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HBV: The importance of NUC-Peg IFN combination

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Disclosures

Advisory Board/Speaker Bureau for:

- BMS, ROCHE, GILEAD SCIENCES, GSK, ABBVIE, MSD, ARROWHEAD, ALNYLAM, JANSSEN

Outine of the presentation

- Background and rationale
- "De-novo combination" for untreated patients
- "Switch to" Peg-IFN for NUC treated patients
- "Add-on" Peg-IFN for NUC treated patients
- Predictors of response

10 years of treatment with ETV or TDF in CHB

Achievements

- Excellent virological and biochemical responses (>95%)
- Histological progression to cirrhosis prevented
- Histological improvement of fibrosis (cirrhosis regression?)
- Decompensation prevented, portal hypertension improved
- HCC risk decreased but not abolished
- Improved survival

Unsolved issues

- Safety issues in some TDF treated patients (>>TAF)
- HCC risk during long-term NUC therapy
- NUC stopping rules
- Low HBsAg rates

How to improve HBsAg decline/loss in long-term NUC treated patients ?

- Continue ETV / TDF long-term
- New strategies based on “current” drugs
  - “de-novo combo” NUC and PEG
  - “switch” NUC to PEG
  - “add-on” PEG to NUC
  - Stop NUC (“stop to flare” strategy)
  - New strategies based on “new” drugs

How to improve HBsAg decline/loss in long-term NUC treated patients ?

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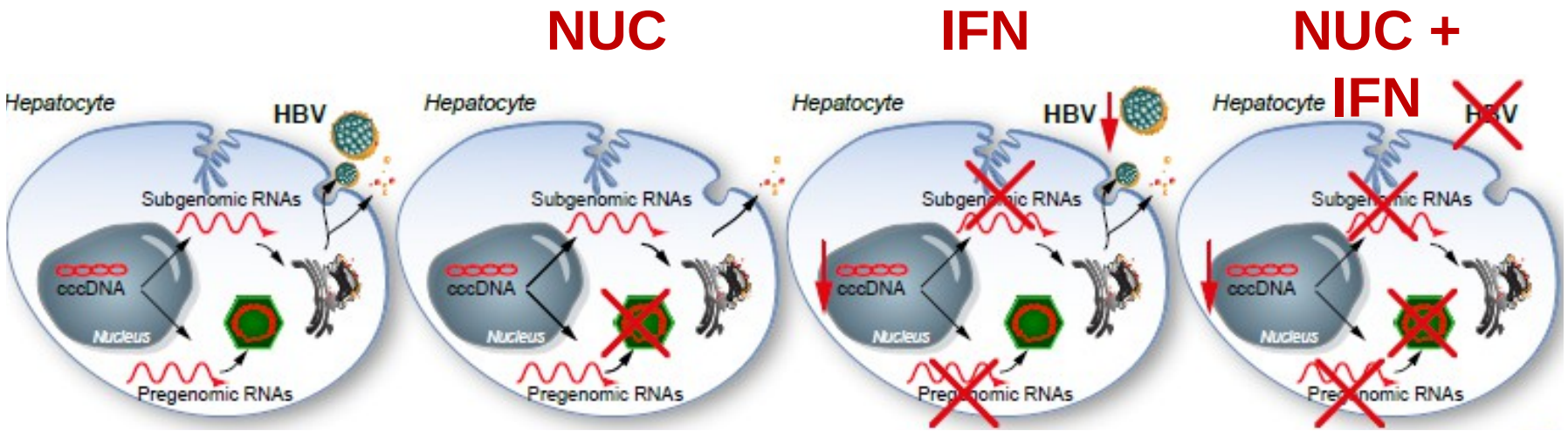
- New strategies based on “new” drugs

IFN and NUC have different mechanisms of action



Studies in patients and humanized mice indicate that combination treatments suppressing both HBV replication (NUCs) and cccDNA transcription (IFNα) may trigger significant antigen decline (HBe and HBs) – combination needs to be done in a smart way

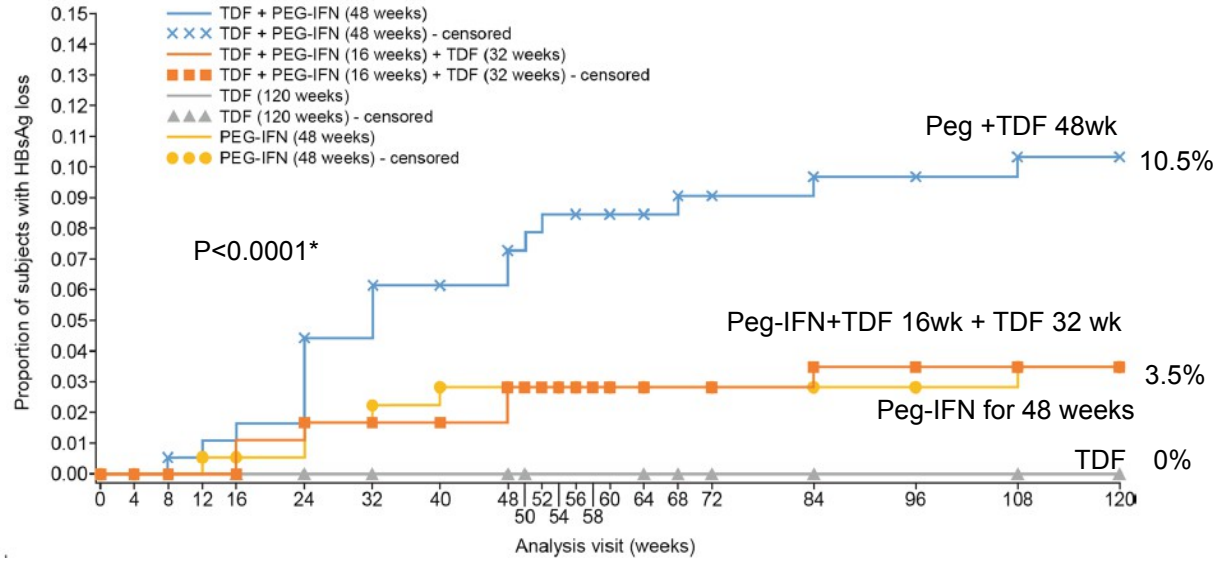
Adapted from Thimme & Dandri, J Hepatol 2012;58:205-9

“De-novo combo” Peg-IFN + NUC

”De-novo combo” IFN+TDF versus monotherapy for untreated CHB patients A multicenter international study - Week 120 Analysis

