Kronik Hepatit B infeksiyonu Antiviral tedavi kesilmesi/kesilememesi

Dr. Süda TEKİN

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İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Bölümü

Olgu 1

- B.K. , Siverek/Şanlıurfa
- 34 yaşında, kadın
- 12 yıllık evli, çalışmıyor
- 4 çocuğu var. İki çocuk HBsAg (+)
- Anne ve bir kardeş HBsAg (+)
- Geliş tarihi 21 şubat 2011

Olgu 1

Öykü;

- 10 yıldır HBV taşıyıcılığı biliniyor.
- İlk çocuk evde doğum
- **2007→ Lamivudin** tedavisi

HBsAg +, HBeAg +, HBVDNA: 24000 IU/ml,
ALT: 48, **HAİ:7**, **F:2**).

- Lamivudin tedavisi **2 yıl** kullanan hasta,

3. gebeliğinin başında tedaviyi kesmiş
(tedavinin 1. yılında HBV DNA neg, ALT N, HBeAg +)

Olgu 1

21.02.2011

HBsAg	**+**
Anti HBs	-
Anti HCV	-
Anti HDV	-
HBe Ag	+
Anti HBe	-
HBV DNA	**13200 IU/ml**

- Gebeliğin 27. haftasında hasta kontrole geldi
- **HBV DNA 128000 IU/ml**

Reaktivasyon

Hasta bilgilendirilip onamı alınarak gebeliğin 29. haftasında **Tenofovir** tedavisi başlandı

Olgu 2
İlk tanı-Şubat 2011

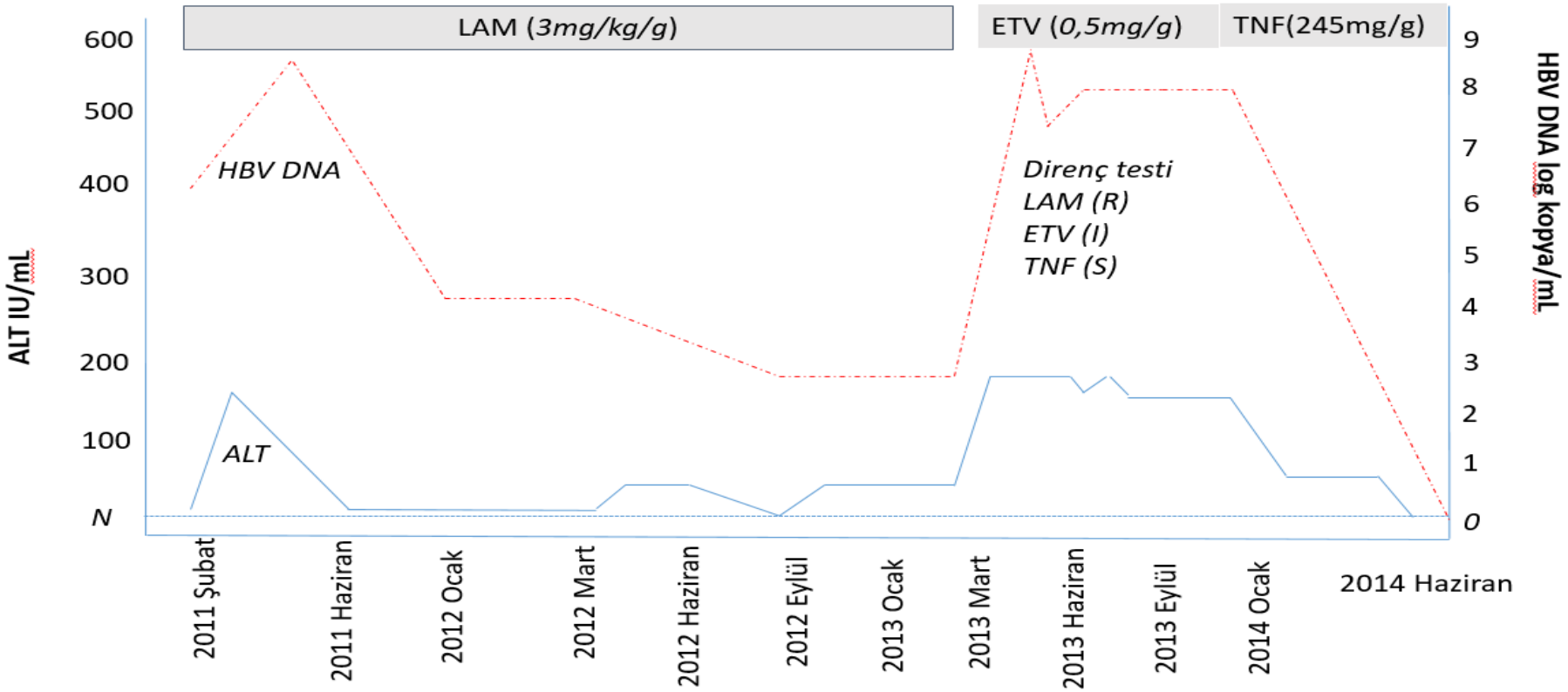
- M.S., 35 yaşında erkek hasta, Urfa
- Anne ve 2 kardeş kronik HBV
- 13 yıldır infekte, IFN tedavisi yıllar önce almış
- Lamivudin verilmiş, etkisiz kanısıyla entekavirle devam

✓ **HBsAg (+)**, **HBeAg (+)**, AntiHBe(-),

- Anti HCV (-), anti HDV (-)
- AST: 26 IU/mL, ALT: **76** IU/mL
- HBV DNA: **$2x10^7$** kopya/mL
- KC USG: ince granüler paternde artış

Takip - Mart 2013

- AST: **140** IU/mL, ALT: **194** IU/mL
- HBV DNA: **$2x10^9$** k/mL
- Biyopsi: **F4**, HAİ **12**



Olgu 2	Sekans analizi
Genotip	**D**, subtip D1
RT domain mutasyonu	H124D, Y135S, V173L, L180M, M204V, N248H
SHB protein mutasyonu	T127P, E164D, I195M
SHB protein escape mutasyonu	E164D (HBIg escape mutasyon), I195M (LAM, LdT ADAPVEM'i)

İlaç	Mutasyon	Direnç analizi
Lamivudine, Zeffix®	173L,180M,204V	R
Adefovir, Hepsera®	**yok**	S
Entecavir, Baraclude®	204V,180M	I
Tenofovir DF	yok	S
Telbivudine, Tyzeka®, Sebivo®	204V	R

Takip

- AST: **140** IU/mL, ALT: **194** IU/mL
- HBV DNA: **$2x10^9$** k/mL, Biyopsi: **F4**, **HAİ 12**
- Tedavi: 2014 **Tenofovir** 1x1 tb

✓ **Kontrol mayıs 2016**;

Genel durumu iyi, şikayeti yok

✓ HBsAg (+), HBeAg (-), **AntiHBe (+)**, anti HDV (-)

- AST: 22 IU/mL, ALT: 26 IU/mL, AFP normal
- HBV DNA <34 kopya/mL
- KC dinamik MR: Normal

Antiviral tedavi kesilsin mi?

