Hepatit B'de Güncelleme

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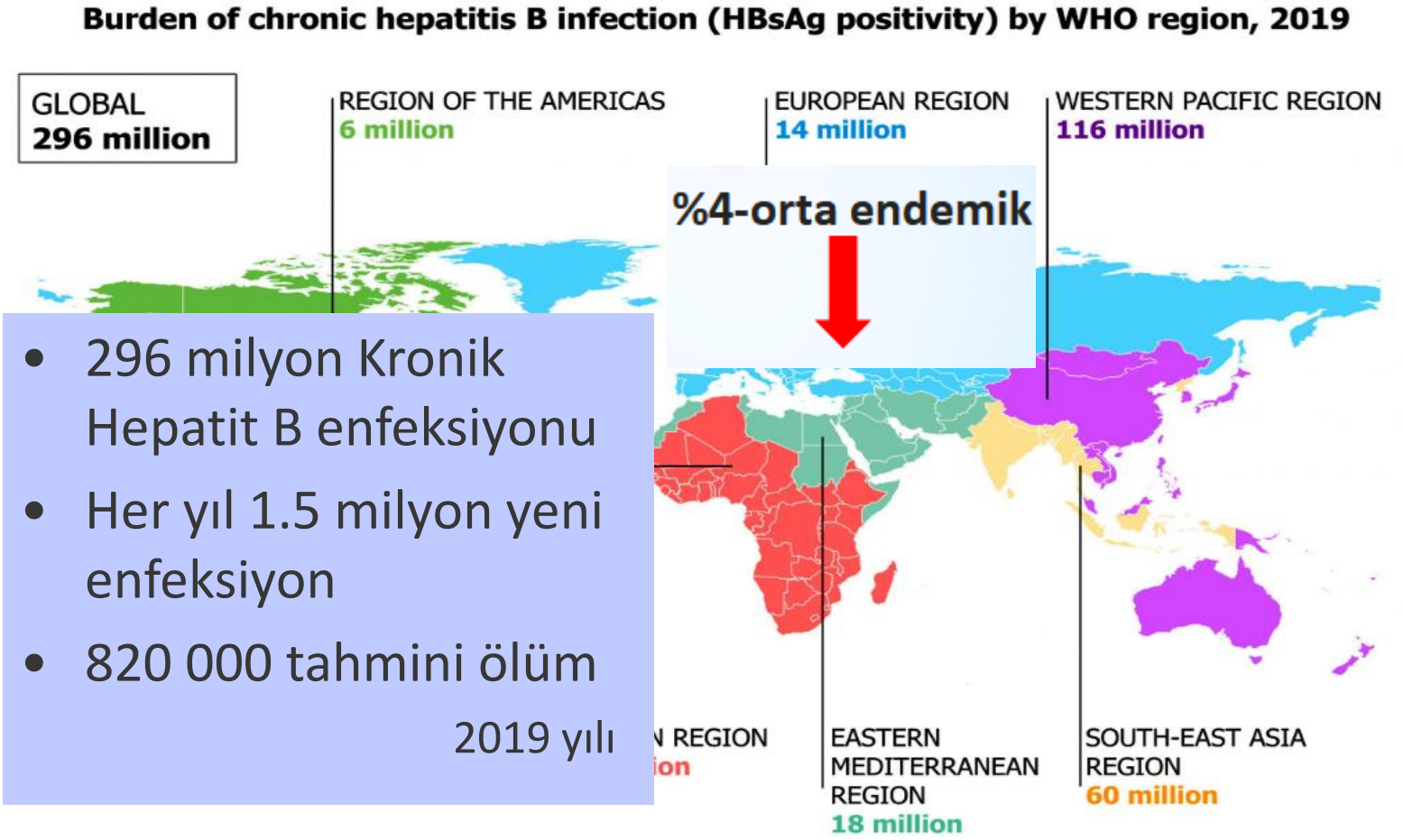
Ondokuz Mayıs Üniversitesi
Tıp Fakültesi

Epidemiyoloji



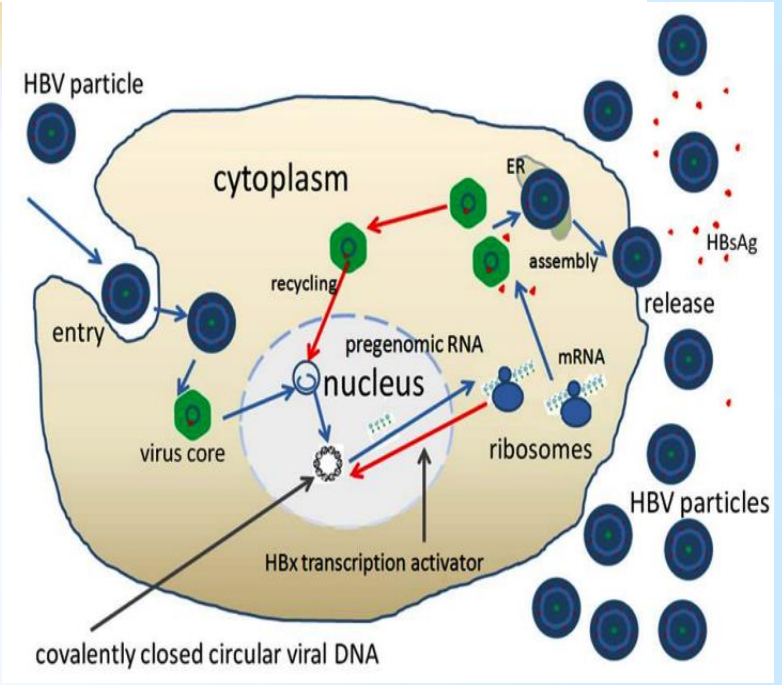
- 296 milyon Kronik Hepatit B enfeksiyonu
- Her yıl 1.5 milyon yeni enfeksiyon
- 820 000 tahmini ölüm

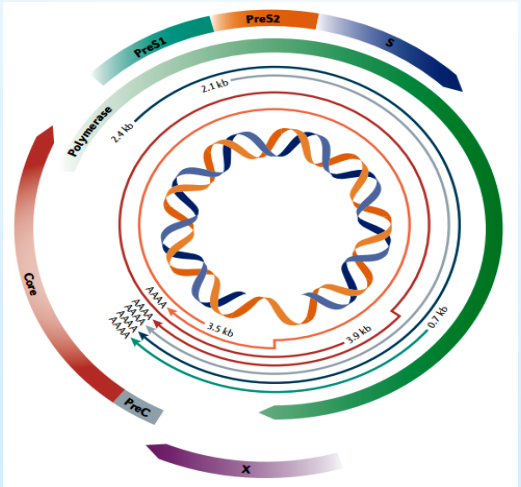
2019 yılı

https://www.who.int/news-room/fact-sheets/detail/hepatitis-b

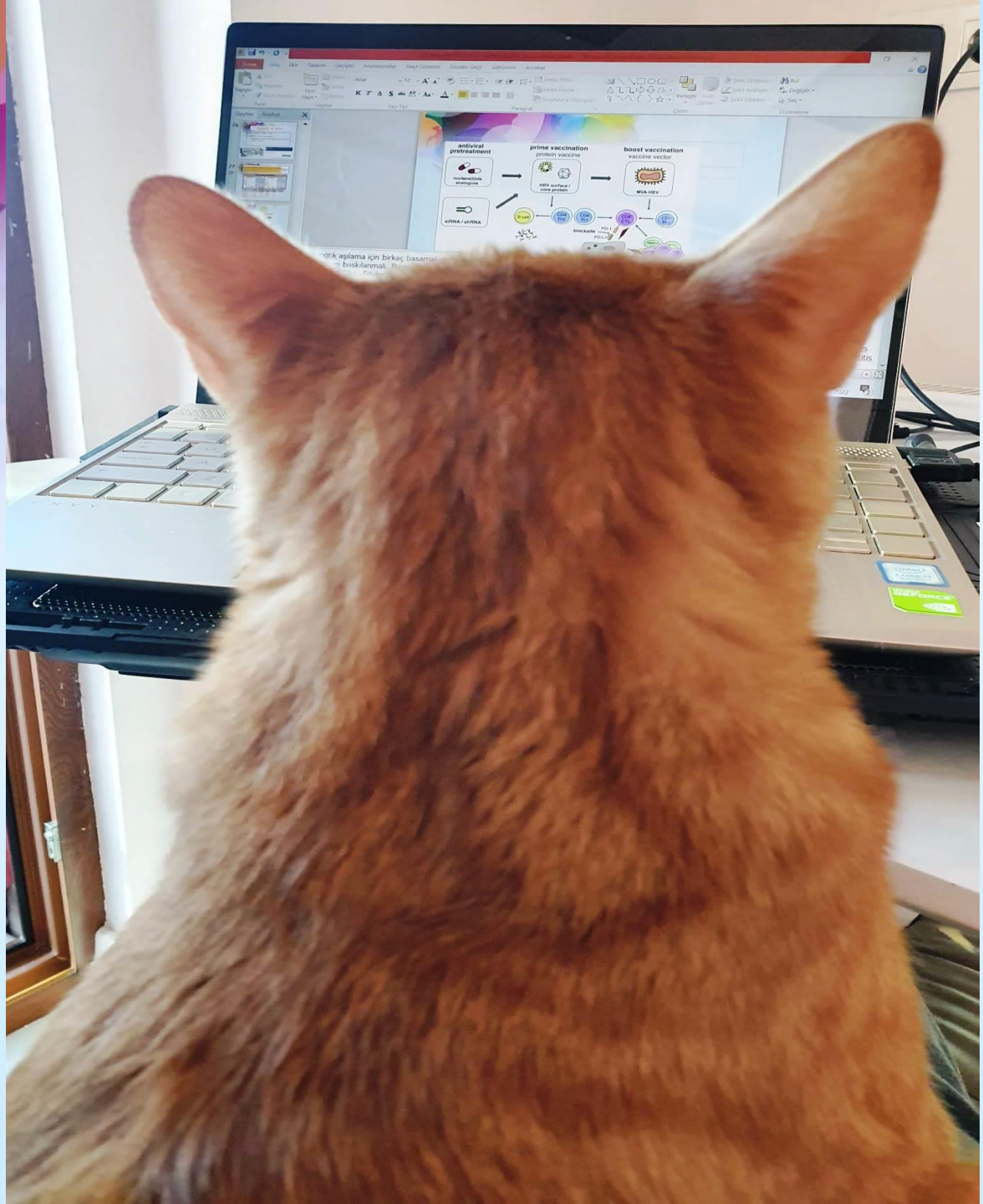
Patogenez

1. HBV hepatosite bağlanır
2. Genom nükleokapsidden ayrılıp çekirdeğe girer
3. Çekirdekte rcDNA'nın cccDNA'ya dönüştürülmesi
4. Pregenomik RNA; e,kor,polimeraz proteinleri
5. Kısa RNA: x,yüzey proteinleri
6. Pregenom kor partikülleri içinde yerleşir
7. HBV DNA oluşumu
8. Kor partikülü zarf proteinleri ile çevrilir
9. Hepatosit dışına salınır





- preS/S ORF:yüzey glikoproteinleri (L, M, S HBsAg)
- preC/C ORF: HBeAg öncülü precore proteini
- Nükleokapsid (C) proteini
- X ORF:X proteini
- P ORF:DNA polimeraz


antiviral pretreatment
prime vaccination
protein vaccine
boost vaccination
vaccine vector
MVA-HBV
siRNA / shRNA
blockade

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Virology®

VIRUS-CELL INTERACTIONS

MafF Is an Antiviral Host Factor That Suppresses Transcription from Hepatitis B Virus Core Promoter

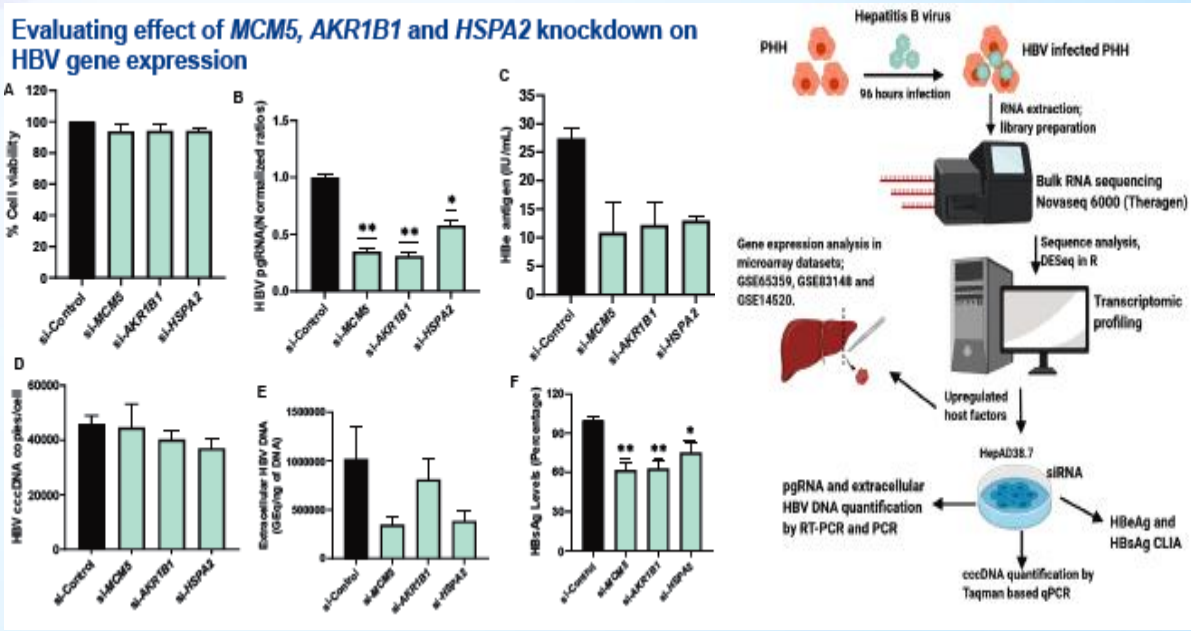
- Maf bZIP transkripsiyon faktorü F (MafF) HBV'ye karşı konak savunmasını destekler
- MafF ekpresyonu s-IL-1b veya TNF-a ile artar
- İmmün klirens döneminde bu sitokinlerle korele şekilde önemli oranda eksprese olur

Ibrahim MK, eta l. J Virol. 2021 12;95(15):e0076721.

Identification of Novel Host-factors in the Patho-biology of Hepatitis B Virus (HBV) Infection

CO. Owino [1,2], Balakrishnan Chakrapani Narmada [1], Giridharan Periyasamy[1], Pablo Bifani[2], DasGupta Ramanuj[1]
1 Genome Institute of Singapore
2 Department of Microbiology and Immunology, National University of Singapore, Singapore

- **Yeni yolaklar;** EMT, Matrisone, AURK, PECAM ve VEGFR
- **Olası konak faktörleri**: AKR1B1, HSPA2 ve MCM5



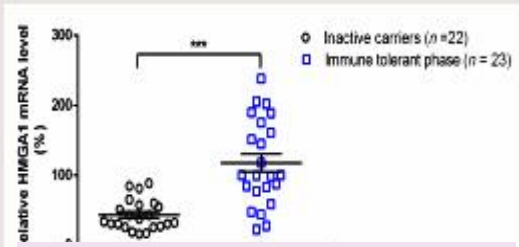
Oral P. Owino CO, **EASL 2021** poster no: 851

8.Jan;67(1):56-70.

Host factor HMGA1 promotes cccDNA transcription and HBV replication via an HBx-mediated positive feedback loop

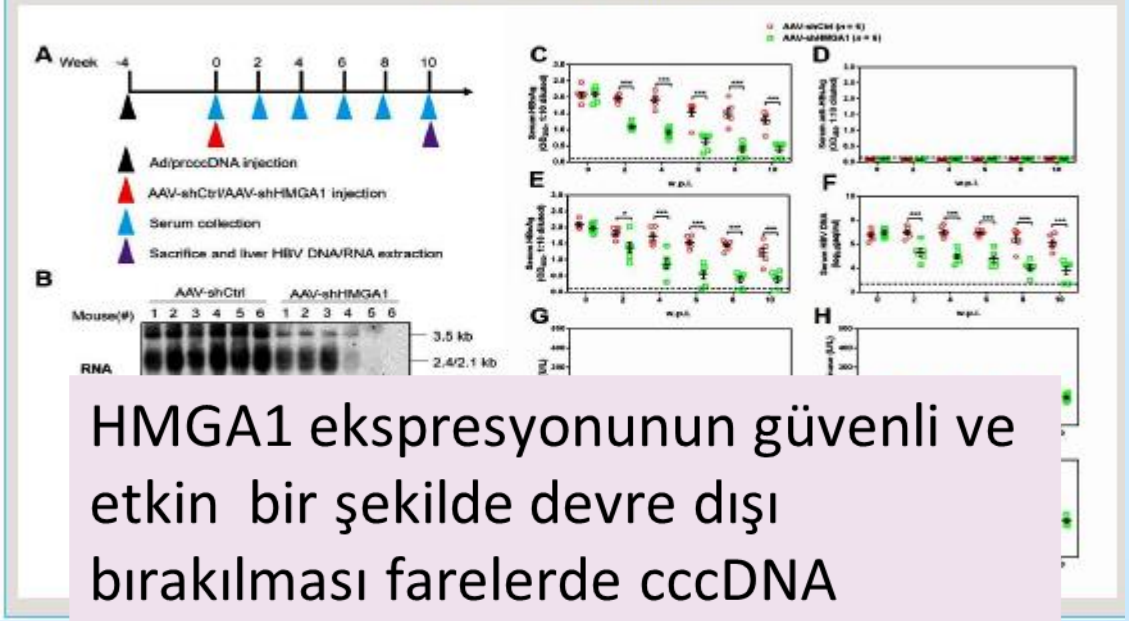
ZL Shen[1,2], JW Wu[1], ZX Gao[2], JY Wang[1], HX Zhu[1], RC Mao[1], XY Wang[2], Q Deng[2], J Liu[2], YH Xie[2], and JM Zhang[1,2]
1Huashan Hospital, Fudan University, Shanghai, People's Republic of China
2Shanghai Medical College, Fudan University, Shanghai, People's Republic of China

The levels of HMGA1 expression w much higher in IT phase.



