OLGU SUNUMU

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KLİMİK Hepatit Akademisi 2015
Çanakkale

Sunum Planı

- Olgu
- HBV genom-mutasyon
- Direnç tanımları
- Antiviral direnç yaklaşım-tedavi
- Takip
- Soru-cevap

Olgu

- 55 yaşında Erkek hasta
- HBsAg: Pozitif (1994-2000)
- HbeAg: Negatif
- HBV DNA (PCR): >10.000.000 IU/ml
- AST: 64 ALT: 72
- AFP: 1.4
- Hepatit Delta Ag: Negatif
- Anti HCV: Negatif
- Anti HIV: Negatif
- Batın USG: Normal bulgular
- Boy: 176 cm Kilo: 78 kg BMI: 25.2 kg/m^2

KC İğne biyopsisi yaparım?

- Evet
- Hayır

Uluslararası Klinik Kılavuzlar

Kılavuz	KC İğne biyopsisi rolü
EASL	• KC iğne biyopsisi (veya noninvaziv marker) tedavi öncesi ya ALT ya da HBV DNA düzeyi yüksek >2,000 IU/mL[3] hastalarda nekroinflamasyonun derecesi veya fibroz saptanmasında önerilir • Siroz klinik bulgularının olduğu veya tedavinin endike olduğu vakalarda biyopsi gerekli değil
APASL	• 40 yaş üstü HBV replikasyonu olan ve persistan olarak yüksek ALT (≥2x NÜS)[1]
AASLD	• Kronik Hepatit Biyopsi önerilir (HBsAg(+) >6 ay; HBV DNA >20,000 IU/mL; ALT/AST düzeylerinde kalıcı veya aralıklı yükseklik)[2]

1. EASL Clinical Practice Guidelines Panel. *J Hepatol*.2012. Liaw Y-F et al., *Hepatol Int*. 2008;2:263–283 3. Lok ASF & McMahon BJ, *Hepatology*. 2007;45:507-39.

Uluslararası Klinik Kılavuzlar

Kılavuz	KC İğne biyopsisi rolü
Italya[1]	• Noninvaziv değerlendirme ile altta yatan karaciğer hasarından kuşkulanılmasında • Yüksek ALT düzeyi olan hastalarda ve sınırda HBV-DNA (2,000 - 20,000 IU/ml arası) olan hastalarda karaciğer hasarının HBV ye bağlı olduğundan emin olunmsı ve KC yağlanması dahil diğer karaciğer hasarı yapan nedenleri dışlamak için
Almanya[2]	• Kronik hepatit tanısı ve prognozunun değerlendirilmesinde biyopsi tüm hastalarda önemli
VHSD[3]	• Tedavi düşünülen hastalarda biyopsi gerekli ve önemli

1. Carosi G, Rizzetto M. Italian Clinical Guidelines. *Dig Liver Dis*. 2008;40:603-17 2. Cornberg M, Protzer U, Dollinger M, et al., Z Gastroenterol. 2007;45:1281-328. 3. Balik I, Tabak F. Viral Hepatitle Savaşım Derneği (VHSD) Guidelines 2011.

Olgu

- KC iğne biyopsi: (2000)

  Biyopsi sonucu: (Ishak)

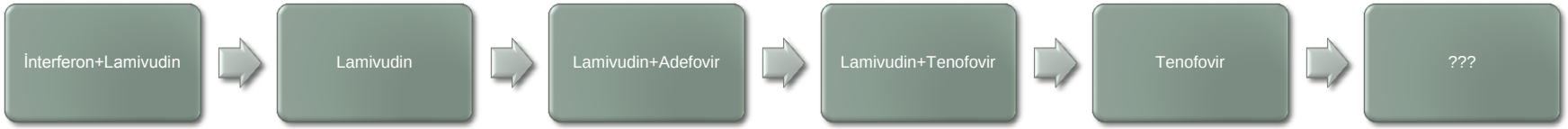
  - Kronik Hepatitis
    - HAI: 8/18
    - Fibrozis:3/4

Tedavi

rtM204V
rtA181T
rtM552V
rtL528M

Direnç Analizi
???

Direnç Analizi



2000-2001 2001-2004 2004-2010 2010-2013 2013-2015

TARİH	AST	ALT	ALBUMİN	HBV DNA (PCR) (IU/ML)
06.06.2002	151	264	3.9	
02.04.2003	39	65	4.1	0
08.07.2003	83	185	4	
20.10.2003	68	152	4.2	0
12.12.2003	65	131	4	
11.03.2004	145	332	3.7	
27.04.2004	89	168	4.2	6520000
23.06.2004	76	125	4.4	
15.09.2004	77	144	4.2	3490000
29.11.2004	76	140	4.2	366000
08.03.2005	47	79	4	0
12.04.2005	55	95	4.1	0
16.08.2005	46	55	4.4	0
07.12.2005	69	85	4.1	0
31.01.2006	216	333	4.2	0
20.03.2006	75	126	4.1	0
14.06.2006	50	86	4.2	0
17.01.2007	48	76	4.1	0
21.07.2007	42	54	4.1	0
11.02.2008	48	51	4.2	
30.11.2008	51	55	4.4	
12.02.2009	38	45	4.7	0
21.05.2009	40	48	5.2	
23.12.2009	49	56	4.1	0
12.03.2010	65	79	4.4	23000
21.03.2010	74	82	4.3	53000
18.06.2010				145
27.09.2010	42	48	4.7	0

LAM

LAM + ADV

LAM + TNF

TARİH	AST	ALT	ALBUMİN	HBV DNA (PCR) (IU/ML)
13.01.2011	38	42	4.3	0
05.04.2011	35	40	4.2	0
16.03.2012	32	44	4.1	0
06.03.2013	71	67	4.1	192
24.06.2013	70	80	4.2	0
03.04.2014	70	73	4.6	0
21.12.2014	57	55	4.5	0