HBV infeksiyonu boyutu

- Dünyada **257 milyon** kişi KHBV infekte
- Sadece 2015 yılında **887000** kişi HCC, siroz vb. komplikasyondan **öldü**

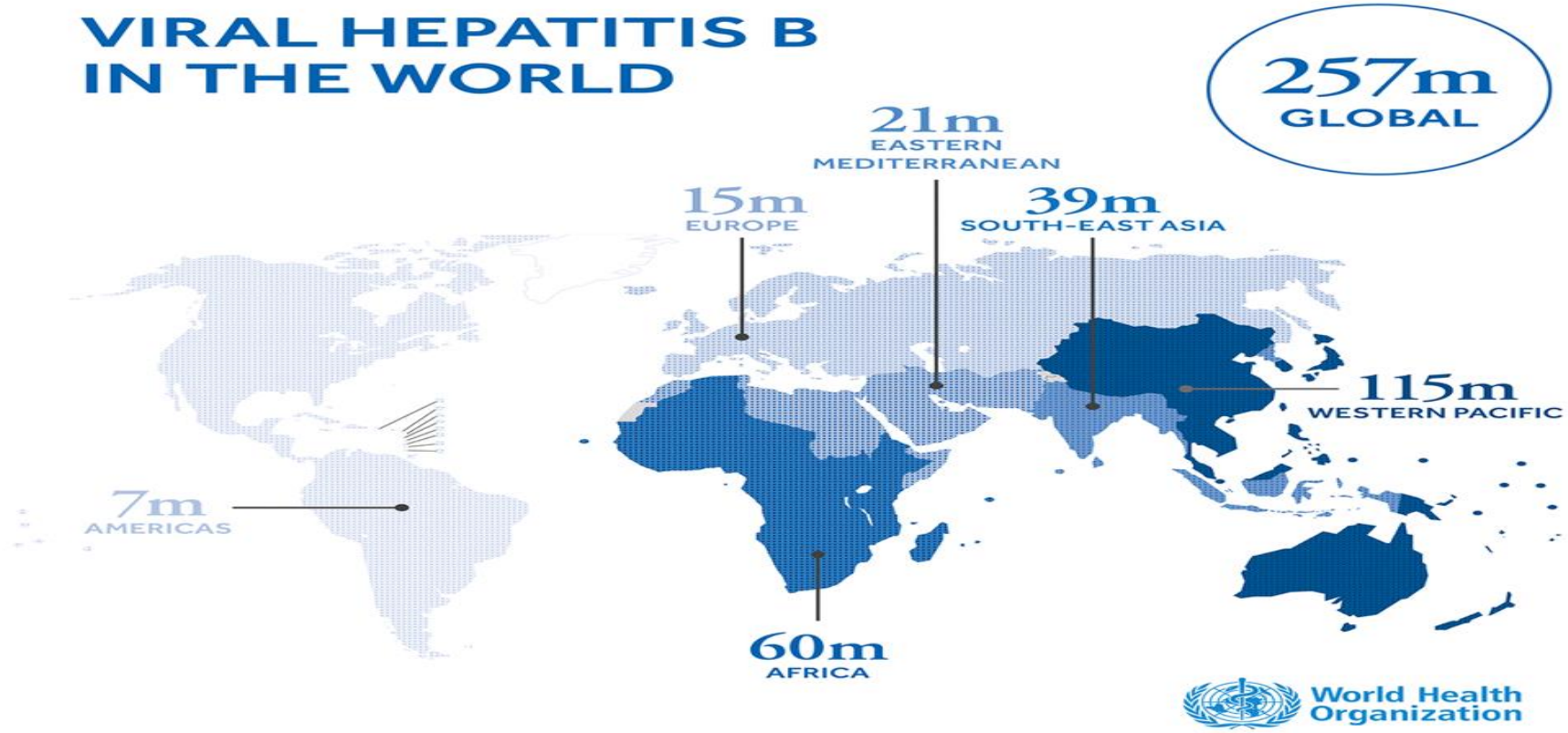
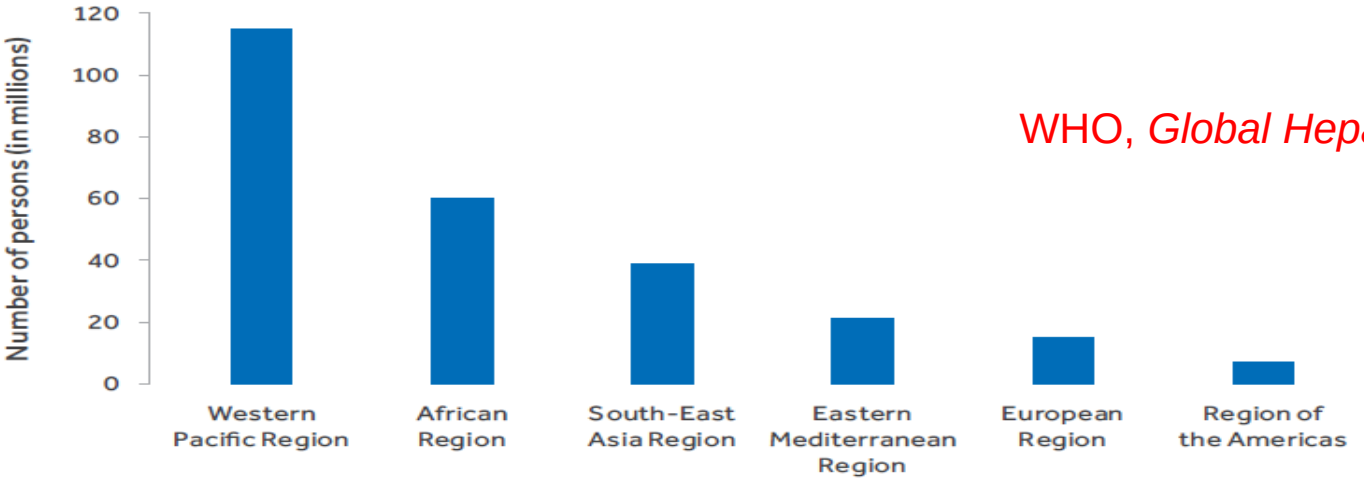


Table 2 (with graph). Prevalence of HBV infection (HBsAg) in the general population by WHO region, 2015: the WHO African and Western Pacific regions have the highest prevalence and the largest number of persons living with HBV



WHO, *Global Hepatitis Report*, 2017

Clinical Practice Guidelines

EASL JOURNAL OF HEPATOLOGY

Journal of Hepatology **2017** vol. 67 | 370–398

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

European Association for the Study of the Liver*

HEPATOLOGY

AASLD AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

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

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

Norah A. Terrault,[1] Anna S.F. I
Robert S. Brown Jr.,[7] Natalie H.

