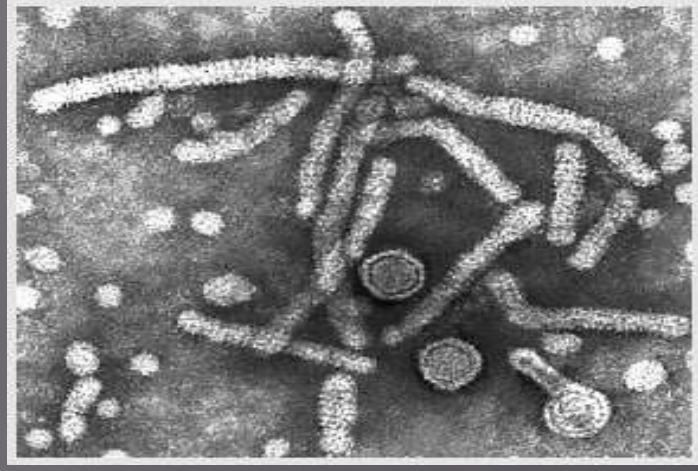
Kronik Hepatit b tanı ve Tedavi

Ediz Tütüncü

EMEK ASİSTAN EĞİTİM PROGRAMI

27 Nisan 2022, Ankara

HBV



Hepatit B virüsü (HBV), bilinen en küçük zarflı DNA virüsleri olan *Hepadnaviridae* ailesinin bir üyesidir.

- Yüksek doku ve tür özgüllüğü,
- Kendine özgü genomik organizasyonu
- Asimetrik replikasyon mekanizması

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Global epidemiology of hepatitis B virus infection: New estimates of age-specific HBsAg seroprevalence and endemicity

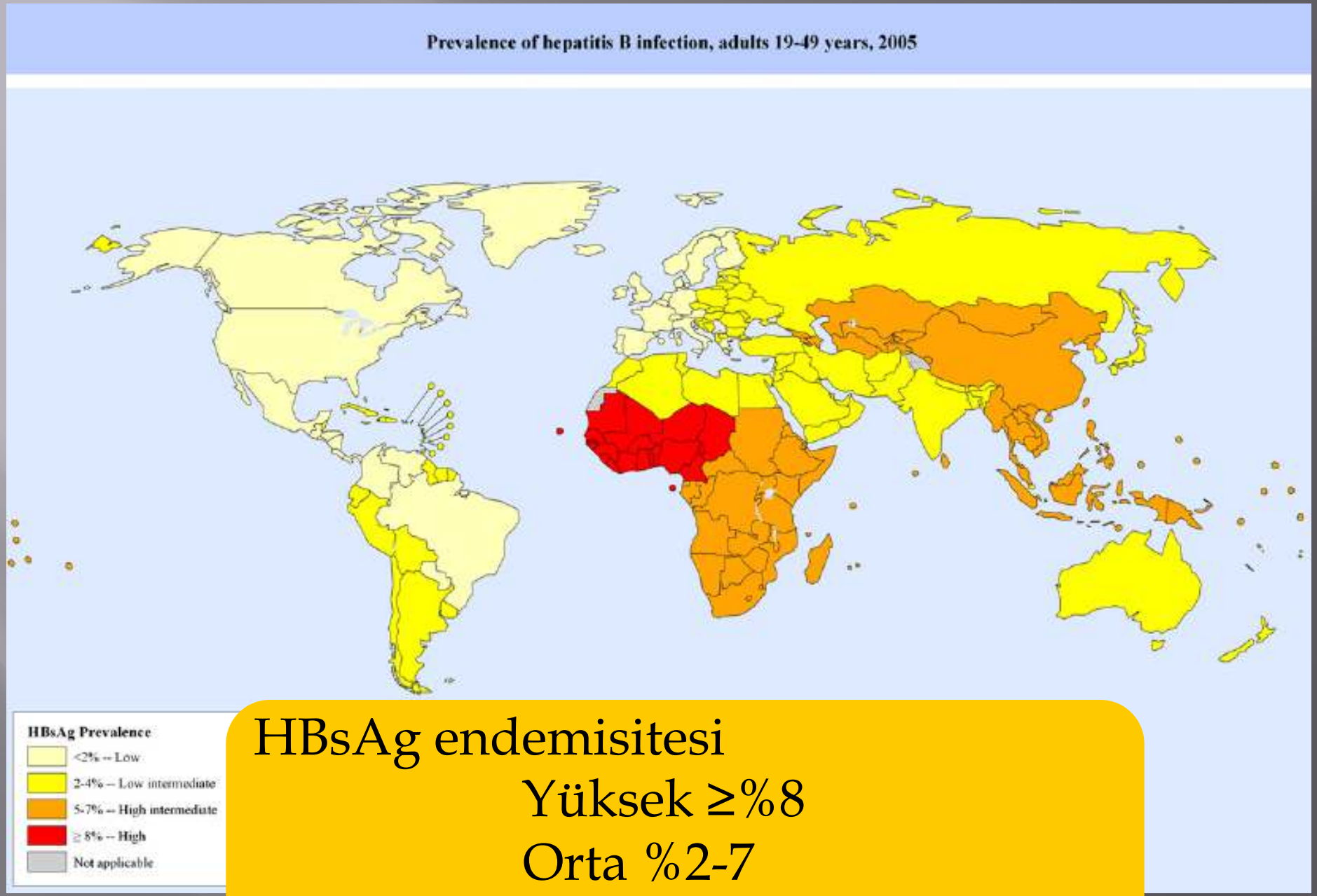
J.J. Ott[a], G.A. Stevens[a], J. Groeger[b], S.T. Wiersma[a,*]

[a] World Health Organization, 20, Avenue Appia, 1211 Geneva 27, Switzerland
[b] Centers for Disease Control and Prevention, Atlanta, GA, USA

Sistematik derleme

1980-2007 seroprevalans verisi

Ott JJ et al. Vaccine 2012;30:2212



HBsAg endemisitesi

Yüksek ≥%8

Orta %2-7

Düşük <%2

e 2012;30:2212

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Global epidemiology of hepatitis B virus infection: New estimates of age-specific HBsAg seroprevalence and endemicity

J.J. Ott[a], G.A. Stevens[a], J. Groeger[b], S.T. Wiersma[a,*]

[a] World Health Organization, 20, Avenue Appia, 1211 Geneva 27, Switzerland
[b] Centers for Disease Control and Prevention, Atlanta, GA, USA

Table 1
Overview: Global HBsAg and people chronically infected.

Year	Males		Females		Both	
	Persons HBsAg positive	Prevalence	Persons HBsAg positive	Prevalence	Persons HBsAg positive	Prevalence
1990	118 million	4.4	105 million	4.0	223 million	4.2
2005	127 million	3.9	113 million	3.5	240 million	3.7

240 milyon kronik enfekte olgu/dünya

Ott JJ et al. Vaccine 2012;30:2212

ORIGINAL ARTICLE VIROLOGY

Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a fieldwork TURHEP study

N. Tozun[1], O. Ozdogan[2], Y. Cakaloglu[3], R. Idilman[4], Z. Karasu[5], U. Akarca[5], S. Kaymakoglu[6] and O. Ergonul[7]

1) *Acibadem University School of Medicine*, 2) *Marmara University School of Medicine*, 3) *Istanbul Memorial Hospital, Istanbul*, 4) *Ankara University Faculty of Medicine, Ankara*, 5) *Ege University Faculty of Medicine, Izmir*, 6) *Istanbul University Istanbul Faculty of Medicine and* 7) *Koc University School of Medicine, Istanbul, Turkey*

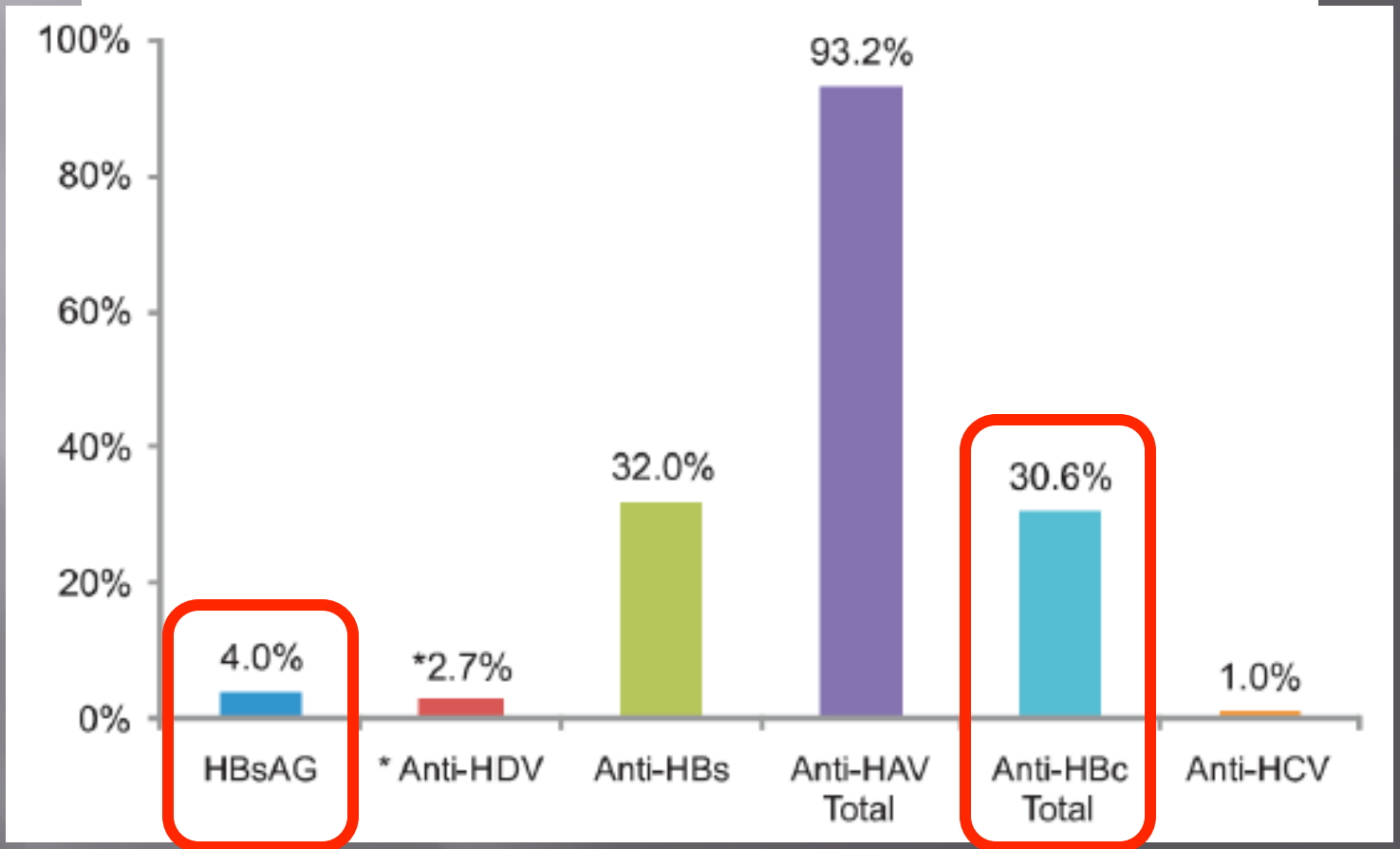
TKAD 2010

n=5460

Tozun N et al. Clin Microbiol Infect. 2015;21(11):1020

TURKHEP 2010

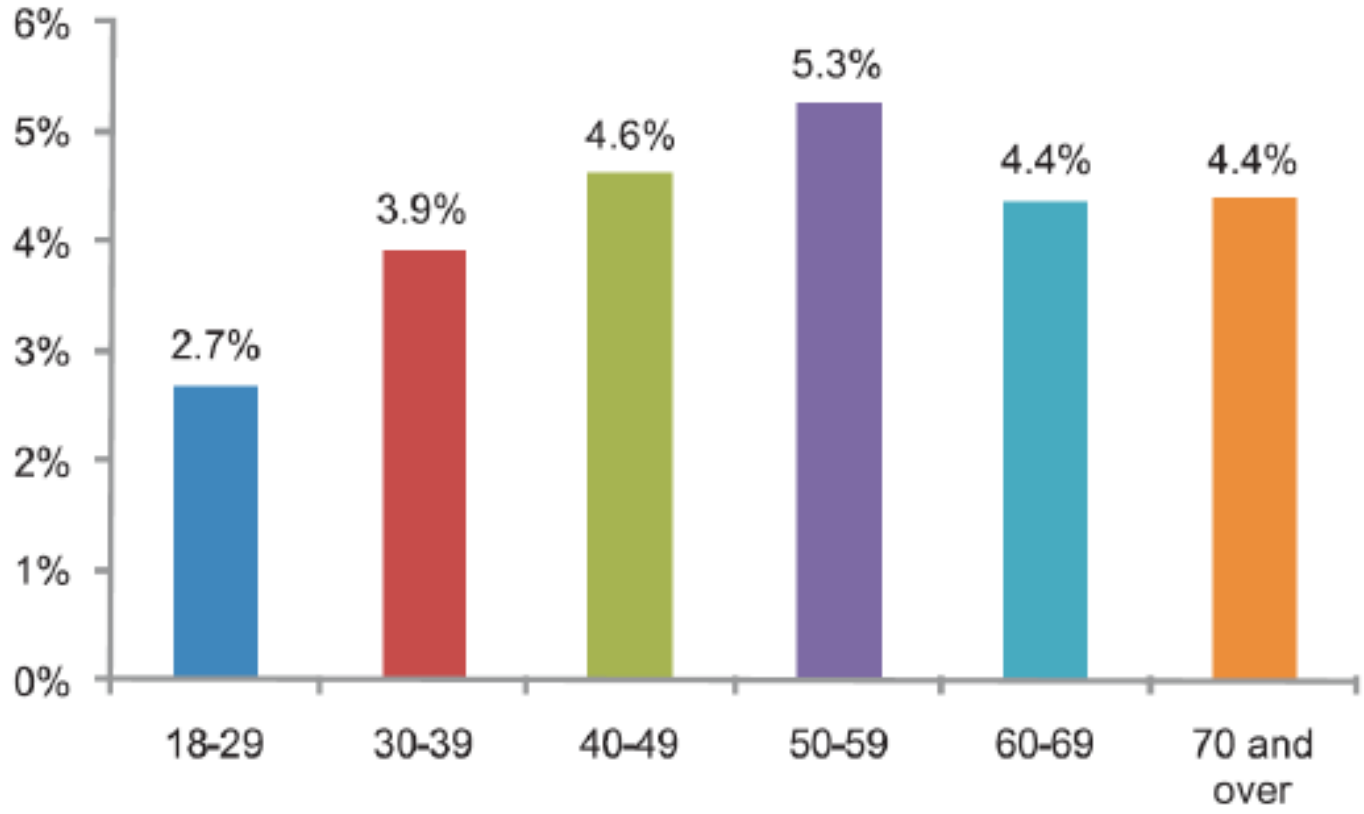
Şekil 2. Tüm populasyonda Hepatit virusları taşıyıcılık oranları



Tozun N et al. Clin Microbiol Infect. 2015;21(11):1020

TÜRKHEP 2010

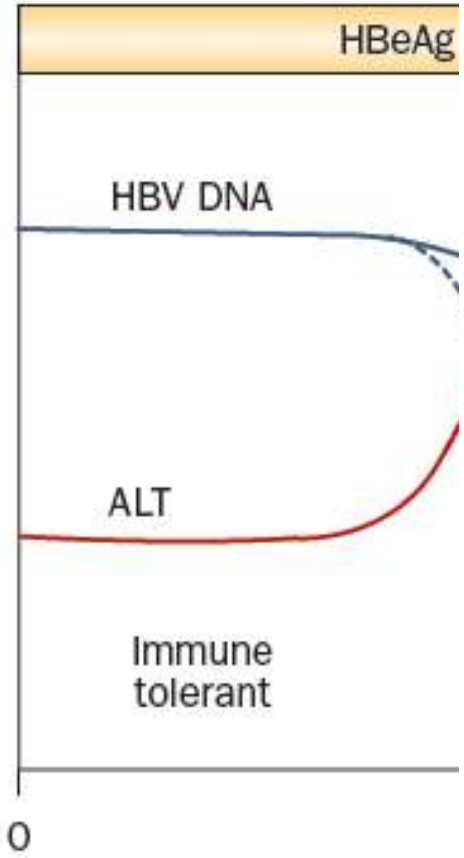
Şekil 5. Hepatit B virusu sıklığının yaşa göre dağılımı



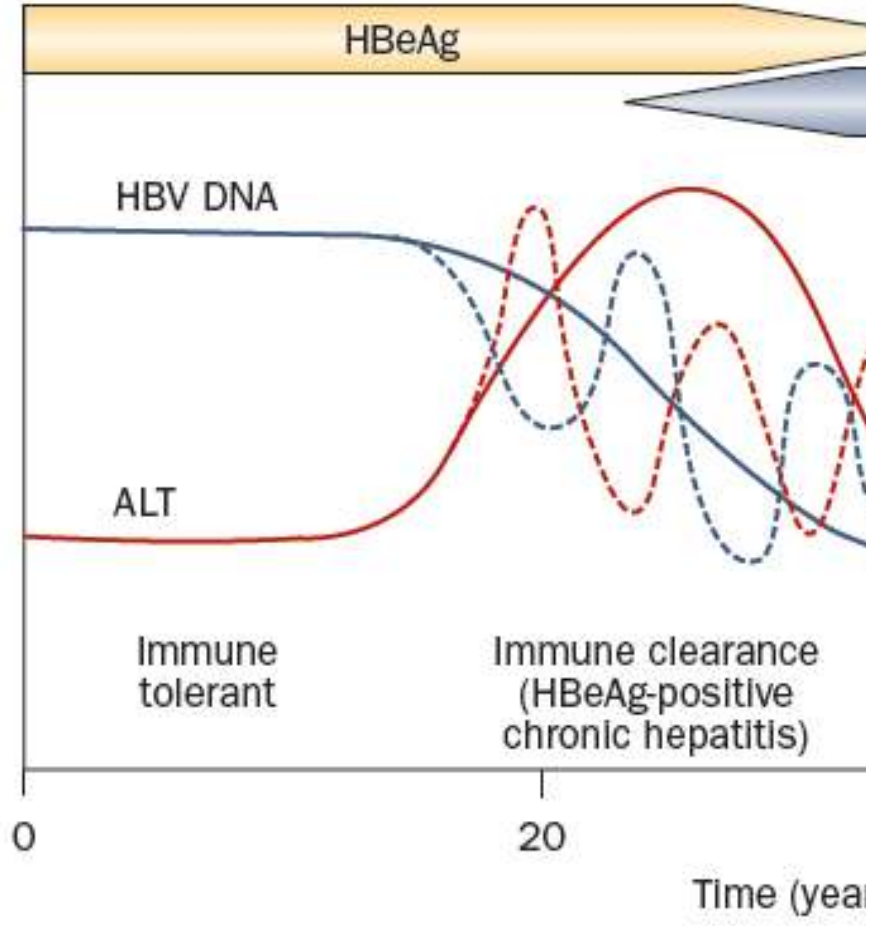
Akut HBV enfeksiyonu

Kronik HBV

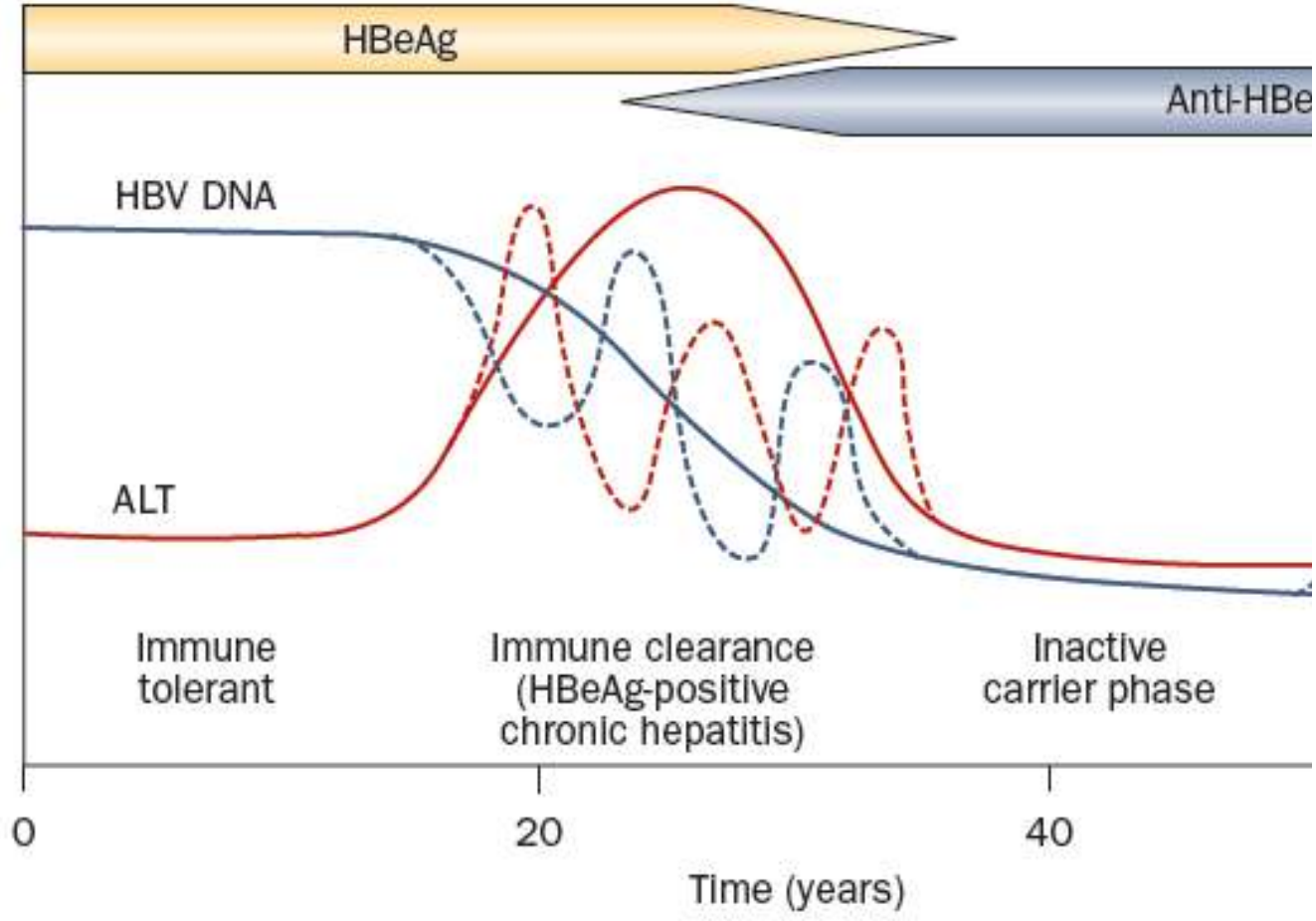
İyileşme %10-90



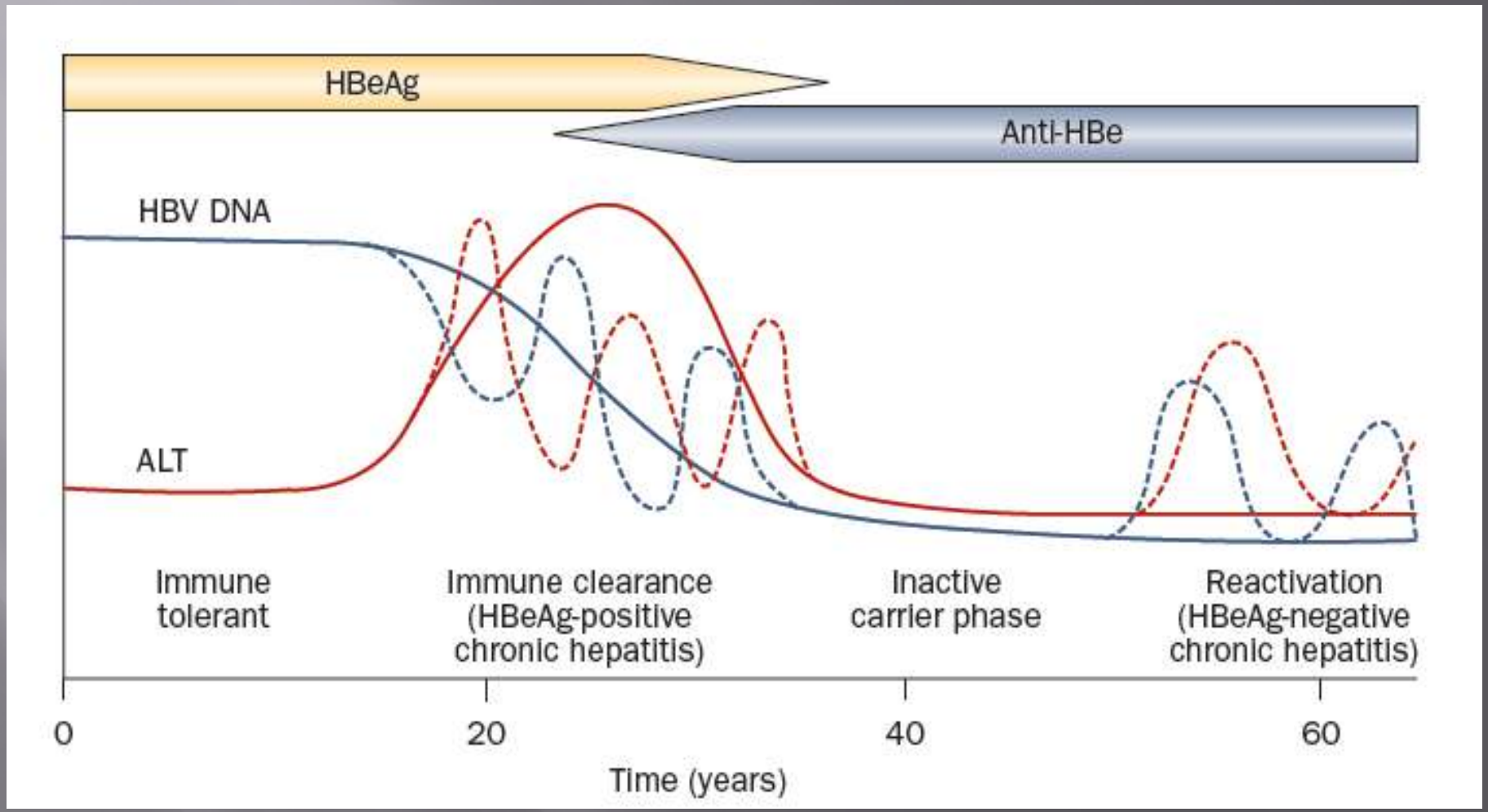
Kwon H et al. Nat Rev Gastroent Hepatol 2011;8:275



Kwon H et al. Nat Rev Gastroent Hepatol 2011;8:275



Kwon H et al. Nat Rev Gastroent Hepatol 2011;8:275



Kwon H et al. Nat Rev Gastroent Hepatol 2011;8:275

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European Association for the Study of the Liver*

EASL CPG. J Hepatol 2017;67:370

	HBeAg pozitif		HBeAg negatif	
	Kronik enfeksiyon	**Kronik hepatit**	**Kronik enfeksiyon**	**Kronik hepatit**
HBsAg	Yüksek	Yüksek/orta	Düşük	Orta
HBeAg	Pozitif	Pozitif	Negatif	Negatif
HBV DNA	$>10^7$ IU/ml	10^4-10^7 IU/ml	<2000 IU/ml	>2000 IU/ml
ALT	Normal	Yüksek	Normal	Yüksek
Karaciğer hasarı	Yok/minimal	Orta/ileri	Yok	Orta/ileri
Eski terminoloji	İmmüntoleran	İmmünreaktif	İnaktif taşıyıcı	HBeAg negatif kronik hepatit

EASL CPG. J Hepatol 2017;67:370

Akut HBV enfeksiyonu

Kronik HBV

İyileşme %10-90

İnaktif
%80

Aktif
%20

Akut HBV enfeksiyonu

Kronik HBV

İyileşme %10-90

İnaktif
%80

Aktif
%20

HCC
%2-5

Siroz
Karaciğer yetmezliği
%50

Tanı sonrası siroz gelişimi için
5 yıllık kümülatif insidans %8-20,

Kompanse sirozlu hastalarda hepatik dekompansasyon için
5 yıllık kümülatif insidans %20,

Dekompanse siroz
5 yıllık sağkalım %14-35,

Siroz geliştikten sonra
HCC insidansı %2-5/ yıl

EASL CPG. J Hepatol 2017;67:370

The Natural History of Chronic Hepatitis B Virus Infection

Brian J. McMahon

Kronik hepatit B enfeksiyonunun iki önemli sonucu siroz ve HCC, karaciğer ilişkili ölümlere neden oluyor.

McMahon BJ. Hepatology 2009;49:S45

< Previous Article

Journal of Hepatology
Volume 45, Issue 4, Pages 529–538, October 2006

Next Article >

The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide☆

Joseph F. Perz, Gregory L. Armstrong, Leigh A. Farrington, Yvan J.F. Hutin, Beth P. Bell

Received: January 9, 2006; Received in revised form: May 3, 2006; Accepted: May 16, 2006; Published Online: June 23, 2006

DOI: http://dx.doi.org/10.1016/j.jhep.2006.05.013

Global olarak,

Siroz olgularının %30,

HCC olgularının %53'ü

HBV ile ilişkilidir.

Perz JF. J Hepatol 2006;45:529

Clinicopathologic features and risk factors for hepatocellular carcinoma: Results from a single center in southern Turkey

Hepatosellüler karsinomun klinikopatolojik özellikleri ve risk faktörleri: Türkiye'nin güney bölümünde tek merkez sonuçları

Birol ÖZER[1], Ender SERİN[1], Uğur YILMAZ[1], Yüksel GÜMÜRDÜLÜ[1], Özlem B. SAYGILI[2], Fazilet KAYASELÇUK[3], Sedat BOYACIOĞLU[1]

Başkent University Faculty of Medicine, Departments of Gastroenterology[1], Radiology[2], Pathology[3], Adana Teaching and Medical Research Center, Adana

1999-2002, 226 siroz,

Hepatit B %35,4

Hepatit C %36,7

35 HCC

Hepatit B %65,7

Hepatit C %28,6

Özer B et al. Turk J Gastroenterol 2003;14:85

Published in final edited form as:
Cancer. 2019 August 01; 125(15): 2621–2630. doi:10.1002/cncr.32129.

