Kronik Hepatit B

Güncel Tedaviler ve Sonuçları

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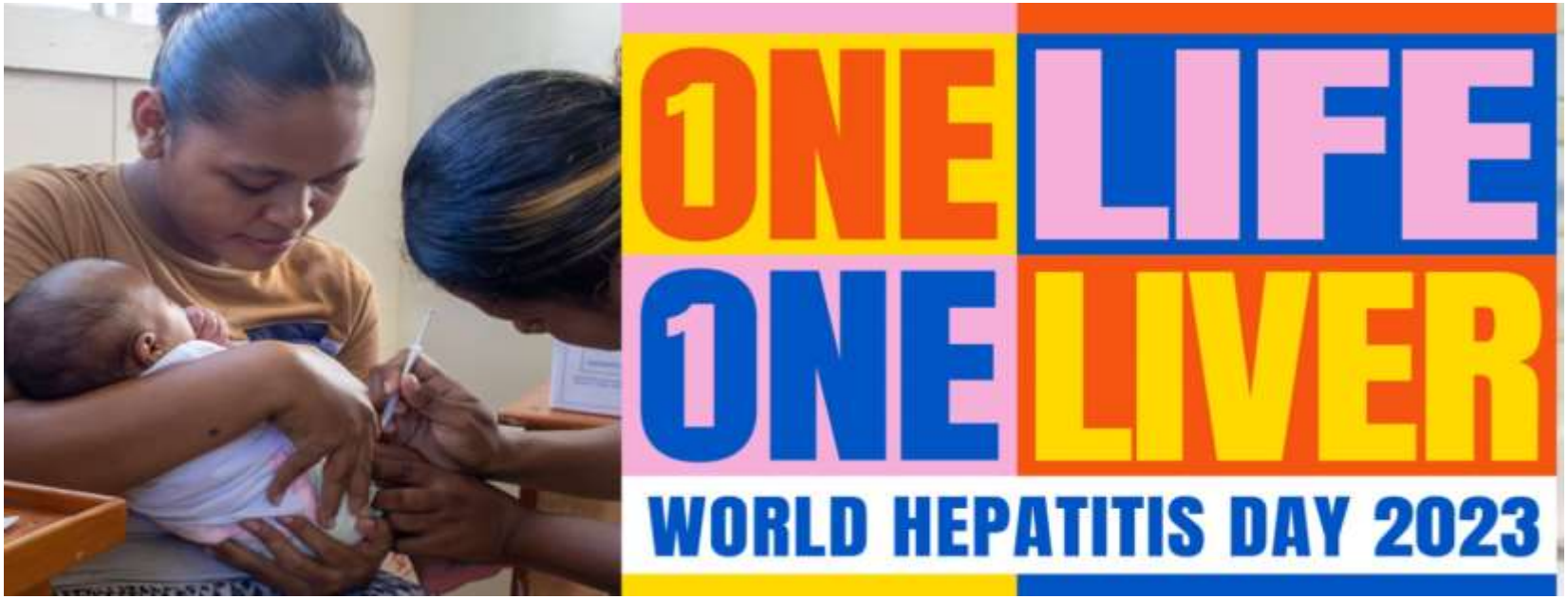
Koç Üniversitesi Tıp Fakültesi
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı

UVHS XIII
29.09.2023

Neler konuşulacak?

- Kronik Hepatit B
  - ✓ Tedavi endikasyonları
  - ✓ Güncel tedaviler
- Tedavi sonuçları
- Gerçek yaşamdan veriler
- Soru & Katkı



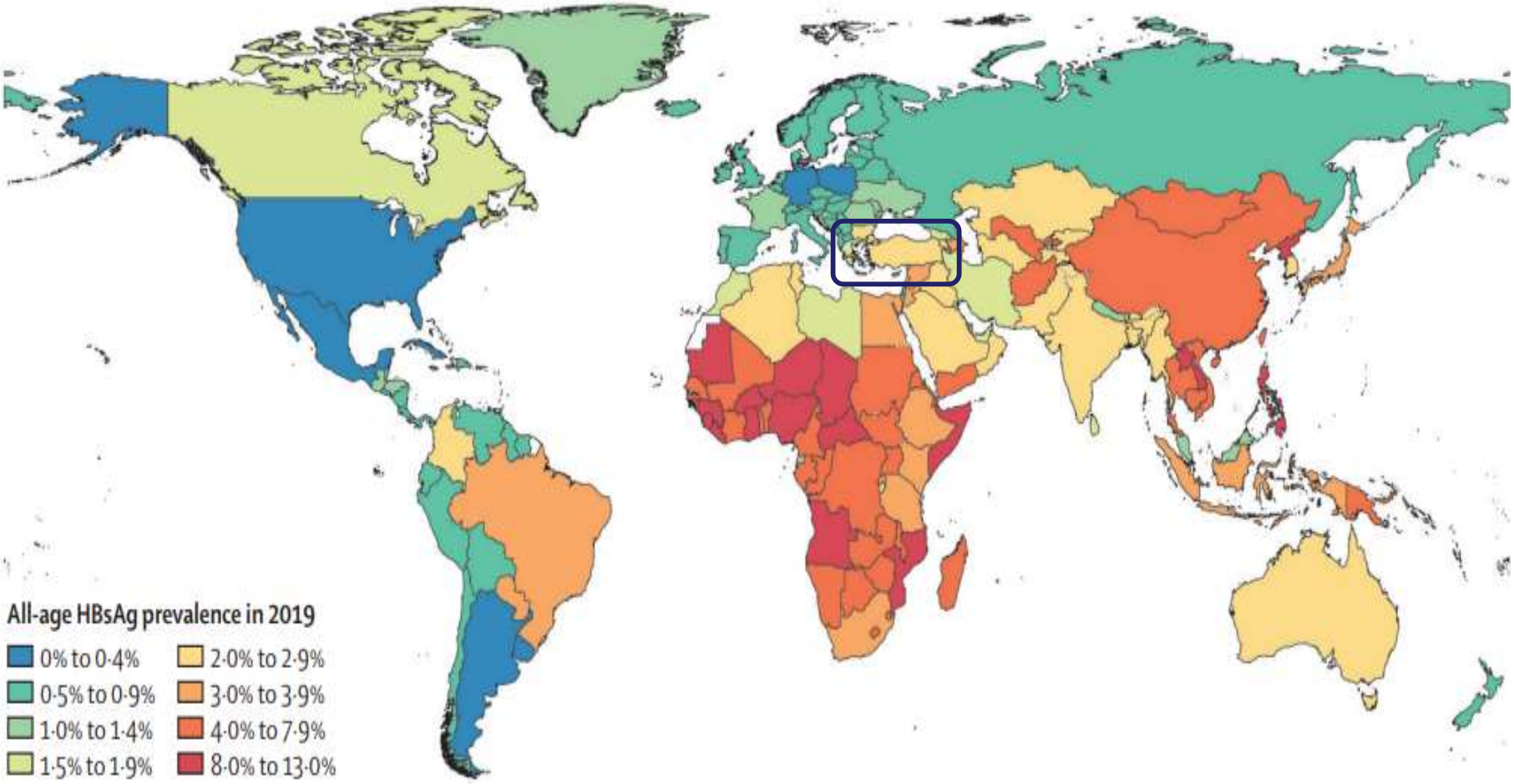
Nobel-prize winning scientist Dr. Blumberg

- **350 milyon** insan kronik viral hepatit infeksiyonu ile yaşıyor.
- Hepatit **B** ve hepatit **C her yıl**
  - **1,1 milyon ölüm**
  - **3 milyon** yeni infeksiyon

Hepatitis B

Wen-Juei Jeng, George V Papatheodoridis, Anna S F Lok

Global HBsAg veya KHB virus infeksiyonu prevalansı



Lancet. 2023; 401: 1039–52.

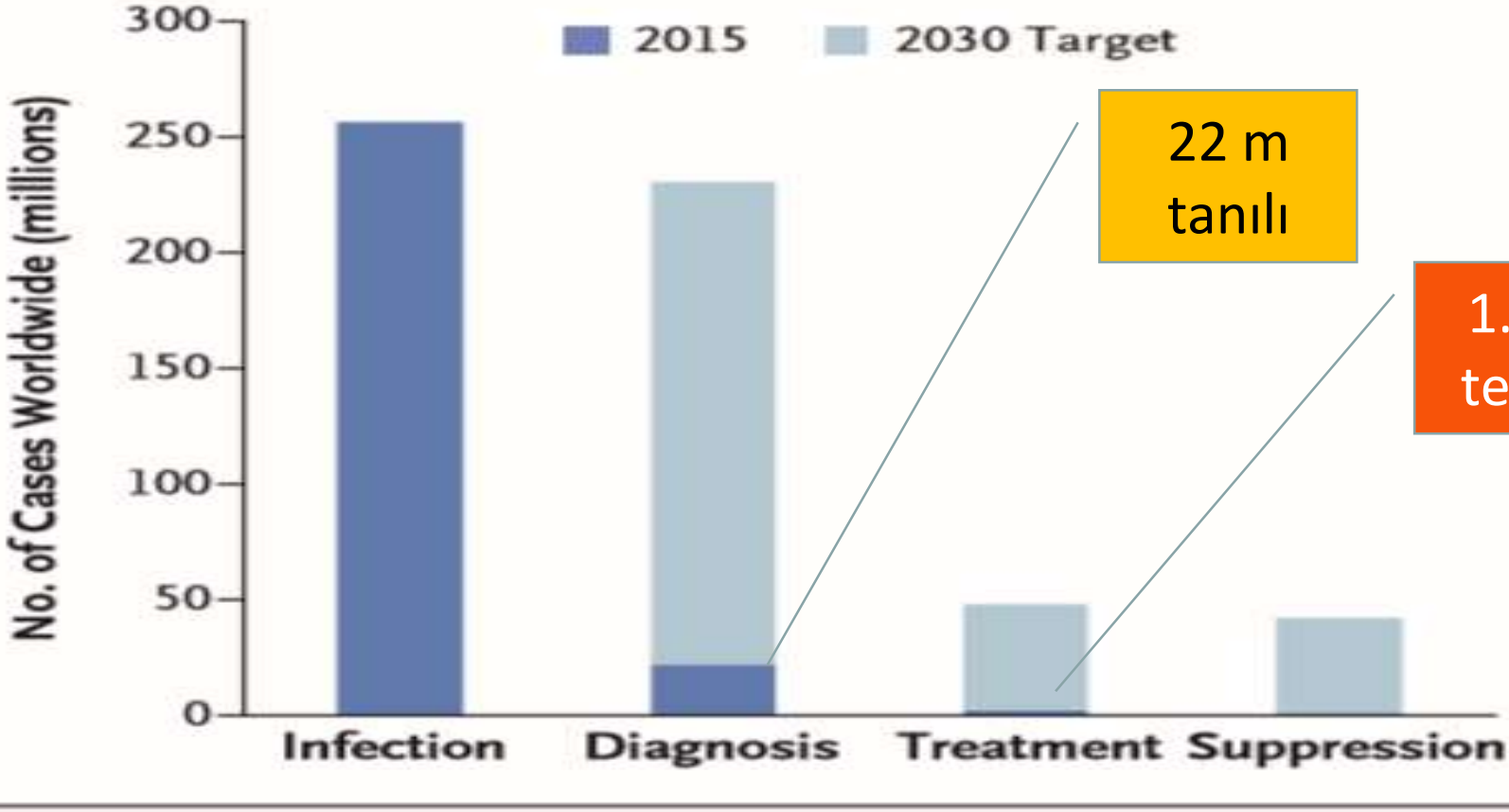
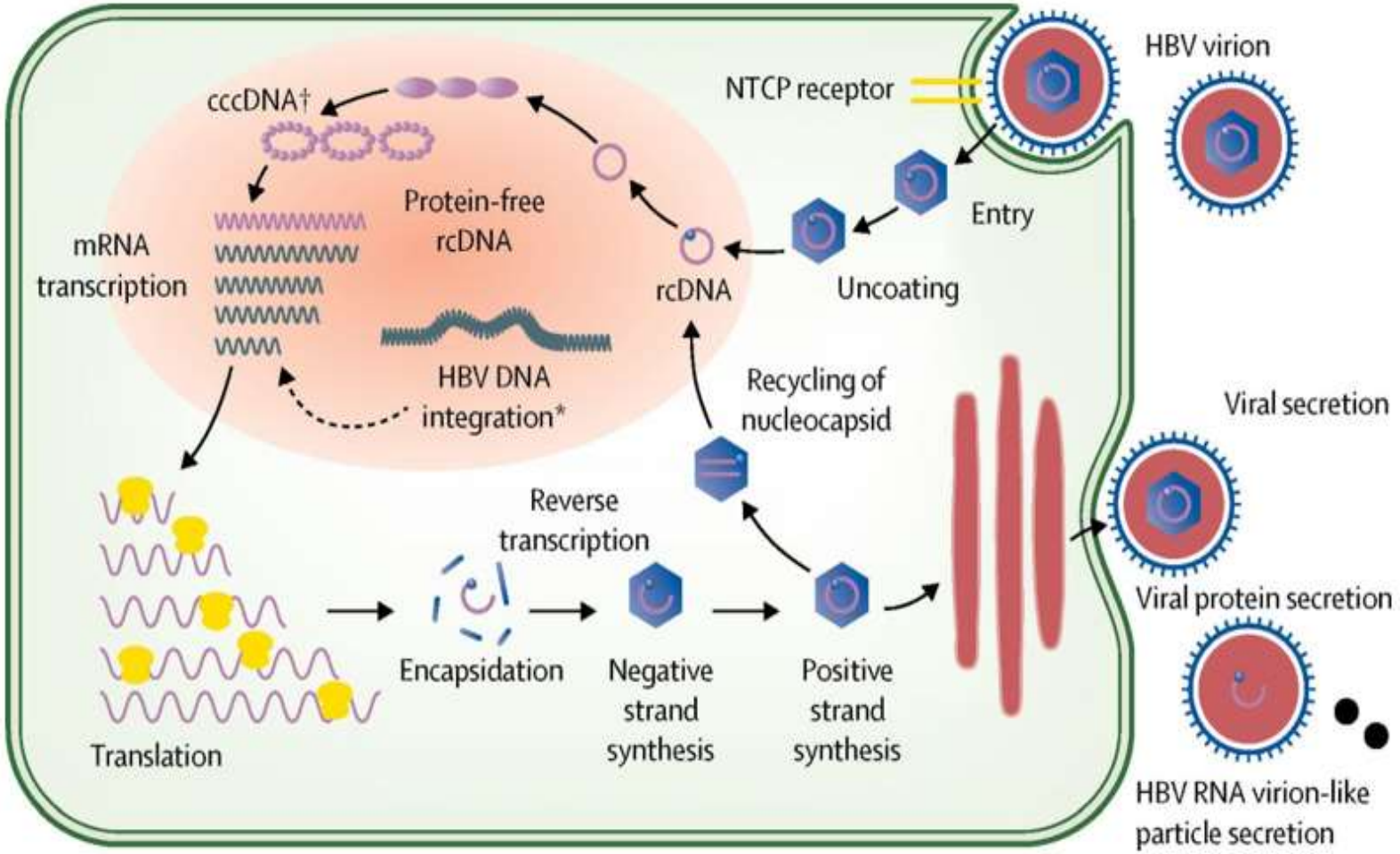