Kronik Hepatit B Virusu İnfeksiyonunun Yönetimi: Türk Klinik Mikrobiyoloji ve İnfeksiyon Hastalıkları Derneği Viral Hepatit Çalışma Grubu Uzlaşı Raporu

Management of Chronic Hepatitis B Virus Infection: A Consensus Report of the Study Group for Viral Hepatitis of the Turkish Society of Clinical Microbiology and Infectious Diseases

Klimik Dergisi 2014; 27(Özel Sayı 1): 2-18.

Sıla Akhan[1], Aynur Aynıoğlu[2], Atahan Çağatay[3], İbak Gönen[4], Özgür Günal[5], Teoman Kaynar[6], Ziya Kuruüzüm[7], Murat Sayan[8], Berivan Tunca[9], Necla Tülek[10], Hüseyin Üçkardeş[11], Ayşe Yavuz[12], Orhan Yıldız[13], Neziha Yılmaz[14], Esma Yüksel[15]

HBV'nin doğal seyri

	HBeAg positive Chronic *infection*	HBeAg positive Chronic hepatitis	HBeAg negative Chronic *infection*	HBeAg negative Chronic hepatitis
HBsAg	High	High/Intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10E7 IU/mL	10E4-10E7 IU/mL	<2,000 IU/mL°°	>2,000 IU/mL
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative Chronic hepatitis

*Persisitently or intermittently

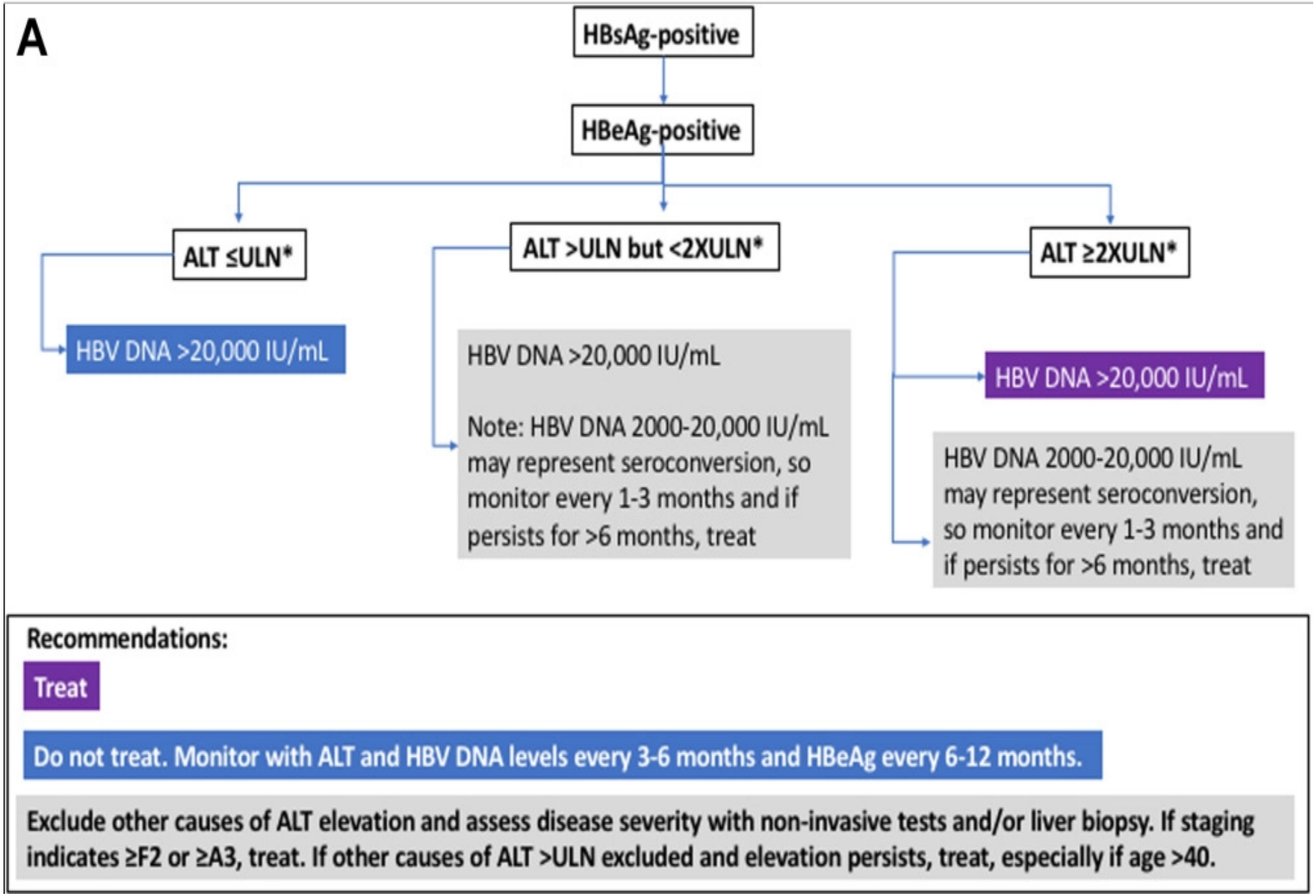
°° HBV-DNA levels can be between 2,000 and 20,000 IU/mL in some patients without sings of chronic hepatitis