Incidence of Hepatocellular Carcinoma among Older Americans Attributable to Hepatitis C and Hepatitis B, 2001-2013

Meredith S. Shiels, Ph.D.[1], **Eric A. Engels, M.D.**[1], **Elizabeth L. Yanik, Ph.D.**[2], **Katherine A. McGlynn, Ph.D.**[1], **Ruth M. Pfeiffer, Ph.D.**[1], and **Thomas R. O'Brien, M.D.**[1]

2001-2013 arasında HCC sıklığında %43 artış

HCV ilişkili HCC sıklığı 4,2 → 8,2 /100000
HBV ilişkili HCC sıklığı 1,3 → 1,8 /100000

Shiels MS et al. Cancer 2019;125:2621

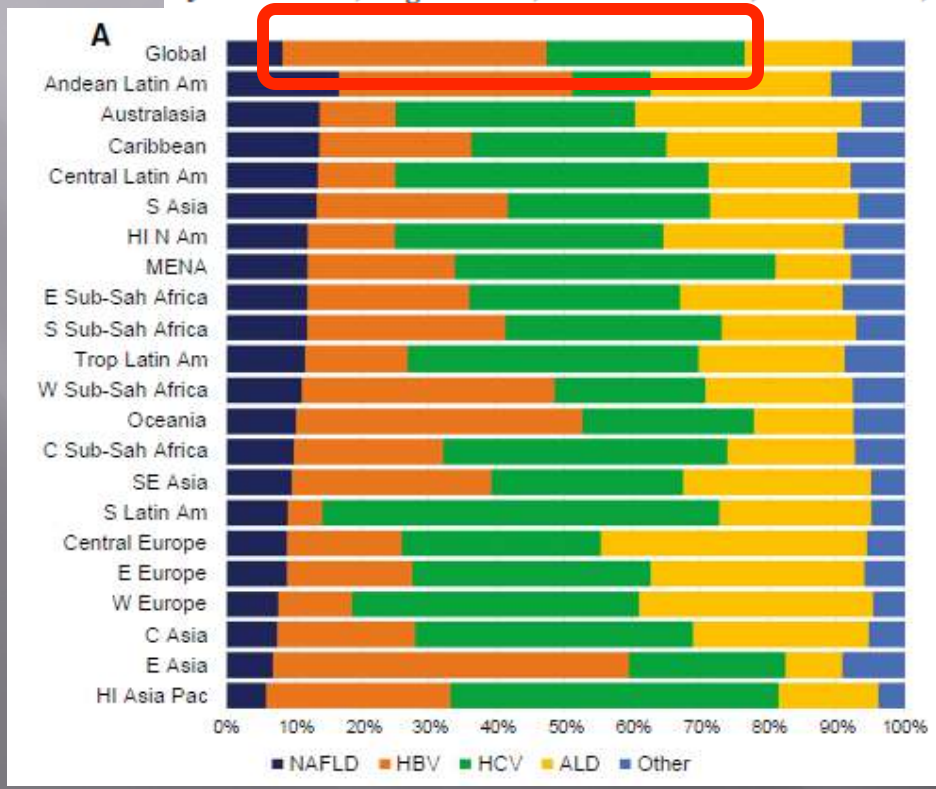
HEPATOLOGY

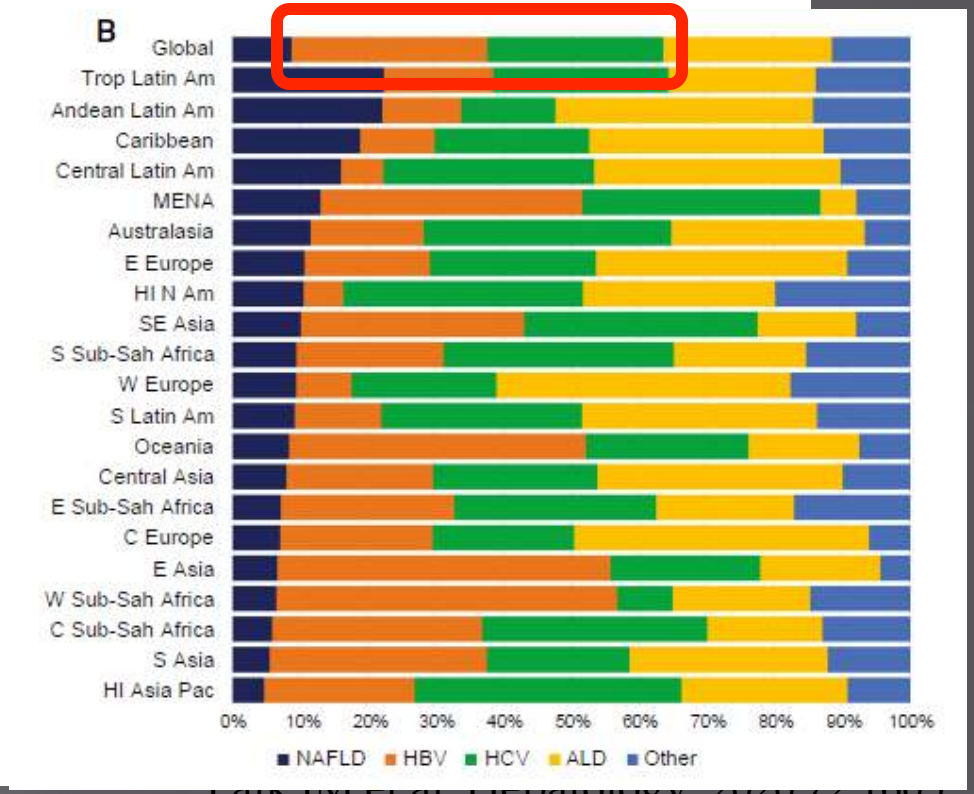
AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

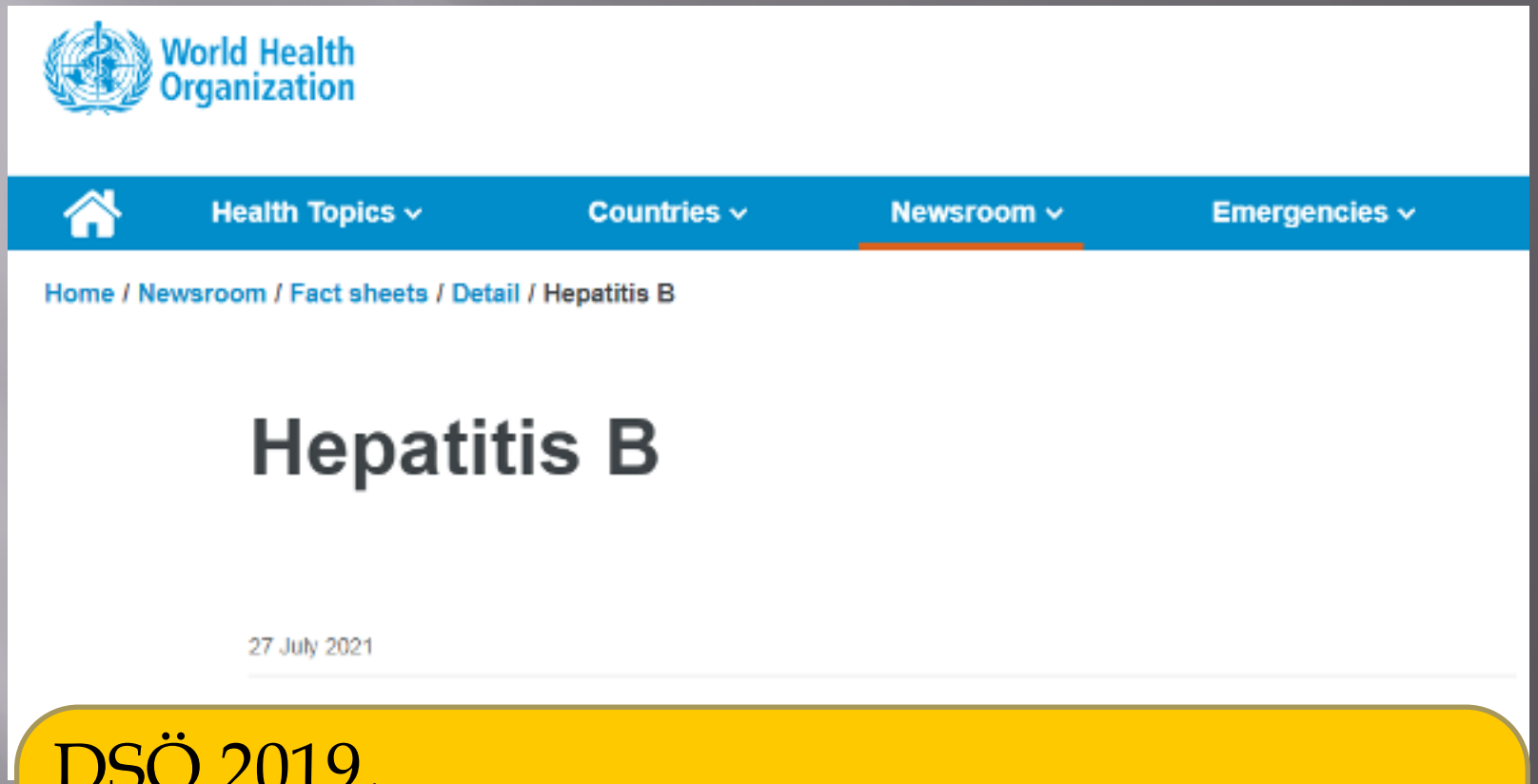
HEPATOLOGY, VOL. 72, NO. 5, 2020

Changes in the Global Burden of Chronic Liver Diseases From 2012 to 2017: The Growing Impact of NAFLD

James M. Paik,[1] Pegah Golabi,[1] Youssef Younossi,[2] Alita Mishra,[3] and Zobair M. Younossi [1,3]



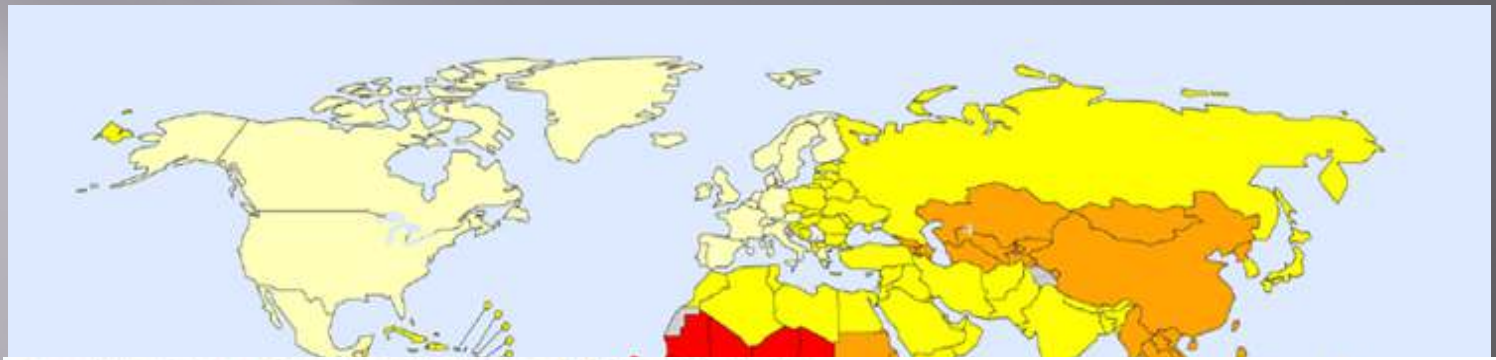


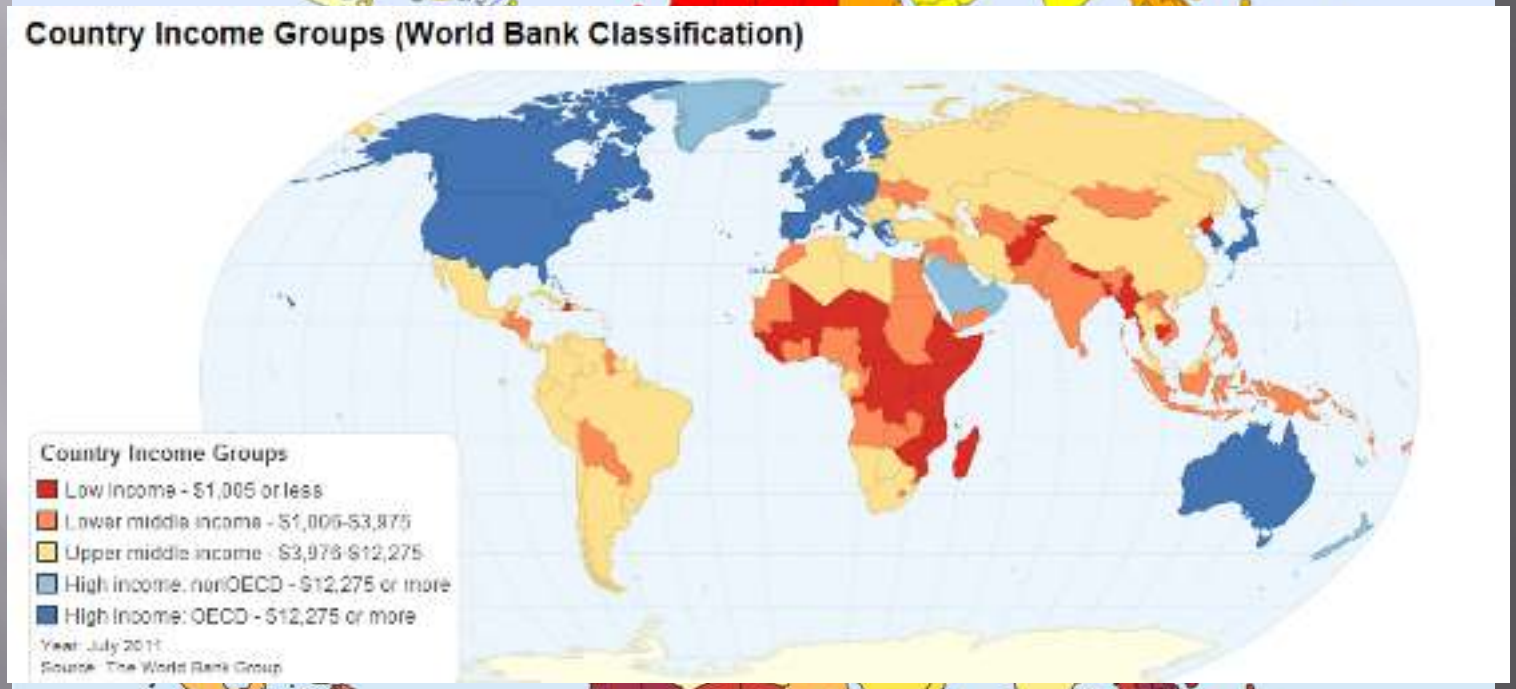


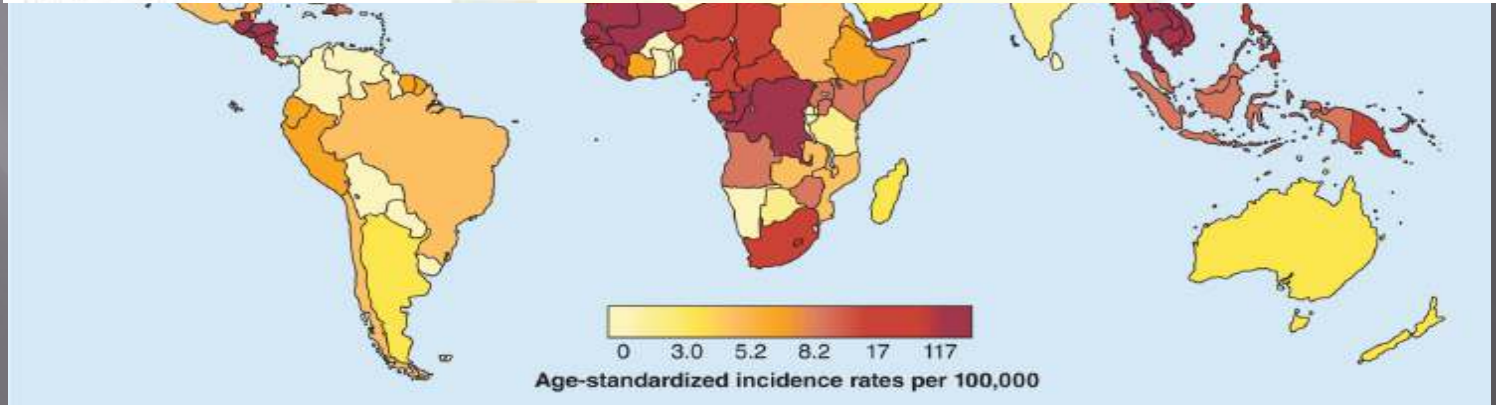
DSÖ 2019,

1,5 milyon yeni olgu/yıl
296 milyon kronik hepatit B
820000 ölüm

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




Country Income Groups (World Bank Classification)
Country Income Groups
Low income - $1,005 or less
Lower middle income - $1,006-$3,975
Upper middle income - $3,976-$12,275
High income: nonOECD - $12,275 or more
High income: OECD - $12,275 or more
Year: July 2011
Source: The World Bank Group


0 3.0 5.2 8.2 17 117
Age-standardized incidence rates per 100,000

Hastalığın spektrumu değişkenlik gösterir

Hastalığın doğal seyri ile ilişkili faktörler

Konak

- erkek cinsiyet,
- ileri yaş,
- sürekli yüksek ALT düzeyleri ya da rekürren alevlenmeler,
- siroz,
- diyabet,
- HCV, HDV, HIV koinfeksiyonları,
- obesite

Viral

- HBeAg varlığı,
- sürekli yüksek HBV DNA varlığı,
- HBV genotipi (C>B),
- core promoter mutasyonları,

Çevresel

- alkol, sigara,
- aflatoksin

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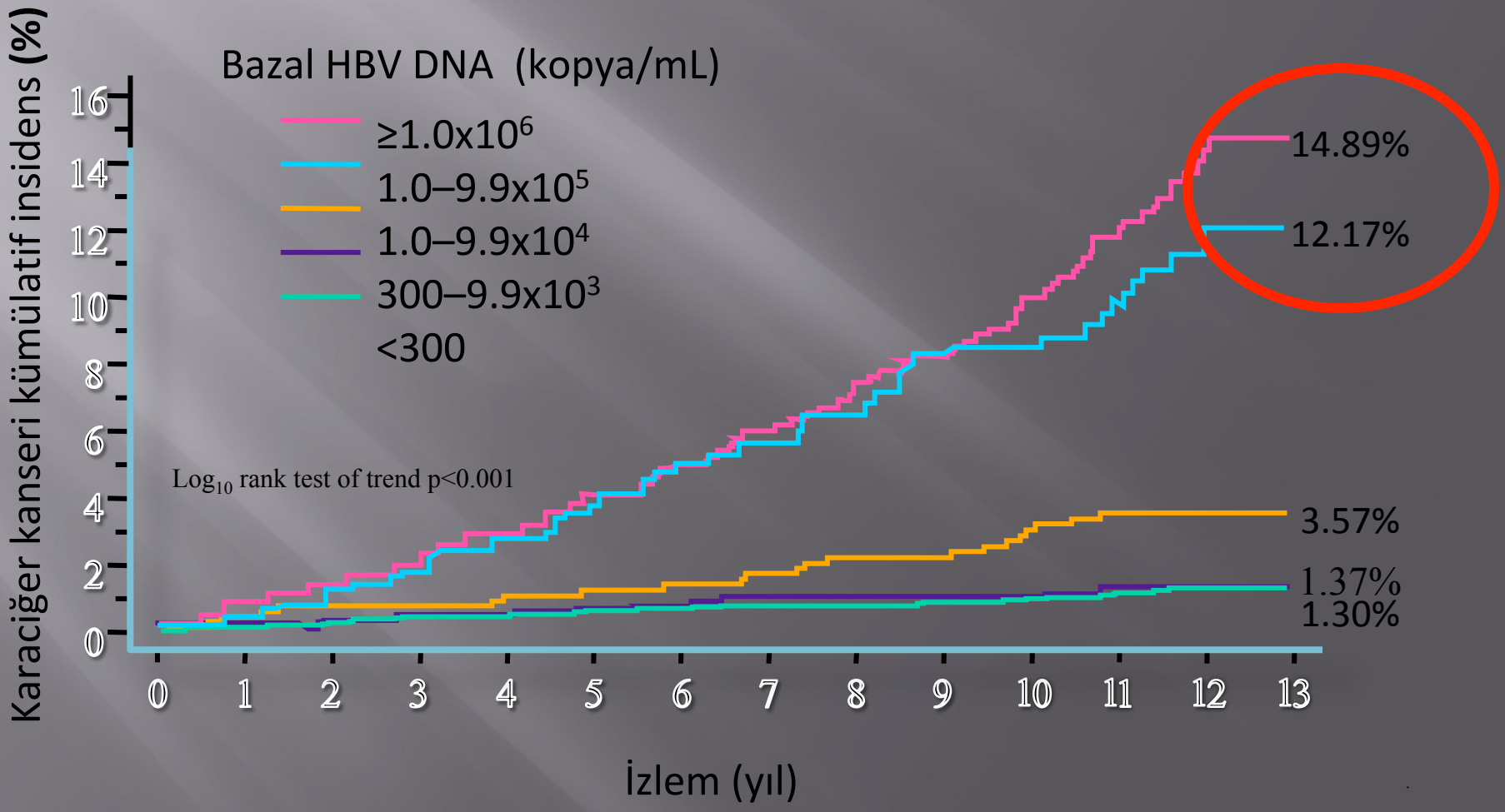
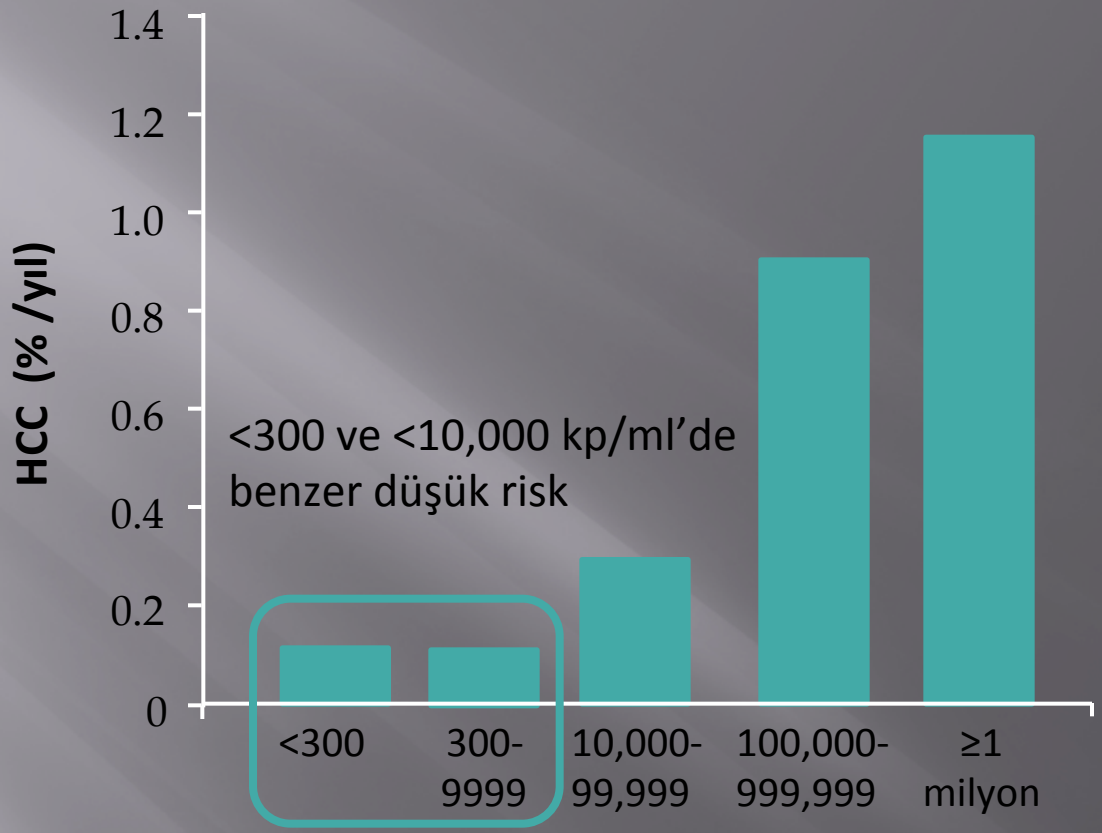
Kronik HBV enfeksiyonun uzun dönem sonuçları ve hastalık progresyonu ile en yakından ilişkili gösterge HBV replikasyonunun düzeyidir.

EASL CPG. J Hepatol 2017;67:370

Yüksek Bazal HBV DNA Düzeyleri ve HCC Gelişimi REVEAL (n=3,653)



Chen CJ et al. JAMA 2006;295:65



HBV DNA <10,000 kopya/ml olması HCC riskinin düşük olmasıyla ilişkilidir.

Chen CJ et al. JAMA 2006;295:65

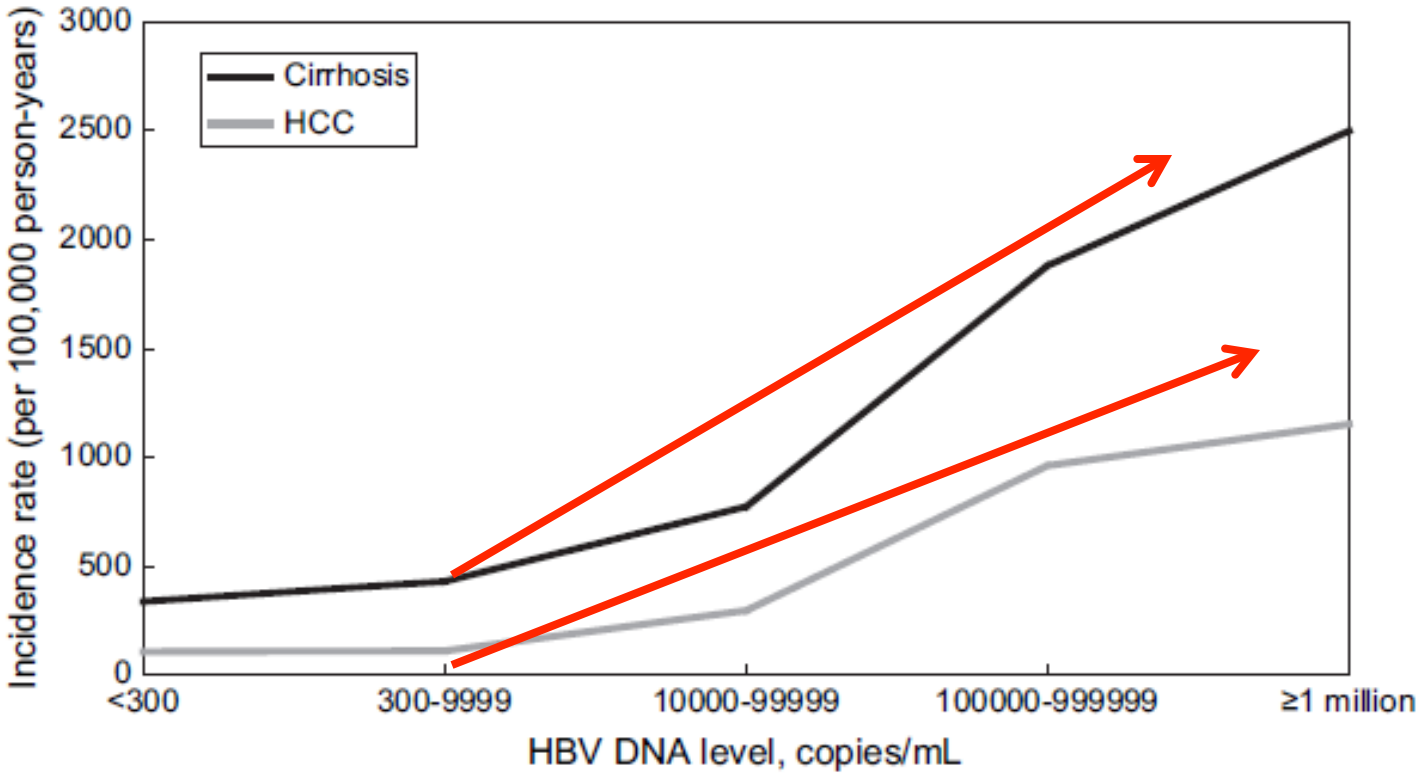
ELSEVIER
SAUNDERS

CLINICS IN
LIVER DISEASE

Clin Liver Dis 11 (2007) 797–816

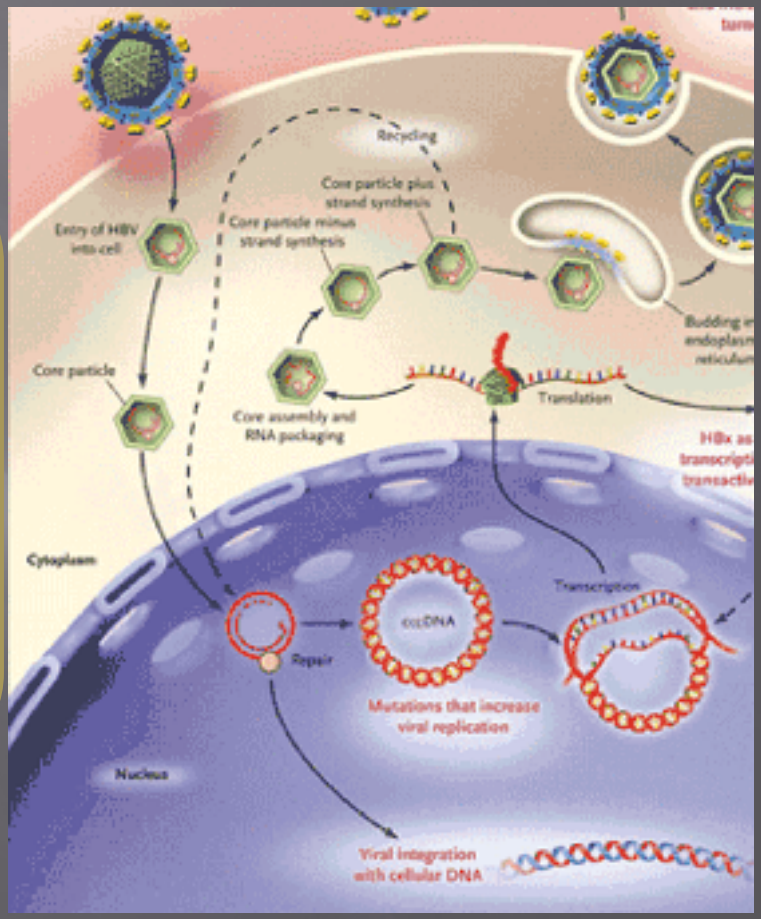
Long-Term Outcomes in Hepatitis B: The REVEAL-HBV Study

Chien-Jen Chen, ScD[a,b,*] Uchenna H. Iloeje, MD, MPH[c]



2007;11:797

Enfekte hepatositlerin nükleusundaki cccDNA nedeniyle, HBV enfeksiyonunun tam anlamıyla eradikasyonu olanaklı değildir.



