

Hepatitis B/D: Was gibt es Neues?

11. Jahrestagung GGHBB
48. Lebertag

20.01.2017

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Charité – Universitätsmedizin Berlin, CCM



Mögliche Interessenkonflikte

Kongresse, Reise-/Übernachtungskosten, Beratungshonorare

AbbVie

Bayer

BMS

Gilead

Gore



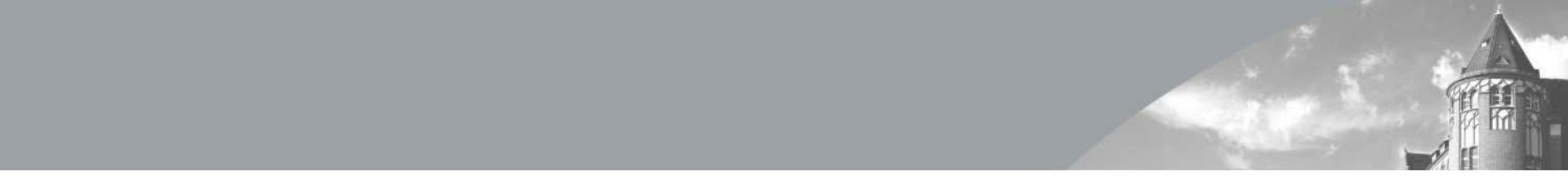
Was gibt es Neues?





Übersicht

- Aktueller Stand der Therapie
- Weiterentwicklungen
- Neue Targets
- Hepatitis D
- Hepatitis B und Schwangerschaft



Übersicht

- **Aktueller Stand der Therapie**
- **Weiterentwicklungen**
- **Neue Targets**
- **Hepatitis D**
- **Hepatitis B und Schwangerschaft**



Aktueller Stand der Therapie

Zugelassene Therapien

- pegIFN α



Aktueller Stand der Therapie

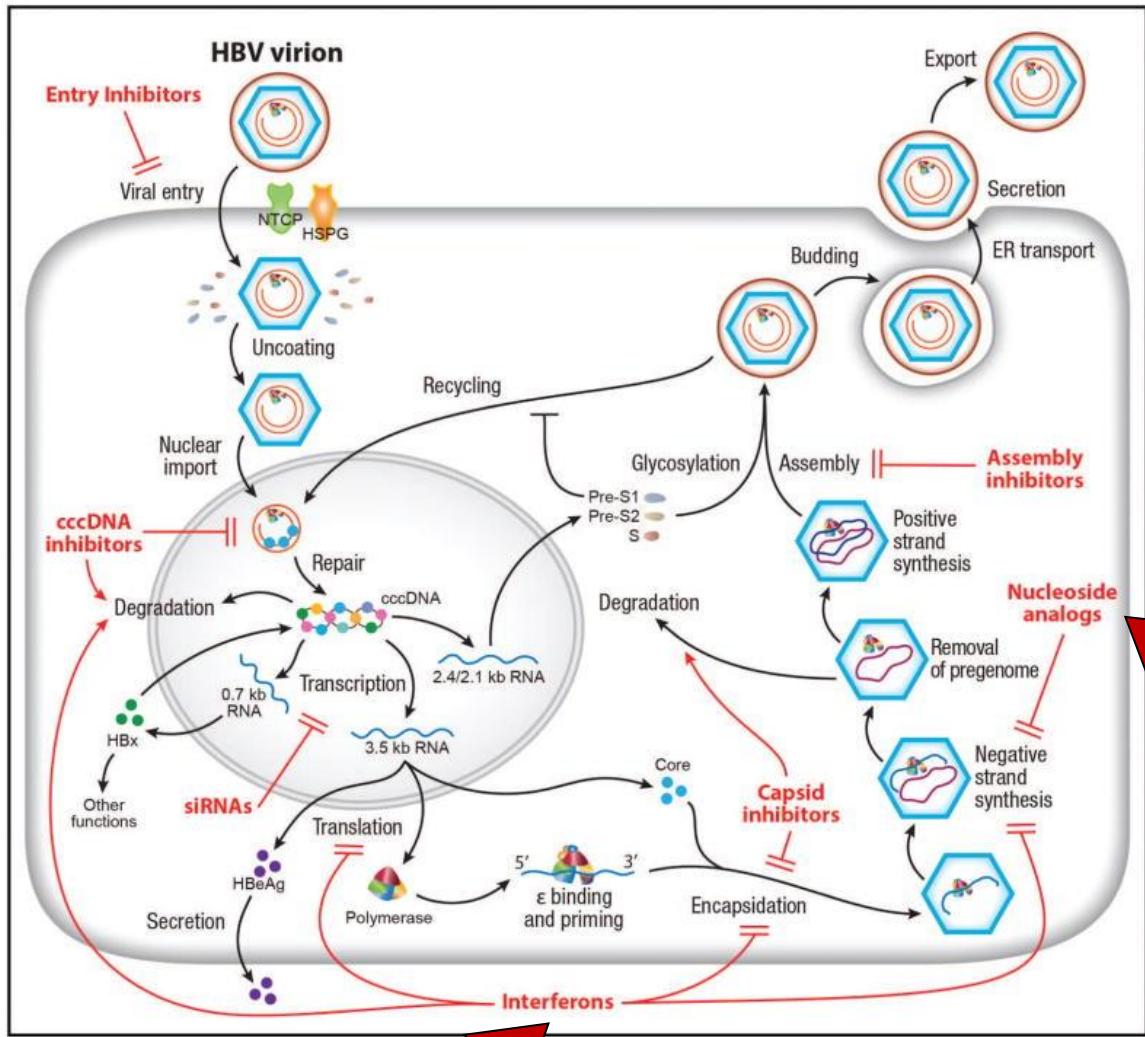
Zugelassene Therapien

- pegIFN α
- Nukleos(t)id analoga

Lamivudin LAM

Entecavir ETV

Tenofovir TDF (Tenofovir-Disoproxil-Fumarat)

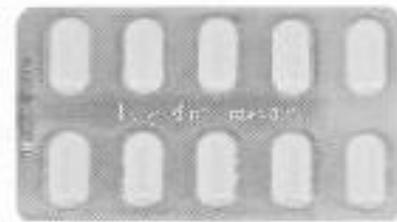


Liang et al., Hepatology 2015



pegIFN vs. NAs

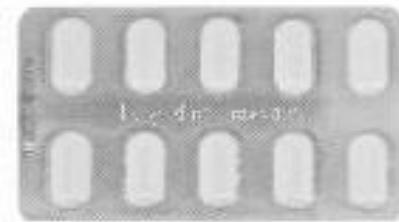
	(PEG-)IFN	NAs
Advantages	<ul style="list-style-type: none">Finite durationAbsence of resistanceHigher rates of anti-HBe and anti-HBs seroconversion with 12 mo of therapy	<ul style="list-style-type: none">Potent antiviral effectGood toleranceOral administration
Disadvantages	<ul style="list-style-type: none">Moderate antiviral effectInferior tolerabilityRisk of adverse eventsSubcutaneous injections	<ul style="list-style-type: none">Indefinite durationRisk of resistanceUnknown long-term safety



EASL CPG 2012

pegIFN vs. NAs

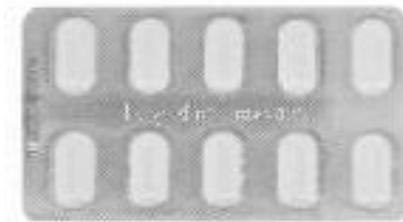
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EASL CPG 2012

pegIFN vs. NAs

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Disadvantages	<ul style="list-style-type: none">Moderate antiviral effectInferior tolerabilityRisk of adverse eventsSubcutaneous injections	<ul style="list-style-type: none">Indefinite durationRisk of resistanceUnknown long-term safety



EASL CPG 2012

Nukleotidanaloga (Tenofovir)

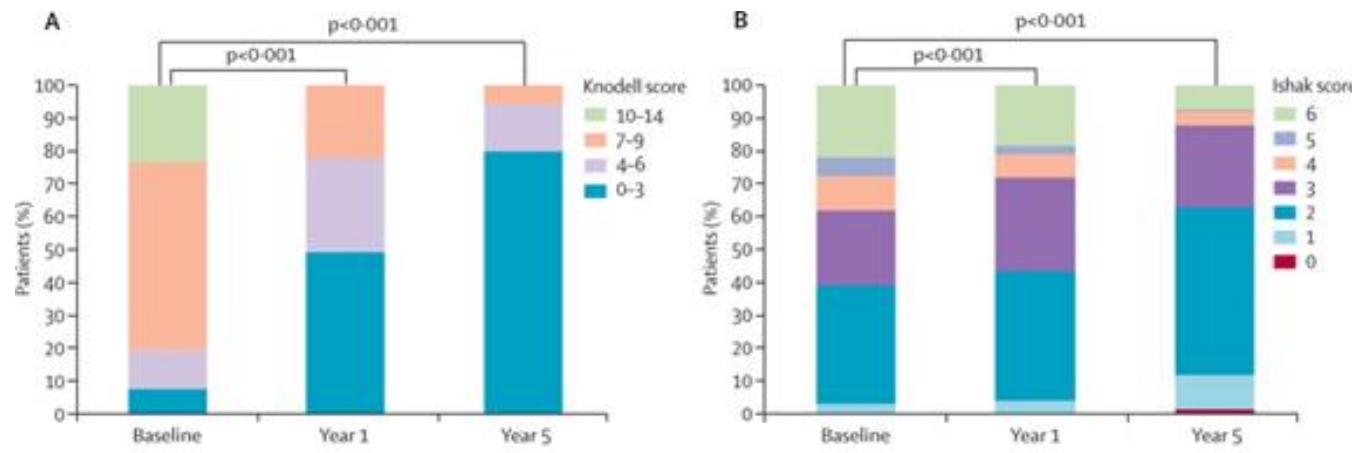


Figure 2. Histology results over 5-year treatment phase

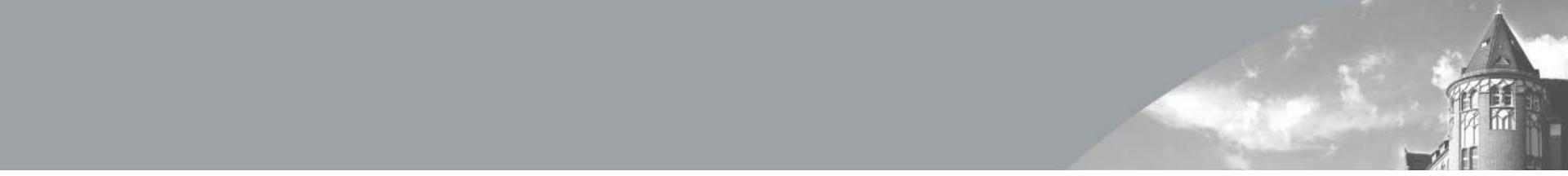
- (A) Distribution of Knodell necroinflammatory scores in 348 patients with results available at each time point
- (B) Distribution of Ishak fibrosis scores in 348 patients with baseline and year 5 data

Marcellin et al., Lancet 2013



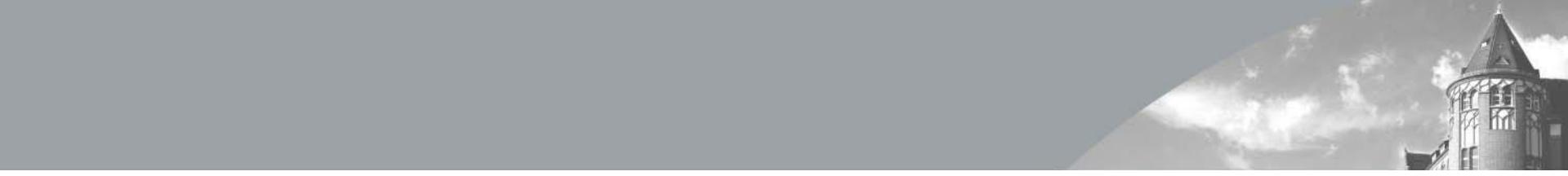
Aktueller Stand der Therapie

- Verhinderung von Komplikationen



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Aktueller Stand der Therapie

- Verhinderung von Komplikationen
 - Suppression v. HBV, keine Heilung
 - Risiko für HCC sinkt, aber nicht auf 0
-
- Verlust von HBeAg ca. 40-50% in 5 Jahren
 - Verlust von HBsAg ca. 10% in 5 Jahren

Versuche mit Kombination

NA + pegIFN simultan

NA + pegIFN sequentiell

Chan et al., Ann Intern Med 2005
Su et al., J Hepatol 2014
Ning et al., J Hepatol 2014
Marcellin et al., Hepatology 2014
Liang et al., Hepatology 2015