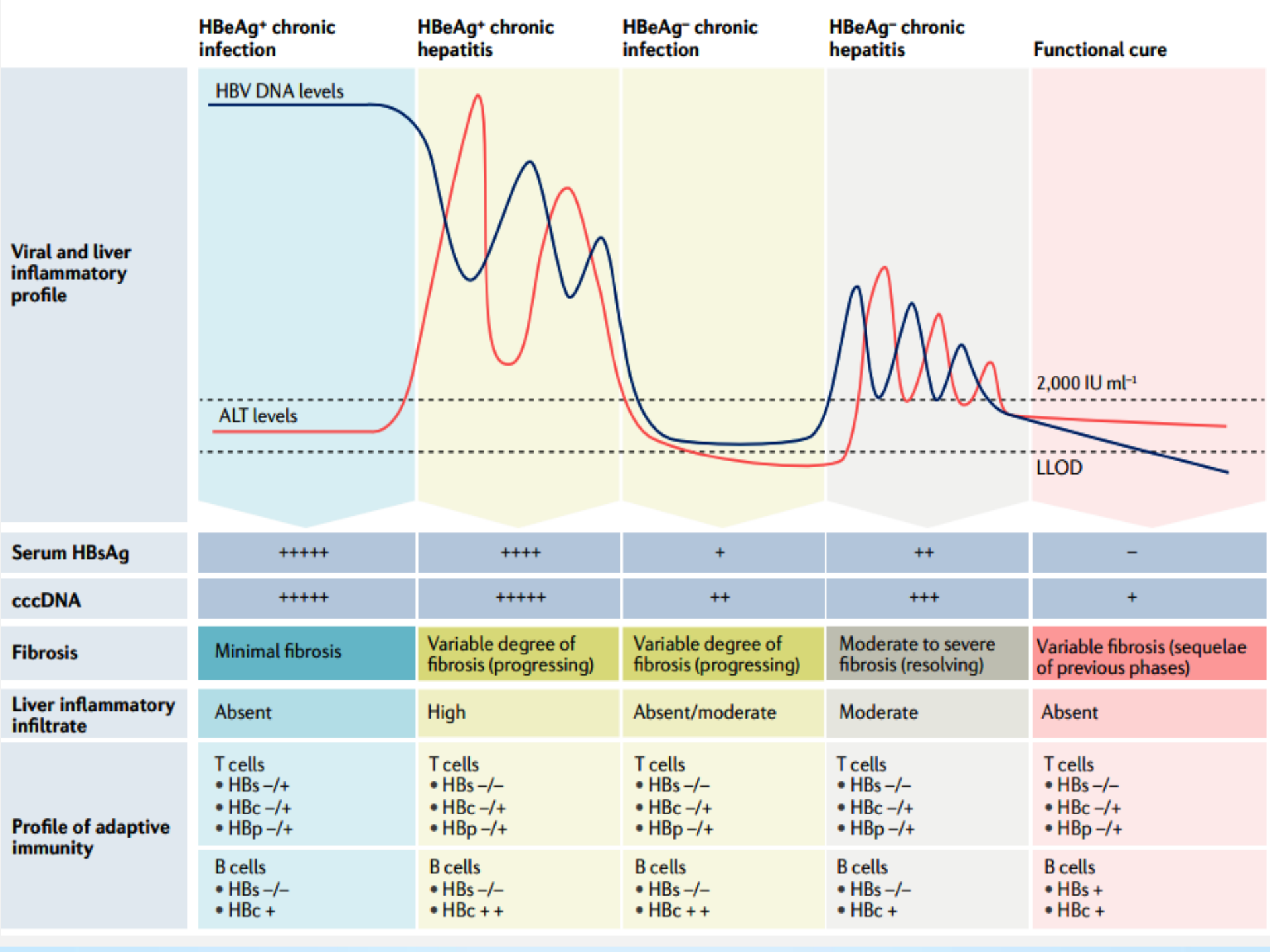
HMGA1 ekspresyonu immun toleran dönemde inaktif taşıyıcılara göre çok daha yüksek bulunmuştur

Knockdown of HMGA1 expression by AAV-shHMGA1 cleared cccDNA persistence in mice.



HMGA1 ekspresyonunun güvenli ve etkin bir şekilde devre dışı bırakılması farelerde cccDNA kalıcılığını temizlemiştir

Oral P. Shen ZL, **EASL 2021** poster no: 143


HBeAg+ chronic infection
HBeAg+ chronic hepatitis
HBeAg− chronic infection
HBeAg− chronic hepatitis
Functional cure
Viral and liver inflammatory profile
HBV DNA levels
ALT levels
2,000 IU ml−1
LLOD
Serum HBsAg
+++++
++++
+
++
−
cccDNA
+++++
+++++
++
+++
+
Fibrosis
Minimal fibrosis
Variable degree of fibrosis (progressing)
Variable degree of fibrosis (progressing)
Moderate to severe fibrosis (resolving)
Variable fibrosis (sequelae of previous phases)
Liver inflammatory infiltrate
Absent
High
Absent/moderate
Moderate
Absent
Profile of adaptive immunity
T cells
• HBs −/+
• HBc −/+
• HBp −/+
T cells
• HBs −/−
• HBc −/+
• HBp −/+
T cells
• HBs −/−
• HBc −/+
• HBp −/+
T cells
• HBs −/−
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• HBc +
B cells
• HBs +
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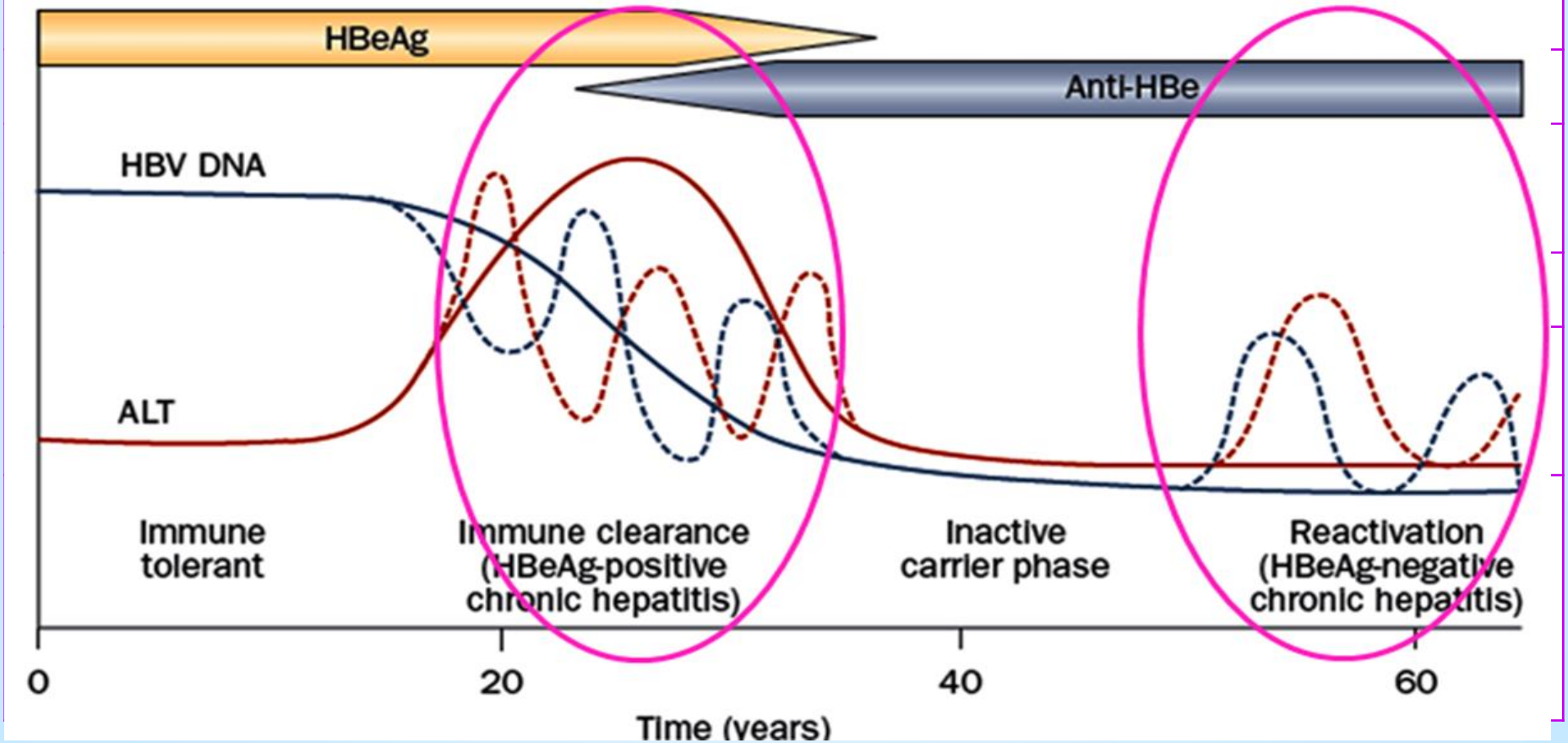
	HBeAg pozitif		HBeAg negatif	
	Kronik enfeksiyon	Kronik hepatit	Kronik enfeksiyon	Kronik hepatit



EASL J Hepatol. 2017 Aug;67(2):370-398.

Kimleri tedavi etmeliyiz?

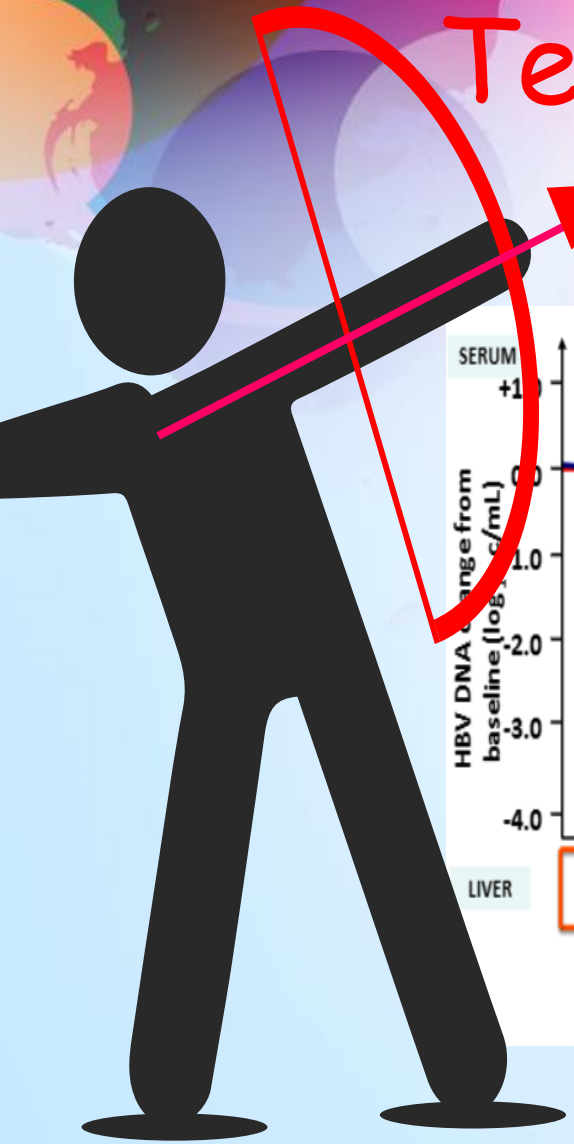
Rehberler	HBeAg pozitif			HBeAg Negative		
	HBV DNA, IU/mL	ALT	KC Hasarı	HBV DNA, IU/mL	ALT	KC Hasarı
AASLD[1]	> 20,000	≥ 2 x NÜS	Bakılmaz	≥ 2000	≥ 2 x NÜS	Bakılmaz
	Bakılmaz	Bakılmaz	Siroz	Bakılmaz	Bakılmaz	Siroz
EASL[2]	> 2000	> NÜS*	Orta derecede inflamasyon veya firbrozis*	> 2000	> NÜS*	Orta derecede inflamasyon veya firbrozis*
	> 20,000	> 2 x NÜS	Bakılmaz	> 20,000	> 2 x NÜS	Bakılmaz

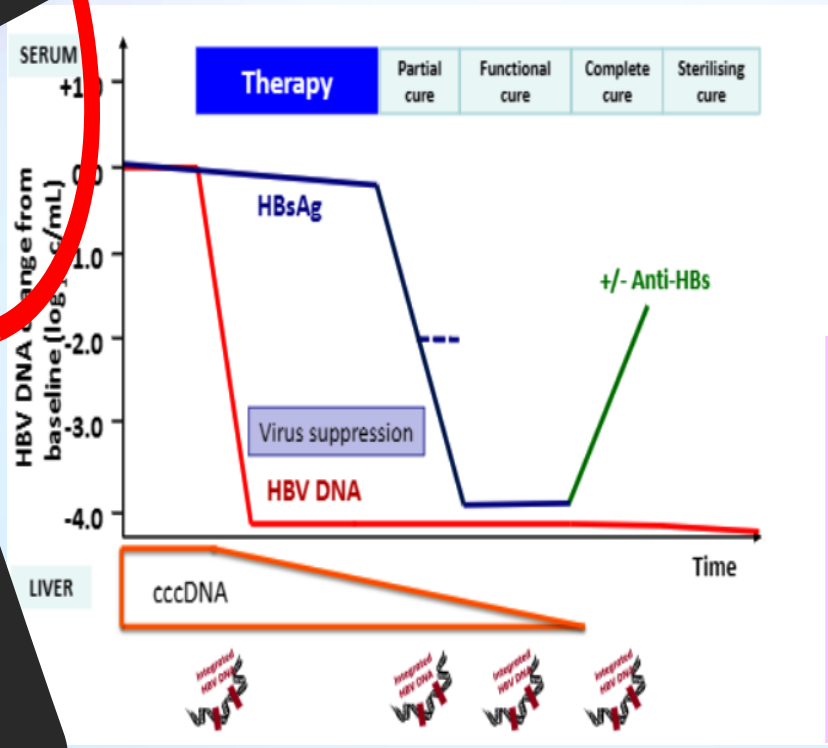
SUT:

HBV DNA >2.000 IU/ml HAI ≥6 veya fibrozis ≥2

Tedavide amaç? Kür?

Kür tanımı??





- Parsiyel kür:

  HBsAg:pos, persistan
  HBV DNA:neg

- **Fonksiyonel kür**:

  Sürekli HBsAg:neg,
  HBV DNA:neg
  ±AntiHBs

Tedavi

ETV

TDF

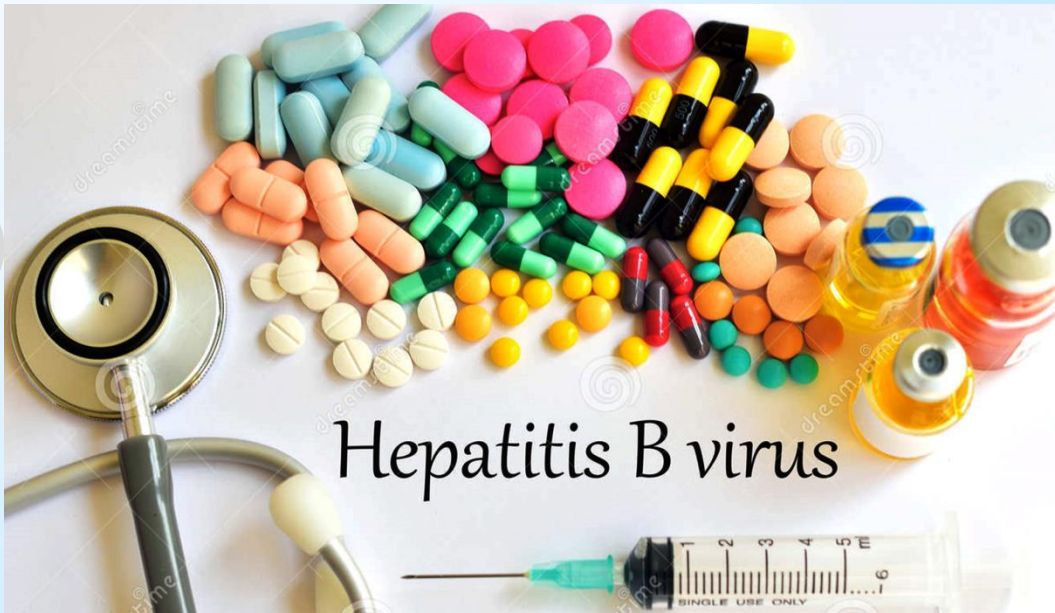
TAF

Peg IFN

ADF

LAM

LdT



TAF for Prevention of HBV Vertical Transmission

- Çok merkezli, TDF karşılaştırmalı (N =
- **Hastaların özellik**
  - Maternal yaş >2
  - Gebeliğin tüm d
  - Tedavi naiv KHB
  - Daha önce tanı- almış KHB hasta

  (ilk tedavileri non- olan sonradan geçenler)

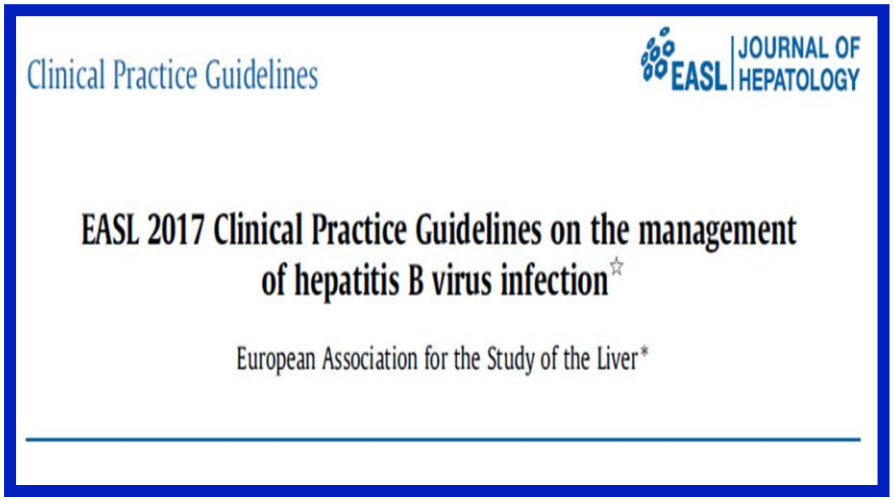
- **Annede**
  - HBV DNA negatif
  - ALT %95 oranında normal
  - HBeAg serokonversiyonu benzer (%22,%21)
- Perinatal bulaş %0
- TAF ve TDF'de anti-HBs: 99.0% ve 100%

Özellikler	TAF (n = 102)*	TDF (n = 104)
	3)	33.8 (8.3)
	3)	39 (37.5)
	5)	9.5 (0.5) 0
		0
	7)	14 (13.4)
	7)	13 (12.5)
	)	9 (8.7)
	)	9 (8.7)
	)	5 (4.8)
	)	5 (4.8)
	*	0
	‡	0

itis media; 6 aylıkken tedavi ile

Zeng. AASLD 2021. Abstr OA19.

