DEĞİŞEN SUT
DEĞİŞEN UYGULAMALAR

E. Ediz Tütüncü

XVII. Türk Klinik Mikrobiyoloji ve İnfeksiyon Hastalıkları Kongresi

26 Mart 2015, Antalya

Sunum planı

- 2009 SUT rasyoneli
- Etkin viral baskılanma
- Direncin klinik sonuçları/Optimal direnç profili
- Etkinlik / Gerçek yaşam verileri
- Histolojik düzelme
- Maliyet etkinlik

29 Eylül 2008 PAZARTESİ Resmî Gazete Sayı : 27012 (Mükerrer)

TEBLİĞ

Sosyal Güvenlik Kurumu Başkanlığından:

2008 YILI SOSYAL GÜVENLİK KURUMU SAĞLIK UYGULAMA TEBLİĞİ

5) Kronik hepatit-B'de:

6 aydan daha uzun süredir ALT düzeyinin 2 katından yüksek, HBV DNA seviyesi HBe Ag pozitif olanlarda 10^5 kopya/ml ve daha yüksek, HBe Ag negatif olanlarda 10^4 kopya/ml ve daha yüksek olması koşuluyla biyopsi şartı aranmaksızın çocuk veya erişkin gastroenteroloji veya enfeksiyon hastalıkları uzman hekimleri tarafından düzenlenen ilaç kullanım uzman hekim raporuna dayanılarak bu uzman hekimler veya iç hastalıkları uzman hekimleri tarafından reçete edilmesi halinde antivirallerin bedeli ödenir.

Antiviral tedavi almakta olan hastaların raporlarının yenilenmesinde, HBV DNA ve ALT yüksekliği bulunması koşulu aranmadan, başlama kriterlerine uygun olduğunu gösteren,

teşhisin konulduğu raporun fotokopisinin yeni rapora eklenmesi veya başlama kriterlerine uygun olduğunu gösteren, teşhisin konulduğu raporda belirtilen HBV DNA ve ALT değerleri ile raporun tarih ve sayısının, yeni raporda açık olarak belirtilmesi yeterlidir.

6) Teşhise esas olan bulgular ilaç kullanım uzman hekim raporunda belirtilecektir.

2009/91 GENELGE VE 2009/98 GENELGE İLE SAĞLIK UYGULAMA TEBLİĞİNDE YAPILAN DEĞİŞİKLİKLER

"12.7.13 Hepatit Tedavisi 17.07.2009 tarihinden geçerli 2009/91 sayılı GENELGE

(1) Akut ve Kronik viral hepatit tedavisinde kullanılan ilaçlar çocuk veya erişkin gastroenteroloji veya enfeksiyon hastalıkları uzman hekimlerinden biri tarafından düzenlenen ilaç kullanım raporuna dayanılarak bu uzman hekimler ile çocuk hastalıkları veya iç hastalıkları uzman hekimleri tarafından reçete edilir.

Sosyal Güvenlik Kurumundan:

SOSYAL GÜVENLİK KURUMU SAĞLIK UYGULAMA TEBLİĞİ

BİRİNCİ BÖLÜM 5
GENEL HÜKÜMLER 5

(5) Erişkin hastalarda oral antiviral tedaviye;

a) HBV DNA $\leq 10^7$ kopya/ml (2.000.000 IU/ml) ise günde 100 mg lamivudin veya 600 mg telbivudin ile başlanır. Tedavinin 24 üncü haftasında HBV DNA 50 IU/ml (300 kopya/ml) ve üzerinde olan hastalarda diğer oral antiviraller kullanılabilir.

b) HBV DNA $>10^7$ kopya/ml (2.000.000 IU/ml)olanlarda diğer oral antivirallerden biri ile tedaviye başlanabilir.

c) Çocuk hastalardan, HBV DNA seviyesi 10.000 (10^4) kopya/ml (2.000 IU/ml) veya üzerinde olan hastalarda lamivudin tedavisine 3mg/kg/gün dozunda başlanabilir.

2009 SUT gerekçesi

AASLD PRACTICE GUIDELINES

Chronic Hepatitis B: Update 2009

Anna S. F. Lok[1] and Brian J. McMahon[2]

This guideline has been approved by the American Association for the Study of Liver Diseases and represents the position of the Association. It has been endorsed by the Infectious Diseases Society of America.

Preamble

These guidelines have been written to assist physicians and other health care providers in the recognition, diagnosis, and management of patients chronically infected

Chronic Hepatitis B, were considered in the development of these guidelines.[3-7] The recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. They are intended to be flexible. Specific recommendations are based on relevant published information. In an attempt to characterize the quality of evidence supporting recommendations, the Practice Guidelines Committee of the AASLD requires a category to be assigned and reported with each recommendation

- Tedavi öncesi HBV DNA düzeyleri,
- Viral baskılanmanın hızı,
- Tedavi süresi,
- Hasta uyumu

Lok ASF et al. Hepatology 2009;50:1

Online Submissions: wjg.wjgnet.com
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2007 August 14; 13(30): 4085-4090
World Journal of Gastroenterology ISSN 1007-9327
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RAPID COMMUNICATION

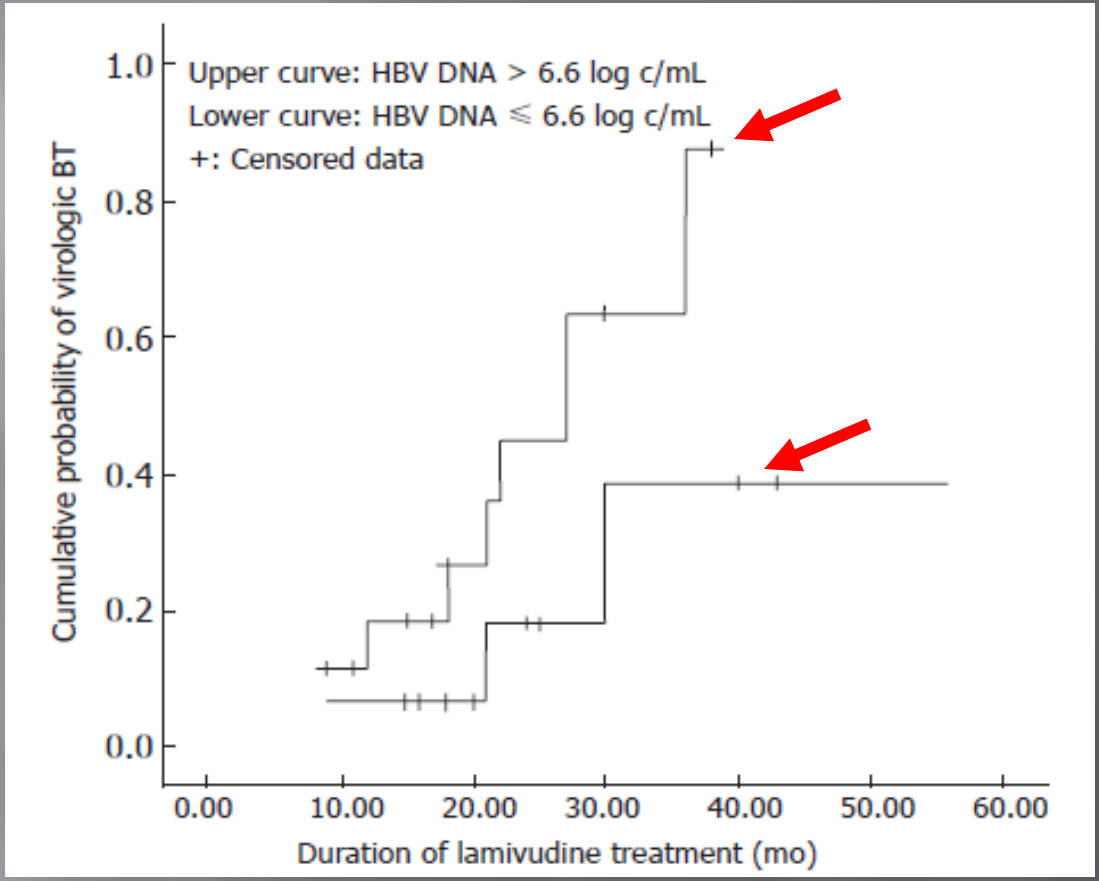
Baseline HBV DNA level is the most important factor associated with virologic breakthrough in chronic hepatitis B treated with lamivudine

Hee Bok Chae, Hie-Won Hann

Table 1 Baseline characteristics of patients (mean ± SD)

	All patients (n = 79)	Breakthrough (n = 24)	Non-breakthrough (n = 55)
Age (yr)	47 ± 12	47 ± 13	47 ± 11
Female (%)	32	29	33
Family history of CHB (%)	47	46	55
ALT (IU/L)	149 ± 44	98 ± 20	171 ± 63
Total bilirubin (mg/dL)	1.1 ± 1.1	1.3 ± 1.4	1.0 ± 0.9
Albumin (g/dL)	4.4 ± 0.4	4.2 ± 0.5	4.3 ± 0.4
(INR)	1.07 ± 0.12	1.09 ± 0.15	1.06 ± 0.08
Cirrhosis (%)	30	36	24
HBeAg-positive (%)	43	56	36
HBV DNA $\log_{10}$ copies/mL[a]	6.0 ± 1.6	6.6 ± 1.5	5.7 ± 1.5
Mean duration of lamivudine treatment (mo)	26 ± 10	29 ± 11	25 ± 10
3 log < HBV DNA < 5 log (%)	19	3	16
HBV DNA ≥ 5 log (%)	60	21	39

Gastroenterol 2007;13:4085



Tedavi öncesi HBV DNA	36. ay direnç
> 6.6 log kopya/ml	%88
≤ 6.6 log kopya/ml	%39

Chae HB et al. World J Gastroenterol 2007;13:4085

Hepatol Int (2008) 2:494–497
DOI 10.1007/s12072-008-9095-9

ORIGINAL ARTICLE

Pretreatment and on-treatment predictors of viral breakthrough in lamivudine therapy for chronic hepatitis B

Shahinul Alam · Golam Azam · Golam Mustafa · Nooruddin Ahmad · Belalul Islam · Provat Kumar Podder · Mobin Khan

Tedavinin altıncı ayında HBV DNA pozitifliğinin devamı viral kırılma için iyi bir belirteçtir.

Alam S et al. Hepatol Int 2008;2:494

GASTROENTEROLOGY 2009;136:486–495

2-Year GLOBE Trial Results: Telbivudine Is Superior to Lamivudine in Patients With Chronic Hepatitis B

YUN–FAN LIAW,* EDWARD GANE,‡ NANCY LEUNG,§ STEFAN ZEUZEM,‖ YUMING WANG,¶ CHING LUNG LAI,# E. JENNY HEATHCOTE,** MICHAEL MANNS,‡‡ NATALIE BZOWEJ,§§ JUNQI NIU,‖‖ STEVEN–HUY HAN,¶¶ SEONG GYU HWANG,## YILMAZ CAKALOGLU,*** MYRON J. TONG,‡‡‡ GEORGE PAPATHEODORIDIS,§§§ YAGANG CHEN,‖‖‖ NATHANIEL A. BROWN,¶¶¶ EFSEVIA ALBANIS,### KARIN GALIL,¶¶¶ and NIKOLAI V. NAOUMOV###; The GLOBE Study Group

*Liver Research Unit, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan; ‡Department of Gastroenterology, Middlemore Hospital, Auckland, New Zealand; §Department of Medicine, Alice Ho Miu Ling Nethersole Hospital, Hong Kong, China; ‖Department of Medicine 1, J.W. Goethe Univeristy Hospital, Frankfurt, Germany; ¶Xi Nan Hospital, Third Military Medical University, Chongqing, China; #University Department of Medicine, Queen Mary Hospital, Hong Kong, China; **Department of Medicine, Division of Gastroenterology, University of Toronto, Toronto, Ontario, Canada; ‡‡Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; §§Department of Liver Transplantation, California Pacific Medical Center, San Francisco, California; ‖‖Department of Hepatology, First Hospital, University of Jilin, Guangzhou, China; ¶¶Pfleger Liver Institute, UCLA School of Medicine, Los Angeles, California; ##Department of Internal Medicine, Pochon CHA University, Bundang Cha Hospital, Kyunggi-Do, Republic of Korea; ***Istanbul University, Istanbul, Turkey; ‡‡‡Phleger Liver Institute, Division of Digestive Diseases, David Geffen School of Medicine, University of California, Los Angeles, California; §§§2nd Department of Internal Medicine, Athens University Medical School, Hippokration Hospital, Athens, Greece; ‖‖‖First Affiliated Hospital, Zhejiang University, Hangzhou, China; ¶¶¶Idenix Pharmaceuticals, Cambridge, Massachusetts; and ###Novartis AG, Basel, Switzerland

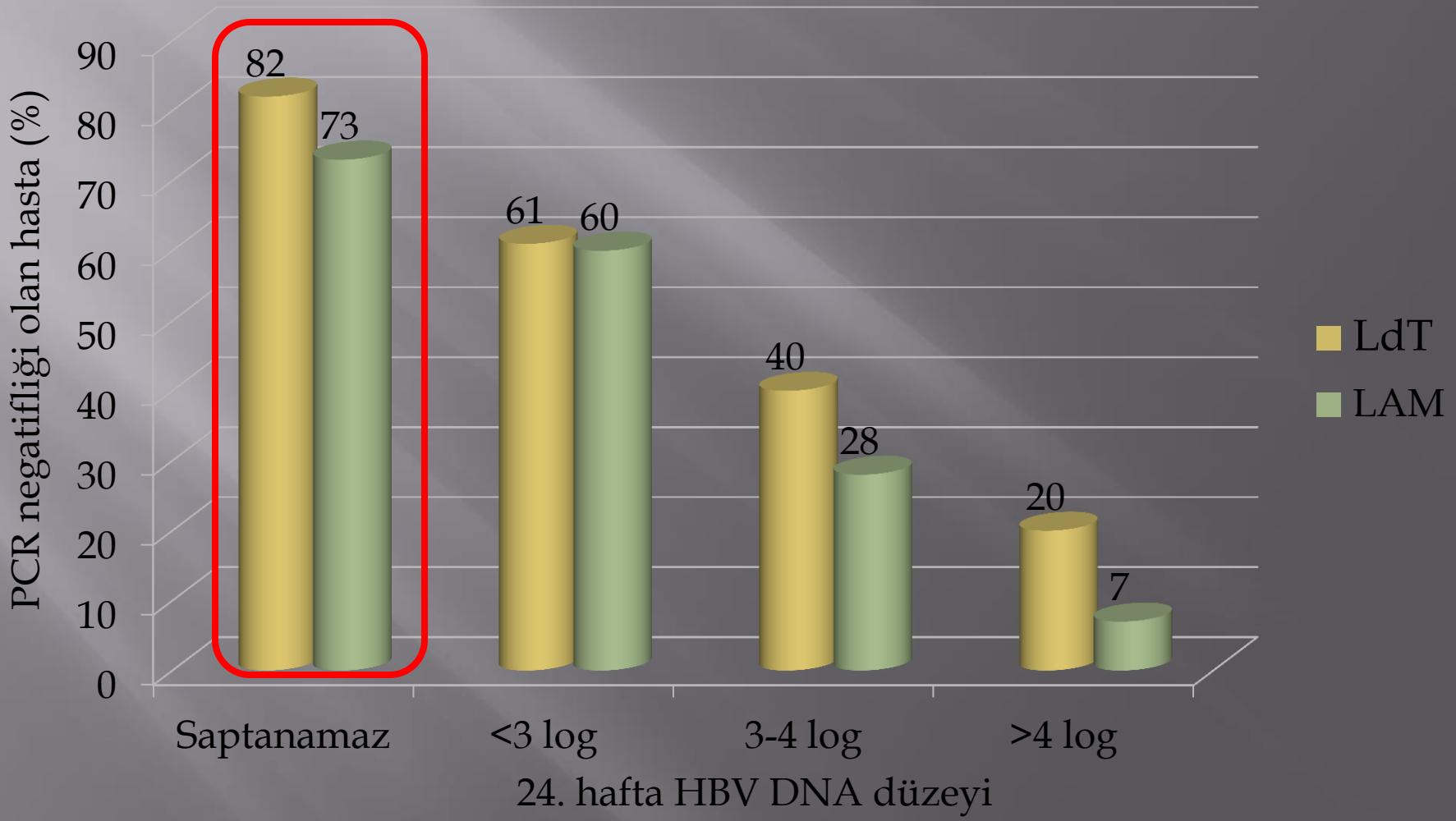
921 HBeAg (+)

446 HBeAg (-)

LAM vs LdT

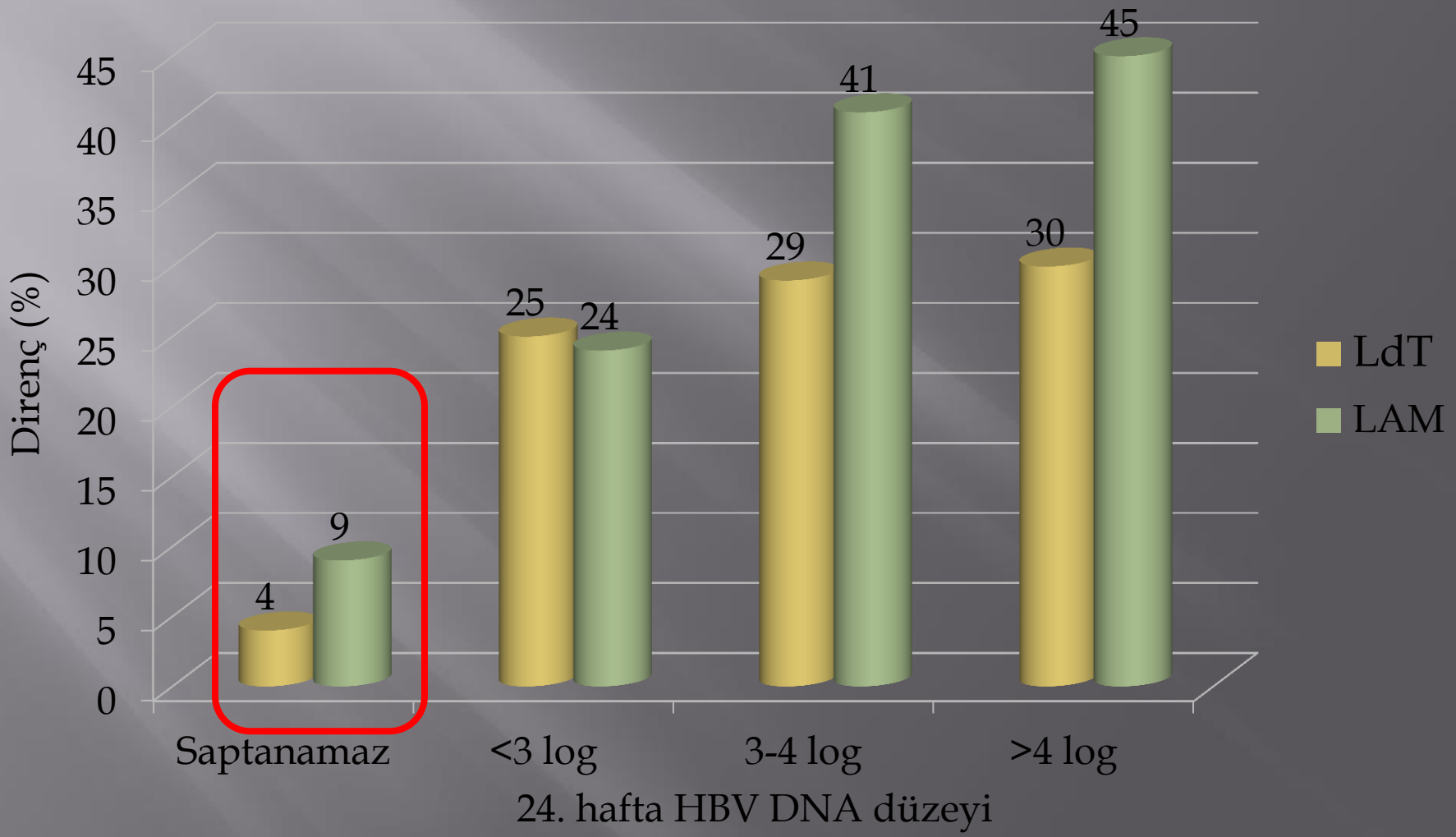
Liaw YF et al. Gastroenterology 2009;136:486