Versuche mit Kombination

NA + pegIFN simultan

NA + pegIFN sequentiell

Daten (noch) nicht ausreichend für generelle Empfehlung

Chan et al., Ann Intern Med 2005

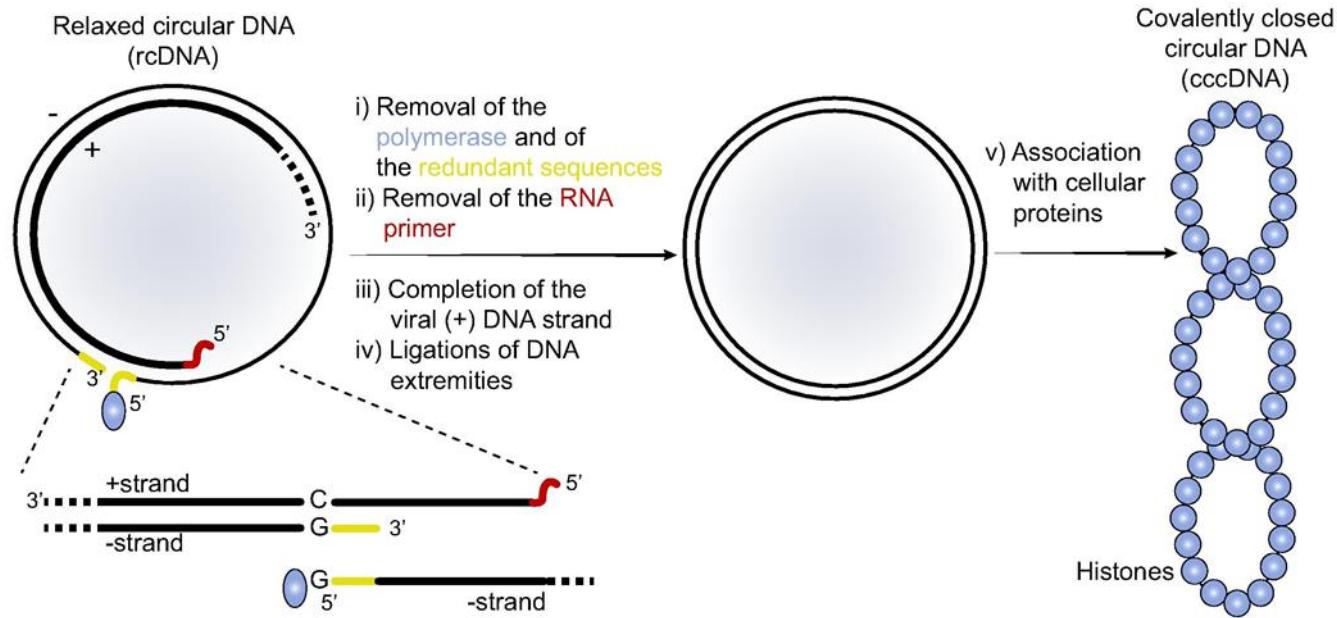
Su et al., J Hepatol 2014

Ning et al., J Hepatol 2014

Marcellin et al., Hepatology 2014

Liang et al., Hepatology 2015

cccDNA



- supercoiling
- Minichromosom
- ca. 1-10 Moleküle pro infizierter Hepatozyt

Lucifora, Protzer, J Hepatol 2016

Heilung?

funktionelle Heilung

- HBsAg-Verlust
- mit/ohne anti-HBs Serokonversion
- HBV-DNA nicht detektierbar
- transkriptionell inaktive cccDNA

=> erlaubt Einstellung der Behandlung



Heilung?

funktionelle Heilung

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=> erlaubt Einstellung der Behandlung

komplette Heilung

- wie funktionelle Heilung
- + physische Elimination der cccDNA

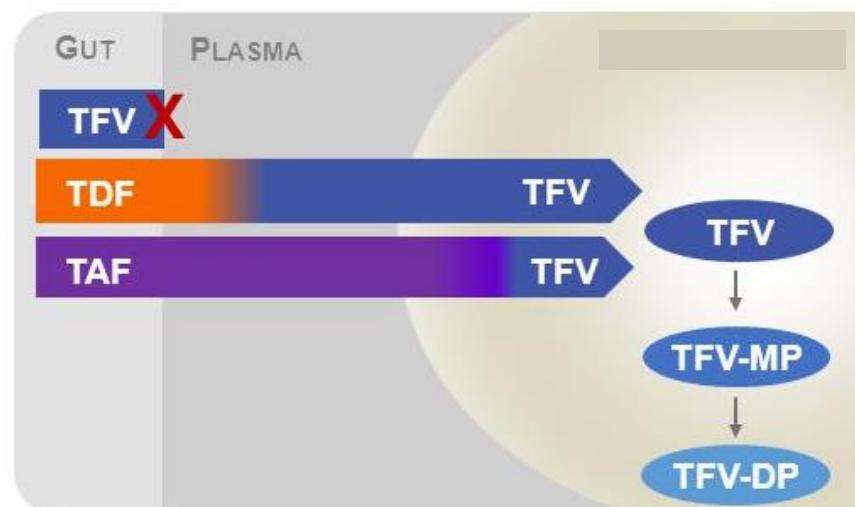
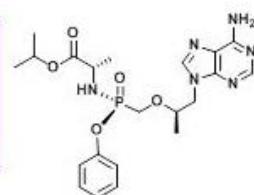
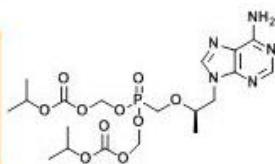
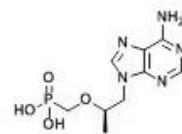


Übersicht

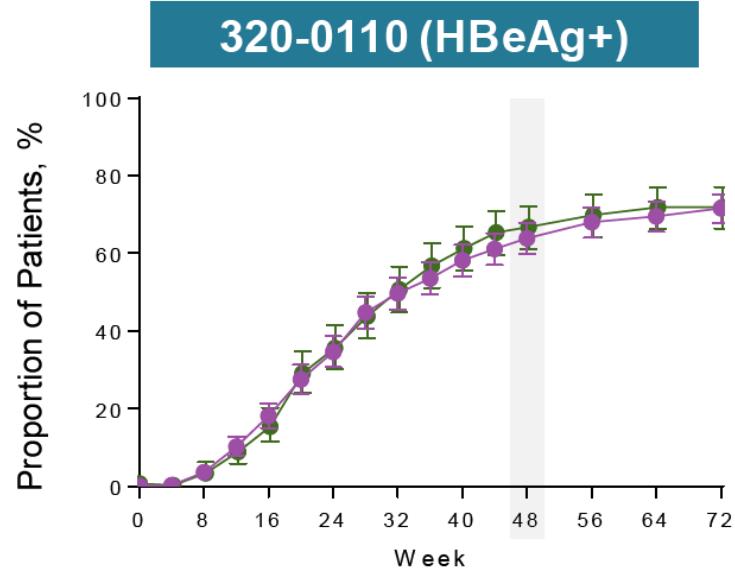
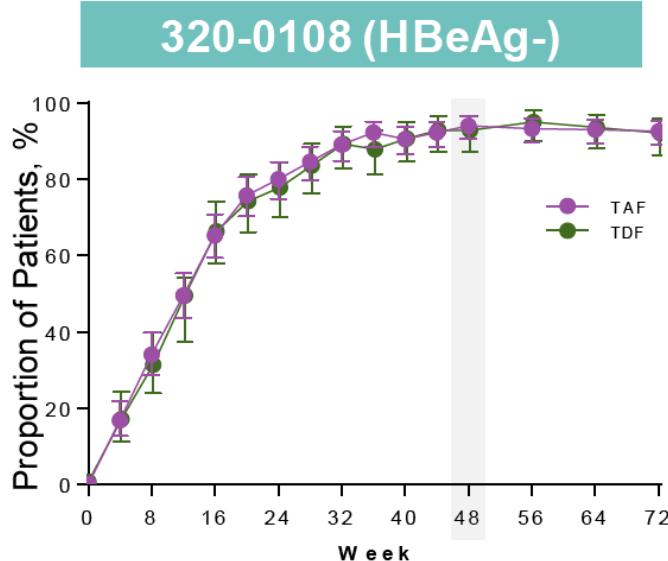
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Tenofovir Alafenamide (TAF)



Tenofovir Alafenamid (TAF)



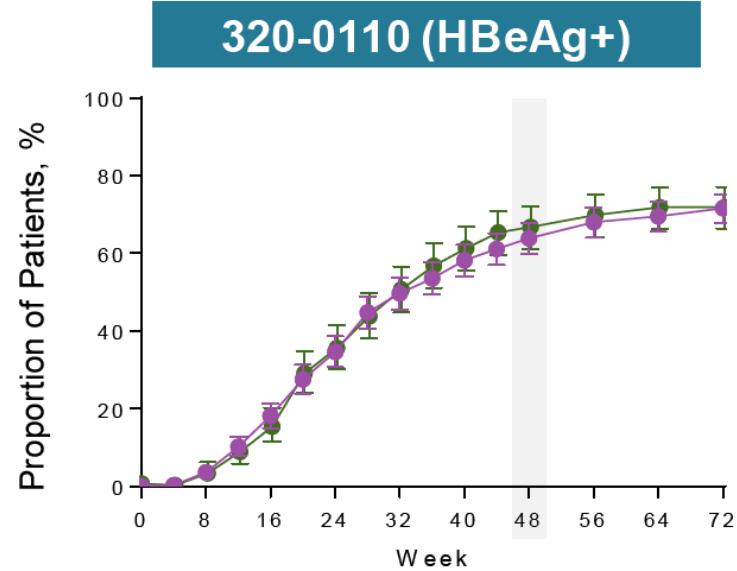
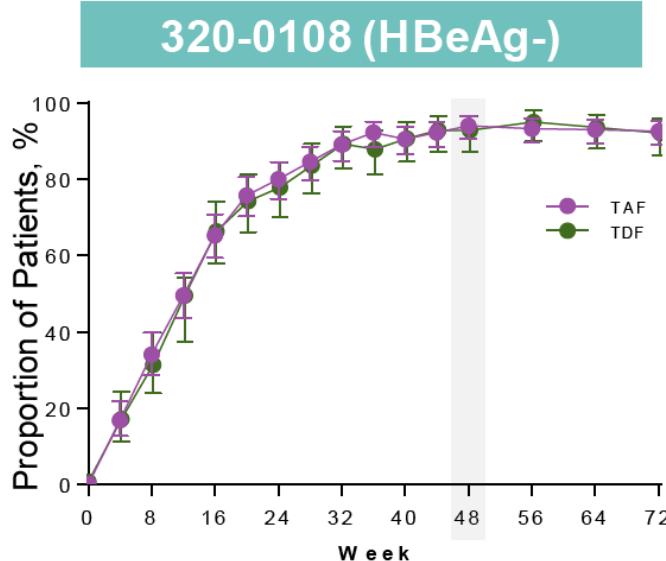
HBeAg-		HBeAg+	
TAF n=285	TDF n=140	TAF n=581	TDF n=292

Primary: HBV DNA <29 IU/mL

Patients, %	92.6	92.1	71.6	71.9
Difference in proportions (95% CI), %	+0.6 (-5.3, +6.4)	-0.9 (-7.0, 5.2)		
p-value	0.84		0.78	

