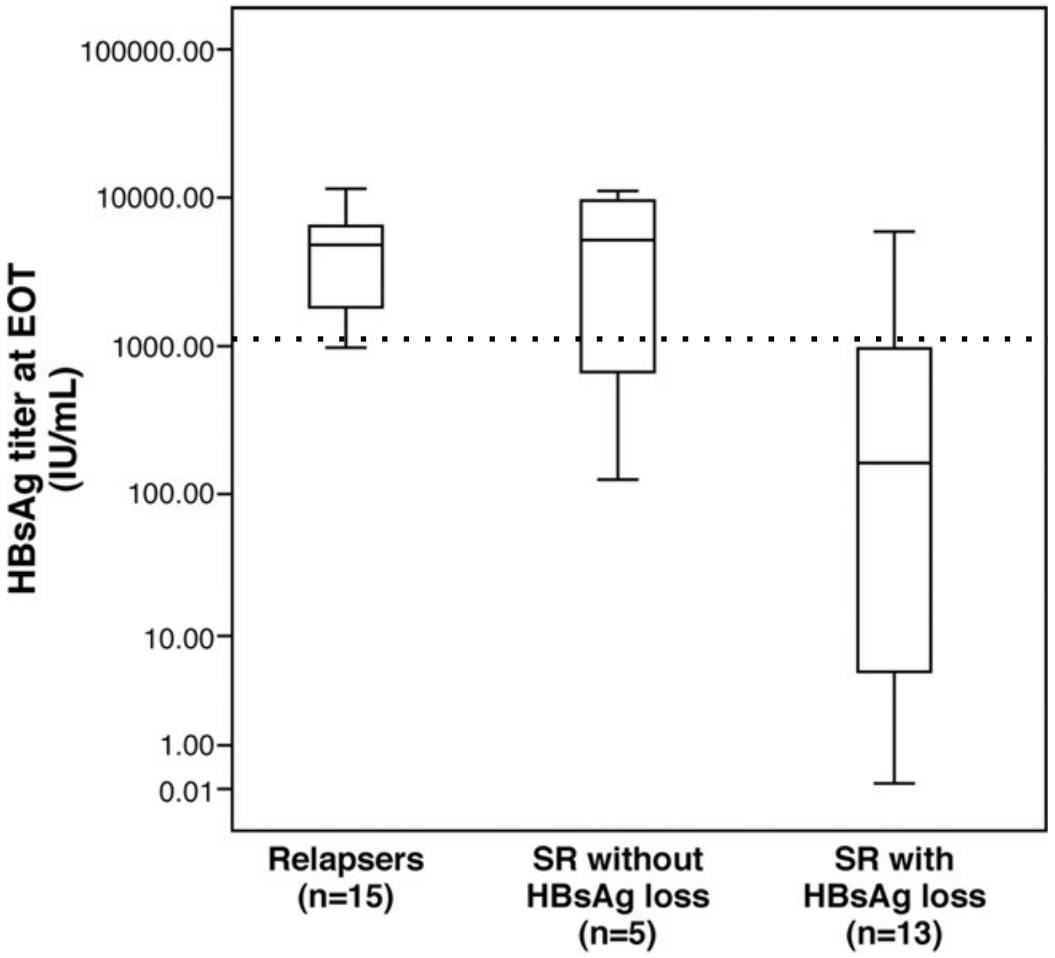
- 33 patients with undetectable HBV DNA levels who had discontinued ADV therapy were followed for 67–72 months
- Initially, 100% had a virological relapse and 76% had a hepatitis flare
- The 5.5-year rate of HBsAg clearance in patients with a sustained response was 72%
- No patient achieving HBsAg loss reverted to HBsAg positivity
- 69% of patients with HBsAg loss, achieved HBsAg seroconversion



Hadziyannis SJ, et al. Gastroenterol 2012;143:629–36.

*Persistently HBV DNA undetectable and persistently normal ALT; ADV: adefovir

Predictors of HBsAg loss: qHBsAg at end of therapy



Multivariate analysis by timepoint:

- No previous IFN use
- Higher baseline ALT
- Lower baseline HBV DNA
- Higher end of treatment ALT level
- Lower end of treatment qHBsAg

Multivariate analysis combining timepoints:

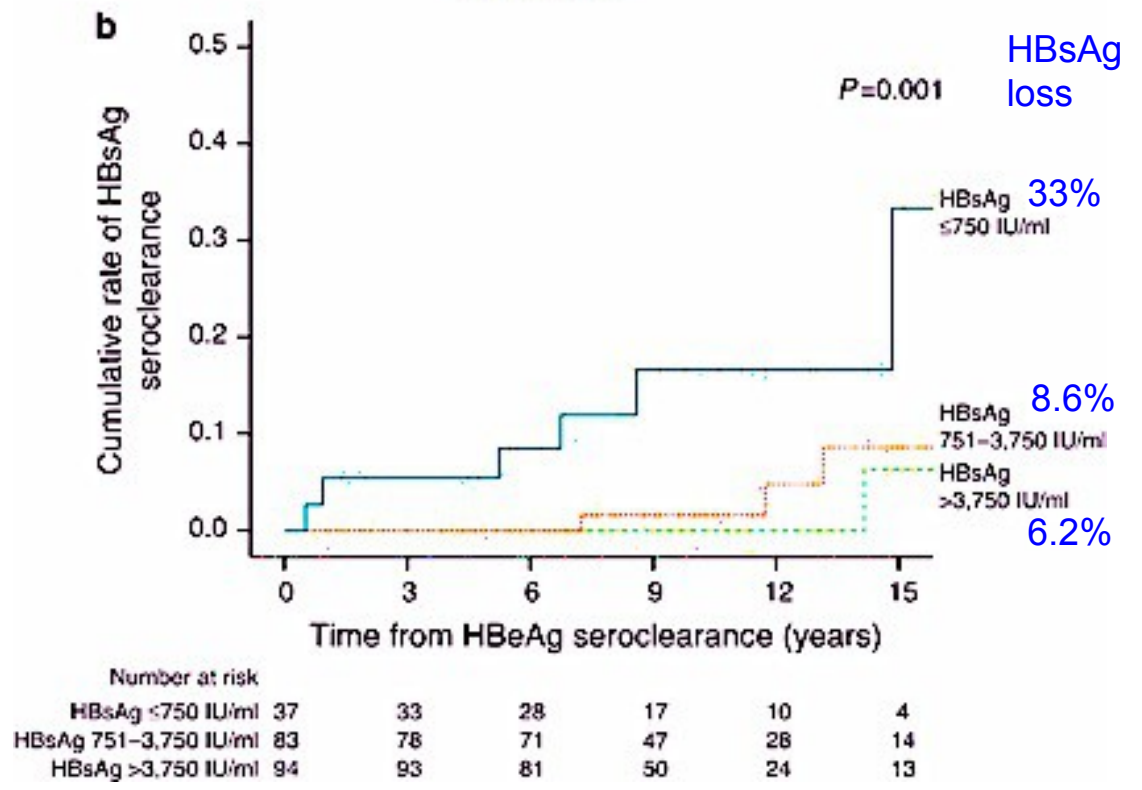
- No significant variables

SR= sustained response
- Persistent Undetectable HBV DNA
- HBV DNA<2000Iu/ml + normal ALT

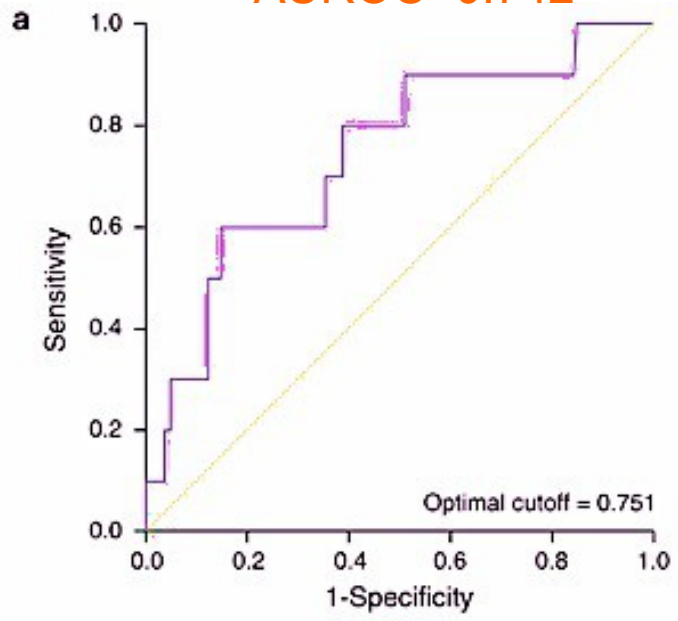
Hadziyannis SJ, et al. *Gastroenterology.* 2012;143:629-636.