Figure 4. Global Continuum of Care for HBV Infection and 2030 WHO Elimination Targets.

Intervention	Indicator	2015 Baseline	2020 Target	2030 Target
HBV vaccination	% of infants with HEPB3 vaccination	84	90	90
Prevention of maternal HBV transmission	% of infants with HBV vaccination ≤12 hr after birth	39	50	90

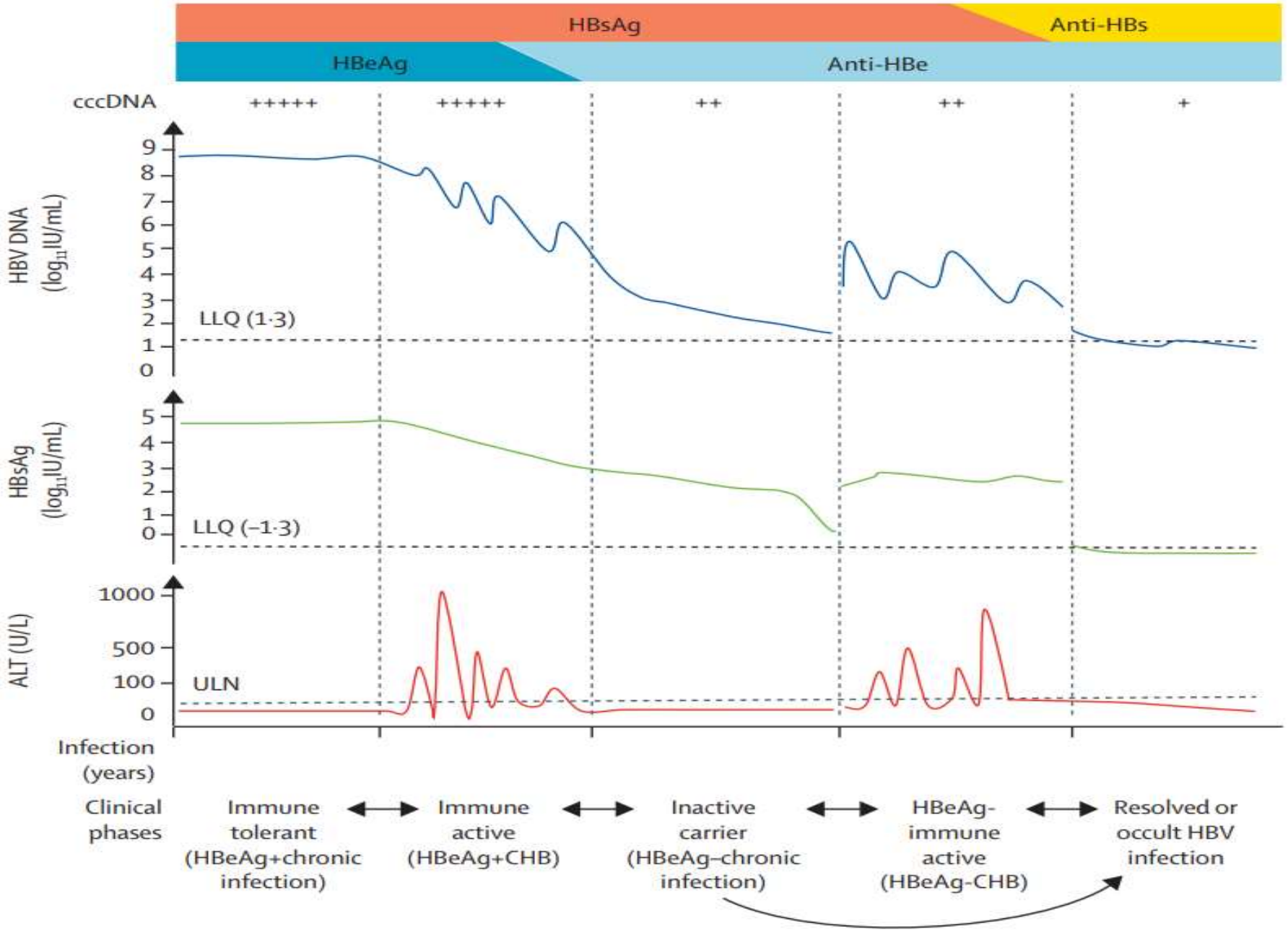
N Engl J Med. 2019; 380: 2041-50.

Hepatit B virusu yaşam döngüsü ve Kronikleşme



Kronik HBV infeksiyonu: **HBs Ag**'nin **en az 6 ay** serumda saptanması

- ✓ Hastaların çoğunluğu **asemptomatik**



Lancet. 2023; 401: 1039-52.

KHB Fazları ve Yönetimi

	HBeAg pozitif
	Kronik infeksiyon Faz 1
HBsAg	Yüksek
HBeAg	Pozitif
HBV DNA	$>10^7$ IU/ml
ALT	Normal
Karaciğer Hastalığı	Yok/Hafif
Eski Terminoloji	İmmün tolerans

HBeAg pozitif kronik infekte hastaların İzlemi

- **Yaş > 30** ve/veya ailede **HSK** veya **siroz öyküsü** varsa **karaciğer biyopsisi** yapılarak tedavi açısından değerlendirilmelidir.

Hastalar; **3-6 ayda** bir **ALT**, **6-12** ayda bir **HBeAg kontrolü** yapılmalıdır.

KHB Fazları ve Yönetimi

	HBeAg pozitif
	Kronik Hepatit Faz 2
HBsAg	Yüksek veya orta
HBeAg	Pozitif
HBV DNA	10^4-10^7 IU/ml
ALT	Yüksek
Karaciğer Hastalığı	Orta/Şiddetli
Eski Terminoloji	İmmün reaktif HBeAg pozitif

- ✓ Karaciğerde orta veya şiddetli **nekroinflamasyon** ve **fibroz hızla** ilerleyebilir
- ✓ Çocuklukta daha yavaş
- ✓ Yetişkinlik döneminde infekte olan kişilerde **hızla** ulaşılır.

Yılda % 5-15 spontan **HBeAg serokonversiyonu**

KHB Fazları ve Yönetimi

	HBeAg Negatif
	Kronik infeksiyon Faz 3
HBsAg	Düşük
HBeAg	Negatif
HBV DNA	<2000 IU/ml
ALT	Normal
Karaciğer Hastalığı	Yok
Eski Terminoloji	İnaktif taşıyıcılık

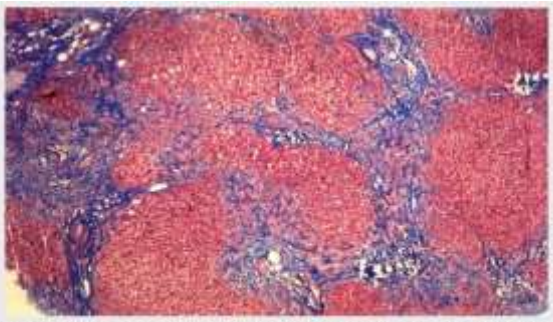
- **Siroza** ilerleme veya **HSK riski** düşüktür HBsAg kaybı ve/veya **serokonversiyo**n hastaların **%1-3**'ünde kendiliğinden olabilir
- Bu durum **serum HBsAg<1000 IU/ml**

KHB Fazları ve Yönetimi

	HBeAg Negatif
	Kronik Hepatit Faz 4
HBsAg	Orta
HBeAg	Negatif
HBV DNA	>2000 IU/ml
ALT	Yüksek
Karaciğer Hastalığı	Orta/Şiddetli
Eski Terminoloji	HBeAg negatif kronik Hepatit

- ✓ **ALT** değerlerinde dalgalanma veya sürekli **yüksek**
- ✓ Karaciğer histolojisi **nekroinflamasyon** ve **fibrozu** gösterir

- ✓ HBeAg ekspresyonunu bozan veya ortadan kaldıran **precore** ve/veya bazal **core promotör** bölgelerindeki HBV **varyantları**



Parankimde rejenere olan hepatositlerden oluşan nodüller ve bunları çevreleyen fibrotik bantlarla karakterli siroz

HBV'nin doğal seyri

HBsAg negatif faz Faz 5	
HBsAg	Negatif
Anti-HBc	Pozitif
Anti-HBs	Pozitif veya negatif
HBV DNA	Genellikle negatif
Karaciğerde HBV-DNA (cccDNA**)**	Genellikle pozitif
ALT	Normal
Karaciğer Hastalığı	➢**Siroz gelişmeden** HBsAg kaybı, siroza ilerleme, HSK gelişimi ve dekompanzasyon riskini azaltır, yaşam beklentisi artar. ➢HBsAg kaybından önce siroz gelişmişse HSK riski devam eder ➢Bu hastalarda **immünosüpresyon HBV reaktivasyonu** olb
Eski Terminoloji	**Okült hepatit**

EASL 2017. HBV. *J Hepatol* 2017

Doğal seyri etkileyen faktörler

İnfeksiyonun alındığı **yaş**	Karaciğer hastalığının devamlı aktif olması, **sık alevlenmeler**
İnfeksiyonun süresinin uzun olması	Metabolik faktörler (DM, obezite)
Erkek cinsiyet	Karaciğer kanseri için **aile öyküsü**
Alkol tüketimi (>50 g etanol/gün)	Yüksek coğrafik **endemi**site
HCV, HDV ve HIV **koinfeksiyon**u	**CD4 < 200/mL** olması
Fibroz evresinin ileri olması	
HBV **genotipi** ; **A**: Siroz riski düşük, HSK gelişebilir **C**: Hepatit ve HSK riski yüksek **D**: Anti-HBe (+) HSK riski yüksek	

KHB

Kimlere tedavi verilmeli?