Buti et al., EASL ILC 2016; Chan et al., EASL ILC 2016

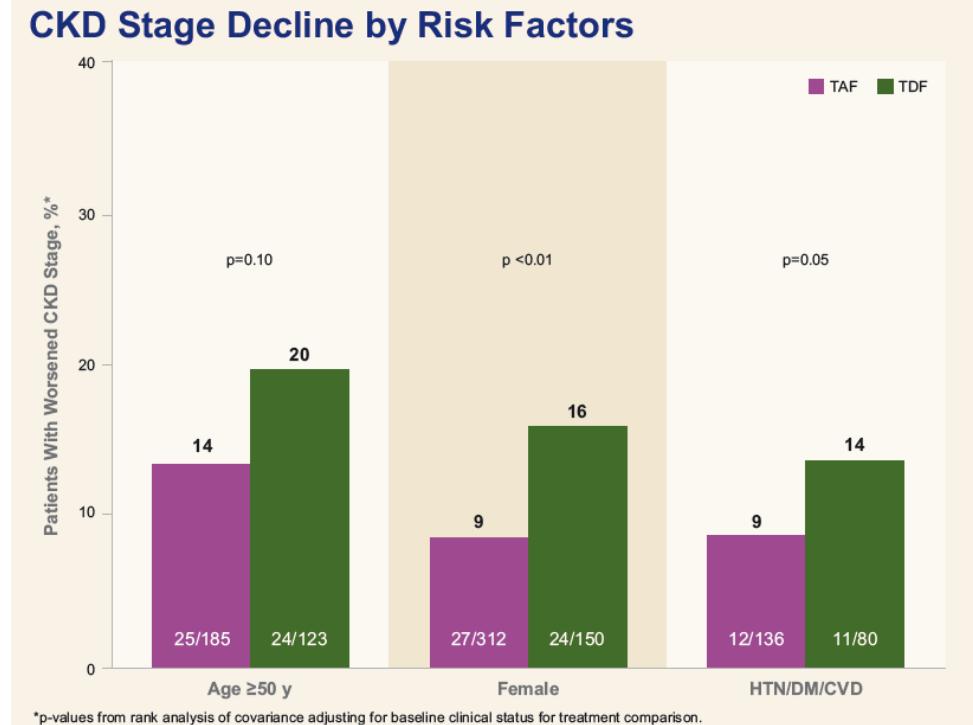
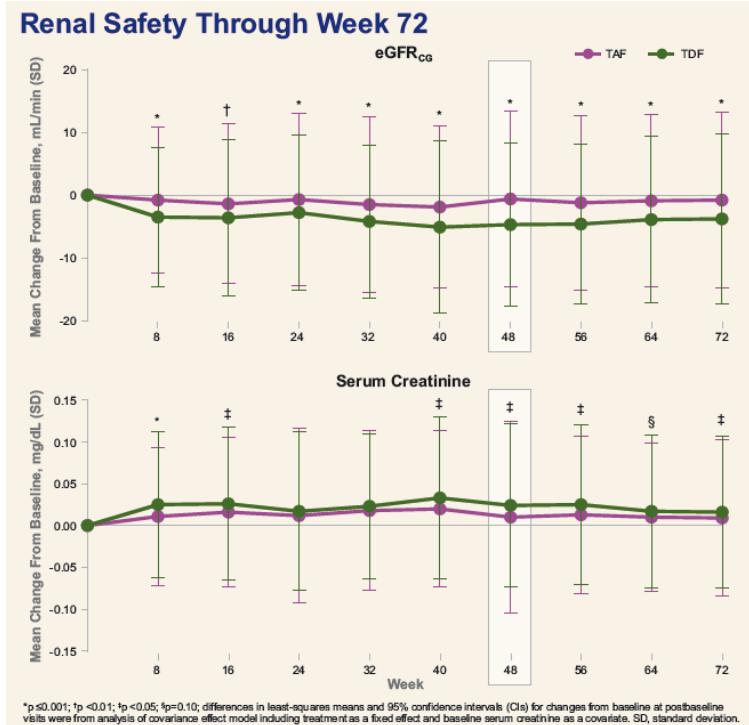
Tenofovir Alafenamid (TAF)



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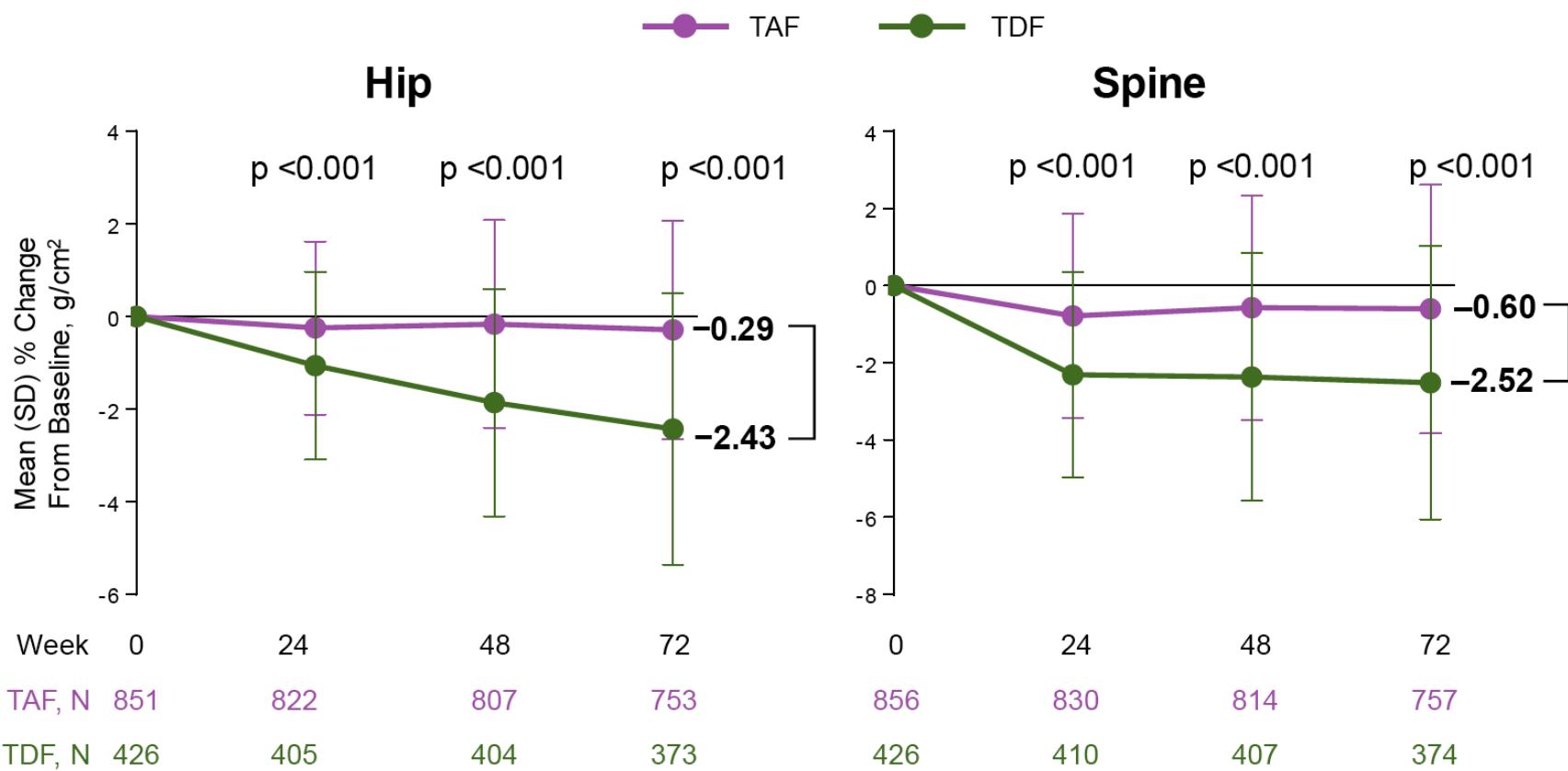
Buti et al., EASL ILC 2016; Chan et al., EASL ILC 2016

Tenofovir Alafenamide (TAF)



Agarwal et al. AASLD 2016, #1844

Tenofovir Alafenamide (TAF)



Seto et al., AASLD 2016, #67

Tenofovir Alafenamid (TAF)

- Option in besonderen Fällen
- seit Mitte Januar 2017 zugelassen
(Kombi-Präparat für HIV schon länger)
- verfügbar in D voraussichtlich ab April 2017



Übersicht

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Neue Targets – kein leichter Weg





Immunmodulatoren 1: Vakzine

NEW AND EXPERIMENTAL THERAPIES

GS-4774 therapeutic vaccine shows little efficacy in people with hepatitis B

Liz Highleyman

Published: 08 December 2016

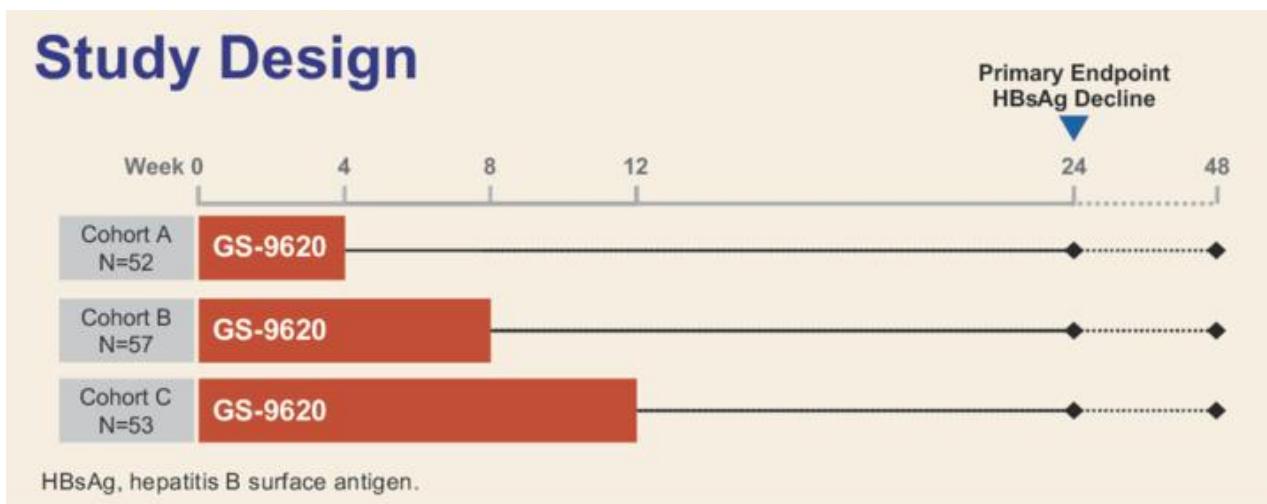
[Produced in collaboration with hivandhepatitis.com](#)



Harry Janssen, presenting at AASLD 2016. Photo by Liz Highleyman, hivandhepatitis.com