HBeAg(+) hastalarda 24. hafta HBV DNA düzeyi ile 104. haftada PCR negatifliği arasındaki ilişki



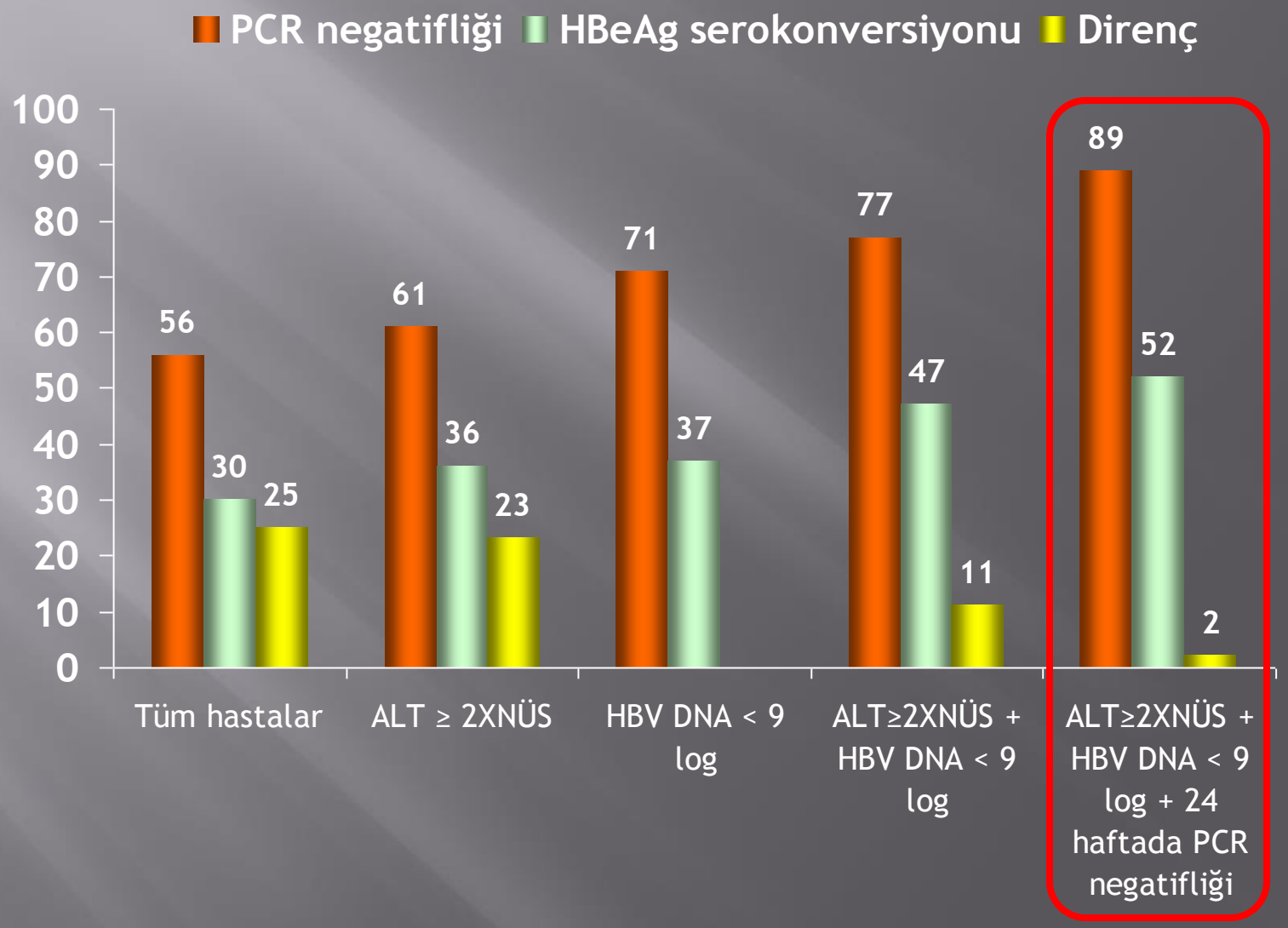
Liaw YF et al. Gastroenterology 2009;136:486

HBeAg(+) hastalarda 24. hafta HBV DNA düzeyi ile 104. haftada direnç arasındaki ilişki



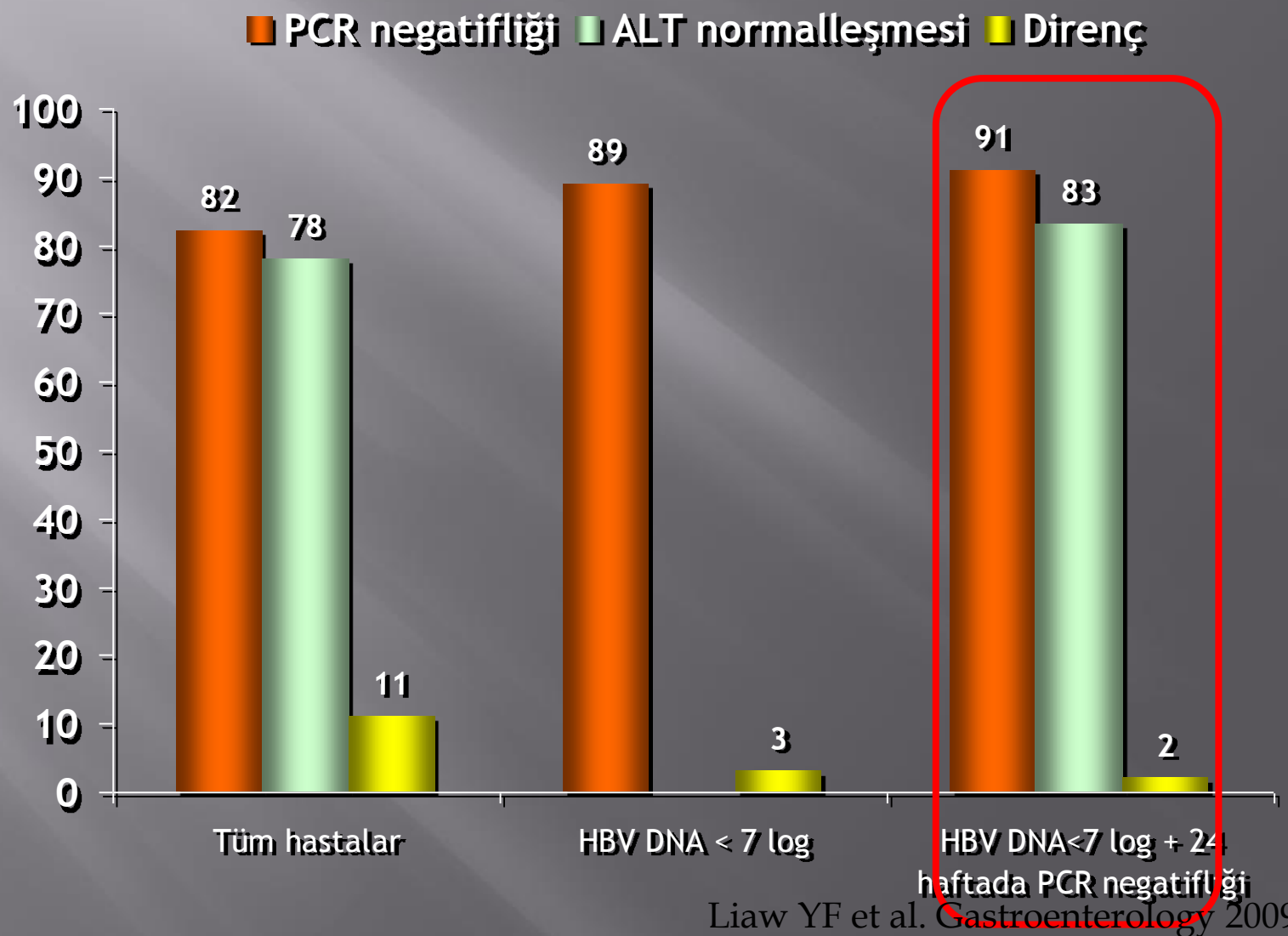
Liaw YF et al. Gastroenterology 2009;136:486

HBeAg (+) hastalarda altgrup analizleri



Liaw YF et al. Gastroenterology 2009;136:486

HBeAg (-) hastaların alt grup analizi



Liaw YF et al. Gastroenterology 2009;136:486

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2007;5:890–897

REVIEW

Report of an International Workshop: Roadmap for Management of Patients Receiving Oral Therapy for Chronic Hepatitis B

EMMET B. KEEFFE,* STEFAN ZEUZEM,‡ RAYMOND S. KOFF,§ DOUGLAS T. DIETERICH,‖ RAFAEL ESTEBAN–MUR,¶ EDWARD J. GANE,# IRA M. JACOBSON,** SENG G. LIM,‡‡ NIKOLAI NAOUMOV,§§ PATRICK MARCELLIN,¶¶ TEERHA PIRATVISUTH,‖‖ and FABIEN ZOULIM##

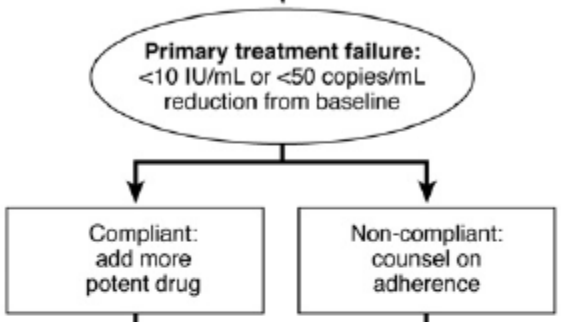
Keeffe EB et al. Clin Gastroenterol Hepatol 2007;5:890

HBV YOL HARİTASI YAKLAŞIMI

12. haftada primer yanıtsızlık değerlendirmesi

Virolojik yanıt

Başlangıç HBV DNA düzeyinde >1 log IU/ml



24. haftada etkinliğin değerlendirilmesi

Tam virolojik yanıt

HBV DNA<60 IU/ml

Kısmi virolojik yanıt

HBV DNA 60-2000

Yetersiz virolojik yanıt

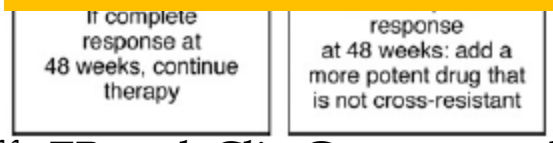
HBV DNA>2000 IU/ml

Düşük genetik bariyeri olan ilaç

İlaç ekleme

Yüksek genetik bariyeri olan ilaç

48. haftada değerlendirme



Keeffe EB et al. Clin Gastroenterol Hepatol 2007;5:890

Clinical Practice Guidelines

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

EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection

European Association for the Study of the Liver*

Introduction

Our understanding of the natural history of hepatitis B virus (HBV) infection and the potential for therapy of the resultant disease is continuously improving. New data have become available since the previous EASL Clinical Practice Guidelines (CPGs) prepared in 2008 and published in early 2009 [1]. The objective of this manuscript is to update the recommendations for the optimal management of chronic HBV infection. The CPGs do not fully address prevention including vaccination. In addition, despite the increasing knowledge, areas of uncertainty still exist and therefore clinicians, patients, and public health authorities must con-

been increasing over the last decade as a result of aging of the HBV-infected population and predominance of specific HBV genotypes and represents the majority of cases in many areas, including Europe [4,9,10]. Morbidity and mortality in CHB are linked to persistence of viral replication and evolution to cirrhosis and/or hepatocellular carcinoma (HCC). Longitudinal studies of untreated patients with CHB indicate that, after diagnosis, the 5-year cumulative incidence of developing cirrhosis ranges from 8% to 20%. The 5-year cumulative incidence of hepatic decompensation is approximately 20% for untreated patients with compensated cirrhosis [2–4,11–13]. Untreated patients with decompensated cirrhosis have a poor prognosis with a 14–35%

İlk seçenek olarak optimal direnç profiline sahip, en potent ilaçlar, tenofovir ve entekavir kullanılmalıdır (A1).

EASL CPG. J Hepatol 2012;57:167

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Tedaviye onaylı 7 ilaçla da başlanabilir ancak uzun süreli tedavi gereksinimi göz önüne alındığında PEG IFN alfa, tenofovir ya da entekavir tercih edilmelidir.

Lok ASF et al. Hepatology 2009;50:1

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Uzun süreli tedavide yüksek ilaç direnci oranları göz önüne alındığında lamivudin ve telbivudin tercih edilmemelidir.

Lok ASF et al. Hepatology 2009;50:1

Hepatol Int (2012) 6:531–561
DOI 10.1007/s12072-012-9365-4

GUIDELINES

Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update

Yun-Fan Liaw · Jia-Horng Kao · Teerha Piratvisuth · Henry Lik Yuen Chan · Rong-Nan Chien · Chun-Jen Liu · Ed Gane · Stephen Locarnini · Seng-Gee Lim · Kwang-Hyub Han · Deepak Amarapurkar · Graham Cooksley · Wasim Jafri · Rosmawati Mohamed · Jin-Lin Hou · Wan-Long Chuang · Laurentius A. Lesmana · Jose D. Sollano · Dong-Jin Suh · Masao Omata

Received: 22 December 2011 / Accepted: 8 March 2012 / Published online: 17 May 2012
© Asian Pacific Association for the Study of the Liver 2012

Tenofovir ve entekavirin viral baskılanma ve ilaç direnci profilleri lamivudin ve adefovire göre daha iyidir ve ilk seçenek tedavi bu iki ilaçtan biri olmalıdır.

Liaw YF et al. Hepatol Int 2012;6:531

Kronik hepatit B tedavisi için ilk sırada önerilen ilaçlar peginterferon, tenofovir ve entekavirdir.

Etkin viral baskılanma

Optimal direnç profili

Kronik HBV infeksiyonu tedavisinde antiviral ilaç direnci niçin dikkate alınmalı?