740 untreated HBeAg pos and neg CHB patients randomized to 4 treatment arms

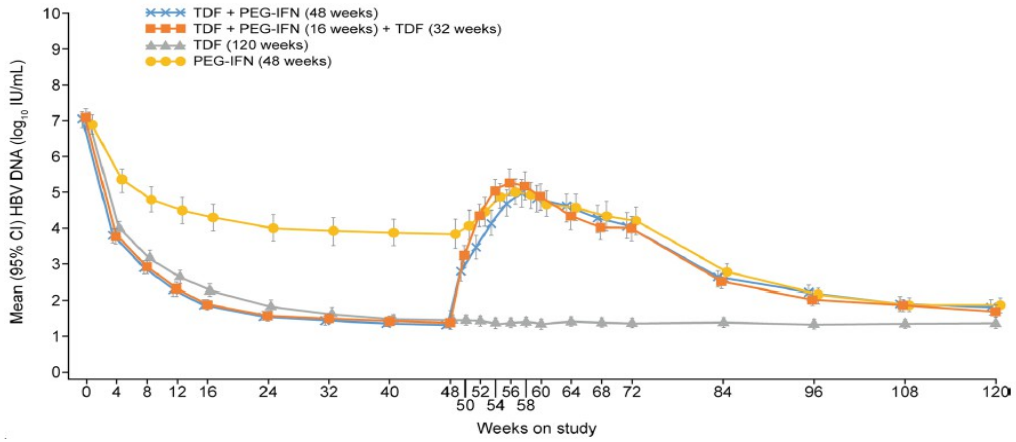
HBsAg loss over time



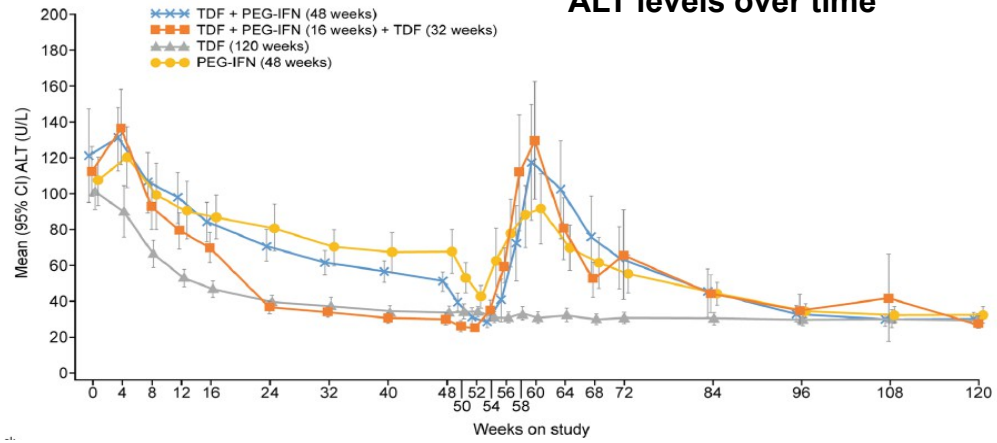
*group A vs C ($P < 0.001$ for both) or D

Conclusions:
Although the higher rates of HBsAg loss are encouraging, they are not at a level that should warrant a change in clinical practice.
Further research is required to establish the most effective combination strategy and also the patients most likely to benefit from such an approach.

HBV-DNA over time



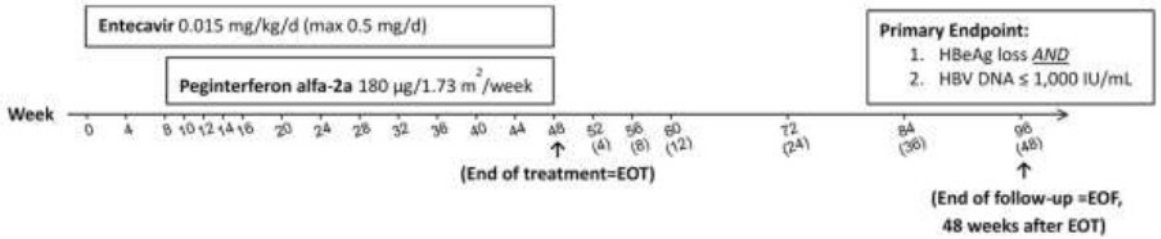
ALT levels over time



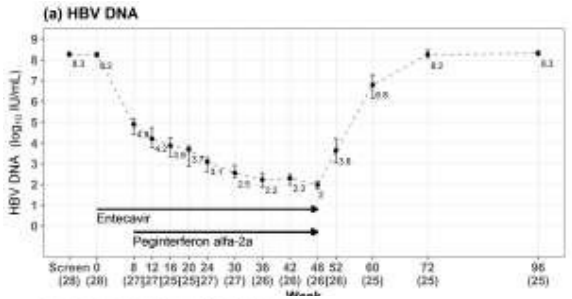
Ahn Sang Hoon et al, DDS 2018

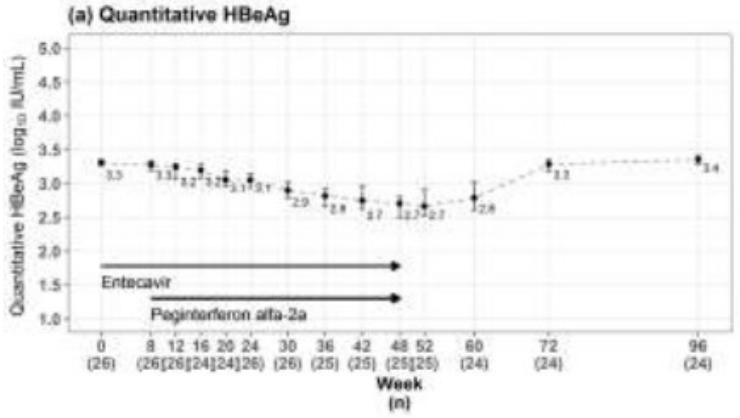
“De-novo combo” Peg-IFN and ETV in 28 adults HBeAg-positive IT patients
A US multicenter uncontrolled study

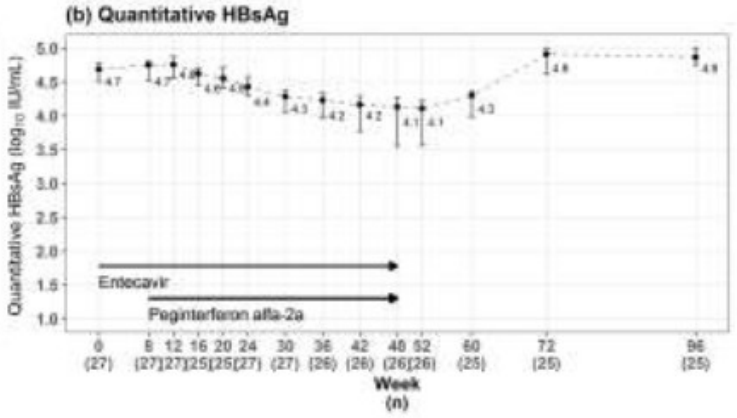
Study design



Changes of HBV markers over time







Efficacy endpoints

	End of Treatment (EOT)		End of Follow-up (EOF)	
Endpoints	**n=28 (%)**	**95% Confidence Intervals (%)**	**n=28 (%)**	**95% Confidence Intervals (%)**
HBsAg loss	0 (0)	(0.0-12.3)	0 (0)	(0.0-12.3)
HBsAg seroconversion	0 (0)	(0.0-12.3)	0 (0)	(0.0-12.3)
HBeAg loss**	1 (4)	(0.1-18.3)	1 (4)	(0.1-18.3)
HBeAg seroconversion	1 (4)	(0.1-18.3)	1 (4)	(0.1-18.3)
HBV DNA< 20 IU/mL	5 (18)	(6.1-36.9)	0 (0)	(0.0-12.3)
HBV DNA≤ 1000 IU/mL	26 (93)	(76.5-99.1)	0 (0)	(0.0-12.3)
ALT< 1x ULN	11 (39)	(21.5-59.4)	13 (46)	(27.5-66.1)
ALT< 1.5 x ULN	16 (57)	(24.5-62.8)	21 (75)	(55.1-89.3)
Primary Endpoint:				
HBeAg loss** & HBV DNA≤ 1000 IU/mL	1 (4)	(0.1-18.3)	0 (0)	(0.0-12.3)

ed using all enrolled participants.

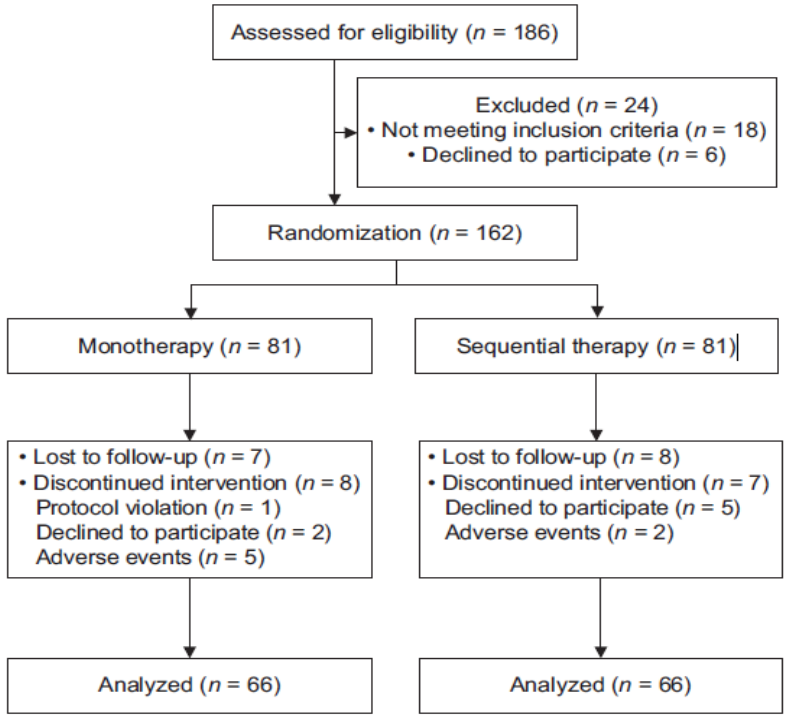
crepant qualitative (positive) and quantitative (negative) HBeAg results over time was not regarded as HBeAg

Conclusion: A lead-in strategy of 8 weeks of ETV followed by ETV + Peg-IFN for 40 weeks had limited efficacy in adults in the IT phase of chronic HBV infection and cannot be recommended.