Janssen et al., AASLD 2016, #231

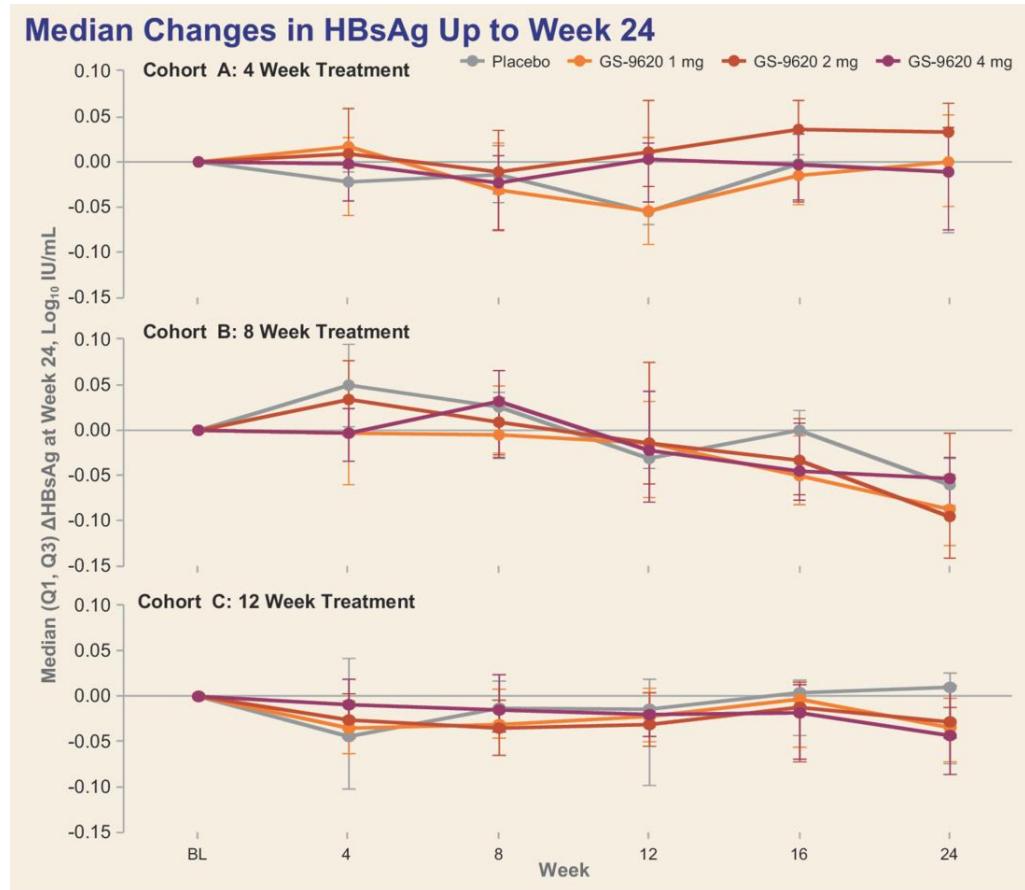
Immunmodulatoren 2: TLR7-Agonist



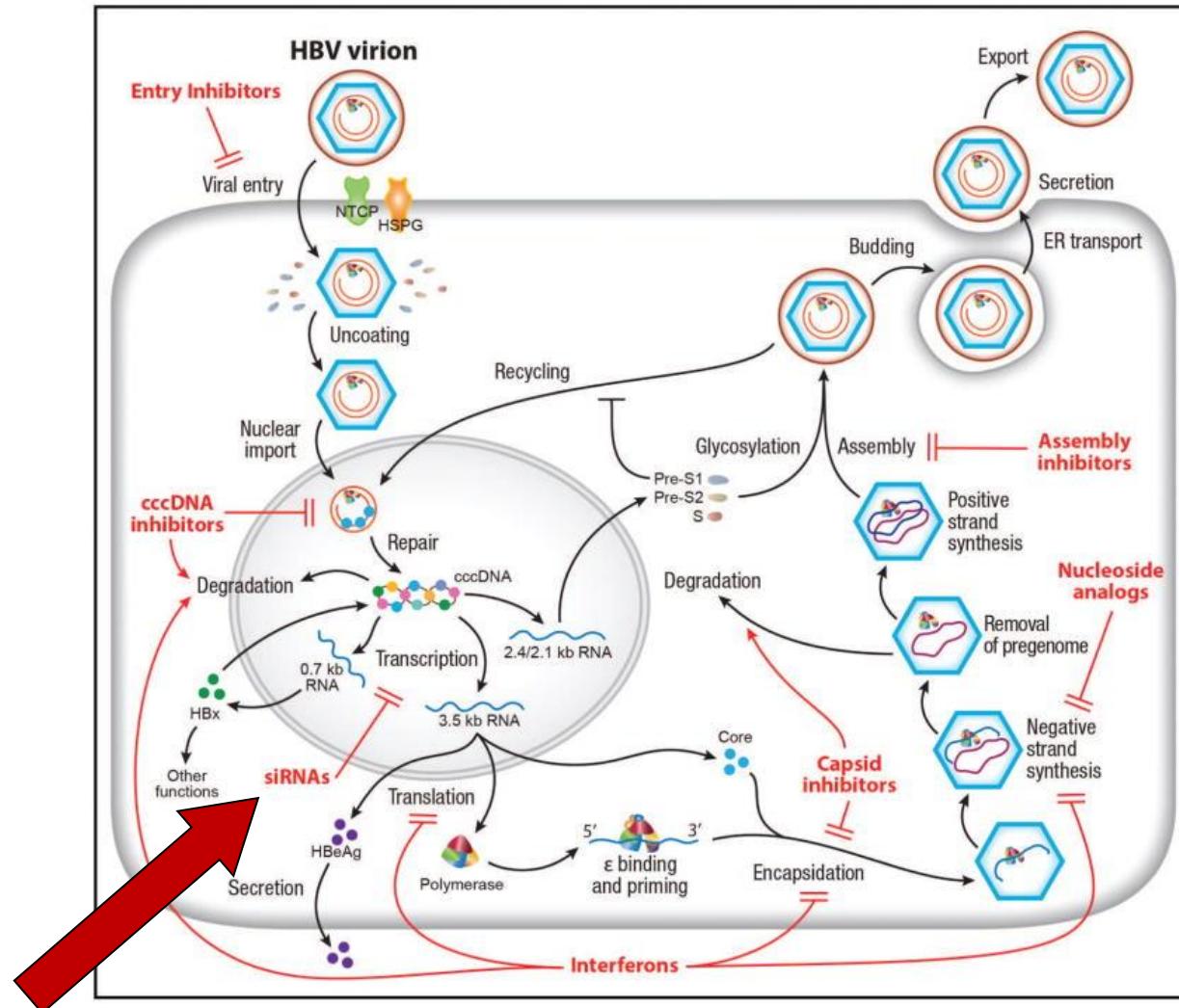
Janssen et al., AASLD 2016, #1851



Immunmodulatoren 2: TLR7-Agonist



Janssen et al., AASLD 2016, #1851



siRNA =

small interfering RNA



HOME ABOUT US CLINICAL TRIAL FORUM

FDA Places Hold on Arrowhead's Phase 2 HBV Clinical Trial

NOVEMBER 10, 2016

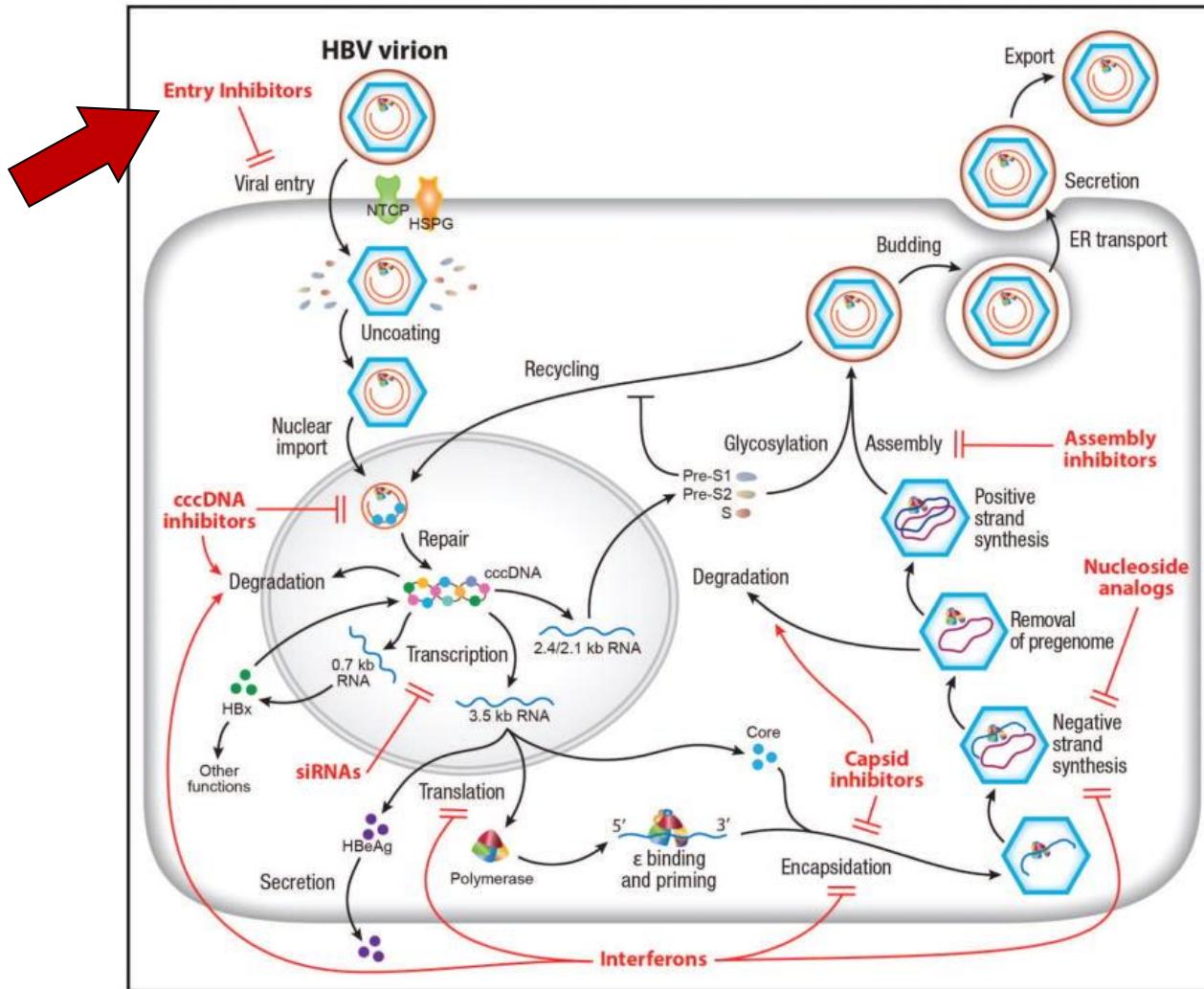


BY DANIELA SEMEDO, PHD

IN HEPATITIS B, NEWS.



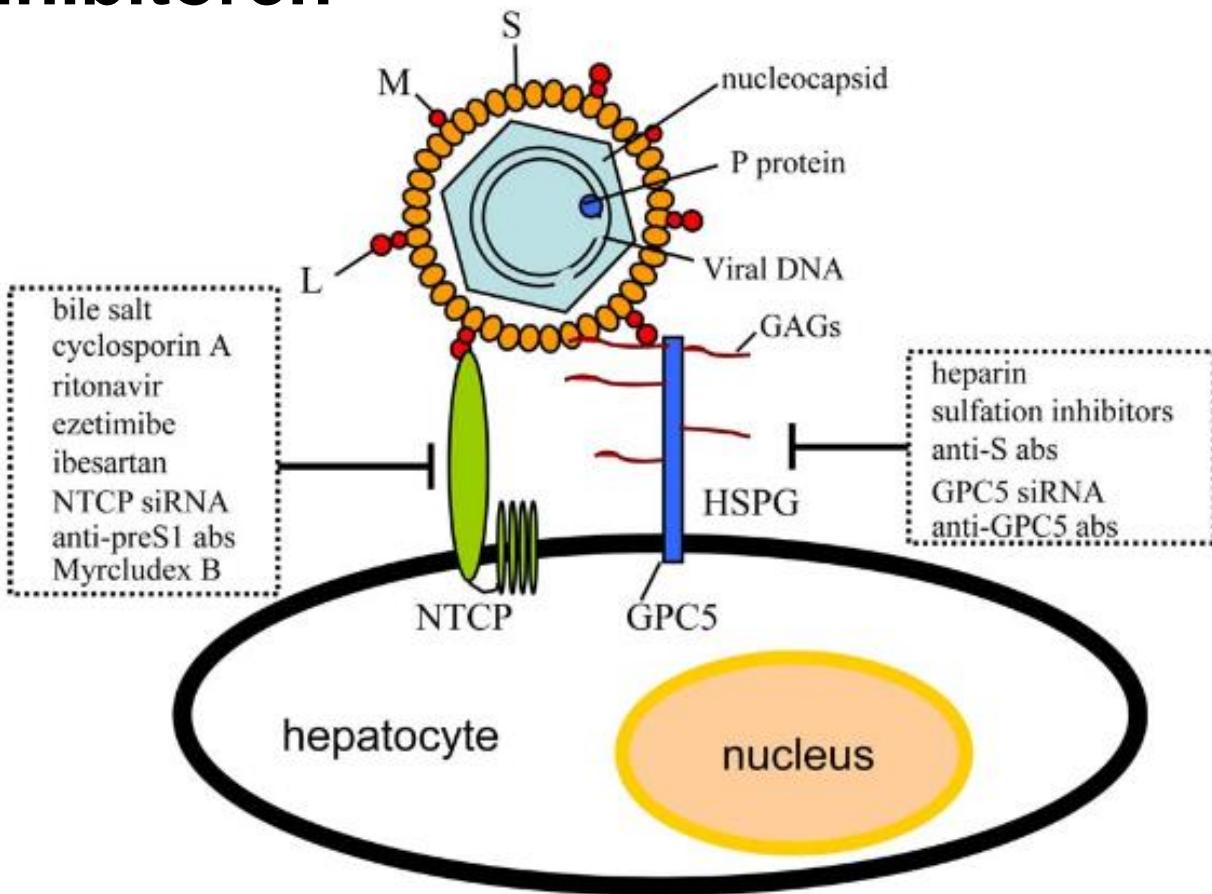
The U.S. Food and Drug Administration (FDA) placed a hold on Arrowhead Pharmaceuticals' Heparc-2004 Phase 2 clinical trial evaluating [ARC-520](#), the company's investigational medicine for the treatment of chronic hepatitis B virus (HBV) infection.



Liang et al., Hepatology 2015



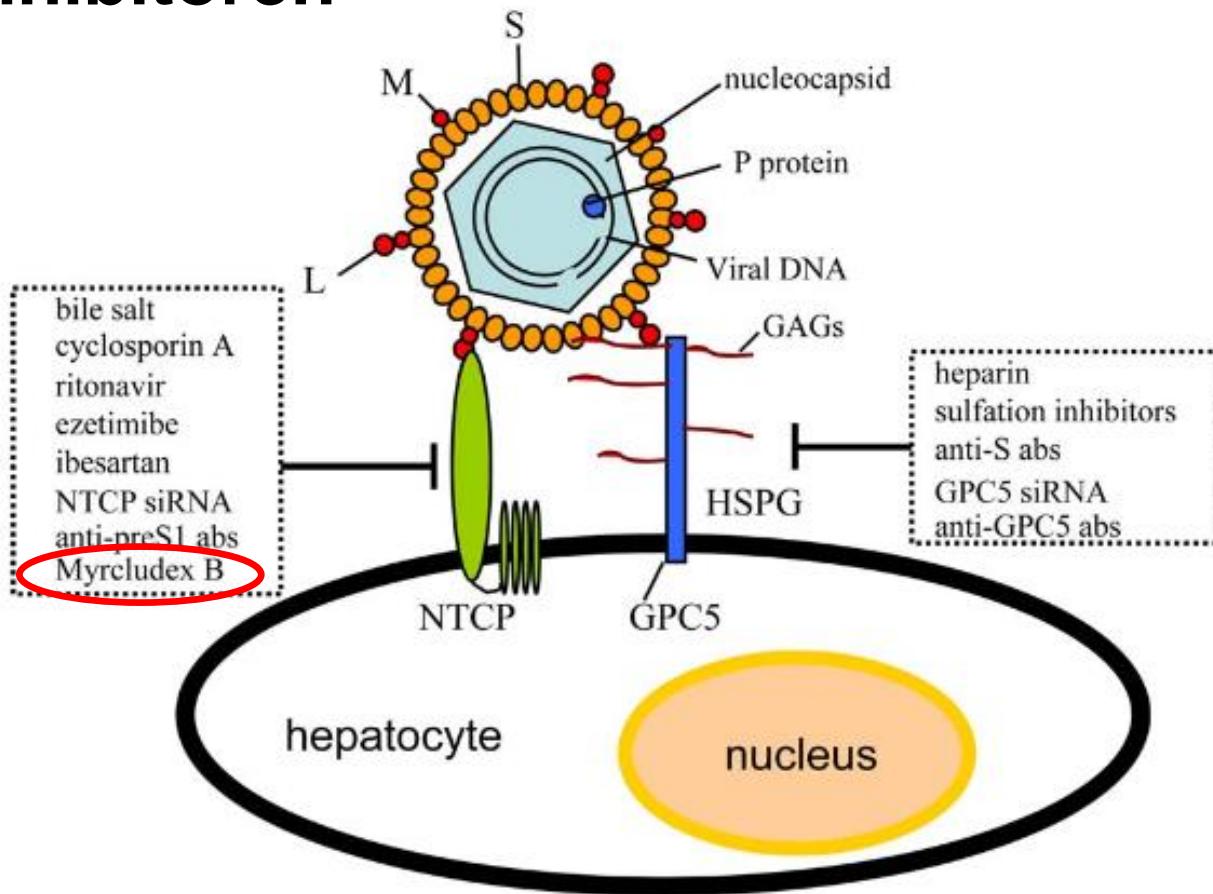
Entry-Inhibitoren



Li, Wands, Hepatology 2016 (Editorial)