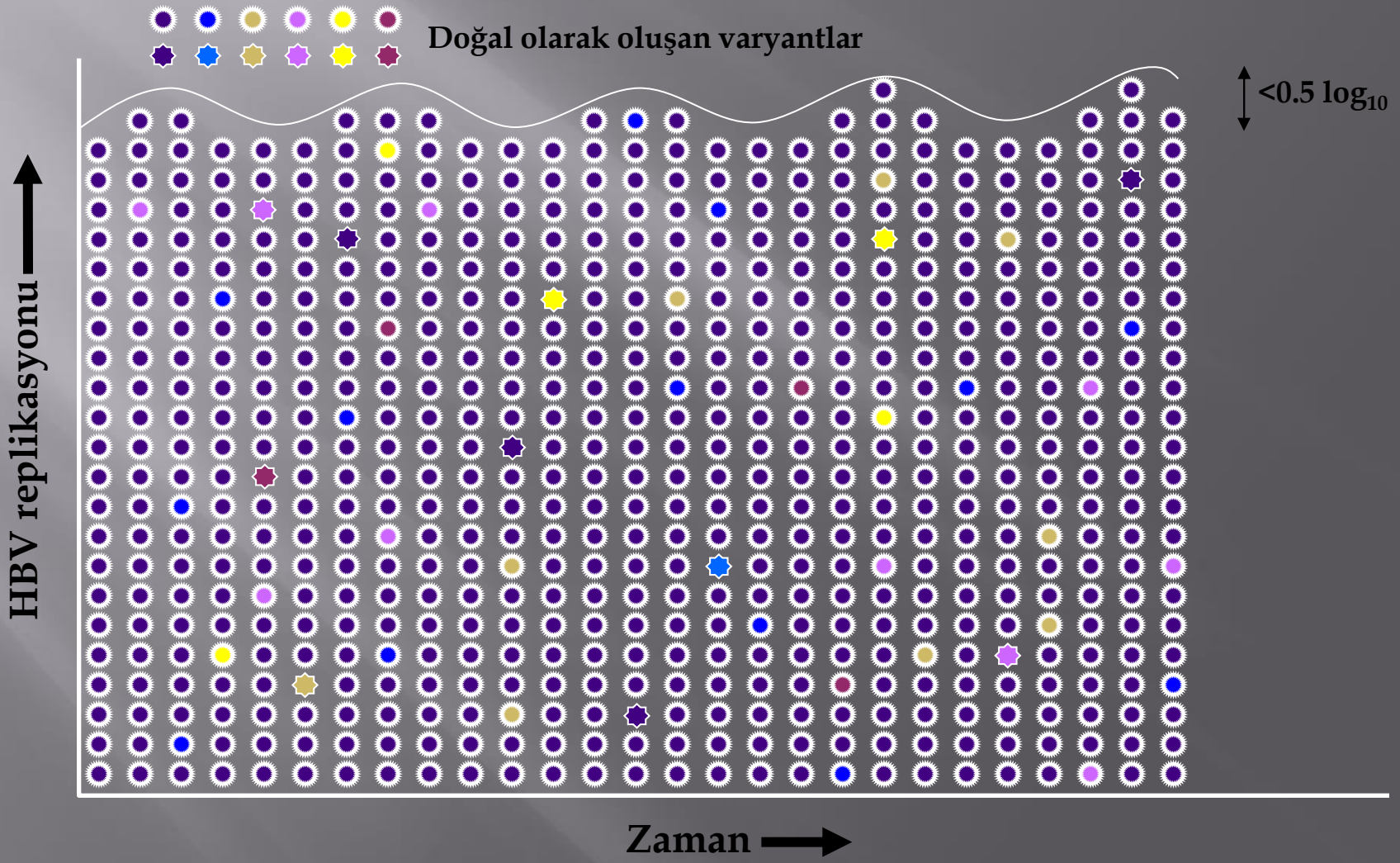
Tek hedef

HBV polimeraz

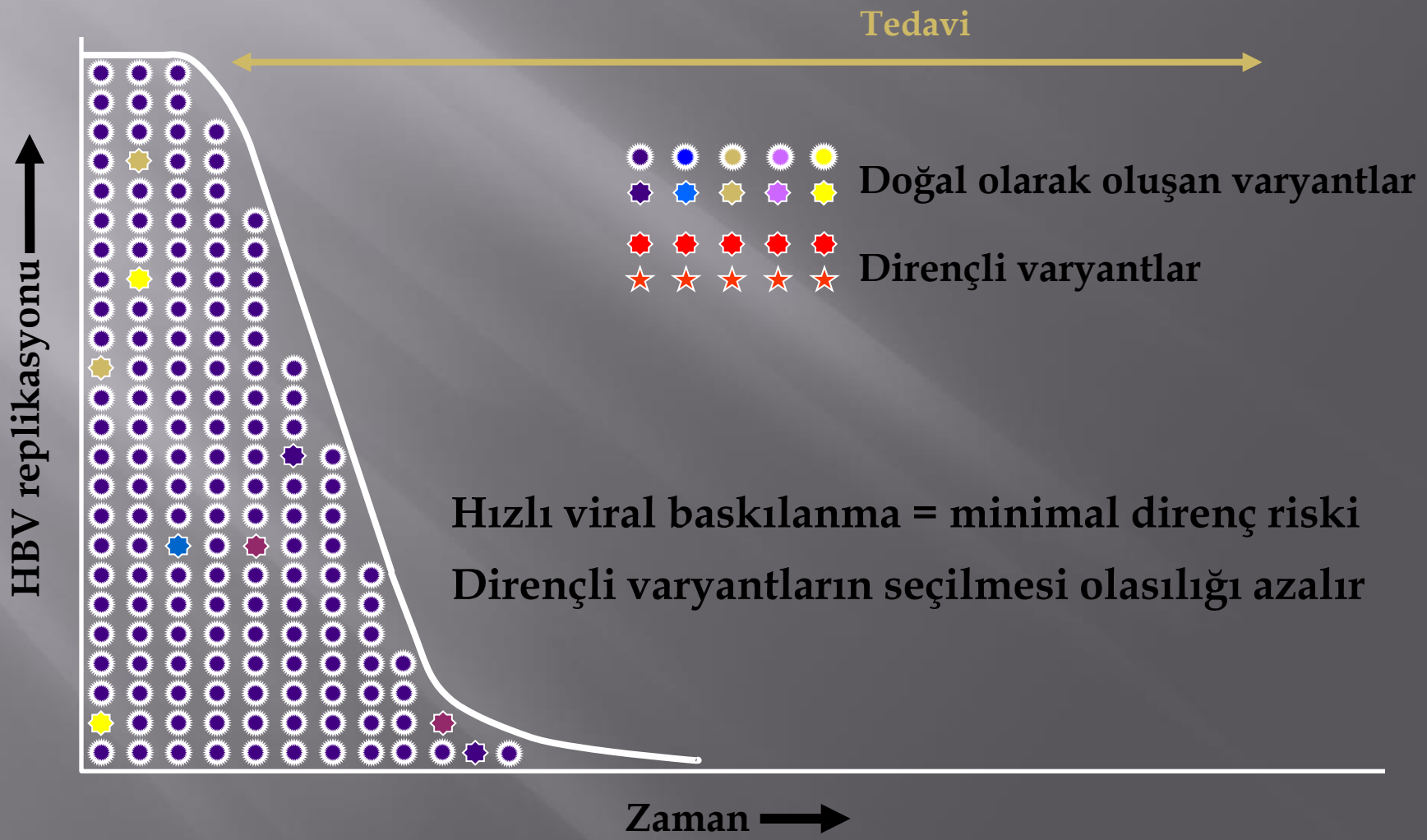
Tek sınıf ilaç (nükleozid/nükleotid analogları)

Etkin viral baskılanma

Ortamda antiviral ilaç yokken viral popülasyon



Replikasyonun maksimum süpresyonu direnç gelişimini minimize eder

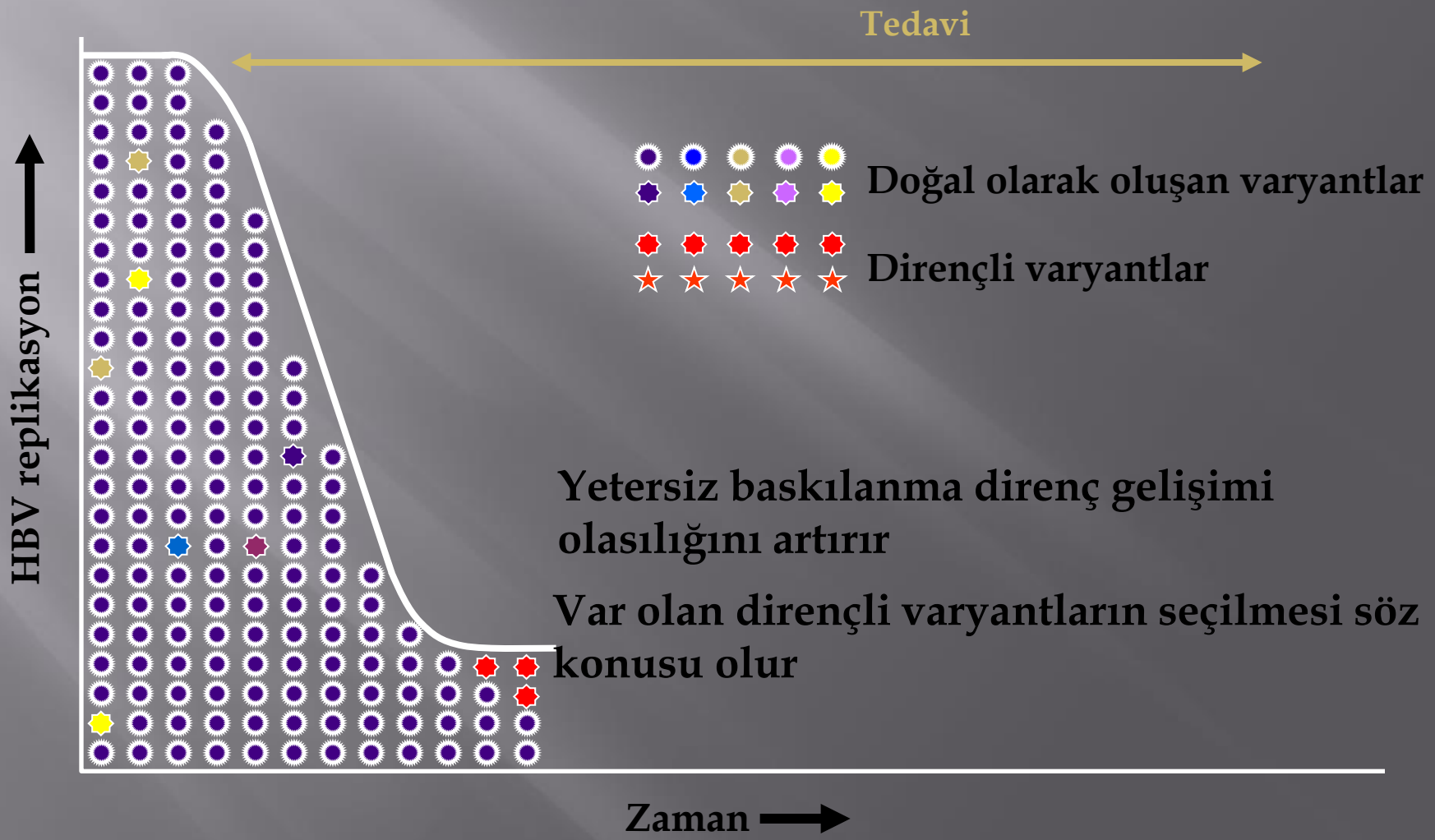


Hızlı viral baskılanma = minimal direnç riski

Dirençli varyantların seçilmesi olasılığı azalır

Replikasyonun yetersiz baskılanması dirençli varyantların seçilmesine olanak sağlar

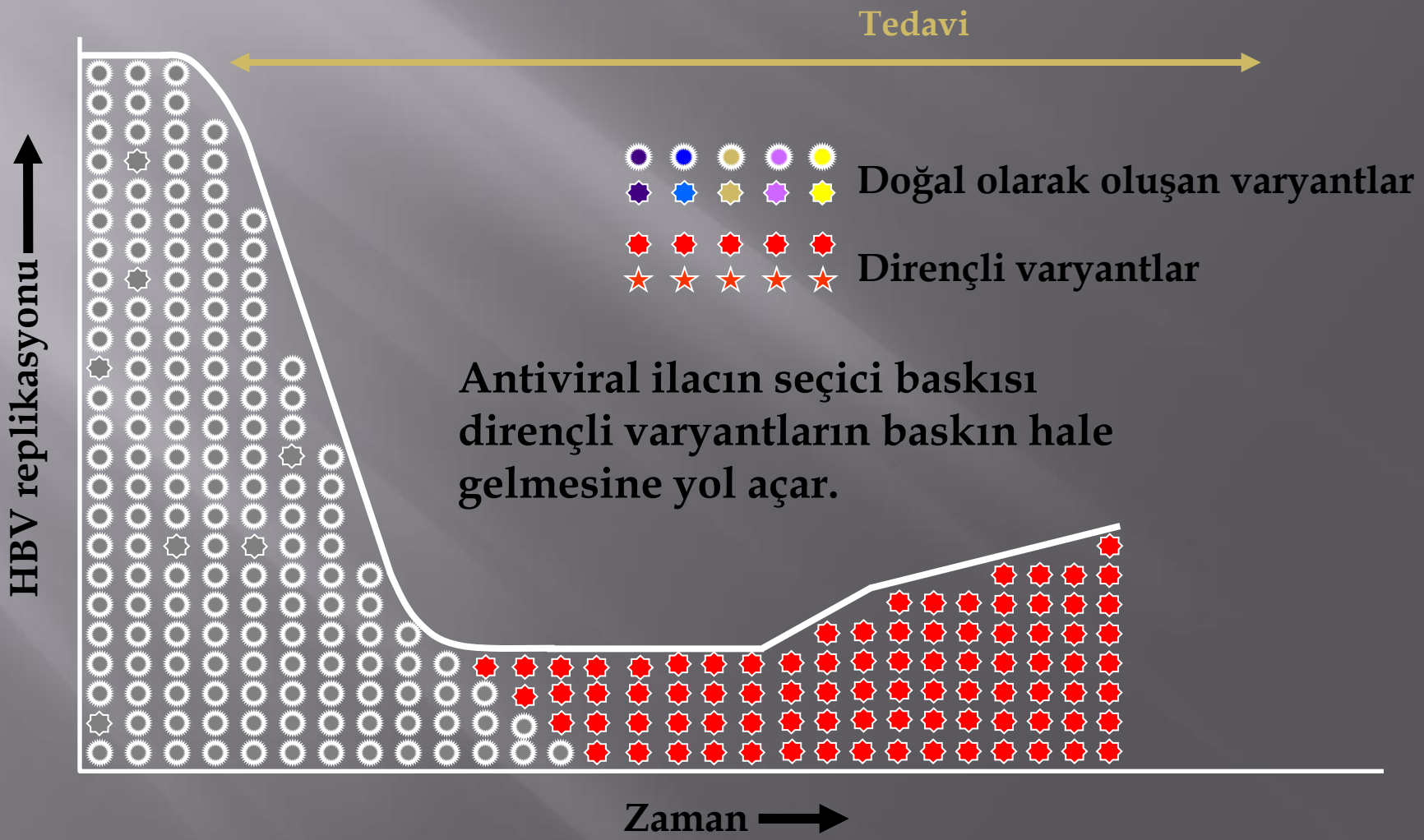
Replikasyonun yetersiz baskılanması dirençli varyantların seçilmesine olanak sağlar



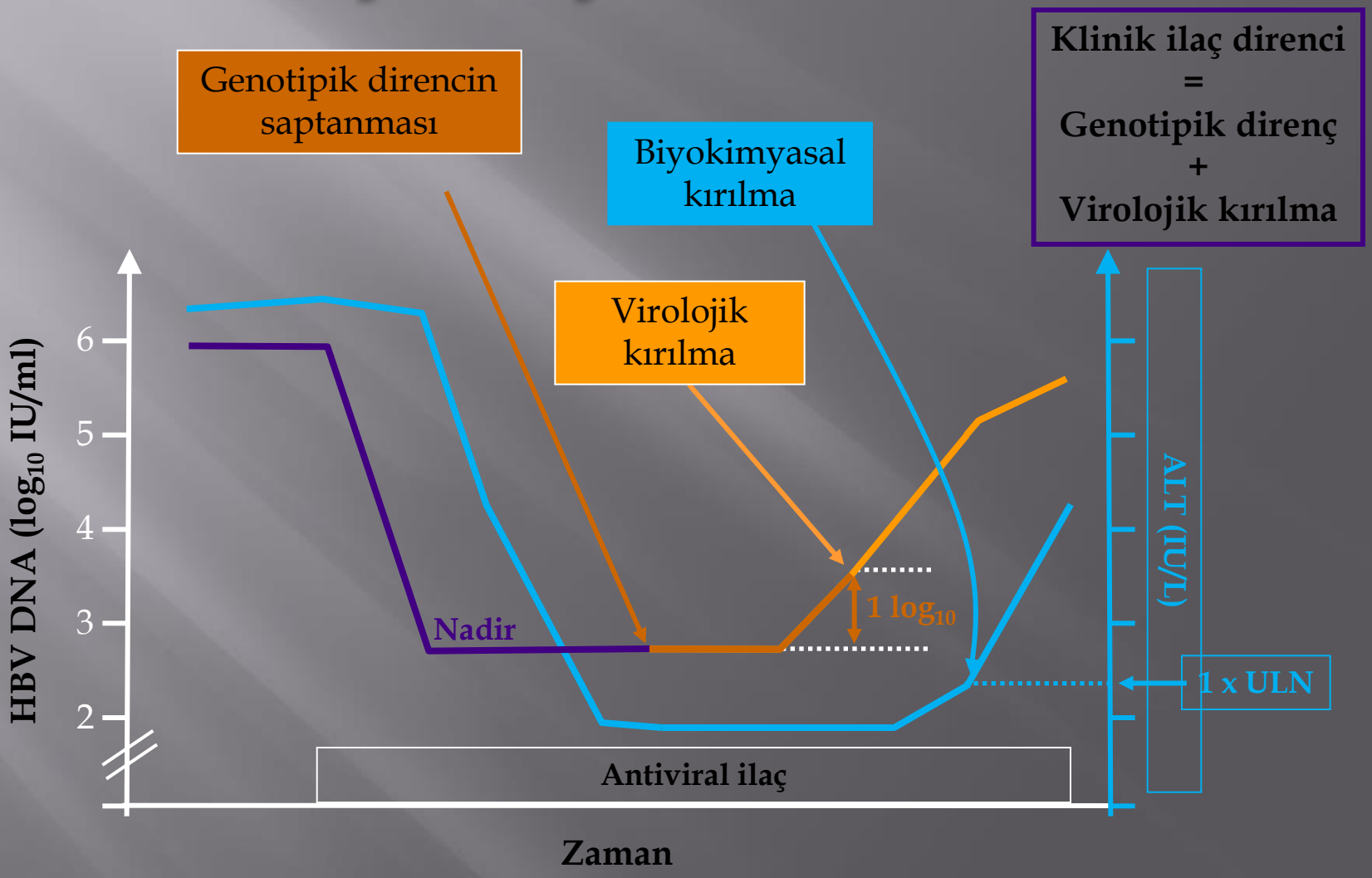
Yetersiz baskılanma direnç gelişimi olasılığını artırır

Var olan dirençli varyantların seçilmesi söz konusu olur

Replikasyonun yetersiz baskılanması dirençli varyantların seçilmesine olanak sağlar



Genotipik direnç, virolojik ve biyokimyasal kırılma



Sosyal Güvenlik Kurumundan:

SOSYAL GÜVENLİK KURUMU SAĞLIK UYGULAMA TEBLİĞİ

BİRİNCİ BÖLÜM 5
GENEL HÜKÜMLER 5

Etkin viral baskılanmayı / tedaviye yanıtı değerlendirmek için 24. hafta uygun mudur?