EASL 2017. HBV, J Hepatol 2017

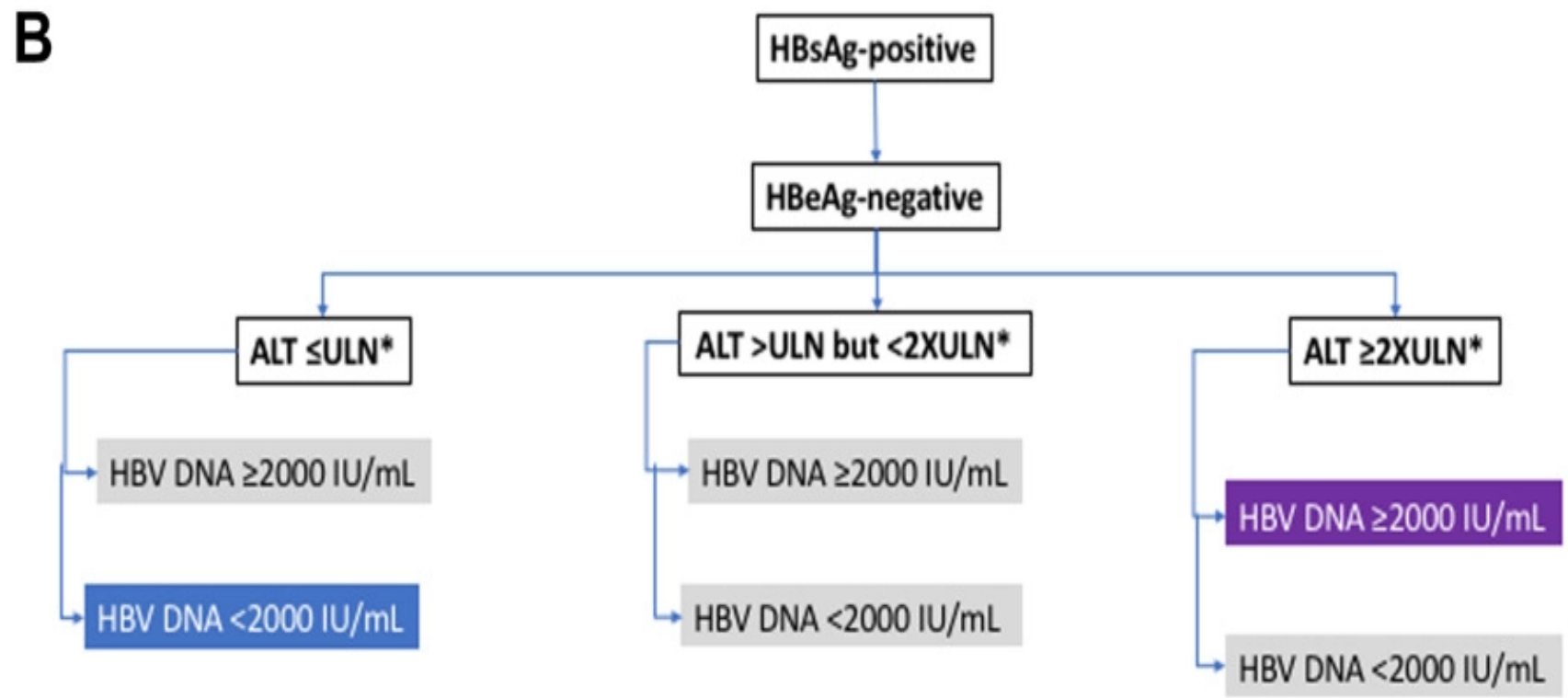
HBV Yönetim

	KHB		İmmün-tolerans KHB	İmmün-aktif KHB		İnaktif KHB
HBeAg	Pozitif	Negatif	Pozitif	Pozitif	Neg	Neg
HBV DNA (IU / mL)	> 20,000	2,000-20,000	> 1 milyon	> 20.000	> 2.000	<2,000
ALT / AST	Normal veya Yüksek		N veya minimum Y	Aralıklı veya sürekli Y		Normal
KC biyopsisi	Kronik hepatit		Fibroz ve inflamasyon yok	Kronik hepatit		Nekroinflamasyon yok

AASLD 2018 Hepatitis B Guidance



AASLD 2018 Hepatitis B Guidance



Recommendations:

Treat

Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBsAg annually.

If ALT ≤ULN, monitor ALT and HBV DNA every 3 months for 1 year, then every 6 months.
If ALT elevated, exclude other causes of ALT elevation and assess disease severity with non-invasive tests and/or liver biopsy. If staging indicates ≥F2 or ≥A3, treat. If persistent ALT >ULN with HBV DNA ≥2000 IU/mL, treat, especially if age >40.

**The upper limits of normal for ALT in healthy adults is reported to be 29 to 33 U/L for males and 19 to 25 U/L for females. An upper limit of normal for ALT of 35 U/L for males and 25 U/L for females is recommended to guide management decisions.*

AASLD 2018 Hepatitis B Guidance

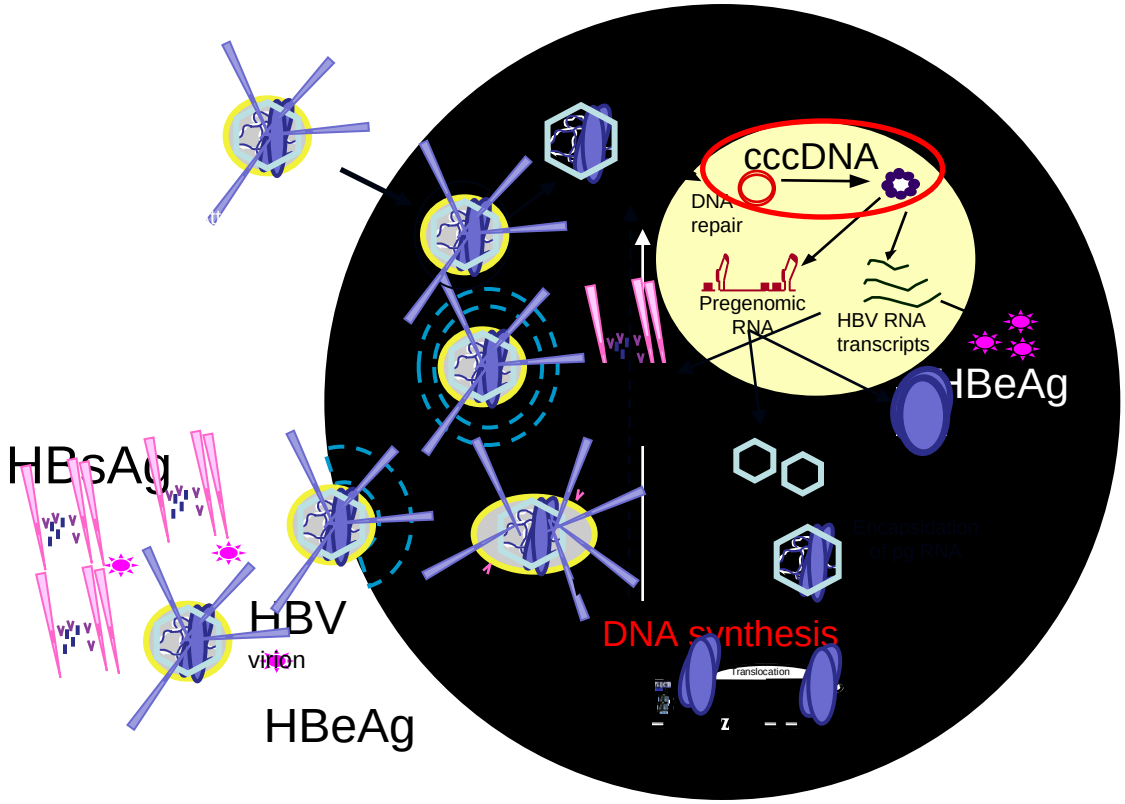
TABLE 2. Efficacy of Approved First-Line Antiviral Therapies in Adults with Treatment-Naïve Chronic Hepatitis B and Immune-Active Disease (Not Head-to-Head Comparisons)

HBeAg Positive	Peg-IFN*	Entecavir†	Tenofovir Disoproxil Fumarate†	Tenofovir Alafenamide‡
% HBV-DNA suppression	30-42 (<2,000-40,000 IU/mL)	61 (<50-60 IU/mL)	76 (<60 IU/mL)	73 (<29 IU/mL)
(cutoff to define HBV-DNA suppression)§	8-14 (<80 IU/mL)			
% HBeAg loss	32-36	22-25	—	22
% HBeAg seroconversion	29-36	21-22	21	18
% Normalization ALT	34-52	68-81	68	—
% HBsAg loss	2-7	4-5	8	1
	11 (at 3 years posttreatment)			

HBeAg Negative	Peg-IFN	Entecavir	Tenofovir Disoproxil Fumarate†	Tenofovir Alafenamide‡
% HBV-DNA suppression	43 (<4,000 IU/mL)	90-91 (<50-60 IU/mL)	93 (<60 U/mL)	90 (<29 IU/mL)
(cutoff to define HBV-DNA suppression)‖	19 (<80 IU/mL)			
% Normalization ALT¶	59	78-88	76	81
% HBsAg loss	4	0-1	0	<1
	6 (at 3 years posttreatment)			

AASLD 2018 Hepatitis B Guidance

Neden Nükleos(t)id Tedavisi ile Kür Nadirdir?