© Dave Granlund (@ PoliticalCartoons.com)

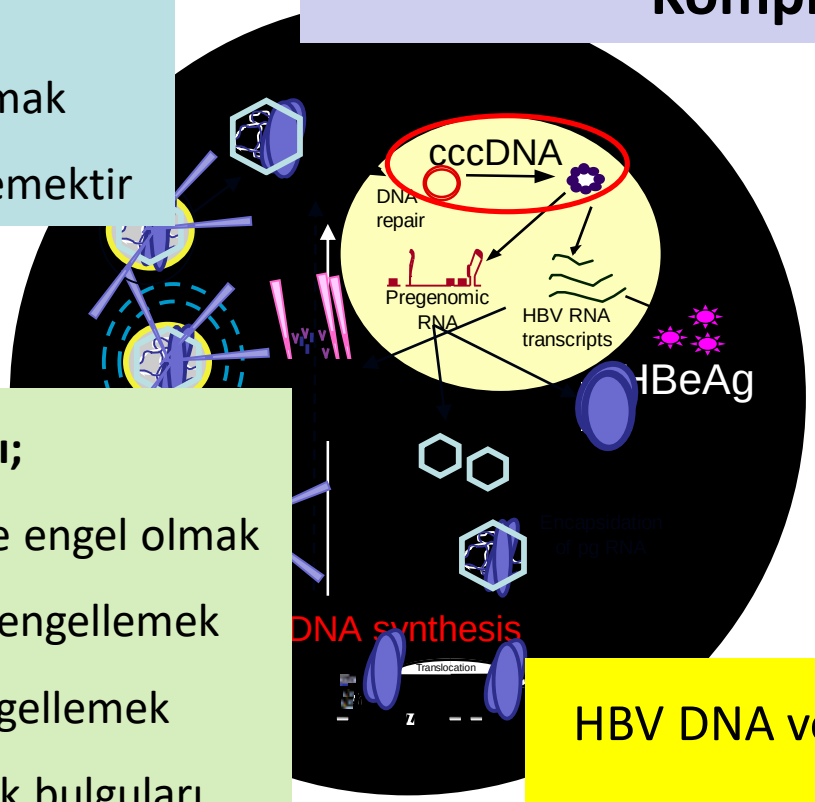
Kronik HBV infeksiyonunda Tedavinin Hedefleri

Tedavinin ana amacı;

- Hastalığın ilerleyişini engellemek
- Yaşam kalitesini artırmak
- HSK gelişimini engellemektir

Hepatositte "de novo" **cccDNA** sentezi

"Komplet kür"



Tedavinin diğer faydaları;

- Anneden bebeğe geçişe engel olmak
- HBV bulaşını azaltmak/engellemek
- HB reaktivasyonunu engellemek
- HBV ilişkili ekstrahepatik bulguları tedavi etmektir

HBV DNA ve HBsAg seroklirensi

"Fonksiyonel kür"

Grimm D, et al. *Hepatol Int*. 2011; 5: 644-53.

How to achieve functional cure of HBV: Stopping NUCs, adding interferon or new drug development?

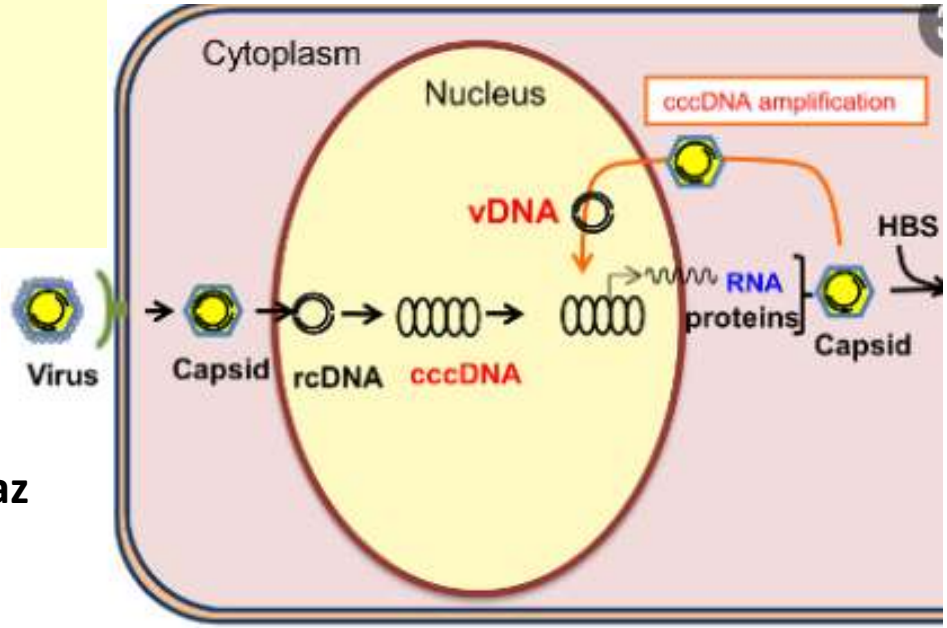
Grace L.H. Wong[1], Ed Gane[2], Anna S.F. Lok[3,*]

HBV komplet kür tedavisinin önündeki engeller;

✓HBV replikasyonu ve antijen üretimi için **rezervuarlar** yer almaktadır (**cccDNA** ve **entegre HBV DNA**)

✓Yüksek **viral yük** (HBV DNA ve HBsAg)

✓**Bozulmuş** doğal ve kazanılmış **bağışıklık**



qHBsAg **<1000 IU/ml → düşük replikatif faz** intrahepatik **cccDNA düzeyleri**

J Hepatology. 2022; 76: 1249-62.

Kronik HBV İnfeksiyonunda İlk Değerlendirme

- Öykü
- Fizik muayene
- HBV infeksiyonu belirteçleri (**HBsAg, HBeAg/anti HBe, HBV DNA**)

Hastanın **yaşı**

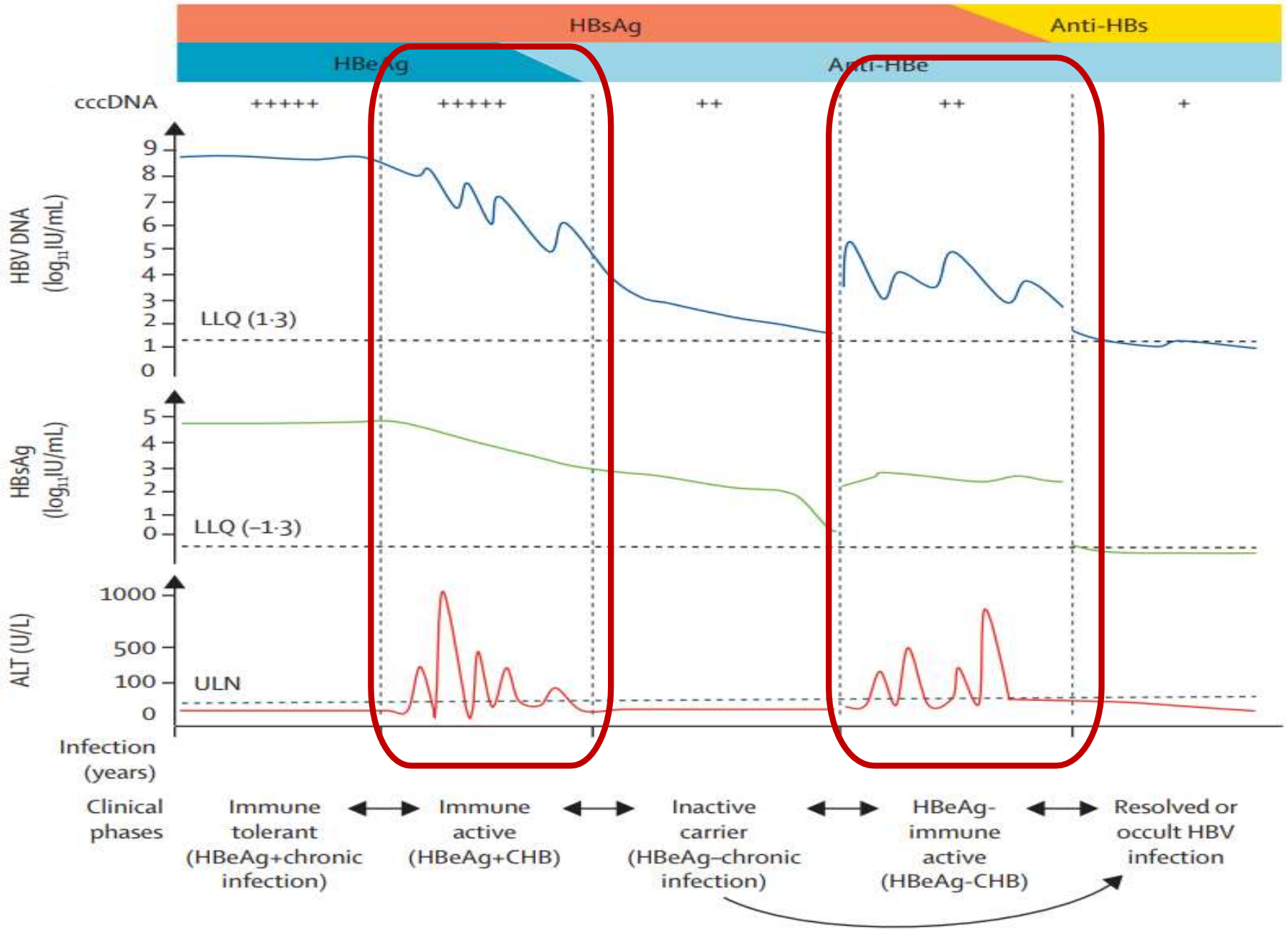
Eşlik eden durumlar;

- Alkol kullanımı
- Otoimmün hastalıklar
- Hepatosteatoz
- Hepatit **D** / Hepatit **C** / **HIV** ko-infeksiyon
- HAV (anti HAV **negatif** ise **aşılanmalı**)