JOURNAL OF VIRAL HEPATITIS
JVH

Journal of Viral Hepatitis, 2013, **20**, e37–e46 doi:10.1111/jvh.12025

Efficacy and safety of continuous 4-year telbivudine treatment in patients with chronic hepatitis B

Y. Wang,[1] S. Thongsawat,[2] E. J. Gane,[3] Y.-F. Liaw,[4] J. Jia,[5] J. Hou,[6] H. L. Y. Chan,[7] G. Papatheodoridis,[8] M. Wan,[9] J. Niu,[10] W. Bao,[11] A. Trylesinski[12] and N. V. Naoumov[12]

[1]*Institute of Infectious Diseases, Southwest Hospital, Third Military Medical University, Chongqing, China;* [2]*Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand;* [3]*New Zealand Liver Unit, Auckland City Hospital, Auckland, New Zealand;* [4]*Liver Research Unit, Chang Gung Memorial Hospital & University, Taipei, Taiwan;* [5]*Liver Research Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China;* [6]*Hepatology Unit and Department of Infectious Diseases, Nanfang Hospital, Guangzhou, China;* [7]*Medicine and Therapeutics, Chinese University of Hong Kong, Hong Kong, China;* [8]*Academic Department of Medicine, Hippokration General Hospital, Athens, Greece;* [9]*Department of Infectious Diseases, ChangHai Hospital of the Second Military Medical University, Shanghai, China;* [10]*Department of Hepatology, First hospital of Jilin University, Jilin, China;* [11]*Novartis Pharma Corporation, East Hanover, NJ, USA; and* [12]*Novartis Pharma AG, Basel, Switzerland*

Faz III GLOBE ve 015 çalışmalarından, bu çalışmaların sonunda telbivudine genetik direnci olmayan 596 hasta, 2 yıl

Wang Y et al. J Viral Hepat 2013;20:e37

JOURNAL OF VIRAL HEPATITIS
JVH

Journal of Viral Hepatitis, 2013, **20**, e37–e46 doi:10.1111/jvh.12025

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4 yılı tamamlayan 502 hasta

HBeAg (+)	HBeAg (-)
(n=293)	(n=209)

4. yıl sonunda HBV DNA (-)

%76.2	%86.4

Wang Y et al. J Viral Hepat 2013;20:e37

JOURNAL OF VIRAL HEPATITIS
JVH

Journal of Viral Hepatitis, 2013, **20**, e37–e46 doi:10.1111/jvh.12025

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Kümülatif 4 yıllık direnç oranı

HBeAg (+)	HBeAg (-)
%10.6	%10

Wang Y et al. J Viral Hepat 2013;20:e37

Original Paper

Digestion

Digestion 2013;88:266–271
DOI: 10.1159/000356312

Received: August 6, 2013
Accepted: September 30, 2013
Published online: December 12, 2013

Lamivudine Treatment Failure Risks in Chronic Hepatitis B Patients with Low Viral Load

Seyfettin Koklu[a] Murat Taner Gulsen[g] Yasar Tuna[h] Hayretdin Koklu[b]
Osman Yuksel[a] Baris Yilmaz[c] Cetin Karaca[i] Huseyin Ataseven[j]
Rahmet Guner[d] Metin Kucukazman[e] Cem Kockar[k] Mehmet Demir[l]
Orhan Kursat Poyrazoglu[m] Mehmet Ibis[b] Tugrul Purnak[f] Sezgin Etgul[a]
Erhan Alkan[h] Sahin Coban[c] Suut Gokturk[i] Murat Biyik[j] Ozlem Baykal[k]
Omer Basar[h] Nimet Koklu[n] Gonca Tatar[a] Halis Simsek[a]

548 hasta LAM tedavisi, LVL

HBeAg (+), HBV DNA $<10^9$ kopya/ml

HBeAg (-), HBV DNA $<10^7$ kopya/ml

46 hasta LAM tedavisi, HVL

Koklu S et al. Digestion 2013;88:266

Original Paper

Digestion

Digestion 2013;88:266–271
DOI: 10.1159/000356312

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Lamivudine Treatment Failure Risks in Chronic Hepatitis B Patients with Low Viral Load

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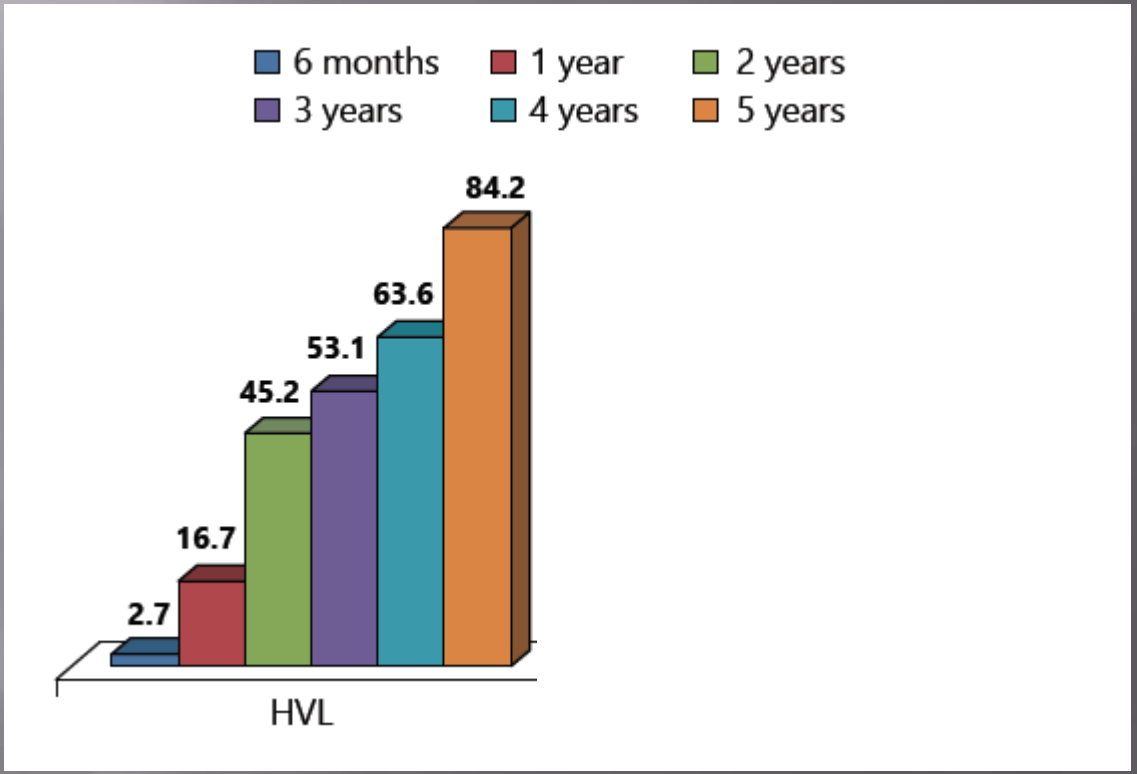
Rahmet Guner[d] Metin Kucukazman[e] Cem Kockar[k] Mehmet Demir[l]

Düşük viral yükü olan hastalarda LAM ile tedavi başarısızlığı görülür mü?

LAM ile tedavi başarısızlığı olasılığını azaltacak bir HBV DNA düzeyi var mıdır?

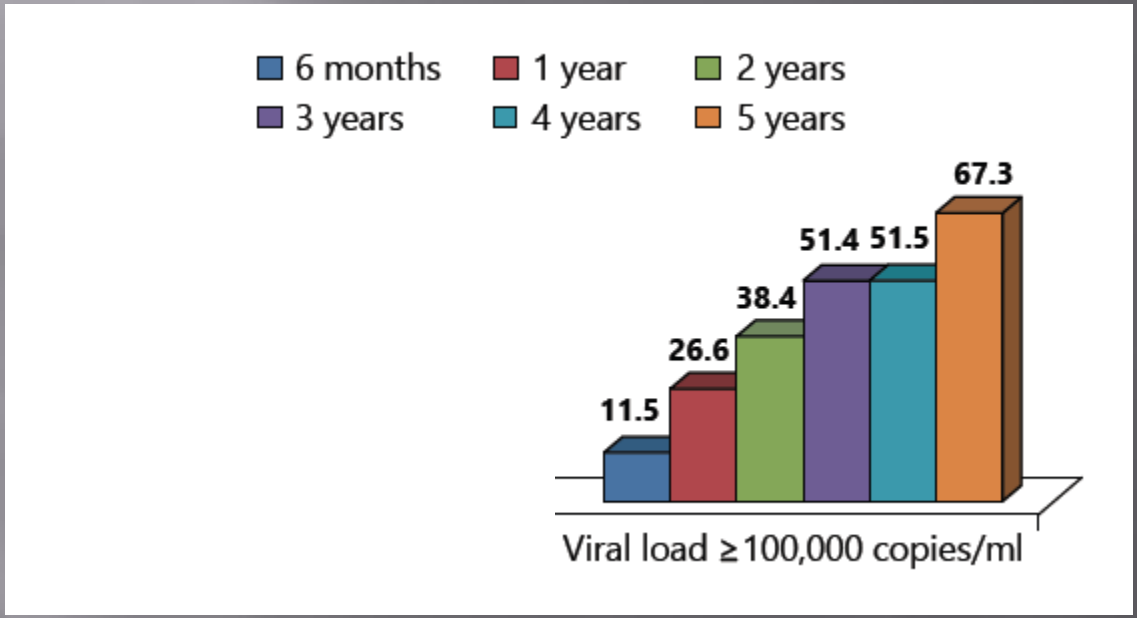
Erken virolojik yanıt gerçekten LAM tedavi başarısını öngördürür mü?

Koklu S et al. Digestion 2013;88:266



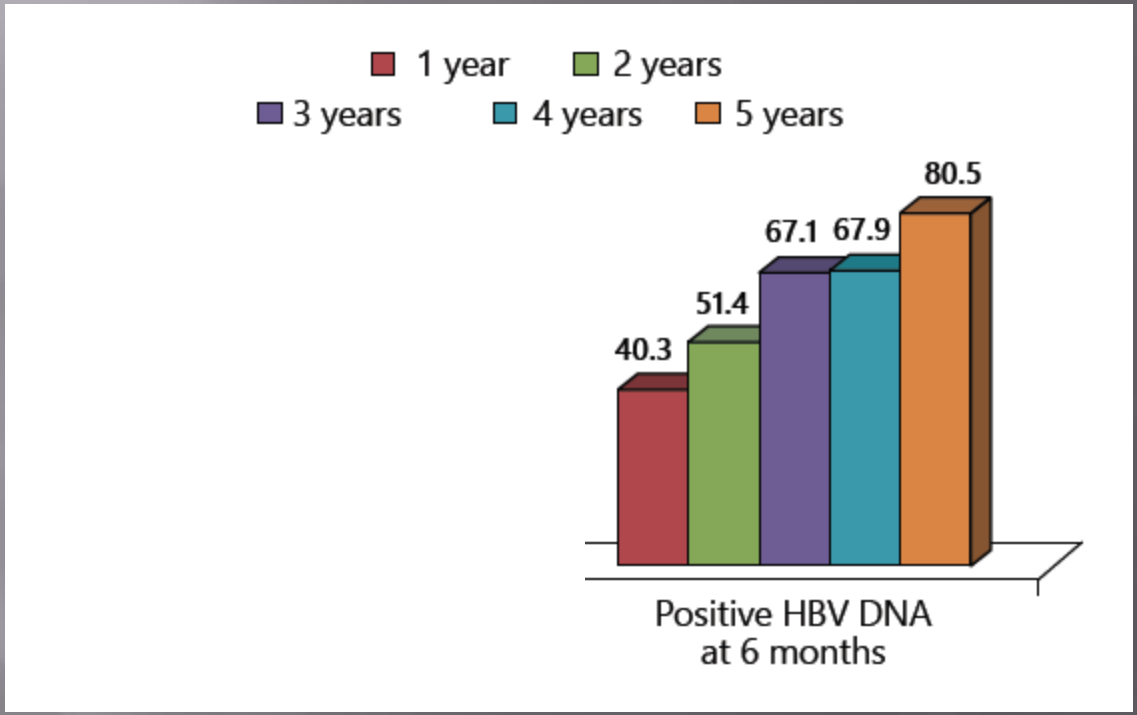
Düşük viral yükü olan hastalarda LAM ile tedavi başarısızlığı görülür mü?

Koklu S et al. Digestion 2013;88:266



LAM ile tedavi başarısızlığı olasılığını azaltacak bir HBV DNA düzeyi var mıdır?

Koklu S et al. Digestion 2013;88:266



Erken virolojik yanıt gerçekten LAM tedavi başarısını öngördürür mü?

Koklu S et al. Digestion 2013;88:266

Sonuç olarak,

Başlangıçta düşük HBV DNA düzeyleri ve 24. haftada HBV DNA < 50 IU/ml olması, LAM ya da LdT için uzun dönem yanıtı öngörmede yeterli değildir.

Antiviral direncinin olası klinik sonuçları

Antiviral direncinin olası klinik sonuçları

ELSEVIER

Journal of Hepatology 39 (2003) S133–S138

Journal of Hepatology

www.elsevier.com/locate/jhep

Hepatitis B virus resistance to antivirals: clinical implications and management

Fabien Zoulim*

INSERM U 271 and Liver Department, Institut Universitaire de France, 151 Cours Albert Thomas, F-69003 Lyon, France

HBV DNA düzeylerinde yükselme,

ALT alevlenmesi,

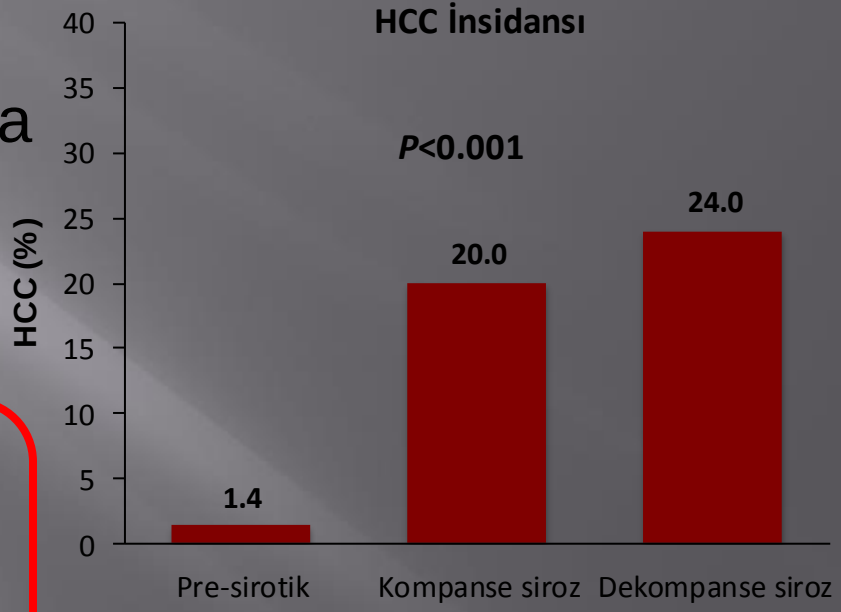
Karaciğer hastalığının histolojik progresyonu,

Karaciğer transplantasyonu gereksinimi

Zoulim F et al. J Hepatol 2003;39:S133

Genotip D Sirotik Hepatit B'li hastalarda HCC Gelişimi

- 661 KHB hasta
- HCC gelişimi: 57 (8.6%) hasta
- HCC gelişimi ile ilgili faktörler (çok değişkenli analiz):
  - Siroz (P = 0.000)
  - **Düşük genetik bariyerli ilaç rejimi (p=0.02)**
  - **Direnç-virolojik kırılma (p = 0.04)**



Direnç/virolojik kırılma gelişmesi, düşük genetik bariyerli NA ile tedavi ve sirotik evrede olmak NA ile tedavi edilen KHB'li hastalarda HCC gelişme riskini arttırmaktadır.

Gokturk S, et al. AASLD 2013. Washington, DC. #990

Antiviral direncinin olası klinik sonuçları

HBV variants	Lamivudin	Telbivudin	Entekavir	Adefovir	Tenofovir
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.

Contents lists available at ScienceDirect

Digestive and Liver Disease

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

Liver, Pancreas and Biliary Tract

Role of hepatitis B virus genetic barrier in drug-resistance and immune-escape development

Valentina Svicher[a,1], Valeria Cento[a,1], Romina Salpini[a], Fabio Mercurio[a], Maria Fraune[b], Bastian Beggel[b], Yue Han[c], Caterina Gori[d], Linda Wittkop[e], Ada Bertoli[f], Valeria Micheli[g], Guido Gubertini[g], Roberta Longo[h], Sara Romano[h], Michela Visca[h], Valentina Gallinaro[i], Nicoletta Marino[j], Francesco Mazzotta[j], Giuseppe Maria De Sanctis[i], Hervè Fleury[e], Pascale Trimoulet[e], Mario Angelico[a], Giuseppina Cappiello[h], Xin Xin Zhang[c], Jens Verheyen[b], Francesca Ceccherini-Silberstein[a], Carlo Federico Perno[a,*]

Virüsün ilaç baskısından kurtulması için gereken nükleotid değişikliklerinin sayısı ve tipi olarak tanımlanır.

Svicher V et al. Dig Liver Dis 2011;43:975

Liver INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE LIVER

Liver International ISSN 1478-3223

Hepatitis B virus resistance to antiviral drugs: where are we going?

Fabien Zoulim[1,2,3]

1 INSERM, U871, Lyon, France
2 Université de Lyon, 69001 Lyon, France
3 Hepatology Department, Hospices Civils de Lyon, 69002 Lyon, France

Dirence karşı yüksek bariyeri olan ilaçlar ile

düşük direnç oranları,

direnç gelişimiyle ilişkili komplikasyonların sıklığında azalma

Zoulim F et al. Liver Int 2011;31(S1):111

Optimal direnç profili

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*

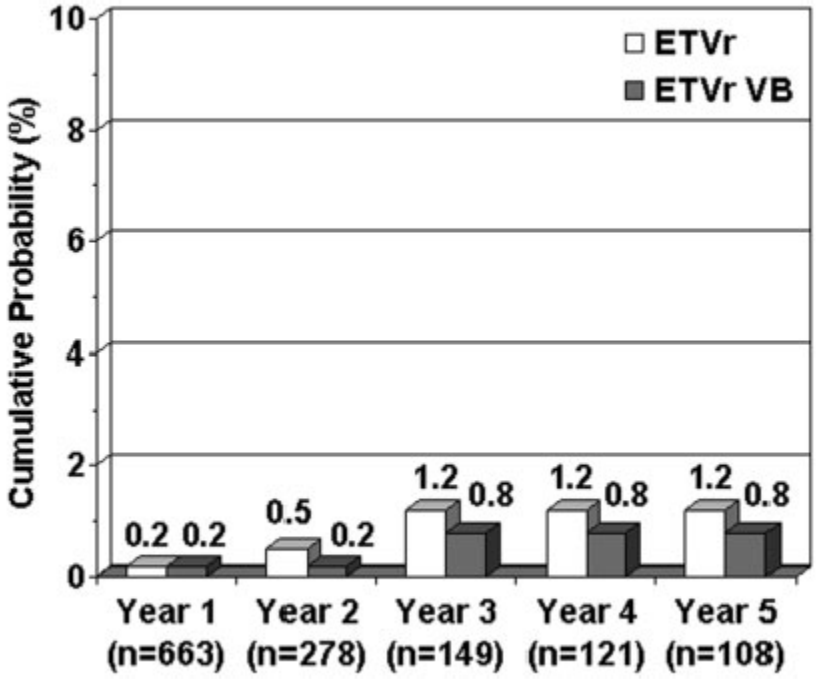
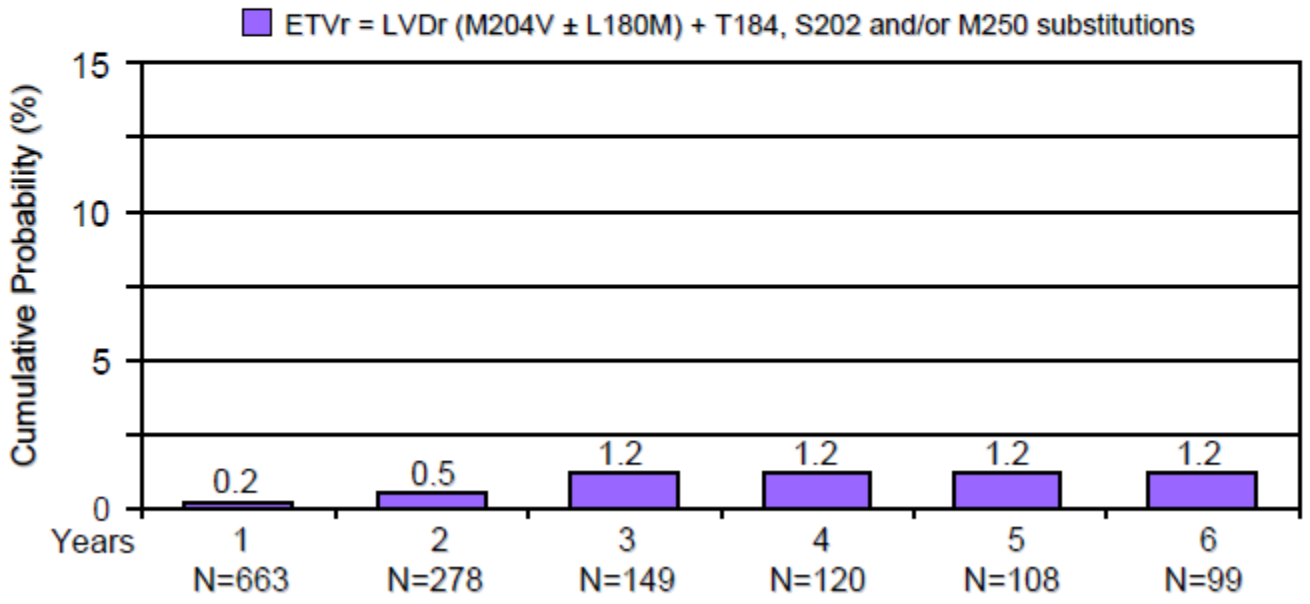


Fig. 1. Cumulative probabilities of ETVr in nucleoside-naïve patients.