qHBsAg as a predictor of HBsAg loss 1y after HBeAg seroconversion

n=775 HBeAg seroconverters (45% on antiviral therapy)



qHBsAg cutoff ≤750 IU/ML
AUROC=0.742

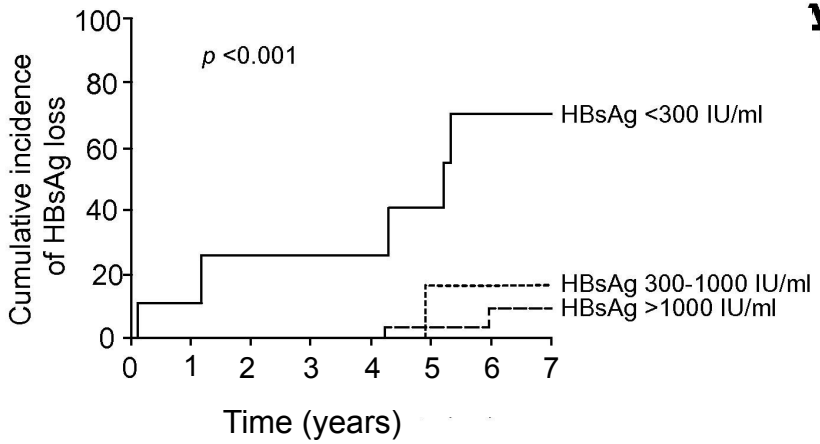


HBsAg level 1y post HBeAg seroconversion for predicting HBsAg loss

Fung, Am J Gastro Sept 2014;109:1764–1770

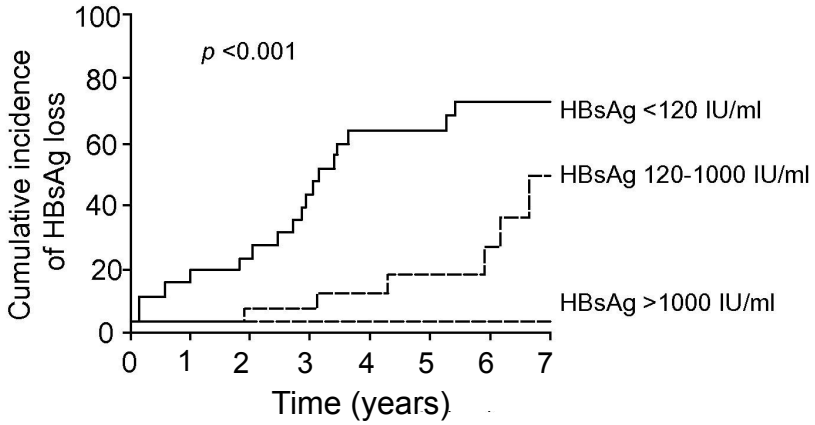
qHBsAg as a predictor of HBsAg loss at the end of lamivudine treatment

HBeAg positive



No. at risk HBsAg								
<300 IU/ml	9	6	6	6	6	4	2	1
300-1000 IU/ml	13	11	10	10	9	5	3	2
>1000 IU/ml	61	49	38	32	30	20	15	7