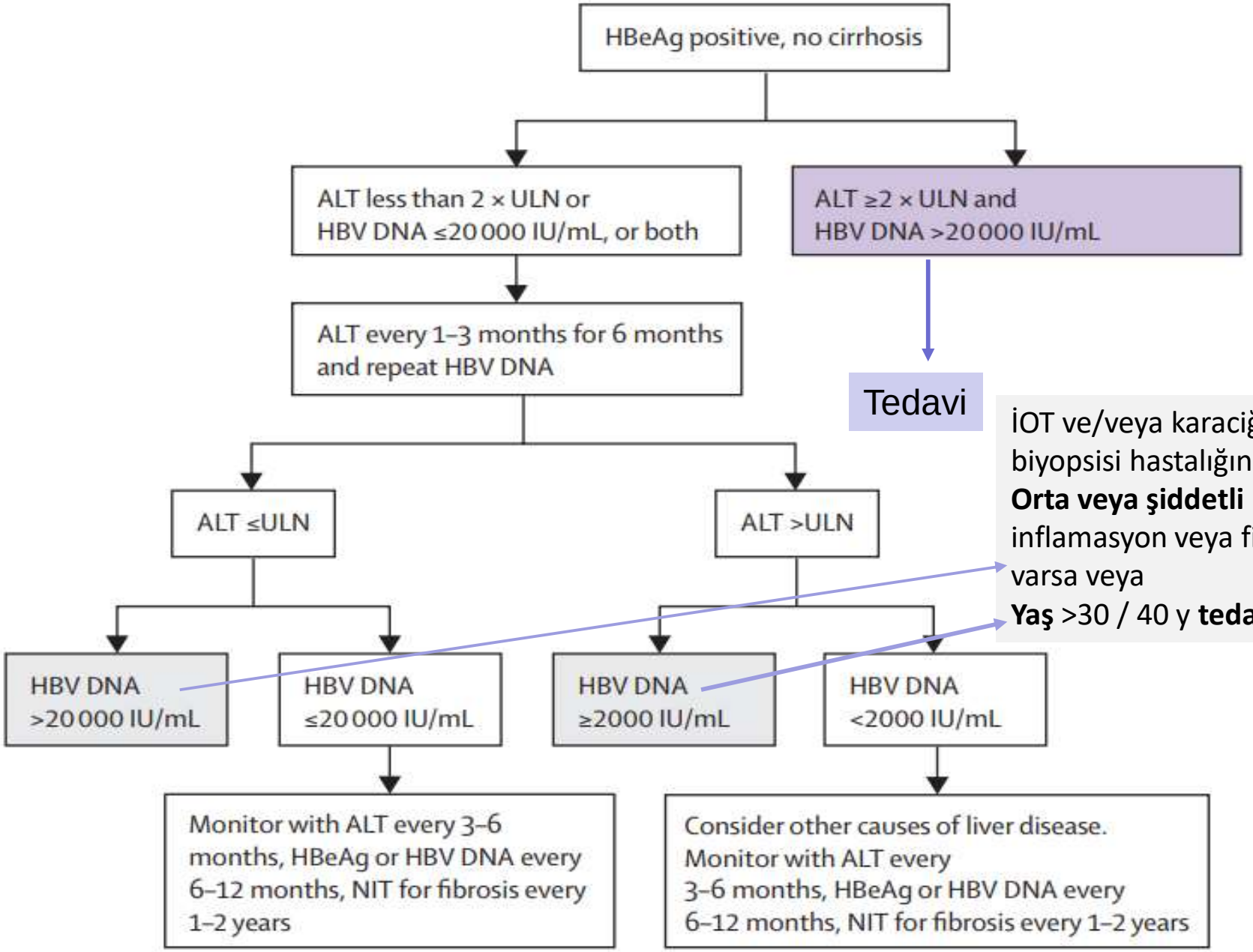
Karaciğer **hastalığı aktivitesinde** belirteçleri

- AST, ALT, GGT, Alkalen fosfataz
- Bilirubinler
- Serum albumin ve gama globulinler
- Hemogram, protrombin zamanı
- Hepatik USG
- Karaciğer biyopsisi veya noninvazif testler (fibro-scan, elastografi vb.)

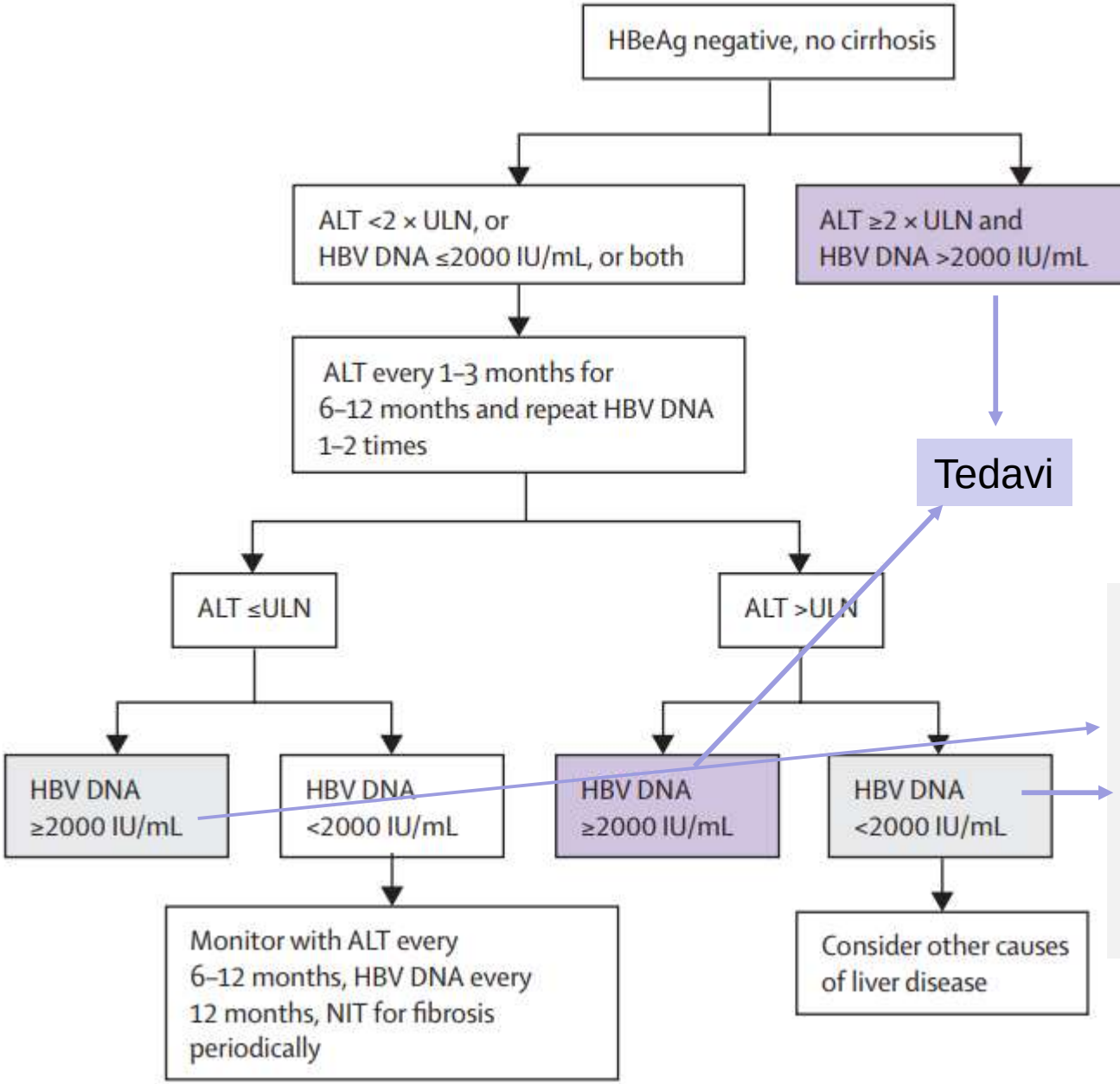
EASL 2017. HBV. *J Hepatol* 2017



Lancet. 2023; 401: 1039-52.



Lancet. 2023; 401: 1039–52.



İOT ve/veya karaciğer biyopsisi hastalığın ciddiyeti **Orta veya şiddetli** inflamasyon veya fibroz varsa **tedavi**
Yoksa yakın **izleme** (ALT ; 3-6 ayda bir, HBV DNA; 6-12 ayda bir, İOT her 1-2 yılda)

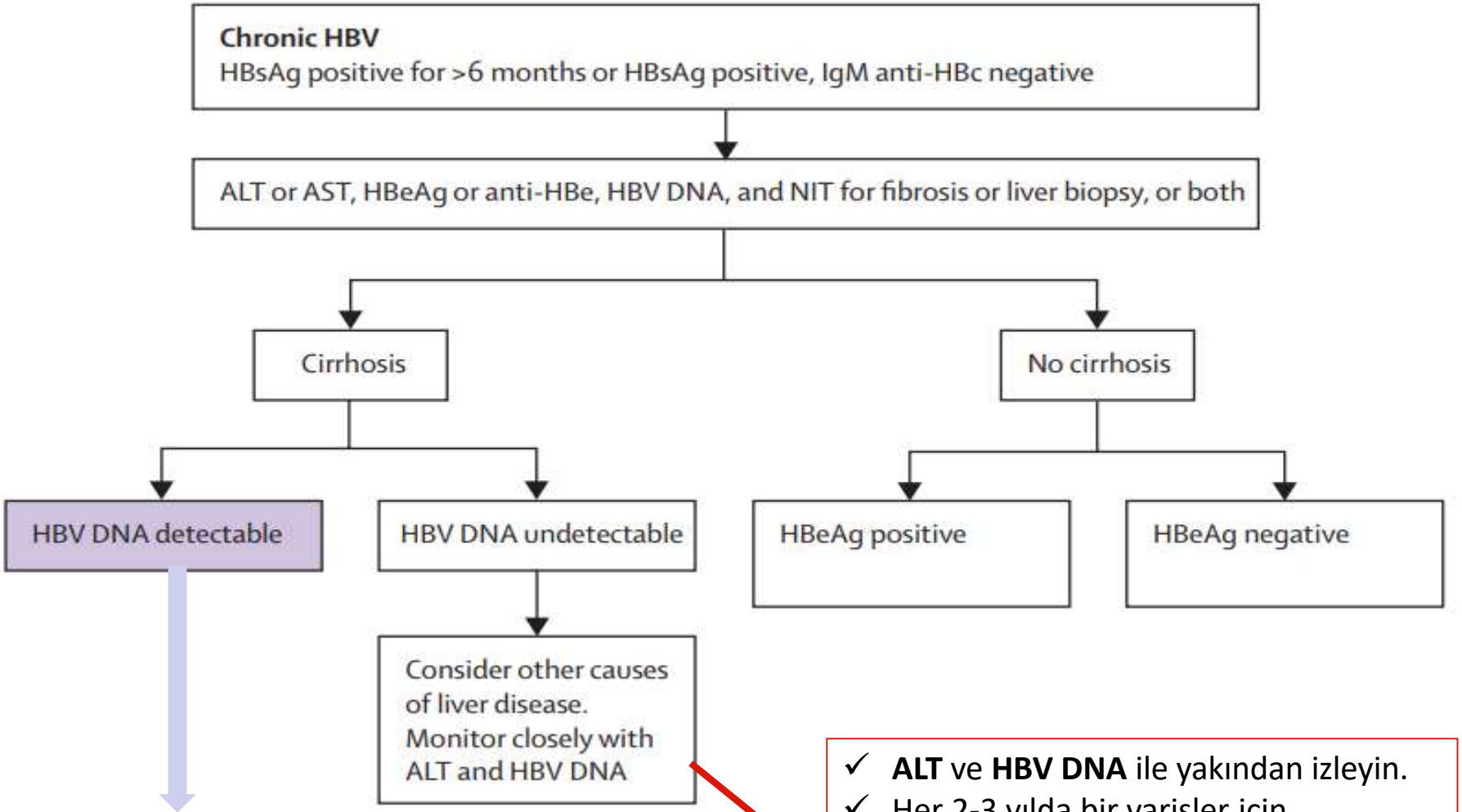
Lancet. 2023; 401: 1039–52.

Table 2 | Current guidelines on eligibility for antiviral treatment in patients with chronic HBV infection

Guidelines[a]	Patients without liver cirrhosis						Patients with cirrhosis	
	HBeAg positive			HBeAg negative			Regardless of HBeAg	
	HBV DNA (IU/ml)	Serum ALT[b]	Liver pathology	HBV DNA (IU/ml)	Serum ALT[b]	Liver pathology	Compensated	Decompensated
AASLD[62]	>20,000	≥2 times ULN	Not required	>2,000	≥2 times ULN	Not required	HBV DNA detectable regardless of ALT levels	HBsAg positive regardless of HBV DNA or ALT levels
	>20,000	1–2 times ULN	≥F2 or ≥A2	>2,000	>ULN	≥F2 or ≥A2		
APASL[63]	>20,000	≥2 times ULN	Not required	>2,000	≥2 times ULN	Not required	HBV DNA >2,000 IU/ml if normal ALT	HBV DNA detectable regardless of ALT levels
	>20,000	1–2 times ULN	≥F2 or ≥A2	>2,000	1–2 times ULN	≥F2 or ≥A2	HBV DNA detectable if elevated ALT	
EASL[61]	>20,000	>2 times ULN	Not required	>20,000	>2 times ULN	Not required	HBV DNA detectable regardless of ALT levels	HBV DNA detectable regardless of ALT levels
	>2,000	>ULN	At least moderate inflammation or fibrosis	>2,000	>ULN	At least moderate inflammation or fibrosis		
WHO[146]	≥20,000	≥ULN	Not required	≥20,000	≥ULN	Not required	Data on ALT or HBV DNA not required	Data on ALT or HBV DNA not required

AASLD: American Association for the Study of Liver Diseases
AATA: Asian American Treatment Algorithm
APASL: Asian Pacific Association for the Study of the Liver
EASL: European Association for the Study of the Liver
JSH, Japan Society of Hepatology

Hsu YC. ***Nat Rev Gastroenterol Hepatol.2023;***20:524-37.