Tedavinin amacı

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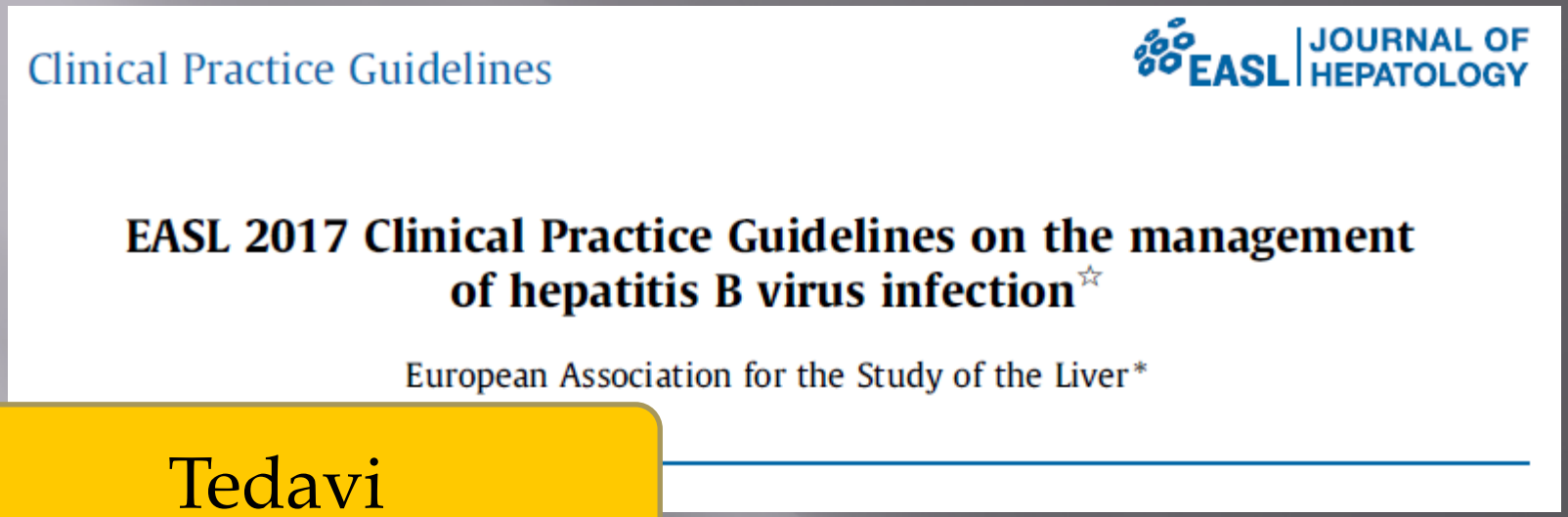
Hastalığın siroz, dekompanse siroz, son dönem karaciğer yetmezliği, HCC ve ölüme ilerlemesine engel olarak yaşam kalitesini ve sağkalımı arttırmak.

EASL CPG. J Hepatol 2017;67:370

“HBV replikasyonu kalıcı biçimde baskılanabilirse, eşlik eden histolojik aktivitedeki azalma siroz ve HCC riskini azaltacaktır.”



Tedavi

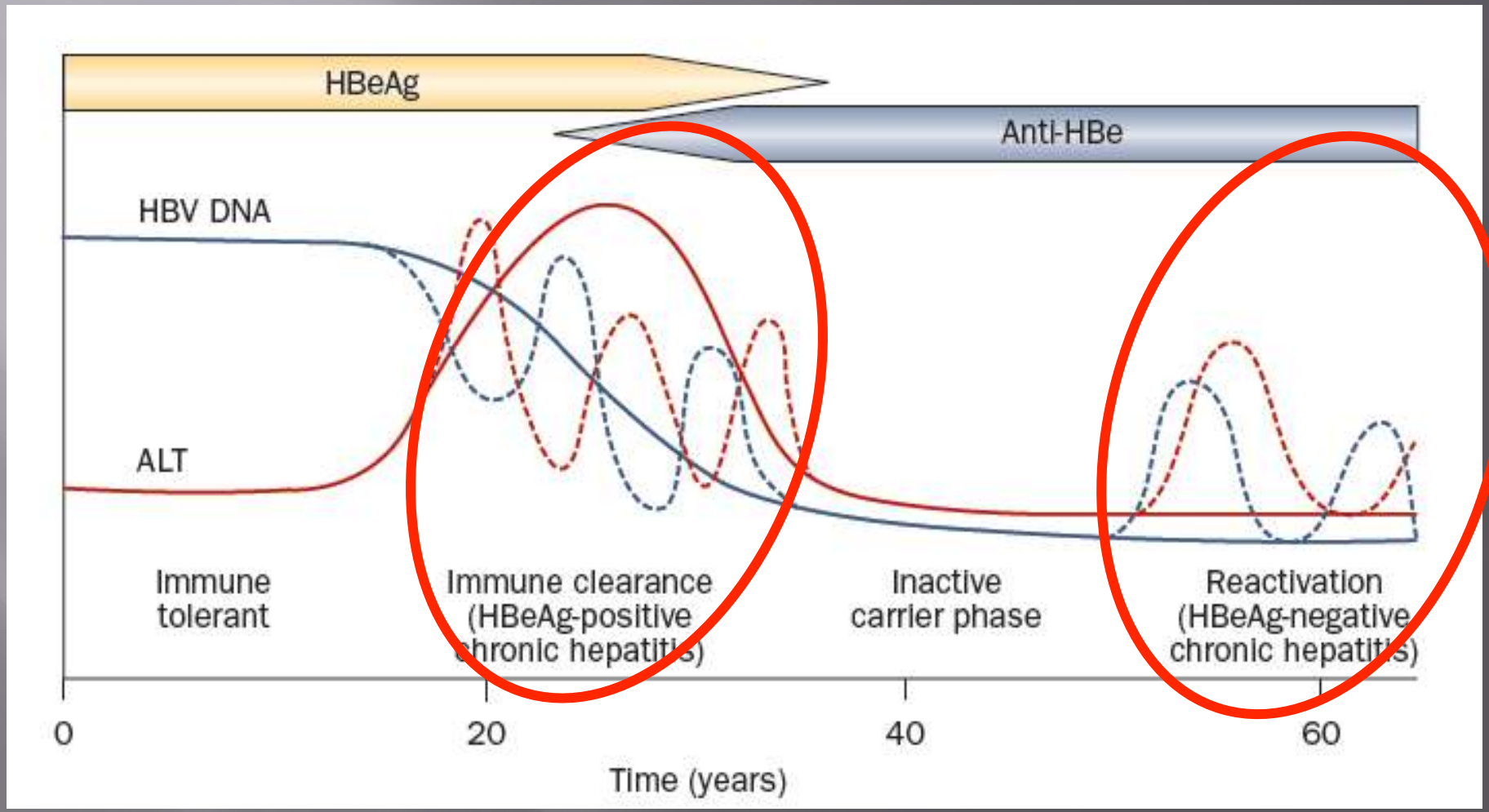
Viral baskılanma

Biyokimyasal iyileşme

Histolojik düzelme

Komplikasyonlar ↓

EASL CPG. J Hepatol 2017;67:370



Kwon H et al. Nat Rev Gastroent Hepatol 2011;8:275

Sorular

Kimler tedavi edilmelidir? / Hangi koşulda tedavi başlanmalıdır?

Hangi ilaçla tedaviye başlanmalıdır?

Tedaviye yanıtı nasıl değerlendirmeliyiz?

Tedavi ne zaman sonlandırılmalıdır?

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

PRACTICE GUIDELINE

AASLD Guidelines for Treatment of Chronic Hepatitis B

Norah

Hepatol Int (2016) 10:1–98
DOI 10.1007/s12072-015-9675-4

GUIDELINES

Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update

S. K. Sarin[1] · M. Kumar[1] · G. K. Lau[2,27] · Z. Abbas[3] · H. L. Y. Chan[4] · C. J. Chen[5] · D. S. Chen[6] · H. L. Chen[7] · P. J. Chen[8] · R. N. Chien[9] · A. K. Dokmeci[10] · Ed Gane[11] · J. L. Hou[12] · W. Jafri[13] · J. Jia[14] · J. H. Kim[15] · C. L. Lai[16] · H. C. Lee[17] · S. G. Lim[18] · C. J. Liu[7] · S. Locarnini[19] · M. Al Mahtab[20] · R. Mohamed[21] · M. Omata[22] · J. Park[23] · T. Piratvisuth[24] · B. C. Sha
S. S. Zhe

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Received: 2

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Kimler tedavi edilmeli / Hangi koşulda tedavi başlanmalıdır?

Karaciğer hastalığının derecesi ve evresi,

HBV replikasyonunun durumu,

Siroz ve HCC açısından risk,

Tedaviden kaynaklanan riskler (yan etkiler, direnç, maliyet),

Spontan remisyon beklentisi

İlk değerlendirme

Öykü, aile öyküsü, fizik inceleme, eşlik eden hastalıklar

HbeAg ve antiHBe

HBV DNA düzeyi,

Anti-HAV IgG

Serum HBsAg düzeyi ve genotip tayini

EASL CPG. J Hepatol 2017;67:370

İlk değerlendirme

Karaciğer hastalığının ağırlığının değerlendirilmesi

Biyokimyasal parametreler
ALT, AST, ALP, GGT, Bil, albumin, tam kan sayımı, PT

Karaciğer biyopsisi

Non invaziv yöntemler

EASL CPG. J Hepatol 2017;67:370

Tedavi kararı

Serum HBV DNA düzeyleri

Serum ALT düzeyleri

Karaciğer hastalığının derecesi ve evresi

EASL CPG. J Hepatol 2017;67:370

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HBeAg pozitif ya da negatif kronik hepatit hastaları
DNA>2000 IU/ml, ALT>NÜS, orta derecede nekroinflamasyon ya da fibroz varlığı,

HBV DNA ve ALT düzeyinden bağımsız olarak kompanse/dekompanse sirotik hastalar,

EASL CPG. J Hepatol 2017;67:370

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Fibroz düzeyinden bağımsız olarak DNA>20000 IU/ml ve ALT>2xNÜS

>30 yaş, HBeAg +, DNA>20000 IU/ml, ALT<NÜS

HCC ya da siroz için aile öyküsü olan hastalar

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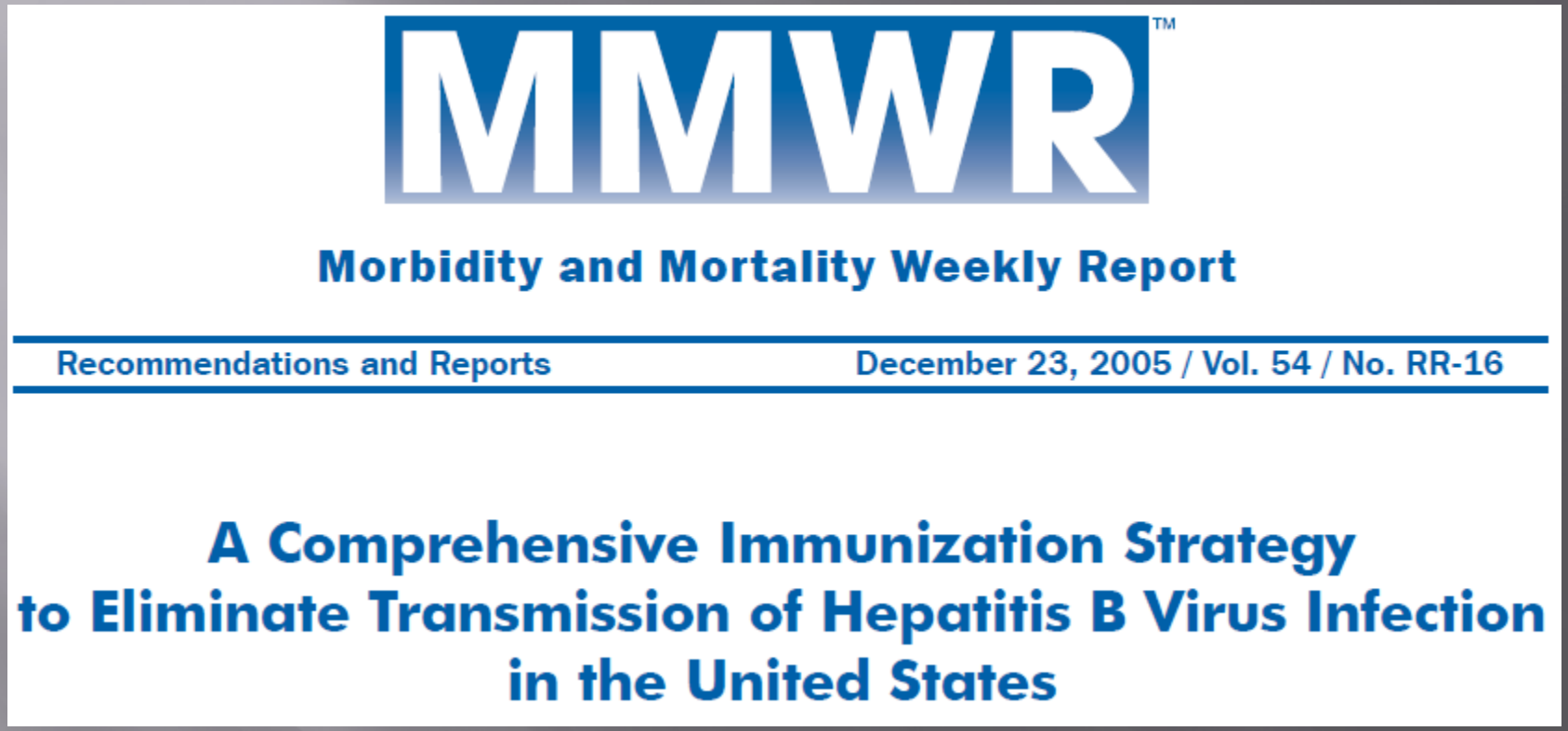
Gebeler,

EASL CPG. J Hepatol 2017;67:370

Anneden bebeğe bulaş



MMWR™

Morbidity and Mortality Weekly Report

Recommendations and Reports — December 23, 2005 / Vol. 54 / No. RR-16

A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States

HBsAg pozitif annelerden bebeklerine bulaş olasılığı %90'a kadar ulaşmaktadır.

Mast EE et al. MMWR Recomm Rep 2006;55(RR-16):1

Clinics in Liver Disease

Volume 11, Issue 4, November 2007, Pages 945–963

Chronic Hepatitis B

Hepatitis B in Pregnancy

Maya Gambarin-Gelwan, MD

Yeni edinilen HBV enfeksiyonu olgularının %50'si vertikal bulaşla gerçekleşmektedir.

Gambarin Gelwan M. Clin Liver Dis 2007;11:945

Perinatal bulaş

Universal maternal tarama uygulamaları ve infantların pasif ve aktif immünizasyonu ile anneden bebeğe bulaş %90-95 olasılıkla engellenmektedir.

Doğumdan sonra 12 saat içinde 0,5 ml **HBIg** ve
Hepatit B aşısı, 0, 1 ve 6. aylarda

Mast EE et al. MMWR Recomm Rep 2006;55(RR-16):1

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2012;10:452–459

REVIEW

An Algorithm for Risk Assessment and Intervention of Mother to Child Transmission of Hepatitis B Virus

CALVIN Q. PAN,* ZHONG-PING DUAN,‡ KALYAN R. BHAMIDIMARRI,§ HUAI-BIN ZOU,‡ XIAO-FENG LIANG,‖ JIE LI,¶ and MYRON J. TONG#

*Division of Liver Diseases, Mount Sinai Medical Center, Mount Sinai School of Medicine, New York, New York; ‡Artificial Liver Center, Beijing Youan Hospital, Capital Medical University, Beijing, China; §Center for Liver Disease, University of Miami-Miller School of Medicine, Miami, Florida; ‖National immunization Program, Chinese Centre for Disease Control and Prevention, Beijing, China; ¶Public Health College, Beijing University Medical School, Beijing, China; and #Pfleger Liver Institute and Division of Digestive Diseases, University of California School of Medicine, Los Angeles, California

HBV DNA >200000 IU/ml gebelerde perinatal bulaş riskini azaltmak için ek önlemlere gereksinim vardır.

Pan CQ et al. Clin Gastroenterol Hepatol 2012;10:452

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*

Gebeler,

İmmünsupresif tedavi ya da kemoterapi alan hastalar,

EASL CPG. J Hepatol 2017;67:370

Gastroenterology 2015;148:215–219

AGA SECTION

American Gastroenterological Association Institute Guideline on the Prevention and Treatment of Hepatitis B Virus Reactivation During Immunosuppressive Drug Therapy

K. Rajender Reddy,[1] Kimberly L. Beavers,[2] Sarah P. Hammond,[3] Joseph K. Lim,[4] and Yngve T. Falck-Ytter[5]

[1]Division of Gastroenterology and Hepatology, University of Pennsylvania, Philadelphia, Pennsylvania; [2]Division of Gastroenterology and Hepatology, Medical University of South Carolina, Charleston, South Carolina; [3]Division of Infectious Diseases, Brigham & Women's Hospital, Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts; [4]Division of Gastroenterology and Hepatology, Yale University School of Medicine, New Haven, Connecticut; and [5]Division of Gastroenterology and Hepatology, Department of Medicine, Case and VA Medical Center, Case Western Reserve University, Cleveland, Ohio

"İmmünsüpresif tedaviye bağlı gelişen HBVr" başlığının gözden geçirilmesi ve güncellenmesi

Abciximab	Belimumab	Daclizumab	Ipilimumab	Omalizumab	Tocilizumab
Adalimumab	Bezlotoxumab	Denosumab	Ixekizumab	Palivizumab	Trastuzumab
Alefacept	Canakinumab	Efalizumab	Natalizumab	Panitumumab	Secukinumab
Alemtuzumab	Certolizumab	Golimumab	Nivolumab	Pembrolizumab	Ustekinumab
Basiliximab	Cetuximab	Inflectra	Olaratumab	Rituximab	

>80 FDA onaylı monoklonal antikor

>80% son 10 yılda onaylandı...

Gastroenterology 2015;148:215–219

AGA SECTION

American Gastroenterological Association Institute Guideline on the Prevention and Treatment of Hepatitis B Virus Reactivation During Immunosuppressive Drug Therapy

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Özellikle başlangıç viral yükü yüksek olan ya da immünsüpresif tedavinin daha yoğun olacağı hastalarda

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HIV, HCV, HDV koinfekte hastalar,

Ekstrahepatik manifestasyonu olan hastalar,

Ağır akut hepatit B

EASL CPG. J Hepatol 2017;67:370

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Tedavi seçiminde

- hastalığın aktivitesi, evresi,
- HBeAg varlığı,
- HBV DNA ve ALT düzeyleri,
- eşlik eden hastalıklar,
- önceki tedavi öyküsü

dikkate alınmalıdır.

EASL CPG. J Hepatol 2017;67:370

Tedavi sonlanım noktaları

- HBsAg kaybı
- HBeAg kaybı
- Biyokimyasal yanıt, ALT normalizasyonu
- HBV DNA baskılanması

EASL CPG. J Hepatol 2017;67:370

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İdeal sonlanım noktası HBsAg kaybı
"Fonksiyonel kür"

EASL CPG. J Hepatol 2017;67:370

Table 1 | Response rates (%) to approved therapies for HBeAg-positive and HBeAg-negative chronic hepatitis B

Treatment response parameters	Approved therapies						
	Lamivudine	Adefovir dipivoxil	Entecavir	Telbivudine	Tenofovir disoproxil	PEG-IFN*	PEG-IFN plus lamivudine*
HBeAg-positive patients at week 48 or 52							
Histologic improvement‡	49–62	53–68	72	65	74	38	41
Undetectable HBV DNA	40–44	21	67	60	76	25	69
HBeAg seroconversion	16–21	12	21	22	21	27	24
HBsAg loss	<1	0	2	0	3	3	3
HBeAg-positive patients during extended treatment§							
Undetectable HBV DNA	NA	39(5.0)	94(5.0)	79(4.0)	77(4.0)	13‖ (4.5)	26‖ (4.5)
HBeAg seroconversion	47 (3.0)	48 (5.0)	41 (5.0)	42 (4.0)	31 (3.0)	37‖ (4.5)	36‖ (4.5)
HBsAg loss	0–3 (2.0–3.0)	2(5.0)	5 (2.0)	1 (2.0)	10 (4.0)	8‖ (4.5)	15‖ (4.5)
HBeAg-negative patients at week 48 or 52							
Histologic improvement‡	60–66	64–69	70	67	72	48	38
Undetectable HBV DNA	60–73	51	90	88	93	63	87
HBsAg loss	<1	NA	<1	<1	0	4	3
HBeAg-negative patients during extended treatment§							
Undetectable HBV DNA	6 (4.0)	67 (5.0)	NA	84(4.0)	86(3.0)	18‖ (4.0)	13‖ (4.0)
HBsAg loss	<1 (4.0)	5 (5.0)	NA	<1 (2.0)	0 (4.0)	8‖ (4.0)	8‖ (4.0)

Kwon H et al. Nat Rev Gastroent Hepatol 2011;8:275

Clinical Practice Guidelines

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

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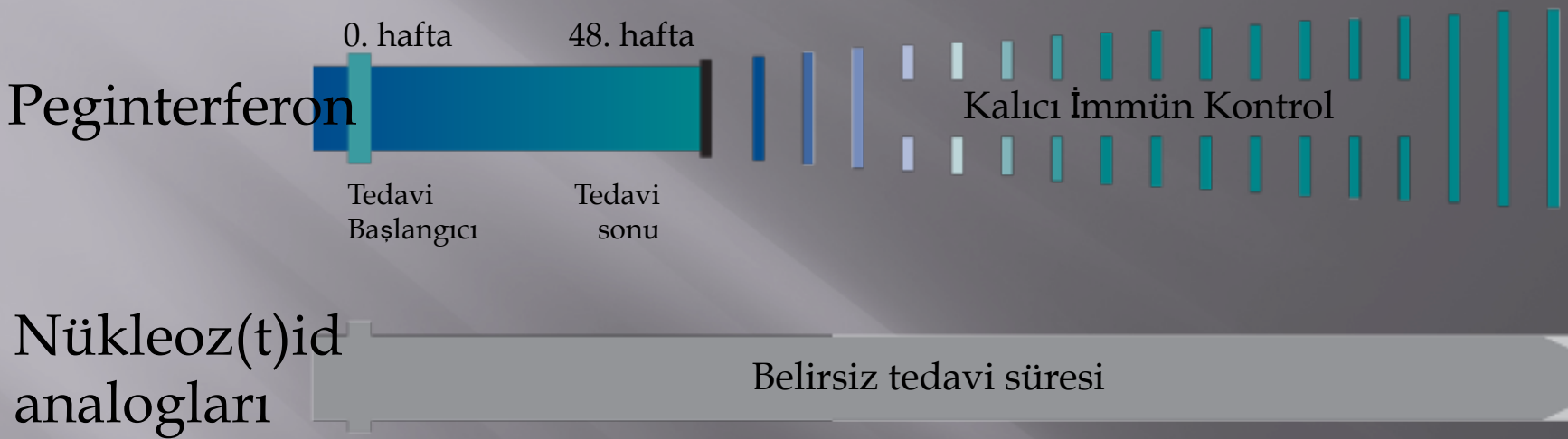
İdeal sonlanım noktası HBsAg kaybı

Tedavi sonrası kalıcı virolojik yanıt

Tedavi altında sürdürülebilir viral baskılanma

EASL CPG. J Hepatol 2017;67:370



PEG IFN ya da NA ile süresi belirli tedavi

NA ile uzun süreli tedavi

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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. Lok,[2] Brian J. McMahon,[3] Kyong-Mi Chang,[4] Jessica P. Hwang,[5] Maureen M. Jonas,[6] Robert S. Brown Jr.,[7] Natalie H. Bzowej,[8] and John B. Wong[9]

Kronik hepatit B tedavisinde tercih edilmesi önerilen seçenekler

PEG-IFN, ETV, TDF, TAF

Terrault NA et al. Hepatology 2018;67:1560

EASL CPG. J Hepatol 2017;67:370

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LAM, ADV, TBV tercih edilmemeli…

Terrault NA et al. Hepatology 2018;67:1560

EASL CPG. J Hepatol 2017;67:370

Clinical Practice Guidelines

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

European Association for the Study of the Liver*

PEG-IFN, süresi belirli bir tedavi yaklaşımı ile uzun dönemli immünolojik kontrol sağlanması ve direnç sorunu olmaması,

Tedavi yanıtının değişkenliği ve yan etki profili

EASL CPG. J Hepatol 2017;67:370

Clinical Practice Guidelines

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

European Association for the Study of the Liver*

Grip benzeri tablo, myalji, baş ağrısı, halsizlik,
Saç dökülmesi,
Kemik iliği baskılanması,
Enjeksiyon yerinde lokal reaksiyonlar

EASL CPG. J Hepatol 2017;67:370

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*

PEG-IFN, uzun süreli tedavi almak istemeyen ve kompanse karaciğer hastalığı olan genç yetişkinlerde iyi bir seçenek…

EASL CPG. J Hepatol 2017;67:370

Benefits and Risks of Interferon Therapy for Hepatitis B

Robert Perrillo

48 hafta PEG IFN tedavisi sonrasında biyokimyasal ve virolojik yanıt,

- HBeAg pozitif hastaların ~1/3'ü,
- HBeAg negatif hastaların %40'ı

HBeAg pozitif hastaların %80,
HBeAg negatif hastaların %50'sinde yanıtın kalıcı olduğu söylenebilir.