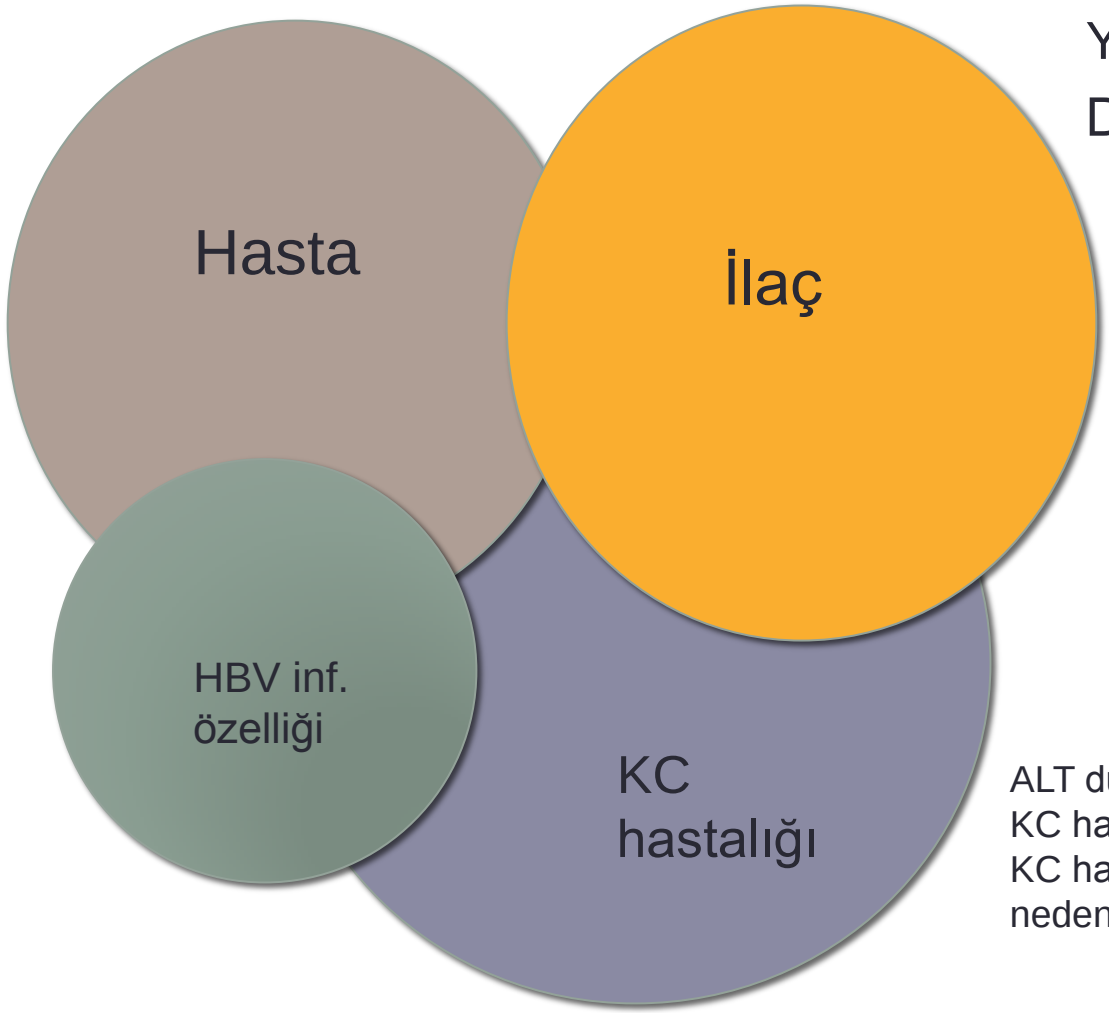
LAM
+
TNF

TNF

HBV hasta yönetimi

Yaş
Kontrendikasyonlar
Önceki tedavi
Komorbid hastalıklar
Koinfeksiyonlar
Genetik
Uyum
Kişinin istekleri

Etkinlik
Yan etki
Direnç profili



HBeAg
HBV DNA
Genotip
Viral heterogenity

ALT düzeyi
KC hastalığı derecesi
KC hasarı kofaktör nedenler

HBV hasta yönetimi

- Uygun ilaç verildi mi?
- İzlemi uygun yapıldı mı?

Table 1 European Association for the Study of the Liver guidelines compared to other international guidelines

Criteria	EASL 2012[6]	AASLD 2009[7]	APASL 2012[8]
HBV DNA treatment threshold			
HBeAg(+) (IU/mL)	2000	20000	20000
HBeAg(-) (IU/mL)	2000	2000-20000	2000
ALT treatment threshold	> ULN	> 2 × ULN	> 2 × ULN
Liver biopsy	Moderate to severe necroinflammation or fibrosis	Not applicable (consider in certain groups)	

ULN: Upper limits of normal; HBeAg: Hepatitis B e antigen; ALT: Alanine aminotransferase; AASLD: American Association for the Study of Liver Diseases; APASL: Asia Pacific Association for the Study of the Liver; EASL: European Association for the Study of the Liver; HBV: Hepatitis B virus.

Antiviral ilaç direnci

- Virüs replikasyonu büyüklüğü ve hızına
- Viral mutasyon sıklığına
- İlaç tarafından selektif seçiciliğe
- Antiviral hedef bölgesinde mutasyon yatkınlığı (intrinsic mutability)

Antiviral direnç ilişkili faktörler

Virüs

- Viral üretim kinetik/dinamik
- Viral temizlik kinetik/dinamik
- RT hata düzeltme hızı
- Viral enzimleri yapısal esnekliği

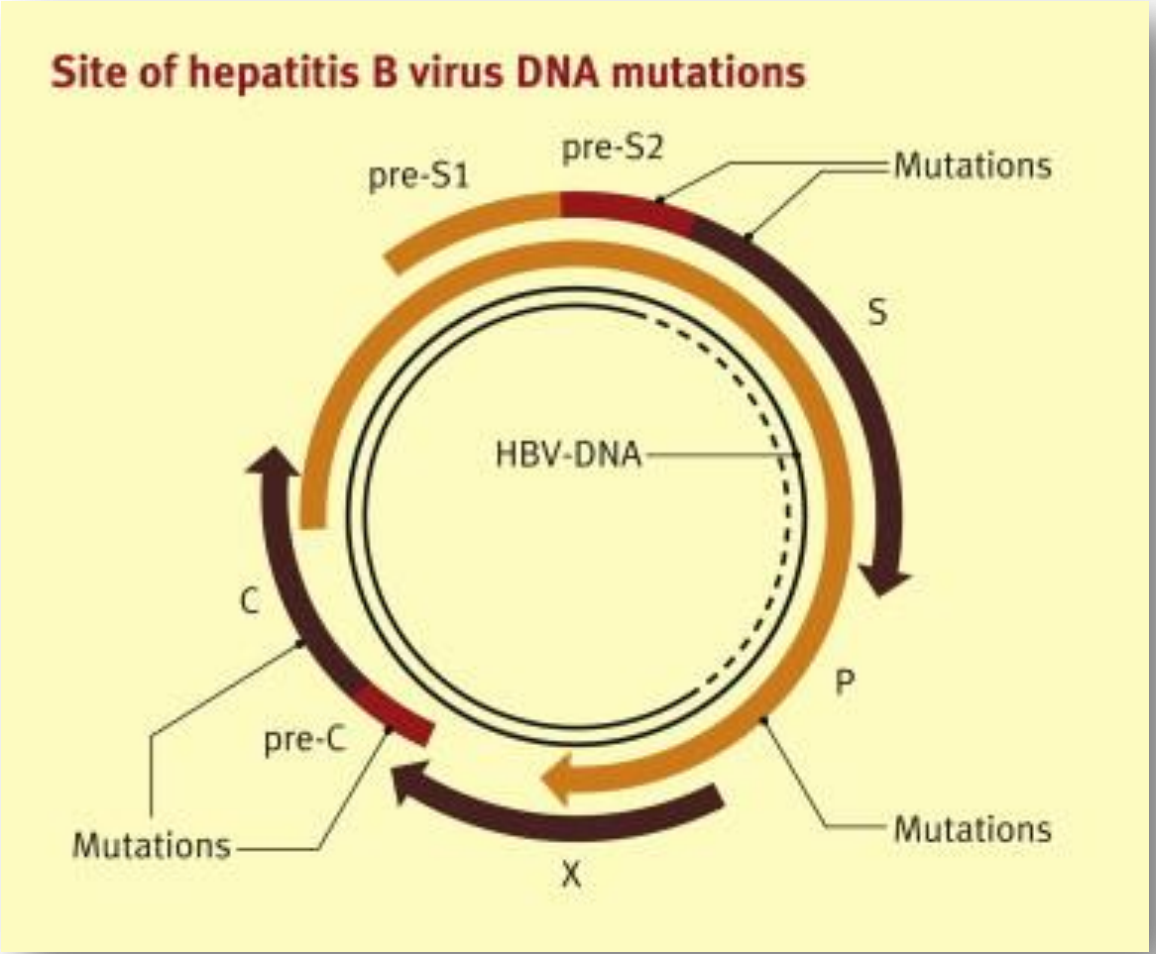
İlaçlar

- Antiviral kombinasyonların Etkinliği
- Farmakokinetik özellikleri
- Farmakodinamik özellikleri (ör. siroz)
- Hedef spesifik ilaçların mutasyon seçiciliği (çapraz direnç)

Hasta

- İlaca uyum
- Anamnezde ilaç kullanımı

HBV genom



Mutimer, David J.; Oo, Ye Htun. Hepatititis B.Published September 1, 2011. Volume 39, Issue 9. Pages 545-549.