Grimm D, et al. Hepatol Int. 2011;5:644-653.

To stop or not to stop: The quest for long-term viral suppression

James Fung, Ching-Lung Lai and Man-Fung Yuen

The University of Hong Kong, Queen Mary Hospital, Hong Kong

*HBeAg (+); HBeAg (-) olduktan 12 ay sonra kesilebilir

**Gebelerde başlanan tedavi doğum sonrası/emzirme döneminde kesilebilir

***HBeAg (-) hastalarda (siroz değilse)
uzun süreli **HBV DNA negatifleşmesi** ve /veya HBsAg titrelerinin <100 IU/mL olmasından sonra kesilebilir

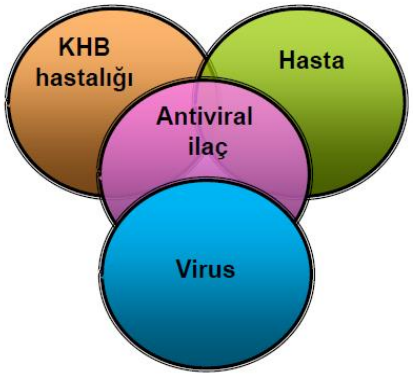
Journal of Gastroenterology and Hepatology **26** (2011) 419–425

To stop or not to stop: The quest for long-term viral suppression

James Fung, Ching-Lung Lai and Man-Fung Yuen

The University of Hong Kong, Queen Mary Hospital, Hong Kong

"Uzun süreli viral baskılama ARAYIŞI…"



Journal of Gastroenterology and Hepatology **26** (2011) 419–425

‘WHO CAN STOP THERAPY?’

Kim cesaret edebilir?

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD

Off-Therapy Durability of Response to Entecavir Therapy in Hepatitis B e Antigen-Negative Chronic Hepatitis B Patients

- HBeAg (-) ETV alan **94** hasta, **39'u siroz**
- Medyan 721 gün izlenmiş

"klinik relaps"=> ALT >2 NUS ile **HBV DNA>2000 IU/mL**

- Relaps %**45.3**
- Sirozlularda **%43.6**, dekompanzasyon **%2.6**
- Lojistik reg analizi => HBV-DNA<**2x 10*5** IU/mL (relaps %29 vs. %53)

Yüksek viral yükte **süre >64 hafta olmalı

HEPATOLOGY 2013;58:1888-1896

Viral Hepatitis

Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Long-term hepatitis B surface antigen (HBsAg) kinetics during nucleoside/nucleotide analogue therapy: Finite treatment duration unlikely

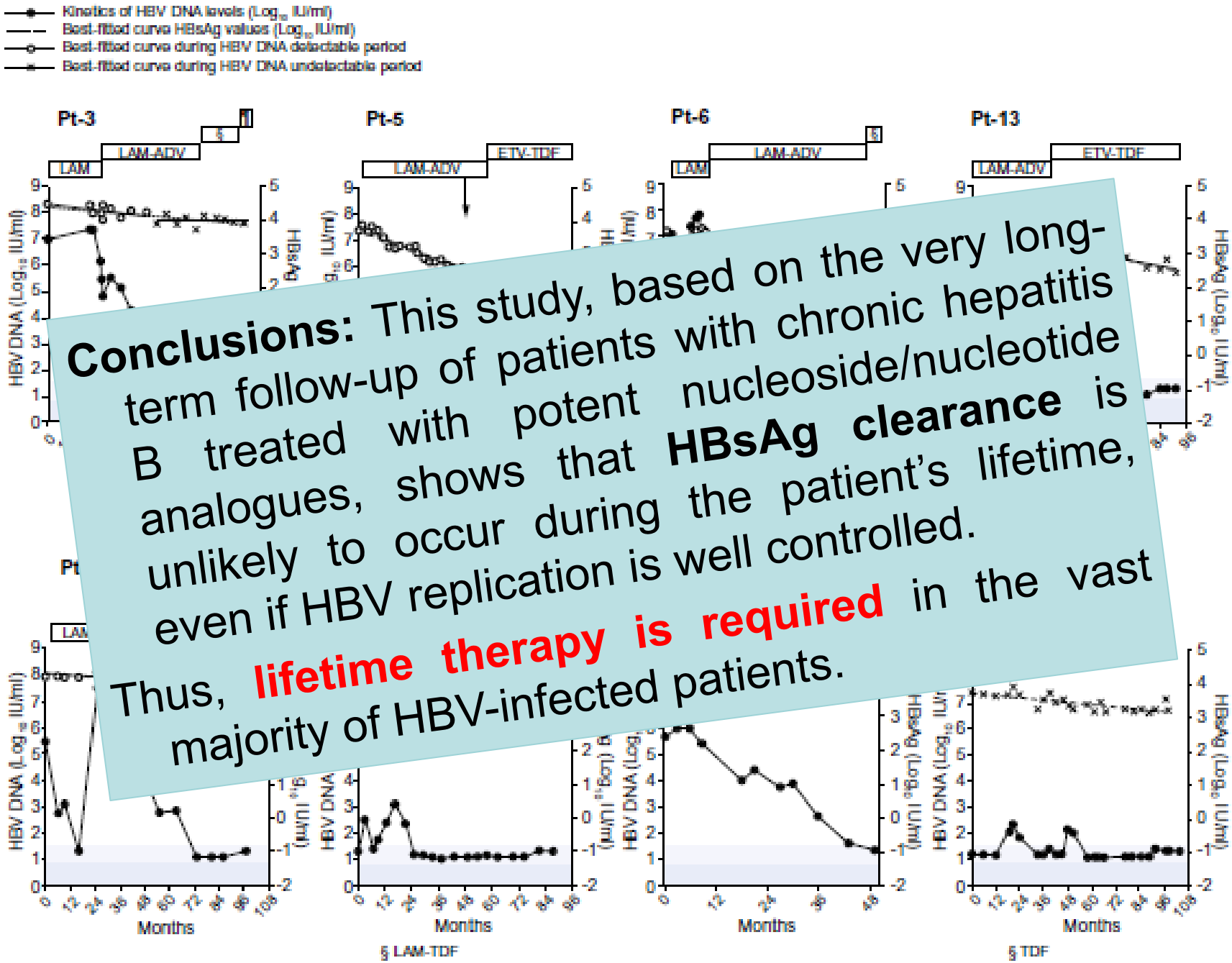
Stéphane Chevaliez[1,2,*], Christophe Hézode[2,3], Stéphane Bahrami[4], Marion Grare[1], Jean-Michel Pawlotsky[1,2]

[1]*National Reference Center for Viral Hepatitis B, C and Delta, Department of Virology, Hôpital Henri Mondor, Université Paris-Est, Créteil, France;* [2]*INSERM U955, Créteil, France;* [3]*Department of Hepatology and Gastroenterology, Hôpital Henri Mondor, Université Paris-Est, Créteil, France;* [4]*Paris Health Economics and Health Services Research Unit, LIC EA 4393, Hôpital Henri Mondor, Université Paris-Est, Créteil, France*

See Focus, pages 641–642

- Toplam 30 hasta (%60 HBeAg negatif)
- Lamivudin, adefovir, entekavir, tenofovir
  - Ortalama tedavi süresi 8.5 yıl

Journal of Hepatology 2013 vol. 58 j 676–683



Conclusions: This study, based on the very long-term follow-up of patients with chronic hepatitis B treated with potent nucleoside/nucleotide analogues, shows that **HBsAg clearance** is unlikely to occur during the patient's lifetime, even if HBV replication is well controlled.