Entry-Inhibitoren



Li, Wands, Hepatology 2016 (Editorial)

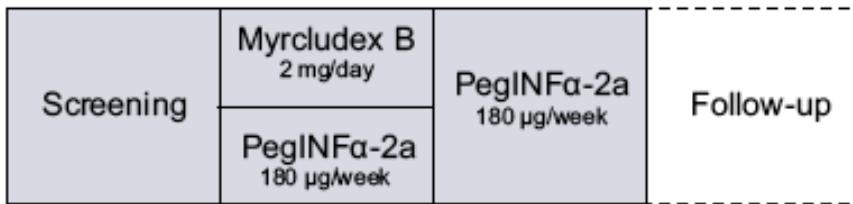
Entry-Inhibitoren – Myrcludex

HBV/HDV - Koinfektion

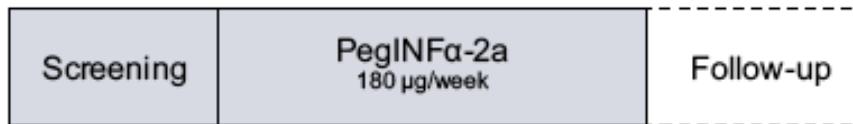
Myr cohort



Myr-IFN cohort



IFN cohort

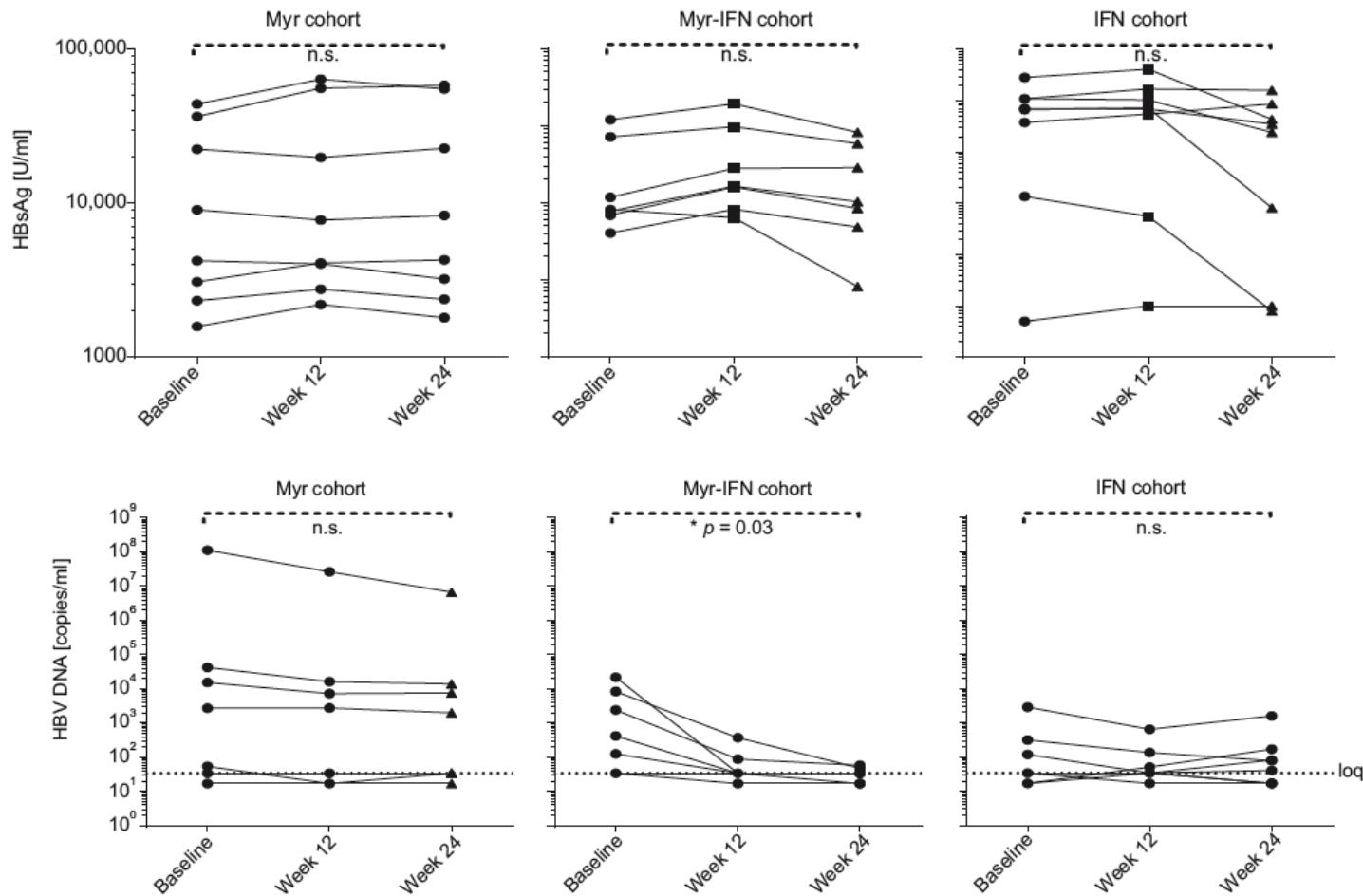


Baseline Week 12 Week 24 Week 36 Week 48 Week 60 Week 72

Bogomolov et al., J Hepatol 2016

Entry-Inhibitoren – Myrcludex

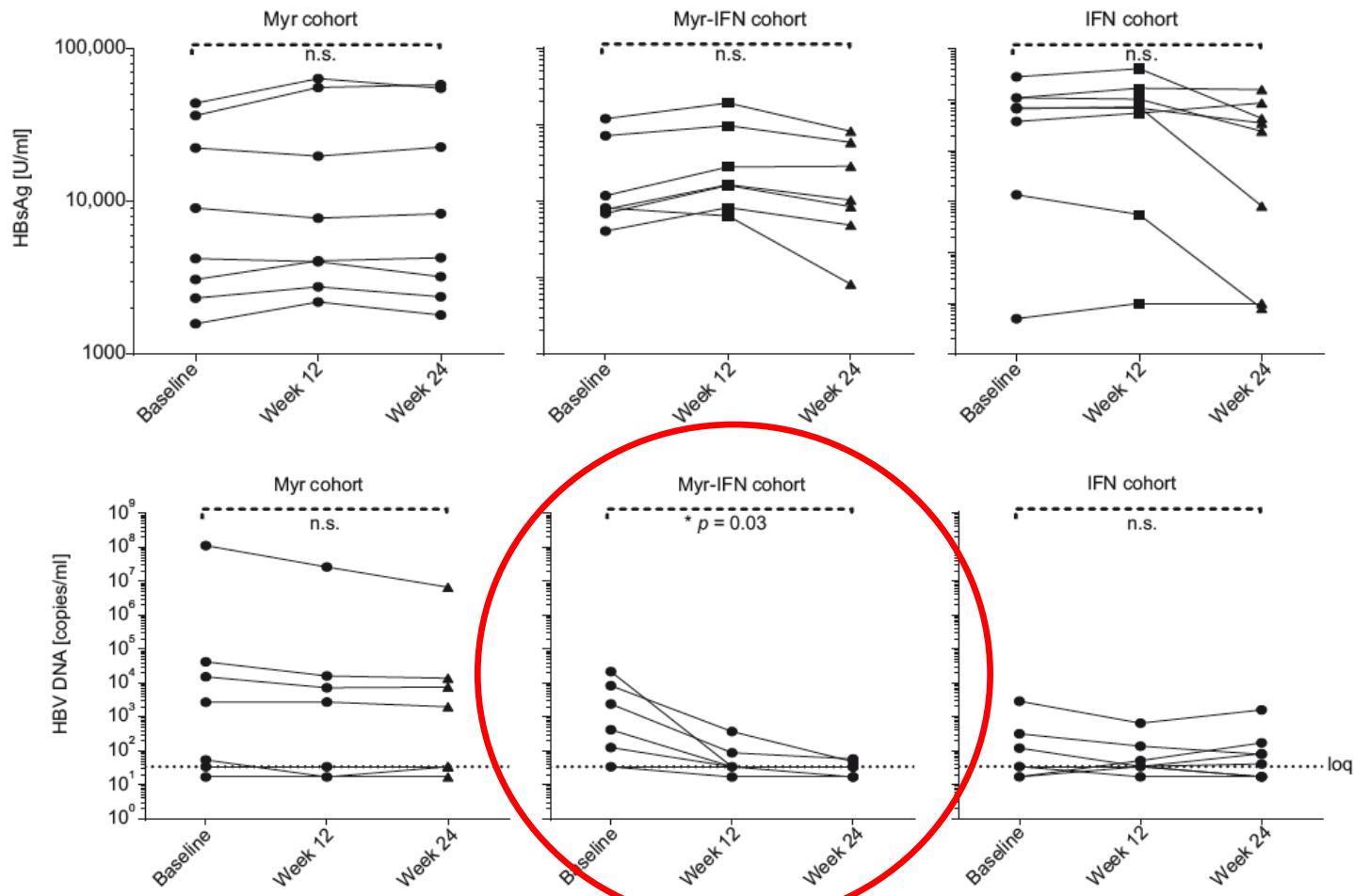
HBV



Bogomolov et al., J Hepatol 2016

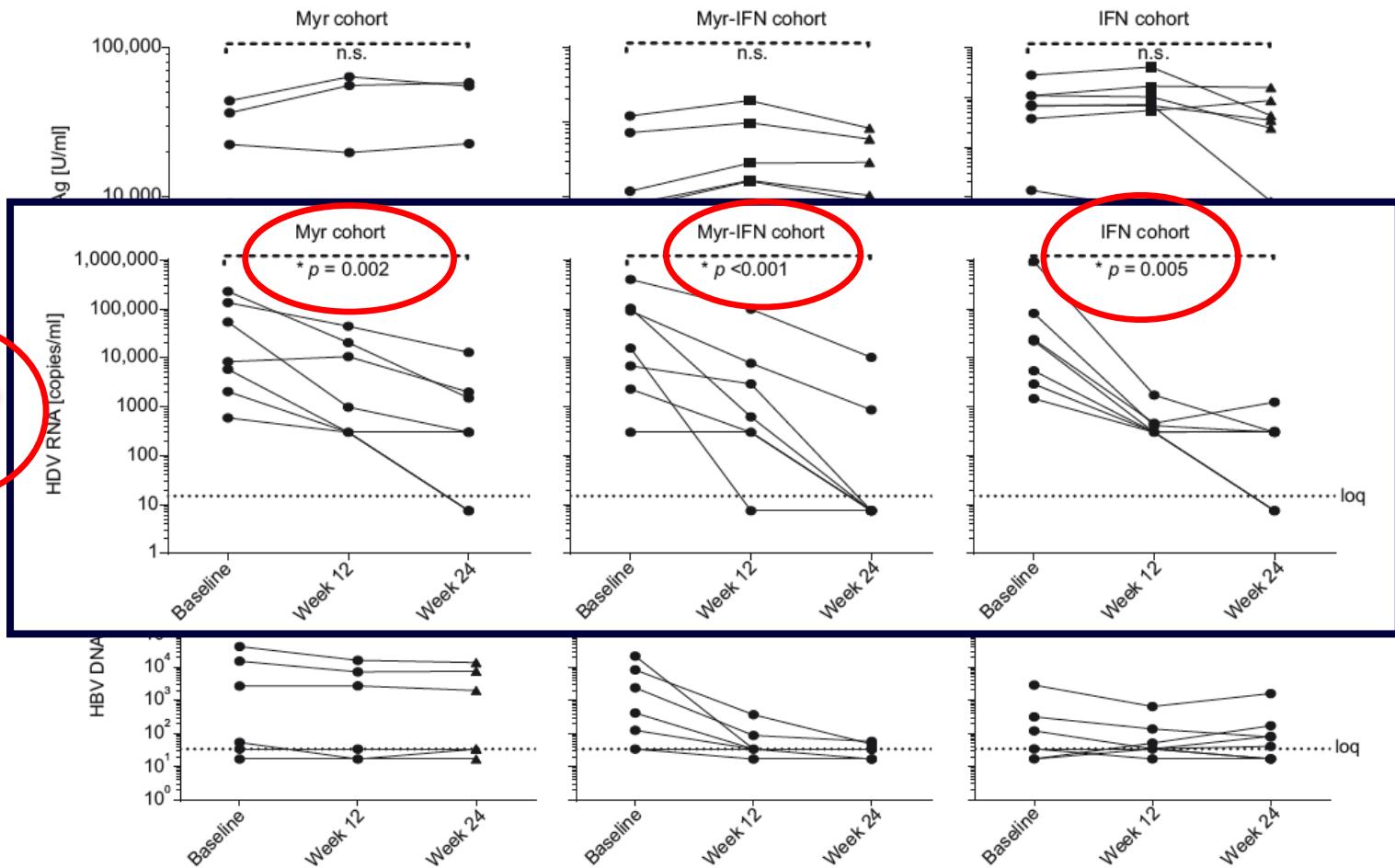
Entry-Inhibitoren – Myrcludex

HBV

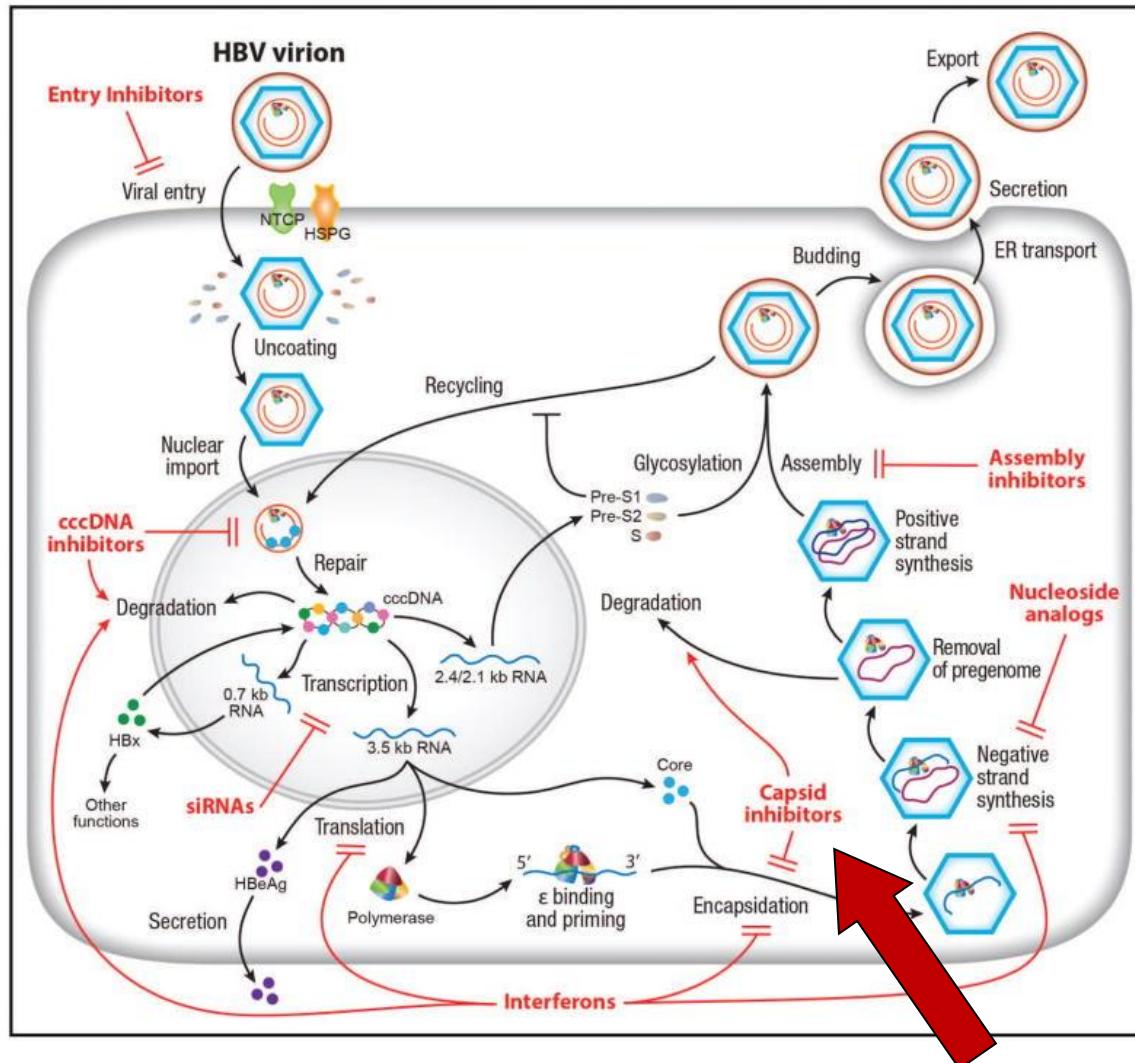


Bogomolov et al., J Hepatol 2016