ALT, HBeAg durumu ve HBV DNA düzeyine bakılmaksızın **tedavi edin**.

- ✓ **ALT** ve **HBV DNA** ile yakından izleyin.
- ✓ Her 2-3 yılda bir varisler için **endoskopi** ve her AFP ile birlikte veya **USG** ile HSK sürveyansı
- ✓ Dekompanse olması durumunda **karaciğer merkezine** başvurun.

Lancet. 2023; 401: 1039–52.

SAĞLIK UYGULAMA TEBLİĞİ

(1) İlk tedaviye başlamak için;

HBV DNA seviyesi **10.000** (10^4) **kopya/ml** (**2.000 IU/ml**) veya **üzerinde olan** hastalar, bu durumun belirtildiği **rapor** ve eki tetkik sonuçlarına (**HBV DNA** sonucu ve **karaciğer biyopsi raporu**) göre;

a) Erişkin hastalarda; karaciğer **biyopsisinde** Histolojik Aktivite İndeksi (**HAI) ≥6** veya **fibroz ≥2**

Tedavi Endikasyonu Olmayanlardaki İzlem

Gösterge	HBV DNA	ALT	Fibroz	İzlem Önerisi
HBeAg pozitif KHBV infeksiyonu, **30 yaş altı**	**Tedavi ölçütlerini karşılamıyor**			**3-6 ay** ara ile KD II-2, ÖD 1
HBeAg-negatif KHBV infeksiyonu	HBV DNA <2,000 IU/ml	**Tedavi ölçütlerini karşılamıyor**		**6-12 a**y arayla KD II-2, ÖD1
HBeAg-negatif KHBV infeksiyonu	HBV DNA ≥ 2,000 IU/ml	**Tedavi ölçütlerini karşılamıyor**		İlk yıl 3 ayda bir, sonrasında 6 ayda bir KD III, ÖD1

EASL 2017. HBV. *J Hepatol* 2017

KHB Tercih edilen antiviraller

Guidelines	HBeAg+ or HBeAg- Without Cirrhosis	Compensated Cirrhosis	Decompensated Cirrhosis
AASLD 2018	TAF*, TDF, ETV, or Peg-IFN	**TAF, TDF or ETV**	TDF or ETV
AATA 2018	TAF, TDF, ETV or Peg-IFN	TAF, TDF or ETV	TDF or ETV
EASL 2017	**TAF, TDF, ETV, or Peg-IFN**	TAF, TDF or ETV; Peg-IFN may be used in selected patients	TAF, TDF or ETV
JSH 2017	TAF, TDF, ETV, or Peg-IFN	TAF, TDF, or ETV	TAF, TDF, or ETV
APASL 2015	TDF, ETV, or Peg-IFN	TDF or ETV; Peg-IFN for well-compensated disease	TDF or ETV
US Algorithm 2015	ETV, TDF or Peg-IFN	TDF or ETV; Peg-IFN may be	ETV or TDF

Tong MJ, Pan CQ, Han SB, et al. An expert consensus for the management of chronic hepatitis B in Asian Americans. Aliment Pharmacol Ther. 2018
EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017; doi: 10.1016/j.jhep.2017.03.021
JSH Guidelines for the Management of Hepatitis B Virus Infection. 2017
Sarin SK, et al. Hepatol Int 2015; doi 10.1007/s12072-015-9675-4; Martin P, et al. Clin Gastroenterol Hepatol 2015;13: 2071–87
Martin P, et al. Clin Gastroenterol Hepatol 2015; Published online July 15, 2015: http://dx.doi.org/10.1016/j.cgh.2015.07.007

Besifovir dipivoxil maleate: a novel antiviral agent with low toxicity and high genetic barriers for chronic hepatitis B

Jeong Eun Song & Jun Yong Park

Pages 2427-2433 | Received 11 May 2021, Accepted 09 Aug 2021, Published online: 19 Aug 2021

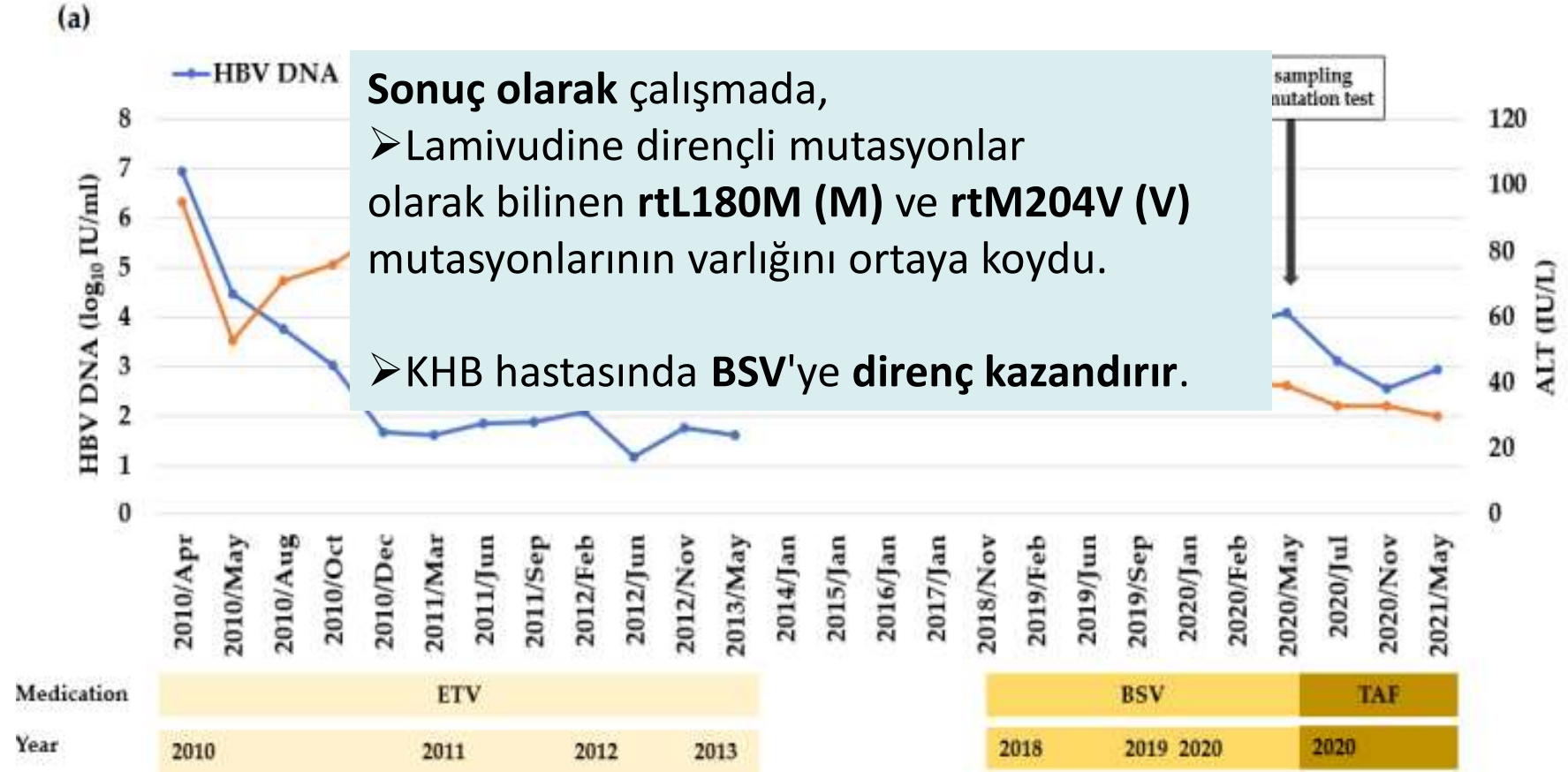
Besifovir dipivoxil maleate (BSV)

- ✓ BSV is a newly developed antiviral agent against HBV.
- ✓ This new agent has **strong antiviral activity** with **low toxicity** and a **high barrier to resistance**.
- ✓ Because there is concern that patients treated with a high dose of BSV require **carnitine** supplementation, BSV with carnitine supplementation is recommended during antiviral therapy.

Identification and Characterization of Besifovir-Resistant Hepatitis B Virus Isolated from a Chronic Hepatitis B Patient

Jong Chul Kim [1,†], Hye Young Lee [2,†], Ah Ram Lee [1], Mehrangiz Dezhbord [1], Da Rae Lee [1], Seong Ho Kim [1], Juhee Won [1], Soree Park [1], Na Yeon Kim [1], Jae Jin Shin [1], Sang Gyune Kim [2], Young Seok Kim [2], Jeong-Ju Yoo [2,*] and Kyun-Hwan Kim [1,*]

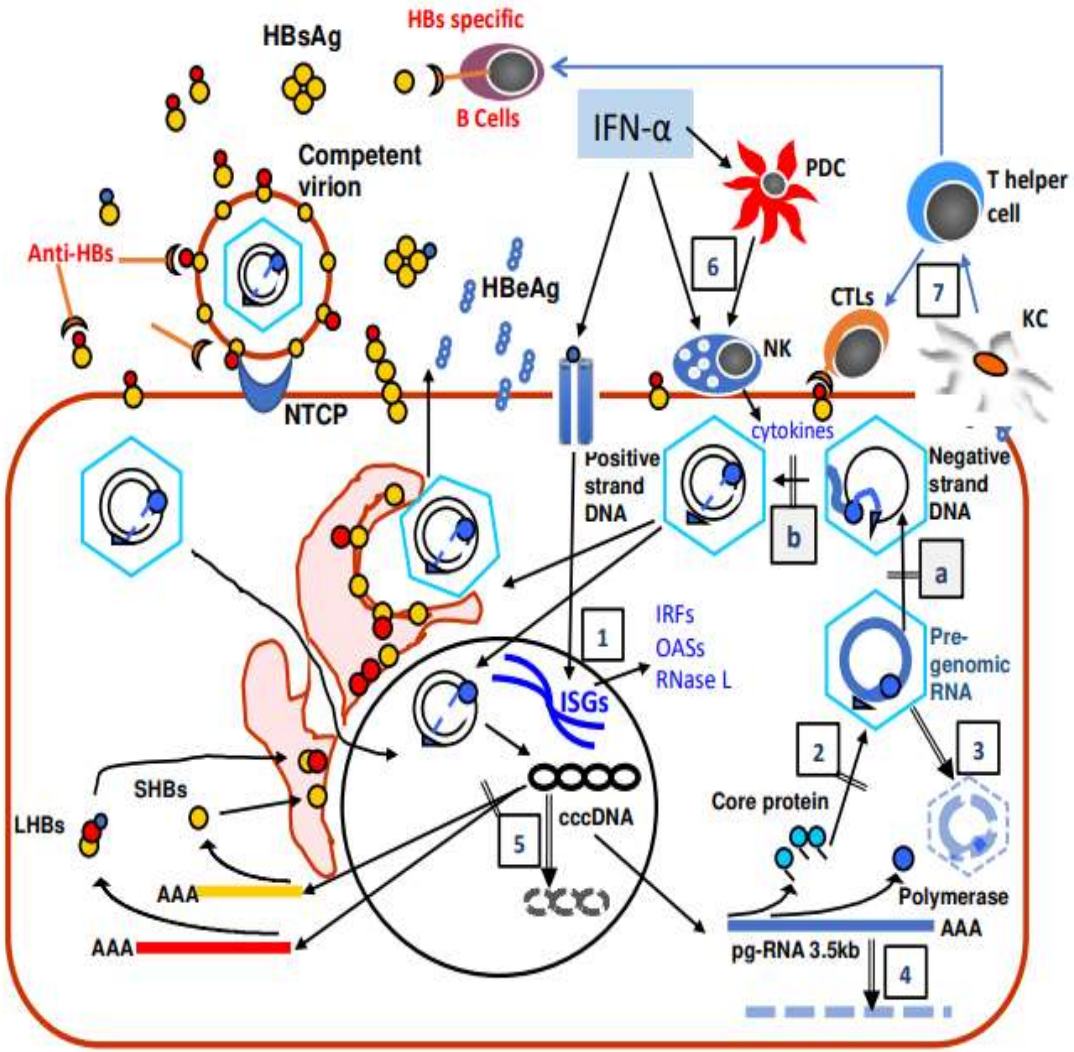
Biomedicines. 2022; 10: 282.