Feld J et al, Hepatology 2019 in press

"De-novo combo" Peg-IFN + ETV versus Peg-IFN mono in HBeAg positive CHB: A Randomized, Multicenter, Phase IIIb Open-Label Study (POTENT Study) - Korea

Study design



Efficacy outcomes in per protocol analysis

Variable	Monotherapy (n = 66)	Sequential therapy (n = 66)	χ^2	P
Primary nonresponse at 12 weeks	8 (12.1)	1 (1.5)	2.07	0.033
Change drug due to elevation of ALT or HBV DNA	7 (10.6)	11 (16.7)	0.21	0.310
HBeAg seroclearance	13 (19.7)	13 (19.7)	0.03	1.000
HBeAb positivity	18 (27.3)	22 (33.3)	0.16	0.449
HBeAg seroconversion	12 (18.2)	12 (18.2)	0.03	1.000
HBV DNA <2000 U/ml	19 (28.8)	19 (28.8)	0.10	1.000
HBeAg seroconversion + HBV DNA <2000 U/ml	8 (12.1)	11 (16.7)	1.83	0.457
HBV DNA <60 U/ml	3 (4.5)	5 (7.6)	0.13	0.466
ALT normalization	30 (45.5)	36 (54.5)	1.12	0.296

Data were presented as n (%). ALT: Alanine aminotransferase; HBV: Hepatitis B virus; DNA: Deoxyribonucleic acid; HBeAg: Hepatitis B e antigen; HBeAb: Hepatitis B e antibody.

Monotherapy= IFN; Sequential therapy= IFN+NUC

Conclusions: The current study shows no differences in HBeAg seroconversion rate, ALT normalization, and HBV-DNA levels between mono-therapy and sequential therapy regimens.

Jun Dae Won et al, Chinese Medical Journal 2018

HBeAg positive CHB: “switch to” Peg-IFN

“Switch to” PEG-IFN long-term ETV treated HBeAg pos patients
The OSST study - China

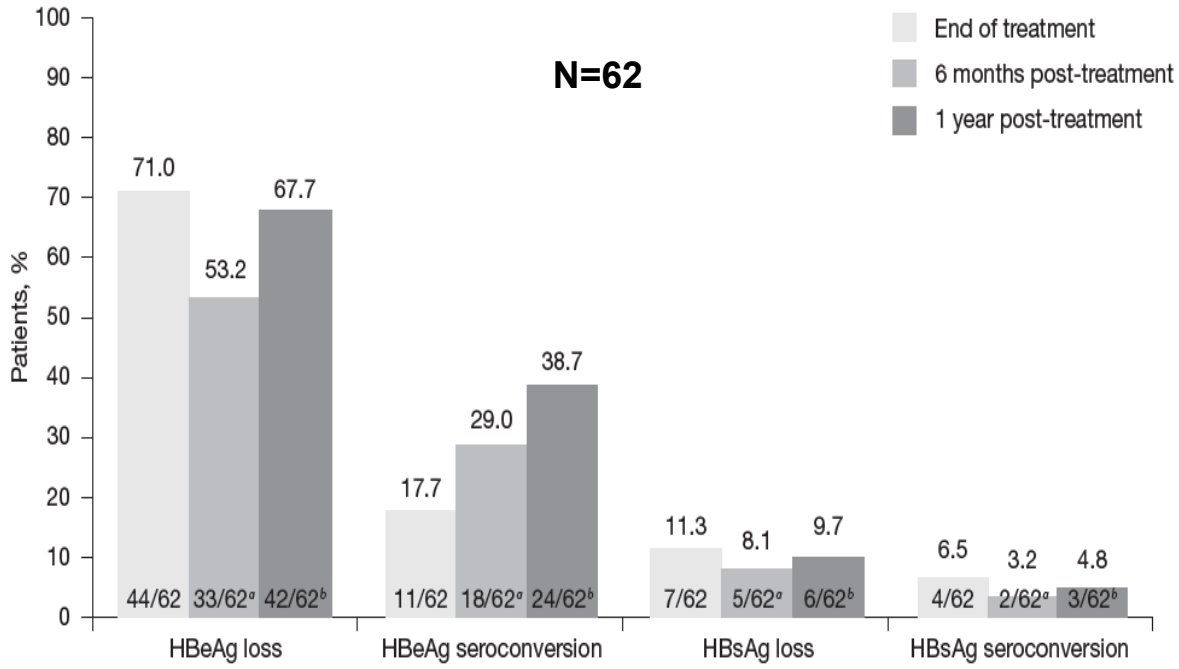
End of treatment analysis (week 48)

	PegIFN alfa2a (n=94)	ETV (n=98)	P value
HBeAg loss	16 (38%)	16 (33%)	NS
HBeAg seroconversion	14 (15%)	6 (6%)	0.046
HBsAg <100 IU/ml	22 (27%)	4 (4.4%)	<0.0001
HBsAg <10 IU/ml	13 (16%)	0	<0.0001
HBsAg loss	8 (8.5%)	0	<0.01
HBsAg seroconversion	4 (4.3%)	0	NS
HBV DNA <1000 cp/mL	59 (72%)	90 (98%)	<0.0001
ALT normal	48 (58%)	84 (94%)	<0.0001

25% HBsAg loss in pts with HBsAg <1500 IU/ml at baseline

Ning Q, et al, J Hepatol 2014

End of follow-up PP analysis for Peg-IFN treated (week 96)



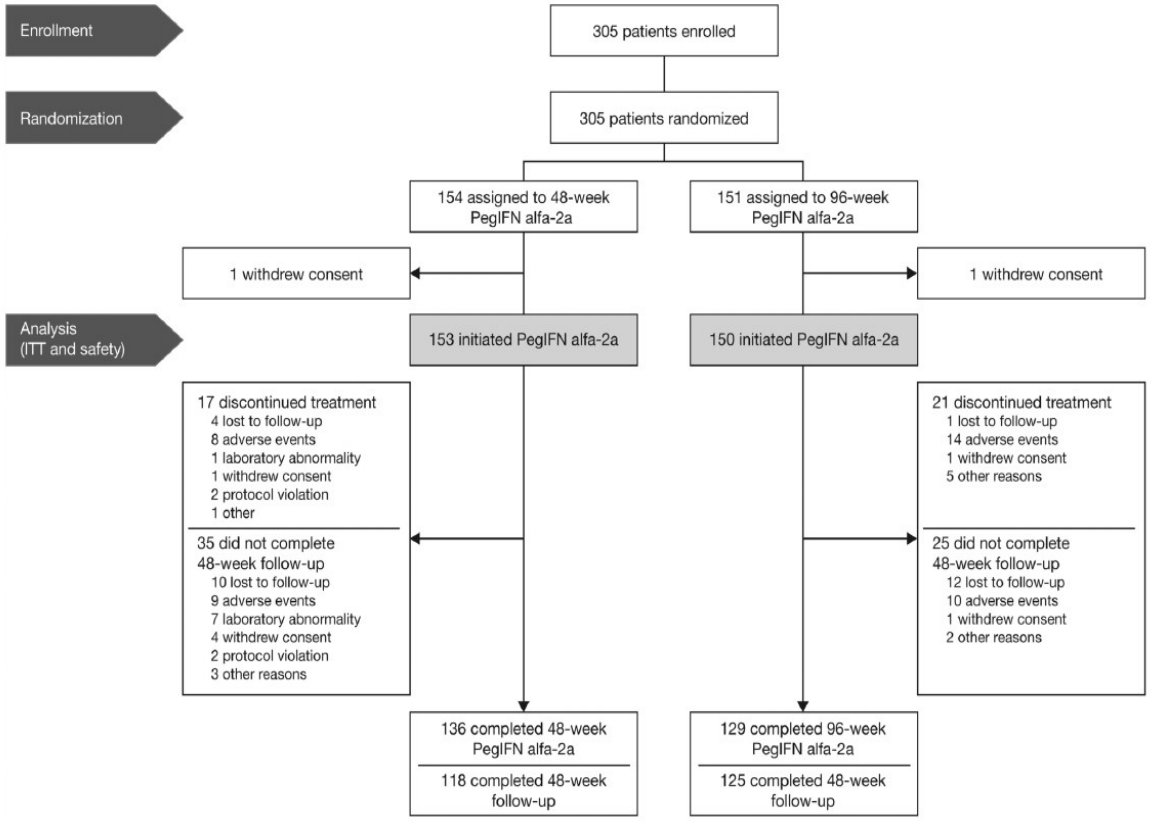
Conclusions: HBeAg seroconversion and HBsAg loss are stable in most patients 1 year after IFN discontinuation