HBV mutasyonlar klinik önemi

Table 1 Hepatitis B virus mutations and their clinical implications

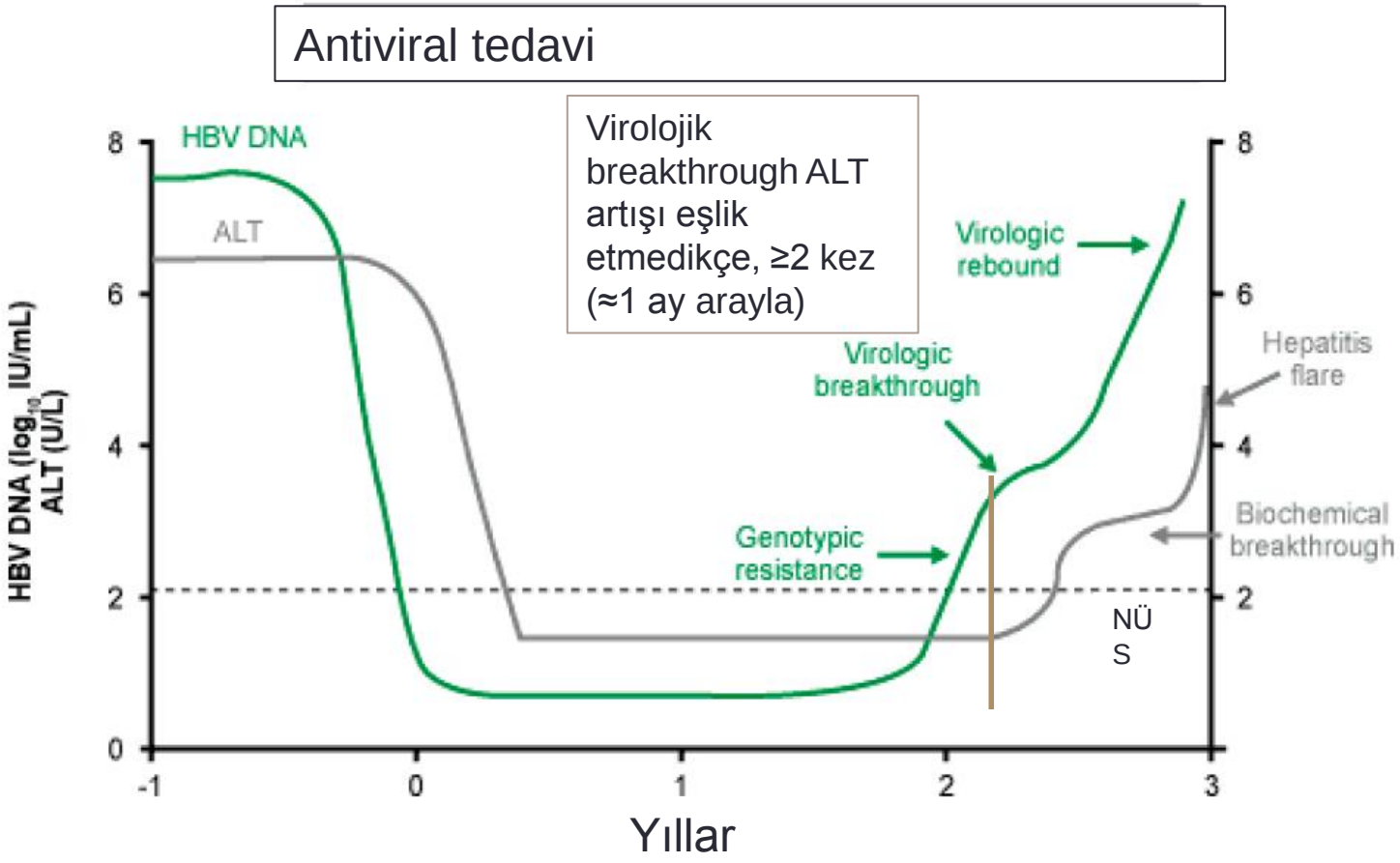
Type of mutation	Clinical implication	Mutation
HBsAg mutations	Vaccine-escape	T116N[24], P120S/E[17,18,25], I/T126A/N/I/S[19,25-28], Q129H/R[26,29,30], M133L[29,30], K141E[16,26,28], P142S[19,20,26,28], D144A/E[19,25,26,30], G145R/A[11-20,31-37]
	OBI	Y100S[50], Q101R[50], P105R[50], T115N[50], T116N[50], G119R[51], P120L[50], R122P[50], T123N[50], C124R/Y[51], T126I/S[50,51], P127H/L[50], Q129P/R[50,51], M133T[50] Y134C[50], S136P[51], C139R[51], T140I[51], K141E[51], S143L[50], D144A[51], G145R/A[51-53], S167L[50], R169H[50], S174N[50], L175S[50], V177A[50], Q181STOP[54]
Basal core promoter /precore mutations	HBeAg-negative hepatitis	T1753C[62], A1762T[59,60], G1764A[59,60], C1766T[62], T1768A[62], G1896A[63,64], G1899A[63,64]
	HCC	C1653T[68], T1753C[68], A1762T[66-68], G1764A[66-68], G1896A[68], G1899A[68]
	Fulminant hepatitis	A1762T[70], G1764A[70], G1862T[69,70], G1896A[70]
X gene mutations	HCC	3′-HBx deletion[82]
Antiviral drug-resistant mutations	LAM/L-dT-resistance	rtL80V/I[84], rtI169T[84], rtV173L[84], rtL180M[84], rtA181T/V[105], rtT184S/G[84], rtS202I[84], rtM204V/I[84], rtQ215S[84]
	ADF-resistance	rtA181T/V[96,105], rtI233V[97,98], rtN236T[96]
	ETV-resistance	rtL180M[85], rtT184G/S[85], rtS202I/G[85], rtM204V[85,108], rtM250V[85]
	TDF-resistance	rtP177G[103], rtA194T[102], rtF249A[103]

Ivana Lazarevic, World J Gastroenterol 2014; 28; 20(24): 7653-7664

HBV direnç

- Yüksek replikasyon hızı (Günde $10^{12\text{-}13}$ viryon)
- HBV polimerazın “proof reading” yeteneğinin olmaması
- Sonuç: günde 10^{11} mutasyon