Perillo R. Hepatology 2009;49:S103

PEG IFN tedavisi öncesi yanıtı öngörme

HBeAg pozitif ve negatif hastalar

- Düşük viral yük,
- Yüksek ALT (2-5xULN)
- Genotip A, B
- Biyopside yüksek aktivite skoru

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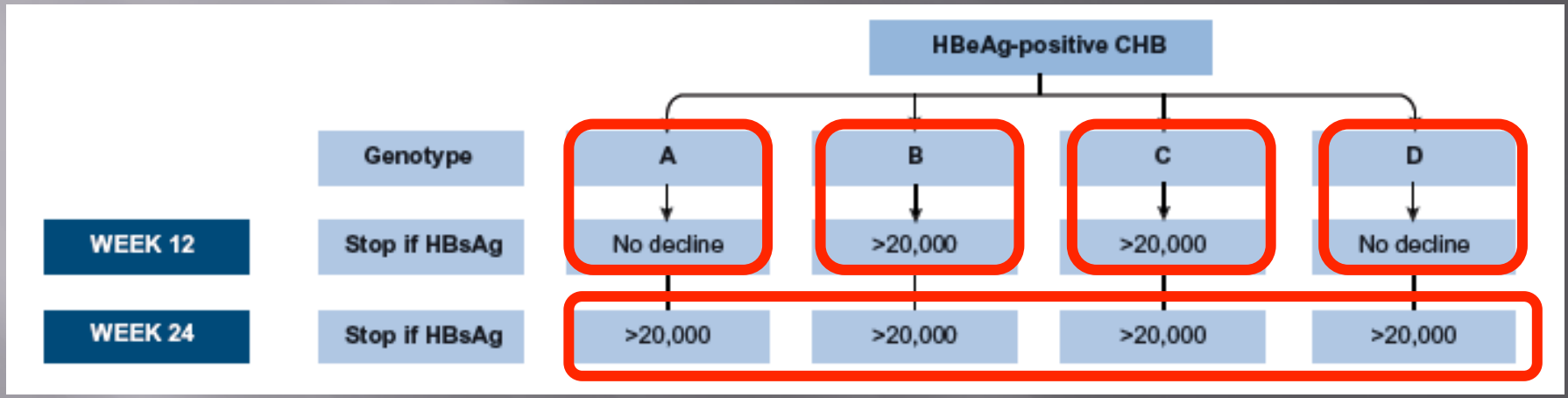
EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection☆

European Association for the Study of the Liver*

PEG-IFN, HBeAg negatif genotip D hastalarda kalıcı virolojik yanıtlar ~%20

EASL CPG. J Hepatol 2017;67:370

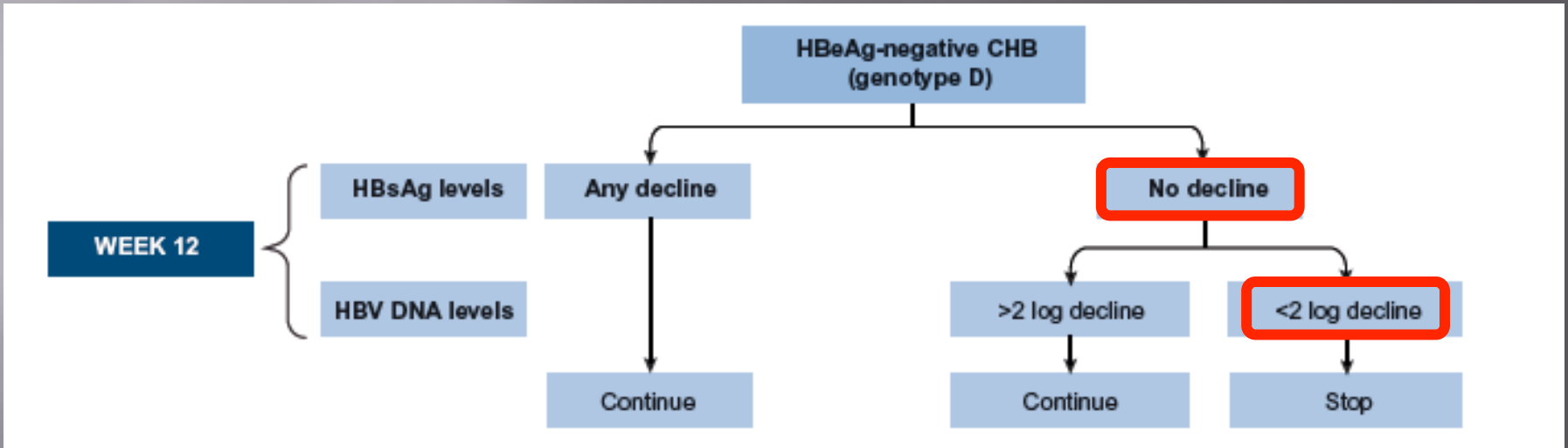
PEG IFN tedavi sırasında yanıtı öngörme



HBeAg pozitif hastalarda,
12. haftada HBsAg<1500 IU/ml
HBeAg serokonversiyonu için ppv %50

EASL CPG. J Hepatol 2017;67:370

PEG IFN tedavi sırasında yanıtı öngörme



HBeAg negatif genotip D hastalarda, 12. haftada HBsAg düzeyinde düşüş olmaması ve HBV DNA düzeyinin 2 log azalmaması tedaviyi kesme kriteridir…

EASL CPG. J Hepatol 2017;67:370

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

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Kronik hepatit B tedavisinde tercih edilmesi önerilen seçenekler

PEG-IFN, ETV, TDF, TAF

Terrault NA et al. Hepatology 2018;67:1560

EASL CPG. J Hepatol 2017;67:370

NAs

Etkin viral baskılanma

Optimal direnç profili

Güvenlik

Etkinlik/Direnç
NAs

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 9, 2006 VOL. 354 NO. 10

A Comparison of Entecavir and Lamivudine for HBeAg-Positive Chronic Hepatitis B

Ting-Tsung Chang, M.D., Robert G. Gish, M.D., Robert de Man, M.D., Adrian Gadano, M.D., José Sollano, M.D., You-Chen Chao, M.D., Anna S. Lok, M.D., Kwang-Hyub Han, M.D., Zachary Goodman, M.D., Ph.D., Jin Zhu, Ph.D., Anne Cross, Ph.D., Deborah DeHertogh, M.D., Richard Wilber, M.D., Richard Colonno, Ph.D., and David Apelian, M.D., Ph.D., for the BEHoLD AI463022 Study Group*

Table 3. Virologic, Biochemical, and Serologic End Points at Week 48.*

End Point	Entecavir (N=354)	Lamivudine (N=355)	Difference Estimate (95% CI)†	P Value
Virologic				
HBV DNA <300 copies/ml by PCR assay — no. (%)	236 (67)	129 (36)	30.3 (23.3 to 37.3)	<0.001
HBV DNA <0.7 MEq/ml by branched-chain DNA assay — no. (%)	322 (91)	232 (65)	25.6 (19.8 to 31.4)	<0.001
Mean change in HBV DNA from baseline by PCR assay — log copies/ml‡	−6.9±2.0	−5.4±2.6	−1.52 (−1.78 to −1.27)	<0.001
Biochemical				
ALT normalization (≤1× ULN) — no. (%)	242 (68)	213 (60)	8.4 (1.3 to 15.4)	0.02
Serologic				
Loss of HBeAg — no. (%)	78 (22)	70 (20)	2.3 (−3.7 to 8.3)	0.45
HBeAg seroconversion — no. (%)	74 (21)	64 (18)	2.9 (−2.9 to 8.7)	0.33
HBsAg loss — no. (%)	6 (2)	4 (1)	0.6 (−1.2 to 2.3)	0.52

Chang TT et al. N Engl J Med 2006;354:1001

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Entecavir versus Lamivudine for Patients with HBeAg-Negative Chronic Hepatitis B

Ching-Lung Lai, M.D., Daniel Shouval, M.D., Anna S. Lok, M.D., Ting-Tsung Chang, M.D., Hugo Cheinquer, M.D., Zachary Goodman, M.D., Ph.D., Deborah DeHertogh, M.D., Richard Wilber, M.D., Richard C. Zink, Ph.D., Anne Cross, Ph.D., Richard Colonno, Ph.D., and Lori Fernandes, M.D., for the BEHoLD AI463027 Study Group*

Table 3. Virologic and Biochemical End Points at Week 48.*

End Point	Entecavir (N=325)	Lamivudine (N=313)	Difference Estimate (95% CI)†	P Value
Virologic				
HBV DNA <300 copies/ml by PCR assay — no. (%)	293 (90)	225 (72)	18.3 (12.3 to 24.2)	<0.001
HBV DNA <0.7 MEq/ml by branched-chain DNA assay — no. (%)	309 (95)	279 (89)	5.9 (1.8 to 10.1)	0.005
Mean change in HBV DNA level from baseline by PCR assay — log copies/ml‡	−5.0±1.7	−4.5±1.9	−0.43 (−0.6 to −0.3)	<0.001
Biochemical				
ALT normalization (≤1.0× ULN) — no. (%)	253 (78)	222 (71)	6.9 (0.2 to 13.7)	0.045

Lai CL et al. N Engl J Med 2006;354:1011

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tenofovir Disoproxil Fumarate versus Adefovir Dipivoxil for Chronic Hepatitis B

Patrick Marcellin, M.D., E. Jenny Heathcote, M.D., Maria Buti, M.D., Ed Gane, M.D., Robert A. de Man, M.D., Zahary Krastev, M.D., George Germanidis, M.D., Sam S. Lee, M.D., Robert Flisiak, M.D., Kelly Kaita, M.D., Michael Manns, M.D., Iskren Kotzev, M.D., Konstantin Tchernev, M.D., Peter Buggisch, M.D., Frank Weilert, M.D., Oya Ovung Kurdas, M.D., Mitchell L. Shiffman, M.D., Huy Trinh, M.D., Mary Kay Washington, M.D., Jeff Sorbel, M.S., Jane Anderson, Ph.D., Andrea Snow-Lampart, B.S., Elsa Mondou, M.D., Joe Quinn, M.P.H., and Franck Rousseau, M.D.

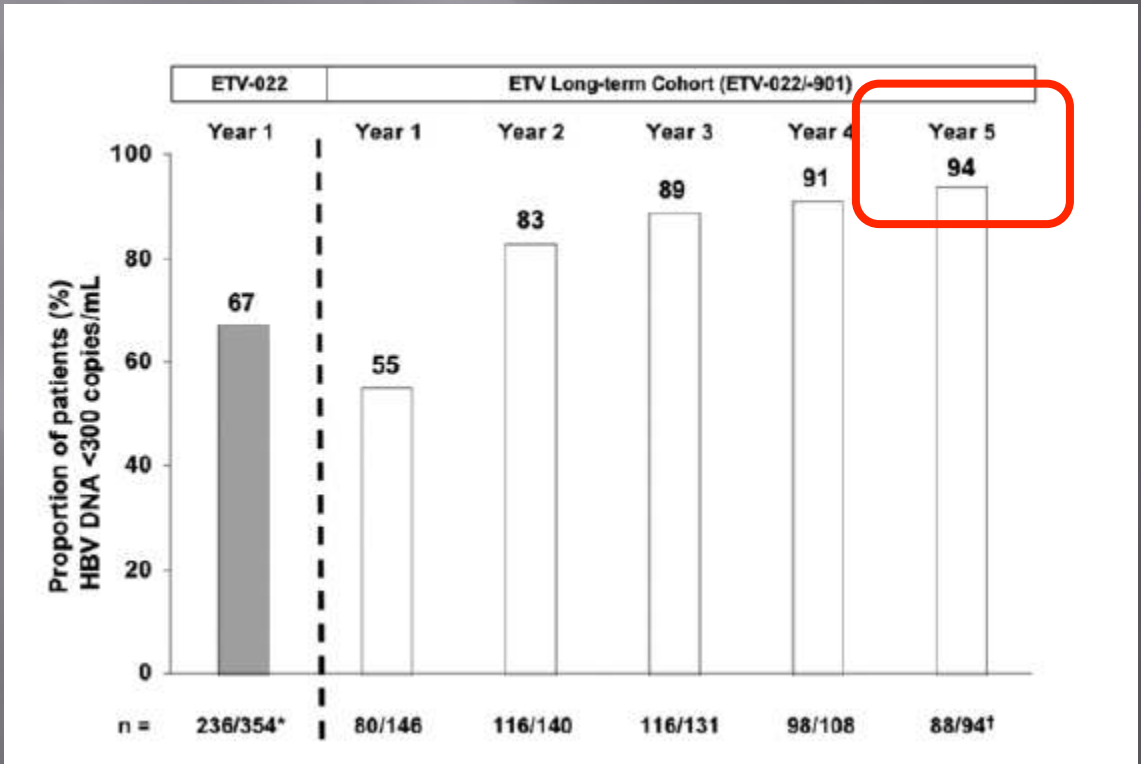
Table 2. Efficacy Results at 48 Weeks.*

Variable	HBeAg-Positive Patients				HBeAg-Negative Patients			
	Tenofovir DF (N=176)	Adefovir Dipivoxil (N=90)	P Value	Stratum-Adjusted Relative Difference % (95% CI)†	Tenofovir DF (N=250)	Adefovir Dipivoxil (N=125)	P Value	Stratum-Adjusted Relative Difference % (95% CI)†
Primary end point								
HBV DNA — no. (%)								
<400 copies/ml, intention-to-treat analysis¶	134/176 (76)	12/90 (13)	<0.001	63.1 (53.8 to 72.3)	233/250 (93)	79/125 (63)	<0.001	30.3 (21.3 to 39.2)
<400 copies/ml, observed data	133/160 (83)	12/84 (14)	<0.001	68.8 (59.4 to 78.3)	233/241 (97)	79/117 (68)	<0.001	29.2 (20.4 to 37.9)
Serologic findings — no. (%)								
HBeAg seroconversion	32/153 (21)	14/80 (18)	0.36	4.7 (−5.5 to 14.9)	—	—		
HBsAg loss	5/158 (3.2)	0/82 (0)	0.02	10.9 (1.9 to 19.9)	0/250 (0)	0/125 (0)		

Marcellin P et al. N Engl J Med 2008;359:2442

Entecavir Treatment for up to 5 Years in Patients with Hepatitis B e Antigen–Positive Chronic Hepatitis B

Ting-Tsung Chang,[1] Ching-Lung Lai,[2] Seung Kew Yoon,[3] Samuel S. Lee,[4] Henrique Sergio M. Coelho,[5] Flair Jose Carrilho,[6] Fred Poordad,[7] Waldemar Halota,[8] Yves Horsmans,[9] Naoky Tsai,[10] Hui Zhang,[11] Daniel J. Tenney,[11] Ricardo Tamez,[12] and Uchenna Iloeje[11]



Chang TT et al. Hepatology 2010;51:422

Dig Dis Sci
DOI 10.1007/s10620-014-3486-7

ORIGINAL ARTICLE

Seven-Year Efficacy and Safety of Treatment with Tenofovir Disoproxil Fumarate for Chronic Hepatitis B Virus Infection

Maria Buti · Naoky Tsai · Joerg Petersen · Robert Flisiak · Selim Gurel · Zahary Krastev · Raul Aguilar Schall · John F. Flaherty · Eduardo B. Martins · Prista Charuworn · Kathryn M. Kitrinos · G. Mani Subramanian · Edward Gane · Patrick Marcellin

Table 1 Biochemical and virologic response to tenofovir disoproxil fumarate at year 7 (week 336)

	By HBeAg status		All
	HBeAg-negative[a]	HBeAg-positive[b]	
HBV DNA < 69 IU/mL [% (*n*/*N*)]			
LTE-TDF[c]	77.3 (269/348)	60.3 (149/247)	70.3 (418/595)
On treatment[d]	99.3 (271/273)	99.4 (159/160)	99.3 (430/433)
HBV DNA < 29 IU/mL [% (*n*/*N*)]			
LTE-TDF[c]	77.1 (269/349)	60.3 (149/247)	70.1(418/596)
On treatment[d]	99.3 (271/273)	99.4 (159/160)	99.3 (430/433)

Buti M et al. Dig Dis Sci 2014 Dec 23;epub

Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial

*Henry L Y Chan, Scott Fung, Wai Kay Seto, Wan-Long Chuang, Chi-Yi Chen, Hyung Joon Kim, Aric Josun Hui, Harry L A Janssen, Abhijit Chowdhury, Tak Yin Owen Tsang, Rajiv Mehta, Edward Gane, John F Flaherty, Benedetta Massetto, Anuj Gaggar, Kathryn M Kitrinos, Lanjia Lin, G Mani Subramanian, John G McHutchison, Young-Suk Lim, Subrat K Acharya, Kosh Agarwal, and the GS-US-320-0110 Investigators**

19 ülke, 161 merkez, çift kör, RCT,

HBeAg pozitif KHB

TAF (n=581) vs TDF (n=292)

48. hafta HBV DNA<29 IU/ml

TAF %64 / TDF %67 (p=0,25)

Chan HLY et al. Lancet Gastroenterol Hepatol 2016;1:185

Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial

*Maria Buti, Edward Gane, Wai Kay Seto, Henry L Y Chan, Wan-Long Chuang, Tatjana Stepanova, Aric-Josun Hui, Young-Suk Lim, Rajiv Mehta, Harry L A Janssen, Subrat K Acharya, John F Flaherty, Benedetta Massetto, Andrea L Cathcart, Kyungpil Kim, Anuj Gaggar, G Mani Subramanian, John G McHutchison, Calvin Q Pan, Maurizia Brunetto, Namiki Izumi, Patrick Marcellin, and the GS-US-320-0108 Investigators**

17 ülke, 105 merkez, çift kör, RCT,

HBeAg negatif KHB

TAF (n=285) vs TDF (n=141)

48. hafta HBV DNA<29 IU/ml

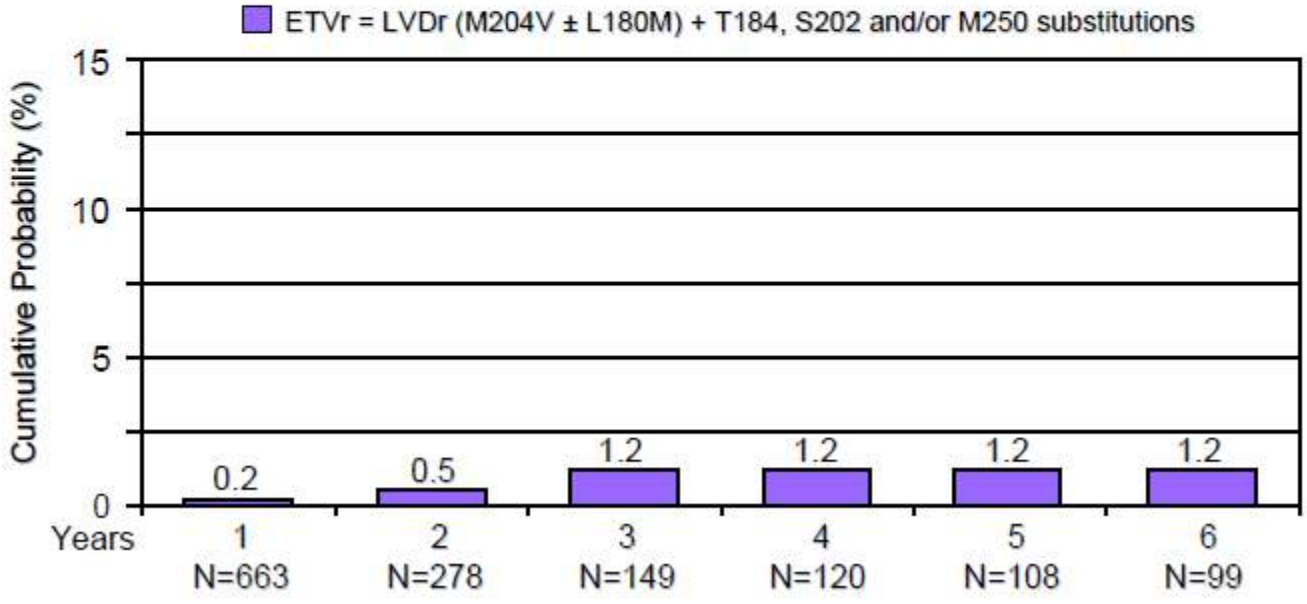
TAF %94 / TDF %93 (p=0,47)

Buti M et al. Lancet Gastroenterol Hepatol 2016;1:196

Long-Term Monitoring Shows Hepatitis B Virus Resistance to Entecavir in Nucleoside-Naïve Patients Is Rare Through 5 Years of Therapy

Daniel J. Tenney, Ronald E. Rose, Carl J. Baldick, Kevin A. Pokornowski, Betsy J. Eggers, Jie Fang, Michael J. Wichroski, Dong Xu, Joanna Yang, Richard B. Wilber, and Richard J. Colonno*

Figure 2. Nucleoside-Naïve Cohort (HBeAg+ & HBeAg-): Cumulative Probability of ETV Resistance Through 6 Years



Dig Dis Sci
DOI 10.1007/s10620-014-3486-7

ORIGINAL ARTICLE

Seven-Year Efficacy and Safety of Treatment with Tenofovir Disoproxil Fumarate for Chronic Hepatitis B Virus Infection

Maria Buti · Naoky Tsai · Joerg Petersen · Robert Flisiak · Selim Gurel · Zahary Krastev · Raul Aguilar Schall · John F. Flaherty · Eduardo B. Martins · Prista Charuworn · Kathryn M. Kitrinos · G. Mani Subramanian · Edward Gane · Patrick Marcellin

437 hasta,
Yedinci yıl değerlendirmesi

Tenofovir direnci yok

Buti M et al. Dig Dis Sci 2014 Dec 23;epub

J Gastroenterol (2019) 54:182–193
https://doi.org/10.1007/s00535-018-1502-y

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Long-term outcome of entecavir treatment of nucleos(t)ide analogue-naïve chronic hepatitis B patients in Japan

Fumitaka Suzuki[1,2] · Tetsuya Hosaka[1] · Yoshiyuki Suzuki[1] · Hitomi Sezaki[1] · Norio Akuta[1] · Shunichiro Fujiyama[1] · Yusuke Kawamura[1] · Masahiro Kobayashi[1] · Satoshi Saitoh[1] · Yasuji Arase[1] · Kenji Ikeda[1] · Mariko Kobayashi[3] · Rie Mineta[3] · Yukiko Suzuki[3] · Hiromitsu Kumada[1]

1094 naiv KHB hastası, 10 yıllık ETV etkinliği

%42 HBeAg pozitif,

%23 sirotik

Suzuki F et al. J Gastroenterol 2019;54:182

J Gastroenterol (2019) 54:182–193
https://doi.org/10.1007/s00535-018-1502-y

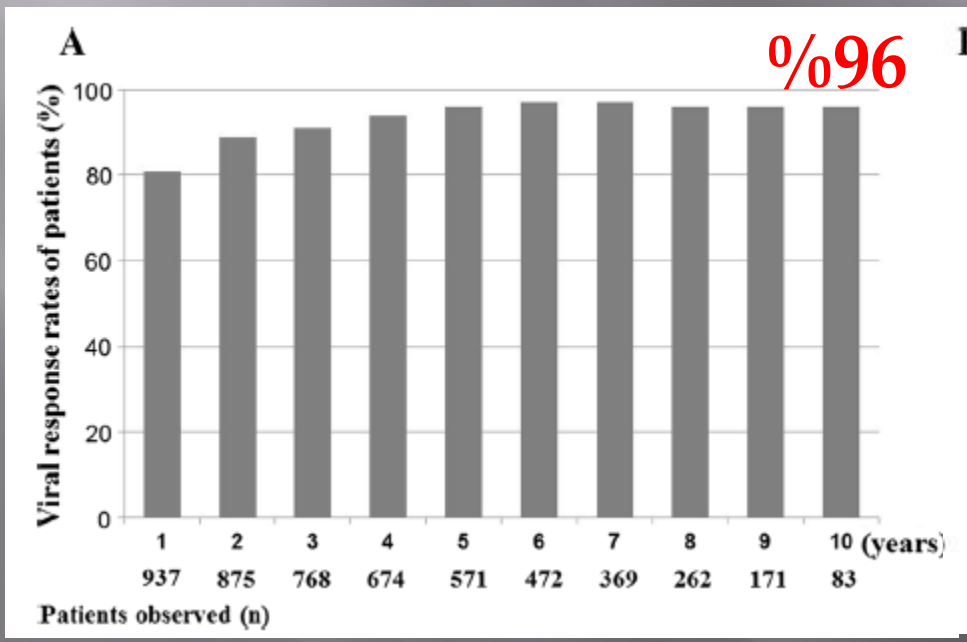
The Japanese Society of Gastroenterology

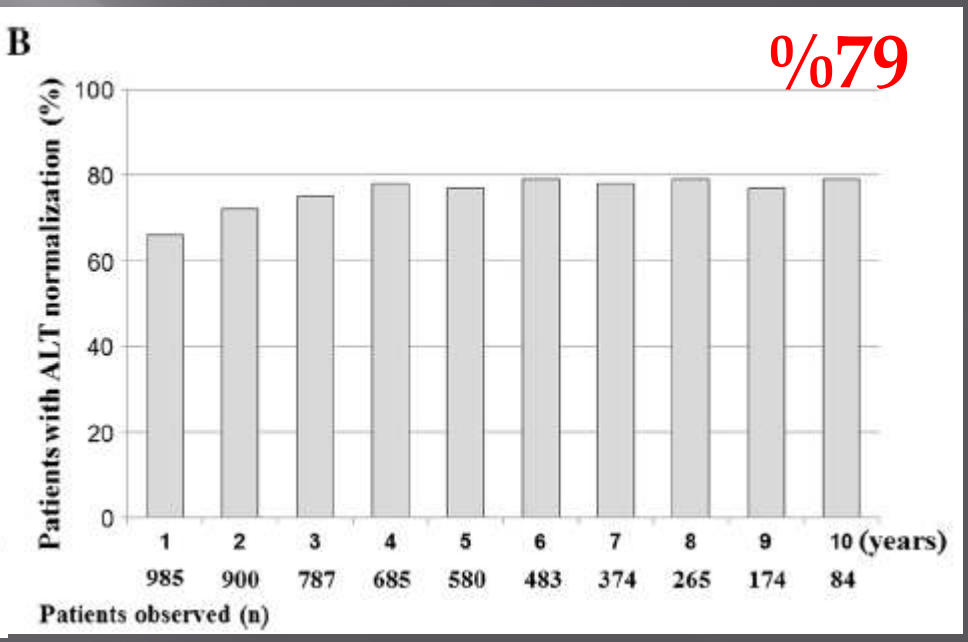
CrossMark

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Long-term outcome of entecavir treatment of nucleos(t)ide analogue-naïve chronic hepatitis B patients in Japan

Fumitaka Suzuki[1,2] · Tetsuya Hosaka[1] · Yoshiyuki Suzuki[1] · Hitomi Sezaki[1] · Norio Akuta[1] · Shunichiro Fujiyama[1] · Yusuke Kawamura[1] · Masahiro Kobayashi[1] · Satoshi Saitoh[1] · Yasuji Arase[1] · Kenji Ikeda[1] · Mariko Kobayashi[3] · Rie Mineta[3] · Yukiko Suzuki[3] · Hiromitsu Kumada[1]





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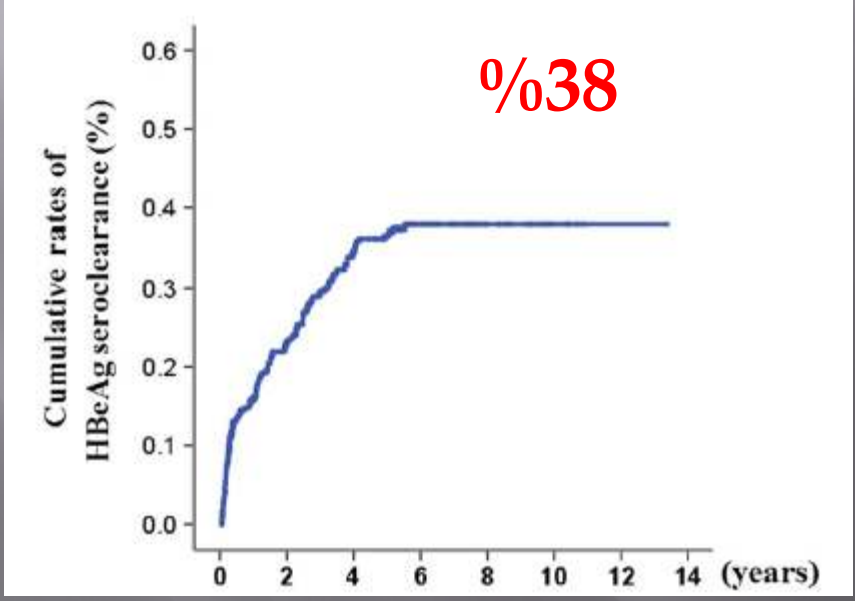

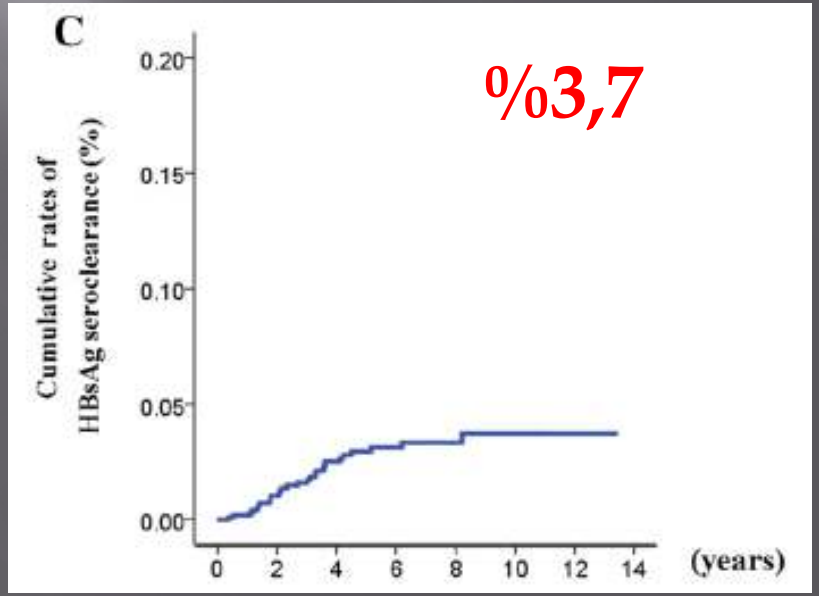

Suzuki F et al. J Gastroenterol 2019;54:182

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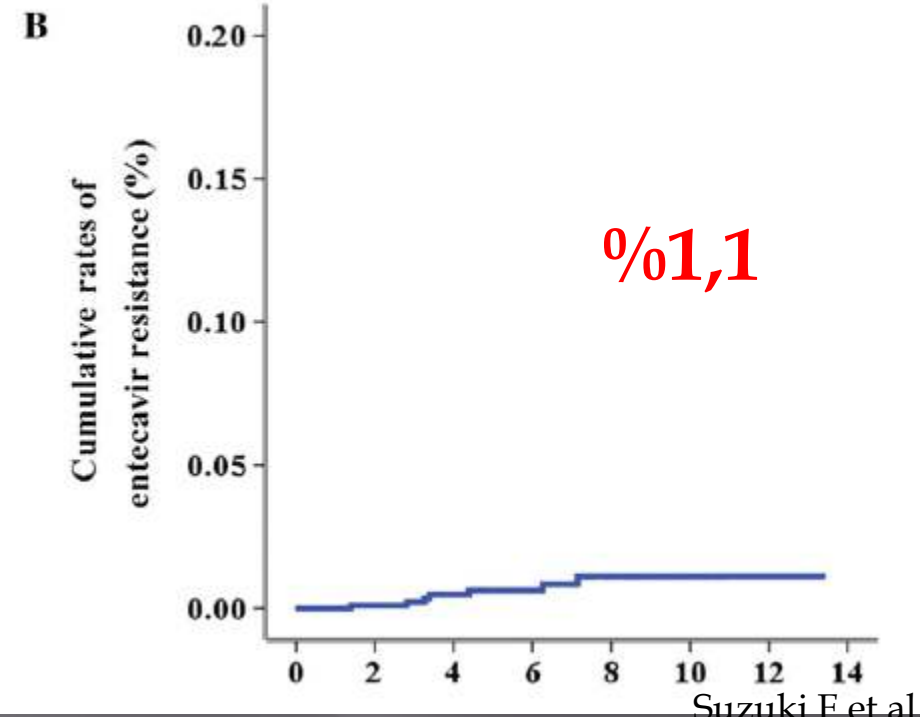

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Suzuki F et al. J Gastroenterol 2019;54:182

VIRAL HEPATITIS

Liver INTERNATIONAL WILEY

Ten-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B virus infection

Patrick Marcellin[1] | David K Wong[2] | William Sievert[3] | Peter Buggisch[4] | Jörg Petersen[4] | Robert Flisiak[5] | Michael Manns[6,7] | Kelly Kaita[8] | Zahari Krastev[9] | Samuel S Lee[10] | Andrea L Cathcart[11] | Gerald Crans[11] | Marjoleine Op den Brouw[12] | Belinda Jump[11] | Anuj Gaggar[11] | John Flaherty[11] | Maria Buti[13]

641 naiv KHB hastası, 10 yıllık TDF etkinliği

%32 HBeAg pozitif,

Marcellin P et al. Liver Int 2019;39:1868

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	HBeAg status		
	HBeAg-negative[b]	HBeAg-positive[c]	All
HBV DNA <69 IU/mL, % (n/N)	100 (118/118)	97.5 (78/80)	99.0 (196/198)
HBV DNA <29 IU/mL, % (n/N)	100 (118/118)	97.5 (78/80)	99.0 (196/198)
ALT normalisation, % (n/N)	83.0 (88/106)	77.9 (60/77)	80.9 (148/183)
HBeAg loss, % (n/N)	–	52.2 (12/23)	52.2 (12/23)
HBeAg seroconversion, % (n/N)	–	27.3 (6/22)	27.3 (6/22)
HBsAg loss, % (n/N)	3.4 (4/117)	4.9 (4/81)	4.0 (8/198)

Marcellin P et al. Liver Int 2019;39:1868

VIRAL HEPATITIS

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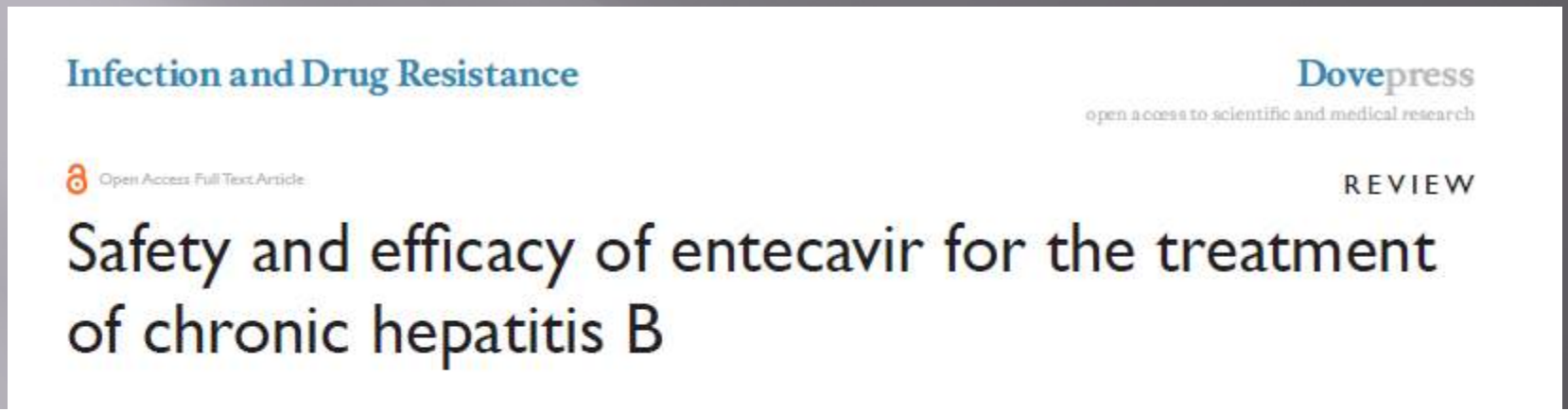
	By initial treatment assignment		
	TDF-TDF n = 389	ADV-TDF n = 196	All n = 585[a]
Patients who discontinued because of AEs, n (%)	10 (2.6)	1 (0.5)	11 (1.9)
Renal impairment, n (%)			
Serum creatinine increase of 0.5 mg/dL from baseline	9 (2.3)	4 (2.0)	13 (2.2)
Creatinine clearance <50 mL/min	4 (1.0)	3 (1.5)	7 (1.2)
Serum phosphate <2 mg/dL	6 (1.5)	4 (2.0)	10 (1.7)

Marcellin P et al. Liver Int 2019;39:1868

Güvenlik



Infection and Drug Resistance

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REVIEW

Safety and efficacy of entecavir for the treatment of chronic hepatitis B

Therapeutic Advances in Gastroenterology *Review*

Efficacy and safety of tenofovir disoproxil fumarate in patients with chronic hepatitis B

Andrés Duarte-Rojo and E. Jenny Heathcote

Ther Adv Gastroenterol
(2010) 3(2) 107–119
DOI: 10.1177/1756283X09354562
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http://www.sagepub.co.uk/

Nükleosid/nükleotid analogları ile uzun süreli tedavinin yan etkiler yönünden yönetilebilir olduğu kabul edilmektedir.