Han M et al, et al, AVT 2016

“Switch to” PEG-IFN long-term ETV treated HBeAg pos patients
The “New Switch” study - China

303 patients with HBeAg loss and HBV DNA <200 IU/ml on NUC were randomized to 48 or 96 week peg-IFN

Study design



End of IFN / End of post-IFN follow-up

	48-week Peg-IFN alfa-2a, *n* = 153	96-week Peg-IFN alfa-2a, *n* = 150	*P*	48-week Peg-IFN alfa-2a, *n* = 153	96-week Peg-IFN alfa-2a, *n* = 150	*P*
HBsAg response						
HBsAg loss	22 (14.4)	31 (20.7)	0.1742	15 (9.8)	23 (15.3)	0.1670
HBsAg loss sensitivity analysis						
HBsAg loss by LOCF imputation method	23/153 (15.0)	35/150 (23.3)	0.0794			
HBsAg loss by PP analysis	17/101 (16.8)	26/108 (24.1)	0.2319			
HBsAg seroconversion	20 (13.1)	24 (16.0)	0.5163	14 (9.2)	18 (12.0)	0.4586
HBeAg response						
Maintained HBeAg loss	132 (86.3)	124 (82.7)	0.4293	95 (62.1)	107 (71.3)	0.1129
HBeAg seroconversion	84 (54.9)	91 (60.7)	0.3524	78 (51.0)	83 (55.3)	0.4902
Virologic response						
Maintained virologic suppression (HBV DNA <200 IU/mL)	117 (76.5)	111 (74.0)	0.6900	53 (34.6)	73 (48.7)	0.0146
Virologic relapse (HBV DNA >2000 IU/mL)	4 (2.6)	11 (7.3)	0.0674	19 (12.4)	24 (16.0)	0.4127
Biochemical response*						
ALT ≤1 × ULN	76 (49.7)	92 (61.3)	0.0494	90 (58.8)	104 (69.3)	0.0723
ALT 1 to ≤5 × ULN	61 (39.9)	38 (25.3)	0.0073	16 (10.5)	8 (5.3)	0.1356
ALT >5 × ULN	1 (0.7)	2 (1.3)	0.6200	1 (0.7)	1 (0.7)	1.0000

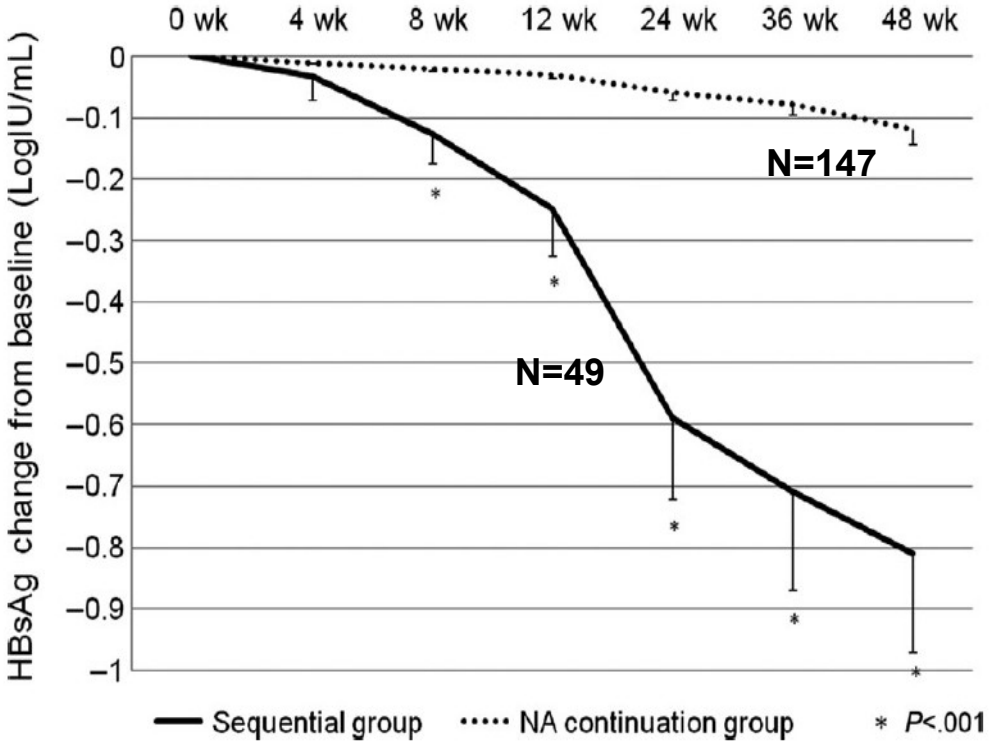
*33 and 83 patients did not have ALT test results at end of treatment and end of follow-up, respectively.

Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ITT, intention-to-treat; LOCF, last observation carried forward; Peg-IFN, pegylated-interferon; PP, per protocol; ULN, upper limit of normal.

Peng Hu et al, Journal of Clinical and Translational Hepatology 2018

"Switch to" Peg-IFN long-term NUC treated CHB patients
The Japanese Red Cross Hospital Liver Study Group

49 NUC patients were switched to 48-week PEG-IFN vs 147 NUC patients



HBsAg <100 IU/mL 35% vs 15%, p=0.002
HBsAg loss: 4% vs 0%, p=0.01

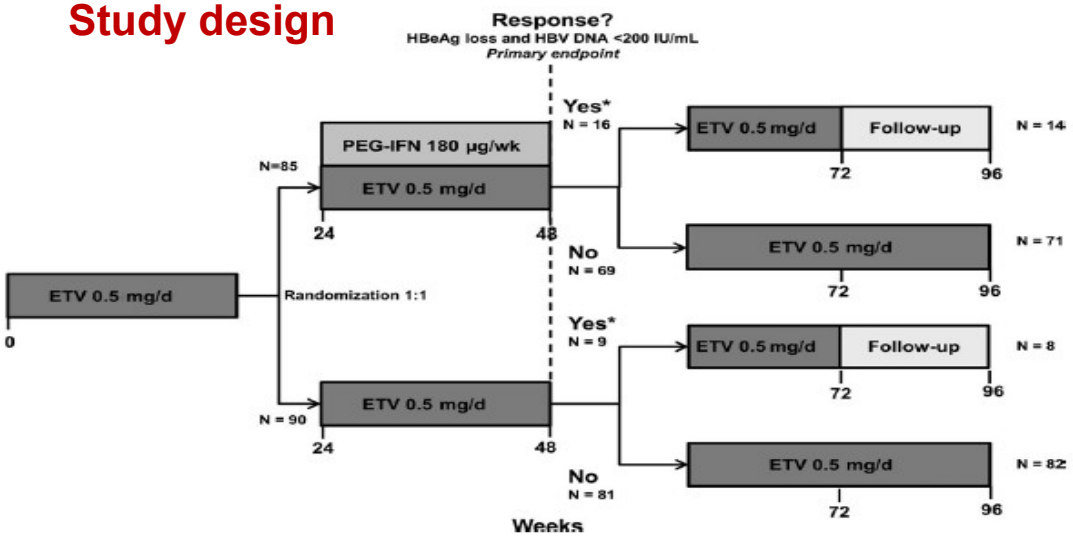
- HBsAg reduction at week 48 was 0.81±1.1 log IU/mL in IFN group, and 0.11±0.3 log IU/mL, in the NUC group (*P*<0.001).
- HBsAg reduction ≥1.0 logIU/ml was achieved in 29% and 2% of the IFN group and NUC group (*P* <0.001).
- In HBeAg pos pts, HBeAg seroconversion was higher in the sequential group (44% vs 8%, *P*<0.001).
- In HBeAg-negative patients, only patients switched to IFN achieved HBsAg loss.
- No patient needed to restart NA because of HBV DNA increase and ALT flares.
- HBsAg decline at week 12 of 0.2 log IU/mL was the best predictor of response (AUROC 0.96, PPV 72%, NPV 97%)