Tedaviyi kesebilir miyiz?

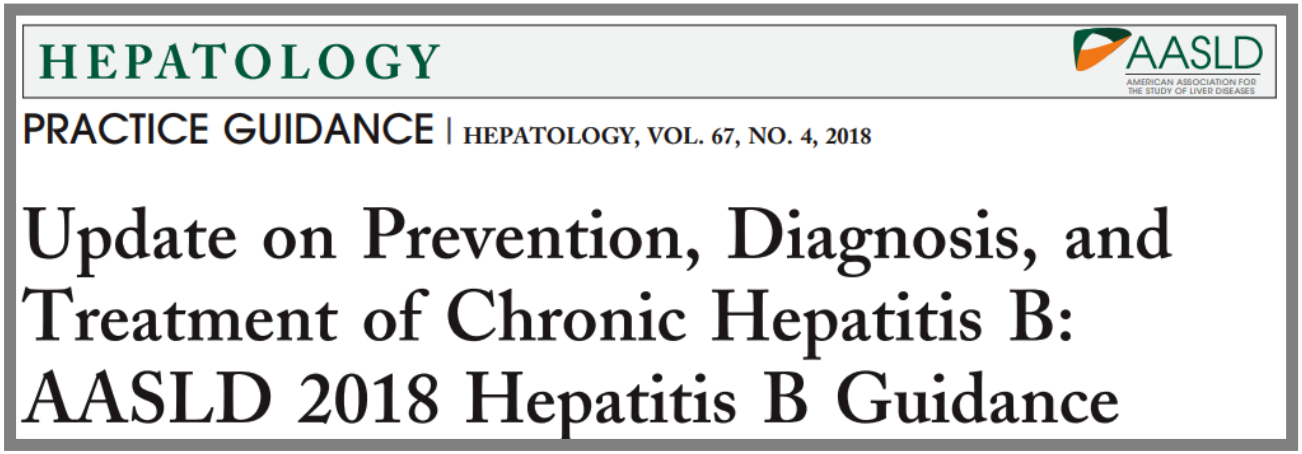

Clinical Practice Guidelines

EASL | JOURNAL OF HEPATOLOGY

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection☆

European Association for the Study of the Liver*

- HBsAg kaybı ± AntiHBs serokonv
- HBeAg + viral suprese, ve HBeAg serokonv sağlanırsa
- HBeAg -nonsirotik en az 3 yıl tedavi almış virolojik supresyon devam eden hastalar


HEPATOLOGY

AASLD

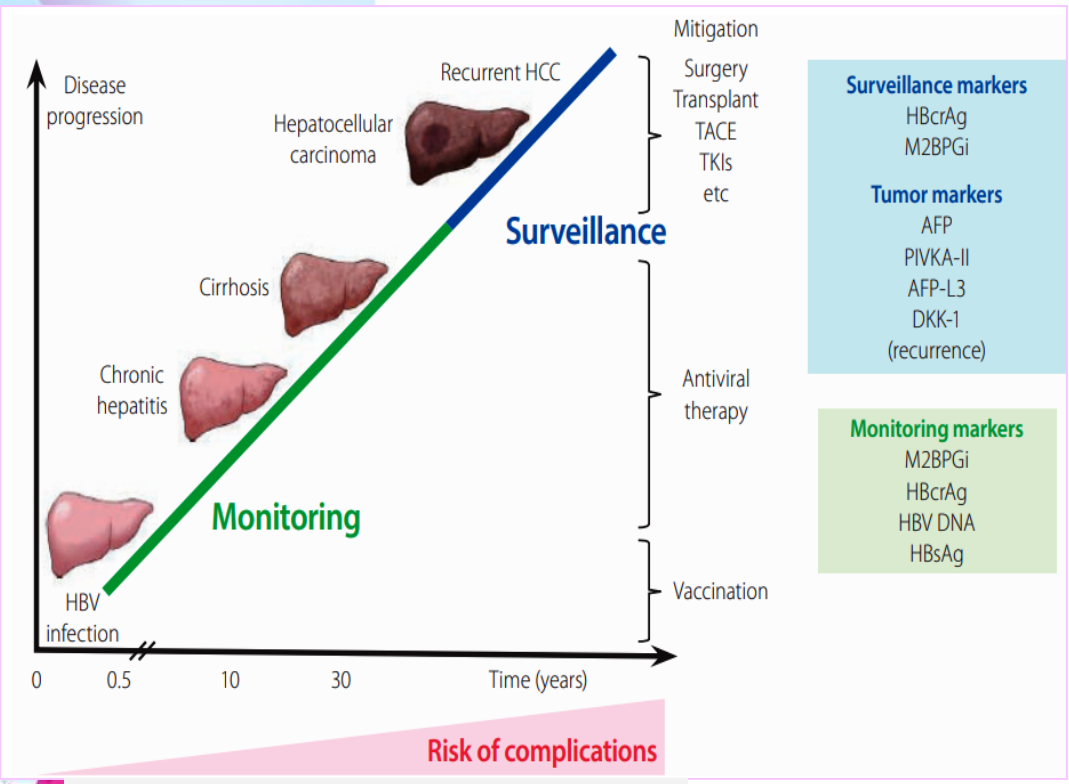
PRACTICE GUIDANCE | HEPATOLOGY, VOL. 67, NO. 4, 2018

Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance

HBsAg kaybı öncesi NA kesilebilir mi?

- Virolojik, biyokimyasal, klinik relaps
- Çok iyi hasta uyumu
- Çok yakın hasta takibi
- Yaklaşık hastaların %50'sinde tekrar tedavi
- Fonksiyonel kür tahmini; qHBsAg,..

Tanıda yeni ne var?

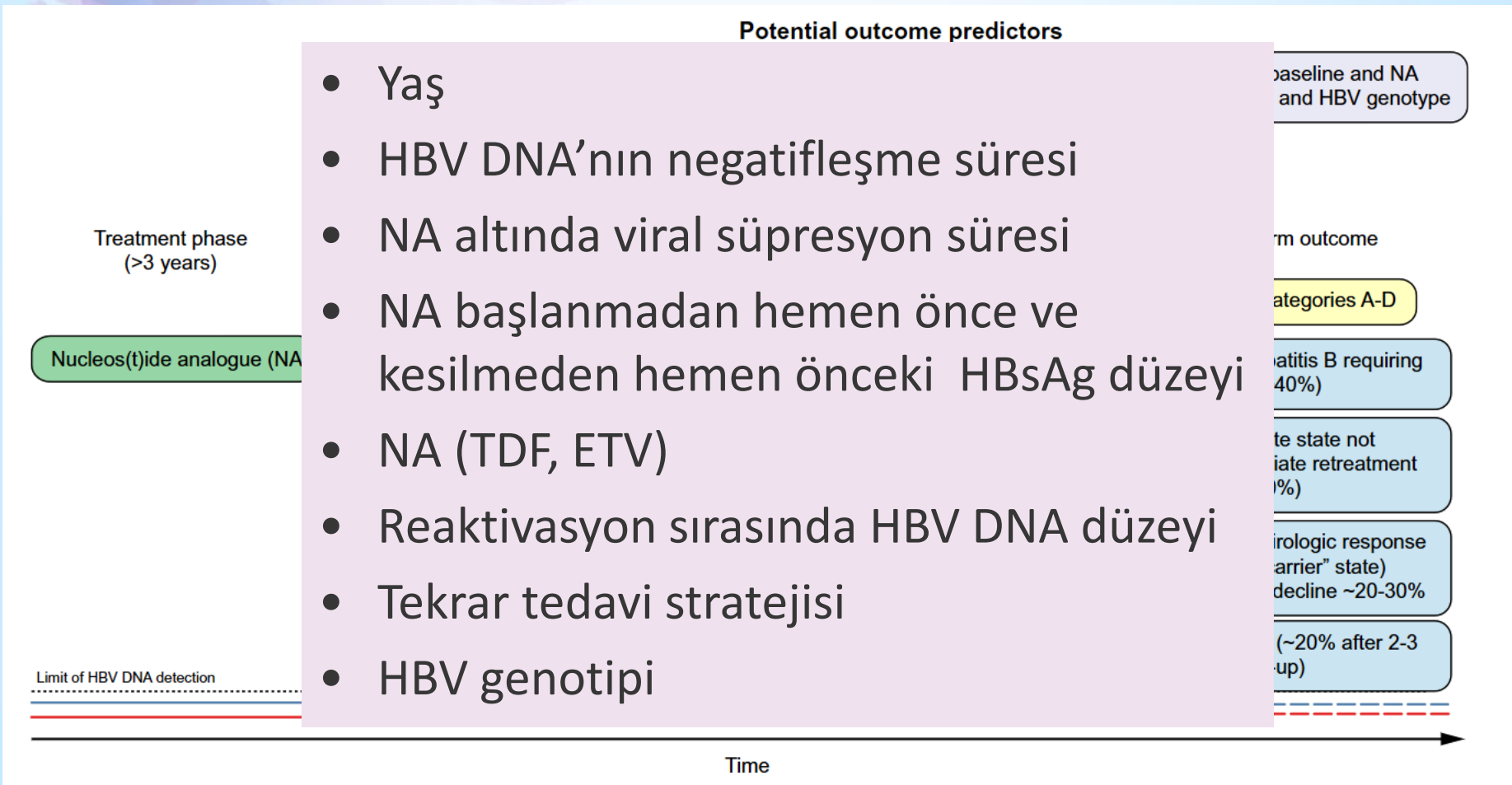


- qHBsAg
- HBV RNA
- HBcrAg
- qAntiHBc
- Soluble inflamatuar mediatörler
  - IP-10 or CXCL-10

- Mac-2-binding protein glycosylation isomer (M2BPGi) _fibrozis, HCC

Cornberg M,et al. J Hepatol. 2020 ;72(3):539-557.
Inoue T, et al. Clin Mol Hepatol. 2020 ;26(3):261-279.

HBeAg-negatif KHB hastalarında uzun dönem NA tedavisinin kesilmesi sonrasındaki tipik seyir



- Yaş
- HBV DNA'nın negatifleşme süresi
- NA altında viral süpresyon süresi
- NA başlanmadan hemen önce ve kesilmeden hemen önceki HBsAg düzeyi
- NA (TDF, ETV)
- Reaktivasyon sırasında HBV DNA düzeyi
- Tekrar tedavi stratejisi
- HBV genotipi

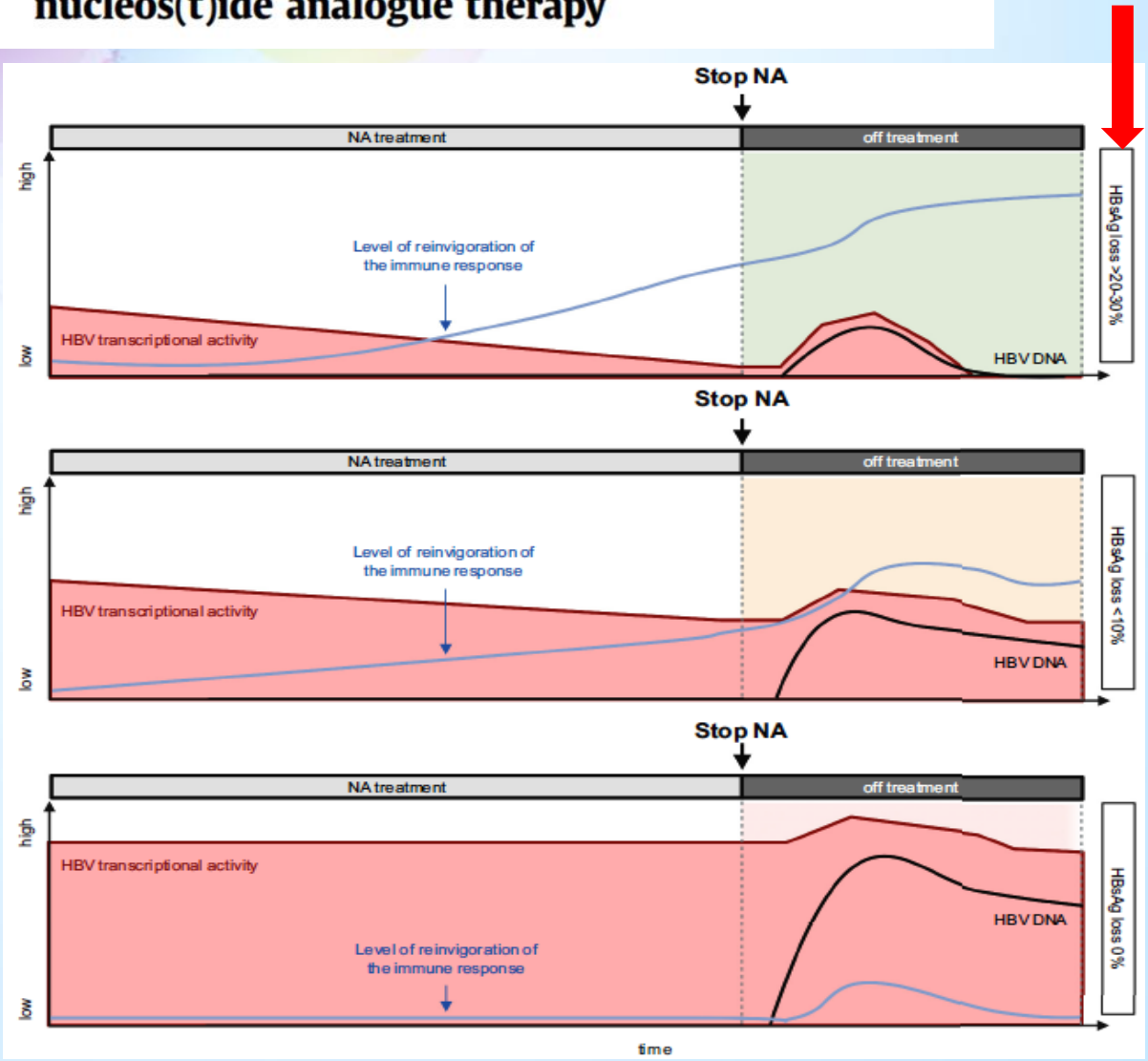
Expert Opinion

JOURNAL OF HEPATOLOGY

The times they are a-changing – A refined proposal for finite HBV nucleos(t)ide analogue therapy

Fonksiyonel kür şansı tedavi kesilmesine bağlı

Alevlenmeler yararlı mı zararlı mı olacak**??**



Berg T., J Hepatol. 2021 Aug;75(2):474-480.

Original research

Discontinuation of nucleot(s)ide analogue therapy in HBeAg-negative chronic hepatitis B: a meta-analysis

- 37 çalışma
- NA kesildikten sonra ≥ 12 ay takip edilen hastalar
- Sonuç: 12. ayda
  - VR: % 63
  - KR: % 35
  - >48 ay takip HBsAg kaybı%27

Hall SAL, et al. Gut. 2021 Sep 7:gutjnl-2020-323979.