Duarte Rojo A et al. Ther Adv Gastroenterol 2010;3:107

Osborn M. Infection and Drug Resistance 2011;4:55

Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/jgh.12213

REVIEW

Long-term therapy for chronic hepatitis B: Hepatitis B virus DNA suppression leading to cirrhosis reversal

Patrick Marcellin and Tarik Asselah

Service d'Hépatologie, Hôpital Beaujon, University of Paris, Clichy, France

Gerek RCT gerekse de RL çalışmaları, potent NA ile KHB olgularında viral replikasyonun etkin ve güvenli bir biçimde uzun süreli baskılanabileceğini ortaya koymuştur.

Marcellin P et al. J Gastroenterol Hepatol 2013;28:912

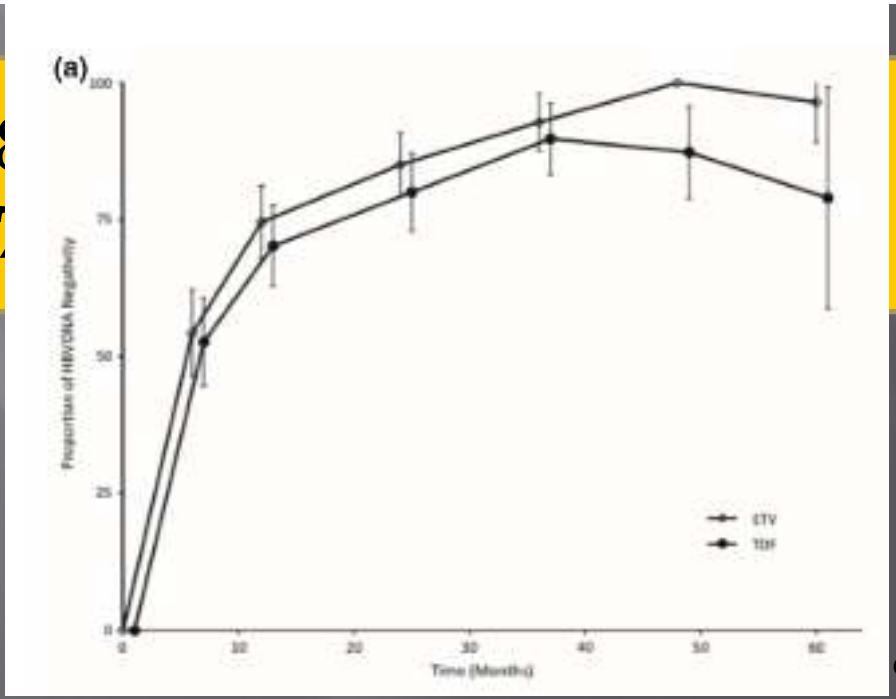
ETV vs TDF

JOURNAL OF VIRAL HEPATITIS
JVH
Journal of Viral Hepatitis, 2015, 22, 504–510 doi:10.1111/jvh.12358

Long-term entecavir or tenofovir disoproxil fumarate therapy in treatment-naïve chronic hepatitis B patients in the real-world setting

R. Idilman,[1] F. Gunsar,[2] M. Koruk,[3] O. Keskin,[1] C. E. Meral,[2] M. Gulsen,[2] A. H. Elhan,[4] U. S. Akarca[2] and C. Yurdaydin[1] [1]*Department of Gastroenterology, Ankara University School of Medicine, Ankara, Turkey;* [2]*Department of Gastroenterolog* *Gaziantep University Faculty of Medicine, Gaziantep, Turkey;*

ETV (n=18
TDF (n=17

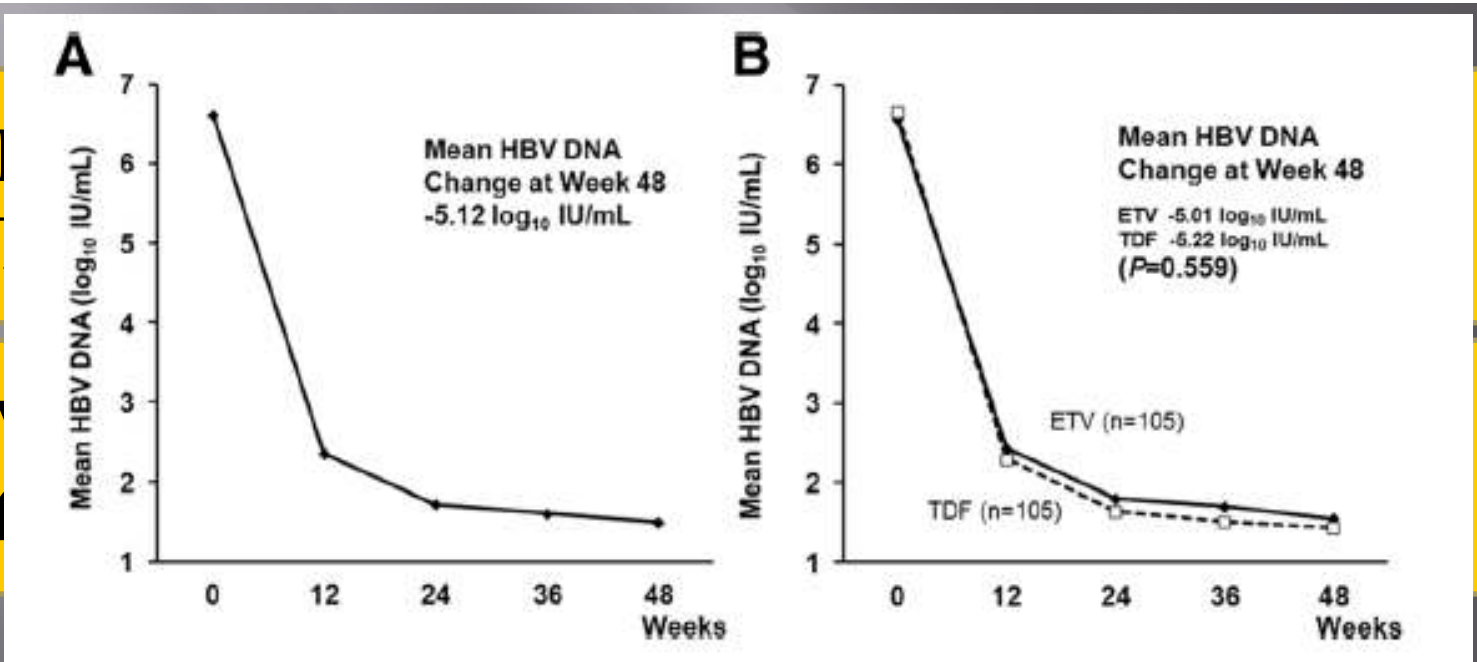


et al. J Viral Hep 2015;22:504

RESEARCH ARTICLE Open Access

Comparison of the long-term efficacy between entecavir and tenofovir in treatment- naïve chronic hepatitis B patients

Ji Won Park[1,2], Kyeong Min Kwak[3,4], Sung Eun Kim[1], Myoung Kuk Jang[5], Ki Tae Suk[6], Dong Joon Kim[6], Sang Hoon Park[7], Myung Seok Lee[7], Hyoung Su Kim[5*] and Choong Kee Park[1]



Park JW et al. BMC Gastroenterol 2017;17:39

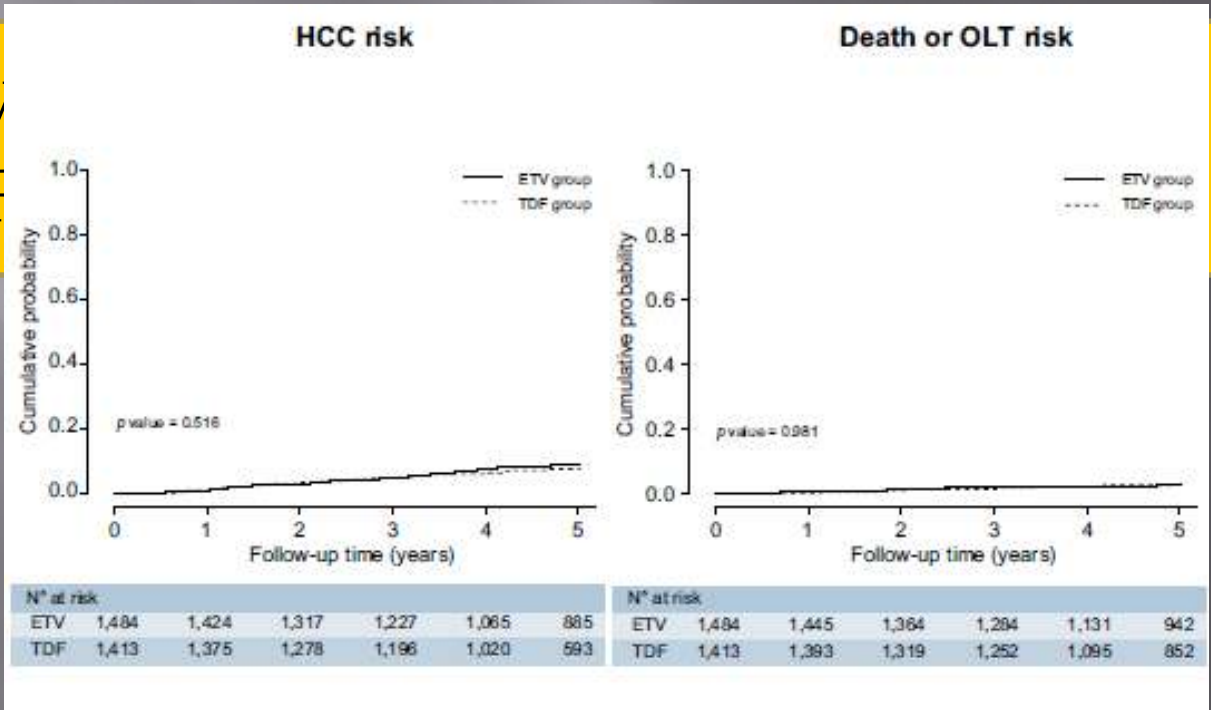
Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

A multicenter study of entecavir *vs.* tenofovir on prognosis of treatment-naïve chronic hepatitis B in South Korea

Seung Up Kim[1,2,3,†], Yeon Seok Seo[4,†], Han Ah Lee[4], Mi Na Kim[5], Yu Rim Lee[6], Hye Won Lee[1,3], Jun Yong Park[1,2,3], Do Young Kim[1,2,3], Sang Hoon Ahn[1,2,3], Kwang-Hyub Han[1,2,3], Seong Gyu Hwang[5], Kyu Sung Rim[5], Soon Ho Um[4], Won Young Tak[6], Young Oh Kweon[6], Beom Kyung Kim[1,2,3,*], Soo Young Park[6,*]

ETV
TDF



Kim SU et al. J Hepatol 2019;71:456

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PLOS ONE

Comparison of Efficacy and Safety of Tenofovir and Entecavir in Chronic Hepatitis B Virus Infection: A Systematic Review and Meta-Analysis

Weixia Ke, Li Liu, Chi Zhang, Xiaohua Ye, Yanhui Gao, Shudong Zhou, Yi Yang*

Department of Epidemiology and Biostatistics and Guangdong Key Lab of Molecular Epidemiology, School of Public Health, Guangdong Pharmaceutical University, Guangzhou, Guangdong, China

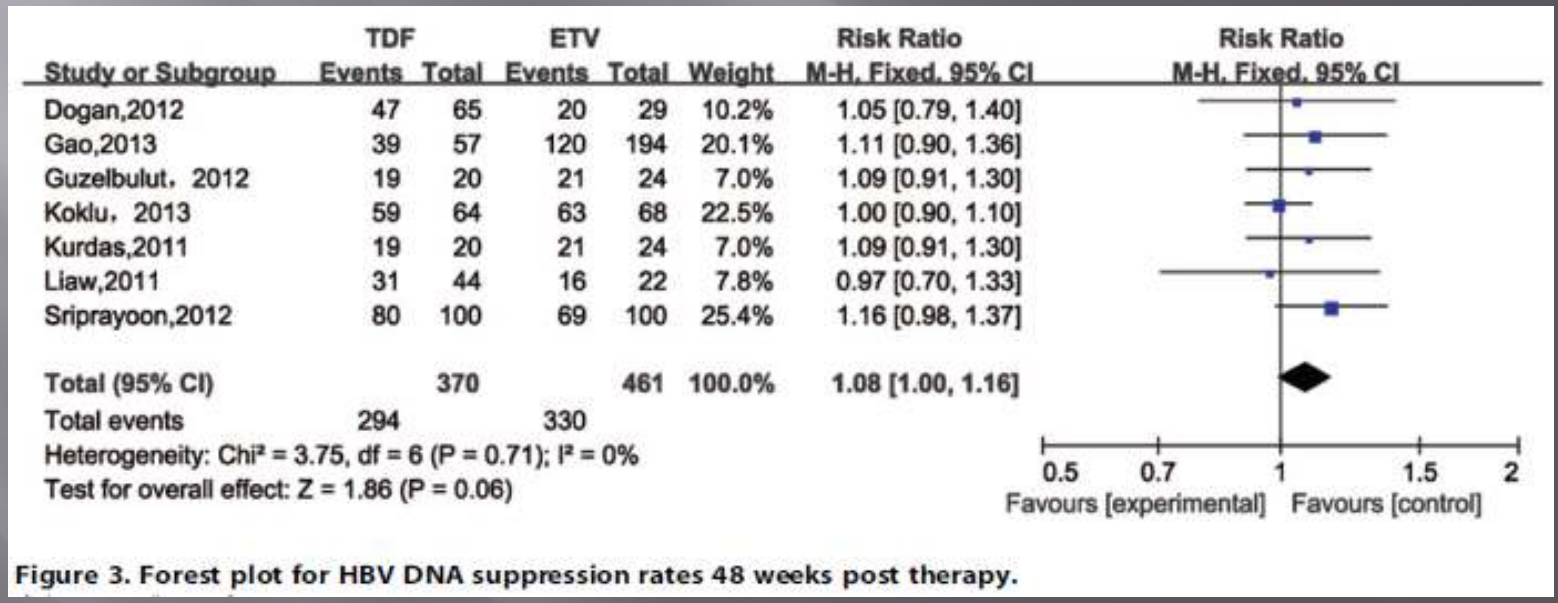

Figure 3. Forest plot for HBV DNA suppression rates 48 weeks post therapy.

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PLOS ONE

Comparison of Efficacy and Safety of Tenofovir and Entecavir in Chronic Hepatitis B Virus Infection: A Systematic Review and Meta-Analysis

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Department of Epidemiology and Biostatistics and Guangdong Key Lab of Molecular Epidemiology, School of Public Health, Guangdong Pharmaceutical University, Guangzhou, Guangdong, China

Figure 5. Forest plot for ALT normalization rates 48 weeks post therapy.

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PLOS ONE

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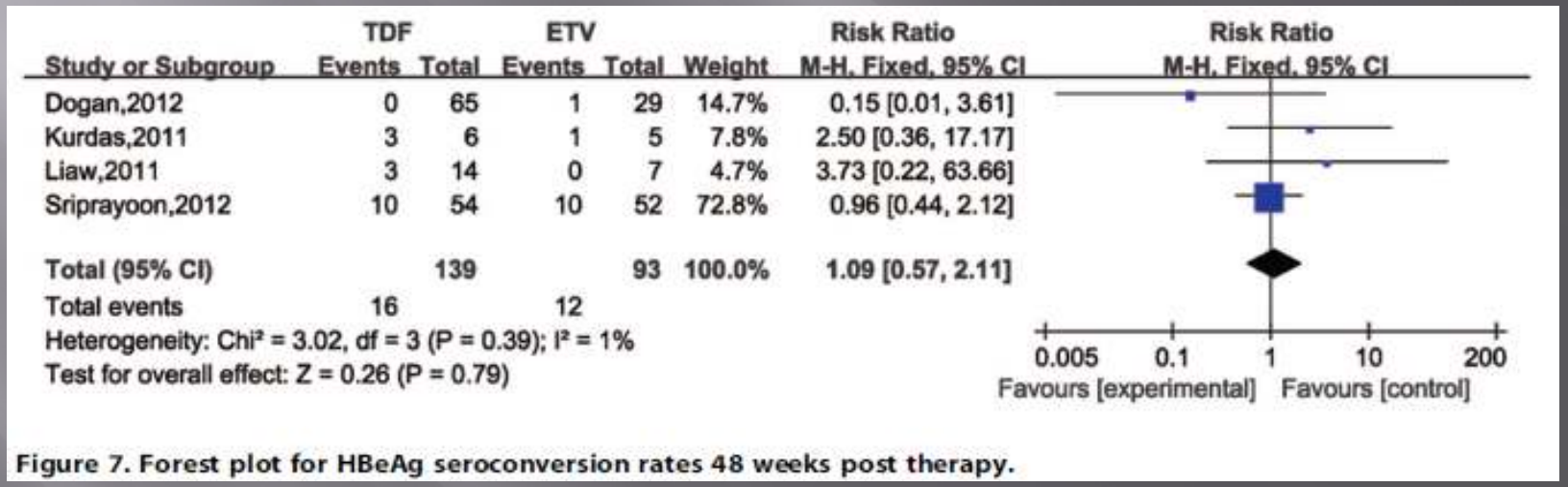

Figure 7. Forest plot for HBeAg seroconversion rates 48 weeks post therapy.

OPEN ACCESS Freely available online

PLOS ONE

Comparison of Efficacy and Safety of Tenofovir and Entecavir in Chronic Hepatitis B Virus Infection: A Systematic Review and Meta-Analysis

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Department of Epidemiology and Biostatistics and Guangdong Key Lab of Molecular Epidemiology, School of Public Health, Guangdong Pharmaceutical University, Guangzhou, Guangdong, China

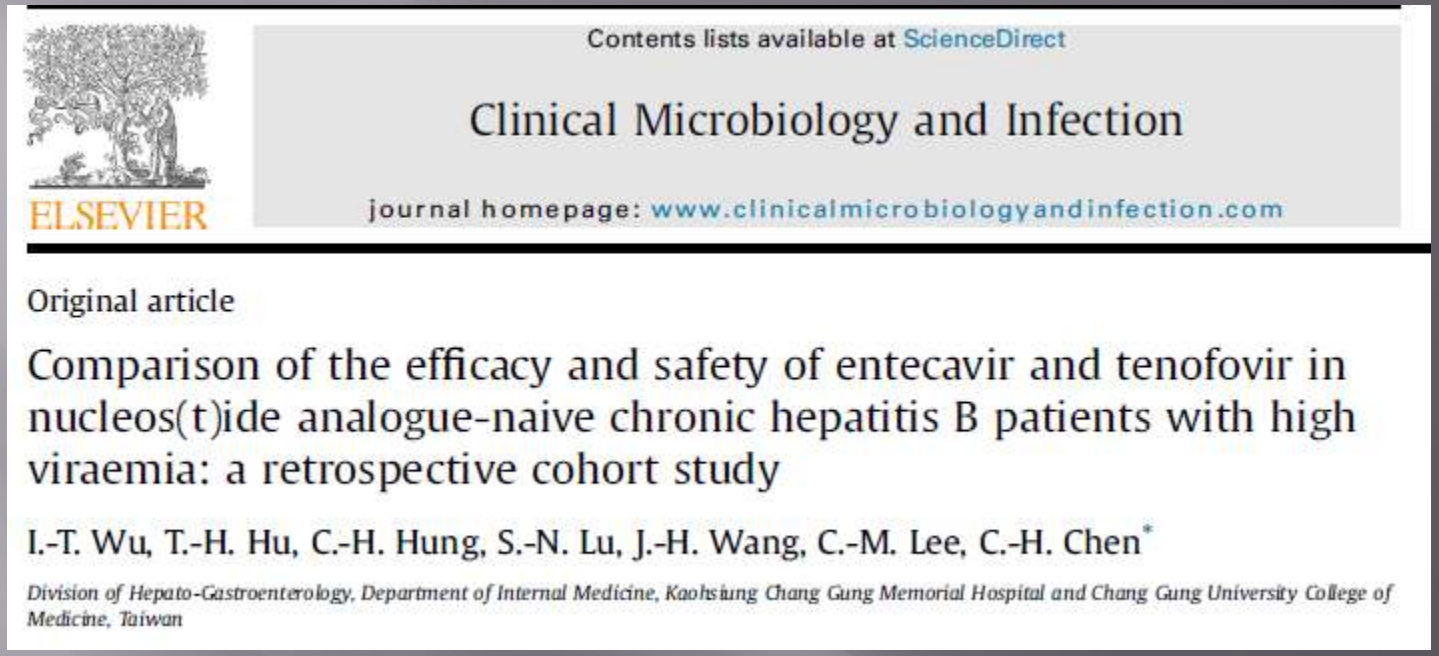
HBV DNA baskılanması, HBeAg serokonversiyonu, ALT normalizasyonu açısından ETV ile TDF benzer etkinliğe sahip,

ETV ve TDF ile uzun dönemde

>%90 HBV DNA baskılanması

~%30 eAg serokonversiyonu

Ke W et al. PLoS ONE 9(6): e98865



Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

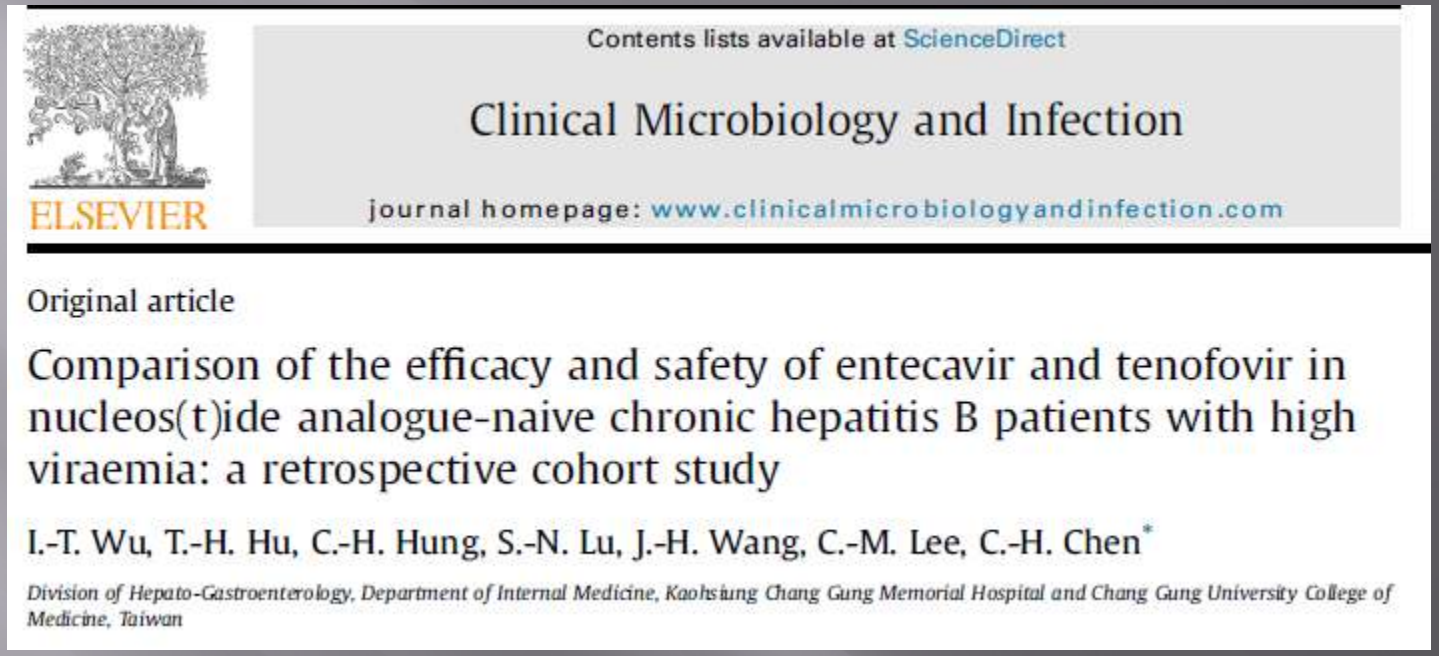
Comparison of the efficacy and safety of entecavir and tenofovir in nucleos(t)ide analogue-naive chronic hepatitis B patients with high viraemia: a retrospective cohort study

I.-T. Wu, T.-H. Hu, C.-H. Hung, S.-N. Lu, J.-H. Wang, C.-M. Lee, C.-H. Chen*

Division of Hepato-Gastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taiwan

419 naiv KHB hastası, HBV DNA>10^6 IU/ml
ETV (n=313) vs TDF (n=106)

Wu IT et al. Clin Microbiol Infect 2017;23:464



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Division of Hepato-Gastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taiwan

3 yıllık kümülatif virolojik yanıt TDF vs ETV

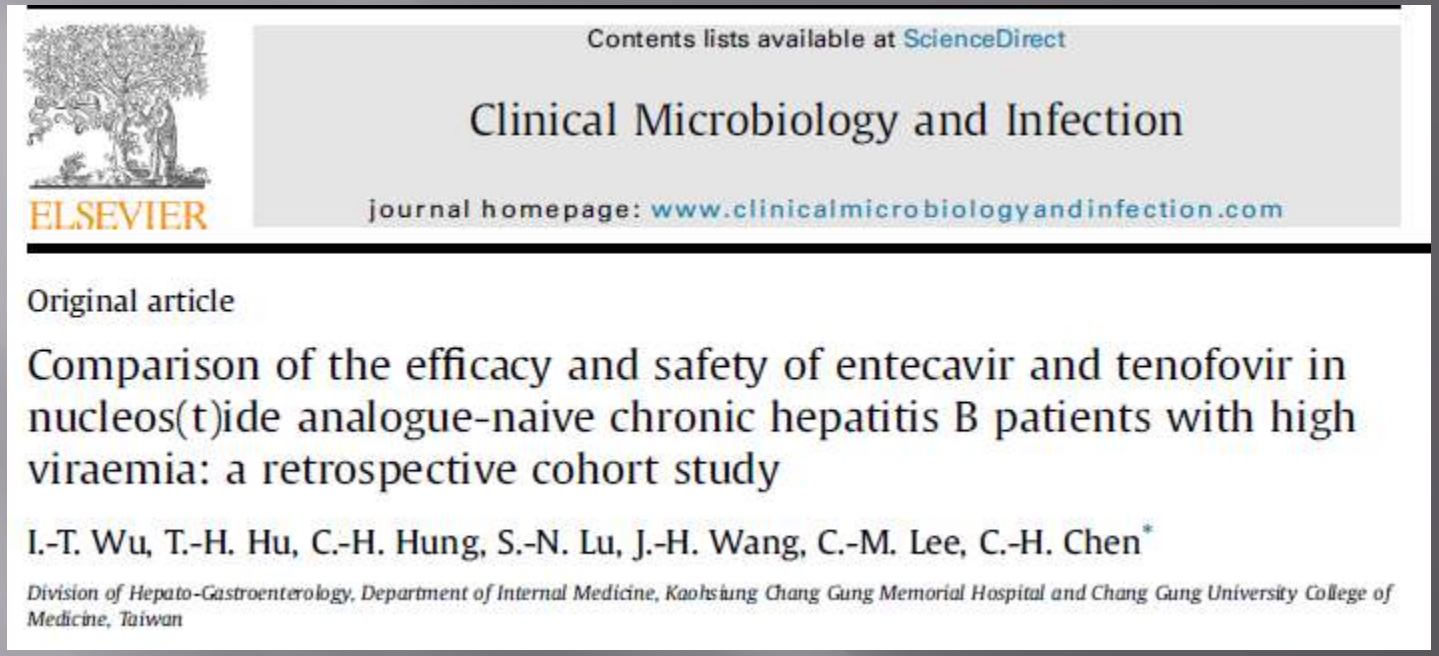
HBeAg pozitif %96,4 vs %92,1 (p=0,26)