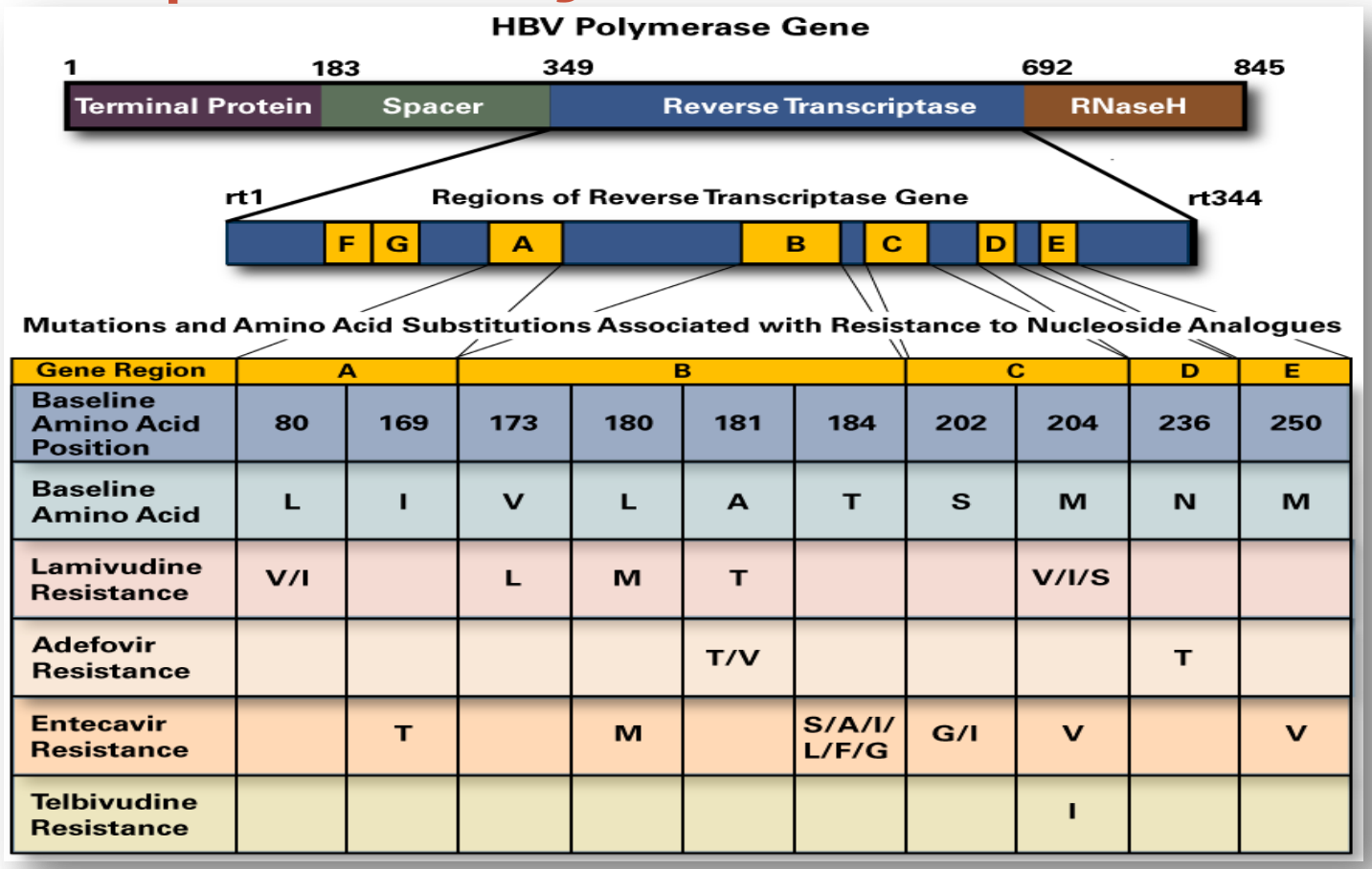
Direnç Tanımları



Virolojik breakthrough:Antiviral tedavi alan olgularda, virolojik yanıt sonrası, HBV DNA düzeyinde ≥ 1 log (10 kat) IU/ml artış olması veya PCR ile negatif olan HBV DNA'nın pozitifleşmesi.

University of Washington, Hepatititis web study

Genotipik Direnç

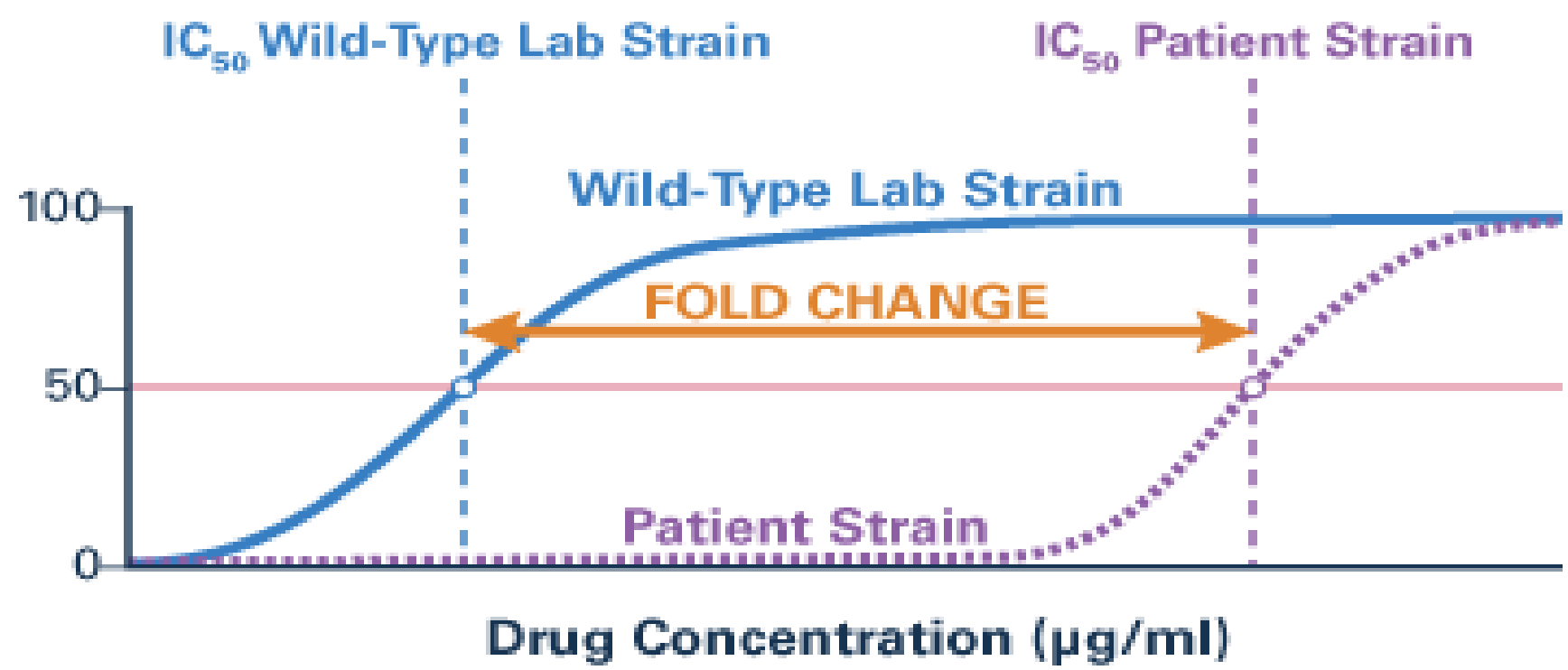


Gene Region	A		B				C		D	E
Baseline Amino Acid Position	80	169	173	180	181	184	202	204	236	250
Baseline Amino Acid	L	I	V	L	A	T	S	M	N	M
Lamivudine Resistance	V/I		L	M	T			V/I/S		
Adefovir Resistance					T/V				T	
Entecavir Resistance		T		M		S/A/I/ L/F/G	G/I	V		V
Telbivudine Resistance								I		

Primer ilaç direnç mutasyonları:HBV pol geni üzerinde antiviral ajana duyarlılığı azaltan a.a değişiklikleridir

Sekonder kompansatuar mutasyonlar:Viral fitness ‘viral polimeraz aktivitesini’ düzelten, HBV’nin replikasyon kapasitesini onaran a.a

Fenotipik Direnç



Saptanan mutasyonla birlikte tedavide kullanılan nükleoz(t)id analoguna karşı duyarlılığın azaldığının in-vitro gösterilmesi

Çapraz Direnç

Table 5 (revised). Cross-resistance data for the most frequent resistant HBV variants. The amino-acid substitution profiles are shown in the left column and the level of susceptibility is given for each drug: S (sensitive), I (intermediate/reduced susceptibility), R (resistant) [140].