RETRACT-B: Nucleos(t)ide Analogue Cessation in Patients With CHB

- Retrospektif kohort
- **HBeAg (-),** viral süprese 1552 KHB hastası
- Medyan takip süresi 18.4 (7.9-39.4)

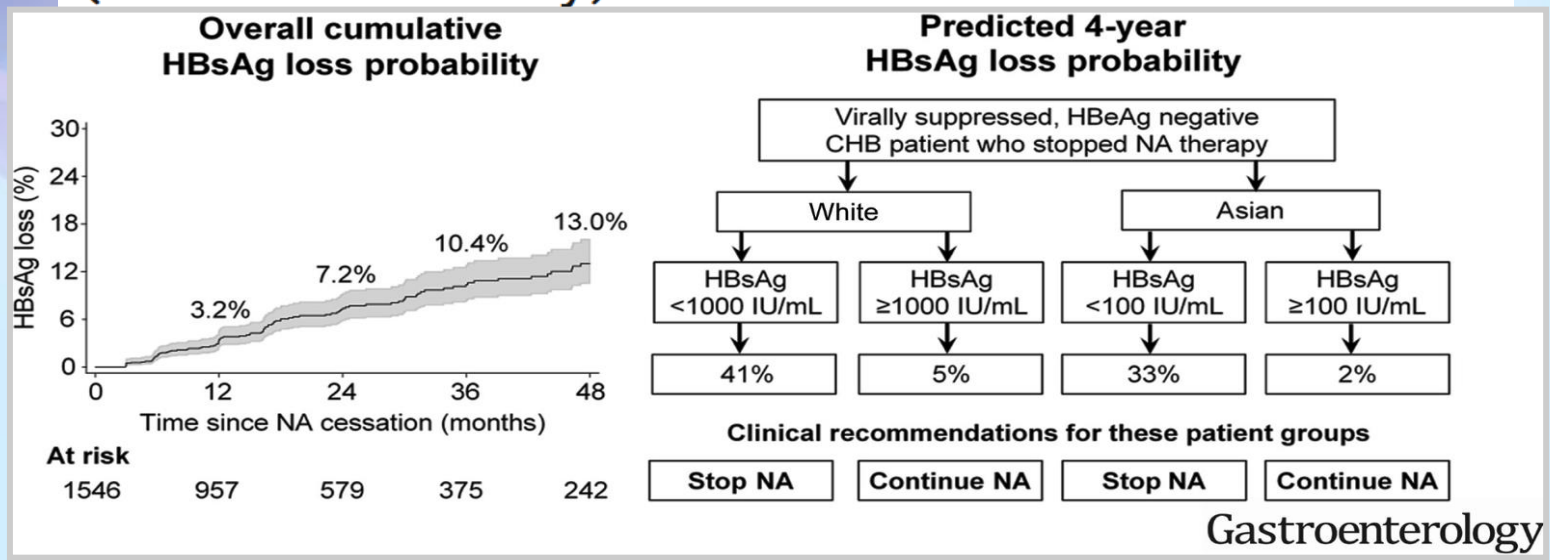
Hasta Özellikleri %	N = 1552
Yaş	52.9 ± 11.2
Erkek	72.3
Irk ▪ Asyalı ▪ Beyaz	 87.6 11.3
HBV genotype B	42.7

Tedavi kesilmeden önceki Hasta Özellikleri	N = 1552
NA, % ▪ **ETV** ▪ **TDF** ▪ Diğer	 **63** **27.1** 8.9
Medyan NA süresi, yıl	3.0 (3.0-3.6)
Peg-IFN alma öyküsü, %	8.6
HBeAg negatiflik, %	84
Sirozlu sayısı, %	11

Hirode G, et al. (RETRACT-B Study). Gastroenterology. 2022 ;162(3):757-771.e4.

Multicenter Study > Gastroenterology. 2022 Mar;162(3):757-771.e4.
doi: 10.1053/j.gastro.2021.11.002. Epub 2021 Nov 9.

Off-Therapy Response After Nucleos(t)ide Analogue Withdrawal in Patients With Chronic Hepatitis B: An International, Multicenter, Multiethnic Cohort (RETRACT-B Study)

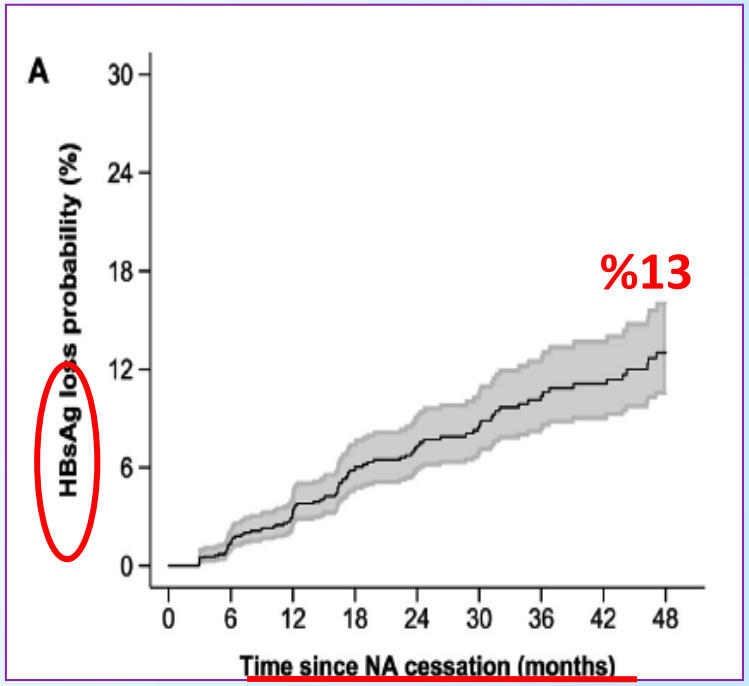


- **Tedavi kesilmesi için en iyi adaylar**
- Viral süprese
- HBeAg negatif
- Nonsirotik
- Düşük HBsAg (beyazlarda<1000 IU/mL, Asyalılarda <100 IU/mL)

Hirode G, et al. (RETRACT-B Study). Gastroenterology. 2022 ;162(3):757-771.e4.

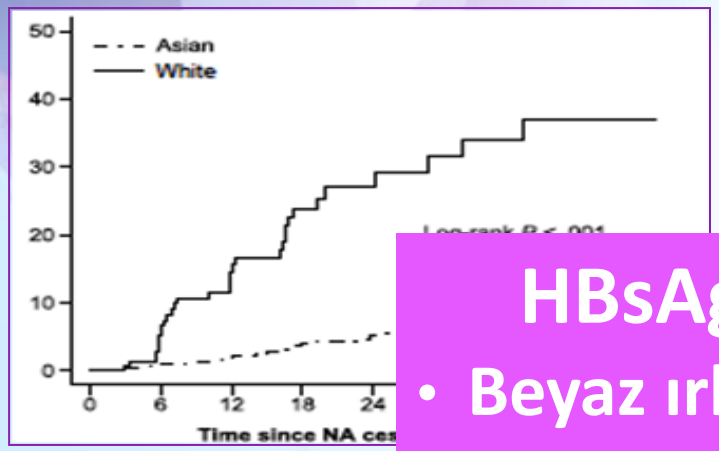
RETRACT-B: Tedavi kesildikten sonraki sonuçlar

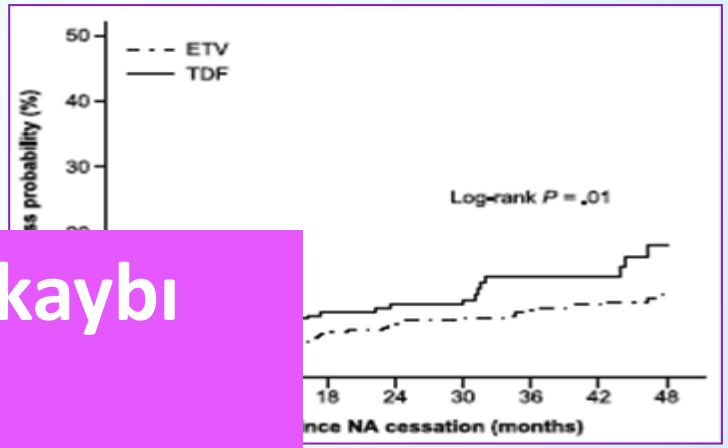
Tedavi kesildikten sonraki hasta özellikleri	**N = 1532**
Ortalama HBsAg, log_{10} IU/mL	2.6±0.8
Medyan ALT x NÜS (aralık)	0.6 (0.4-0.8)
HBsAg kaybı, % **12 ay sonra** **48 ay sonra**	 **3.2** **13.0**
HBsAg, N,% <100IU/mL 100-1000IU/mL >1000IU/mL	225 (14.5) 682 (43.9) 463 (29.8)



Hirode G, et al. (RETRACT-B Study). Gastroenterology. 2022 ;162(3):757-771.e4.

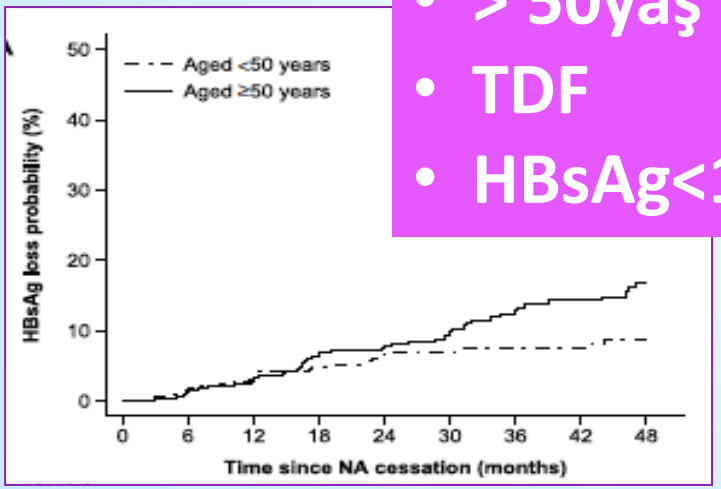
RETRACT-B: Tedavi kesildikten sonraki sonuçlar

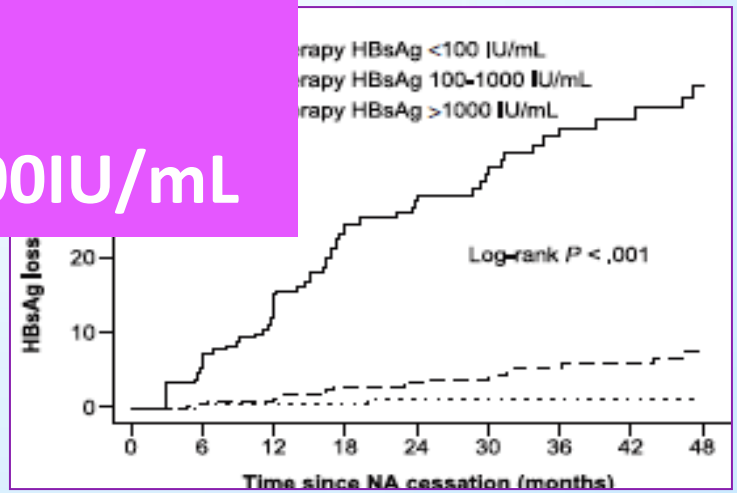




HBsAg kaybı

- Beyaz ırk
- > 50yaş
- TDF
- HBsAg<100IU/mL

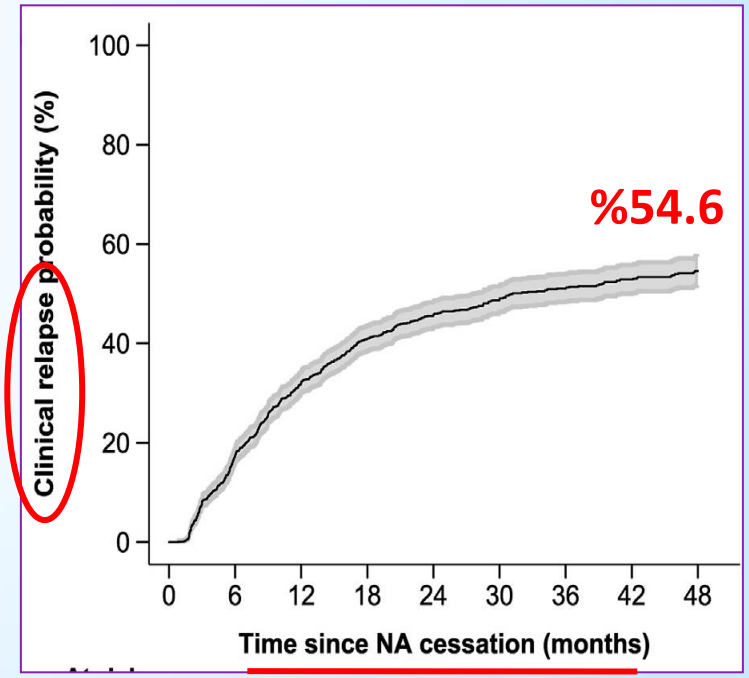




Hirode G, et al. (RETRACT-B Study). Gastroenterology. 2022 ;162(3):757-771.e4.

RETRACT-B: Tedavi kesildikten sonraki sonuçlar

Relaps	N = 1532
Virolojik relaps, % 12 ay 48 ay	 68.9 83.4
Biyokimyasal relaps, % 12 ay 48 ay	 38.1 61.1
Klinik relaps, % **12 ay** **48 ay**	 **31.9** **54.6**
Tekrar tedavi başlanma oranı, % **12 ay** **48 ay**	 **29.8** **54.7**



EASL
The Home of Hepatology

Functional cure based on pegylated interferon α in long-term nucleoside analog suppressed HBeAg negative chronic hepatitis B: A multicenter real-world study (everest project in China), a sequential report - the predictors for HBsAg loss

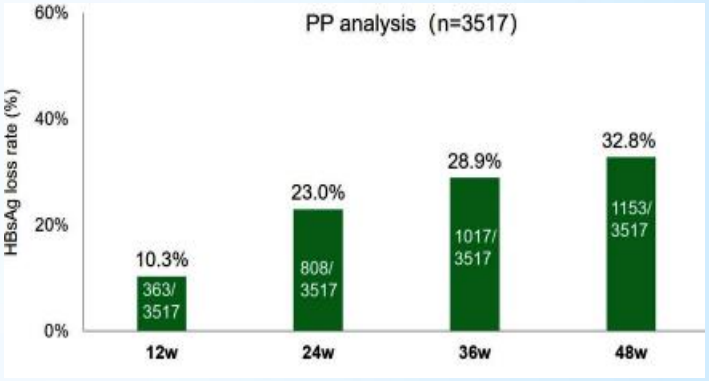
Ze-Qian Wu[1], Dong-Ying Xie[1], Lei Fu[2], Wen-Hua Zhang[3], Jia Wei[4], Jia Shang[5], Guojun Li[6], Ying Guo[7], Jia-Hong Yang[8], Yu-Juan Guan[9], Jia-Bin Li[10], Jia-Bao Chang[11], Guang-Yu Huang[12], Yan-Zhong Peng[13], Ming-Hua Lin[14], Yi-Lan Zeng[15], Jia Li[16], Jia-Ji Jiang[17], Yong-Fang Jiang[18], Ye Gu[19], Jia-Wei Geng[20], Zhi-Liang Gao[1]

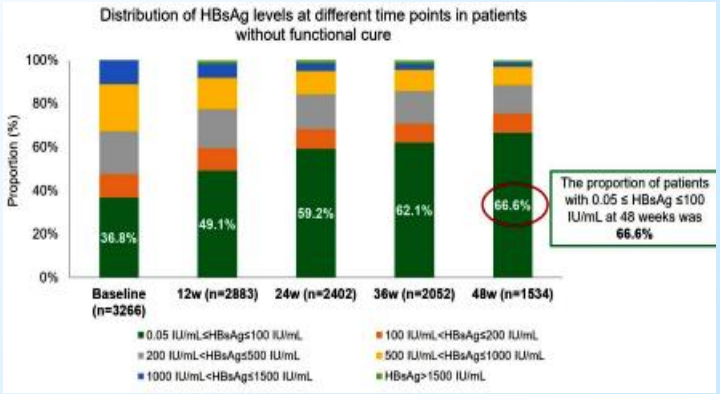
中国慢性乙型肝炎临床治愈(珠峰)工程项目

- >1 yıl NA alan, HBeAg (-) HBV DNA <100 IU/ml
- 48-96 hft peg-IFN
- 48. hft.da
  - %32.8 HBsAg kaybı
  - %66.6 HBsAg≤100 IU/mL

- **Fonksiyonel Kür Prediktörleri**
- Bazal HBsAg düşükse, 24.hft.da başlangıca göre hızlı azalmışsa ve 12. hft.da ALT yükselmeleri varsa

- NA ile viral yükü süprese edilmiş HBeAg (-) hastalarda **Peg IFN** ile **fonksiyonel kür** sağlanabilir





HBsAg kaybının klinik önemi

- <50 yaş spontan gelişen HBsAg kaybı
- HBsAg seroklirens süresi?

- Siroz riski
- Transplantasyon ihtiyacı
- HCC riski
  - Hem sirotik hem nonsirotik olgularda HCC riski azalır

Moini M, et al. Viruses. 2022 Mar 22;14(4):657.