HBeAg negatif %98,2 vs %98,6 (p=0,64)

HBeAg kaybı

%53,8 vs %47,4 (p=0,89)

Wu IT et al. Clin Microbiol Infect 2017;23:464



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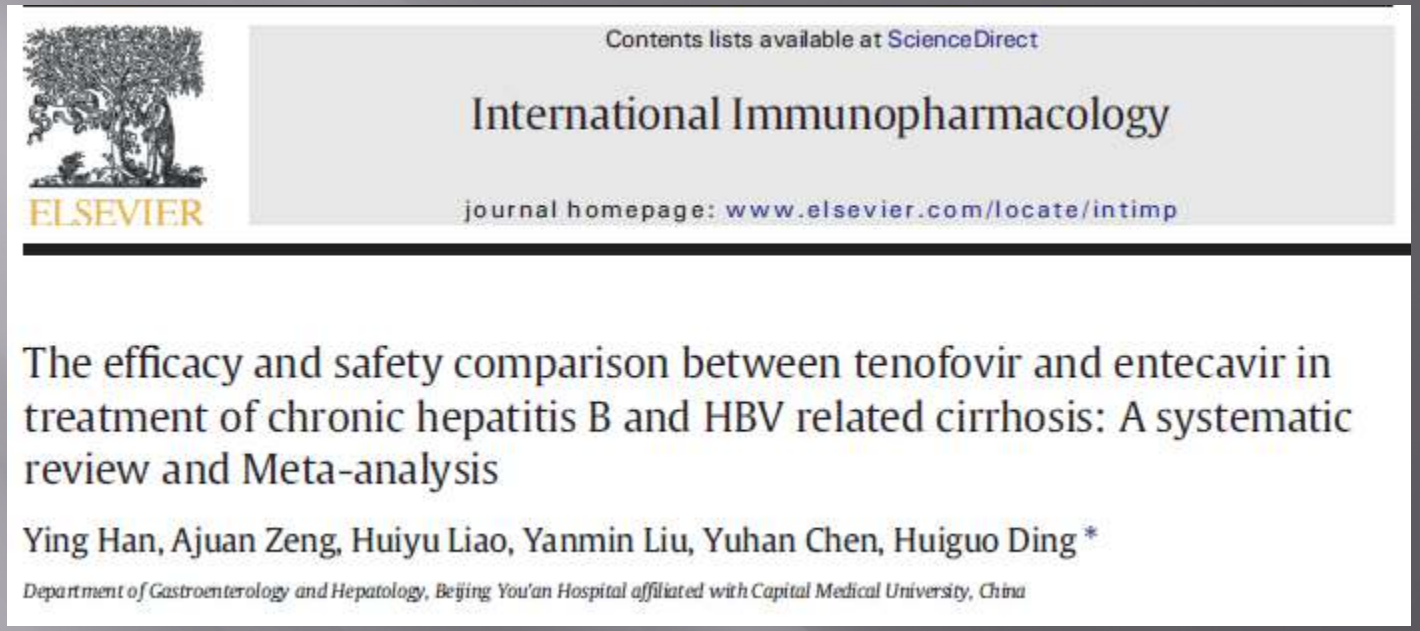
Division of Hepato-Gastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taiwan

Yüksek viral yükü olan KHB hastalarında ETV ve TDF benzer etkinliğe sahiptir…

Wu IT et al. Clin Microbiol Infect 2017;23:464


Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

The efficacy and safety comparison between tenofovir and entecavir in treatment of chronic hepatitis B and HBV related cirrhosis: A systematic review and Meta-analysis

Ying Han, Ajuan Zeng, Huiyu Liao, Yanmin Liu, Yuhan Chen, Huiguo Ding *

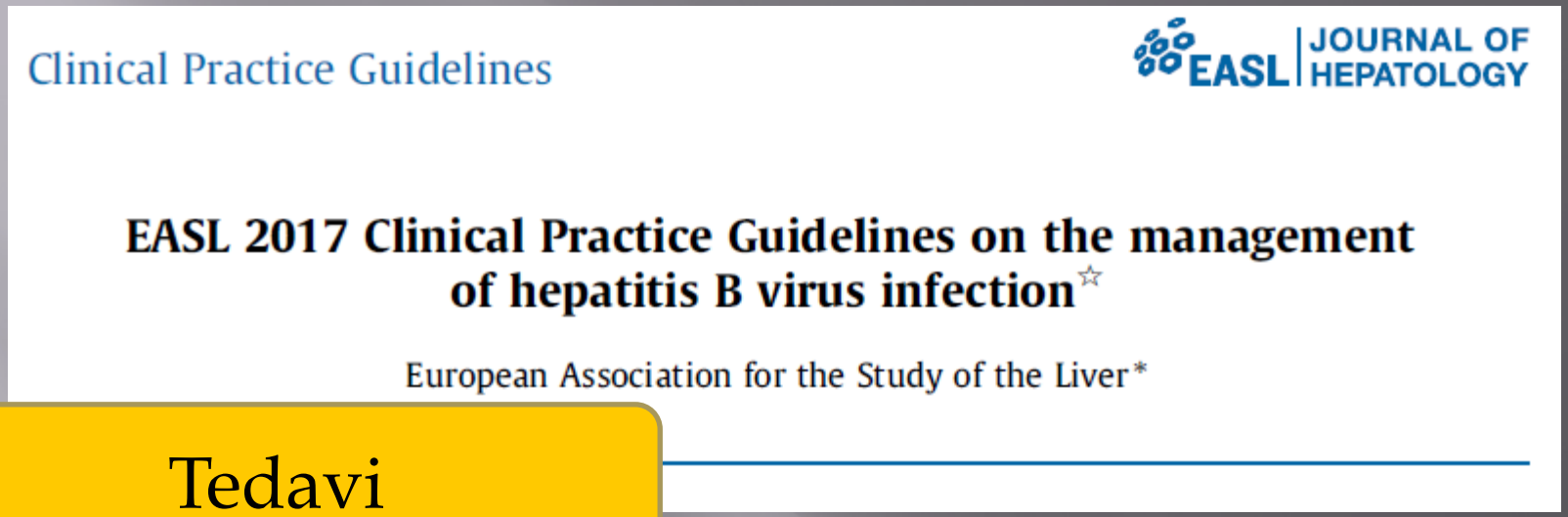
Department of Gastroenterology and Hepatology, Beijing You'an Hospital affiliated with Capital Medical University, China

20 çalışma, metaanaliz

Sirotik KHB hastalarında ETV ve TDF etkinlikleri arasında fark yoktur.

Han Y et al. Int Immunopharmacol 2017;42:168

Histolojik düzelme



Tedavi

Viral baskılanma

Biyokimyasal iyileşme

Histolojik düzelme

Komplikasyonlar ↓

EASL CPG. J Hepatol 2017;67:370

Journal of Hepatology 38 (2003) S38–S53

Journal of Hepatology

www.elsevier.com/locate/jhep

Liver fibrosis – from bench to bedside

Scott L. Friedman*

Division of Liver Diseases, P.O. Box 1123, Mount Sinai School of Medicine, 1425 Madison Ave. Room 1170F, New York, NY 10029, USA

Kronik hepatit seyrinde görülen hepatik fibrozis, süregiden karaciğer hasarına karşı gelişen tipik bir yara iyileşmesi sürecidir.

Friedmann SL. J Hepatol 2003;38:S38

ELSEVIER

Journal of Hepatology 38 (2003) S38–S53

Journal of Hepatology

www.elsevier.com/locate/jhep

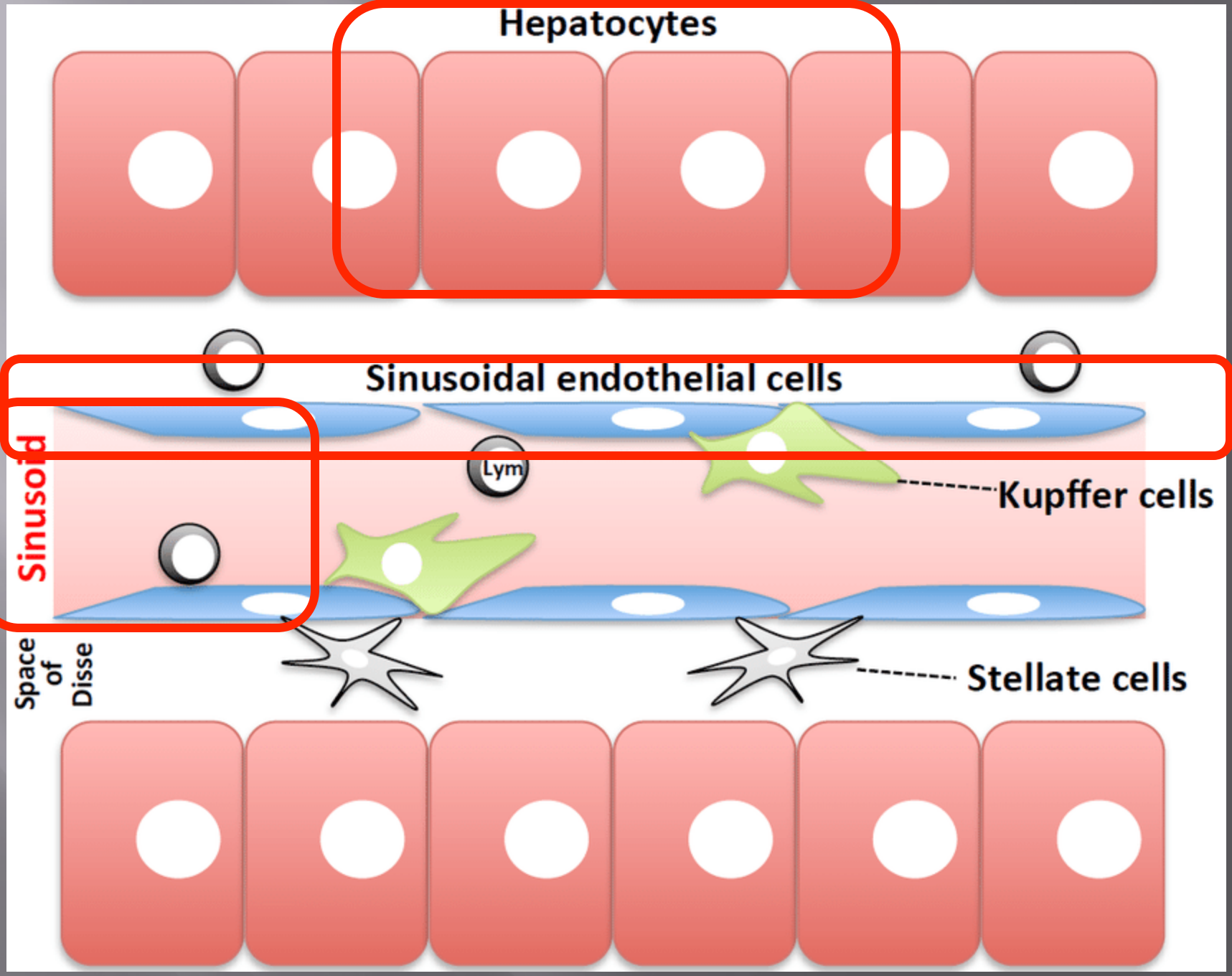
Liver fibrosis – from bench to bedside

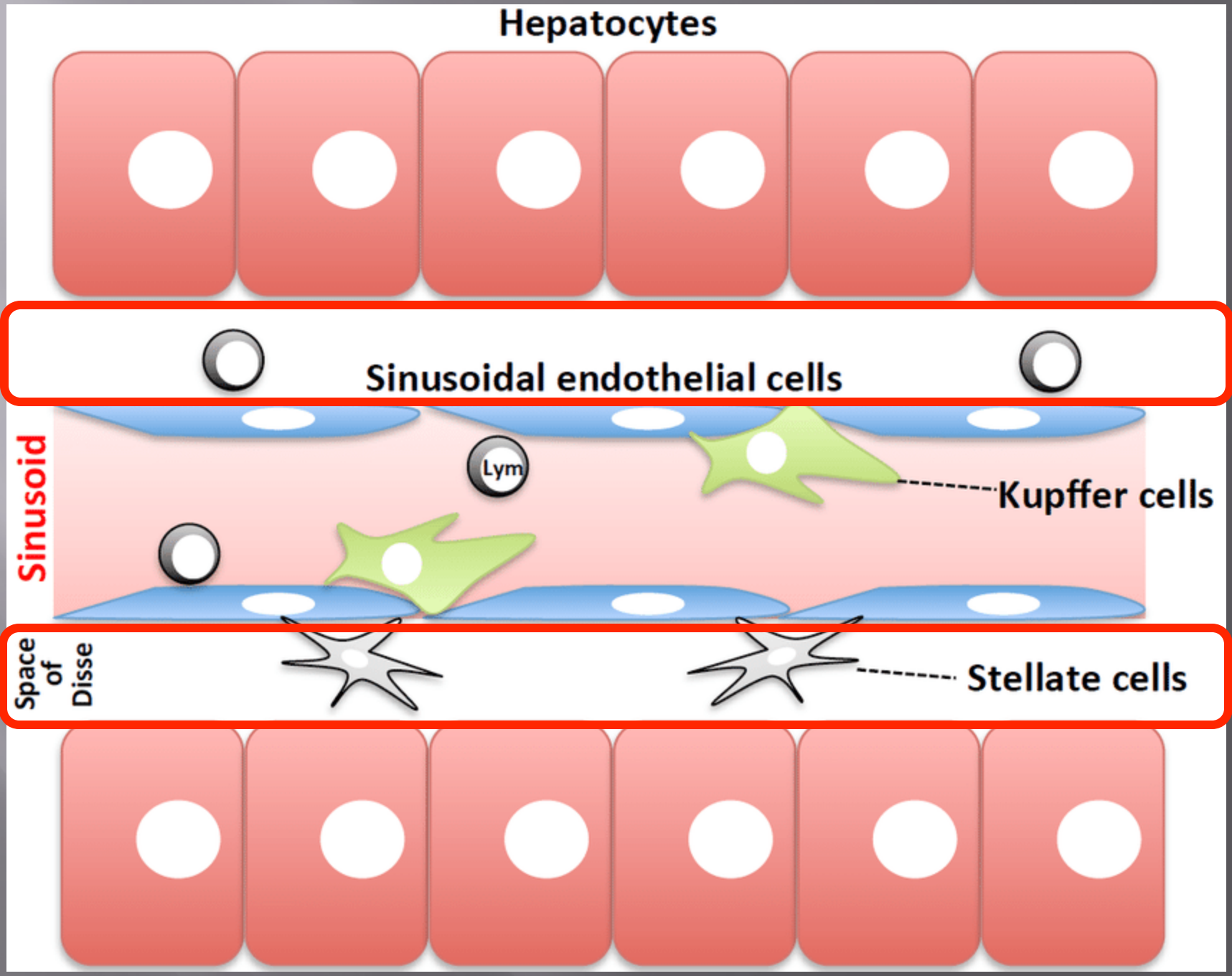
Scott L. Friedman*

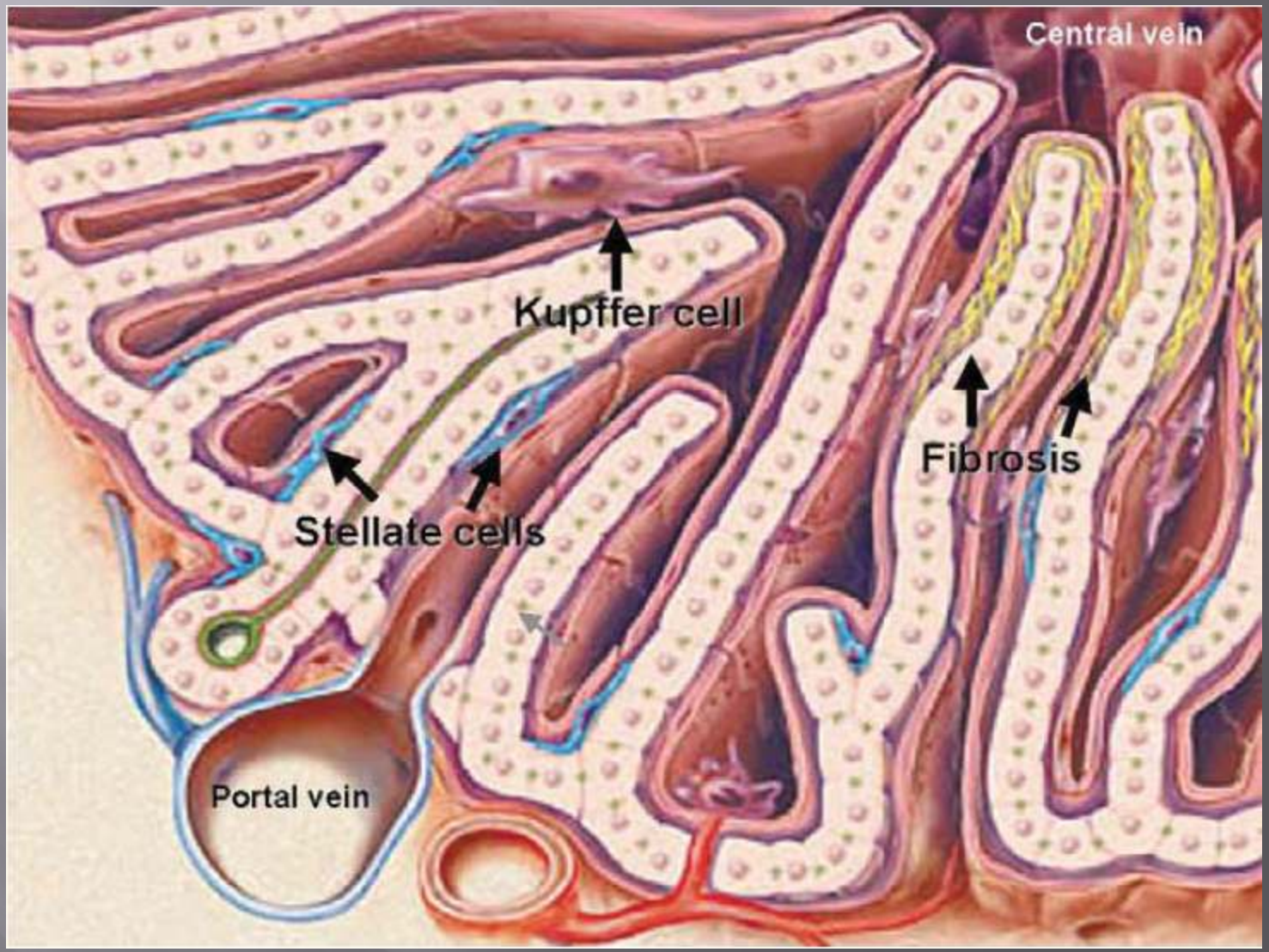
Division of Liver Diseases, P.O. Box 1123, Mount Sinai School of Medicine, 1425 Madison Ave. Room 1170F, New York, NY 10029, USA

Hepatik parankimal fibrozisin son dönem sonucu olarak nodül formasyonu ve hepatik fonksiyonlardaki bozulma siroz olarak tanımlanır.

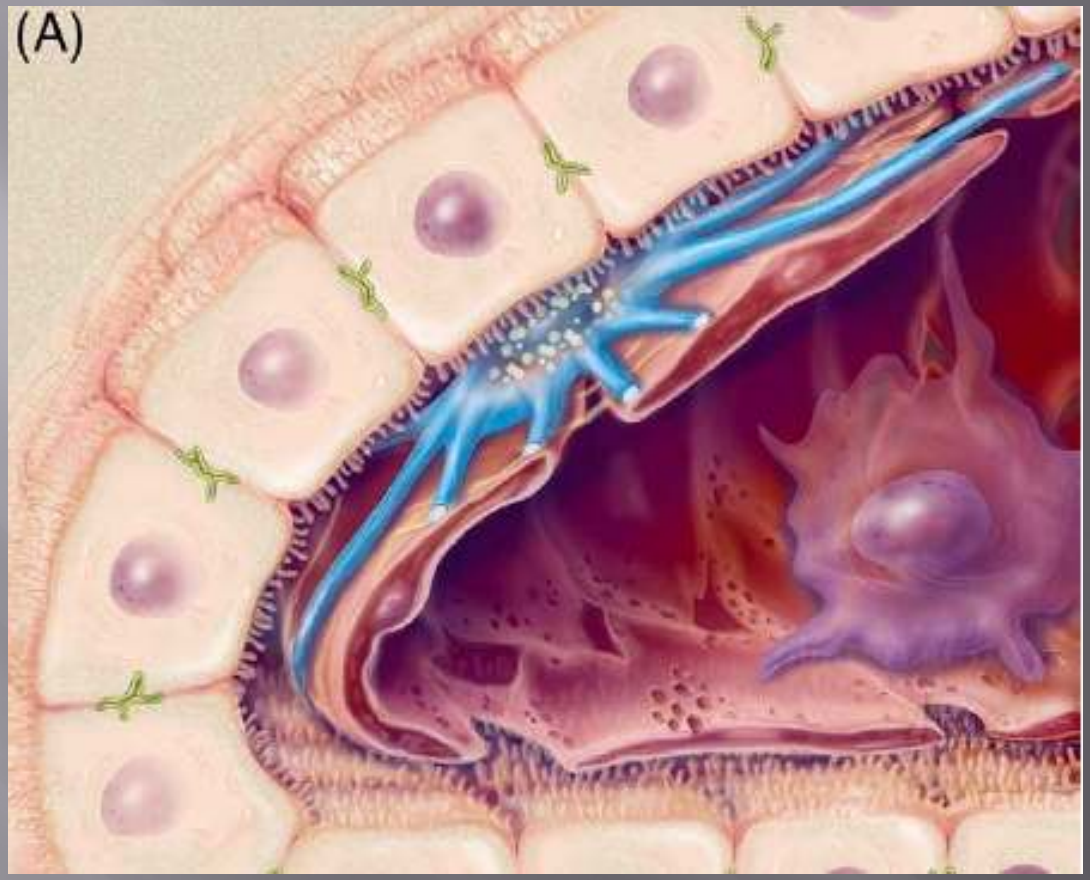
Friedmann SL. J Hepatol 2003;38:S38


Hepatocytes
Sinusoidal endothelial cells
Sinusoid
Lym
Kupffer cells
Space of Disse
Stellate cells


Hepatocytes
Sinusoidal endothelial cells
Sinusoid
Lym
Kupffer cells
Space of Disse
Stellate cells

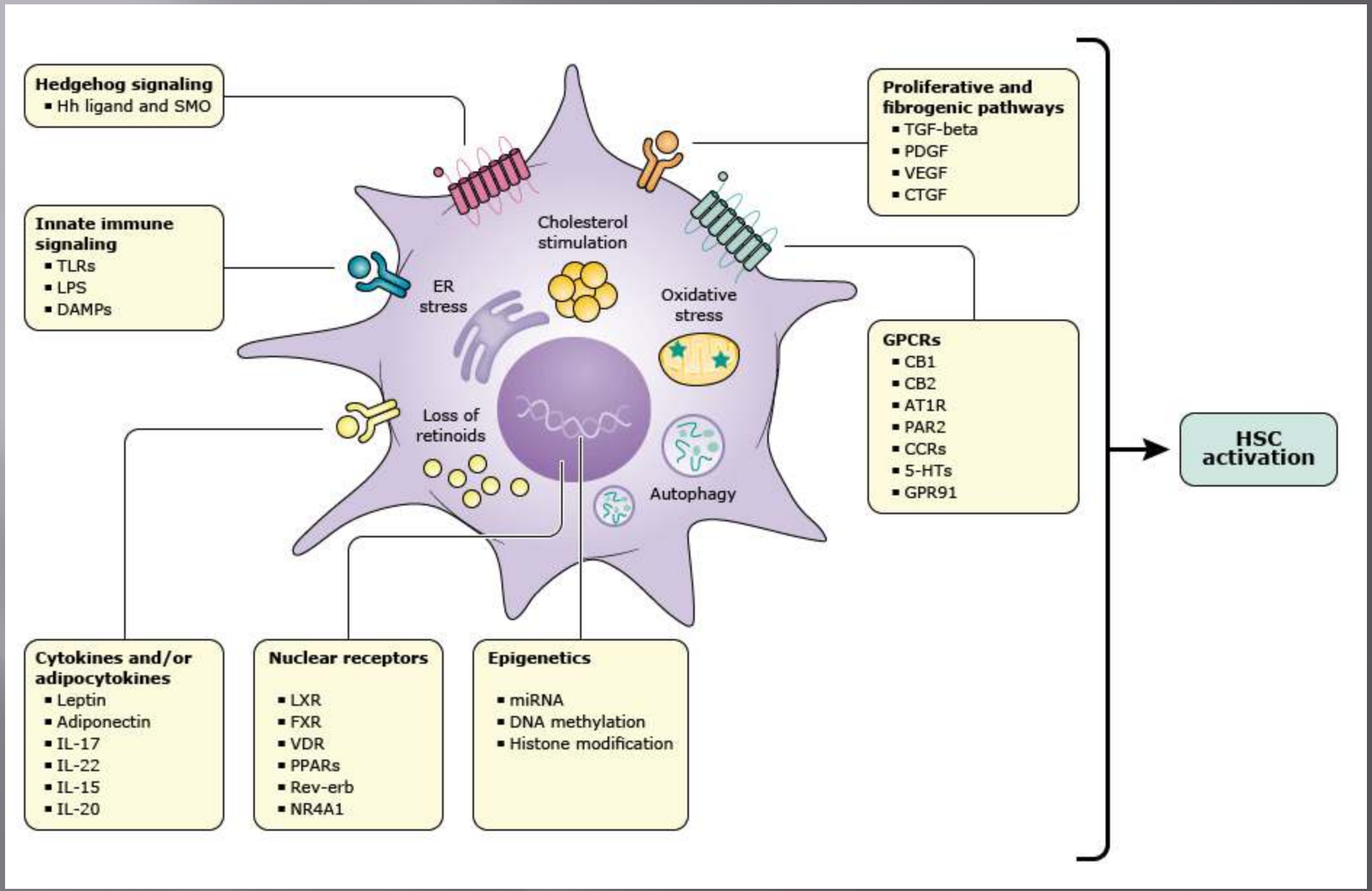


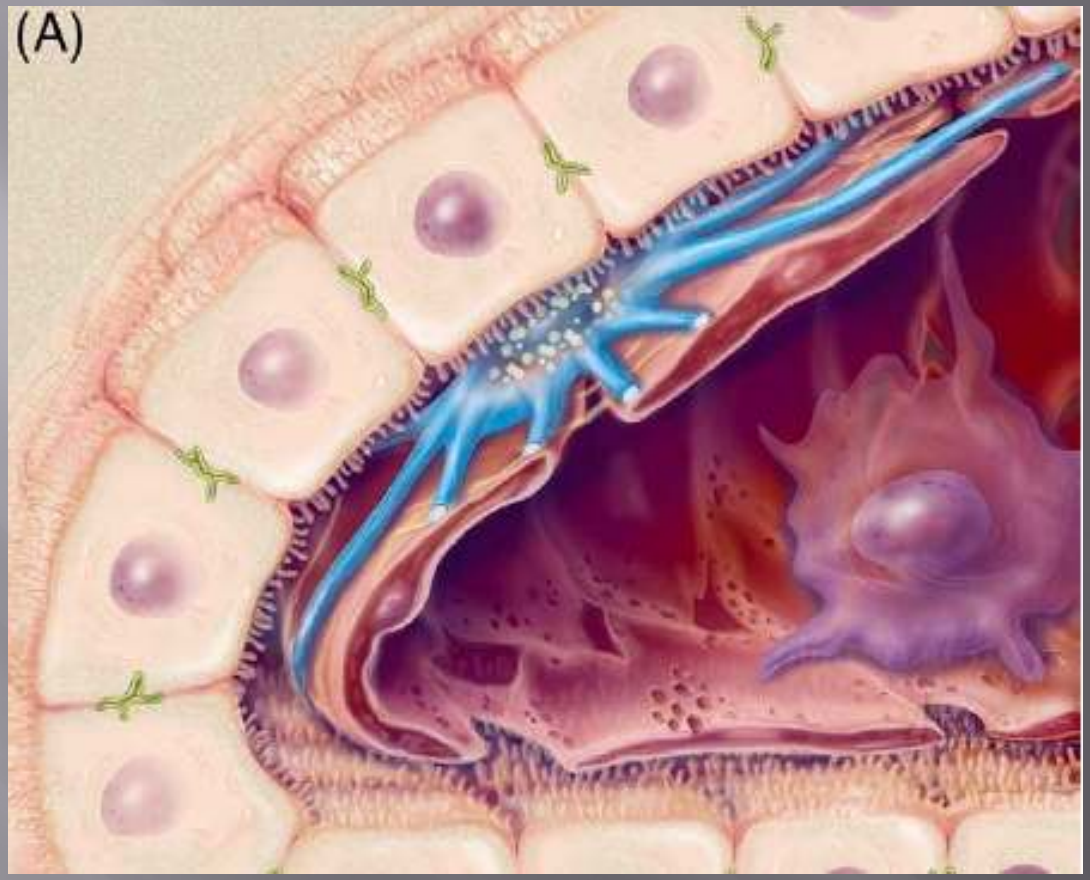
Friedmann SL. J Hepatol 2003;38:S38



Subendotelyal boşlukta, düşük dansiteli, çözünenlerin transportuna izin veren bir ekstraselüler matriks bulunur.