HBV variant	Level of susceptibility				
	Lamivudine	Telbivudine	Entecavir	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

*Single M204V mutation is not usually detected in clinical practice; its cross-resistance profile has been mainly studied *in vitro*.

Corrigendum to: ‘‘EASL clinical practice guidelines: Management of chronic hepatitis B virus infection’’ [J Hepatol 2012;57:167–185]

Nucleos(t)id analogları

1.L-Nucleoside

- lamivudin (LAM)
- emtrisitabin (FTC)
- telbivudin (LdT)
- klevudin (L-FMAU)

2.Acyclic Phosphonate

- adefovir (ADV)
- tenofovir (TDF)

3.Cyclopentane/pentene Ring

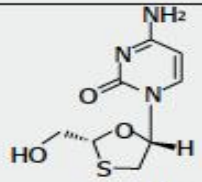
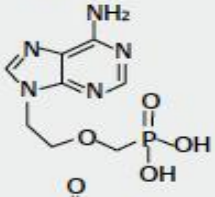
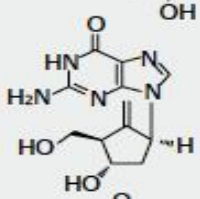
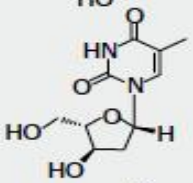
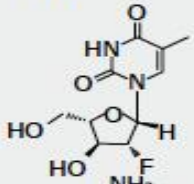
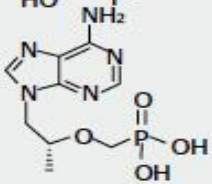
- entekavir (ETV)
- abakavir/karbovir (ABC)

Mutasyon

- İlacın etkinliğini viral DNA'ya bağlanma affinitesi azalır
  - Sterik Hindrans:mutasyon sonucu polimeraz, doğal substrata kıyasla, ilaca daha düşük oranda bağlanır
  - Katalitik etkinlik: Viral DNA'ya bağlanmak için suboptimal bir geometri oluşur

Doo, Gastroenterology;2001.

Nucleos(t)id analogları

Molecule	Structure	Year of FDA approval	*In vitro* IC_{50} (μmol/L)[23]	Resistant mutations	5 yr cumulative resistance rate[25-31]
Lamivudine		1998 (for adults) and 2000 (for children) in United States	3.3[23]	rtL80V/I rtV173L rtL180M rtM204I/V	70%
Adefovir		2002 (United States)	6.3[23]	rtA181T/V rtN236T	29%-65%[57]
Entecavir		2005 (United States)	0.01[23]	rtI169T rtL180M rtT184S/A/I/L rtS202G/I rtM204I/V rtM250I/V	1.2%-1.5%
Telbivudine		2006 (United States)	0.19[24]	rtA181T/V rtM204I	34% (3 yr)
Clevudine		2006 (South Korea)	0.9[23]	rtL180M rtM204I/V	30% (3 yr)
Tenofovir		2008 (United States)	2.5[23]	rtA181T/V rtA194T rtN236T	0%

Jeong Han Kim, World J Gastroenterol 2014: 21; 20(19): 5708-5720

Tedavi-süre

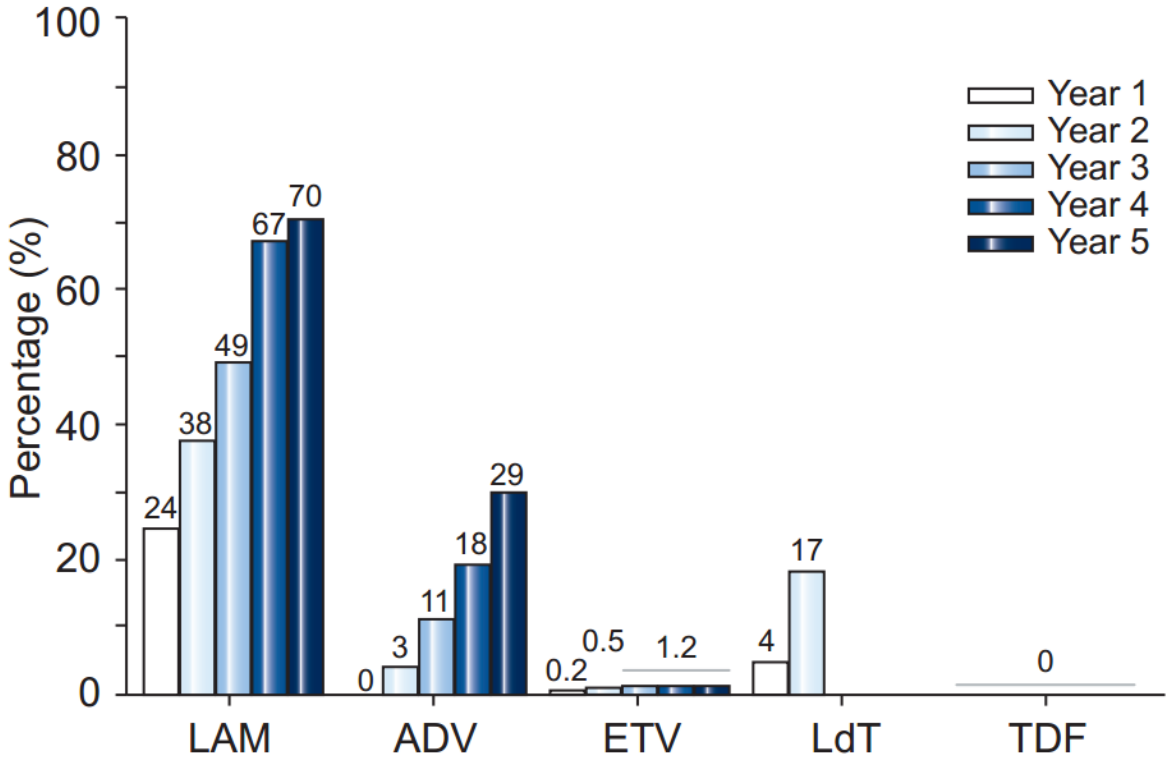
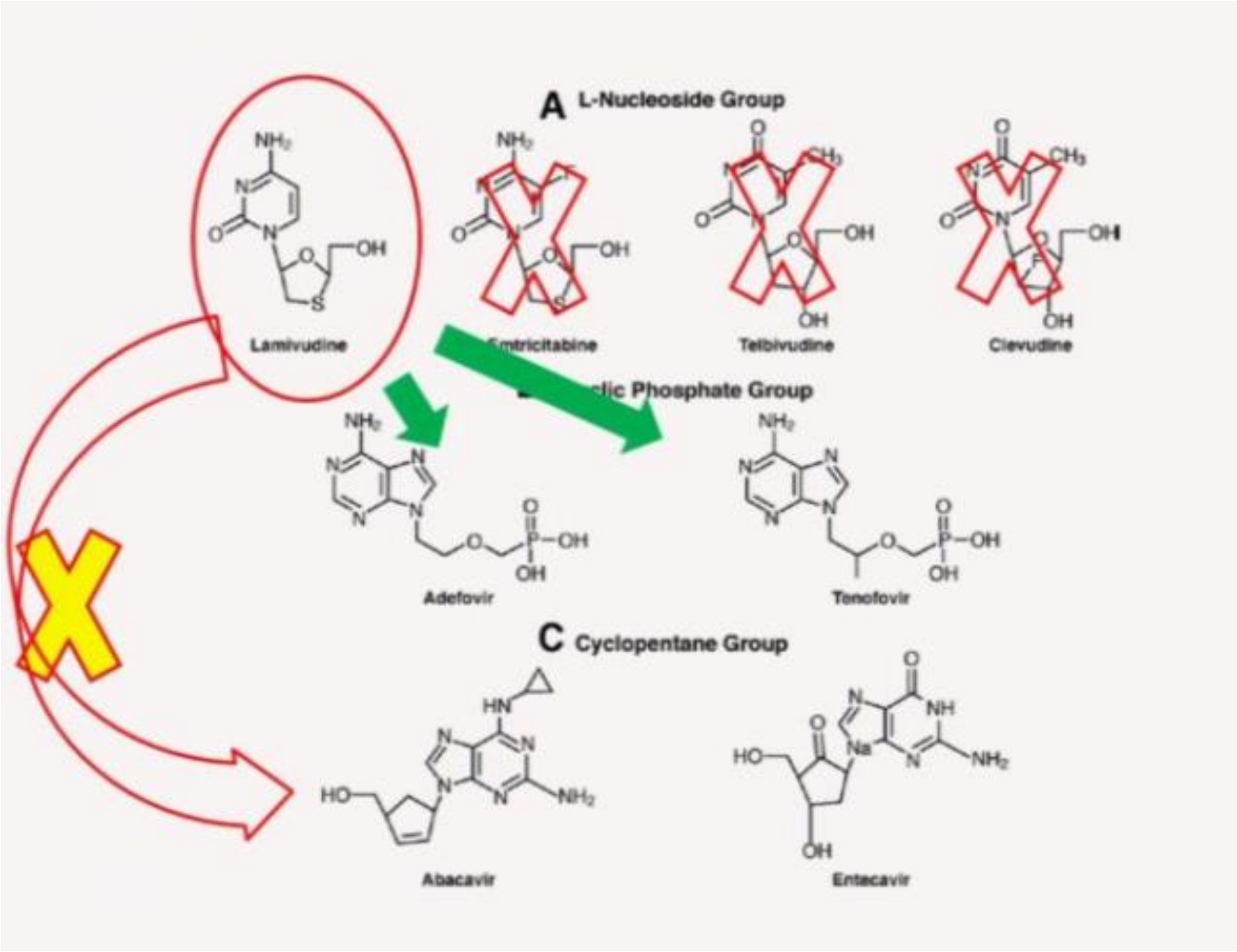