Tedavide yenilikler?

viruses

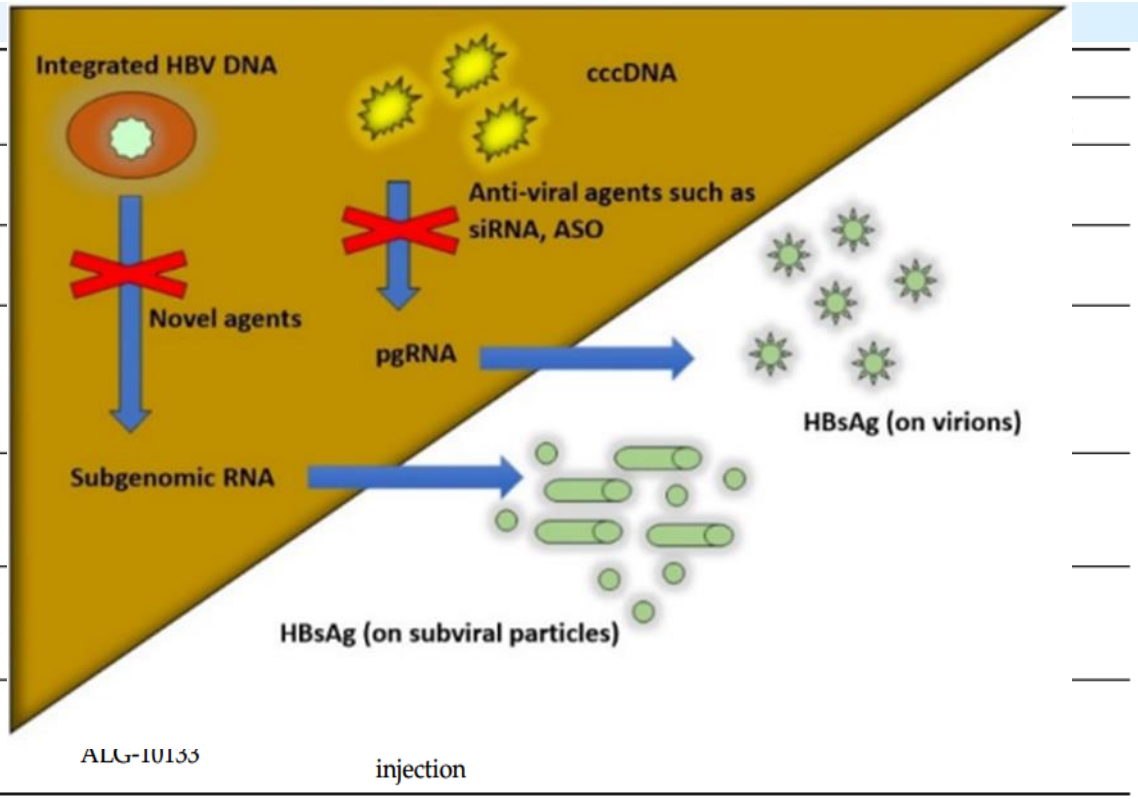
MDPI

Review

HBsAg Loss as a Treatment Endpoint for Chronic HBV Infection: HBV Cure

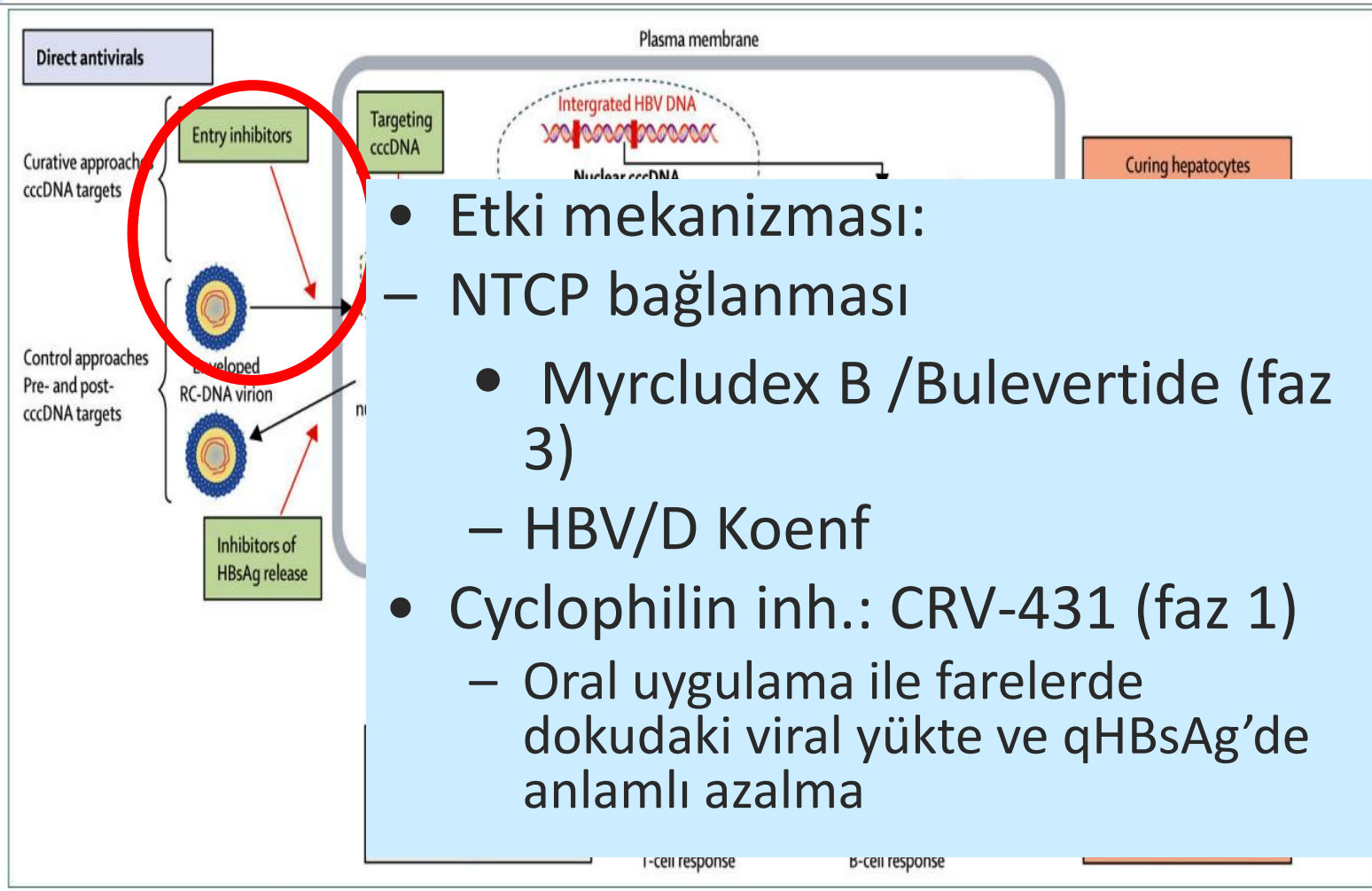
Maryam Moini [1] and Scott Fung [2,*]

Agent & Mode of Action
Nucleos(t)ideAnalogs (NA)
Interferons
Capsid assembly modulator (CAM)
Small interfering RNA (siRNA)
Antisense oligonucleotide (ASO)
Nucleic acid polymer (NAP)



Moini M, et al. Viruses. 2022 Mar 22;14(4):657.

Viral giriş inhibitörleri



- Etki mekanizması:
  - NTCP bağlanması
    - Myrcludex B /Bulevertide (faz 3)
      - HBV/D Koenf
- Cyclophilin inh.: CRV-431 (faz 1)
  - Oral uygulama ile farelerde dokudaki viral yükte ve qHBsAg'de anlamlı azalma

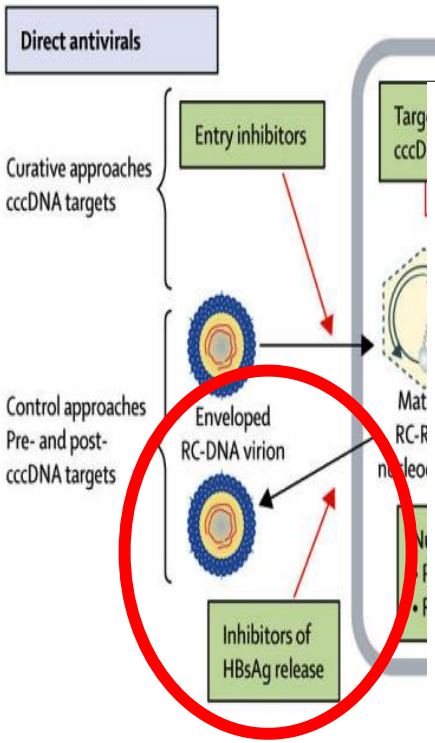
STRONG INTRAHEPATIC DECLINE OF HEPATITIS D VIRUS RNA AND ANTIGEN AFTER 48 WEEKS OF TREATMENT WITH BULEVIRTIDE IN CHRONIC HBV/HDV CO-INFECTED PATIENTS: INTERIM RESULTS FROM A MULTICENTER, OPEN-LABEL, RANDOMIZED PHASE 3 CLINICAL TRIAL (MYR301)

- Bulevirtide (BLV, Hepcludex®)
- HBV/HDV reseptor (NTCP) bloke eden ilk giriş inibitörü.
- Kronik HDV'de onaylandı
- Sodium taurocholate co-transporting polypeptide (NTCP)
- 48. hft sonuçları
  - İntrahepatik HBV DNA/RNA'de azalma olmamış
  - İntrahepatik HDV RNA ve HDAg+ hücrelerde 48 hft sonra azalma

2021 AASL Abstrakt ödülü

PO. 223.Lena Allweiss L,et al.AASLD 2021 ABSTRACTS

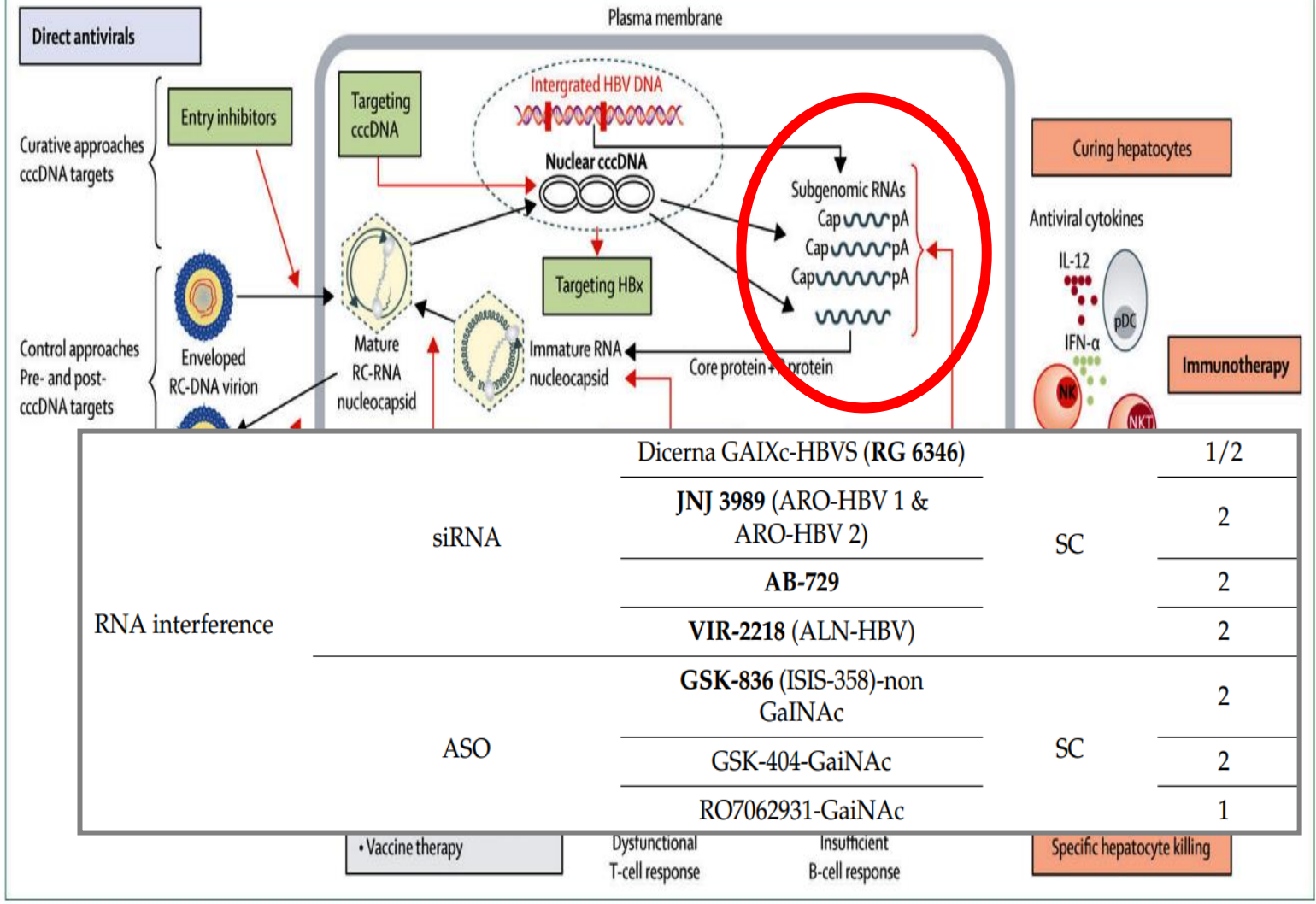
HBsAg salınım inhibisyonu



- **Nükleik asit polimerleri (NAP)**
  - REP 2139 ve REP 2165
  - Faz 2 çalışma, REP 2139/REP 2165 + TDF +PEG-IFN
  - Tedavi süresi: 24 hft
  - Sonuç:
    - % 60 hastada HBsAg < 0.05 IU/mL
    - %35 HBsAg seroklirensi
- **S-antigen Transport-inhibiting Oligonucleotide Polymers (STOPS)**
  - ALG-010133
  - NAP'den daha potent
  - İntegre HBV DNA'dan HBsAg salınımını 100 kat daha fazla önler

Mak LY, Viruses. 2021 Jun 18;13(6):1169

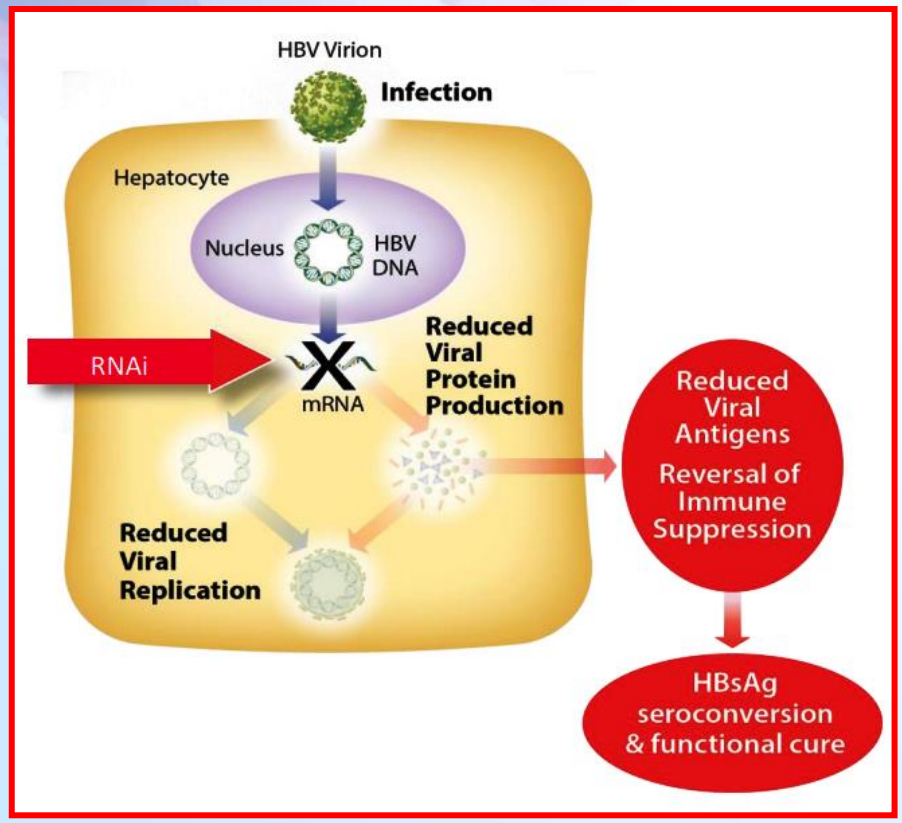
RNA interferansı



RNA interference	siRNA	Dicerna GAIXc-HBVS (**RG 6346**)	SC	1/2
		JNJ 3989 (ARO-HBV 1 & ARO-HBV 2)		2
		AB-729		2
		VIR-2218 (ALN-HBV)		2
	ASO	**GSK-836** (ISIS-358)-non GaINAc	SC	2
		GSK-404-GaiNAc		2
		RO7062931-GaiNAc		1

Mak LY, Viruses. 2021 Jun 18;13(6):1169

siRNA



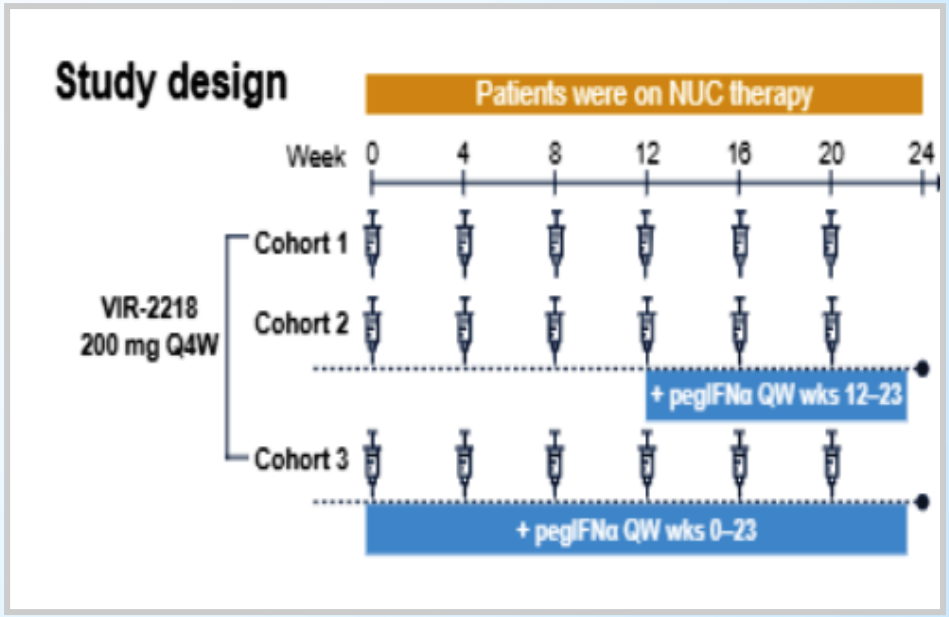
- siRNA integreDNA ve cccDNA transkriptini baskılayan X genindeki korunmuş bölgeyi hedefleyerek
  - HBV'ye karşı etkin bağışıklık yanıtı
  - Direkt antiviral etki

Seto WK,et al Clinical Liver Disease 2016;8:4, 83-86

Vir Biotechnology Presents New Data Evaluating the Potential for VIR-2218 and VIR-3434 to Achieve a Functional Cure for Chronic Hepatitis B Virus (HBV) Infection at AASLD The Liver Meeting®

November 12, 2021

- **VIR-2218**
  - **ESC+ teknolojisini içeren klinikteki ilk siRNA**
- 64 viral suprese KHB hastası
- Faz 2 sonuçları



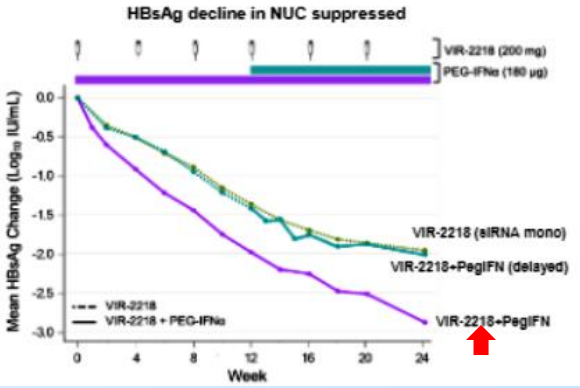
Oral P. Yuen MF et al. **EASL** 2021 Publication #93

Vir Biotechnology Presents New Data Evaluating the Potential for VIR-2218 and VIR-3434 to Achieve a Functional Cure for Chronic Hepatitis B Virus (HBV) Infection at AASLD The Liver Meeting®

November 12, 2021

- **VIR-2218**
- 24hft SC VIR-2218 ± PEG-IFN-α tedavisi
  - VIR-2218 + PEG-IFN-α alan hastalarda HBsAg'de >2 log10 IU/mL azalma
  - %95 HBsAg <100 IU/mL
  - %55 HBsAg < 10 IU/mL
  - **3 hastada HBsAg kaybı** bunların 2'sinde anti-HBs serokonv.