Thus, **lifetime therapy is required** in the vast majority of HBV-infected patients.

Journal of Hepatology 2013; 58: 676–83

INVITED REVIEW

Annals of Gastroenterology (2014) **27,** 105-112

The role of HBsAg levels in the current management of chronic HBV infection

Christoph Höner zu Siederdissen, Markus Cornberg

- HBsAg; HBV'de farklı fazların tespitinde çok yararlı
- Düşük HBsAg seviyeleri konağın immün kontrolüyle ilişkili
- Düşük seviyeler HCC için oldukça düşük risk

DOI: 10.1111/liv.13314

REVIEW ARTICLE

WILEY Liver INTERNATIONAL

When can we stop nucleoside analogues in patients with chronic hepatitis B?

Liver International 2017; 37: 52-8.

Chern Hao Chong[1] | Seng Gee Lim[1,2]

WHO CAN STOP THERAPY?

*Hasta seçimi

** **qHBsAg** yardımcı olabilir

*** **HBsAg** seroklirensi veya **KVY** izlenmeli

DOI: 10.1111/liv.13314

REVIEW ARTICLE

WILEY Liver INTERNATIONAL

When can we stop nucleoside analogues in patients with chronic hepatitis B?

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Chern Hao Chong[1] | Seng Gee Lim[1,2]

- ✓ HBeAg serokonversiyon, NA kesilmesi→ **%50** klinik relaps
- ✓ APASL; HBeAg (-) HBV DNA 6 ay / 3 negatifse kesilmiş →
  - %70.5 virolojik relaps
  - %43.6 klinik relaps
- ✓ HBeAg (-) 36. ayda %30.1 remisyon, alevlenme nadir
- ✓ HBeAg (-), qHBsAg düşükse NA kesilen %20-39 seroklirens
- ✓ Tedavi kesilmesinde **qHBsAg** önemli belirteç ancak **eşik** seviye net değil

HBeAg serokonversiyonundan sonra tedavi kesilen hastalardaki relapslar, farklı çalışmalar;

Author	n	FU	Sero-reversion	Relapse	Consolidation improves durability
Chi[36]	35	3 y	20%	74%	25% ≥3 y 53% <1 y
Fong[37]	54	30 mo	32%	69% viral 37% clinical	No effect
Fung[17]	22	5 y	9%	44%	Not assessed
Jun[38]	52	18 mo		52.7%	Consolidation≥18 mo and early virological response at 6 mo
Kuo[39]	135	5 y	19.1%	51.9%	Not significant on multivariate analysis
Kuo[40]	124	2 y	44.3%	68.4%	LAM consolidation therapy ≥48 wk -HR 2.44 and age<34
Lee[41]	31	72 wk	29%	56.3%	Consolidation no effect
Pan[42]	136	48 mo	NA	41.7%	Age, baseline ALTand consolidation (11 mo) was sign by multivariate analysis
Qiu[15]	112	52 wk	NA	48.2%	Not significant, multivariate analysis—age and qHBsAg level
Ryu[43]	85	2 y	16%	31%	Age and precore mutant were sign in multivariate analysis, not duration of consolidation
Song[12]	34	2 y	38%	49.2%	Duration of consolidation therapy significant

Liver International 2017; 37: 52-8.

HBeAg (-) KHB tedavi kesilen hastalardaki relapslar, farklı çalışmalar;

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

Liver International 2017; 37: 52-8.

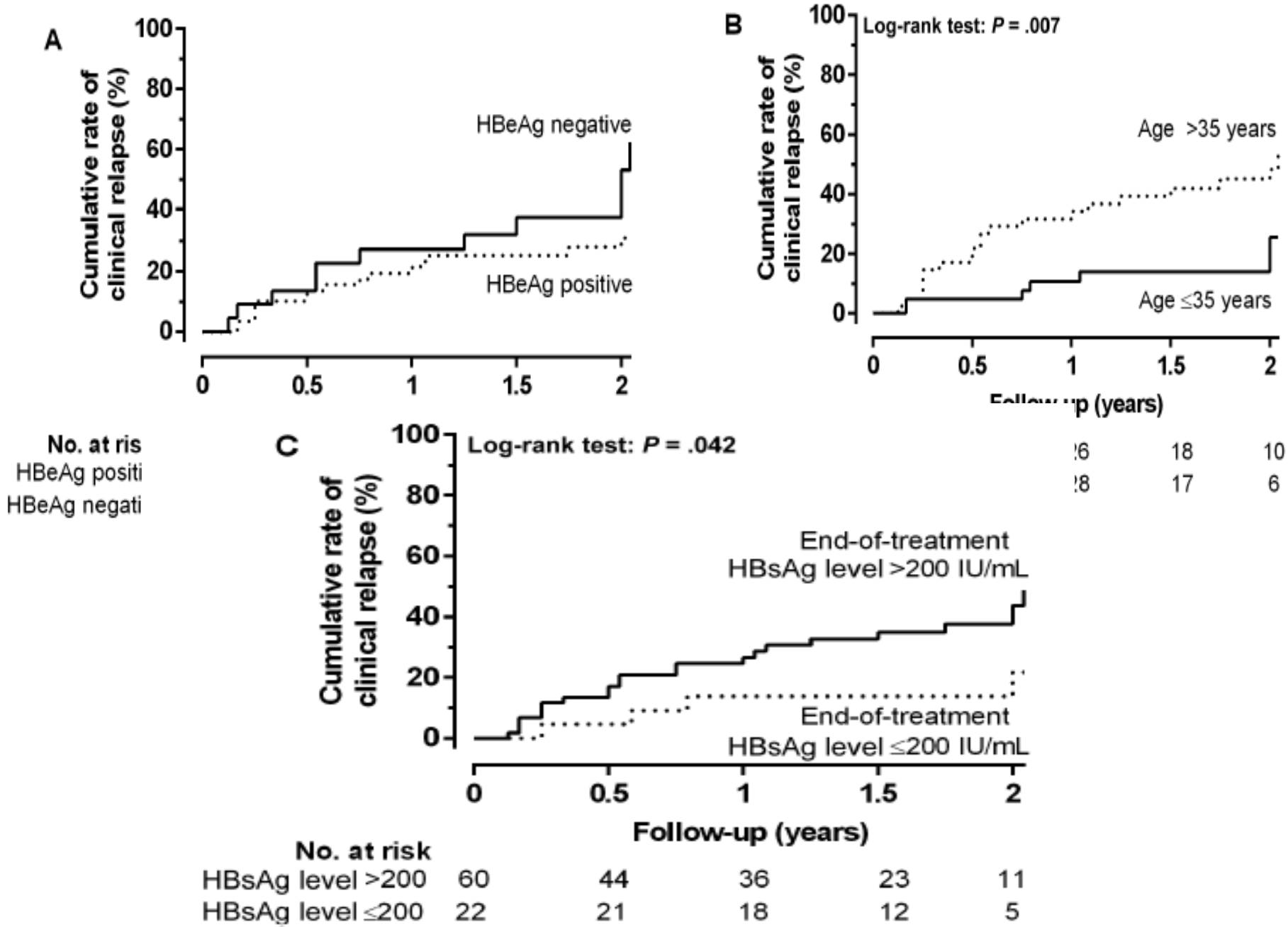
The Journal of Infectious Diseases
MAJOR ARTICLE