Hepatology 2009;49:1503

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



Tenney DJ et al. DDW 2009;P. W1805

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*

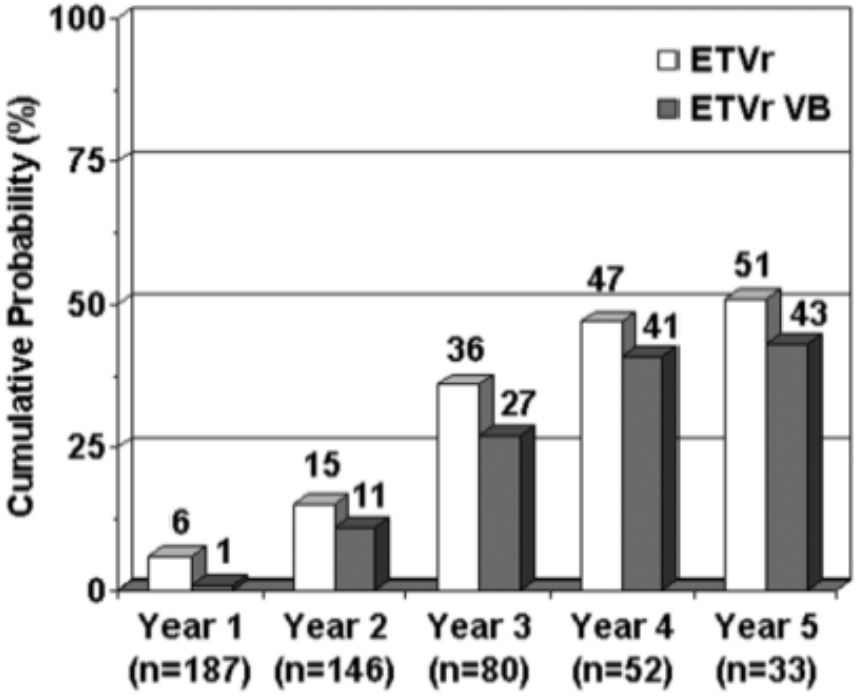
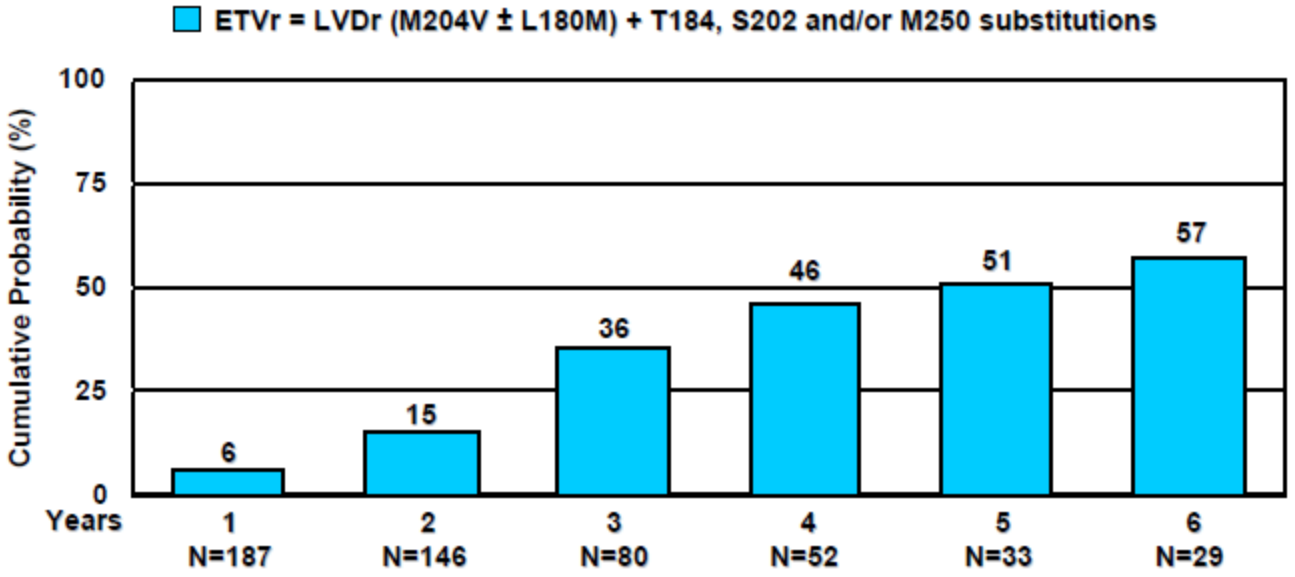


Fig. 3. Cumulative probabilities of ETVr in LVD-refractory patients.

Hepatology 2009;49:1503

Figure 4. Lamivudine-Refractory Cohort (HBeAg+): Cumulative Probability of ETV Resistance Through 6 Years



Tenney DJ et al. DDW 2009;P. W1805

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

No Detectable Resistance to Tenofovir Disoproxil Fumarate After 6 Years of Therapy in Patients With Chronic Hepatitis B

Kathryn M. Kitrinos,[1] Amoreena Corsa,[1] Yang Liu,[1] John Flaherty,[1] Andrea Snow-Lampart,[1] Patrick Marcellin,[2] Katyna Borroto-Esoda,[1] and Michael D. Miller[1]

585 hasta,
288 hafta

Kitrinos KM et al. Hepatology 2014;59:434

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

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

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

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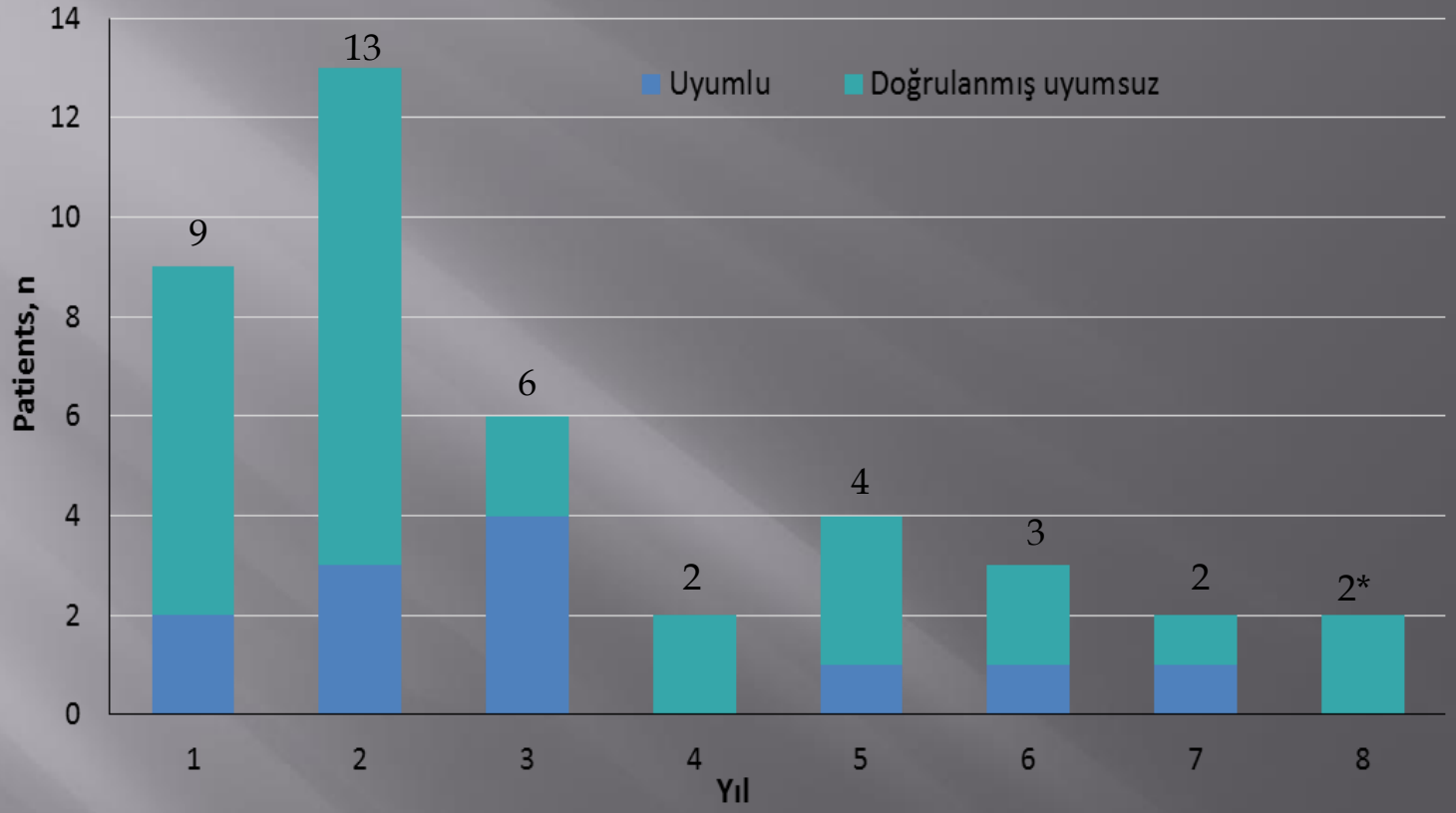
Tenofovir direnci yok

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



Sekiz yılda virolojik kırılma saptanan hastalar

Corsa, AASLD, 2014, Poster #1707

Corsa AASLD 2014, poster #1707

AAC
Journals.ASM.org

Efficacy of Tenofovir in Patients with Lamivudine Failure Is Not Different from That in Nucleoside/Nucleotide Analogue-Naïve Patients with Chronic Hepatitis B

Bulent Baran,[a] Ozlem Mutluay Soyer,[a] Asli Cifcibasi Ormeci,[a] Suut Gokturk,[a] Sami Evirgen,[a] Hamza Ugur Bozbey,[b] Filiz Akyuz,[a] Cetin Karaca,[a] Kadir Demir,[a] Fatih Besisik,[a] Derya Onel,[c] Mine Gulluoglu,[d] Selim Badur,[c] Sabahattin Kaymakoglu[a]
Istanbul University, Istanbul Faculty of Medicine, Departments of Gastroenterohepatology,[a] Internal Medicine,[b] Microbiology,[c] and Pathology,[d] Capa, Istanbul, Turkey

TDF teda … ları,
WT'e ber … şüş
kinetiği gö …

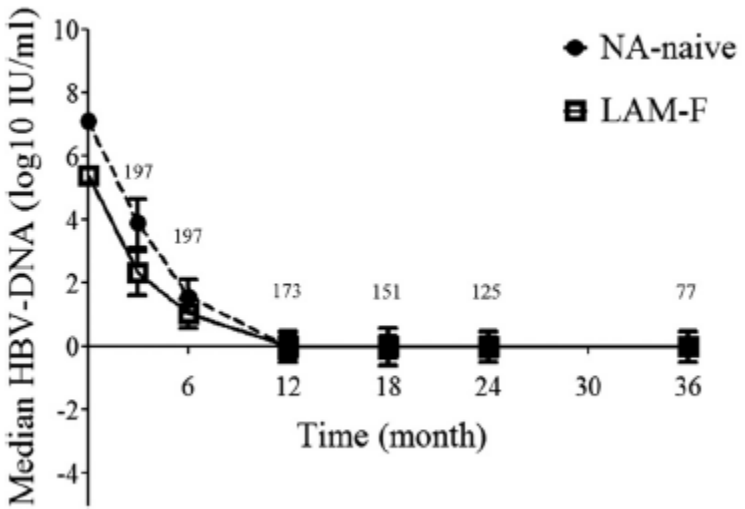


FIG 2 Changes in the median HBV DNA level were similar in the two groups.

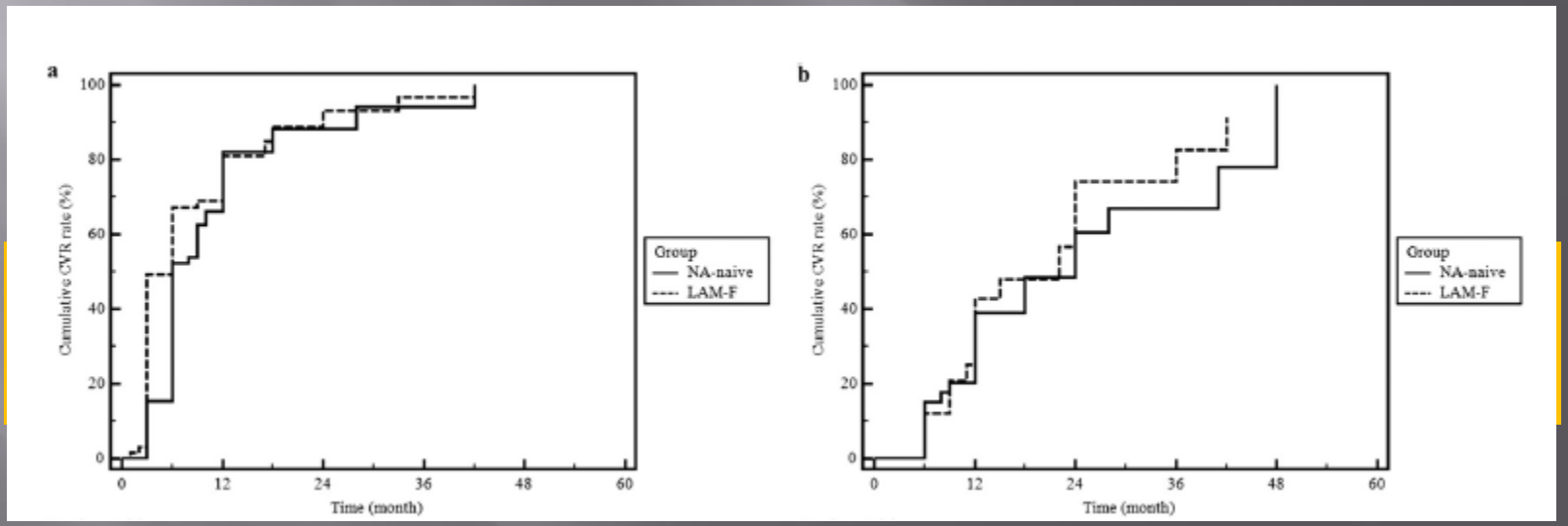
Baran B et al. Antimicrob Agents Chemother 2013;57:1790