Sonuç olarak çalışmada,

- Lamivudine dirençli mutasyonlar olarak bilinen **rtL180M (M)** ve **rtM204V (V)** mutasyonlarının varlığını ortaya koydu.
- KHB hastasında **BSV**'ye **direnç kazandırır**.

Kronik Hepatit B'de IFN-α ve NA'nın etki mekanizmaları



Interferon-α

1. **Generic antiviral activity** mediated by IFN-stimulated genes (ISGs)
2. **Blocking formation of RNA-containing core particles**
3. **Accelerated decay of replication-competent core particles**
4. **Degradation of pre-genomic-RNA**
5. **Degradation and inhibition of cccDNA transcription** by epigenetic regulation
6. **Boosting of innate immunity** by NK cells activation
7. **Delayed increase of adaptive immunity responses** in responder patients

Nucleos(t)ide Analogs

a. **blocking reverse transcription** from pre-genomic RNA to HBV-DNA (chain termination)

b. **inhibition of the first or second step of HBV protein priming** by competing with dGTP or dAMP by entecavir and tenofovir

Colombatto P, *Viruses*. 2022, 14, 701.

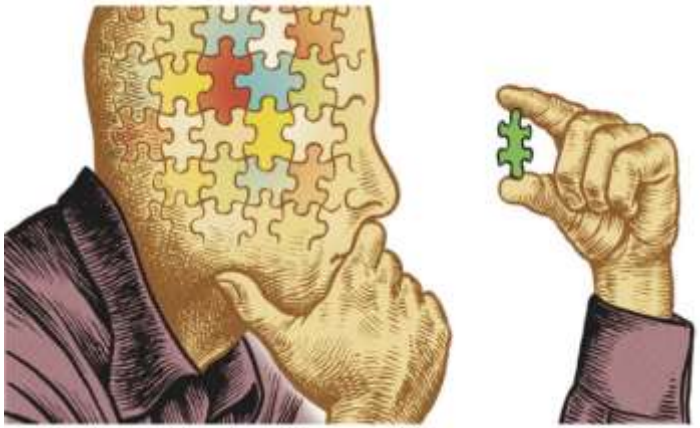
ETV, TDF veya TAF ile tedavi edilen hastalarda İzlem

- ✓ NA alan hastalarda **ALT** ve **HBV DNA** periyodik değerlendirilmeli (EI, G1) .
- ✓ **Böbrek hastalığı** riski taşıyan hastalar TDF ile tedavi edilen tüm hastalar, en azından tahmini glomerüler filtrasyon hızı (**eGFR**) ve **serum fosfat** seviyeleri (EII-2, G1) periyodik böbrek takibine alınmalıdır
- ✓ **Böbrek** sorunu gelişim riski taşıyan ve/veya **altta yatan böbrek** veya **kemik** hastalığı olan TDF kullanan hastalarda, **önceki LAM maruziyetine** bağlı olarak **ETV** veya **TAF**'ye geçiş düşünülmelidir (Kanıt düzeyi II-2/I, G1)

1. **Osteoporosis**
2. **Renal alteration****

eGFR \60 ml/min/1.73 m2 Albuminuria [30 mg/24 h or moderate dipstick proteinuria, Low phosphate (\2.5 mg/dl) Hemodialysis

EASL HBV guidelines. *J Hepatology* 2017: 67; 370-98.



KHB’de Tedavi

Gerçek Yaşam Verileri

KHB'de Uzun Süreli Tedavi Sonuçları

Table 2. Summary of studies reporting HBsAg loss in patients with chronic hepatitis B who had stopped nucleos(t)ide analogues (modified from Kao *et al.*).[35]

Author/study design	N	NUC	Cirrhosis (%)	Tx (years)	Consolidation Tx (months)	FU (months)	HBsAg loss
HBeAg-positive							
Liem/RCT	18	ETV/TDF	0	7.9	41	18	0% (*vs.* 0% in control)
Cao/Pros	60	Mixed	0	4	25	24	10%[#]
Liu/Pros	138	Mixed	0	2.4	21	120	0%
Su/Pros	28	ETV/TDF	0	3.1	26	48	0%
Chi/Pros	71	Mixed	0	3.9	26	31	4%
He/Retro	97	Mixed	n.a.	2.8	48	12	0%
Chen/Retro	148	LAM/ETV	0	2.7	-	96	19.6%
Kuo/Retro-Pros	154	ETV/TDF	0	3.1	>12	24	4.7% (ETV) 0% (TDF)
Song/Retro	262	Mixed	20.6	2.9	17.5	73.3	9.5% (median FU 6.1 yr)

J Hepatology. 2022; 76: 1249-62.

KHB'de Uzun Süreli Tedavi Sonuçları

Author/study design	N	NUC	Cirrhosis (%)	Tx (years)	Consolidation Tx (months)	FU (months)	HBsAg loss
HBeAg-negative							
Hadziyannis/Pros	33	ADV	0	4–5	45	69	39.4%
Berg /RCT	21	TDF	0	>4	>42	36	19% (*vs.* 0% in control)
Liem/RCT	27	ETV/TDF	0	7.4	85	18	4% (*vs.* 5% in control)
Van Bommel/RCT	79	Mixed	0	>4	n.a.	24	10.3% at 96 weeks (*vs.* 0% in control)
Cao/Pros	22	Mixed	0	4	35	48	10%[#]
Papatheodoridis/Pros	57	ETV/TDF	0	>4	64	18	25%
Liu/Pros	85	Mixed	0	2.4	21	120	14%
Su/Pros	72	ETV/TDF	0	3.1	26	48	0%
Chi/Pros	29	Mixed	0	3.9	106	31	10%
Jeng/Retro-Pros	691	ETV/TDF	45	2.9	25	36	13% by 6 years
Chen/Retro	263	LAM/ETV	0	2.9	-	96	33.1%
Kuo/Retro-Pros	353	ETV/TDF	0	3.1	>12	36	10% (ETV) 15.4% (TDF)
Chen/Retro-Pros	250	ETV	0	3.2	>12	58	20.8%
Song/Retro	226	Mixed	36.4	2.7	25	73.3	14.6% (median FU 6.1 yr)
Hirode/Retro	1,183	Mixed	5	3	-	17	15% by 4 years

J Hepatology. 2022; 76: 1249-62.

HBeAg pozitif / HBeAg negatif KHB'de onaylanmış tedavilerin etkinliği

	Pegylated interferon alfa 48–52 weeks (post therapy)		Entecavir (on therapy)		Tenofovir disoproxil fumarate (on therapy)		Tenofovir alafenamide (on therapy)	
	6 months	3 years	1 year	7–10 years*	1 year	10 years†	1 year	5 years‡
HBeAg positive								
ALT normalisation	32–41%	57%	68%	78–79%	68%	78%	72%	76%
HBeAg seroconversion	29–32%	35%	21%	38%	21%	27%	10%	27%
HBV DNA undetectable§	7–14%	25%	67%	80–97%	76%	98%	64%	93%
HBsAg clearance	3–7%	11%	2%	4%	3%	5%	1%	1%
HBeAg negative								
ALT normalisation	59%	31%	78%	78–79%	76%	83%	83%	76%
HBV DNA undetectable§	19%	23–26%	90%	80–97%	93%	100%	94%	93%
HBsAg clearance	4%	8–14%	0	4%	0	3%	0	1%

Lancet. 2023; 401: 1039-52.

NA Tedavisi altında Direnç Gelişen Hasta Yönetimi

Resistance pattern	Recommended rescue strategies
LAM resistance	Switch to TDF or TAF
TBV resistance	Switch to TDF or TAF
ETV resistance	Switch to TDF or TAF
ADV resistance	If LAM-naïve: switch to ETV or TDF or TAF If LAM-resistance: switch to TDF or TAF If HBV DNA plateaus: add ETV*** or switch to ETV
TDF or TAF resistance**	If LAM-naïve: switch to ETV If LAM-R: add ETV*
Multidrug resistance	Switch to ETV plus TDF or TAF combination

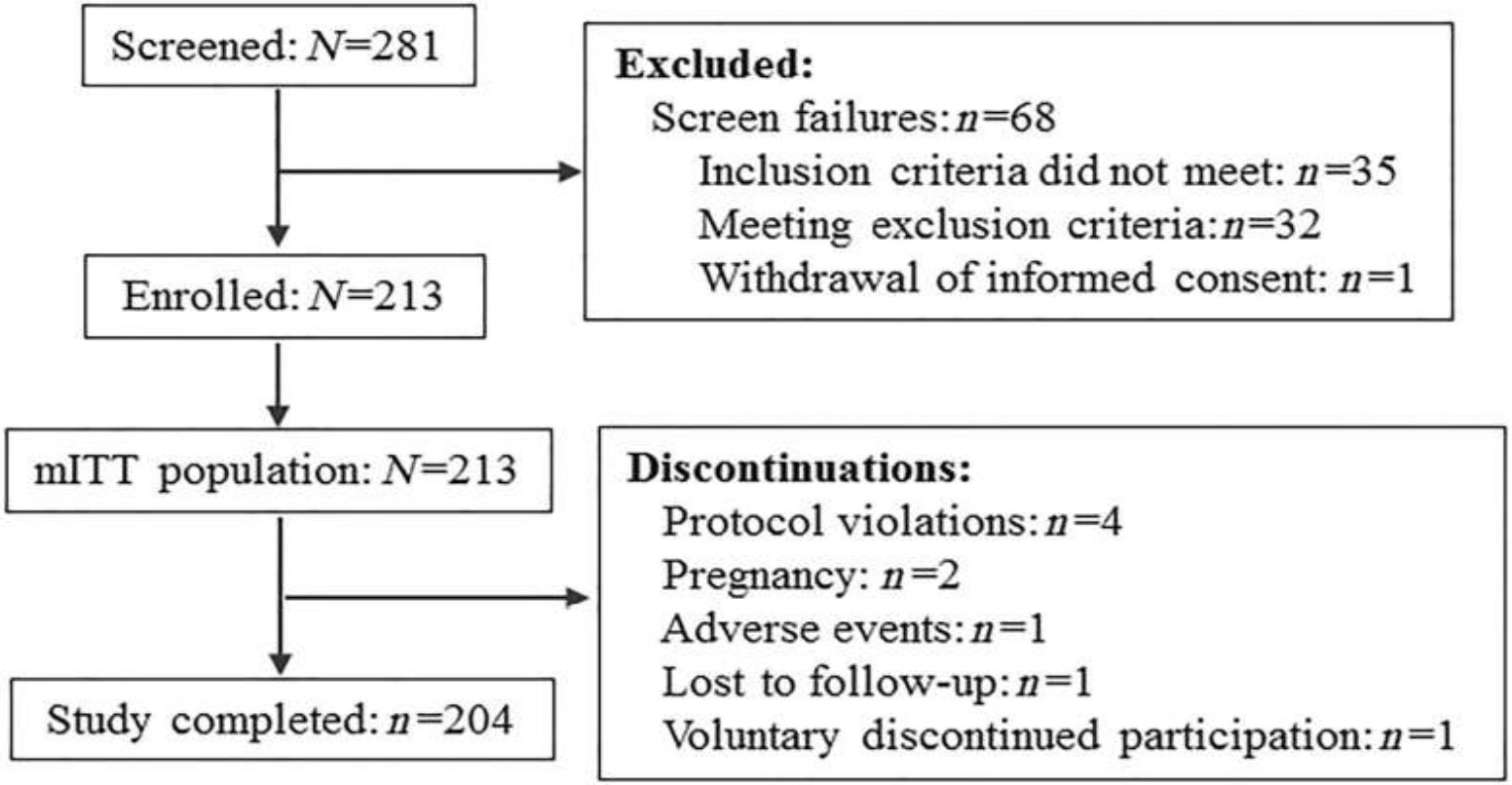
De novo combination therapy with two NAs with **high barrier** to resistance (**ETV, TDF, TAF**) is **not recommended** (EI, G1)

EASL HBV guidelines. *J Hepatology* 2017: 67; 370-98.