Entry-Inhibitoren – Myrcludex

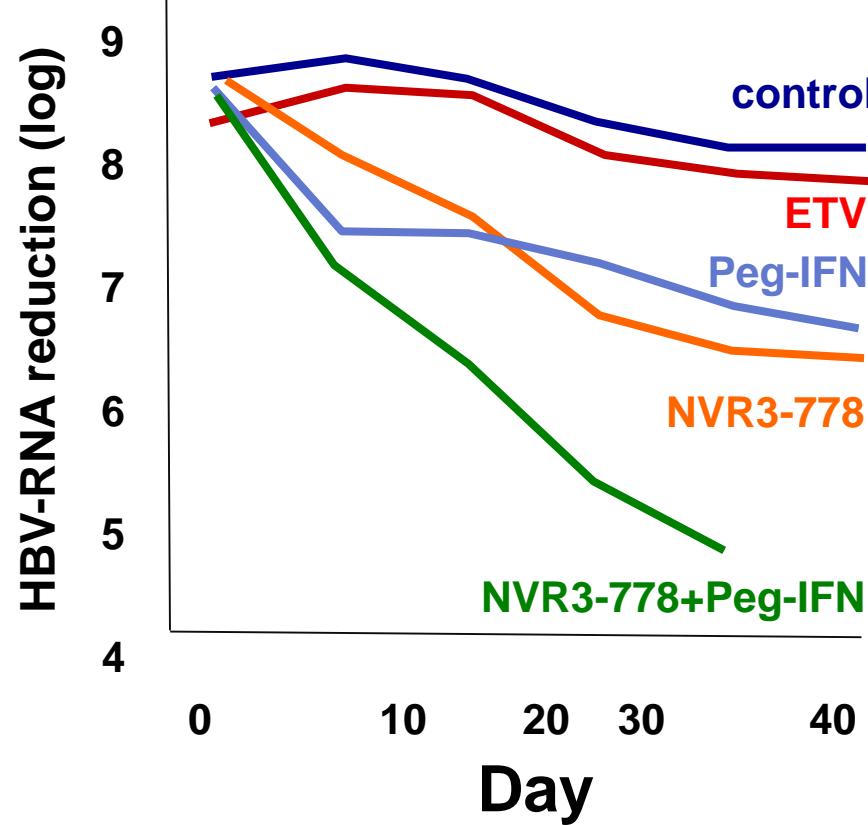
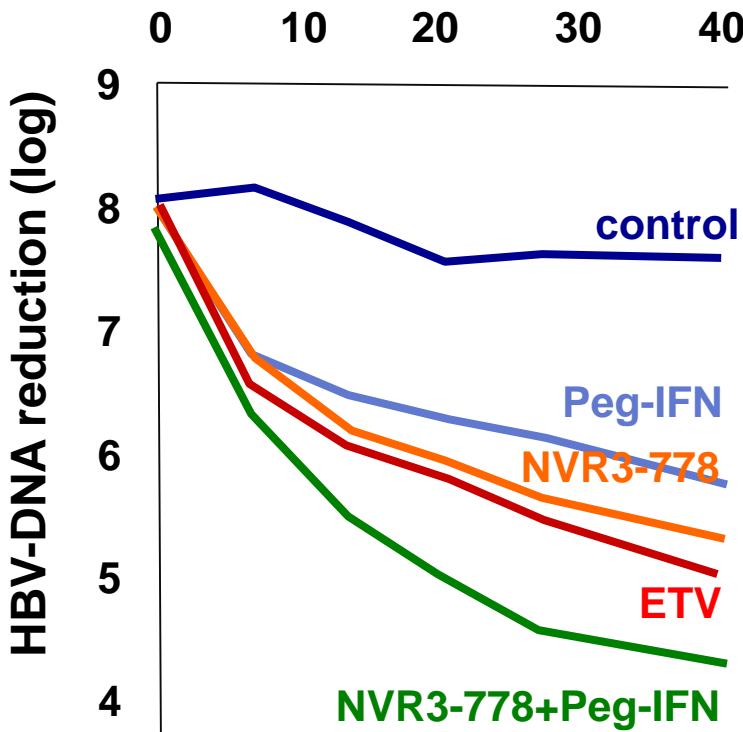


Bogomolov et al., J Hepatol 2016



Kapsidinhibitoren

Day

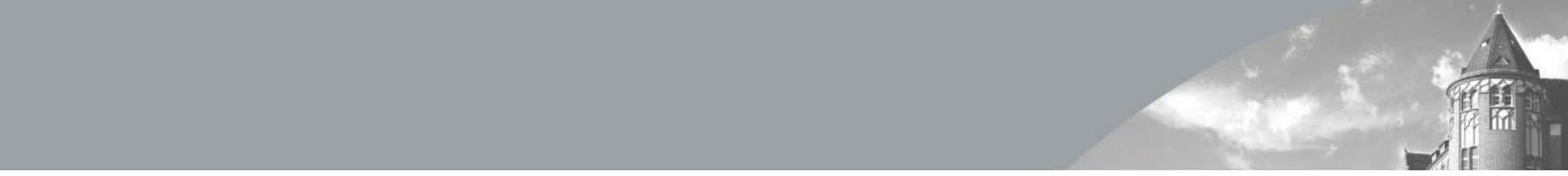


Lam et al. AASLD 2015, #33



Kapsidinhibitoren

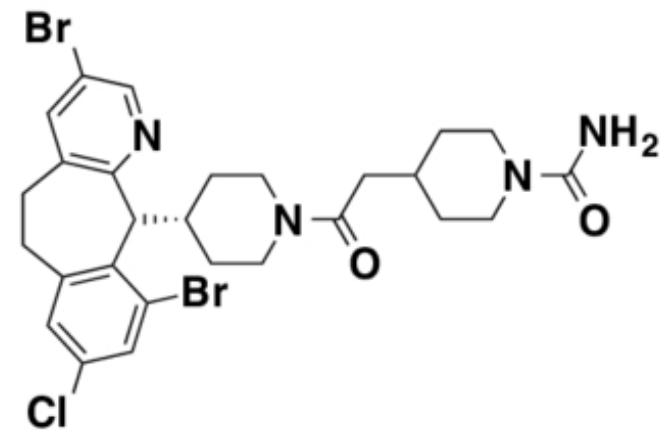
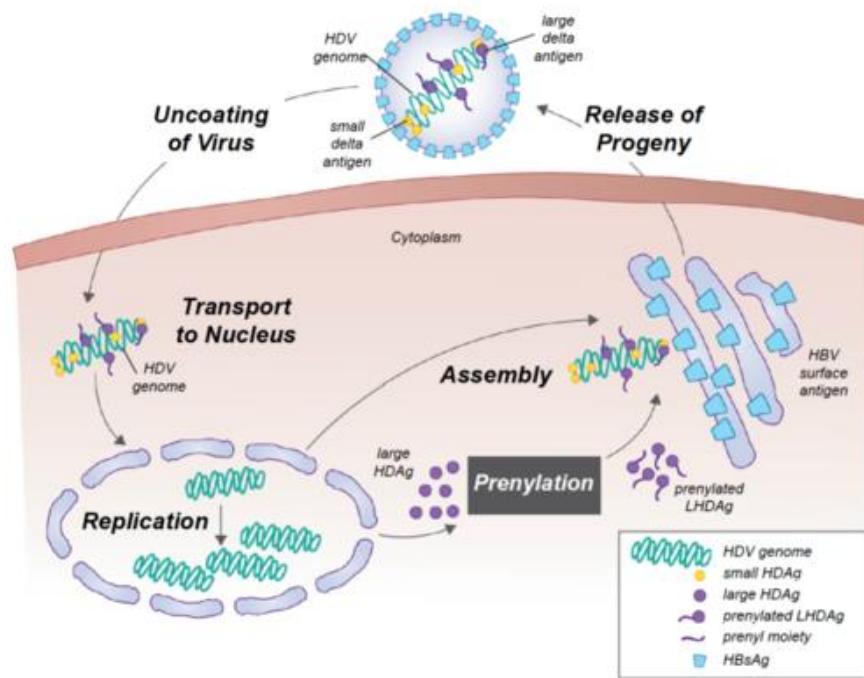
- #232 AB-423 in Kombination mit si-RNA (in vitro)
- #233 AB-423 in Kombination mit anderen Hepatitis B Therapien (in vitro)
- #234 JNJ-56136379 verhindert de novo Infektion (in vitro)
- #1881 JNJ-56136379 Sicherheit und Pharmakokinetik (Phase I)
- #1883 NVR3-778 Sicherheit und Pharmakokinetik (Phase I)