AAC
Journals.ASM.org

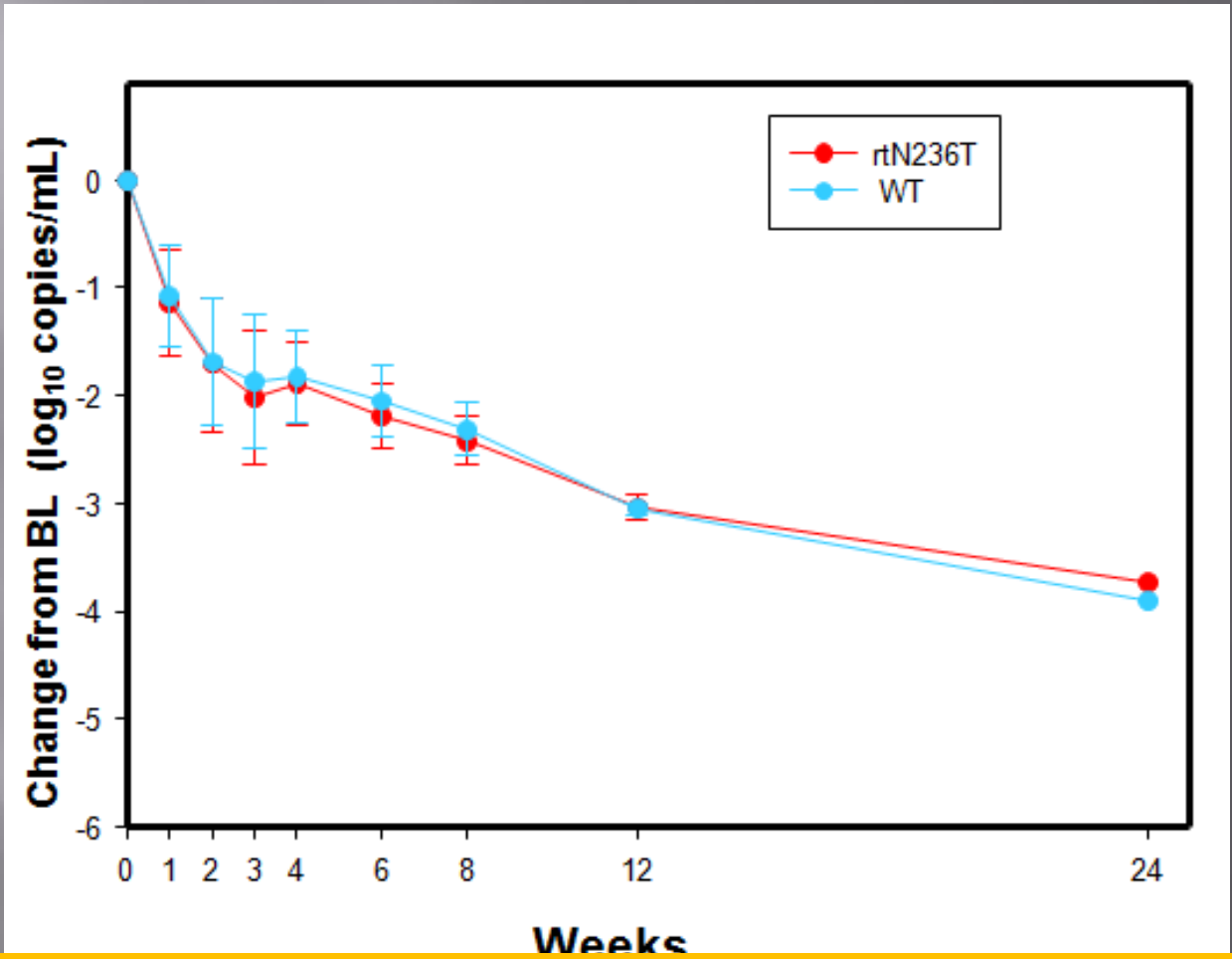
Efficacy of Tenofovir in Patients with Lamivudine Failure Is Not Different from That in Nucleoside/Nucleotide Analogue-Naïve Patients with Chronic Hepatitis B

Bulent Baran,[a] Ozlem Mutluay Soyer,[a] Asli Cifcibasi Ormeci,[a] Suut Gokturk,[a] Sami Evirgen,[a] Hamza Ugur Bozbey,[b] Filiz Akyuz,[a] Cetin Karaca,[a] Kadir Demir,[a] Fatih Besisik,[a] Derya Onel,[c] Mine Gulluoglu,[d] Selim Badur,[c] Sabahattin Kaymakoglu[a]

Istanbul University, Istanbul Faculty of Medicine, Departments of Gastroenterohepatology,[a] Internal Medicine,[b] Microbiology,[c] and Pathology,[d] Capa, Istanbul, Turkey



Baran B et al. Antimicrob Agents Chemother 2013;57:1790



TDF tedavisi ile rtN236T subpopulasyonları, WT'e benzer biçimde erken HBV DNA düşüş kinetiği gösterirler.

Sosyal Güvenlik Kurumundan:

SOSYAL GÜVENLİK KURUMU SAĞLIK UYGULAMA TEBLİĞİ

BİRİNCİ BÖLÜM 6
GENEL HÜKÜMLER 6

(3) Oral antiviral tedaviye;

a) Erişkin hastalarda; günde 100 mg lamivudin veya 600 mg telbivudin veya 245 mg tenofovir veya 0,5 mg

İlk seçenek olarak dirence karşı yüksek genetik bariyeri olan ilaçların seçilmesi uzun dönemde başarılı tedavi olasılığını artırır.

Uluslararası kılavuzlar

AASLD PRACTICE GUIDELINE UPDATE

Chronic Hepatitis B: Update 2009

Anna S. F. Lok[1] and Brian J. McMahon[2]

Based on these new findings, the recommendation for first-line oral antiviral medications has been changed to tenofovir or entecavir, and adefovir has been moved to second-line oral antiviral medication.

Clinical Practice Guidelines

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

EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection

European Association for the Study of the Liver*

Entecavir and tenofovir are potent HBV inhibitors with a high barrier to resistance [67,70,78,85,92,123] (Fig. 1). Thus, they can be confidently used as first-line monotherapies [1] (**A1**).

APASL guidelines for HBV management

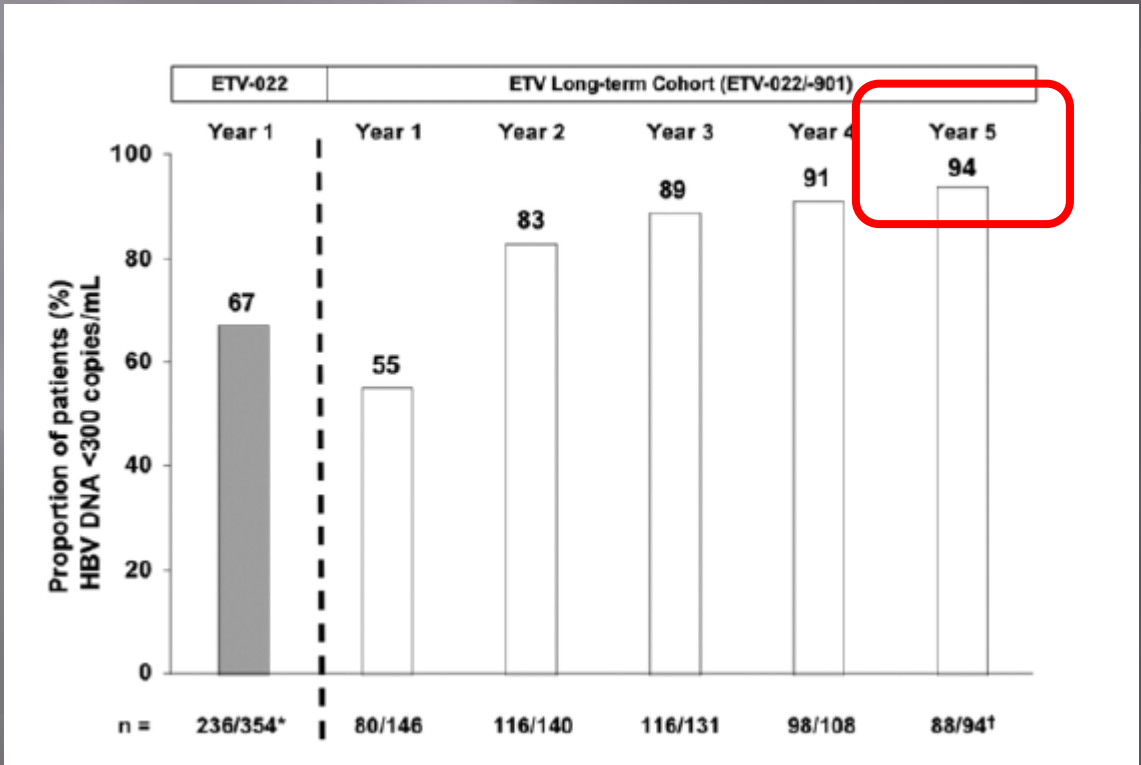
Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update

considered [5]. In general, the first-line therapy should be either ETV or TDF, and the second-line therapy should be LdT, ADV, and LAM. Nonetheless, pharmacoeconomic

Etkinlik

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

8. Yılda Etkinlik Değerleri

	HBeAg-	HBeAg+
HBV DNA <29 IU/mL (ITT)* %	74	58
HBV DNA <29 IU/mL (gözlenen), %	99.6	97
HBeAg kaybı / serokonversiyon†, %	NA	47/ 31
HBsAg kaybı[a]/serokonversiyon (KM%) ‡	1.1/0.7	12.9/10.3

Marcellin P AASLD 2014, oral #229

Gerçek yaşam

Research Article

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

Long-term continuous entecavir therapy in nucleos(t)ide-naïve chronic hepatitis B patients

Atsushi Ono[1], Fumitaka Suzuki[1,*], Yusuke Kawamura[1], Hitomi Sezaki[1], Tetsuya Hosaka[1], Norio Akuta[1], Masahiro Kobayashi[1], Yoshiyuki Suzuki[1], Satoshi Saitou[1], Yasuji Arase[1], Kenji Ikeda[1], Mariko Kobayashi[2], Sachiyo Watahiki[2], Rie Mineta[2], Hiromitsu Kumada[1]

[1]*Department of Hepatology, Toranomon Hospital, Tokyo, Japan;* [2]*Research Institute for Hepatology, Toranomon Hospital, Tokyo, Japan*

474 hasta,
Medyan takip süresi 2.4 yıl
1, 2, 3, 4. yılda 403, 281, 165, 73 hasta

Ono A et al. J Hepatol 2012;57:508

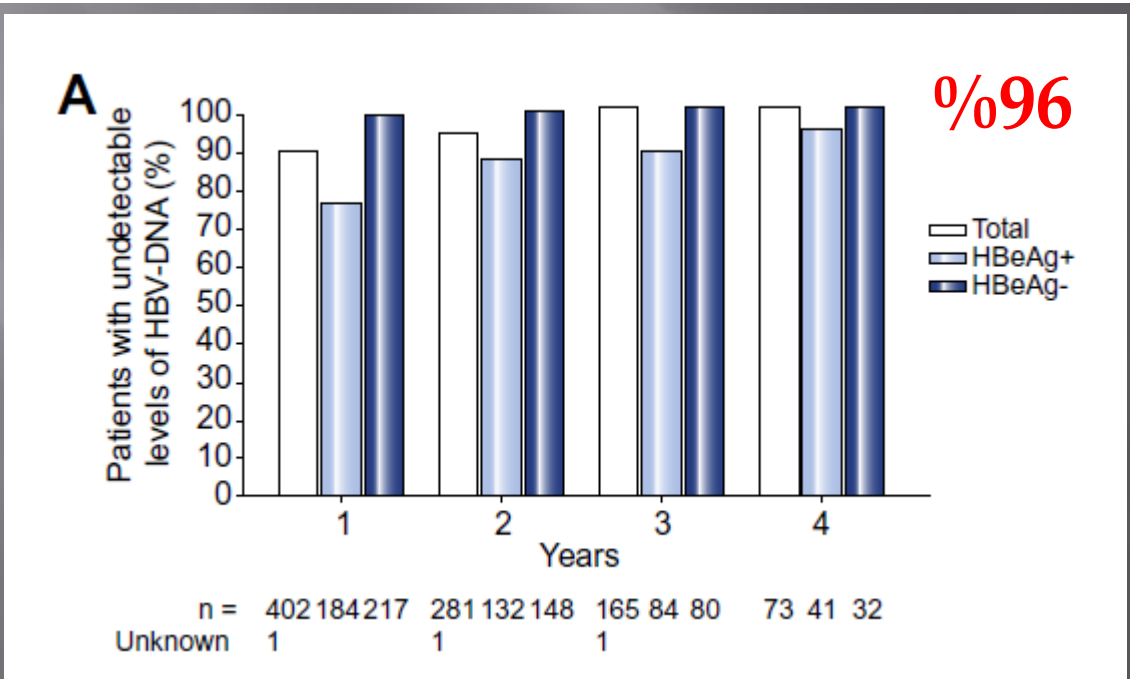
Research Article

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

Long-term continuous entecavir therapy in nucleos(t)ide-naïve chronic hepatitis B patients

Atsushi Ono[1], Fumitaka Suzuki[1,*], Yusuke Kawamura[1], Hitomi Sezaki[1], Tetsuya Hosaka[1], Norio Akuta[1], Masahiro Kobayashi[1], Yoshiyuki Suzuki[1], Satoshi Saitou[1], Yasuji Arase[1], Kenji Ikeda[1], Mariko Kobayashi[2], Sachiyo Watahiki[2], Rie Mineta[2], Hiromitsu Kumada[1]

[1]*Department of Hepatology, Toranomon Hospital, Tokyo, Japan;* [2]*Research Institute for Hepatology, Toranomon Hospital, Tokyo, Japan*



Ono A et al. J Hepatol 2012;57:508

Efficacy and safety of TenofovirDisoproxilFumarate in Turkish patients with chronic hepatitis B: Four year real-life data

BAYKAM N[1,2], TUTUNCU E[3], GUNER R[4], YAMAZHAN T[5], HIZEL K[6], KANDEMIR O[7], INAN D[8].

Clinics of Infectious Diseases and Clinical Microbiology

[1]Hitit University Faculty of Medicine

[2]Ankara Numune Training and Research Hospital,

[3]Diskapi YildirimBeyazitTraining and Research Hospital

[4]Yildirim Beyazit University Faculty of Medicine, Ataturk Training and Research Hospital

[5]EgeUniversity, Faculty of Medicine

[6]Gazi University, Faculty of Medicine

[7]Mersin University, Faculty of Medicine

[8]Akdeniz University, Faculty of Medicine

206 hasta,
1, 2, 3, 4. yılda 206, 177, 118, 67 hasta

Baykam N et al. Yayınlanmamış veri

Efficacy and safety of TenofovirDisoproxilFumarate in Turkish patients with chronic hepatitis B: Four year real-life data

BAYKAM N[1,2], TUTUNCU E[3], GUNER R[4], YAMAZHAN T[5], HIZEL K[6], KANDEMIR O[7], INAN D[8].

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[7]Mersin University, Faculty of Medicine

[8]Akdeniz University, Faculty of Medicine

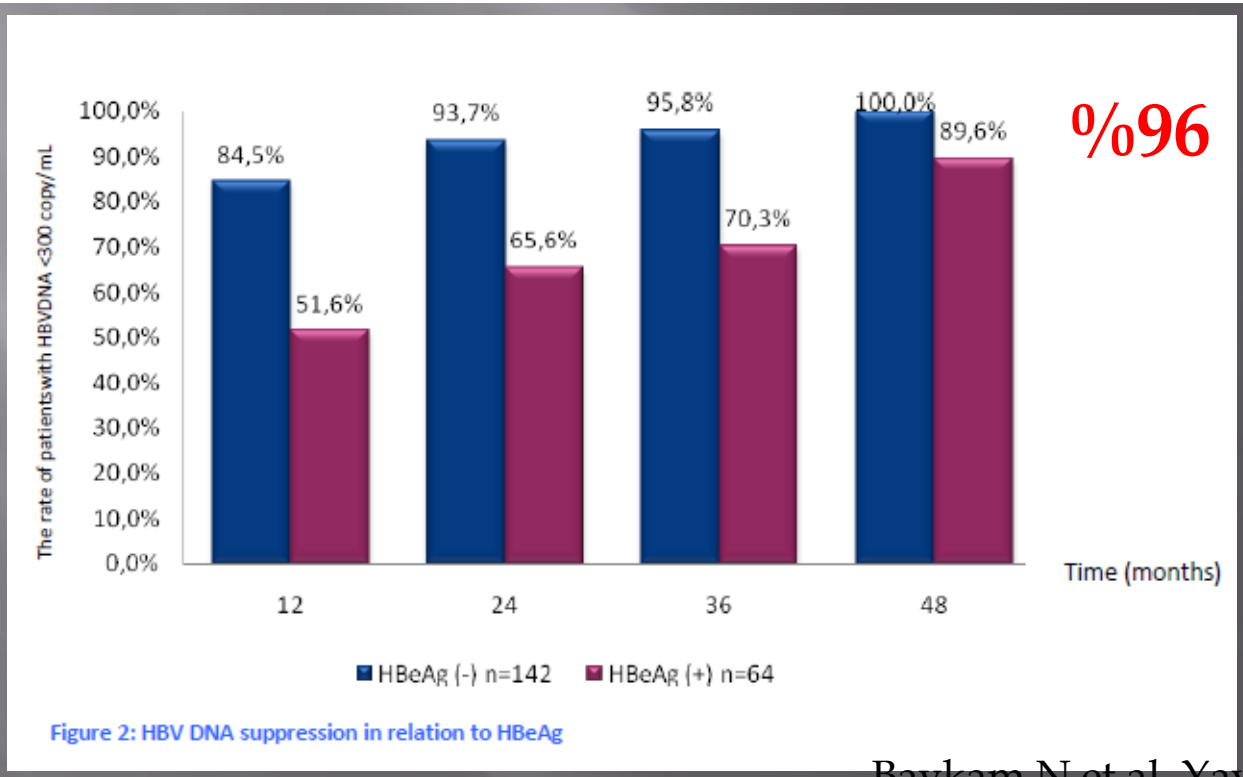

Figure 2: HBV DNA suppression in relation to HBeAg

%96

Baykam N et al. Yayınlanmamış veri

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

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

HBV DNA baskılanması açısından TDF ile ETV benzer etkinliğe sahiptir.