Tenofovir disoproxil fumarate for multiple nucleos(t)ide analogues treatment failure hepatitis B: Is monotherapy enough?

Xieer Liang,* Qing Xie,† Jia Shang,‡ Hong Tang,§ Min Xu,¶ Qinghua Meng,** Jiming Zhang,†† Pujun Gao,‡‡ Jifang Sheng,§§ Hao Wang,¶¶ Jidong Jia,*** Guiqiang Wang,††† Shunquan Wu,‡‡‡ Jingna Ping‡‡‡ and Jinlin Hou*

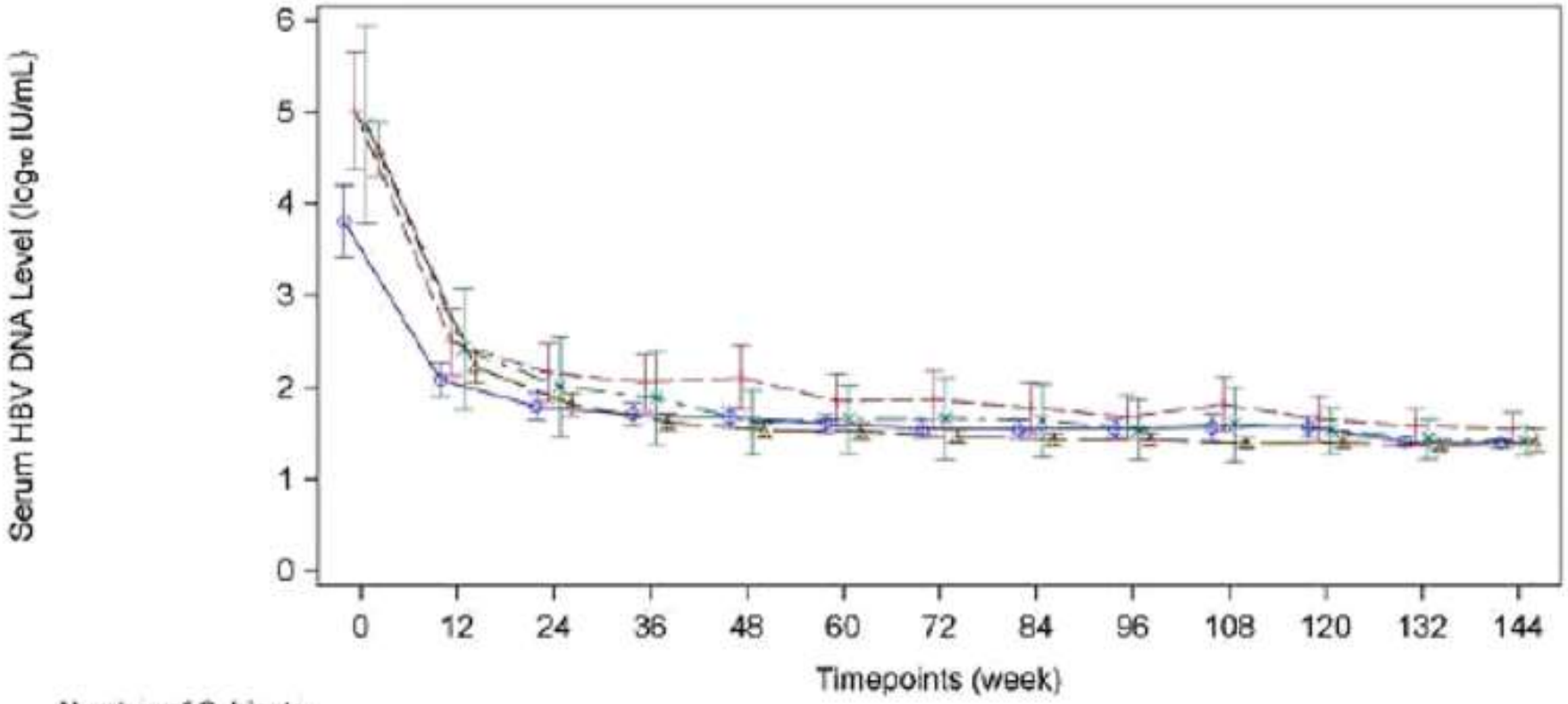
Total **213 patients,** March **2015** and August **2018.**



J Gastroenterol Hepatology. 2022; 37: 471–9.

Table 1 Demographics and clinical characteristics (mITT population)

Characteristics	Total population (n = 213)



Number of Subjects													
Wild type	60	57	56	57	57	57	57	57	57	57	56	57	56
ADV-R single mutation	28	28	28	28	28	28	28	28	28	28	28	28	28
ADV-R double mutation	10	10	10	10	10	10	10	10	10	10	10	10	10
other mutation	115	114	114	114	113	113	112	112	112	110	108	110	110

J Gastroenterol Hepatology. 2022; 37: 471–9.

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Total **213 patients,** March **2015** and August **2018.**

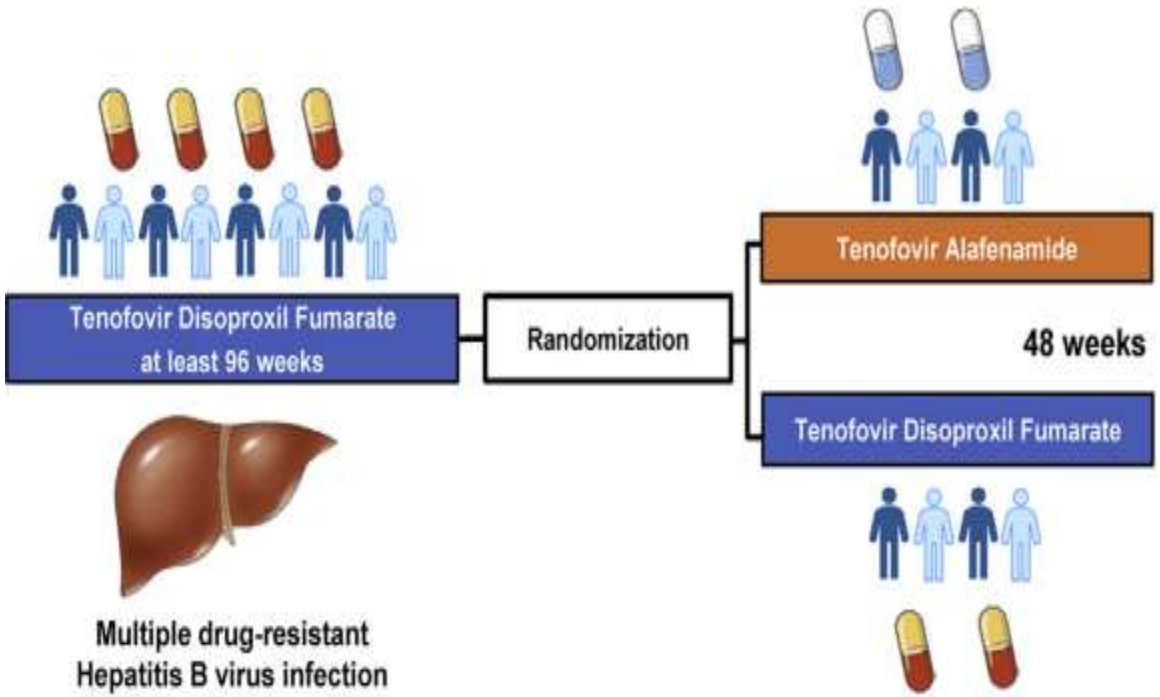
Conclusions

CHB from China who have **failed** prior treatment with **multiple NAs, 144 weeks of TDF** monotherapy is **efficacious** with **77% patients achieving sustained virological** suppression (**HBV DNA < 20 IU/mL**) in the total population and **65.8% in patients with MDR mutations** at baseline.

J Gastroenterol Hepatology. 2022; 37: 471–9.

Tenofovir Alafenamide for Drug-Resistant Hepatitis B: A Randomized Trial for Switching From Tenofovir Disoproxil Fumarate

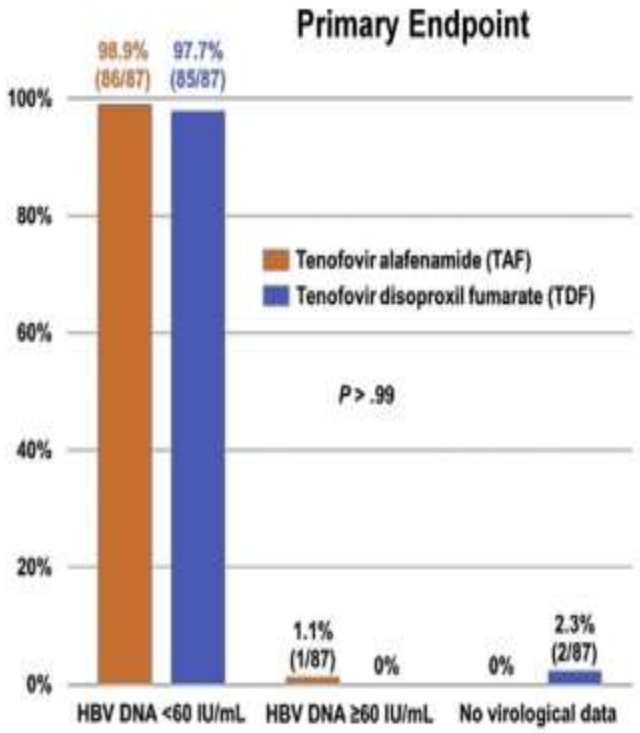
Kwan Soo Byun,[*,a] Jonggi Choi,[‡,a] Ji-Hoon Kim,[*] Yung Sang Lee,[‡] Han Chu Lee,[‡]



TAF 25 mg n=87

Randomized n=174

TDF 300 mg n=87



Clin Gastroenterol Hepatology. 2022;20:427–37

Tenofovir Alafenamide for Drug-Resistant Hepatitis B: A Randomized Trial for Switching From Tenofovir Disoproxil Fumarate

Kwan Soo Byun,[*,a] Jonggi Choi,[‡,a] Ji-Hoon Kim,[*] Yung Sang Lee,[‡] Han Chu Lee,[‡]

Characteristics	Total (N = 174)	TAF (n = 87)	TDF (n = 87)
Age,[a] y	54.8 ± 9.6	56.4 ± 9.4	53.3 ± 9.5
Cirrhosis history,[b] n (%)	35 (20.1)	18 (20.7)	17 (19.5)
Lamivudine resistance, n (%)	160 (92.0)	81 (93.1)	79 (90.8)
Entecavir, n (%)	80 (46.0)	37 (42.5)	43 (49.4)
Adefovir, n (%)	60 (34.5)	28 (32.2)	32 (36.8)
Entecavir and adefovir, n (%)	34 (19.5)	22 (25.3)	12 (13.8)

Clin Gastroenterol Hepatology. 2022;20:427–37

Tenofovir Alafenamide for Drug-Resistant Hepatitis B: A Randomized Trial for Switching From Tenofovir Disoproxil Fumarate

Kwan Soo Byun,[*,a] ... Han Chu Lee,[‡]

- Çoklu ilaca **dirençli** HBV hastalarında, etkinlik kaybı olmaksızın **kemik** ve **böbrek güvenliğinin** iyileştirilmesi için TDF'nin yerine **TAF** kullanılabilir.
- Ancak TAF tedavisiyle **vücut ağırlığı** ve **kolesterol düzeyindeki artışlar** endişe verici olabilir.

Findings

- ✓ Switching to TA... maintaining **viral suppressi...**
- ✓ Showed a decli... nd **renal safety** compared with...
- ✓ Compared with... **ociated with greater increas... HDL cholesterol** levels at week 48 from baseline.