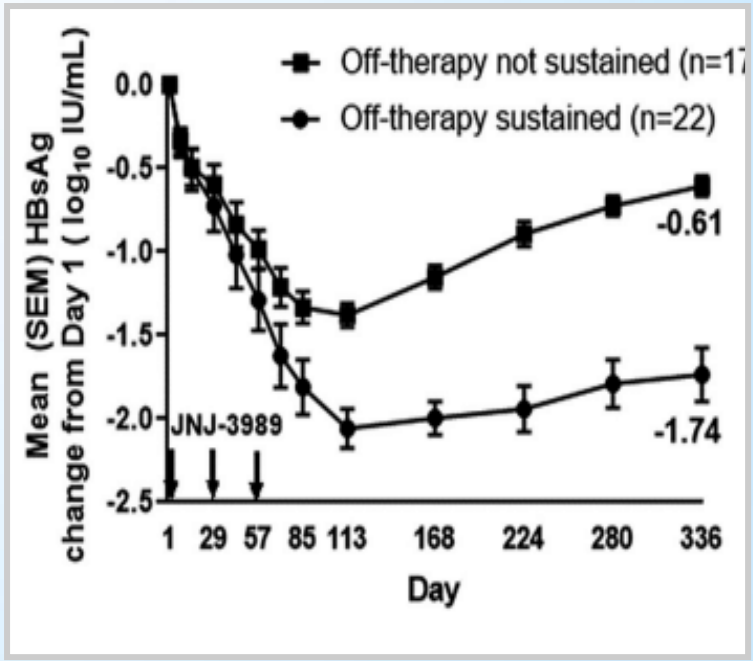
Baseline demographics	Cohort 1 (n=15)	Cohort 2 (n=15)	Cohort 3 (n=17)
HBeAg-positive, n (%)	4 (26.7)	6 (40.0)	6 (35.3)
Mean ±SD age, years	50 ±8.6	47 ±7.8	49 ±6.0
Male, n (%)	13 (86.7)	13 (86.7)	14 (82.4)
Race, n (%)			
Asian	11 (73.3)	13 (86.7)	15 (88.2)
White	0	0	1 (5.9)
Other	4 (26.7)	2 (13.3)	1 (5.9)
Mean ±SD HBsAg Log_{10} IU/mL	3.44 ±0.447	3.20 ±0.676	3.27 ±0.743
Mean ±SD ALT (U/L)	21 ±10.1	25 ±12.4	22 ±11.9
ALT >ULN	1 (6.7)	1 (6.7)	1 (5.9)



Oral P. Yuen MF et al. **EASL 2021** Publication #93

Short-term treatment with **RNA interference therapy**, **JNJ-3989**, results in sustained hepatitis B surface antigen supression in patients with chronic hepatitis B receiving nucleos(t)ide analogue treatment

- JNJ-3989, Faz 2b
- 40 hasta,3 ay, 25–400 mg + NA
  - antiviral etkili
- 39/40 HBsAg'de ≥1.0 log10 azalma
  - 22/39 (%56) hastada son dozdan 9 ay sonra devam eden ≥1.0 log10 azalma



Gane E, et al. Journal of Hepatology 2020 vol. 73 | S19–S57

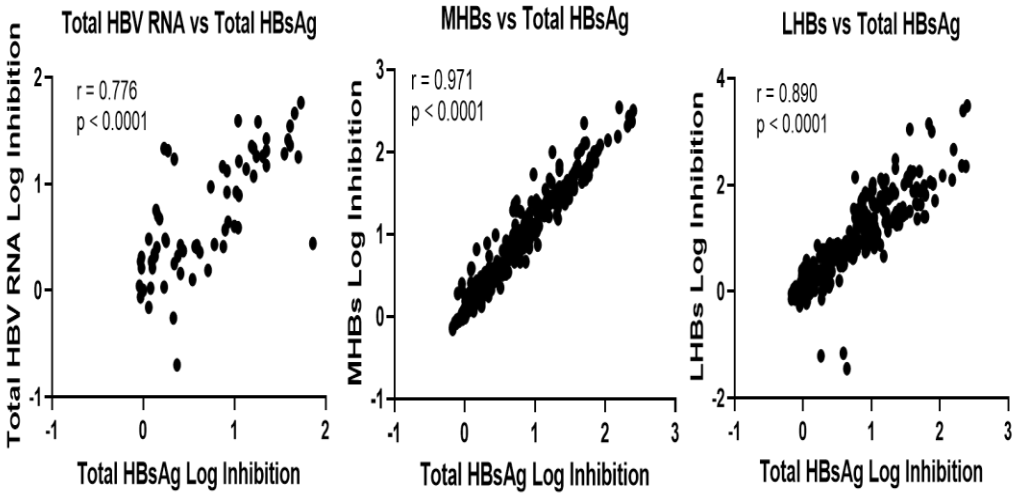
Inhibition of hepatitis B surface antigen by RNA interference therapeutic AB-729 in chronic hepatitis B patients correlates with suppression of all HBsAg isoforms and HBV RNA

- **AB-729 GalNAc-konjuge siRNA**
- **AB-729, HBV RNA transkriptlerini tamamen bloke eden tek ajan**
  - HBx blokasyonu ile viral replikasyonu baskılar
- Tek doz veya multi-dozlarda uygulanan hastalar
  - Total HBV RNA ve pregenomic RNA
  - HBsAg izoformları ve HBsAg immun kompleks

Sonuç

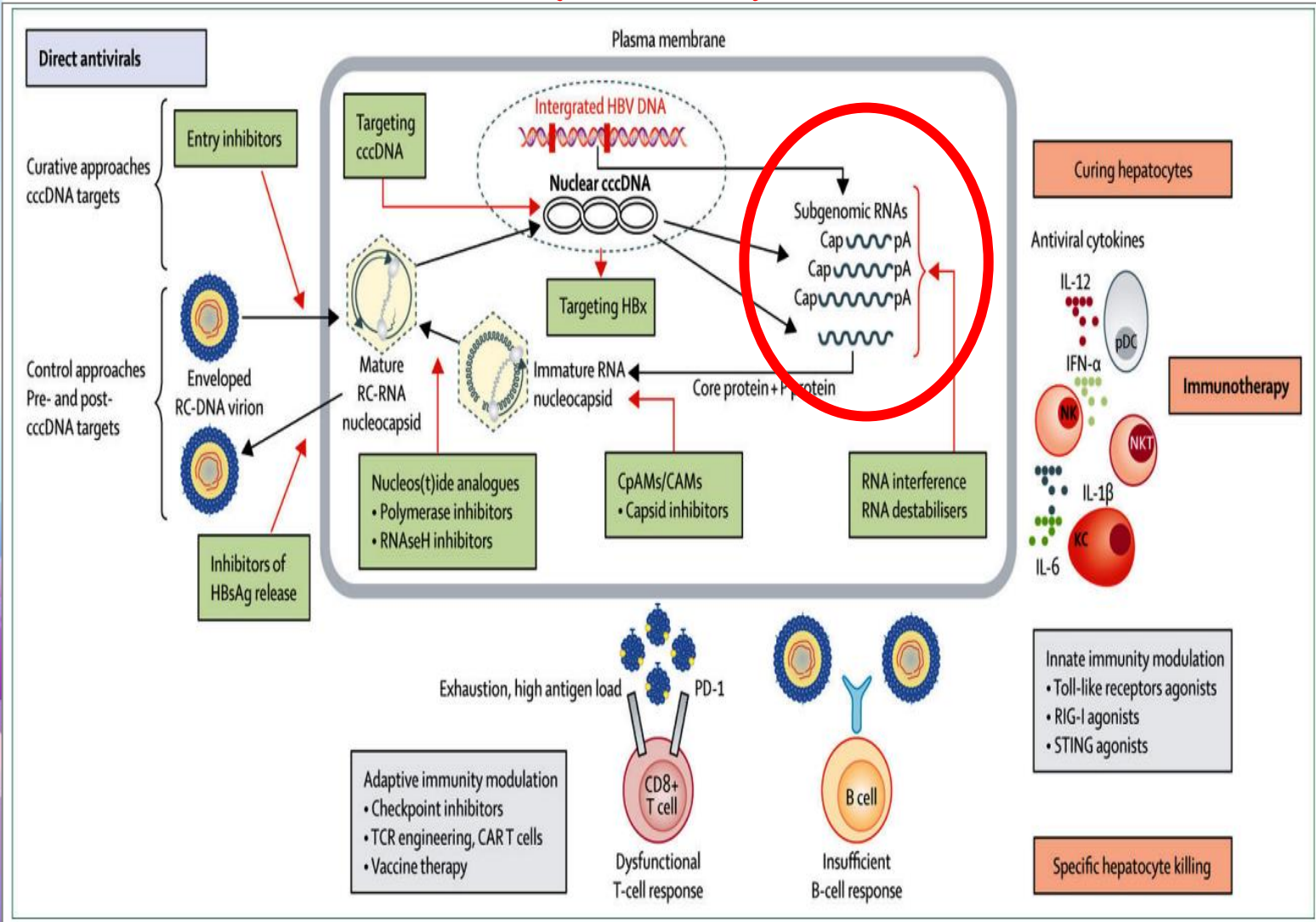
- AB-729 uygulaması sonrası , total HBsAg'deki düşme HBV RNA, pgRNA, LHBs and MHBs HBsAg izoformları ile korele. ($p<0.0001$)

HBV DNA- CHB subjects



Thi EP, et al. ILC 2021; PO-2822

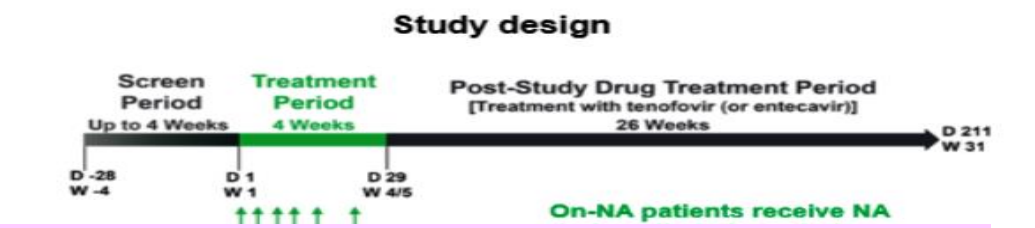
Antisens oligonükleotidler (ASO)



Mak LY, Viruses. 2021 Jun 18;13(6):1169

HBsAg inhibition with **ISIS 505358** in CHB patients on stable NA regimen and in NA-naive CHB patients: phase 2a, randomized, double-blind, placebo-controlled study

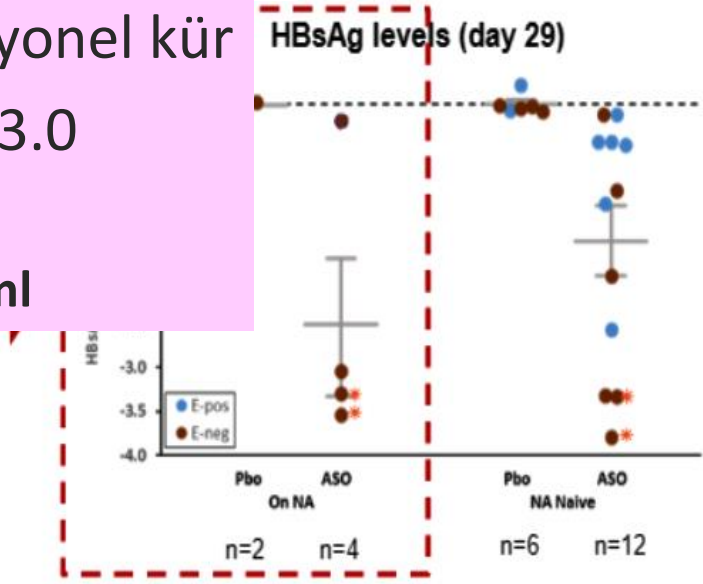
ASO



- GSK3228836-Faz 2a sonuçları
- 4hft tedavi sonrası fonksiyonel kür
  - 6 hastada HBsAg'de >3.0 log_{10} IU/ml azalma
    - **4 hastada < 0.05 IU/ml**

Change in HBsAg from Baseline Mean (SD) log_{10} IU/mL	
Day 29	
p-value (compared to placebo)	

Change in HBV DNA from Baseline Mean (SD) log_{10} IU/mL	Naive Patients	
	Pbo (N=6)	ASO (N=12)
Day 29	-0.001 (0.4710)	-1.655 (1.4791)
p-value (compared to placebo)		p<0.001



nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01513-4

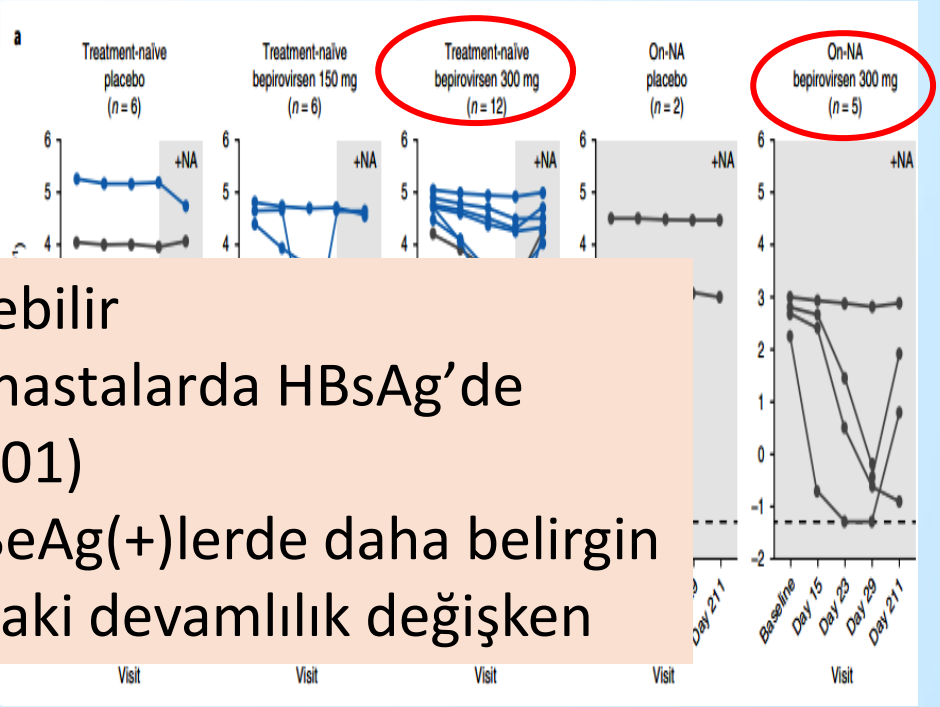
Check for updates

OPEN

Safety, tolerability and antiviral activity of the antisense oligonucleotide bepirovirsen in patients with chronic hepatitis B: a phase 2 randomized controlled trial

Table 3 | HBsAg and HBV DNA at baseline and day 29 in patients with CHB (full analysis population)

	Treatment-naïve			On-NA	
	Bepirovirsen 150 mg ($n=6$)	Bepirovirsen 300 mg ($n=12$)	Placebo ($n=6$)	Bepirovirsen 300 mg ($n=5$)	Placebo ($n=2$)
Baseline HBsAg (log_{10} IU ml^{-1})					
n	6	12	6	5	2
Mean (s.d.)	3.57 (1.244)	3.89 (1.056)	3.21 (1.304)	2.78 (0.363)	3.77 (1.018)
Day 29 HBsAg (log_{10} IU ml^{-1}), LOCF					
n	6				
Mean (s.d.)	3.06 (1.580)				
Change from baseline to day 29 in HBsAg (log_{10}					
n	6				
Mean (s.d.)	−0.50 (0.566)				
P value (versus placebo)	0.245				
Baseline HBV DNA (log_{10} IU ml^{-1})					
n	6				
Mean (s.d.)	7.41 (1.396)				
Day 29 HBV DNA (log_{10} IU ml^{-1}), LOCF					
n	6				
Mean (s.d.)	7.03 (1.451)				
Change from baseline to day 29 in HBV DNA (l					
n	6				
Mean (s.d.)	−0.38 (0.420)				
P value (versus placebo)	0.116	<0.001		NA	