Übersicht

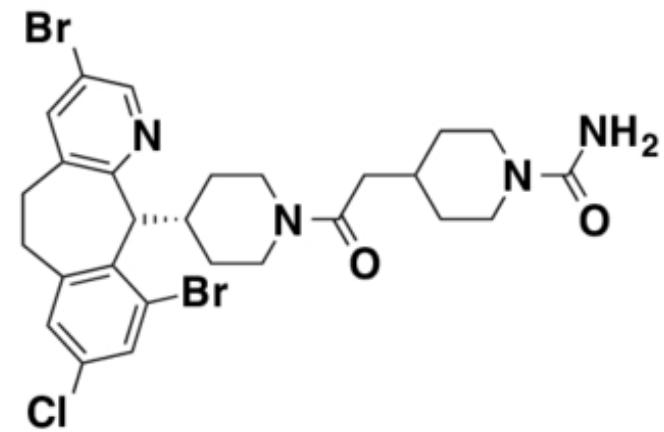
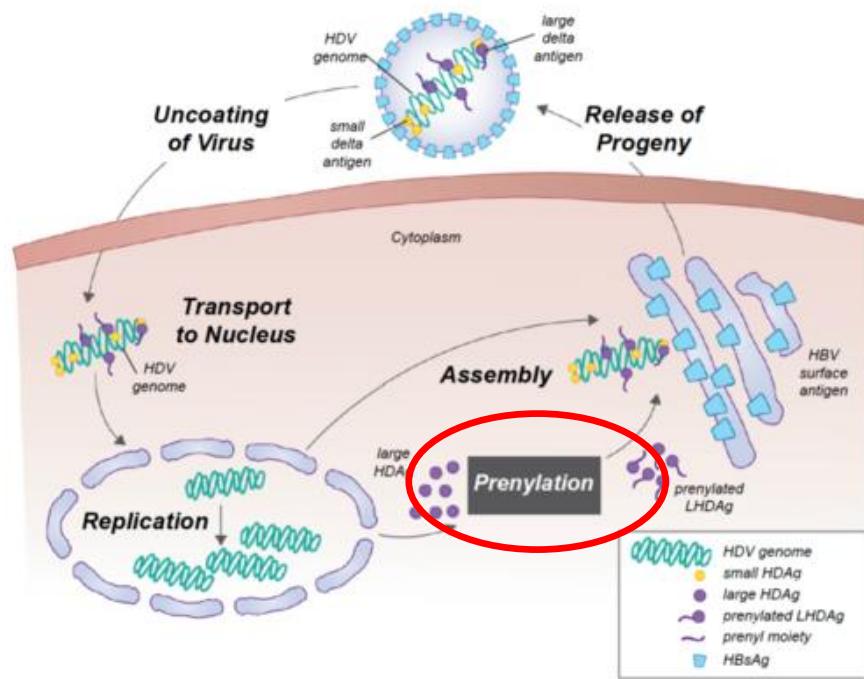
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HBV/HDV – Lonafarnib



Yurdaydin C. et al., AASLD 2016 #1845

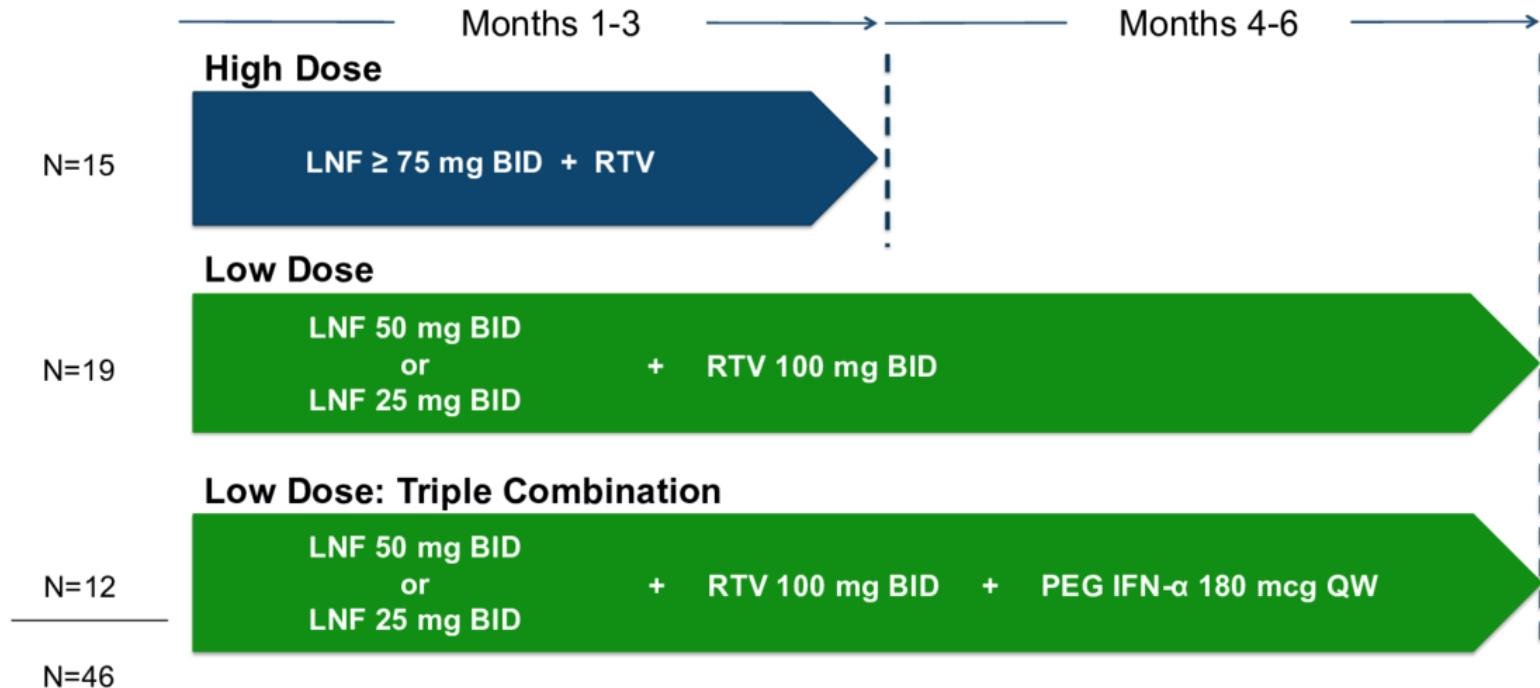
HBV/HDV – Lonafarnib



Yurdaydin C. et al., AASLD 2016 #1845

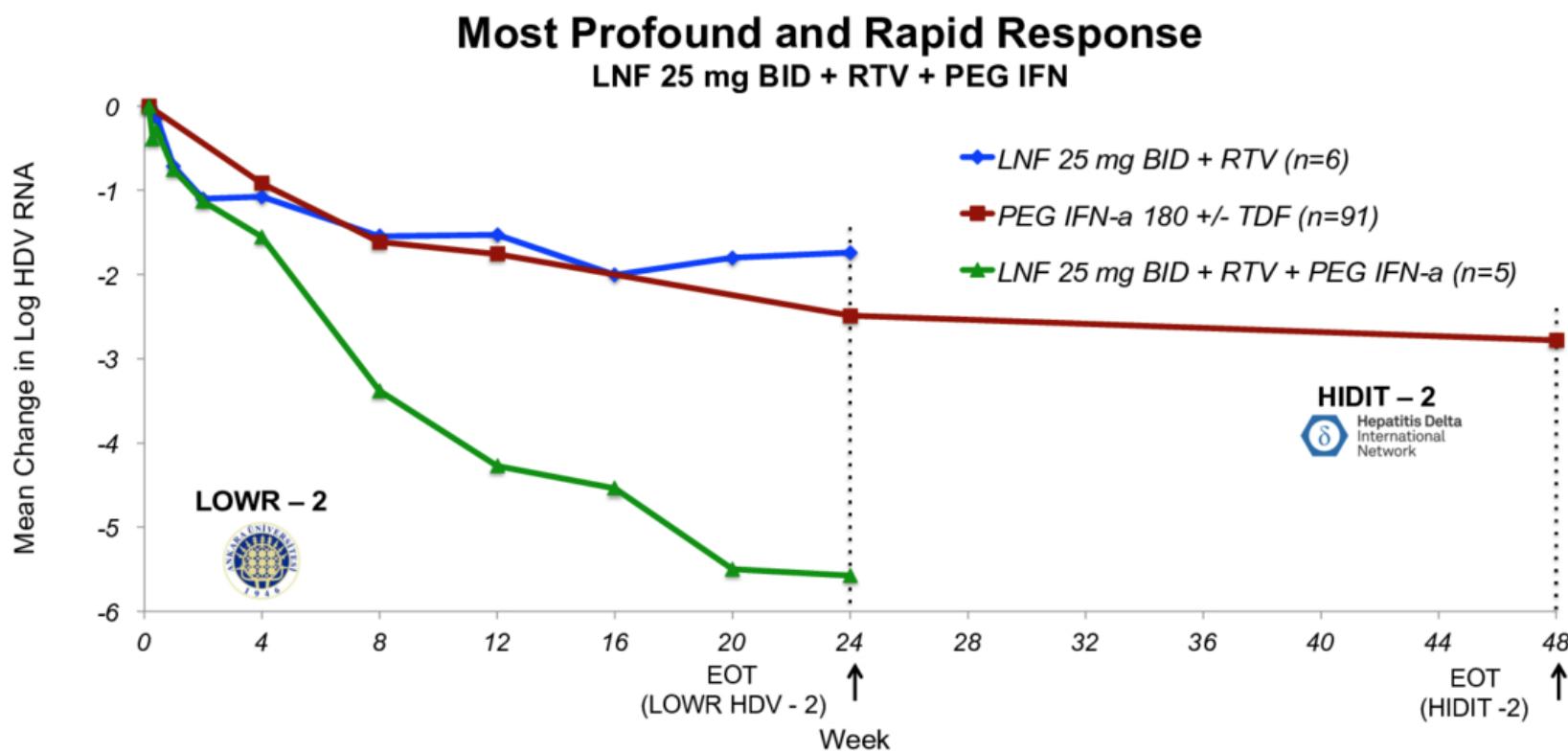
HBV/HDV – Lonafarnib

LOWR HDV – 2: “Dose Finding” Study Tolerability, Longer Dosing, and Triple Combination