Clin Gastroenterol Hepatology. 2022;20:427–37

Original Investigation | Gastroenterology and Hepatology

Risk of Hepatocellular Carcinoma With Tenofovir vs Entecavir Treatment for Chronic Hepatitis B Virus

A Reconstructed Individual Patient Data Meta-analysis

Darren Jun Hao Tan; Cheng Han Ng; Phoebe Wen Lin Tay; Nicholas Syn, MBBS; Mark D. Muthiah, MBBS; Wen Hui Lim; Ansel Shao Pin Tang; Kai En Lim;

- Bu meta-analizde **tenofovir** ve **entekavir** arasında **HSK** riskinde klinik olarak anlamlı bir fark yoktu.
- Klinik kohort çalışmaları arasında tenofovir ve entekavir arasında 3 ve 5 yıllık takiplerde **anlamlı bir fark yoktu**

Characteristic						*P* value[a]
Before propensity score mat						
Age, mean, y	12	11 415	48.90 (46.75-51.04)	47 813	51.48 (49.41-53.55)	.09
Cirrhosis, %	12	11 415	63.92 (27.78-89.08)	47 813	51.52 (18.79-82.99)	.64
Decompensated cirrhosis, %	3	7094	10.82 (7.11-16.12)	3274	14.11 (7.82-24.13)	.46
HBeAg postive, %	12	11 415	46.76 (37.32-56.44)	47 813	41.68 (31.44-52.69)	.49
HBV DNA, mean log IU/mL	11	11 199	5.56 (4.95-6.17)	47 135	5.85 (5.30-6.40)	.49
ALT level, mean, U/L	7	5567	121.23 (90.74-151.72)	11 266	134.77 (108.45-161.10)	.51

JAMA Network Open. 2022;5(6):e2219407.

How to achieve functional cure of HBV: Stopping NUCs, adding interferon or new drug development?

Epizomal cccDNA, HBV yaşam döngüsünde transkripsiyonel olarak görev yapan önemli bir ara maddedir.

HBV RNA'lar için şablon görevindedir.

Bu **mini kromozom** (cccDNA) infekte hepatosit çekirdeğinde bulunur.

Konakçı **immünitesinden korunur** ve **NA'lar tarafından hedeflenmez**.

Table 1. HBsAg seroclearance rates with pegylated-interferon-α or nucleos(t)ide analogue therapy.[93,94]

	HBsAg seroclearance (%)	
Antiviral agents (dose)	**HBeAg-positive**	**HBeAg-negative**
PEG-IFNα-2a (180 ug)	3 (EOT; 5 in genotype A, 3 non-genotype A) 7 (3 years)	7 (EOT; 11 genotype A; 3 non-genotype A) 9 (3 years)
ETV (0.5 mg)	2 (1 year) 3 (5 years)	0 (1 year) 1 (5 years)
TDF (300 mg)	3 (1 year) 5 (10 years)	0 (1 year) 3 (10 years)
TAF (25 mg)	1 (1 year) 4 (3 years)	0 (1 year) 3 (3 years)

EOT, end of treatment; ETV, entecavir; PEG-IFNα, pegylated-interferon α; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

J Hepatology. 2022; 76: 1249-62.

HEPATOLOGY

AASLD

SPECIAL ARTICLE | HEPATOLOGY, VOL. 71, NO. 3, 2020

Guidance for Design and Endpoints of Clinical Trials in Chronic Hepatitis B—Report From the 2019 EASL-AASLD HBV Treatment Endpoints Conference

Markus Cornberg [1-3], Anna Suk-Fong Lok,[4] Norah A. Terrault [5], and Fabien Zoulim[6,7], the 2019 EASL-AASLD HBV

TABLE 1. "Cures" in HBV and their Definitions[1,2]

	Sterilising "Cure"	Idealistic Functional "Cure"	Realistic Functional "Cure"	Attainable Partial Functional "Cure"
Clinical scenario	Never infected	Recovery after acute HBV	Chronic HBV with HBsAg loss	Inactive carrier off treatment
HBsAg	Negative	Negative	Negative	Positive
Anti-HBs	Negative/Positive	Positive	Positive/negative	Negative
HBeAg	Negative	Negative	Negative	Negative
Serum HBV DNA	Not detected	Not detected	Not detected	Low level or not detected
Hepatic cccDNA, transcription	Not detected	Detected	Detected	Detected
	Not active	Not active	Not active	Low level
Integrated HBV DNA	Not detected	Detected?	Detected	Detected
Liver disease	None	None	Inactive, fibrosis regress over time	Inactive
Risk of HCC	Not increased	Not increased	Declines with time	Risk lower vs. active hepatitis

Kronik hepatit B hastalarında antiviral tedavinin kesilmesi

Table 1 Recommendations on discontinuation of antiviral therapy in chronic hepatitis B patients by the European Association for the Study of Liver, American Association for the Study of Liver, and Asian Pacific Association for the Study of Liver guidelines

	HBeAg-positive	HBeAg-negative	Cirrhosis
EASL (2017)	HBsAg seroclearance HBeAg seroconversion and HBV DNA undetectable with at least 12 mo of consolidation therapy	HBsAg seroclearance May be consider before HBsAg loss if undetectable HBV DNA for at least 3 yr (close monitoring for at least 1 yr)	No recommendation until HBsAg loss
AASLD (2018)	HBsAg seroclearance HBeAg seroconversion with at least 12 mo of persistent ALT levels and undetectable HBV DNA (close monitoring every 3 mo for at least 1 yr)	HBsAg seroclearance (close monitoring every 3 mo for at least 1 yr) May be consider if there is a compelling rationale and under careful monitoring every 3 mo for at least 1 yr	No recommendation until HBsAg loss
APASL (2015)	HBeAg seroconversion with undetectable HBV DNA and persistently normal ALT levels with at least 1 yr of consolidation therapy (preferably 3 yr)	HBsAg seroclearance with anti-HBs seroconversion or at least 12 mo of a post-HBsAg clearance consolidation period -After treatment for at least 2 yr with undetectable HBV DNA documented on 3 separate occasions, 6 mo apart	May be consider before HBsAg loss if disease is compensated and under a careful monitoring plan

Medas R, et al. *World J Clin Cases* 2021; 9(24): 6979-86.

Table 2 Durability in HBeAg-positive chronic hepatitis B patients stopping nucleos(t)ide analogs after ≥ 1 year consolidation duration and ≥ 1 year follow-up

Author/Study design	N	NA	LC (%)	Tx duration (yrs)	Consolida-tion (mos)	F/U (mos)	VR*	CR*	HBsAg loss*
Liem [81]/RCT	18	ETV/TDF	0	7.9	41	18	100%	6%	N/A
Fan [121]/RCT	130	LdT/ADV	0	3	22.2	48	54.7	30.8	N/A
Ryu [122]/Pros	61	LAM	21.5	> 24	> 24	24	31%	N/A	N/A
Wang [123]/Pros	125	LAM	0	24–36	16–25	24	30.4%	N/A	N/A
Cao [124]/Pros	60	mixed	0	4	25	24	70.7%#	31%	10% #
Liu [125]/Pros	138	mixed	0	2.4	21	120	30.9%	N/A	0%
Su [103]/Pros	28	ETV/TDF	0	3.1	26	48	65–72.1%#	40.7–46.1%#	0%
Chi [113]/Pros	71	mixed	0	3.9	26	31	85%#	43%	4%
Kuo [40]/Retro	31	LAM	38.7	1.8	> 12	> 12	N/A	34%	N/A
He [126]/Retro	97	mixed	N/A	2.8	48	12	N/A	12.5%	0%
Qiu [127]/Retro	112	ETV	0	2.6	> 12	12	48.2%	N/A	N/A
Chen [104]/Retro	148	LAM/ETV	0	2.7	-	96	55.6%	47.7%	19.6%
Kuo [82]/Retro-Pros	154	ETV/TDF	0	3.1	> 12	24	41.3%(ETV), 72.4%(TDF)	33%(ETV), 63.5%(TDF)	4.7%(ETV), 0%(TDF)
Song [128]/Retro	262	Mixed	20.6	2.9	17.5	73.3	74.8%*[a]	60.6%*[a]	9.5%**

Hepatology International. 2021; 15:833-51.

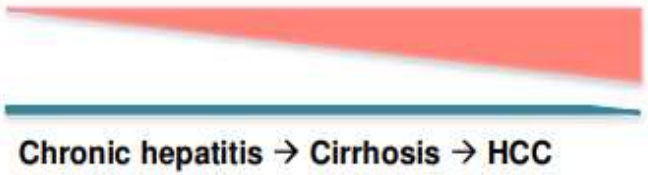
Table 3 Durability in HBeAg-negative chronic hepatitis B patients stopping nucleos(t)ide analogs after ≥ 1 year consolidation duration and ≥ 1 year follow-up

Author/Study design	N	NA	LC (%)	Tx duration (yrs)	Consolidation (mos)	F/U (mos)	VR*	CR*	HBsAg loss*
Hadziyannis [47]/ RCT	33	ADV	0	4–5	45	69	100%	76%	39.4%
Berg [48]/RCT	21	TDF	0	>4	>42	36	76%	23.8%	19%
Liem [81]/RCT	27	ETV/TDF	0	7.4	85	18	100%	19%	4%
Van Bommel [49]/ RCT	79	mixed	0	>4	N/A	24	67.1[a]	8.8%[b]	10.3%**
Cao [124]/Pros	22	mixed	0	4	35	48	70.7%	53%	10%[#]
Papatheodoridis [129]/Pros	57	ETV/TDF	0	>4	64	18	72%	43%	25%
Liu [125]/Pros	85	mixed	0	2.4	21	120	62.3%	N/A	14%
Su [103]/Pros	72	ETV/TDF	0	3.1	26	48	65–72.1%[#]	40.7–46.1%[#]	0%
Chi [113]/Pros	29	mixed	0	3.9	106	31	85%[#]	59%	10%
Jeng [7]/Retro-Pros	691	ETV/TDF	45	2.9	25	36	79.2%	61%	13%
Chen [104]/Retro	263	LAM/ETV	0	2.9	–	96	69.3	58.9	33.1
Kuo [82]/Retro-Pros	353	ETV/TDF	0	3.1	>12	36	69.2%(ETV), 72.1%(TDF)	54.8%(ETV), 59.2%(TDF)	10%(ETV), 15.4%(TDF)
Chen [51]/Retro-Pros	250	ETV	0	3.2	>12	58	71%	56.4%	20.8%
Song [128]/Retro	226	Mixed	36.4	2.7	25	73.3	71.9%*[c]	48%*[c]	14.6%**
Hirode [50]/Retro	1183	Mixed	5	3	–	17	74%[d]	56%[d]	15%[d]

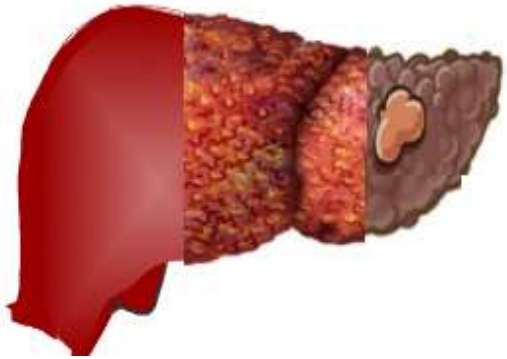
Hepatology International. 2021; 15:833-51.

KHB hastalarının yönetimi ve tedavisi: Kişiselleştirilmiş tıbba doğru

HBV cure vs
HBV infection control



Liver diesease cure vs control



Tedavi seçimi:

- ✓ **HBV infeksiyon profili**: genotip, türler, infeksiyon evresi
- ✓ **Karaciğer hastalığının evresi**: Karaciğer fonksiyonu, fibroz derecesi
- ✓ **Tedavi** durumu; Naif /deneyimli
- ✓ **Konak özellikleri; Y**aş, cinsiyet, eşlik eden hastalıklar

Colombatto P, *Viruses*. 2022; 14: 701.

Sonuç olarak;

- HBV infeksiyonu küresel bir **halk sağlığı** sorunu olmaya devam ediyor
- KHB'li hastalarda **siroz** ve **HSK**'ye ilerleme riski yüksektir
- KHB'nin '**kür**' tedavisi yok
- Terapinin temel amacı **hayatta kalmayı** ve **yaşam kalitesini** iyileştirmektir.
- Yedavide direnç bariyeri **ETV, TDF** ve **TAF** kullanılmakta
- Uzun süreli tedavi, **düşük yan etki** oranıyla viral replikasyonun kontrolünde **yüksek etkinliği** temsil eder
- Hepatit B, güvenli, mevcut ve etkili **aşılarla** önlenebilir.
- **Korunma** tedaviden daha iyidir

Isınan bir gezegende

Birlikte mutlu ve sağlıklı yaşam mümkün...