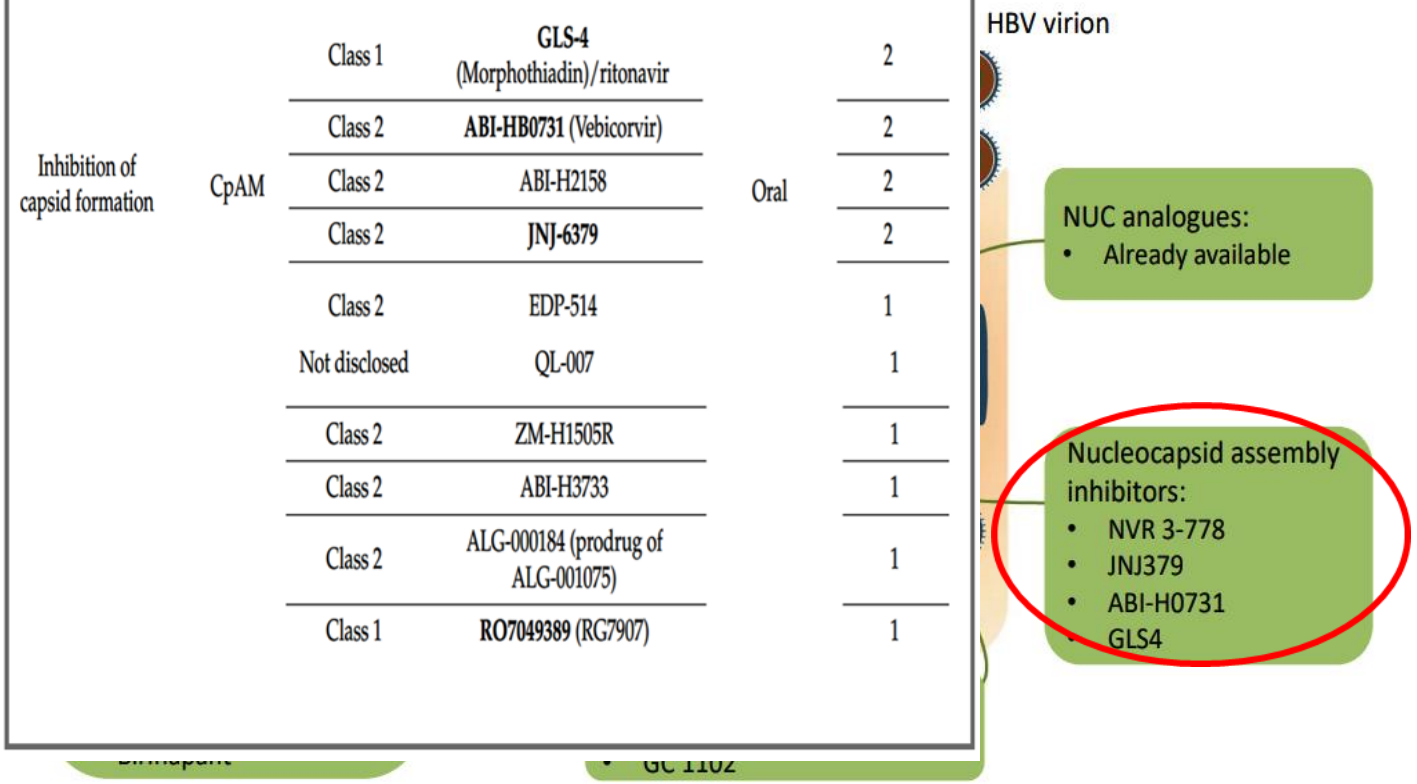


- Güvenli ve tolere edilebilir
- 300mg dozlarda naiv hastalarda HBsAg'de anlamlı azalma(P= 0.001)
- HBsAg'deki düşme HBeAg(+)lerde daha belirgin
- Tedavi sonunda yanıttaki devamlılık değişken

Yuen MF, et al. Nat Med. 2021 Oct;27(10):1725-1734.

Nükleokapsit inhibitörleri

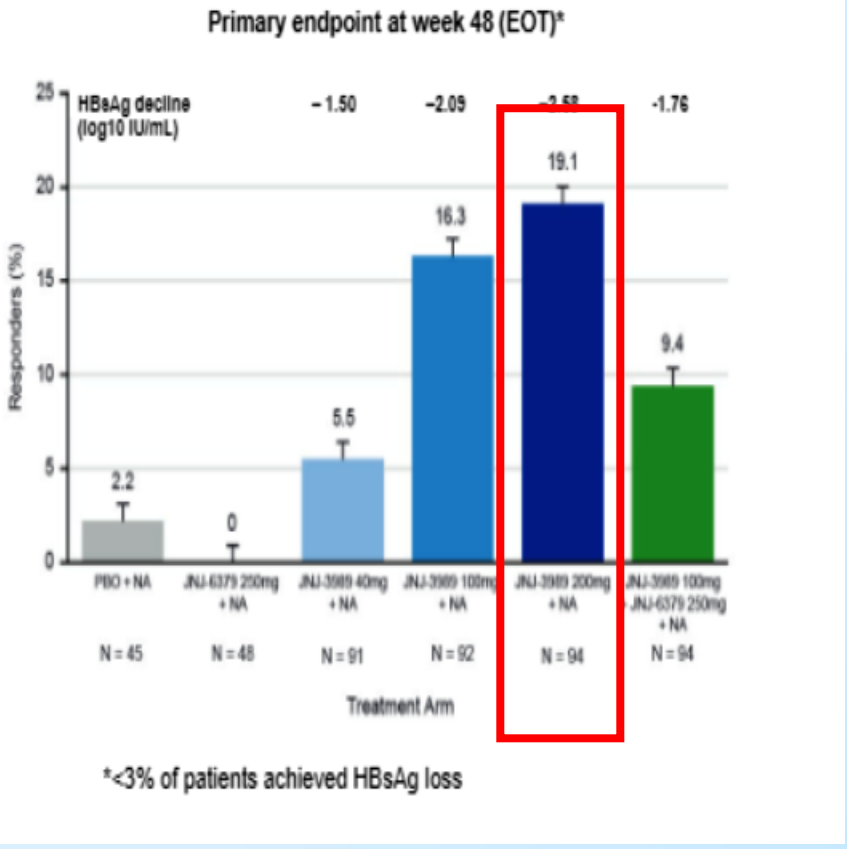
Inhibition of capsid formation	CpAM	Class 1	**GLS-4** (Morphothiadin)/ritonavir	Oral	2
		Class 2	**ABI-HB0731** (Vebicorvir)		2
		Class 2	ABI-H2158		2
		Class 2	**JNJ-6379**		2
		Class 2	EDP-514		1
		Not disclosed	QL-007		1
		Class 2	ZM-H1505R		1
		Class 2	ABI-H3733		1
		Class 2	ALG-000184 (prodrug of ALG-001075)		1
		Class 1	**RO7049389** (RG7907)		1



Mak LY, Viruses. 2021 Jun 18;13(6):1169

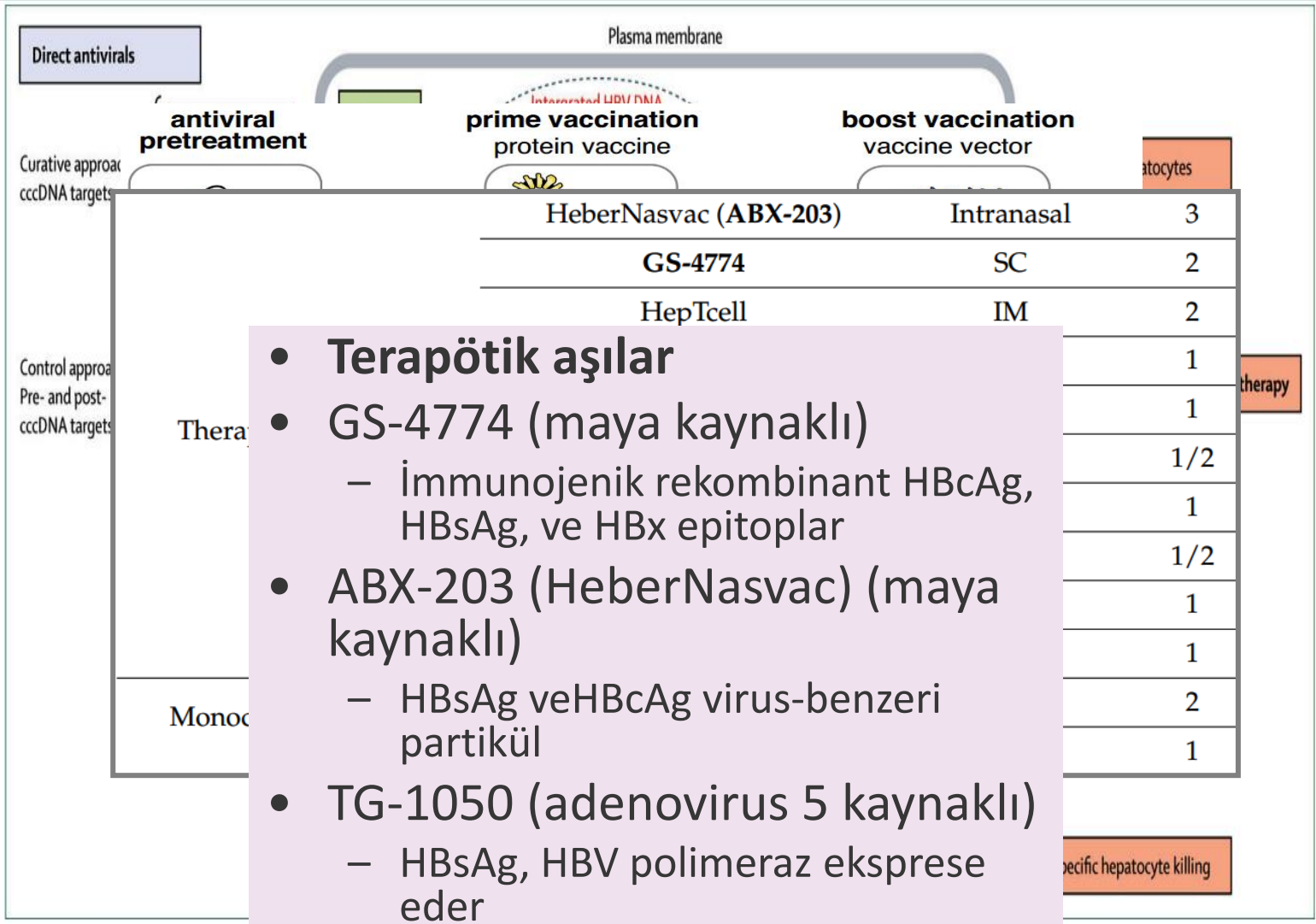
siRNA JNJ-3989 and/or the Capsid Assembly Modulator (CAM) JNJ-6379 for the Treatment of CHB: the Phase 2b REEF-1 Study

- 470 KHB hastası, 6 kol (2:2:2:2:1:1)
- 48hft tedavi, 48 hft takip
- **JNJ-3989** (aylık 40mg,100mg ve 200mg SK enj.) **+ CAM+ NA**
- Sonuç olarak;
  - JNJ-3989 doz bağımlı etki
  - **%19.1** 'i 48 hft sonra primer sonlanım noktasına ulaştı (ALT<3XULN, HBV DNA < ölçülebilir limit, HBsAg<10 IU/mL)



Seto WK,et al Clinical Liver Disease 2016;8:4, 83-86

Terapötik aşılar



HeberNasvac (**ABX-203**)	Intranasal	3
GS-4774	SC	2
HepTcell	IM	2
		1
		1
		1/2
		1
		1/2
		1
		1
		2
		1

- **Terapötik aşılar**
- GS-4774 (maya kaynaklı)
  - İmmunojenik rekombinant HBcAg, HBsAg, ve HBx epitoplar
- ABX-203 (HeberNasvac) (maya kaynaklı)
  - HBsAg veHBcAg virus-benzeri partikül
- TG-1050 (adenovirus 5 kaynaklı)
  - HBsAg, HBV polimeraz eksprese eder

Mak LY, Viruses. 2021 Jun 18;13(6):1169

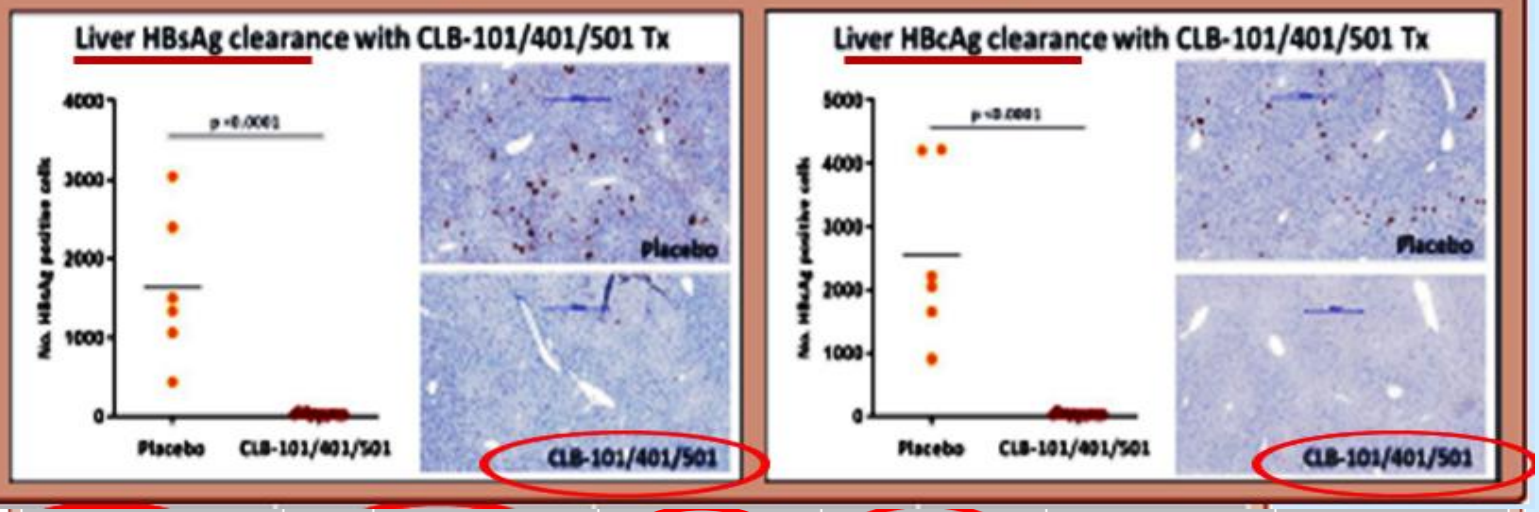
A novel therapeutic vaccine achieves functional cure in a mouse model of chronic hepatitis B

R. WALSH[1,2], S. LOCARNINI[1,2], R. HAMMOND[1,2], M. HYAKUMURA[1,2], C.L. LEE[1,2], J. HO[1,2], R. FARQUHAR[2], A. RUBIO[2], and H.J. NETTER[1,2]

[1]Victorian Infectious Diseases Reference Laboratory, Doherty Institute, Melbourne, Australia. [2]ClearB Therapeutics, Inc., Concord, MA 01742, USA

CLEARB THERAPEUTICS

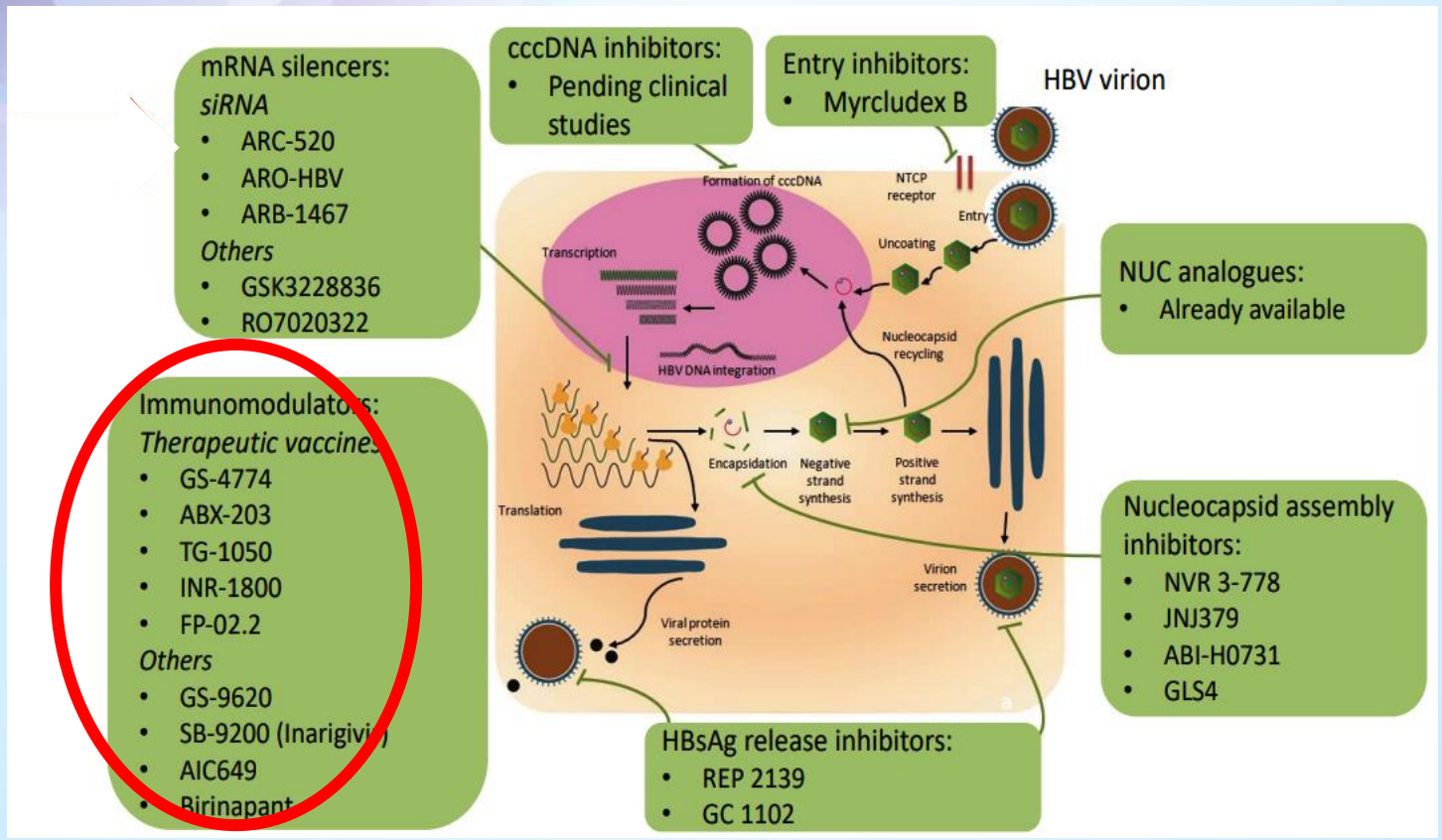
Fig.3 Liver HBsAg and HBcAg IHC



Group	n	PreTx HBsAg IUmL (log10)	EOS HBsAg IUmL (log10)	Effect on HBsAg	Anti-HBs seroconversion (diagnostic)	Anti-HBs IndCP (clearing)
Placebo	8	1657 (3.22)	1391 (3.14)	no	na	na
CLB-101/401/501	**13**	**1955 (3.29)**	**<1, UND**	**> 3 log decline, UND**	**8/13 (62%)**	**yes**
Engerix-B ®	8	907 (2.96)	988 (2.99)	no	no	no