Tamaki N et al, JVH 2017

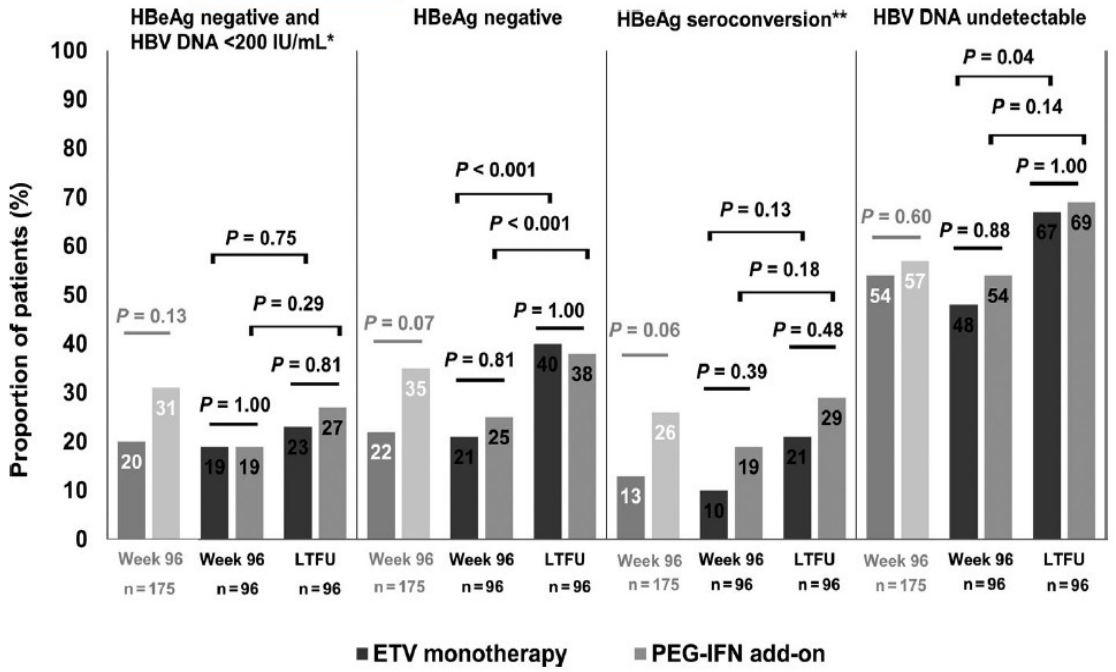
HBeAg positive CHB: “add on” Peg-IFN

"Add-on" Peg-IFN to ETV treated HBeAg-positive CHB
Long-term follow-up of the ARES study

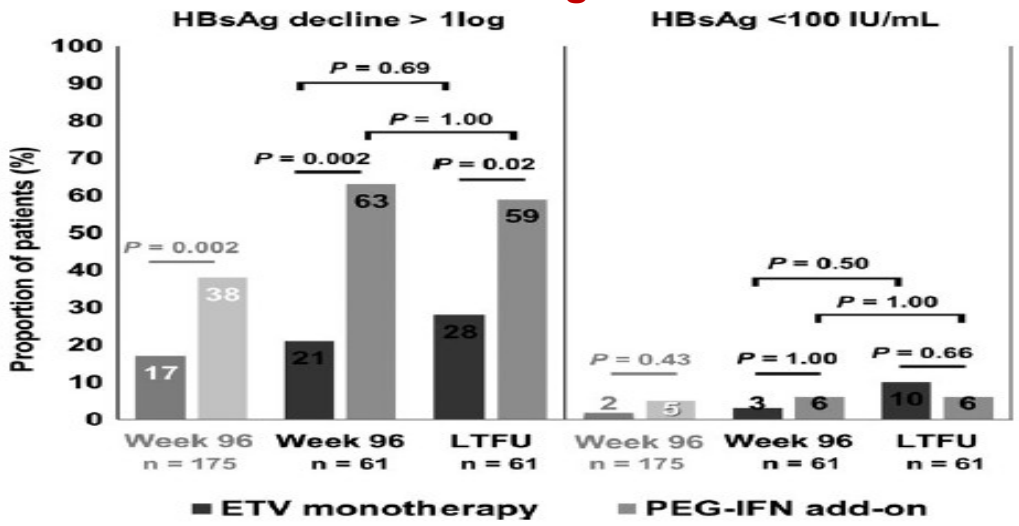
Study design



Efficacy markers



HBsAg levels



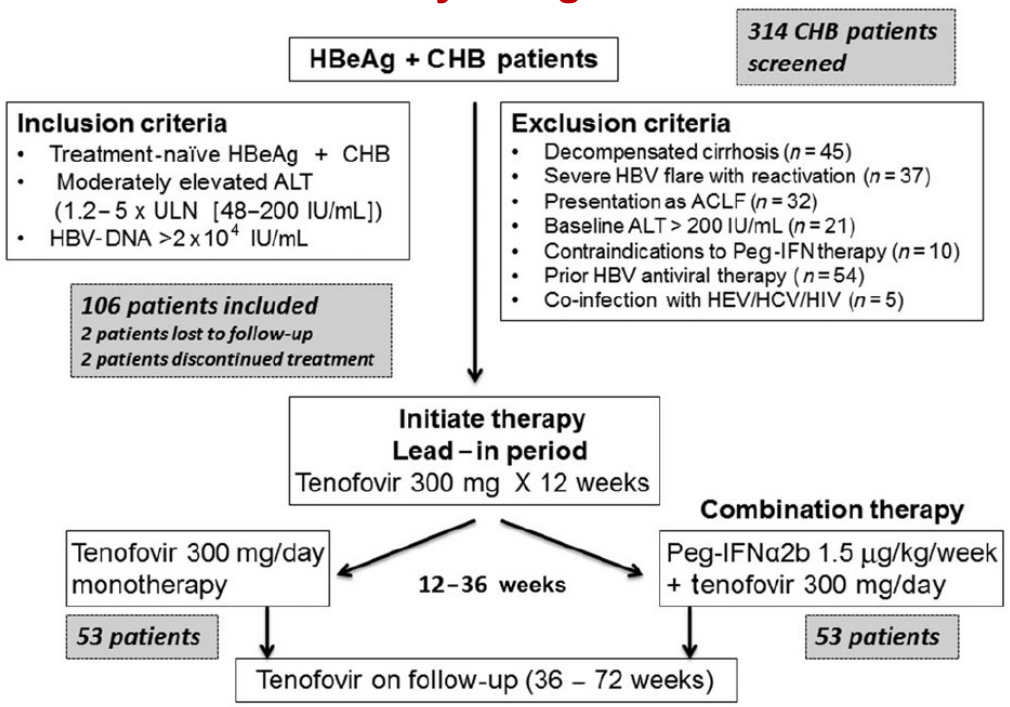
Conclusions

Although early response was stronger in PEG-IFN add-on treated patients, rates of HBeAg loss and combined response became comparable between the treatment arms beyond week 96 of follow-up.