Fig. 1. Cumulative incidence of HBV resistance to lamivudine (LAM), adefovir (ADV), entecavir (ETV), telbivudine (LdT) and tenofovir (TDF) in pivotal trials in nucleos(t)ide-naive patients with chronic hepatitis B. For method of calculation, see Ref. [41]. These trials included different populations, used different inclusion and exclusion criteria and different follow-up end points.

"EASL clinical practice guidelines: Management of chronic hepatitis B virus infection" [J Hepatol 2012;57:167–185]


A L-Nucleoside Group
Lamivudine
Telbivudine
Clevudine
Adefovir
Tenofovir
C Cyclopentane Group
Abacavir
Entecavir

Lamivudin Dirençli hastada Entecavir çapraz direnç

Kümülatif Entecavir Direnci % (n)	Lamivudin almamış % (n)	Lamivudin dirençli % (n)
1. yıl	0.2 (663)	6 (187)
2. yıl	0.5 (278)	15 (146)
3. yıl	1.2 (149)	36 (80)
4. yıl	1.2 (120)	46 (52)
5. yıl	1.2 (106)	51 (33)
6. yıl	1.2 (99)	57 (29)

Tenney Dj, EASL abstarct no:20. 2009 Denmark

Antiviral dirençte yaklaşım

- HBV ilaç direnci mutasyon analizi tedavi yönteminin bir parçası olmalıdır.
- Genetik bariyeri düşük olan ilaç tedavilerindeki rejim değişiklikleri, HBV ilaç direnci analizine göre rasyonel olmalıdır.
- Gereksiz/hatalı ilaç değişikliklerine yol açamamak için kompansatuar mutasyonların mutlaka gösterilmesi ve gereksiz ilaç değişikliği önlenmelidir.
- Etkin bir NA tedavisi ilaca dirençli kökenlerin seçilimini önlemeli ve meydana gelen tüm viral varyantları baskılamalıdır.
- HBV genomunun pol geninde primer ve kompansatuar mutasyonların tümü aynı anda analiz edilmeli ve bu amaçla HBV DNA populasyon sekanslama bir analiz tekniği olarak seçilmelidir.

VHÇG konsensus raporu. 2014 Samsun

Direnç tedavi

Table 1 Guidelines for treatment of resistance

Resistant drug	AASLD 2009[18]	EASL 2012[16]	APASL 2012[17]	KASL 2012[13]
LMV	Add ADV or TDF Stop LMV, switch to Truvada (TDF + FTC)	Switch to TDF Add ADV (If TDF not available)	Add ADV Switch to TDF Switch to IFN-based therapy	Add ADV or TDF Stop LMV, switch to ADV or TDF + other nucleoside analogues Switch to TDF Stop LMV, consider to switch with Peg IFN
ADV	Add LMV Stop ADV, switch to Truvada Stop ADV, switch to or add ETV	NA-naïve; Switch to ETV or TDF Prior LMV-resistance; Switch to TDF + a nucleoside analogue	Add LMV, LdT, or ETV Switch to TDF Switch to IFN-based therapy	With prior LMV resistance, -Stop ADV, switch to TDF + other nucleoside analogues -Add ETV 1mg ADV as a first-line therapy -Stop ADV, switch to TDF + other nucleoside analogues -Add other nucleoside analogue, if rtA181T, add ETV Add nucleotide analogue
ETV	Switch to TDF or Truvada	Switch to TDF Add TDF Add ADV (If TDF not available)	Add TDF or ADV Switch to IFN-based therapy	
LdT	Same treatment as LMV	Switch to TDF Add TDF Add ADV (If TDF not available)	Same treatment as LMV	Same treatment as LMV
CLV TDF		Add ETV, LdT, LMV or FTC (LMV-naïve; Switch to ETV/ prior LMV-resistance; Add ETV)		Same treatment as LMV
Multidrug-resistance		Combination of a nucleoside and a nucleotide (preferably TDF)	ETV + TDF Switch to IFN-based therapy	TDF + ETV 1 mg ADV + ETV 1 mg
Comment	Update is required especially for multidrug-resistance	Recommendation about IFN-based therapy is limited	Recommendation about TDF resistance is limited	Recommendation about TDF resistance and IFN-based therapy is limited