Off-Treatment Hepatitis B Virus (HBV) DNA Levels and the Prediction of Relapse After Discontinuation of Nucleos(t)ide Analogue Therapy in Patients With Chronic Hepatitis B: A Prospective Stop Study

Jiawei Cao,[1,a] Heng Chi,[2,a] Tao Yu,[1] Zhandong Li,[1] Bettina E. Hansen,[2] Xiaoyong Zhang,[1] Chunxiu Zhong,[1] Jian Sun,[1] Jinlin Hou,[1] Harry L. A. Janssen,[2,3,b] and Jie Peng[1,b]

- Siroz olmayan 82 Asyalı, KHB
- HBV DNA >2000 IU, ALT> 2 NUS tedavi devam
- Diğerlerinde NA kesilmiş

JID 2017:215; 581-9.



JID 2017:215; 581-9.

Submit a Manuscript: http://www.f6publishing.com
DOI: 10.3748/wjg.v24.i17.1825
World J Gastroenterol 2018 May 7; 24(17): 1825-1838
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Is it possible to stop nucleos(t)ide analogue treatment in chronic hepatitis B patients?

Elia Moreno-Cubero, Robert T Sánchez del Arco, Julia Pe[illegible] [illegible]duardo Sanz de Villalobos, Joaquín Míquel, Juan Ramón Larrubia

Nereye kadar?

- DSÖ: Dünyada [illegible]lyon KHB var
- Sadece 201[illegible] ilişkili siroz ve HCC nedeniyle 887000 ölüm
- Tedavi ömür boyu;
  - ✓ Kronik başka hastalıkları indükler (DM, metabolik sendrom)
  - ✓ Yan etkiler (böbrek, kemik erimesi vb.)
  - ✓ Maliyet
  - ✓ Gebelerde kullanımı var, fetüste uzun etkileri bilinmiyor

- NA yeni **cccDNA** sentezini durduramıyor
- "**komplet kür**" değil "**fonksiyonel kür**"=> **HBV DNA & HBsAg klirensi**

Table 2 NA treatment cessation recommendations in the current hepatitis B virus guidelines

Society	HBeAg(+)	HBeAg(-)	Cirrhosis
EASL (2017)[9]	HBsAg clearance (safest) HBeAg seroconversion and HBV DNA undetectability with 6-12 mo of ensuing consolidation therapy	HBsAg clearance Selected patients with ≥ 3 yr virological suppression if guaranteed close postNA monitoring for at least 1 yr	Not recommended
AASLD (2016)[20]	HBsAg clearance HBeAg seroconversion with at least 12 mo of persistently normal ALT levels and undetectable serum HBV DNA levels (close monitoring for at least 1 yr)	HBsAg clearance	Not recommended
APASL (2016)[22]	HBeAg seroconversion with undetectable HBV DNA and persistently normal ALT levels with 1-3 yr of consolidation therapy	HBsAg clearance with antiHBs seroconversion HBsAg loss with at least 12 mo of consolidation period After treatment for at least 2 yr with undetectable HBV DNA documented on 3 separate occasions, 6 mo apart	Could be considered in compensated cirrhosis with careful monitoring

World J Gastroenterol 2018; 24: 1825-38.

NA Tedavisinin sonlandırılması
EASL Öneriler

- NAs should be discontinued after confirmed HBsAg loss, with or without anti-HBs seroconversion (Evidence level II-2, grade of recommendation 1).
- NAs can be discontinued in non-cirrhotic HBeAg-positive CHB patients who achieve stable HBeAg seroconversion and undetectable HBV DNA and who complete at least 12 months of consolidation therapy. Close post-NA monitoring is warranted (Evidence level II-2, grade of recommendation 2).
- Discontinuation of NAs in selected non-cirrhotic HBeAg-negative patients who have achieved long-term (≥3 years) virological suppression under NA(s) may be considered if close post-NA monitoring can be guaranteed (Evidence level II-2, grade of recommendation 2).

EASL 2017. J Hepatol 2017; 67: 370–3.

NA Tedavi kesilmesinde yardımcı biyobelirteçler

- **Cinsiyet:** HBeAg (-) kişilerde **K>E iyi** sonuç, kesilebilir
- **Yaş:** İleri yaşlarda relaps yüksek
- **NA tedavi süresi:** HBeAg (-) kişilerde süre >2 yıl ise, kesilebilir
- **ALT:** Tartışmalı, düşük ALT seviyeleri HBsAg kaybında olumlu. Aralıklı dalgalanmalar -''flare''- yaşan**mayan**larda sonuç olumlu
- **HBV DNA:** Düşük titrelerde relaps olasılığı düşük
- **Serum qHBsAg:** Düşük düzeylilerde HBsAg klirensi olasılığı yüksek (Titre = **100-700** IU/mL ise NA kesilebilir)

World J Gastroenterol 2018; 24: 1825-38.

NA kesilmesinde yardımcı virolojik ölçütler

✓ **HBV RNA:** Karaciğer **cccDNA** trankripsiyon aktivitesini gösterir. HBeAg serokonversiyonu için prediktör.