Yurdaydin C. et al., AASLD 2016 #1845

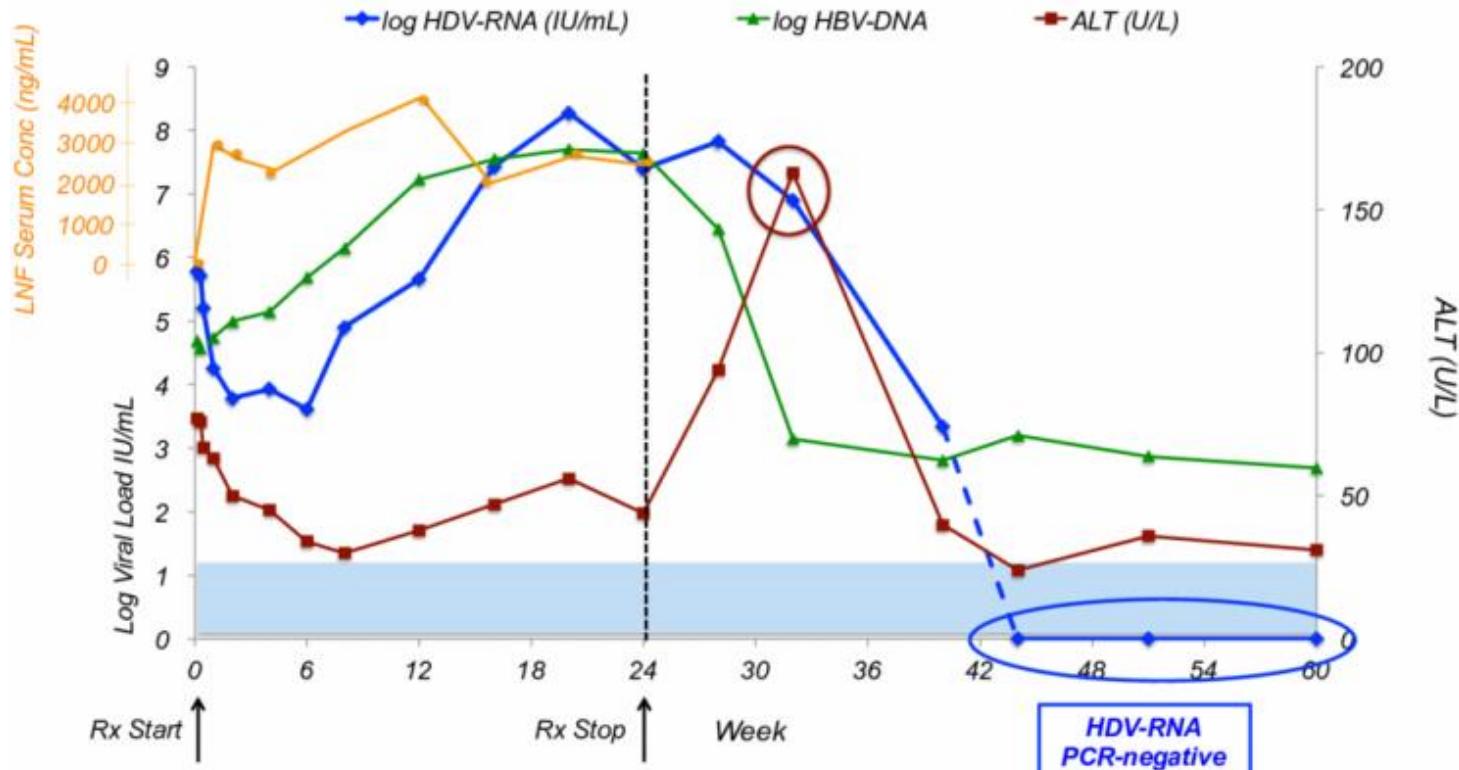
HBV/HDV – Lonafarnib



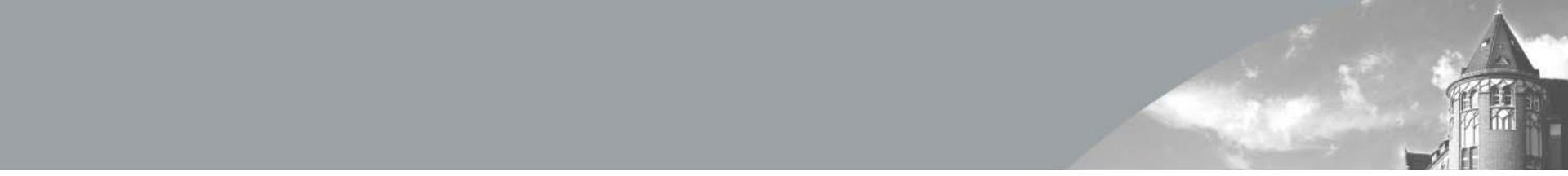
Yurdaydin C. et al., AASLD 2016 #1845

HBV/HDV – Lonafarnib

Patient 3
LNF 50 mg BID + RTV 100 mg BID



Yurdaydin C. et al., AASLD 2016 #1875



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TDF in Schwangerschaft

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load

Calvin Q. Pan, M.D., Zhongping Duan, M.D., Erhei Dai, M.D., Shuqin Zhang, M.D.,
Guorong Han, M.D., Yuming Wang, M.D., Huaihong Zhang, M.D.,
Huaibin Zou, M.D., Baoshen Zhu, M.D., Wenjing Zhao, M.D.,
and Hongxiu Jiang, M.D., for the China Study Group
for the Mother-to-Child Transmission of Hepatitis B*

Pan et al., NEJM 2016

TDF in Schwangerschaft

- HBeAg-positive Mütter
- hohe Viruslast (>200.000 IE/ml)
- TDF von 30.-32. SS-Wo.
bis 4. postpartale Wo.
- aktive + passive Impfung

Pan et al., NEJM 2016



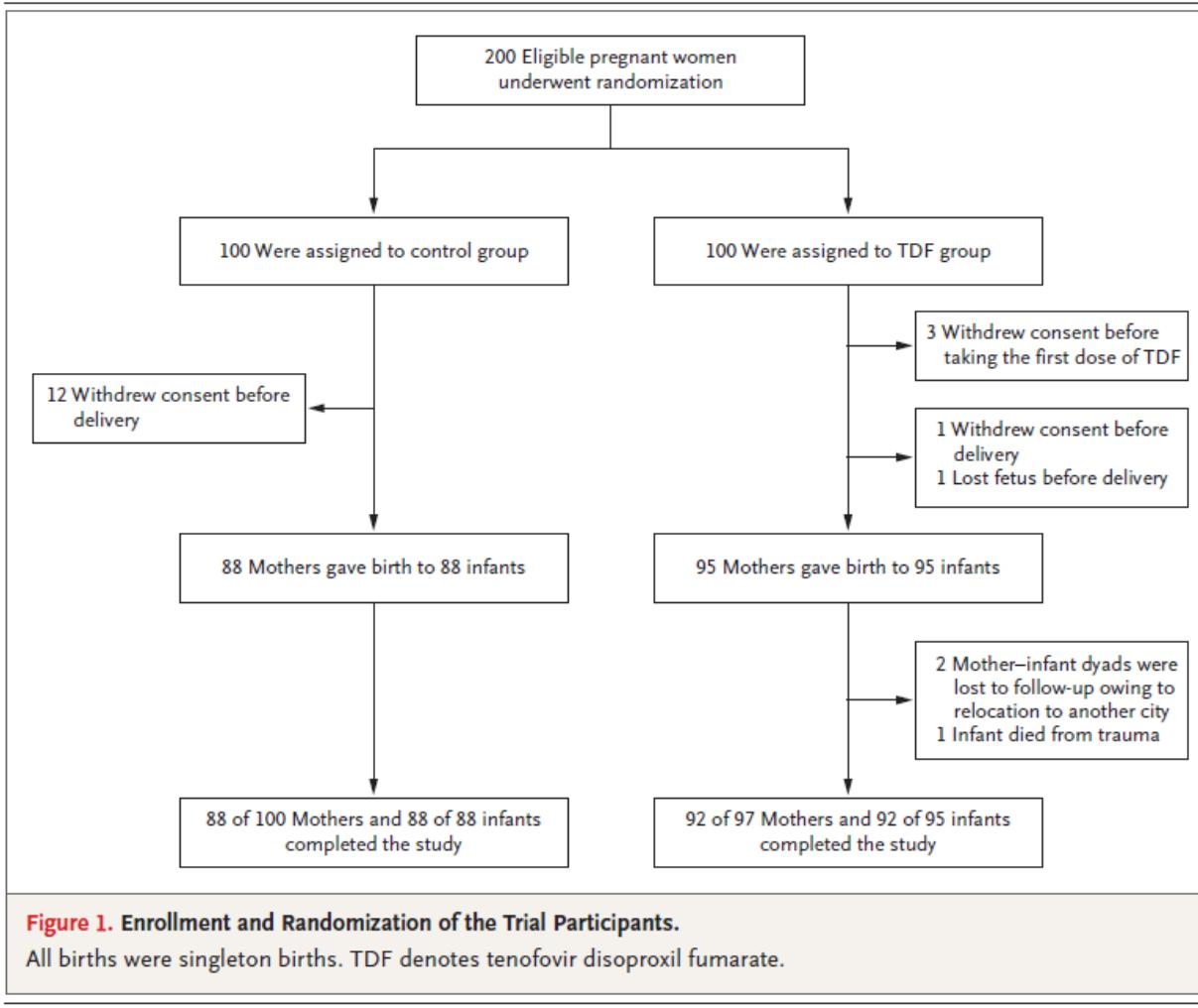
TDF in Schwangerschaft

primäre Endpunkte

- Übertragung HBV Mutter – Kind
- Fehlbildungen bei Geburt

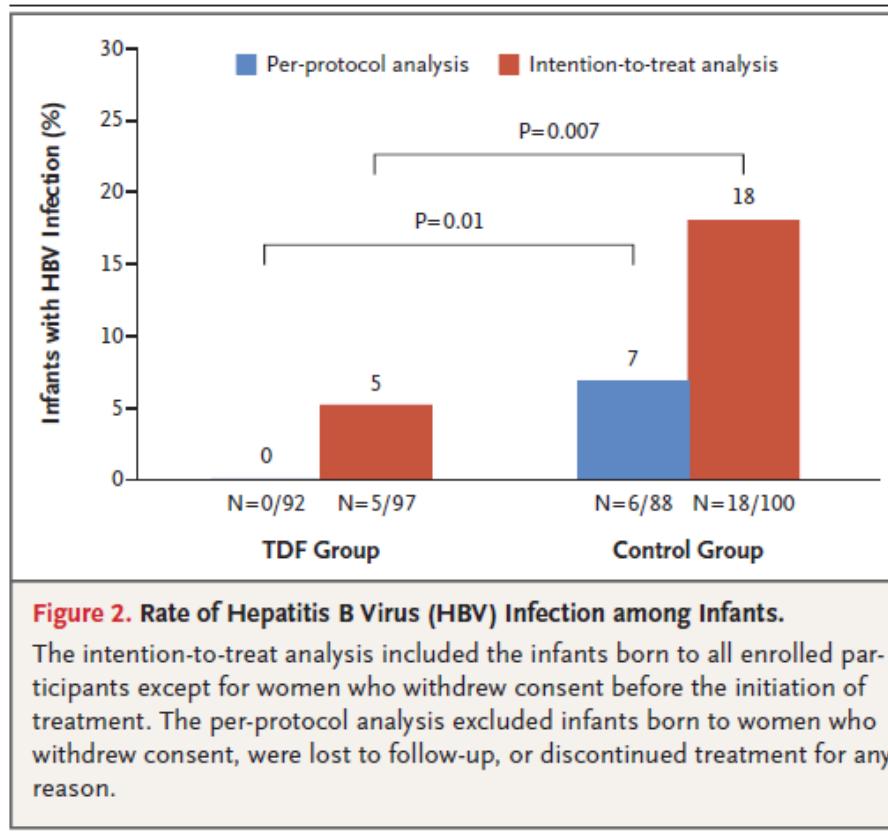
Pan et al., NEJM 2016

TDF in Schwangerschaft



Pan et al., NEJM 2016

TDF in Schwangerschaft



Pan et al., NEJM 2016



TDF in Schwangerschaft

signifikante Unterschiede bei UAW

- ALT-Anstieg
- CK-Anstieg

in der TDF-Gruppe

Pan et al., NEJM 2016

TDF in Schwangerschaft

Table 3. Birth Defects, Malformations, and Adverse Events in Infants.*

Variable	TDF (N=95)	Control (N=88)
	number (percent)	
Birth defect or malformation†	2 (2)	1 (1)
Torticollis	1 (1)	0
Umbilical hernia	1 (1)	0
Hypospadias	0	1 (1)
Adverse event		
Grade 1 or 2 event		
Fever	7 (7)	3 (3)
Skin abnormality		
Rash, including diaper rash	4 (4)	4 (5)
Café-au-lait spots	1 (1)	0
Cough	10 (11)	6 (7)
Diarrhea	6 (6)	1 (1)
Vomiting	2 (2)	1 (1)
Jaundice	2 (2)	1 (1)
Grade 3 or 4 event	3 (3)	1 (1)
Forceps-induced intracranial hemorrhage	1 (1)	0
Pneumonia	2 (2)	0
Bronchitis	0	1 (1)

* There were no significant differences between the two groups in these variables (all $P \geq 0.05$).

† The frequency of congenital deformities or defects among infants who had exposure to TDF (one infant each with umbilical hernia and torticollis) did not differ significantly from that among infants in the control group (2% [95% CI, 0 to 7] vs. 1% [95% CI, 0 to 6], $P = 1.00$).

Pan et al., NEJM 2016

TDF in Schwangerschaft

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Pan et al., NEJM 2016



Zusammenfassung

- **HBV-Infektion noch nicht (komplett) heilbar**



Zusammenfassung

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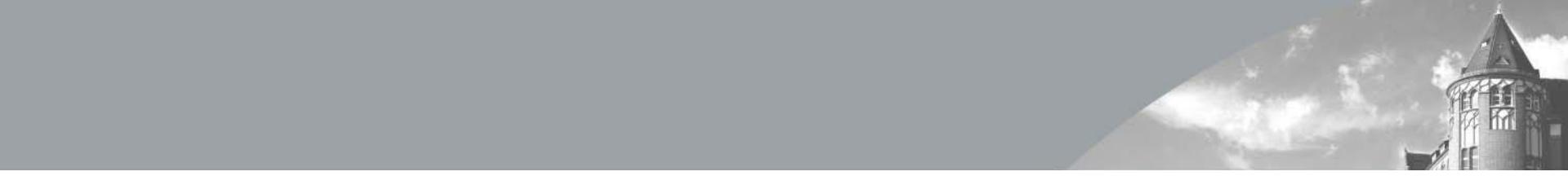


- **testen, testen, testen! (Migr.-Hintergrund, SS, HDV-Ak)**



Vielen Dank!

1) an Eckart Schott für viele Folien



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- 2) für die Aufmerksamkeit**