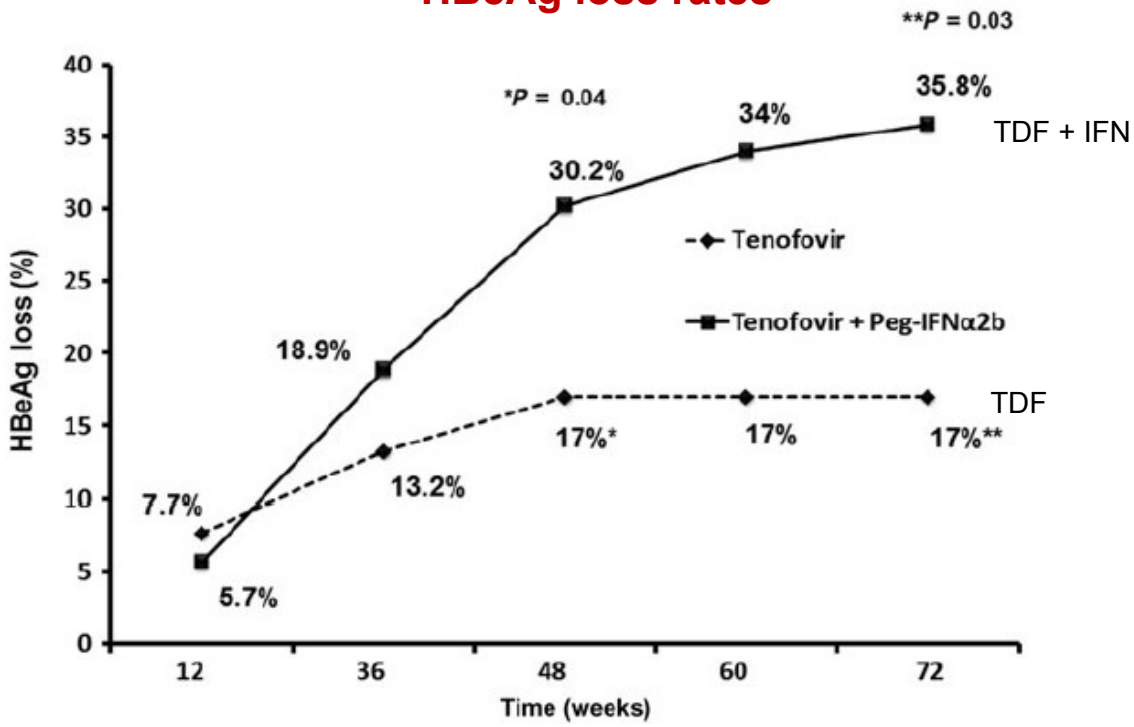
Margo J. H. van Campenhout et al, JVH 2019

"Add-on" Peg-IFN to TDF treated HBeAg positive CHB
A RCT from India

Study design



HBeAg loss rates



Other efficacy markers:

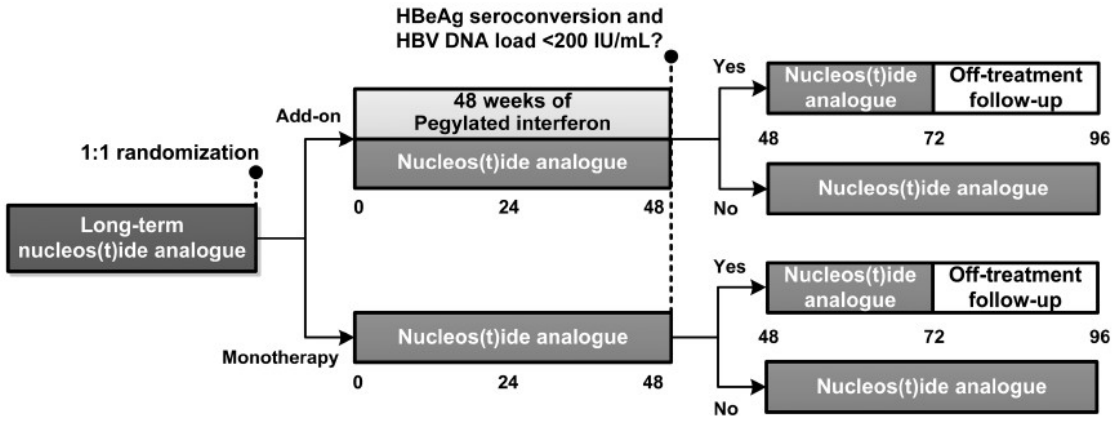
ALT and HBV DNA responses: no differences between groups at any time point

HBsAg loss rates= no differences between groups (6% vs 0%)

Jindal Ankur et al, Hepatology Research 2018

“Add-on” Peg-IFN alfa-2b in NUC treated HBeAg positive patients
A Randomized, Controlled Trial (PEGON)

Study design

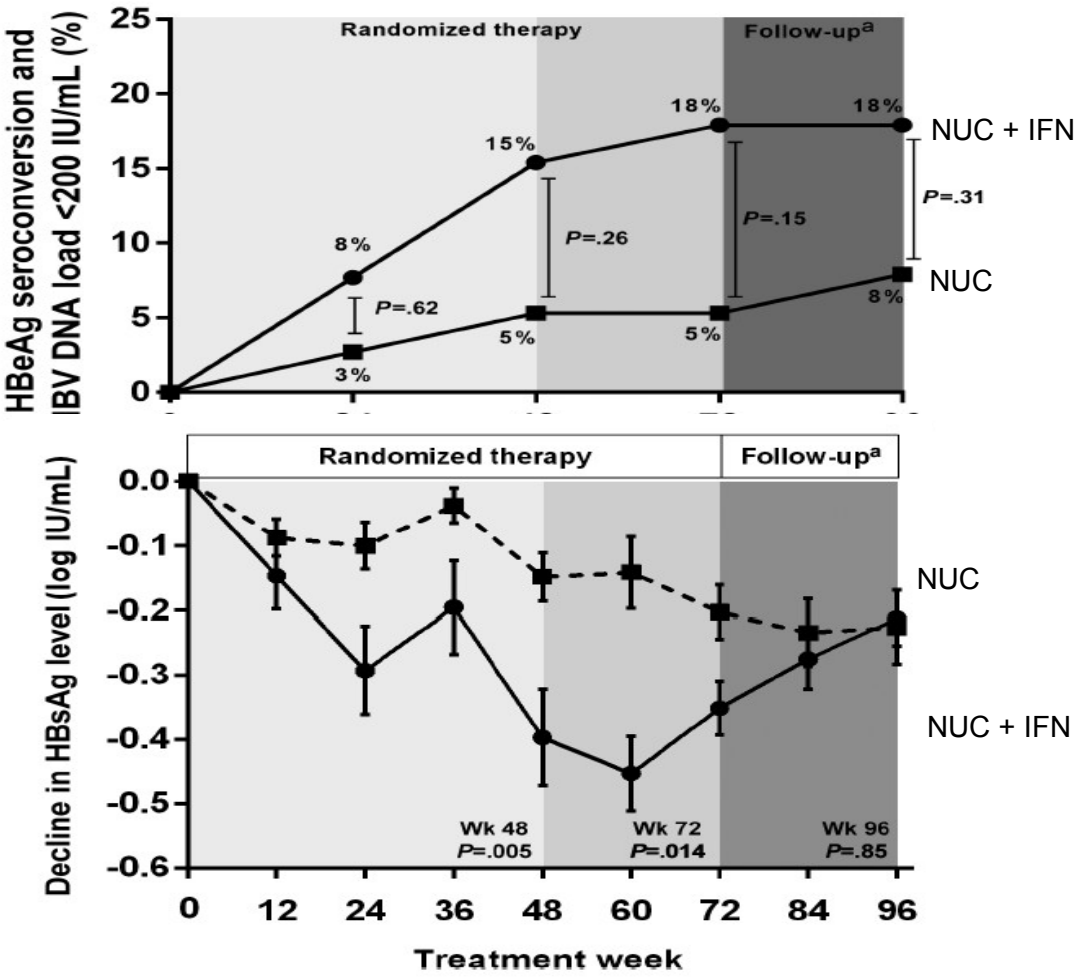


Inclusion criteria:

- 88 patients randomized (98% Asian)
- HBeAg loss but anti-HBe negative
- HBV DNA < 2000 IU/ml
- On ETV or TDF > 1 year

Conclusions: in a predominantly Asian population of HBeAg-positive patients treated with ETV or TDF, Peg-IFN add-on did not lead to significantly more HBeAg seroconversion, compared with continuation of NA monotherapy.