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

TDF ve ETV ile uzun dönemde

>%90 HBV DNA baskılanması

~%30 eAg serokonversiyonu

Histolojik düzelme

Clinical Practice Guidelines

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

EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection

European Association for the Study of the Liver*

Tedavi

Viral baskılanma

Biyokimyasal iyileşme

Histolojik düzelme

EASL CPG. J Hepatol 2012;57:167

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 fibroz 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

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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

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,
TDF 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

Histolojik düzelme

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

Fibroz skorunda düzelme

ISHAK fibroz skorunda ≥1 puan gerileme

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

Histolojik düzelme

304/348 (%87)

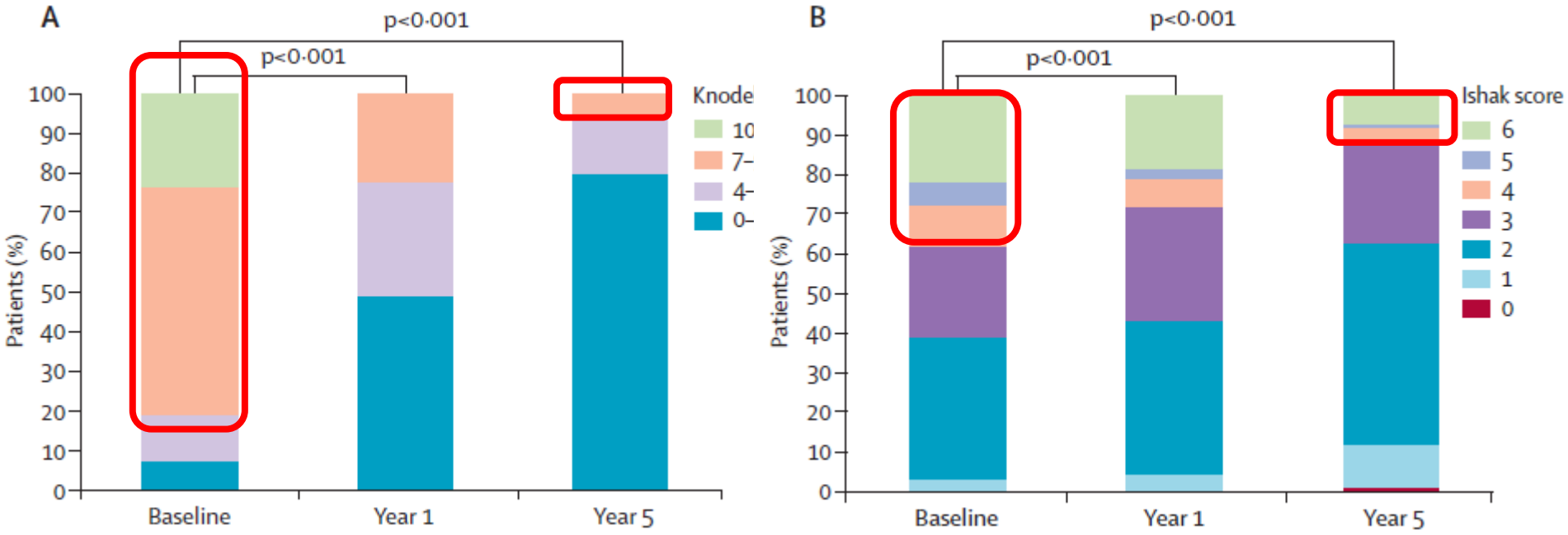
Fibroz skorunda düzelme

176/348 (%51)

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

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

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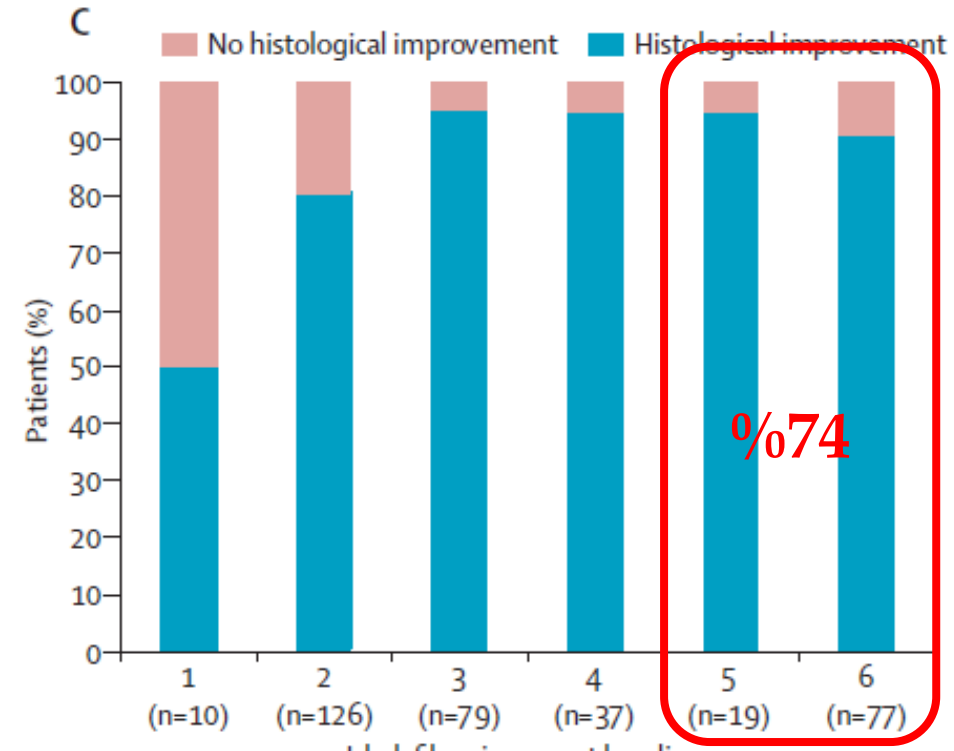

al. Lancet 2013;381:468

JGH 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.

;28:912

Risk of Hepatocellular Carcinoma Across a Biological Gradient of Serum Hepatitis B Virus DNA Level

Chien-Jen Chen, ScD
Hwai-I. Yang, MSc
Jun Su, MD, MSc
Chin-Lan Jen, MSc

Context Serum hepatitis B virus (HBV) DNA level is a marker of viral replication and efficacy of antiviral treatment in individuals with chronic hepatitis B.

Objective To evaluate the relationship between serum HBV DNA level and risk of hepatocellular carcinoma.

Chen CJ. JAMA 2006;295:65

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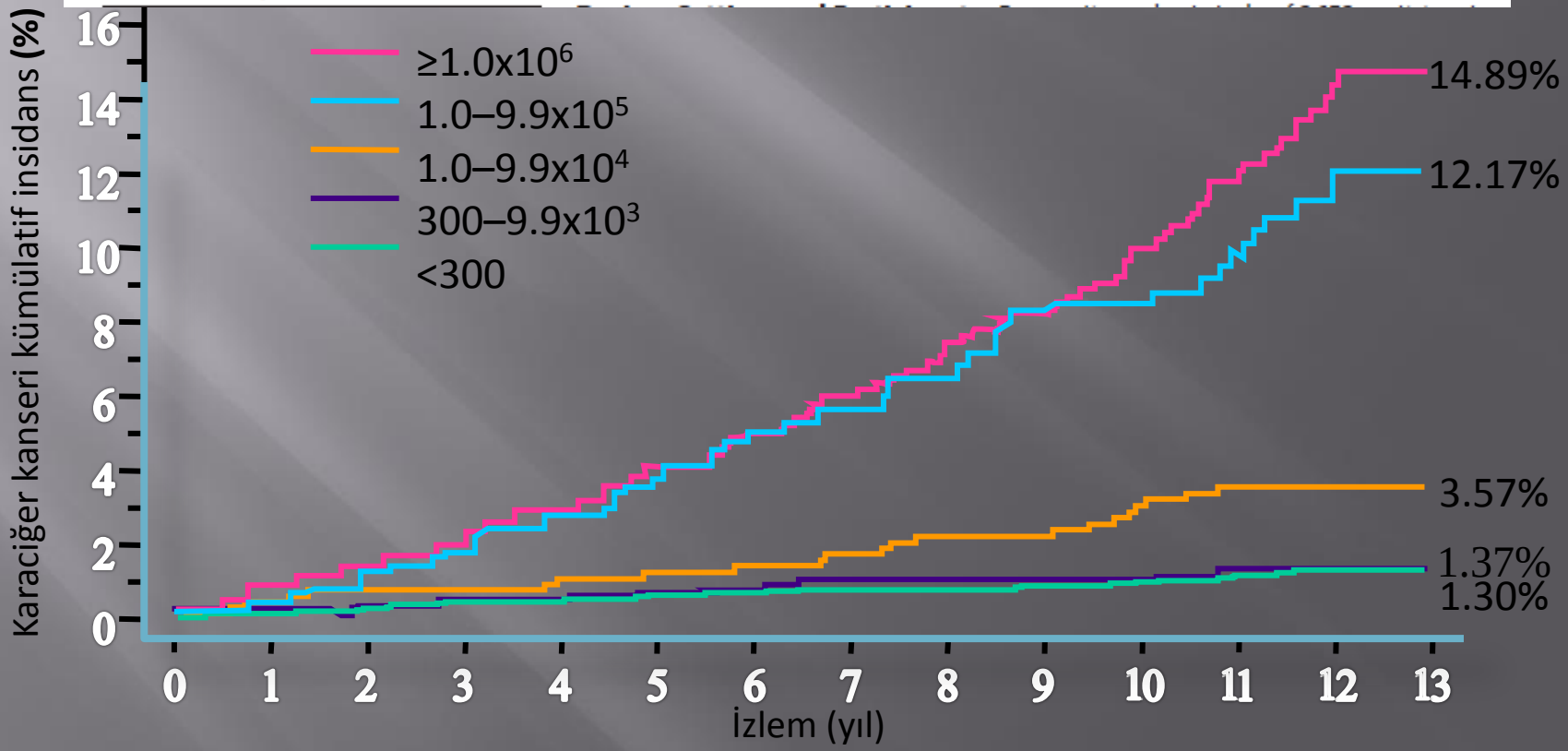
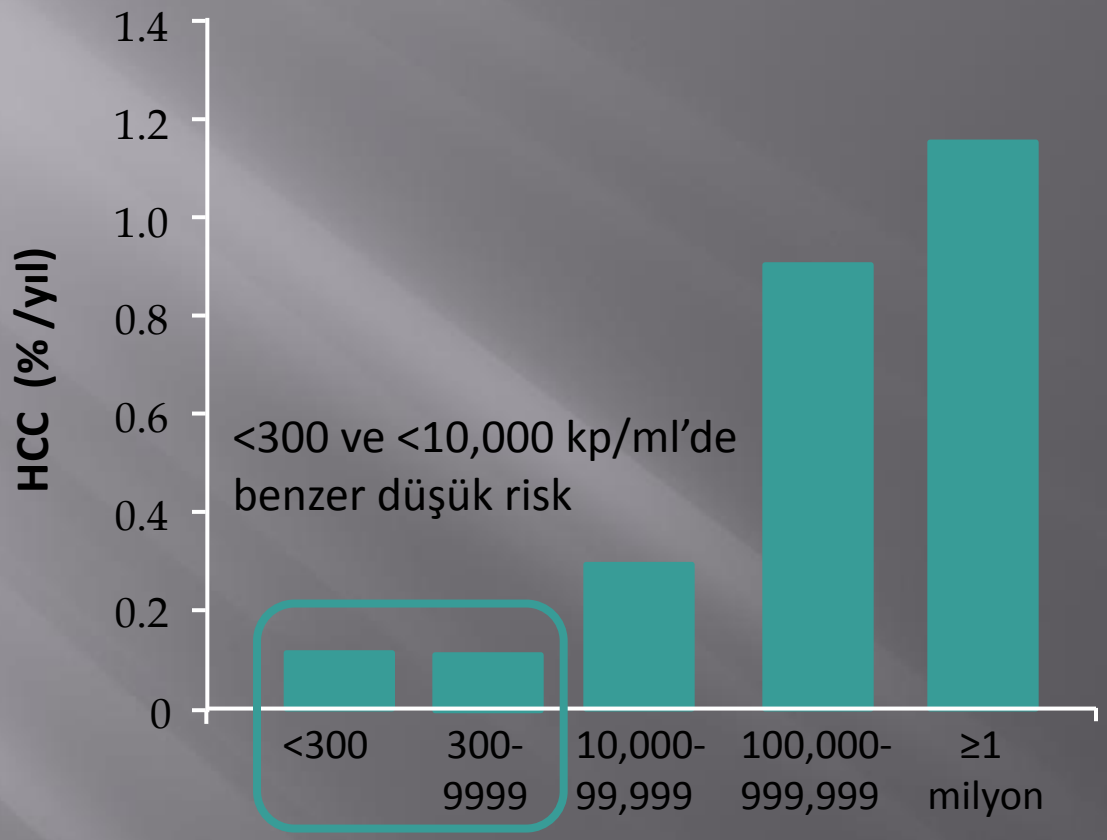
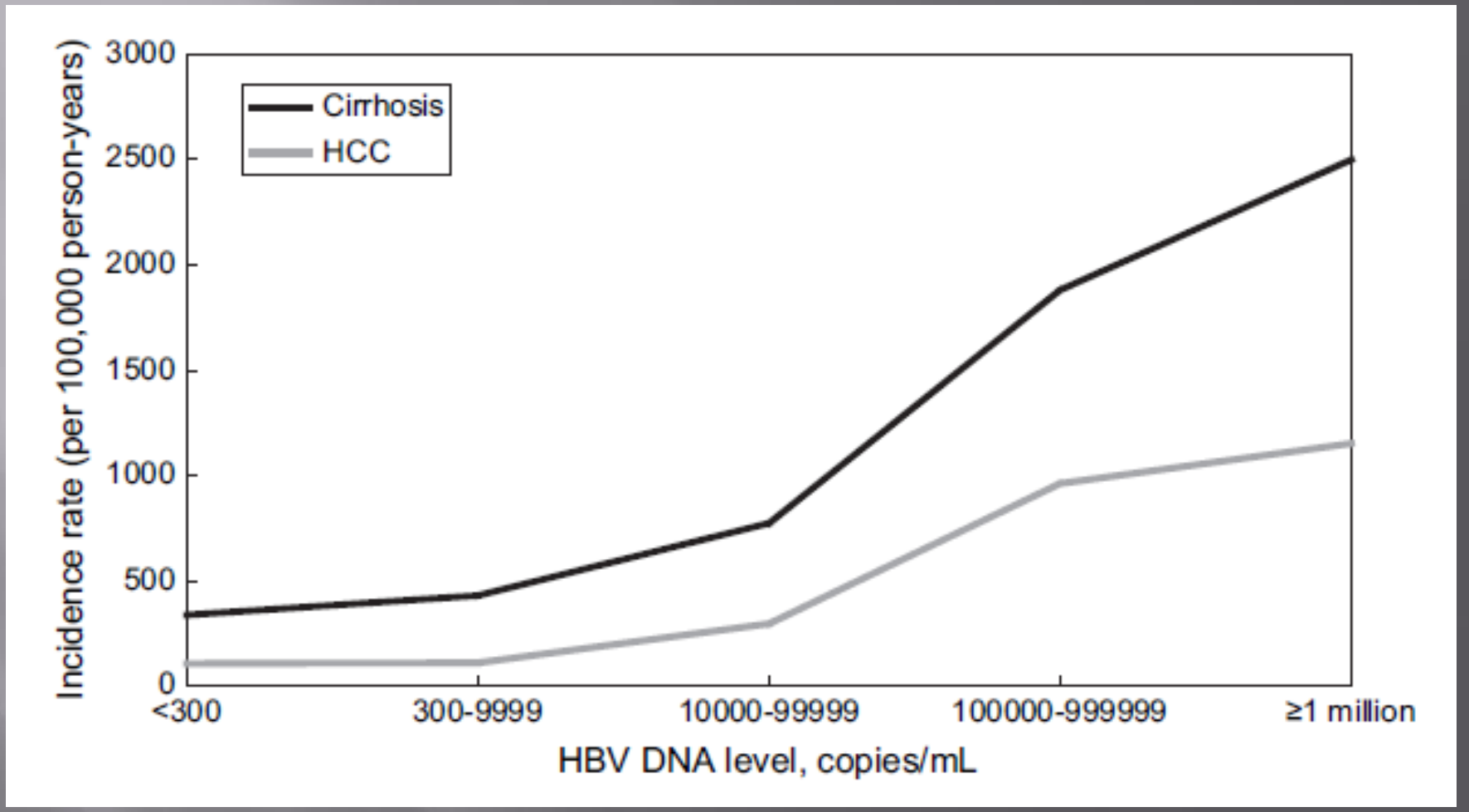


Chen CJ. JAMA 2006;295:65



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

Chen CJ. JAMA 2006;295:65



Chen CJ. Clin Liver Dis 2007;11:797

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

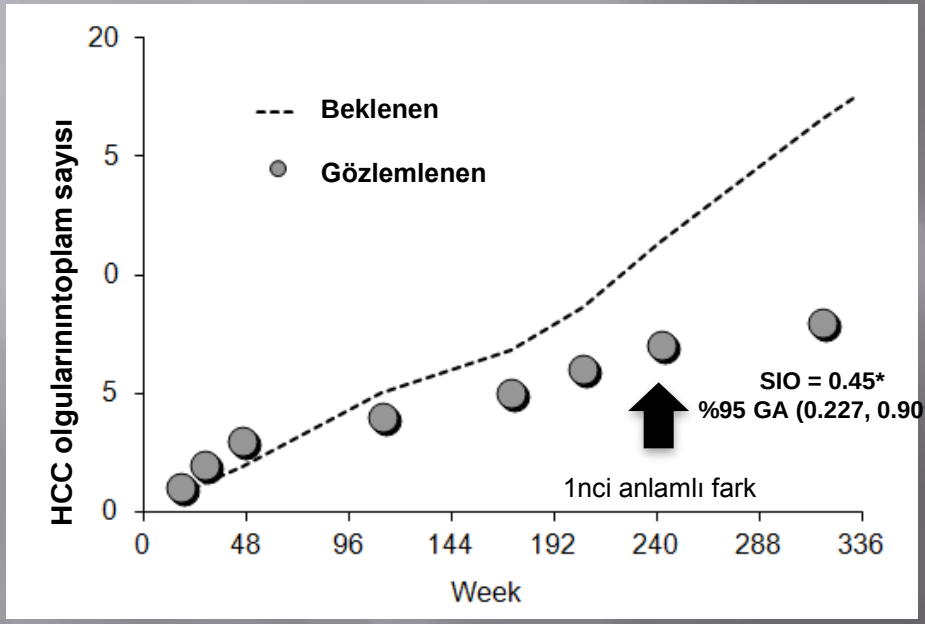
HBeAg pozitif hastalarda yarar daha belirgin.

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

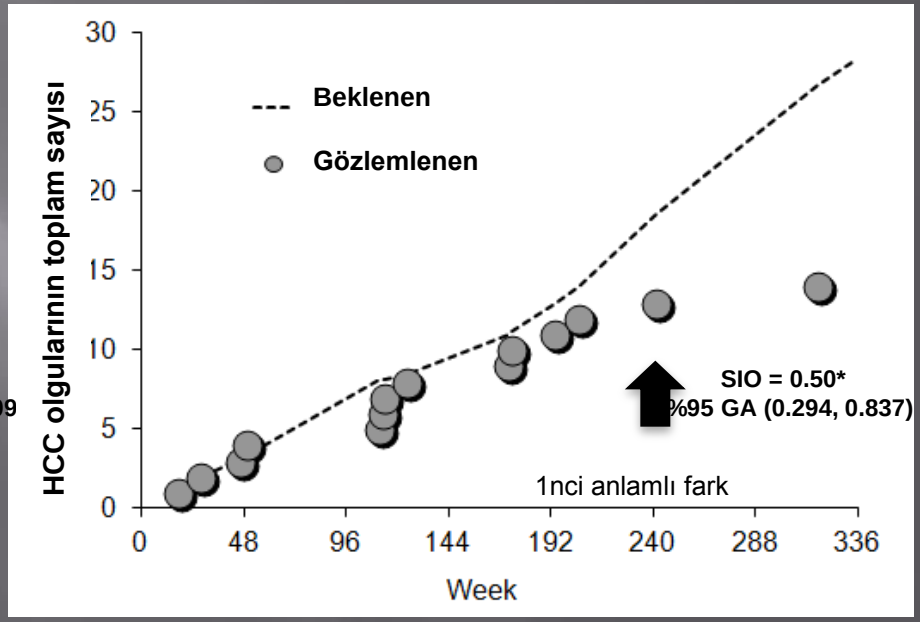
Araştırma 102/103

Gözlemlenen ve Beklenen HCC Olguları

Non-sirotikler
n=482



Tüm Hastalar
n=634



- Araştırma 102/103'te TDF alan hastalarda HCC insidansı REACH-B modeli ile öngörülenden düşüktü
- Non-sirotik hastalarda TDF'in etkisi tedavinin 2-3 yılı arasında belirginleşir ve tedavinin 6.yılında istatistiksel olarak anlamlı (%55 azalma) hale gelmiştir

*Sayısal α-ldüzeyi 0.05 olduğunda istatistiksel olarak anlamlı.