Oral P. Walsh R. EASL2021 Poster no:853

İmmün modülatörler



Seto WK,et al Clinical Liver Disease 2016;8:4, 83-86

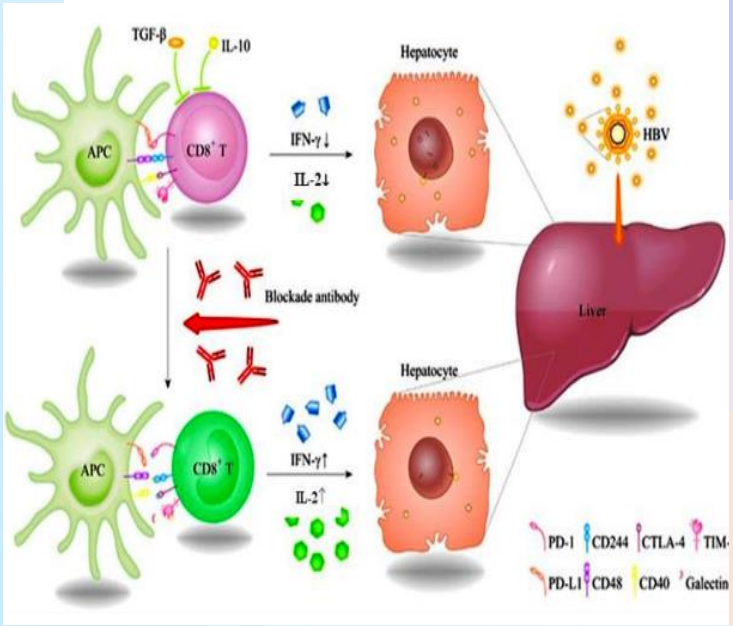
AdisInsight Report | Published: 05 February 2022

Envafolimab: First Approval

Anthony Markham

Drugs **82**, 235–240 (2022) | Cite this article

HBsAg Loss in Chronic Hepatitis B Patients with Subcutaneous PD-L1 Antibody ASC22 (Envafolimab) plus Nucleos(t)ide Analogs Treatment: Interim Results from a Phase IIb Clinical Trial



PD-1/PD-L1 etkileşimi T hücrelerinde yorulmaya neden olur

—— Persistan HBV enfeksiyonu

PD-1/PD-L1 yolak blokajı T hücrelerin restorasyonuna neden olur

——HBV eliminasyonu

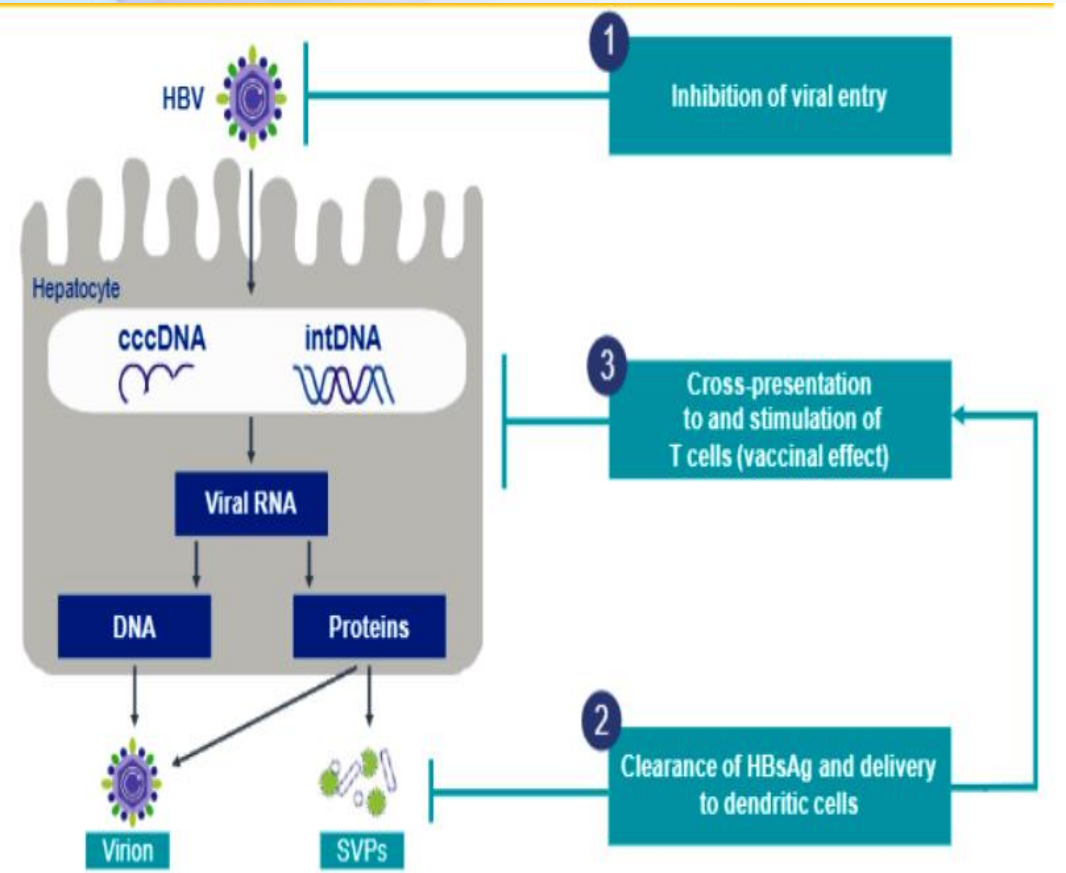
PD-1/PD-L1 inhibitörü ile NA kombinasyonu

—— Kronik HBV kürü?

Markham A.. Drugs. 2022 Feb;82(2):235-240
Cell Death Dis. 2015 19;6:e1694.

Vir Biotechnology Presents New Data Evaluating the Potential for VIR-2218 and VIR-3434 to Achieve a Functional Cure for Chronic Hepatitis B Virus (HBV) Infection at AASLD The Liver Meeting®

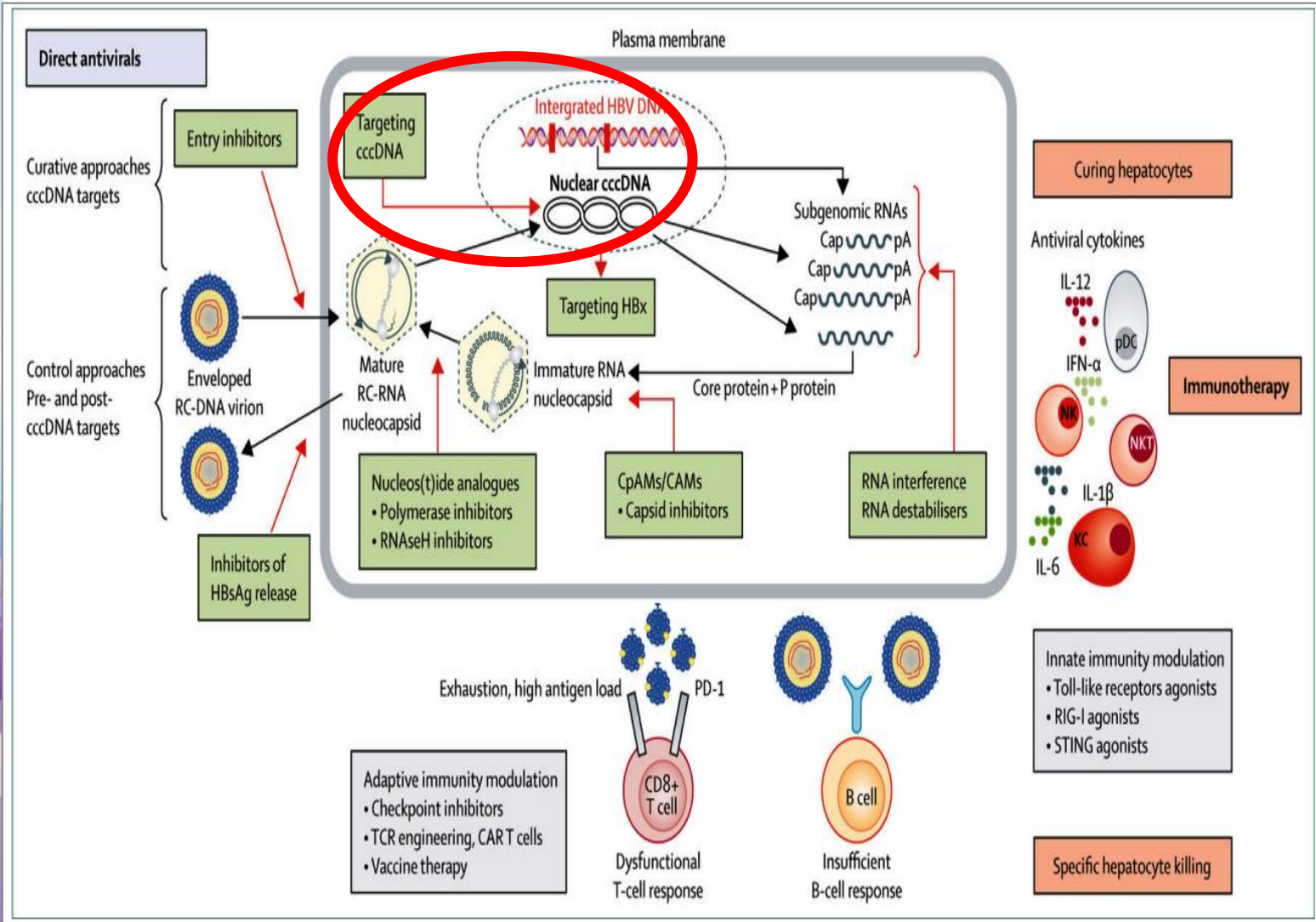
November 12, 2021



- **VIR-3434** Faz 1 sonuçları
- Viral suprese 24 KHB hastası
- **Tek doz** 6 mg, 18 mg, 75 mg veya plasebo
- Bir hafta sonunda tek doz tedavi ile **HBsAg >1 log10 IU/mL azalma**
  - 75 mg alanlarda HBsAg'de >2 log10 IU/mL

Poster P. Florian A. Etal. **EASL 2021** Publication #838

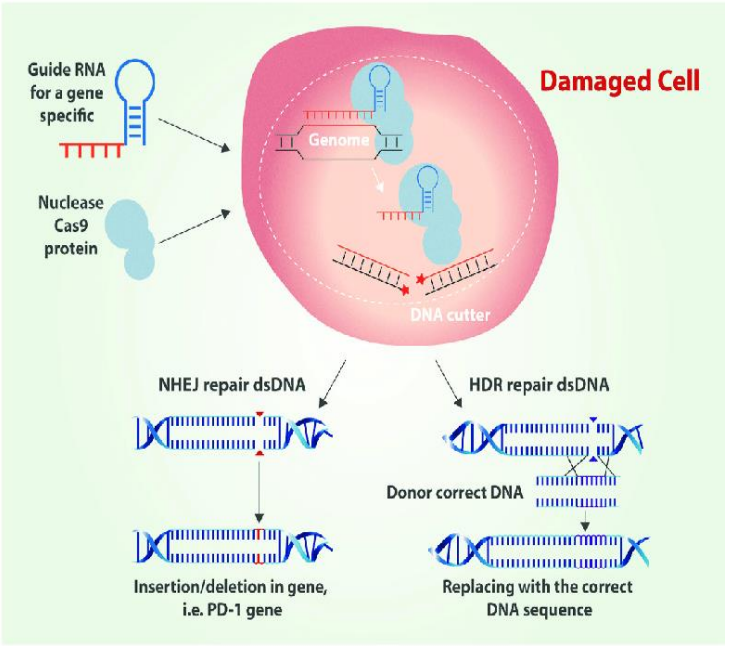
cccDNA'yı hedefleyen



Mak LY, Viruses. 2021 Jun 18;13(6):1169

NOVEL ANTI-HBV COMBINATION TREATMENT USING **CRISPR/Cas9** TARGETING HBV GENOME AND SUPPRESSION OF NHEJ-MEDIATED DNA REPAIR

- DNA onarım mekanizmalarının süpresyonu ve HBV genomunu hedefleyen CRISPR/Cas9'un etkinliği
- HBV genomunu hedefleyen gRNA (HBV-gRNA) düzenlenmiş
- HBV-gRNA/Cas9 transdüksiyonu, intraselüler pregenomik RNA (pgRNA) seviyeleri ile HBV DNA ve HBsAg seviyelerinde önemli ölçüde azalma
- Hepatositlerde **cccDNA'da azalma**



Oral P. No:22 Murai K. ,AASLD 2021 Abstract

Molecular Therapy
Nucleic Acids
Original Article

Permanent Inactivation of HBV Genomes by CRISPR/Cas9-Mediated Non-cleavage Base Editing

- CRISPR/Cas aracılı “baz düzenleyicilerin” DNA'nın bölünmesi olmadan HBV gen ekspresyonunu inaktive edebilir
- Baz düzenleme ile ortaya çıkan bazı nokta mutasyonları, hem polimeraz hem de yüzey genlerinin aynı anda baskılanması
- **Cas9 aracılı baz düzenleme, entegre HBV DNA ve cccDNA'nın kalıcı olarak etkisizleştirilmesi yoluyla KHB'yi iyileştirebilir**

Yang YC, et al. Mol Ther Nucleic Acids. 2020 5;20:480-490.

Hepatit B Aşısı

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 71 / No. 13
April 1, 2022

END HEP 2030

- >18 - <60 yaş tüm erişkinler

Weng MK,et al. MMWR Morb Mortal Wkly Rep. 2022 Apr 1;71(13):477-483.

Sağlık Bakanlığı tarafından yürütülmekte olan Hepatit B Kontrol Programı kapsamında, **Hepatit B aşısı risk grupları** ve bu risk gruplarının dışında, hekimin yüksek risk nedeniyle aşı yapılmasını uygun bulduğu kişilere sağlık kuruluşlarında Hepatit B aşısı uygulaması ücretsiz olarak uygulanabilir

T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü

AŞI PORTALI

Hepatit B Aşısı

JAMA Network | Open

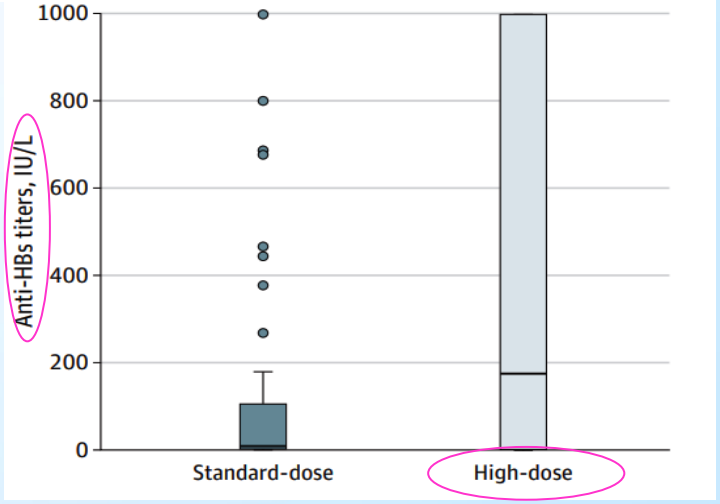
Original Investigation | Gastroenterology and Hepatology

Comparative Efficacy of a High-Dose vs Standard-Dose Hepatitis B Revaccination Schedule Among Patients With HIV

A Randomized Clinical Trial

- %98'i antiretroviral alan, ort CD4 >400, viral yük negatif hastalar
- 40 µg doz 20 µg doza göre daha etkin

(%72, %51 P = 0.03)



Vargas JI, eta al. JAMA Netw Open. 2021;4(8):e2120929.

Hepatit B Aşısı

- Yeni trivalan hepatit B aşısı
- Yaşlılarda daha immunojenik
  - **≥45 yaş**, 24 hft sonra anti-HBs titresi ≥10 mIU /mL (%89.4 vs %73.1)

Vesikari T,Lancet Infect Dis. 2021;21(9):1271.

Son Söz

1.Tedavide yeni amaç fonsiyonel kür mü?

2.Tedavi esnasında mı bırakıldığında mı HBsAg kaybı?

3. Peg-IFN tekrar sahalarda mı?

4. qHBsAg,..

5. Yeni çalışmalar;ASO, NAP, CAM, siRNA,..