Virolgical and serological responses

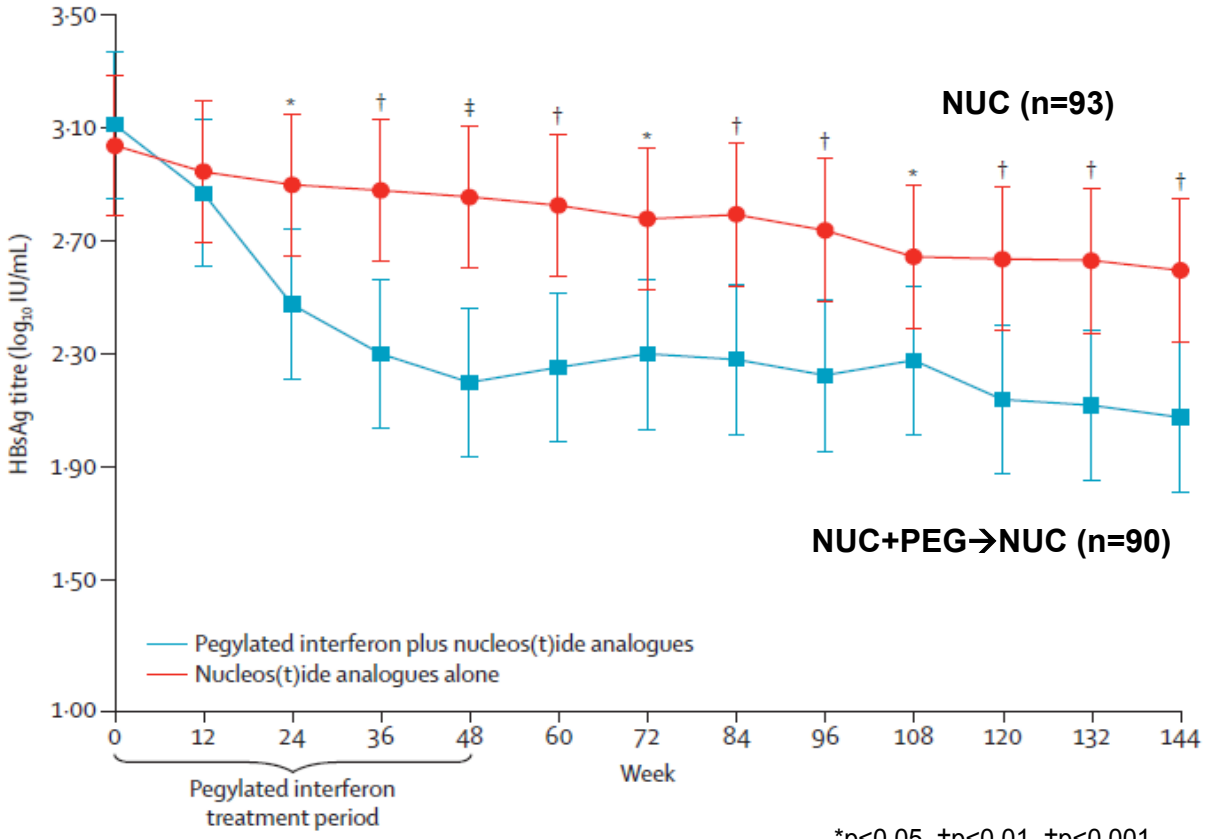


Chi Heng et al, JID 2017

HBeAg negative CHB: “add on” Peg-IFN

"Add-on" PEG-IFN in NUC treated HBeAg neg patients
A RCT multicenter study from France

HBsAg levels



*p<0.05. †p<0.01. ‡p<0.001

HBsAg loss and seroconversion

	Pegylated interferon plus nucleos(t)ide analogues group			Nucleos(t)ide analogues-alone group			
	Week –6 HBsAg titre of <2·25 log_{10} IU/mL	Week –6 HBsAg titre of ≥2·25 log_{10} IU/mL	Total	Week –6 HBsAg titre of <2·25 log_{10} IU/mL	Week –6 HBsAg titre of ≥2·25 log_{10} IU/mL	Total	p value
Intention-to-treat analysis	n=14	n=76	n=90	n=15	n=78	n=93	..
Week 48							
HBsAg loss	3 (21%)	4 (5%)	7 (8%)	0	0	0	0·006
Anti-HBs seroconversion	2 (14%)	2 (3%)	4 (4%)	0	0	0	0·04
Week 96							
HBsAg loss	4 (29%)	3 (4%)	7 (8%)	2 (13%)	1 (1%)	3 (3%)	0·15
Anti-HBs seroconversion	3 (21%)	3 (4%)	6 (7%)	0	1 (1%)	1 (1%)	0·047
Week 144							
HBsAg loss	4 (29%)	5 (7%)	9 (10%)	3 (20%)	1 (1%)	4 (4%)	0·11
Anti-HBs seroconversion	4 (29%)	4 (5%)	8 (9%)	2 (13%)	1 (1%)	3 (3%)	0·09
Full-dose analysis	n=10	n=55	n=65	n=15	n=78	n=93	..
Week 48							
HBsAg loss	3 (30%)	4 (7%)	7 (11%)	0	0	0	0·001
Anti-HBs seroconversion	2 (20%)	2 (4%)	4 (6%)	0	0	0	0·01
Week 96							
HBsAg loss	4 (40%)	3 (5%)	7 (11%)	2 (13%)	1 (1%)	3 (3%)	0·04
Anti-HBs seroconversion	3 (30%)	3 (5%)	6 (9%)	0	1 (1%)	1 (1%)	0·01
Week 144							
HBsAg loss	4 (40%)	5 (9%)	9 (14%)	3 (20%)	1 (1%)	4 (4%)	0·02
Anti-HBs seroconversion	4 (40%)	4 (7%)	8 (12%)	2 (13%)	1 (1%)	3 (3%)	0·02

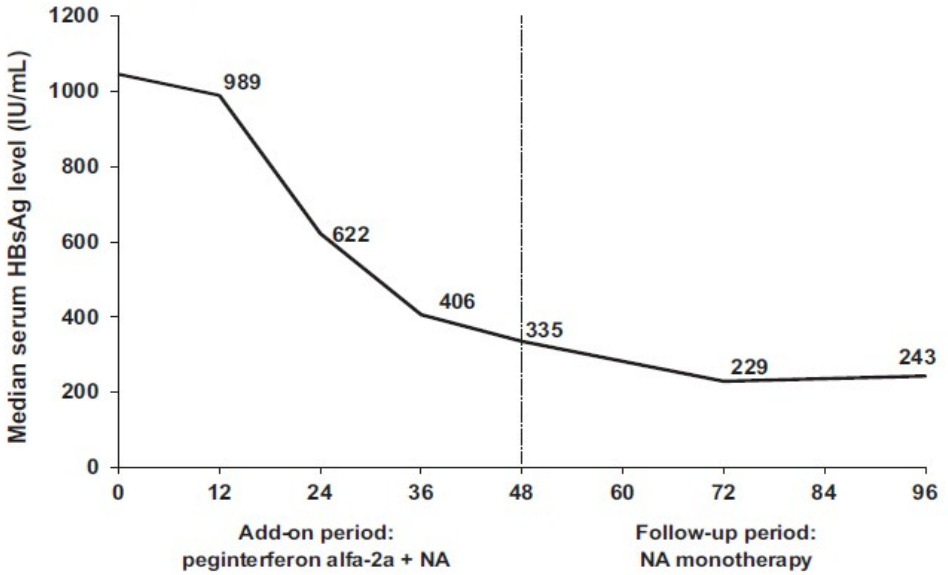
Safety:
AE were more frequent in the PEG+NUC vs NUC
(Grade 3: 29% vs 3%; Grade 4: 21% vs 6%)