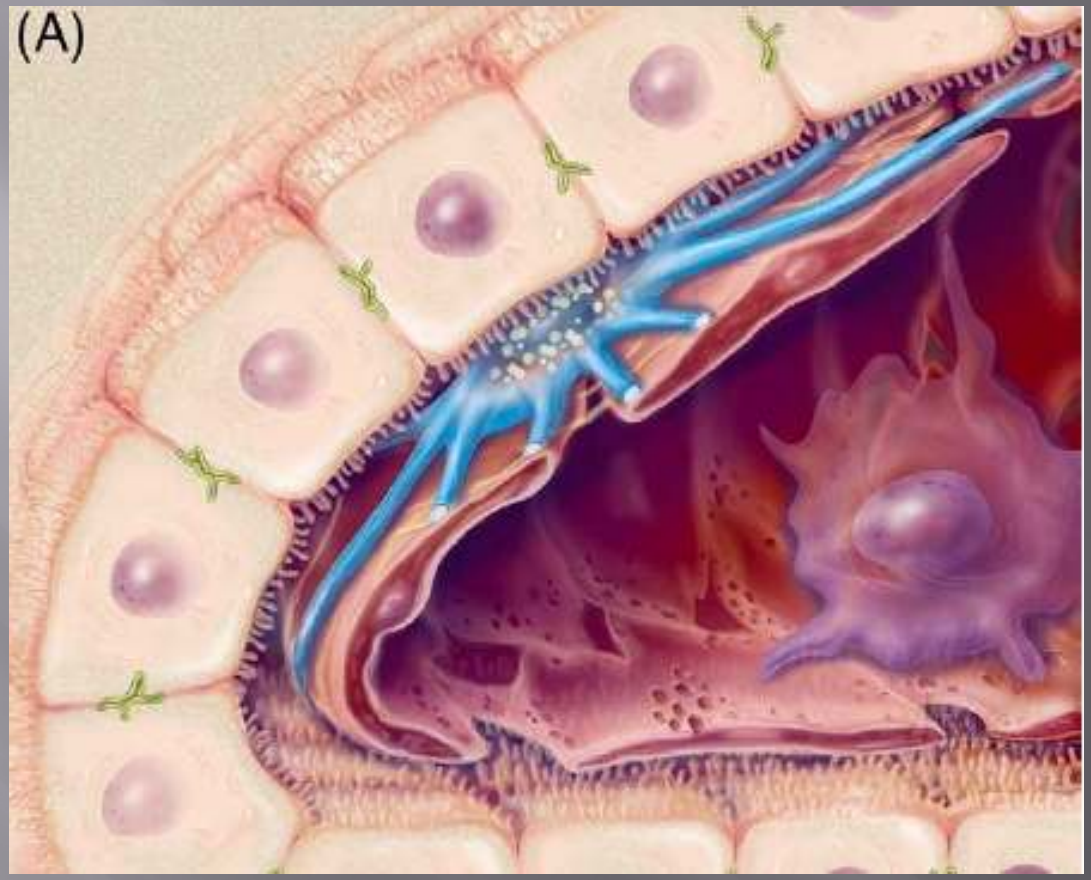
Friedmann SL. J Hepatol 2003;38:S38


Hedgehog signaling
▪ Hh ligand and SMO
Innate immune signaling
▪ TLRs
▪ LPS
▪ DAMPs
Cytokines and/or adipocytokines
▪ Leptin
▪ Adiponectin
▪ IL-17
▪ IL-22
▪ IL-15
▪ IL-20
Nuclear receptors
▪ LXR
▪ FXR
▪ VDR
▪ PPARs
▪ Rev-erb
▪ NR4A1
Epigenetics
▪ miRNA
▪ DNA methylation
▪ Histone modification
Proliferative and fibrogenic pathways
▪ TGF-beta
▪ PDGF
▪ VEGF
▪ CTGF
GPCRs
▪ CB1
▪ CB2
▪ AT1R
▪ PAR2
▪ CCRs
▪ 5-HTs
▪ GPR91
Cholesterol stimulation
ER stress
Oxidative stress
Loss of retinoids
Autophagy
HSC activation



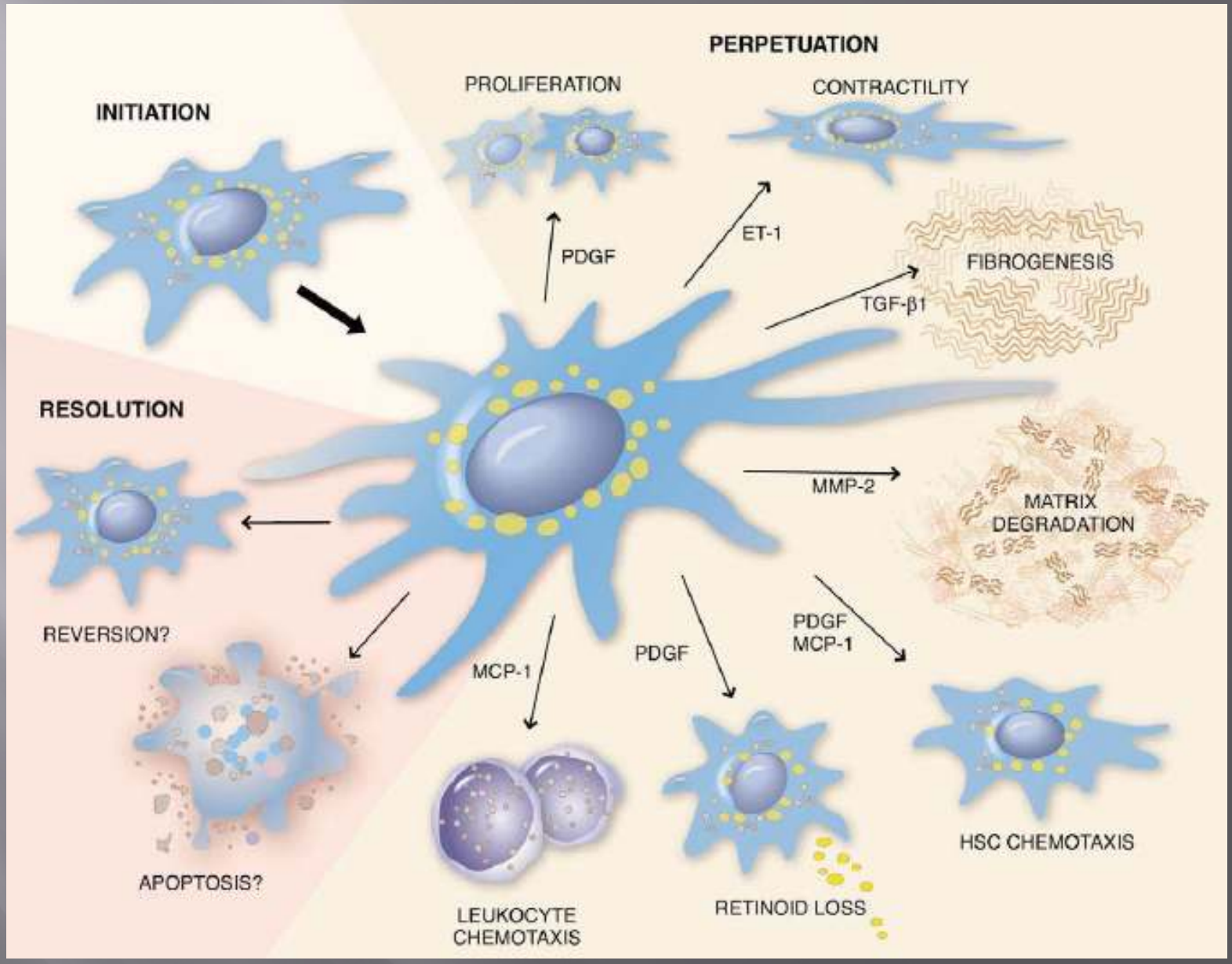
"Aktivasyon",
Stellat hücrelerin proliferatif, fibrojenik, kontraktil myofibroblastlara dönüşmesidir.

Friedmann SL. J Hepatol 2003;38:S38

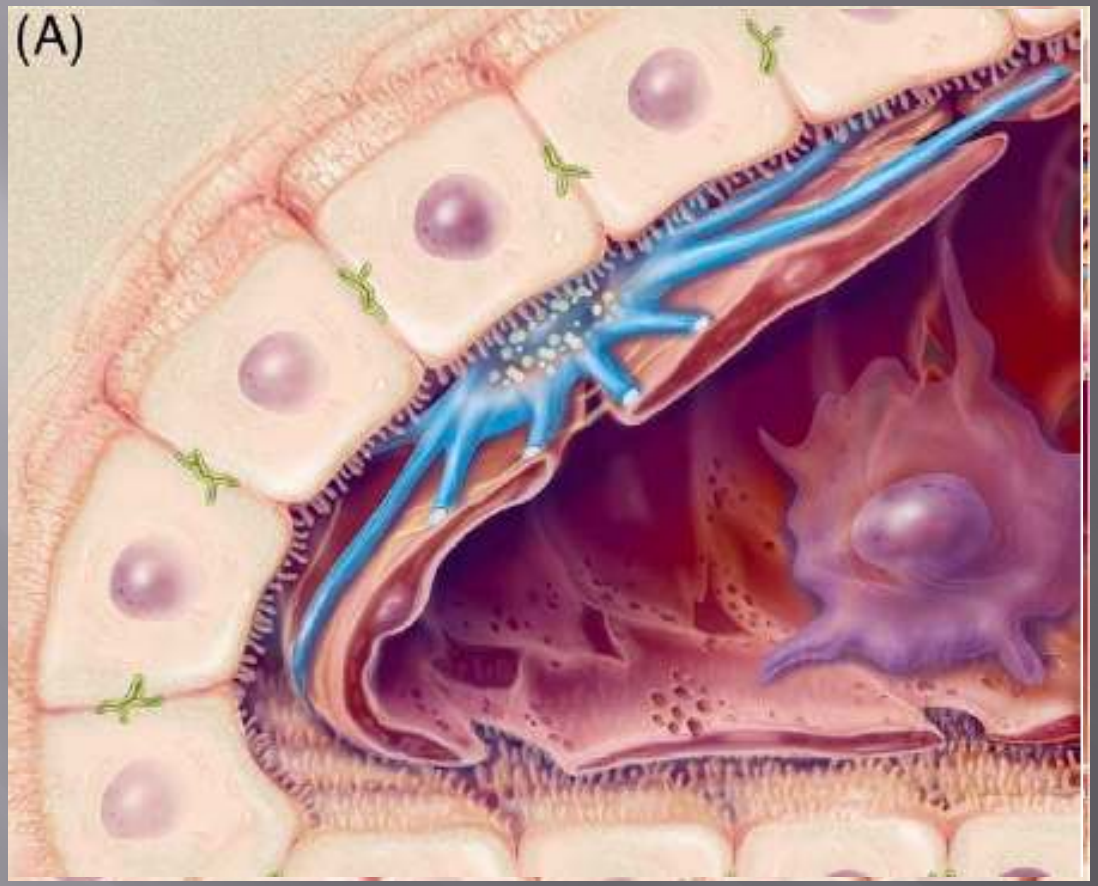


Stellat hücreler karaciğerdeki yara iyileşme sürecini yöneten mediatörlerin, matriks moleküllerinin, proteazların esas kaynağı olan “fibrojenik” hücrelerdir.

Friedmann SL. J Hepatol 2003;38:S38



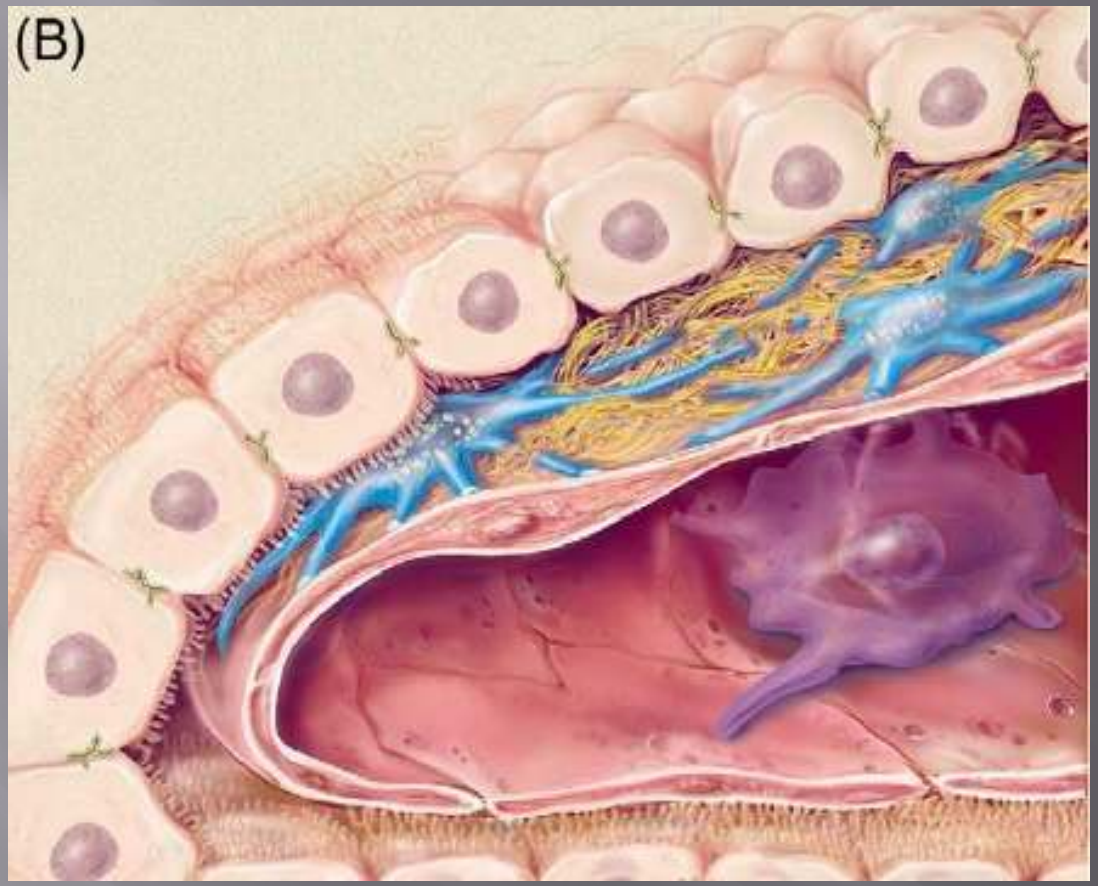
Friedmann SL. J Hepatol 2003;38:S38



Stellat hücre aktivasyonu ve proliferasyonu

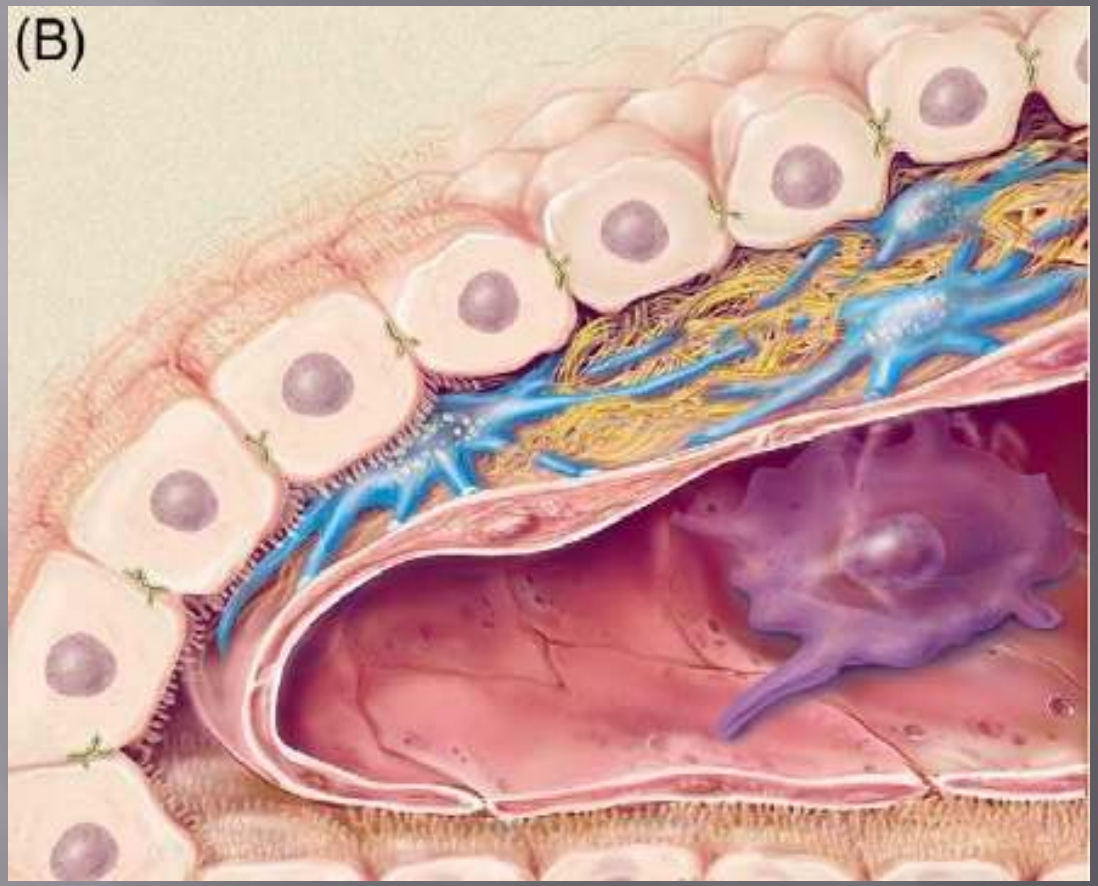
Fibriler matriks birikimi

Friedmann SL. J Hepatol 2003;38:S38



Ekstraselüler matriks bileşenleri,
kollajen tip I, kollajen tip III,
proteoglikanlar, glikoproteinler,
glikozaminoglikanlar

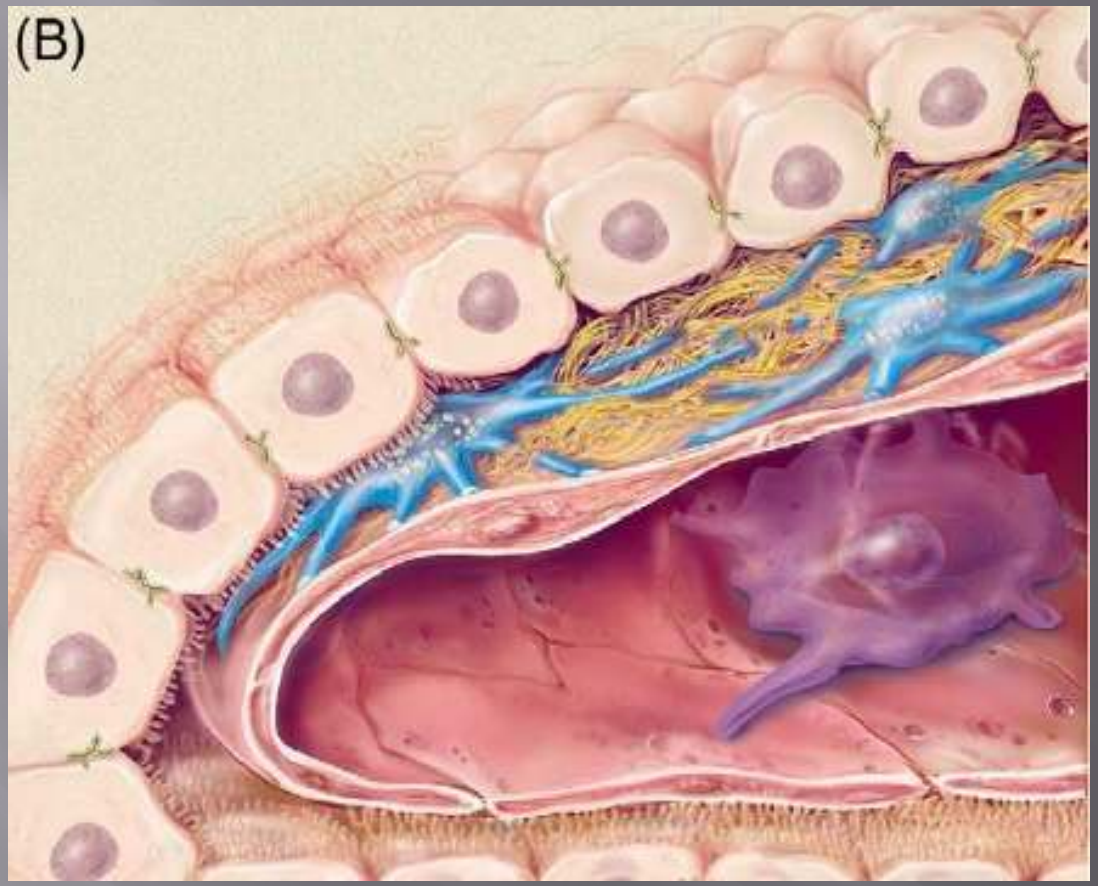
Friedmann SL. J Hepatol 2003;38:S38



Hepatosit mikrovillus kaybı

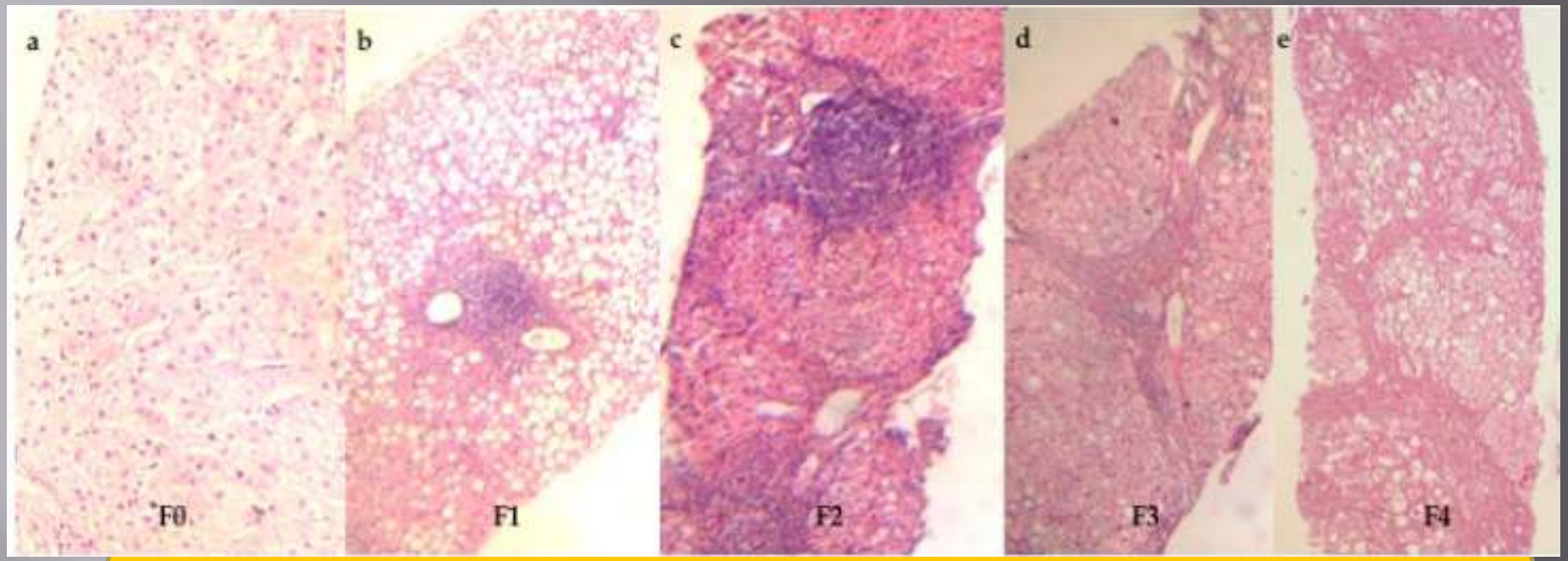
Endotelyal fenestraların kapanması

Friedmann SL. J Hepatol 2003;38:S38



Aktive olan stellat hücrelerle ilişkili olarak kontraktilitenin artması, karaciğerde portal direnci artırır ve portal kan akımını bozar.

Friedmann SL. J Hepatol 2003;38:S38



Histolojik olarak kronik hepatit interface hepatit, köprüleşme nekrozu, portosentral ve portoportal fibröz septalarla seyreden nekroinflamatuvar süreçle karakterizedir.

Friedmann SL. J Hepatol 2003;38:S38

ELSEVIER

Journal of Hepatology 38 (2003) S38–S53

Journal of Hepatology

www.elsevier.com/locate/jhep

Liver fibrosis – from bench to bedside

Scott L. Friedman*

Division of Liver Diseases, P.O. Box 1123, Mount Sinai School of Medicine, 1425 Madison Ave. Room 1170F, New York, NY 10029, USA

Karaciğer fibrozisi, subendotelyal boşluktaki ekstrasellüler matrikste, kollajen ve diğer proteinlerin birikimi ve ortadan kaldırılmasının söz konusu olduğu, dinamik ve kompleks sürecin net sonucudur.

Friedmann SL. J Hepatol 2003;38:S38

Pellicoro *et al. Fibrogenesis & Tissue Repair* 2012, **5**(Suppl 1):S26
http://www.fibrogenesis.com/content/5/S1/S26

Fibrogenesis & Tissue Repair

PROCEEDINGS Open Access

Reversibility of liver fibrosis

Antonella Pellicoro*, Prakash Ramachandran, John P Iredale

From Fibroproliferative disorders: from biochemical analysis to targeted therapies
Frauenchiemsee, Germany. 25-30 September 2010

Karaciğer hastalığının geri dönüşümsüz bir süreç olduğuna dair geleneksel görüş geçmişte kalmıştır.

Karaciğerde fibrozis gelişimi, dinamik ve iki yönde de ilerleyebilecek bir süreçtir.

Pellicoro A et al. Fibrogenesis Tissue Repair 2012;5(S1):S26

Pellicoro *et al. Fibrogenesis & Tissue Repair* 2012, **5**(Suppl 1):S26
http://www.fibrogenesis.com/content/5/S1/S26

Fibrogenesis & Tissue Repair

PROCEEDINGS Open Access

Reversibility of liver fibrosis

Antonella Pellicoro*, Prakash Ramachandran, John P Iredale

From Fibroproliferative disorders: from biochemical analysis to targeted therapies
Frauenchiemsee, Germany. 25-30 September 2010

Hepatik inflamasyona yol açan kronik ya da tekrarlayan stimulus ortadan kaldırıldığında skar dokusunda resolüsyon izlenmektedir.

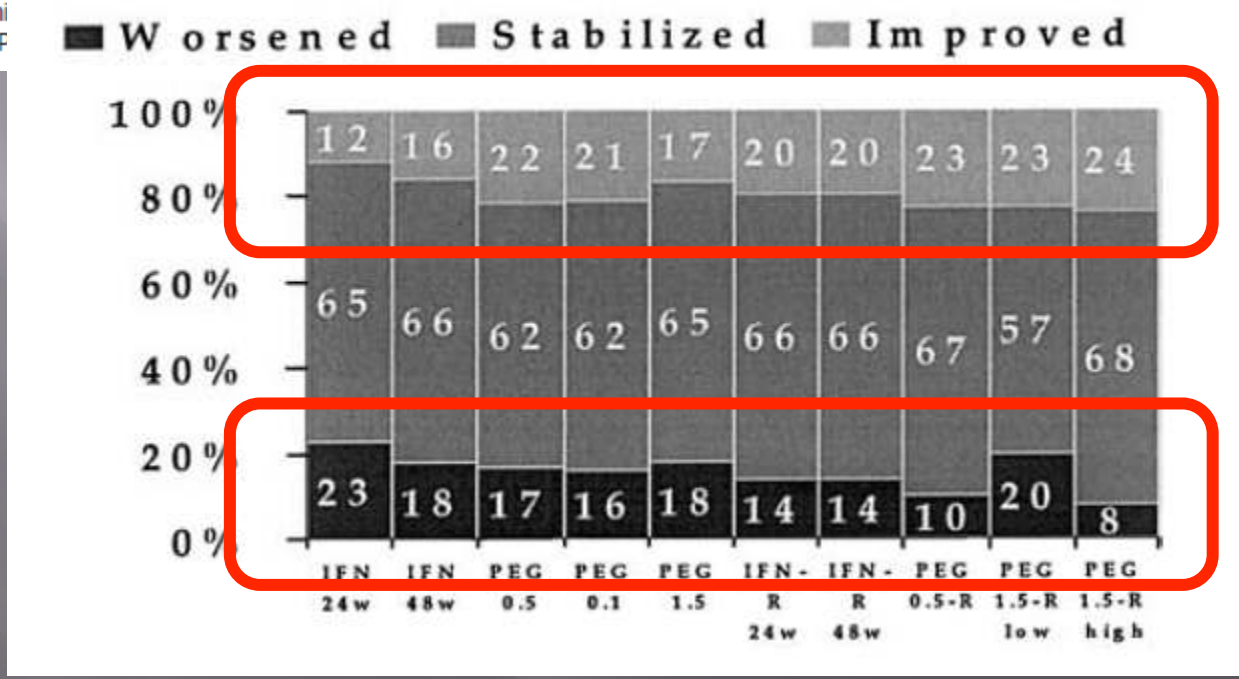
Pellicoro A et al. Fibrogenesis Tissue Repair 2012;5(S1):S26

GASTROENTEROLOGY 2002;122:1303–1313

Impact of Pegylated Interferon Alfa-2b and Ribavirin on Liver Fibrosis in Patients With Chronic Hepatitis C

THIERRY POYNARD,* JOHN McHUTCHISON,† MICHAEL MANNS,§ CHRISTIAN TREPO,‖ KAREN LINDSAY,¶ ZACHARY GOODMAN,# MEI–HSIU LING,** and JANICE ALBRECHT** for the PEG-FIBROSIS Project Group

*Service d'Hépato-Gastroentérologie, Groupe Hospitalier Pitié-Salpêtrière, Université Paris VI, Paris, France; †Scripps Clinic and Research Foundation, al School of Hannover, H Liver Disease, Uni ed Forces Institute of P



erol 2002;122:1303

GASTROENTEROLOGY 2002;122:1303–1313

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*Service d'Hépato-Gastroentérologie, Groupe Hospitalier Pitié-Salpêtrière, Université Paris VI, Paris, France; †Scripps Clinic and Research Foundation, Division of Gastroenterology/Hepatology, La Jolla, California; §Division of Gastroenterology and Hepatology, Medical School of Hannover, Hannover, Germany; ‖Service d'Hépato-Gastroentérologie, Hôtel Dieu, Lyon, France; ¶Division of Gastrointestinal and Liver Disease, University of Southern California, Los Angeles, California; #Department of Hepatic and Gastrointestinal Pathology, Armed Forces Institute of Pathology, Washington, DC; and **Schering-Plough Research Institute, Kenilworth, New Jersey

Tedavi öncesi biyopsisinde siroz saptanan 153 hastanın 75'inde (%49) fibroz geriledi.