Kim WR, et al. EASL 2013. Amsterdam, The Netherlands. Oral #43

Maliyet etkinlik

FORMULARY MANAGEMENT

Evaluation of the Cost-Effectiveness of Entecavir Versus Lamivudine in Hepatitis BeAg-Positive Chronic Hepatitis B Patients

Yong Yuan, PhD; Uchenna H. Iloeje, MD, MPH; Joel Hay, PhD; and Sammy Saab, MD, MPH

ABSTRACT

BACKGROUND: As new treatment options for chronic hepatitis B virus (HBV) become available, evaluations of cost-effectiveness become important. Entecavir is a deoxyguanine nucleoside analogue approved by the U.S. Food and Drug Administration in March 2005 for HBV infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (alanine aminotransferase or aspartate aminotransferase) or histologically active disease. Entecavir has demonstrated greater suppression of viral replication compared with lamivudine, but also has a relatively higher drug acquisition cost in the United States.

gain at an incremental cost of $2,350, with a 3% annual discount. The incremental cost of using entecavir was $3,230 per QALY gained (95% confidence interval [CI], $2,312-$4,528), with 99.3% of PSA-derived estimates below $5,000 per QALY. Results were robust and most sensitive to efficacy, drug cost, and treatment duration.

CONCLUSIONS: Assuming that (1) the efficacy of entecavir after 1 year is sustainable and (2) liver disease risk levels from the REVEAL-HBV study population (a primarily HBeAg-negative group) adequately represent risk for a treated HBeAg-positive patient group, entecavir given for up to 10 years would be highly cost-effective in HBeAg-positive patients.

Maliyet-etkinlik çalışması

LAM vs ETV

ETV, LAM'a göre maliyet etkindir…

Yuan Y et al. J Manag Care Pharm 2008;14:21

« Previous

Journal of Hepatology
Volume 51, Issue 4 , Pages 640-646, October 2009

Next »

Modeling the cost-effectiveness of different oral antiviral therapies in patients with chronic hepatitis B☆

Maria Buti, Max Brosa, Miquel A. Casado, Magdalena Rueda, Rafael Esteban

Received 19 January 2009; received in revised form 16 March 2009; accepted 1 April 2009. published online 20 May 2009.

Kronik hepatit B hastalarında tenofovir maliyet etkin bir tedavi yaklaşımıdır.

Buti M et al. J Hepatol 2009;51:640

Eur J Health Econ (2012) 13:663–676
DOI 10.1007/s10198-012-0413-8

ORIGINAL PAPER

The cost-effectiveness of treating chronic hepatitis B patients in a median endemic and middle income country

Mehlika Toy · Fatih Oguz Onder · Ramazan Idilman · Gokhan Kabacam · Jan Hendrik Richardus · Mithat Bozdayi · Meral Akdogan · Zarife Kuloglu · Aydan Kansu · Solko Schalm · Cihan Yurdaydin

Table 4 Age group specific distribution of chronic hepatitis B in Turkey by HBeAg and stage of liver disease

Age group					Active CHB		Cirrhosis		Chronic hepatitis (no cirrhosis)	
(years)	Population	HBsAg+ (%)	HBeAg+	HBeAg−	HBeAg+	HBeAg−	HBeAg+ (%)	HBeAg− (%)	HBeAg+	HBeAg−
0–14	18,788,587	533,596 (2.84)	283,828	249,768	90,621	47,586	1,818 (2)	2,379 (5)	88,808	45,207
15–24	12,441,662	490,201 (3.94)	176,473	313,729	91,504	45,804	1,830 (2)	2,290 (5)	89,674	43,514
25–34	12,328,944	784,121 (6.36)	159,961	624,160	113,892	132,322	6,834 (6)	9,263 (7)	107,058	123,059
35–44	10,070,734	624,386 (6.20)	62,439	561,947	35,222	96,610	2,466 (7)	14,491 (15)	32,756	82,118
45–54	7,927,348	437,590 (5.52)	22,655	414,935	11,923	74,353	2,981 (25)	20,819 (28)	8,943	53,534
55–64	5,066,402	184,924 (3.65)	12,753	172,170	5,070	41,595	1,673 (33)	21,214 (51)	3,397	20,382
65+	4,893,423	197,205 (4.03)	18,260	178,945	4,565	37,280	0	20,877 (56)	4,565	16,403
Total	71,517,100	3,252,022 (4.57)	736,367	2,515,655	352,797	475,550	17,595 (9)	91,333 (19)	335,202	384,217

CHB chronic hepatitis B, *HBeAg* hepatitis B e antigen, *HBsAg* hepatitis B surface antigen

Toy M et al. Eur J Health Econ 2012;13:663

Eur J Health Econ (2012) 13:663–676
DOI 10.1007/s10198-012-0413-8

ORIGINAL PAPER

The cost-effectiveness of treating chronic hepatitis B patients in a median endemic and middle income country

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Hastalığın doğal seyrinde bırakıldığında nasıl ilerleyeceği ve antivirallerin kullanımıyla bu seyrin ne yönde değişeceğine dair projeksiyon

Toy M et al. Eur J Health Econ 2012;13:663

Treatment	NH*		Lam	
HBeAg status	+	−	+	−
CHB (no cirrhosis)				
Cumulative costs (×1,000 TL (€))	25.7 (12.8)	48.2 (23.9)	31.6 (15.7)	72.6 (36.1)
Cumulative QALYs	14.0	9.3	14.5	9.9
Incremental costs (×1,000 TL (€))[a]	–	–	5.8 (2.9)	24.4 (12.1)
Incremental QALYs[b]	–	–	0.5	0.6
ICER (×1,000 TL (€)/QALY)	–	–	11.2 (5.5)	38.3 (19.0)

QALYs: Kazanılmış kaliteli yaşam süresi

ICER: Maliyet etkinlik oranı

Toy M et al. Eur J Health Econ 2012;13:663

Treatment	NH*		Lam		Lam + ADV		Lam + TDF	
HBeAg status	+	−	+	−	+	−	+	−
CHB (no cirrhosis)								
Cumulative costs (×1,000 TL (€))	25.7 (12.8)	48.2 (23.9)	31.6 (15.7)	72.6 (36.1)	73.4 (36.5)	168.5 (83.8)	54.7 (27.2)	122.5 (60.9)
Cumulative QALYs	14.0	9.3	14.5	9.9	17.0	13.0	17.5	13.8
Incremental costs (×1,000 TL (€))[a]	–	–	5.8 (2.9)	24.4 (12.1)	41.9 (20.8)	120.3 (59.9)	23.2 (11.5)	74.4 (37.0)
Incremental QALYs[b]	–	–	0.5	0.6	3.0	3.7	3.5	4.5
ICER (×1,000 TL (€)/QALY	–	–	11.2 (5.5)	38.3 (19.0)	13.9 (6.9)	32.1 (16.0)	6.6 (3.2)	16.3 (8.1)

Hem TDF hem de ETV ile kazanılmış kaliteli yaşam süresi benzer ve diğer tüm yaklaşımlardan daha yüksek

Treatment							Roadmap
HBeAg sta							−
CHB (no c							
Cumulative							94.8 (47.1)
Cumulative QALYs	17.5	14.9	18.8	16.6	19.0	16.8	12.2
Incremental costs (×1,000 TL (€))[a]	27.1 (13.5)	112.9 (56.2)	14.4 (7.2)	169.9 (84.5)	3.2 (1.6)	117.7 (58.5)	46.6 (23.2)
Incremental QALYs[b]	3.5	5.6	4.8	7.3	5.0	7.6	2.9
ICER (×1,000 TL (€)/QALY)	7.8 (3.9)	20.0 (9.9)	3.0 (1.5)	23.2 (11.6)	0.6 (0.3)	15.6 (7.8)	15.6 (7.9)

Toy M et al. Eur J Health Econ 2012;13:663

Treatment	NH*		Lam		Lam + ADV		Lam + TDF	
HBeAg status	+	−	+	−	+	−	+	−
CHB (no cirrhosis)								
Cumulative costs (×1,000 TL (€))	25.7 (12.8)	48.2 (23.9)	31.6 (15.7)	72.6 (36.1)	73.4 (36.5)	168.5 (83.8)	54.7 (27.2)	122.5 (60.9)
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Incremental QALYs[b]	–	–	0.5	0.6	3.0	3.7	3.5	4.5
ICER (×1,000 TL (€)/QALY)	–	–	11.2 (5.5)	38.3 (19.0)	13.9 (6.9)	32.1 (16.0)	6.6 (3.2)	16.3 (8.1)

Treatment	Peg INF + TDF		ETV		TDF		Roadmap
HBeAg status	+	−	+	−	+	−	−
CHB (no cirrhosis)							
Cumulative costs (×1,000 TL (€))	58.7 (29.2)	161.0 (80.1)	46.0 (22.9)	218.0 (108.5)	34.8 (17.3)	165.9 (82.5)	94.8 (47.1)
Cumulative QALYs	17.5	14.9	18.8	16.6	19.0	16.8	12.2
Incremental costs (×1,000 TL (€))[a]	27.1 (13.5)	112.9 (56.2)	14.4 (7.2)	169.9 (84.5)	3.2 (1.6)	117.7 (58.5)	46.6 (23.2)
Incremental QALYs[b]	3.5	5.6	4.8	7.3	5.0	7.6	2.9
ICER (×1,000 TL (€)/QALY)	7.8 (3.9)	20.0 (9.9)	3.0 (1.5)	23.2 (11.6)	0.6 (0.3)	15.6 (7.8)	15.6 (7.9)

Toy M et al. Eur J Health Econ 2012;13:663

Treatment	NH*		Lam		Lam + ADV		Lam + TDF	
HBeAg status	+	−	+	−	+	−	+	−
CHB (no cirrhosis)								
Cumulative costs (×1,000 TL (€))	25.7 (12.8)	48.2 (23.9)	31.6 (15.7)	72.6 (36.1)	73.4 (36.5)	168.5 (83.8)	54.7 (27.2)	122.5 (60.9)
Cumulative QALYs	14.0	9.3	14.5	9.9	17.0	13.0	17.5	13.8
Incremental costs (×1,000			5.8 (2.9)	24.4 (12.1)	41.9 (20.8)	120.3 (59.9)	23.2 (11.5)	74.4 (37.0)
Incremen								5
ICER (× (€)/QAL								6.3 (8.1)

Maliyet etkinlik oranı en düşük olan ilaç
TDF, ardından ETV

Treatment							Roadmap
HBeAg status	+	−	+	−	+	−	−
CHB (no cirrhosis)							
Cumulative costs (×1,000 TL (€))	58.7 (29.2)	161.0 (80.1)	46.0 (22.9)	218.0 (108.5)	34.8 (17.3)	165.9 (82.5)	94.8 (47.1)
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Incremental costs (×1,000 TL (€))[a]	27.1 (13.5)	112.9 (56.2)	14.4 (7.2)	169.9 (84.5)	3.2 (1.6)	117.7 (58.5)	46.6 (23.2)
Incremental QALYs[b]	3.5	5.6	4.8	7.3	5.0	7.6	2.9
ICER (×1,000 TL (€)/QALY)	7.8 (3.9)	20.0 (9.9)	3.0 (1.5)	23.2 (11.6)	0.6 (0.3)	15.6 (7.8)	15.6 (7.9)

Toy M et al. Eur J Health Econ 2012;13:663

Eur J Health Econ (2012) 13:663–676
DOI 10.1007/s10198-012-0413-8

ORIGINAL PAPER

The cost-effectiveness of treating chronic hepatitis B patients in a median endemic and middle income country

Mehlika Toy · Fatih Oguz Onder · Ramazan Idilman · Gokhan Kabacam · Jan Hendrik Richardus · Mithat Bozdayi · Meral Akdogan · Zarife Kuloglu · Aydan Kansu · Solko Schalm · Cihan Yurdaydin

Kronik hepatit B tedavisinde TDF ya da ETV ile monoterapi, en maliyet etkin ve en fazla sağlık kazanımı elde edilen yaklaşımdır.

Toy M et al. Eur J Health Econ 2012;13:663

Sosyal Güvenlik Kurumundan:

SOSYAL GÜVENLİK KURUMU SAĞLIK UYGULAMA TEBLİĞİ

BİRİNCİ BÖLÜM 6
GENEL HÜKÜMLER 6

(3) Oral antiviral tedaviye;

a) Erişkin hastalarda; günde 100 mg lamivudin veya 600 mg telbivudin veya 245 mg tenofovir veya 0,5 mg entekavir ile başlanır.

b) 2-18 yaş grubu hastalarda tedaviye lamivudin, 12-18 yaş grubu hastalarda lamivudin veya tenofovir, 16-18 yaş grubu hastalarda lamivudin veya tenofovir veya entekavir ile başlanabilir. Çocuk hastalarda lamivudin tedavisine 3mg/kg/gün dozunda (günlük maksimum 100 mg), tenofovir tedavisine 245 mg/gün, entekavir tedavisine 0,5 mg/gün dozunda başlanabilir.

KHB'nin etkin biçimde tedavi edilmesiyle uzun dönemde

Biyokimyasal, serolojik ve virolojik yanıtların artmasını,

Histolojik yanıt elde edilmesi ve fibrozun gerilemesini,

HCC olasılığının azalmasını,

Maliyet etkin

Sosyal Güvenlik Kurumundan:

SOSYAL GÜVENLİK KURUMU SAĞLIK UYGULAMA TEBLİĞİ

BİRİNCİ BÖLÜM 6
GENEL HÜKÜMLER 6

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

VIRAL HEPATITIS

Randomized, Placebo-Controlled Trial of Tenofovir Disoproxil Fumarate in Adolescents With Chronic Hepatitis B

Karen F. Murray,[1] Leszek Szenborn,[2] Jacek Wysocki,[3] Stephen Rossi,[4] Amoreena C. Corsa,[4] Phillip Dinh,[4] John McHutchison,[4] Phillip S. Pang,[4] Luminita M. Luminos,[5] Malgorzata Pawlowska,[6] and Jacek Mizerski[7]

12-18 yaş 106 adolesan,
Çift kör, plasebo kontrollü çalışma,

%91 HBeAg pozitif,
%85 naiv değil

Murray KF et al. Hepatology 2012;56:2018

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VIRAL HEPATITIS

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Virolojik yanıt %89

Murray KF et al. Hepatology 2012;56:2018

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TDF naiv ve naiv olmayan adolesanlarda etkindir ve iyi tolere edilir.

Murray KF et al. Hepatology 2012;56:2018

Sosyal Güvenlik Kurumundan:

SOSYAL GÜVENLİK KURUMU SAĞLIK UYGULAMA TEBLİĞİ

BİRİNCİ BÖLÜM 6
GENEL HÜKÜMLER 6

4.2.13.C - İmmünsupresif ilaç tedavisi, sitotoksik kemoterapi, monoklonal antikor tedavisi uygulanmakta olan hastalarda tedavi

(1) İmmünsupresif ilaç tedavisi veya sitotoksik kemoterapi veya monoklonal antikor tedavisi uygulanmakta olan HBsAg (+) hastalarda, ALT yüksekliği, HBV DNA pozitifliği ve karaciğer biyopsisi koşulu aranmaksızın uygulanmakta olan diğer tedavisi süresince ve bu tedavisinden sonraki en fazla 12 ay boyunca **(Değişik: RG- 25/07/2014-29071 / 26-b md. Yürürlük: 07/08/2014)** ~~lamivudin~~ günde 100 mg lamivudin veya 600 mg telbivudin veya 245 mg tenofovir veya 0,5 mg entekavir kullanılabilir. İmmünsupresif, sitotoksik kemoterapi ve monoklonal antikor tedavisine ilişkin ilaç raporunun tarih ve sayısı reçetede belirtilir.

Clinical Practice Guidelines

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

EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection

European Association for the Study of the Liver*

HBsAg-positive candidates for chemotherapy and immunosuppressive therapy should be tested for HBV DNA levels and should receive pre-emptive NA administration during therapy (regardless of HBV DNA levels) and for 12 months after cessation of therapy (**A1**). There are limited data on the optimal options. Most experience with pre-emptive treatment has been with lamivudine, which may suffice for patients with low (<2000 IU/ml) HBV DNA levels when a finite and short duration of immunosuppression is scheduled [221,222]. In this setting, prophylactic lamivudine reduces the risk of HBV reactivation and the associated morbidity and mortality (**B1**). It is, however, recommended that patients, who have a high HBV DNA level and/or may receive a lengthy and repeated cycles of immunosuppression, should be protected with a NA with high antiviral potency and a high barrier to resistance, i.e. entecavir or tenofovir (**C1**).

EASL CPG. J Hepatol 2012;57:167

Contents lists available at ScienceDirect

European Journal of Internal Medicine

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

Original Article

The role of tenofovir in preventing and treating hepatitis B virus (HBV) reactivation in immunosuppressed patients. A real life experience from a tertiary center

J.S. Koskinas *[,1], M. Deutsch [1], S. Adamidi, M. Skondra, M. Tampaki, A. Alexopoulou, S. Manolakopoulos, D. Pectasides

Second Department of Internal Medicine, Medical School of Athens University, Hippokration General Hospital, Athens, Greece

İmmünsupresif tedavi alan 38 hasta

25 profilaksi

13 reaktivasyon tedavisi

Koskinas JS et al. Eur J Intern Med 2014in press

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Second Department of Internal Medicine, Medical School of Athens University, Hippokration General Hospital, Athens, Greece

Profilaktik tedavi alan hastaların hiçbirinde HBV alevlenmesi izlenmiyor,

Tedavi alan hastaların tamamında altıncı ayda biyokimyasal ve virolojik yanıt elde ediliyor.

Koskinas JS et al. Eur J Intern Med 2014in press

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TDF immünsupresif tedavi alan hastaların profilaksi ve kurtarma tedavisinde etkin ve güvenlidir.

Koskinas JS et al. Eur J Intern Med 2014in press