Bourliere M. et al, Lancet GH 2017

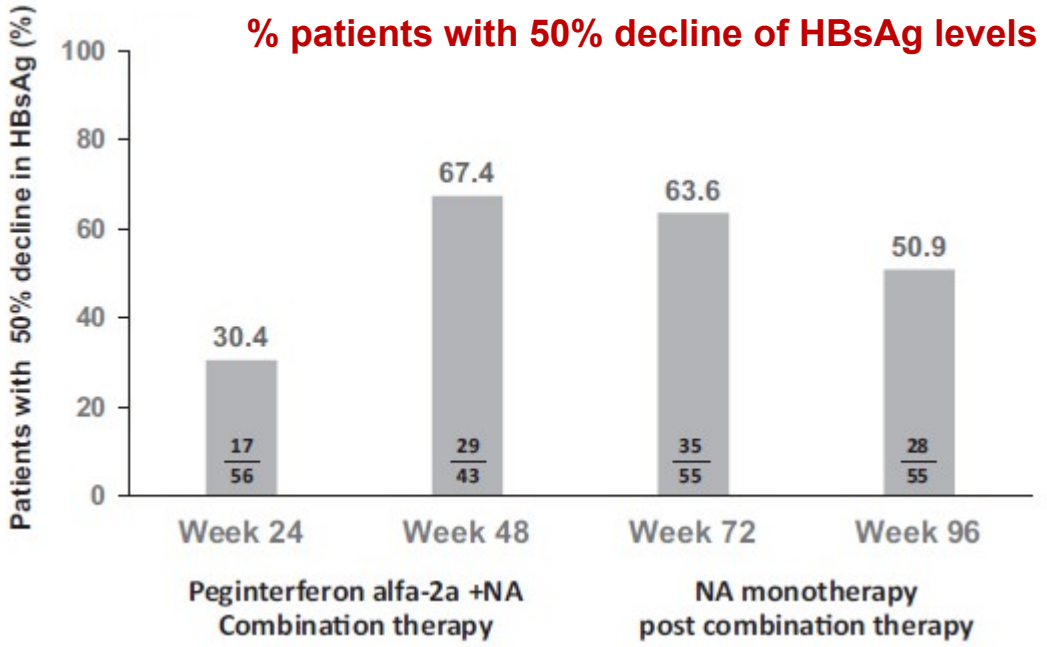
”Add-on” Peg-IFN to NUC treated with HBeAg-negative, genotype D patients The multicenter italian study (HERMES study)

Single arm study enrolling 70 patients with undetectable HBV DNA, normal ALT levels, genotype D and HBsAg >100 IU/ml

HBsAg levels (PP analysis)



% patients with 50% decline of HBsAg levels



Other efficacy markers (96 week): HBsAg <100: 20%; HBsAg loss: 1 patient (1.5%)
Safety: 12% of patients permanently discontinued pegIFN

Lampertico P et al, JVH 2018

Predictors of response ?

“Switch to” PEG-IFN for ETV treated HBeAg pos patients Predictors of HBsAg loss

The OSST study

	%	*n*/total *n*	*P*-value[a]
Sustained HBeAg seroconversion			
Week 12 HBsAg			
<1,500 IU/ml	22.2	6/27	0.0365
≥1,500 IU/ml	2.9	1/35	
Week 24 HBsAg			
<1,000 IU/ml	23.1	6/26	0.0182
≥1,000 IU/ml	2.8	1/36	
End of treatment			
<100 IU/ml	31.6	6/19	0.0025
≥100 IU/ml	2.3	1/43	
HBsAg loss			
Week 12 HBsAg			
<200 IU/ml	75	6/8	<0.0001
≥200 IU/ml	0	0/54	

[a]*P*-value was obtained by Fisher's exact test. HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

HBsAg <200 IU/ml at wk 12: 8/62 (13%) patients

Han M et al, et al, AVT 2016

The New Switch study

	Baseline HBsAg, IU/mL	*n/N* (%)	Week 24 HBsAg, IU/mL*	*n/N* (%)	HBsAg loss at week 48, *n/N* (%)	HBsAg loss at week 96, *n/N* (%)
Overall population, *n* = 303	<1500	138/303 (45.5)	<200	81/138 (58.7)	35/81 (43.2)	
			≥200	45/138 (32.6)	0	
	≥1500	165/303 (54.5)	<200	18/165 (10.9)	5/18 (27.8)	
			≥200	142/165 (86.1)	0	
48-week Peg-IFN alfa-2a, *n* = 153	<1500	68/153 (44.4)	<200	35/68 (51.5)	18/35 (51.4)	
			≥200	26/68 (38.2)	0	
	≥1500	85/153 (55.5)	<200	10/85 (11.8)	4/10 (40.0)	
			≥200	73/85 (85.9)	0	
96-week Peg-IFN alfa-2a, *n* = 150	<1500	70/150 (46.7)	<200	46/70 (65.7)	17/46 (37.0)	27/46[†] (58.7)
			≥200	19/70 (27.1)	0	1/19 (5.3)
	≥1500	80/150 (53.3)	<200	8/80 (10.0)	1/8 (12.5)	1/8 (12.5)
			≥200	69/80 (86.3)	0	2/69 (2.9)

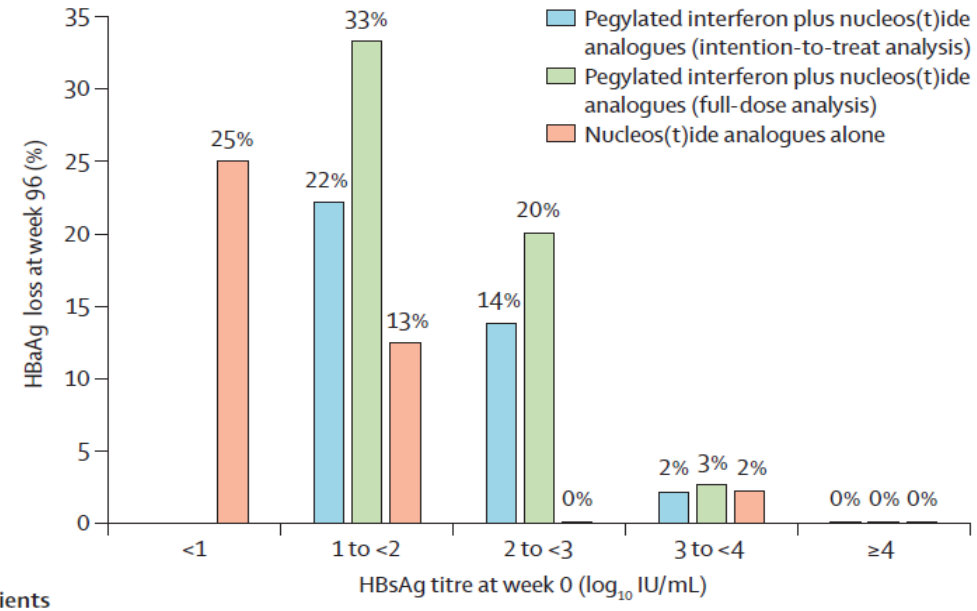
*9 and 8 patients in the 48- and 96-week Peg-IFN alfa-2a arms, respectively, had missing data at week 24;
†13 responders (HBsAg loss) and 14 nonresponders at week 48 had HBsAg loss at week 96.
Abbreviations: HBsAg, hepatitis B surface antigen; Peg-IFN, pegylated-interferon.

HBsAg <1500 IU/ml at baseline + <200 IU/ml at wk 12: 81/303 (27%) patients

Peng Hu et al, Journal of Clinical and Translational Hepatology 2018

“Add-on” PEG-IFN in NUC treated HBeAg neg patients
Predictors of HBsAg loss

HBsAg loss at week 96 according to treatment group stratified by HBsAg leves at baseline



Number of patients					
Pegylated interferon intention-to-treat analysis	0/0	2/9	4/29	1/48	0/4
Pegylated interferon full-dose analysis	0/0	2/6	4/20	1/38	0/1
Nucleos(t)ide analogues alone	1/4	1/8	0/27	1/46	0/8

Predictors of HBsAg loss at week 96

- In the ITT analysis, baseline HBsAg titres were the only predictive factor associated with HBsAg loss at week 96 (OR 0.36; 95% CI 0.17–0.76; p=0.006).
- In the full-dose analysis set, baseline HBsAg levels (OR 0.29, 95%CI 0.12–0.66; p=0.002) and Peg-IFN (OR 5.55, 95% CI 1.02–43.8; p=0.046) were independently associated with HBsAg loss at week 96.
- The benefit in HBsAg loss appeared more marked in patients with baseline HBsAg titres between 2 and 3 logs IU/mL (approx. 1/3 of the patients)

Bourliere M. et al, Lancet GH 2017

PEG-IFN + NUC combination - Summary

- The combination of PEG+NUC with NUC has a strong biological rationale
- Three strategies have been assessed (de-novo combo, switch to, add-on)
- Most studies showed a faster HBsAg decline in the Peg-IFN+NUC vs NUC….

  ……but only few patients cleared HBsAg
- Side effects and cost issues of Peg-IFN must be also considered
- Combination strategies are not recommended for all patients but could be considered for selected patients with favorable baseline and week 12 predictors