- HBeAg(-) kişilerde ölçülemez

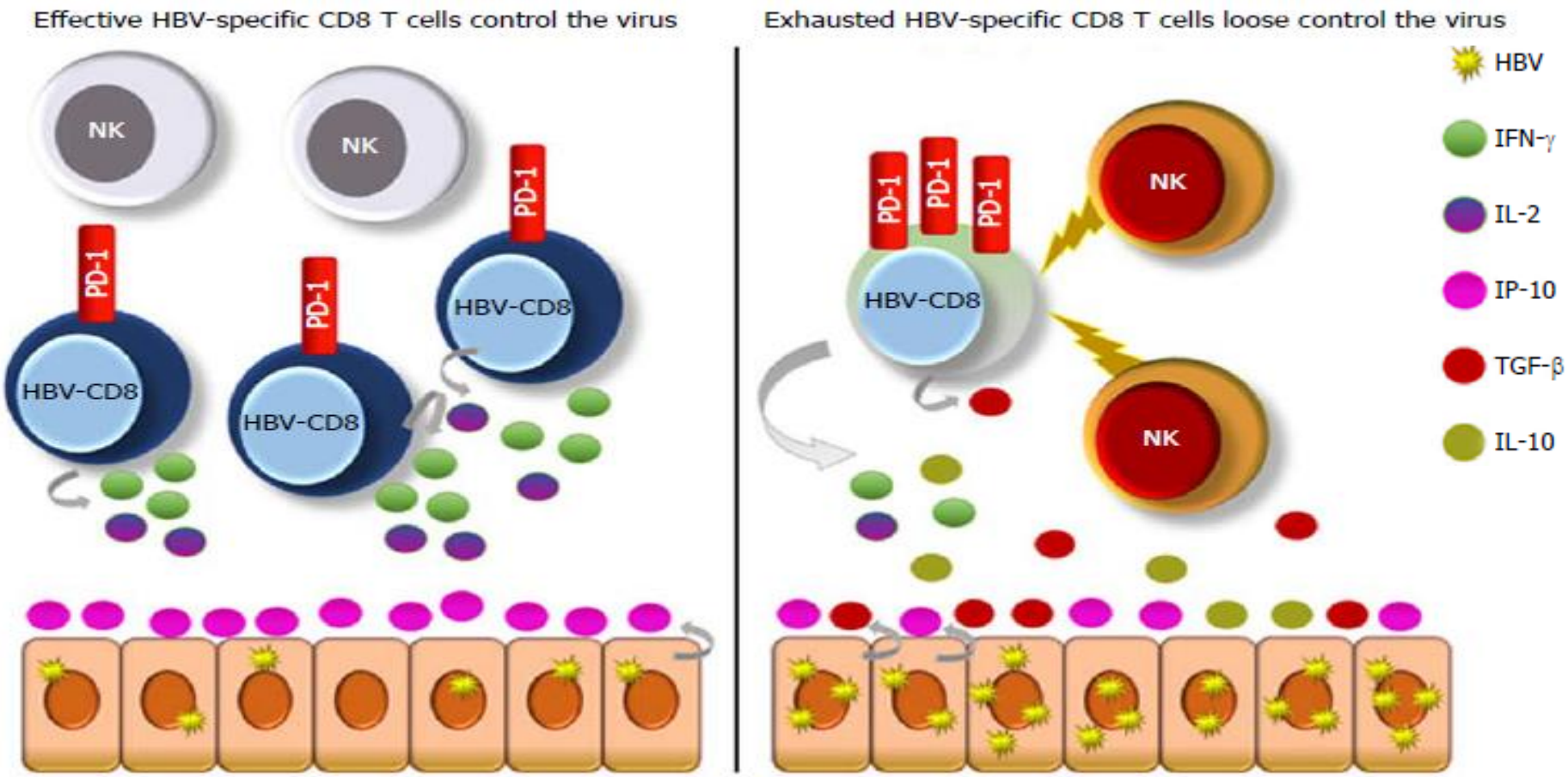
✓ **AntiHBc :** Prediktör belirteç, Asyalı hastalar dışında valide edilebilirse anlamlı olabilir

✓ **HBV core-ilişkili antijen** (**HBcrAg**) = HB**c**Ag, HB**e**Ag ve pre-core protein (**p22cr**) **:** Kantite edilince intrahepatik **cccDNA** seviyesini verir.

➢ **Sonuçta** bunlardan **HBeAg (-) KHB** hastalarında yararlanılır. **HBeAg (+)**'lerde **valide edilmemiştir**.

World J Gastroenterol 2018; 24: 1825-38.

NA kesilmesinde immünolojik olayların etkisi



- KHB'de **HBV-özgül T hücre** yanıtı, **yüksek/sürekli Ag uyarımı** nedeniyle fonksiyonlarını kaybeder → **işlevsiz**
- Böylece immün hasardan korunmuş olurlar

World J Gastroenterol 2018; 24(17): 1825-38.

NA kesilmesinde immünolojik olayların etkisi

Plazma kemokinleri incelenmiş

✓ NA tedavisiyle HBsAg kaybıyla **CXCL10 (IP-10)** bulunmuş

- **IP-10;** virusa yanıt olarak hepatositlerden sentezlenen küçük protein
- CD4 & CD8 T hücrelerinin güçlendiğinin göstergesi

***Üç yıllık entekavir tedavisini takiben IP-10 düzeyinin arttığı gösterilmiş**

World J Gastroenterol 2018; 24(17): 1825-38.
*Papatheodoridis G *J Hepatol* 2014; 60: 62-8.

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REVIEW

Is it possible to stop nucleos(t)ide analogue treatment in chronic hepatitis B patients?

Elia Moreno-Cubero, Robert T Sánchez del Arco, Julia Peña-Asensio, Eduardo Sanz de Villalobos, Joaquín Míquel, Juan Ramón Larrubia

- Farklı immün sistem çalışmaları mevcut
- Özellikle **HBV-özgül CD8 T** hücrelerinin işlevi NA tedavi kesiminde hekimi yönlendirebilir
- Asıl **hedef cccDNA'nın temizlenmesi**
- **Temel bilimler** hasta yönetiminde önemli

- Tedavi için **bireysel** karar

» İmmun reaktif fazda **ileri fibroz yok**

» Persiste eden **HBV DNA >20.000** IU/ml, ALT>2ULN fibroz derecesinden bağımsız

» HBeAg +, > 30 yaş, ALT normal, HBV DNA yüksek

» Ailede **siroz/HCC öyküsü** var veya ekstrahepatik bulgular mevcut

Chronic Hepatitis B Virus Infection: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2018
Clinical/Antimicrobial

- HBV→ Oldukça stabil ‘’cccDNA’’ var
- Replikatif olmayan ‘minikromozom’
- Hayat boyu kalıcı
- Güncel ilaçlarla elimine edilemiyor

*Çalışmalar erişkin, sirozu olmayan bireylerde

**Sonlanım noktaları

- qHBsAg
- HBeAg
- HBV RNA
- HBV core-related antigen (HBcrAg)
- cccDNA kantitasyonu
- HBsAg fragmanları
- HBsAg-anti-HBs immune kompleks

} Miktarları

DRAFT GUIDANCE 2018

Sonuç olarak;

- HBV infeksiyonu tedavisinin kesilmesinde kabul edilen sonlanım noktası **HBsAg kaybıdır**
- Soruların yanıtı **HBV&konak immün** yanıtındaki denge belirleyecektir
- Hücrede **cccDNA**'nın tamamen ortadan kaldırılmasına yönelik etkin tedaviler geliştirilinceye dek tartışmalar sürecektir

XX. TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI KONGRESİ

Kongremizde görüşmek dileğimle...