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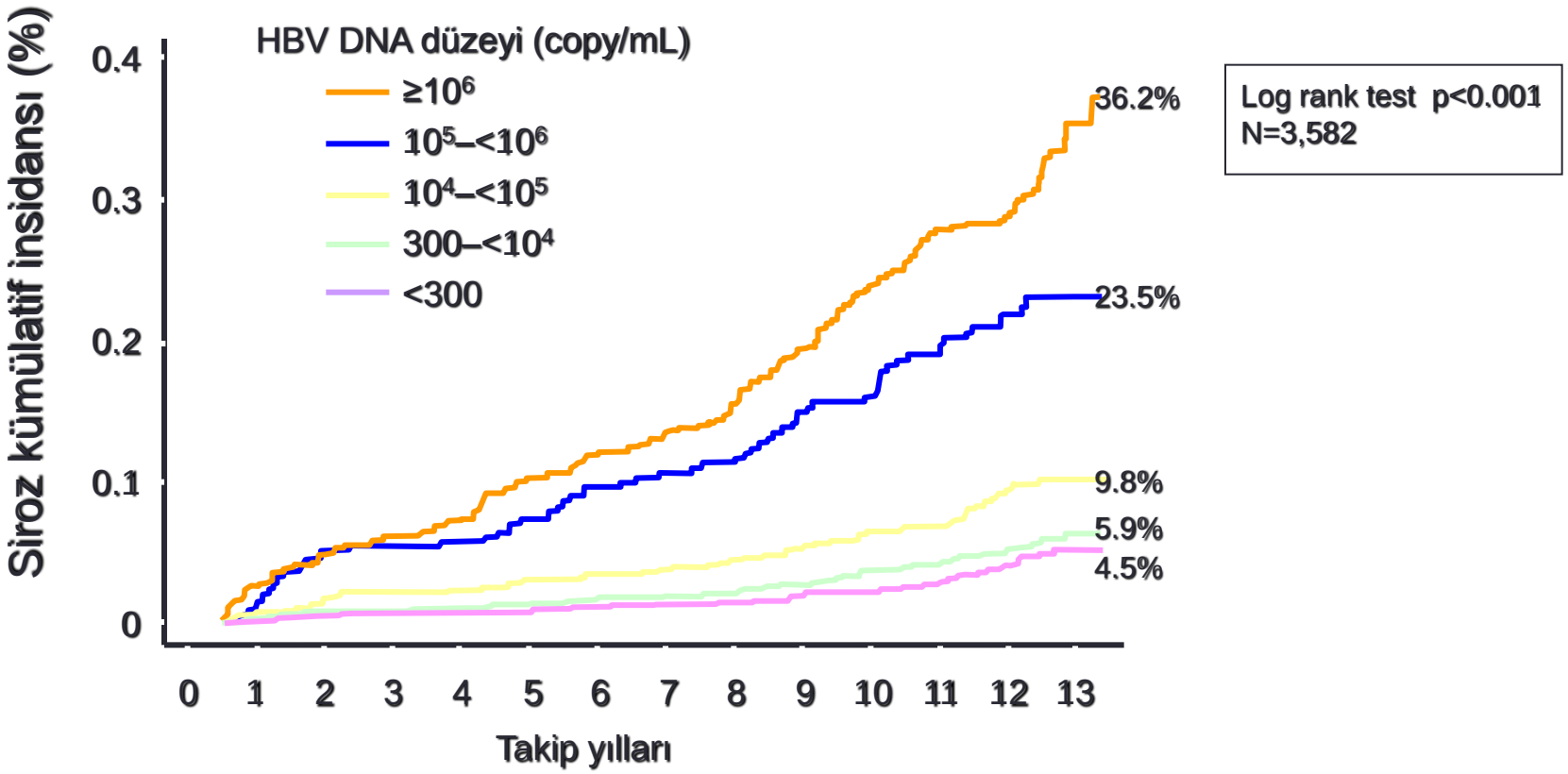
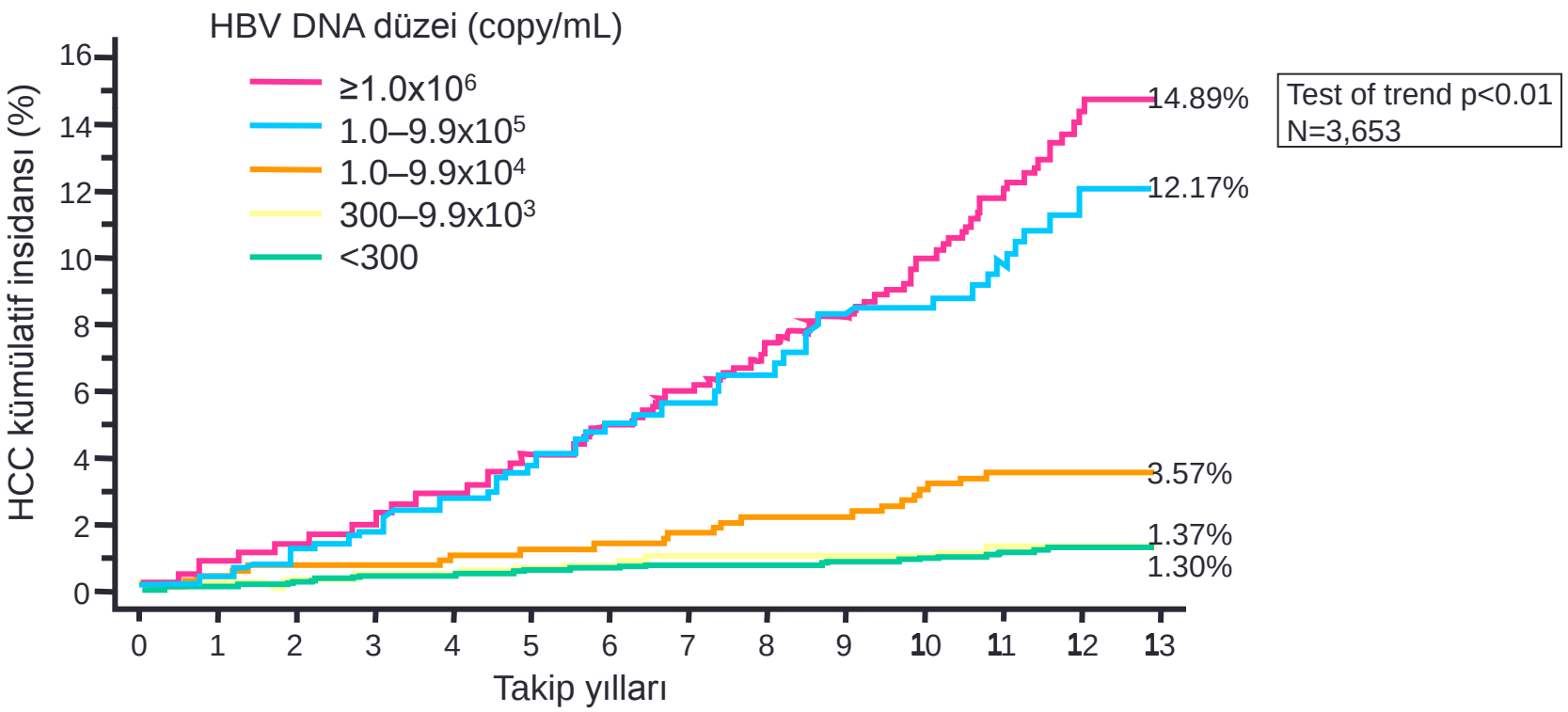
Siroz-viral yük



- HBV DNA düzeyleri siroza ilerleme ile ilşkilidir.