HBeAg negative

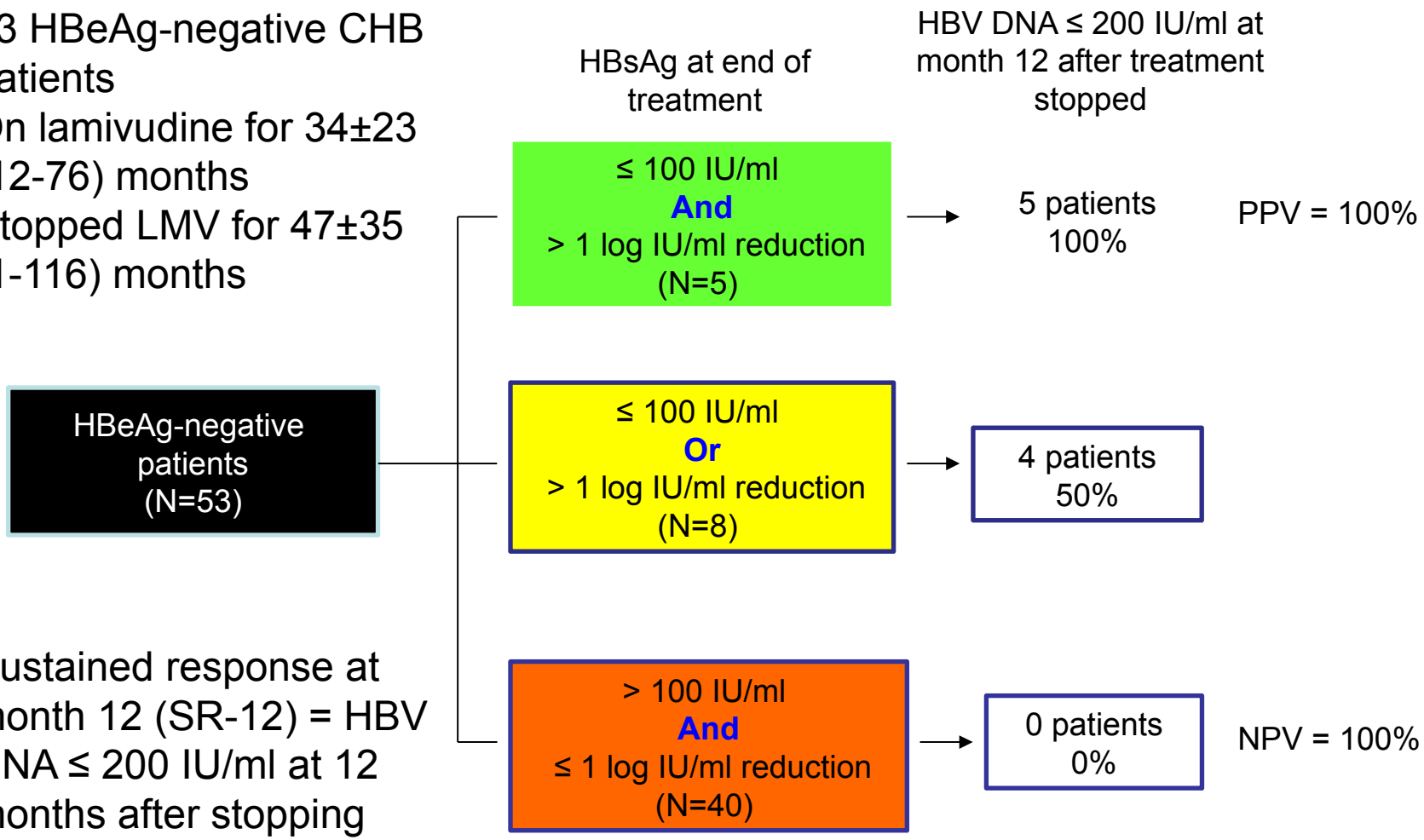


No. at risk HBsAg								
<120 IU/ml	24	20	19	14	9	8	4	4
120-1000 IU/ml	42	31	24	20	16	10	8	4
>1000 IU/ml	39	35	26	21	17	14	8	2

Chen, J Hepatol 2014;61:515–522

Serum qHBsAg at end of treatment can predict response at 12 months post-treatment

- 53 HBeAg-negative CHB patients
- On lamivudine for 34±23 (12-76) months
- Stopped LMV for 47±35 (1-116) months



- Sustained response at month 12 (SR-12) = HBV DNA ≤ 200 IU/ml at 12 months after stopping lamivudine

Chan, Antivir Ther. 2011;16(8):1249-57

HBsAg level to predict HBsAg loss at the end of NUC therapy

study	n	qHBsAg cutoff	Sensitivity	Specificity	AUROC
Chen1	105	≤117.3	95%	76%	0.91
Chan2	53	<100 IU/ml	78%	96%	0.91
		↓ 1 log IU/ml	78%	96%	0.96
Hadziyannis3	39	≤1000 IU/ml	?	?	?

In whom can we stop long term antiviral therapy?

Those who have low quantitative HBsAg level – how low?

- **<1000 IU/ml?**
- **<100 IU/ml?**
- **> 1 log reduction?**
- **Combination of low qHBsAg + reduction in qHBsAg level?**

1Chen, J Hepatol 2014; 61(3): 515-22
2Chan, Antivir Ther. 2011;16(8):1249-57
3Hadziyannis, Gastroenterol 2012;143:629–36

Conclusions

- In HBeAg positive CHB, stopping NUC therapy after seroconversion
  - Viral remission in 61%
  - Biochemical remission in 70%
  - Consolidation therapy could not be shown to affect durability of HBeAg seroconversion
- For HBeAg negative CHB, stopping NUC therapy
  - Viral remission in 45%
  - biochemical remission in 56%
  - NUC therapy>2y improves durability of remission from 35% to 75%
- APASL stopping rules for HBeAg neg CHB on NUCs
  - Viral relapse 70%
  - Biochemical relapse 43%
- Stopping therapy is generally safe, even in cirrhotics
- Stopping therapy can lead to HBsAg seroclearance in as many as 39% of HBeAg neg CHB, and appears durable
- Those with low qHBsAg have the best probability of HBsAg loss
- However, the cutoff level for qHBsAg for stopping therapy is still uncertain and further studies are needed.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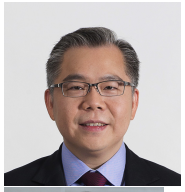
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Lee Yin Mei