Poynard T et al. Gastroenterol 2002;122:1303

Long-Term Entecavir Therapy Results in the Reversal of Fibrosis/Cirrhosis and Continued Histological Improvement in Patients with Chronic Hepatitis B

Ting-Tsung Chang,[1] Yun-Fan Liaw,[2] Shun-Sheng Wu,[3] Eugene Schiff,[4] Kwang-Hyub Han,[5] Ching-Lung Lai,[6] Rifaat Safadi,[7] Samuel S. Lee,[8] Waldemar Halota,[9] Zachary Goodman,[10] Yun-Chan Chi,[11] Hui Zhang,[12] Robert Hindes,[12] Uchenna Iloeje,[12] Suzanne Beebe,[12] and Bruce Kreter[12]

57 hasta,
En az 3 yıl ETV tedavisi,
Biyopsi kontrolü medyan 6 yıl

Chang TT et al. Hepatology 2010;52:886

Long-Term Entecavir Therapy Results in the Reversal of Fibrosis/Cirrhosis and Continued Histological Improvement in Patients with Chronic Hepatitis B

Ting-Tsung Chang,[1] Yun-Fan Liaw,[2] Shun-Sheng Wu,[3] Eugene Schiff,[4] Kwang-Hyub Han,[5] Ching-Lung Lai,[6] Rifaat Safadi,[7] Samuel S. Lee,[8] Waldemar Halota,[9] Zachary Goodman,[10] Yun-Chan Chi,[11] Hui Zhang,[12] Robert Hindes,[12] Uchenna Iloeje,[12] Suzanne Beebe,[12] and Bruce Kreter[12]

Histolojik düzelme

Knodell nekroinflamatuvar skorunda ≥2 puan gerileme ve fibroz skorunda kötüleşme olmaması

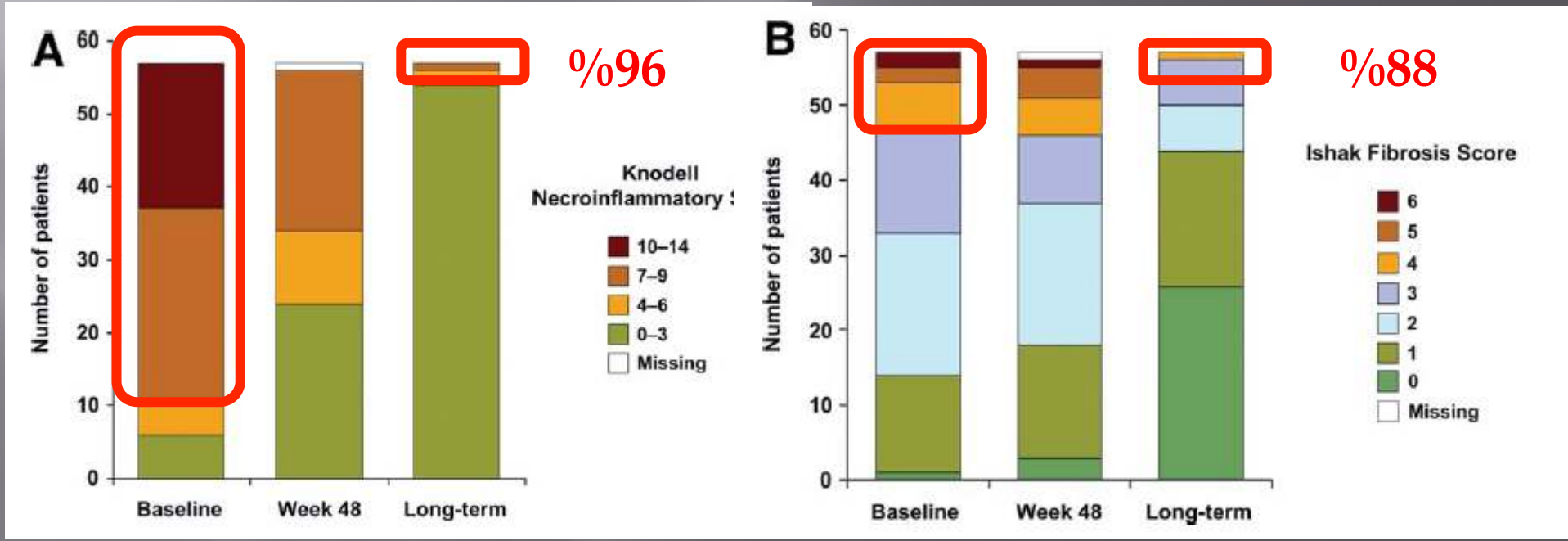
Fibroz skorunda düzelme

ISHAK fibroz skorunda ≥1 puan gerileme

Chang TT et al. Hepatology 2010;52:886

Long-Term Entecavir Therapy Results in the Reversal of Fibrosis/Cirrhosis and Continued Histological Improvement in Patients with Chronic Hepatitis B

Ting-Tsung Chang,[1] Yun-Fan Liaw,[2] Shun-Sheng Wu,[3] Eugene Schiff,[4] Kwang-Hyub Han,[5] Ching-Lung Lai,[6] Rifaat Safadi,[7] Samuel S. Lee,[8] Waldemar Halota,[9] Zachary Goodman,[10] Yun-Chan Chi,[11] Hui Zhang,[12] Robert Hindes,[12] Uchenna Iloeje,[12] Suzanne Beebe,[12] and Bruce Kreter[12]



Chang TT et al. Hepatology 2010;52:886

Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study

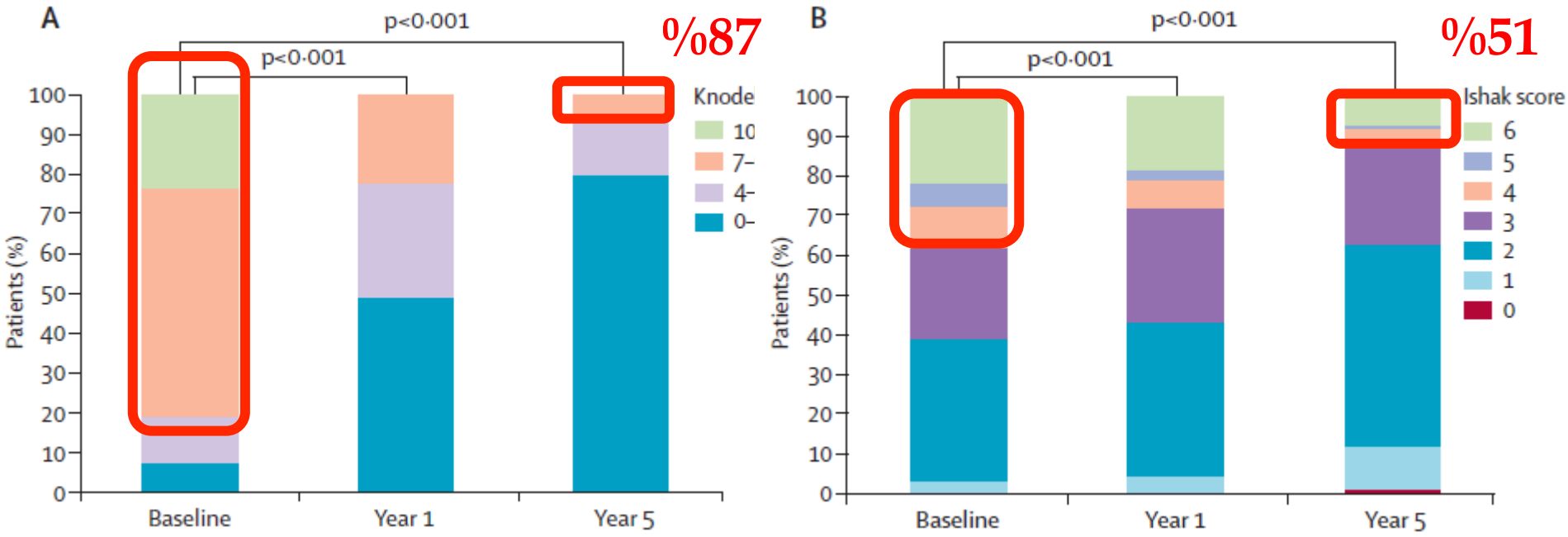
Patrick Marcellin, Edward Gane, Maria Buti, Nezam Afdhal, William Sievert, Ira M Jacobson, Mary Kay Washington, George Germanidis, John F Flaherty, Raul Aguilar Schall, Jeffrey D Bornstein, Kathryn M Kitrinos, G Mani Subramanian, John G McHutchison, E Jenny Heathcote

348 hasta,
TNF tedavisinin 240. haftasını tamamlamış,
Başlangıç, 48. hafta, 240. hafta biyopsi

Marcellin P et al. Lancet 2013;381:468

Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study

Patrick Marcellin, Edward Gane, Maria Buti, Nezam Afdhal, William Sievert, Ira M Jacobson, Mary Kay Washington, George Germanidis, John F Flaherty, Raul Aguilar Schall, Jeffrey D Bornstein, Kathryn M Kitrinos, G Mani Subramanian, John G McHutchison, E Jenny Heathcote



Marcellin P et al. Lancet 2013;381:468

Journal of Gastroenterology and Hepatology
JGHF
doi:10.1111/jgh.12213

REVIEW

Long-term therapy for chronic hepatitis B: Hepatitis B virus DNA suppression leading to cirrhosis reversal

Patrick Marcellin and Tarik Asselah

Service d'Hépatologie, Hôpital Beaujon, University of Paris, Clichy, France

Gerek RCT gerekse de RL çalışmaları, potent NA ile KHB olgularında viral replikasyonun etkin ve güvenli bir biçimde uzun süreli baskılanabileceğini ortaya koymuştur.

Bu ajanlarla tedavi hastalığın ilerlemesini engellemekle kalmaz, aynı zamanda seyrini de değiştirir.

Observational Study > Hepatology. 2015 Jun;61(6):1809-20. doi: 10.1002/hep.27723. Epub 2015 Mar 18.

Long-term effect of antiviral therapy on disease course after decompensation in patients with hepatitis B virus-related cirrhosis

Jeong Won Jang [1 2], Jong Young Choi [1 2], Young Seok Kim [3 2], Hyun Young Woo [4 2], Sung Kyu Choi [5 2], Chang Hyeong Lee [6 2], Tae Yeob Kim [7 2], Joo Hyun Sohn [7 2], Won Young Tak [8 2], Kwang-Hyub Han [9 2]

Affiliations + expand

PMID: 25627342 DOI: 10.1002/hep.27723

707 dekompanse sirotik KHB hastası

5 yıllık transplantasyonsuz sağkalım NA tedavisi alan hastalarda daha yüksek

Jang JW et al. Hepatology 2015;61:1809

Observational Study > Hepatology. 2015 Jun;61(6):1809-20. doi: 10.1002/hep.27723.
Epub 2015 Mar 18.

Long-term effect of antiviral therapy on disease course after decompensation in patients with hepatitis B virus-related cirrhosis

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Affiliations + expand

PMID: 25627342 DOI: 10.1002/hep.27723

Hastaların %34'ü transplantasyon listesinden çıkartıldı…

Jang JW et al. Hepatology 2015;61:1809

HCC riski

Antiviral Therapy 2011; **16**:787–795 (doi: 10.3851/IMP1895)

Review

Does antiviral therapy prevent hepatocellular carcinoma?

Hellan Kwon[1], *Anna S Lok*[1]*

[1]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI, USA

Kwon H et al. Antiviral Ther 2011;16:787

Clinical Gastroenterology and Hepatology 2014;12:885–893

Antiviral Therapy for Chronic Hepatitis B Virus Infection and Development of Hepatocellular Carcinoma in a US Population

Stuart C. Gordon,* Lois E. Lamerato,* Loralee B. Rupp,* Jia Li,* Scott D. Holmberg,‡ Anne C. Moorman,‡ Philip R. Spradling,‡ Eyasu H. Teshale,‡ Vinutha Vijayadeva,§ Joseph A. Boscarino,‖ Emily M. Henkle,¶ Nancy Oja-Tebbe,* and Mei Lu,* for the CHeCS Investigators

*Henry Ford Health System, Detroit, Michigan; ‡Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; §Center for Health Research, Kaiser Permanente Hawaii, Waipahu, Hawaii; ‖Center for Health Research, Geisinger Health System, Danville, Pennsylvania; and ¶Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon

Antiviral tedavi alan hastalarda HCC riski almayanlara göre daha düşüktür. (AHR:0.39)

Gordon SC et al. Clin Gastroenterol Hepatol 2013;12:885

Alimentary Pharmacology & Therapeutics

Meta-analysis: treatment of hepatitis B infection reduces risk of hepatocellular carcinoma

J. J. Y. SUNG, K. K. F. TSOI, V. W. S. WONG, K. C. T. LI & H. L. Y. CHAN

Institute of Digestive Disease, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, NT, Hong Kong, China

Correspondence to:
Prof. J. J. Y. Sung, Department of Medicine and Therapeutics, Prince of Wales Hospital, Shatin, NT, Hong Kong, China.
E-mail: joesung@cuhk.edu.hk

SUMMARY

Background

Chronic hepatitis B (CHB) infection leads to development of hepatocellular carcinoma (HCC), but the effects of treatment in preventing HCC are not clear.

Aim

To study the effects of interferon (IFN) or nucleoside/tide analogue (NA) on the risk of developing HCC in CHB patients.

Sung YYK et al. Aliment Pharmaco Ther 2008;28:1067

Alimentary Pharmacology & Therapeutics

Meta-analysis: treatment of hepatitis B infection reduces risk of hepatocellular carcinoma

J. J. Y. SUNG, K. K. F. TSOI, V. W. S. WONG, K. C. T. LI & H. L. Y. CHAN

IFN tedavisi,
12 çalışma, 2742 hasta

IFN tedavisi ile HCC riski %34 azalıyor

Erken dönem sirotik hastalarda yarar daha belirgin.

Sung YYK et al. Aliment Pharmaco Ther 2008;28:1067

Alimentary Pharmacology & Therapeutics

Meta-analysis: treatment of hepatitis B infection reduces risk of hepatocellular carcinoma

J. J. Y. SUNG, K. K. F. TSOI, V. W. S. WONG, K. C. T. LI & H. L. Y. CHAN

NA tedavisi,
5 çalışma, 2289 hasta

NA tedavisi ile HCC riski %78 azalıyor

HBeAg pozitif hastalarda yarar daha belirgin.

Sung YYK et al. Aliment Pharmaco Ther 2008;28:1067

Hepatology

ORIGINAL ARTICLE

Comparison of tenofovir and entecavir on the risk of hepatocellular carcinoma and mortality in treatment-naïve patients with chronic hepatitis B in Korea: a large-scale, propensity score analysis

Sung Won Lee ,[1,2] Jung Hyun Kwon ,[1,2] Hae Lim Lee,[1,2] Sun Hong Yoo,[1,2] Hee Chul Nam,[1,2] Pil Soo Sung,[1,2] Soon Woo Nam,[1,2] Si Hyun Bae,[1,2]

3022 hasta, %34 sirotik
ETV (n=1583) vs TDF (n=1439)

Antiviral tedavinin başlanmasından sonraki 5 yıl içinde HCC insidansı, tüm nedenlere bağlı mortalite ve KC tx sıklığı

Lee SW et al. Gut 2019;0:1-8 doi:10.1136/gutjnl-2019-318947

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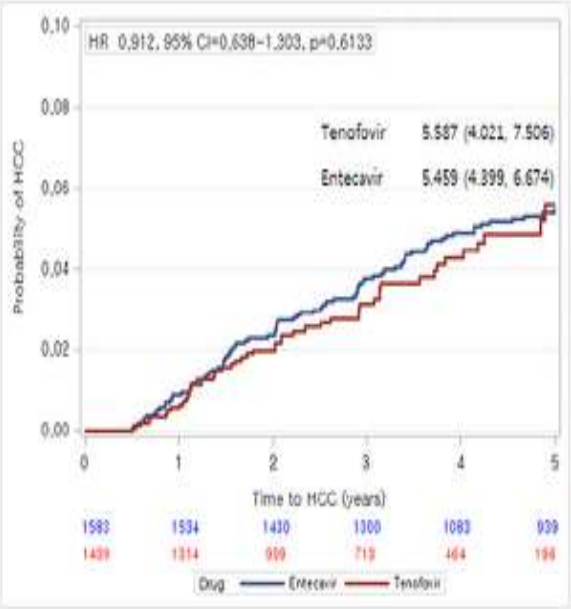
A



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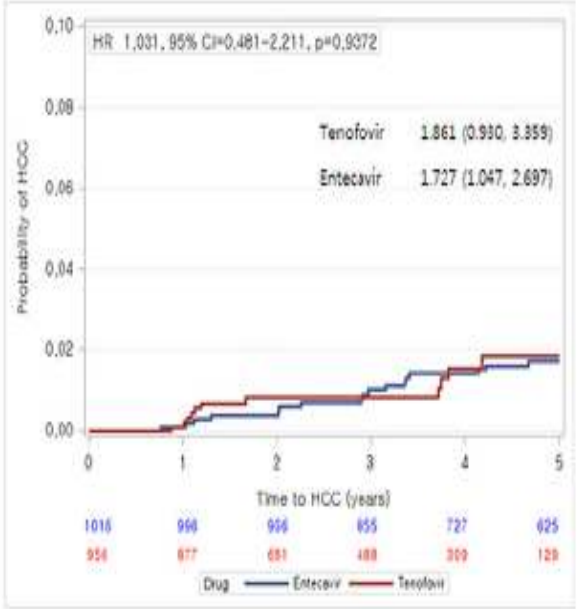

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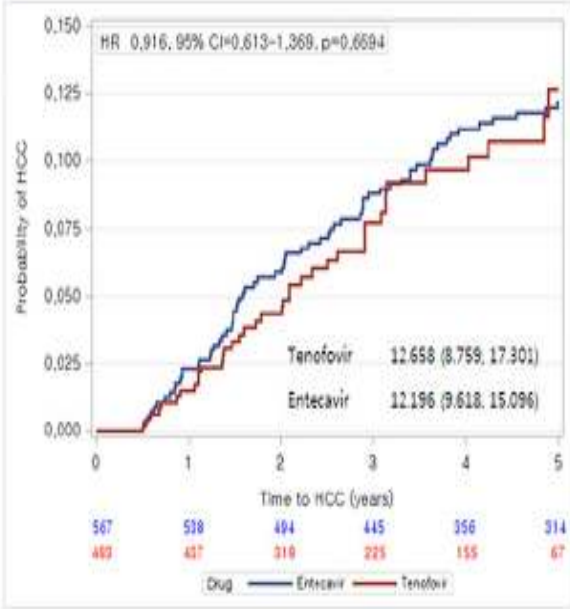

Lee SW et al. Gut 2019;0:1-8 doi:10.1136/gutjnl-2019-318947

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Antiviral tedavinin başlanmasından sonraki 5 yıl içinde HCC insidansı, tüm nedenlere bağlı mortalite ve KC tx sıklığı açısından TDF ve ETV arasında fark yok…

Lee SW et al. Gut 2019;0:1-8 doi:10.1136/gutjnl-2019-318947

Research Article
Viral Hepatitis

JOURNAL OF HEPATOLOGY

A multicenter study of entecavir *vs.* tenofovir on prognosis of treatment-naïve chronic hepatitis B in South Korea

Seung Up Kim[1,2,3,†], Yeon Seok Seo[4,†], Han Ah Lee[4], Mi Na Kim[5], Yu Rim Lee[6], Hye Won Lee[1,3], Jun Yong Park[1,2,3], Do Young Kim[1,2,3], Sang Hoon Ahn[1,2,3], Kwang-Hyub Han[1,2,3], Seong Gyu Hwang[5], Kyu Sung Rim[5], Soon Ho Um[4], Won Young Tak[6], Young Oh Kweon[6], Beom Kyung Kim[1,2,3,*], Soo Young Park[6,*]

2897 hasta, 910 sirotik
ETV (n=1484) vs TDF (n=1413)

ETV ve TDF grupları arasında tedavinin 5. yılında HCC insidansı, tüm nedenlere bağlı mortalite ve KC tx sıklığı açısından fark yok...

Kim SU et al. J Hepatol 2019;71:456

JAMA Oncology | Original Investigation

Risk of Hepatocellular Carcinoma in Patients Treated With Entecavir vs Tenofovir for Chronic Hepatitis B

A Korean Nationwide Cohort Study

Jonggi Choi, MD; Hyo Jeong Kim, MPH; Jayoun Lee, PhD; Songhee Cho, MPH; Min Jung Ko, PhD; Young-Suk Lim, MD, PhD

Ulusal kohort çalışması,
ETV (n=11464)
TDF (n=12692)

HCC insidansı
ETV 1,06/100 hasta yılı
TDF 0,64/100 hasta yılı

Choi J et al. JAMA Oncol 2019;5:30

JAMA Oncology | Original Investigation

Risk of Hepatocellular Carcinoma in Patients Treated With Entecavir vs Tenofovir for Chronic Hepatitis B

A Korean Nationwide Cohort Study

Jonggi Choi, MD; Hyo Jeong Kim, MPH; Jayoun Lee, PhD; Songhee Cho, MPH; Min Jung Ko, PhD; Young-Suk Lim, MD, PhD

Multivariate analiz ile istatistiksel olarak anlamlı biçimde TDF tedavisi daha düşük HCC riski ile ilişkilidir (HR 0,61; 95%CI 0,54-0,70)

Choi J et al. JAMA Oncol 2019;5:30

Notice of Retraction and Replacement. Choi et al. Risk of hepatocellular carcinoma in patients treated with entecavir vs tenofovir for chronic hepatitis B: a Korean nationwide cohort study. *JAMA Oncol.* 2019;5(1):30-36

To the Editor On behalf of our coauthors, we write to report serious errors in our article, "Risk of Hepatocellular Carcinoma in Patients Treated With Entecavir vs Tenofovir for Chronic Hepatitis B: A Korean Nationwide Cohort Study," published online on September 27, 2018, and in the January 2019 issue of *JAMA Oncology*.[1]

Choi J et al. JAMA Oncol 2019;5:30

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Eight-year survival in chronic hepatitis B patients under long-term entecavir or tenofovir therapy is similar to the general population☆

George V. Papatheodoridis[1,*], Vana Sypsa[2], George Dalekos[3], Cihan Yurdaydin[4], Florian van Boemmel[5], Maria Buti[6], John Goulis[7], Jose Luis Calleja[8], Heng Chi[9], Spilios Manolakopoulos[10], Alessandro Loglio[11], Spyros Siakavellas[1], Nikolaos Gatselis[3], Onur Keskın[4], Maria Lehretz[5], Savvoula Savvidou[7], Juan de la Revilla[8], Bettina E. Hansen[9], Anastasia Kourikou[10], Ioannis Vlachogiannakos[1], Kostantinos Galanis[3], Ramazan Idilman[4], Massimo Colombo[12], Rafael Esteban[6], Harry L.A. Janssen[9,13], Thomas Berg[5], Pietro Lampertico[11]

Uzun süreli ETV ya da TDF tedavisi alan sirotik/nonsirotik hastalarda 8 yıllık sağkalım genel popülasyondan farklı değildir…

Papatheodoridis GV et al. J Hepatol 2018;68:1129

HEPATOLOGY

HEPATOLOGY, VOL. 66, NO. 5, 2017

The Risk of Hepatocellular Carcinoma Decreases After the First 5 Years of Entecavir or Tenofovir in Caucasians With Chronic Hepatitis B

George V. Papatheodoridis,[1] Ramazan Idilman,[2] George N. Dalekos,[3] Maria Buti,[4] Heng Chi,[5] Florian van Boemmel,[6] Jose Luis Calleja,[7] Vana Sypsa,[8] John Goulis,[9] Spilios Manolakopoulos,[10] Alessandro Loglio,[11] Spyros Siakavellas,[10] Onur Keskin,[2] Nikolaos Gatselis,[3] Bettina E. Hansen,[5] Maria Lehretz,[6] Juan de la Revilla,[7] Savvoula Savvidou,[9] Anastasia Kourikou,[10] Ioannis Vlachogiannakos,[3] Kostantinos Galanis,[3] Cihan Yurdaydin,[2] Thomas Berg,[6] Massimo Colombo,[12] Rafael Esteban,[4] Harry L.A. Janssen,[5,13] and Pietro Lampertico[11]

>5 yıl TDF/ETV tedavisi alan 1951 KHB hastası

İlk 5 yıl içinde HCC insidansı %1,22
>5 yıl HCC insidansı %0,73 (p=0,05)

Papatheodoridis GV et al. Hepatology 2017;66:1444

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Sirotik hastalarda

İlk 5 yıl içinde HCC insidansı %3,22
>5 yıl HCC insidansı %1,57 (p=0,039)

Papatheodoridis GV et al. Hepatology 2017;66:1444

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>5 yıl TDF/ETV tedavisi alan Kafkas ırkından KHB hastalarında HCC riski azalmaktadır.

Papatheodoridis GV et al. Hepatology 2017;66:1444

De novo kombinasyon

HEPATOLOGY

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. Lok,[2] Brian J. McMahon,[3] Kyong-Mi Chang,[4] Jessica P. Hwang,[5] Maureen M. Jonas,[6] Robert S. Brown Jr.,[7] Natalie H. Bzowej,[8] and John B. Wong[9]

Dirence karşı genetik bariyeri yüksek ilaçlar kullanıldığı sürece, de novo kombinasyon tedavisi gereksizdir.

Terrault NA et al. Hepatology 2018;67:1560

Naiv hastalarda ETV, TDF, TAF ve PEG-IFN ile monoterapi önerilen tedavi yaklaşımıdır.

Tedavi deneyimli hastalar
Virolojik yanıtsızlık
Tedavi başarısızlığı

HEPATOLOGY

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

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

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Uzun süreli NA tedavisine ilişkin en önemli kaygı, antiviral direnç mutasyonlarının seçilmesidir.

Terrault NA et al. Hepatology 2018;67:1560

HBV variants	LAM	LDT	ETV	ADV	TDF/TAF
Wild-type	S	S	S	S	S
M204V	R	S	I	S	S
M204I	R	R	I	S	S
L180M +M204V	R	R	I	S	S
A181T/V	R	R	S	R	I
N236T	S	S	S	R	I
A181T/V + N236T	R	R	S	R	I/R
L180M + M204V/I ± I169T± V173L ± M250V	R	R	R	S	S
L180M + M204V/I ± T184G ± S202I/G	R	R	R	S	S

Mutasyonların cccDNA'da arşivlenmesi ile aynı ilacın tekrar kullanımı olanaksız hale gelir ve çapraz direnç nedeniyle diğer seçenekler kısıtlanır.

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Virolojik kırılma

Başlangıçtaki virolojik yanıttan sonra, HBV - DNA düzeyinde 1 $\log_{10}$ (10 kat) artış olması

Tedavi altında DNA negatifliği sağlanmış hastalarda HBV DNA> 100 IU/ml

Terrault NA et al. Hepatology 2018;67:1560

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Tedavi uyumu mutlaka sorgulanmalı,

HBV DNA düzeyi bir ay arayla doğrulanmalı

Terrault NA et al. Hepatology 2018;67:1560

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

Çapraz direnç olmayan potent ajana geçilmeli,

Çoklu ilaç direnci olmadığı sürece "switch"

EASL CPG. J Hepatol 2017;67:370

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ETV ya da TDF kullanan hastalarda HBV DNA düzeyleri düşme eğilimindeyse, yanıt 96. haftada değerlendirilmelidir.

Terrault NA et al. Hepatology 2018;67:1560

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ETV ya da TDF kullanan hastalarda persistan düşük düzey viremi (HBV DNA<2000 IU/ml) durumunda monoterapiye devam edilmesi önerilir.

Terrault NA et al. Hepatology 2018;67:1560

Tedavinin kesilmesi

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*

Sirotik olmayan HBeAg pozitif hastalarda stabil antiHBe serokonversiyonu sonrası 12 aylık bir konsolidasyon döneminin ardından tedavi kesilebilir…

EASL CPG. J Hepatol 2017;67:370

GASTROENTEROLOGY 2010;139:491–498

Nucleos(t)ide Analogues Only Induce Temporary Hepatitis B e Antigen Seroconversion in Most Patients With Chronic Hepatitis B

JURRIËN G. P. REIJNDERS,* MONIEK J. PERQUIN,* NINGPING ZHANG,*,‡ BETTINA E. HANSEN,*,§ and HARRY L. A. JANSSEN*

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Hastaların çoğunda tedavi ile sağlanan HBeAg serokonversiyonu geçicidir ve eAg serokonversiyonuna bakılmaksızın uzun süreli tedavi gerekli görülmektedir.

Reijnders JGP et al. Gastroenterology 2010;139:491

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*

HBeAg serokonversiyonu uygun bir sonlanım noktası olmayabilir,

HBeAg serokonversiyonuna bakılmaksızın tedavi devamı alternatif yaklaşımdır.

EASL CPG. J Hepatol 2017;67:370

Hepatol Int (2008) 2:263–283
DOI 10.1007/s12072-008-9080-3

OpenAccess

REVIEW ARTICLE

Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update

Yun-Fan Liaw · Nancy Leung · Jia-Horng Kao · Teerha Piratvisuth · Edward Gane · Kwang-Hyub Han · Richard Guan · George K. K. Lau · Stephen Locarnini · for the Chronic Hepatitis B Guideline Working Party of the Asian-Pacific Association for the Study of the Liver

HBeAg negatif hastalarda 6 ay arayla üç kez HBV DNA negatifliği saptanırsa, tedavinin kesilmesi düşünülebilir.

Liaw YF. Hepatol Int 2008;2:263

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*

Optimal tedavi sonlanım noktası HBsAg kaybıdır.

EASL CPG. J Hepatol 2017;67:370

Sonuç

Ülkemizde insidans azalmaya devam etmekle birlikte prevalansın %4 dolayında olduğu bilinmektedir.

Hepatit B tedavisinde amaç eradikasyon değildir.

Hastalığın siroz, dekompanse siroz, son dönem karaciğer hastalığı, HCC ve ölüme ilerlemesine engel olarak sağkalımı ve yaşam kalitesini artırmaktır.

Sonuç

- Serum HBV DNA ve ALT düzeyleri
- Karaciğer hastalığının derecesi ve evresi
- İdeal sonlanım noktası HBsAg kaybı
- Tedavi altında sürdürülebilir viral baskılanma

Sonuç

Naif hastalarda
Dirence karşı genetik bariyeri yüksek NA'ları ve seçilmiş hastalarda PEG-IFN,

KHB'nin etkin biçimde tedavi edilmesiyle uzun dönemde

- Biyokimyasal, serolojik ve virolojik yanıtların arttığı,
- Histolojik yanıt elde edildiği ve fibrozisin gerilediği,
- HCC olasılığının azaldığı,
- Sağkalımın arttığı