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Richard Guan


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Tan Chee Kiat


Teerha Piratvisuth


Pei Cher Chen


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Khin Maung Win


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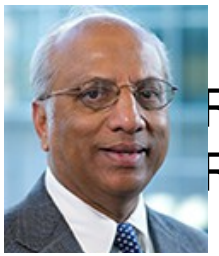
Rajender Reddy


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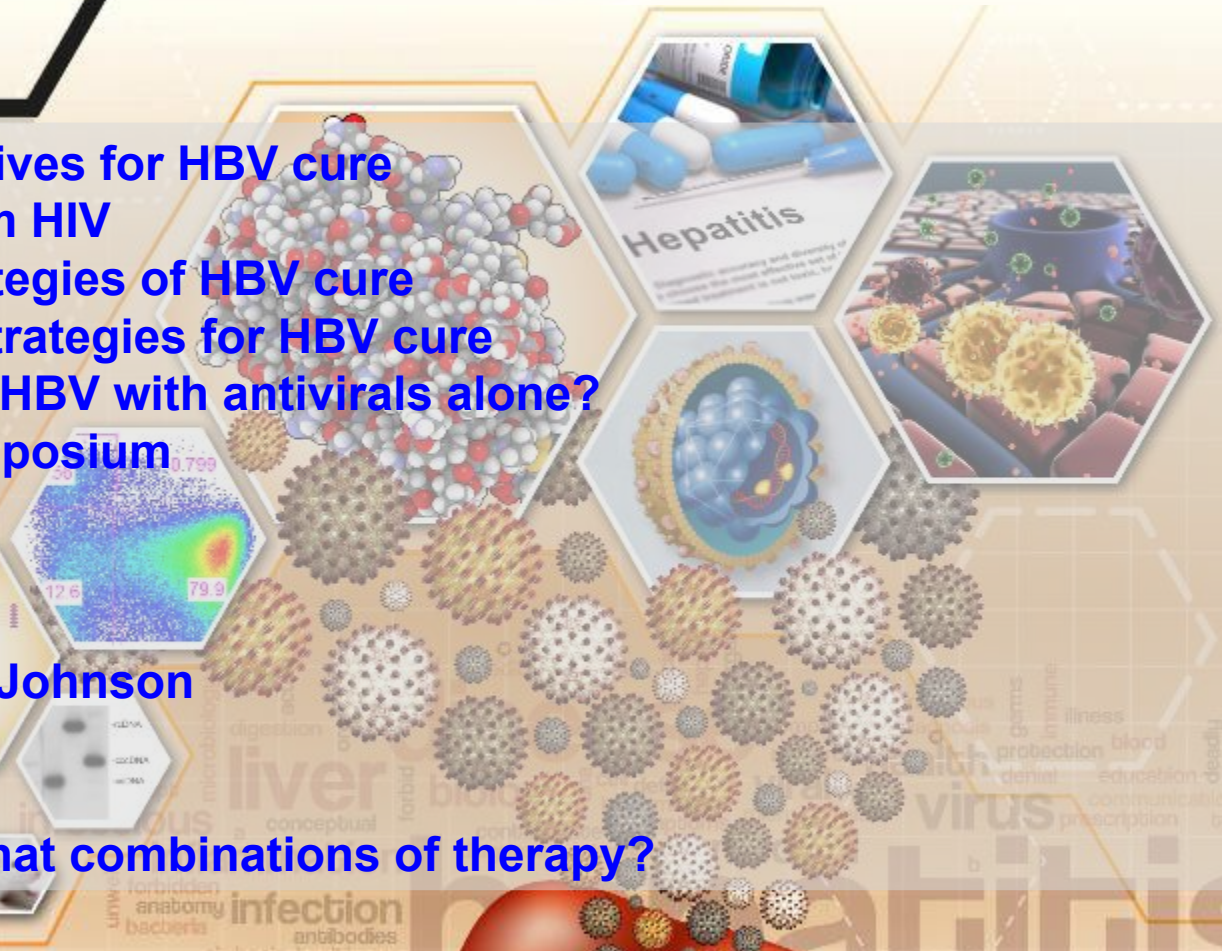
THE SCIENCE OF HBV CURE

2-3 JUNE 2017



- Global initiatives for HBV cure
- Lessons from HIV
- Immune strategies of HBV cure
- Virological strategies for HBV cure
- Can we cure HBV with antivirals alone?
- Industry symposium
  - Gilead
  - Arrowhead
  - Arbutus
  - Johnson & Johnson
  - Roche
  - Abbott
  - How and what combinations of therapy?

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