Iloeje UH,l. *Gastroenterology* 2006;130:678-686.

Hepatoselüler carcinoma-viral yük



- HBV DNA düzeyi ile HCC gelişimi arasındaki ilişki

Chen CJ, . *JAMA* 2006;295:65-73.

Mutasyon

Table 4. Incidence of Clinical End Points According to Evidence of YMDD Mutations.

Clinical End Point	Lamivudine Group		Placebo Group (N=214)
	Negative for YMDD Mutations (N=221)	Positive for YMDD Mutations (N=209)	
	number (percent)		
Total	11 (5)	23 (11)	38 (18)
Increase in Child–Pugh score ≥2	1 (<1)	14 (7)	19 (9)
Hepatocellular carcinoma	8 (4)	9 (4)	16 (7)

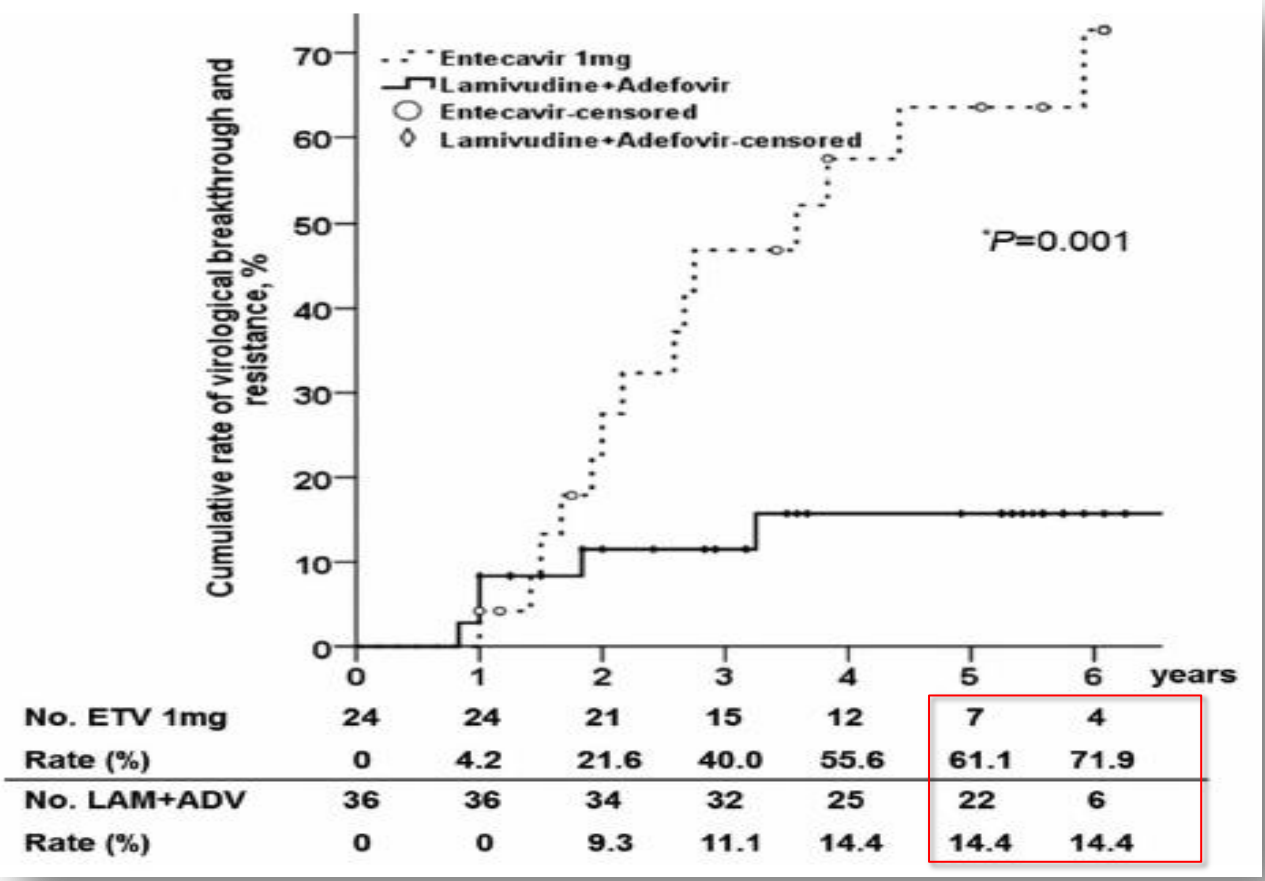
Liaw, N Engl J Med. 2004;351:1521-31.

Original Article

http://dx.doi.org/10.3350/cmh.2014.20.3.267
Clinical and Molecular Hepatology 2014;20:267-273

Long-term outcomes of two rescue therapies in lamivudine-refractory patients with chronic hepatitis B: combined lamivudine and adefovir, and 1-mg entecavir

EunYoung Ze, Eun Kyung Baek, Jong Jin Lee, Han Wook Chung, Dae Geon Ahn, Hwan Jun Cho, Jae Cheol Kwon, Hyung Joon Kim, and HyunWoong Lee



No. ETV 1mg	24	24	21	15	12	7	4
Rate (%)	0	4.2	21.6	40.0	55.6	61.1	71.9
No. LAM+ADV	36	36	34	32	25	22	6
Rate (%)	0	0	9.3	11.1	14.4	14.4	14.4

Hindawi Publishing Corporation
Hepatitis Research and Treatment
Volume 2014, Article ID 615621, 5 pages
http://dx.doi.org/10.1155/2014/615621

Clinical Study

High Dose of Lamivudine and Resistance in Patients with Chronic Hepatitis B

Hamid Ullah Wani, Saad Al Kaabi, Manik Sharma, Rajvir Singh, Anil John, Moutaz Derbala, and Muneera J. Al-Mohannadi

Department of Medicine, Division of Gastroenterology, Hamad Medical Corporation (HMC), 2 South 2, P.O. Box 3050, Doha, Qatar

TABLE 3: Treatment (biochemical and virological response).

	12 months	24 months	36 months	48 months	60 Months
HBV DNA IU/mL Below detection level	35/40 (87.5%)	31/40 (77.4%)	25/40 (62.5%)	20/40 (50%)	16/40 (40%)
Biochemical activity (high ALT)	2/40	normal	normal	normal	normal
HBsAg seroconversion	0%	0%	0%	0%	0%
HBeAg seroconversion	0%	0%	1	2	3
Viral breakthrough	5/40 (12.5%)	9/40 (22.5%)	15/40 (37.5%)	20/40 (50%)	24/40 (60%)

Kombinasyon tedavisi

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REVIEW ARTICLE

Optimal therapy for chronic hepatitis B: hepatitis B virus combination therapy?

Jorg Petersen[1] and Maura Dandri[2]

1 IFI Institute at the Asklepios Klinik St Georg Hamburg, University of Hamburg, Hamburg, Germany
2 Department of Medicine, University Hospital Hamburg Eppendorf, Hamburg, Germany

EASL kılavuzda yer alan :

- Çok selektif vakalarda
- Multirezistan virüs türler
- Birkaç monoterapi ile tedavi başarısızlığı

Kombinasyon tedavisi

Mathematical Medicine and Biology Advance Access published November 13, 2014

Mathematical Medicine and Biology (2014) Page 1 of 21
doi:10.1093/imammb/dqu022

Combination versus sequential monotherapy in chronic HBV infection: a mathematical approach

DANIELA BERTACCHI*

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

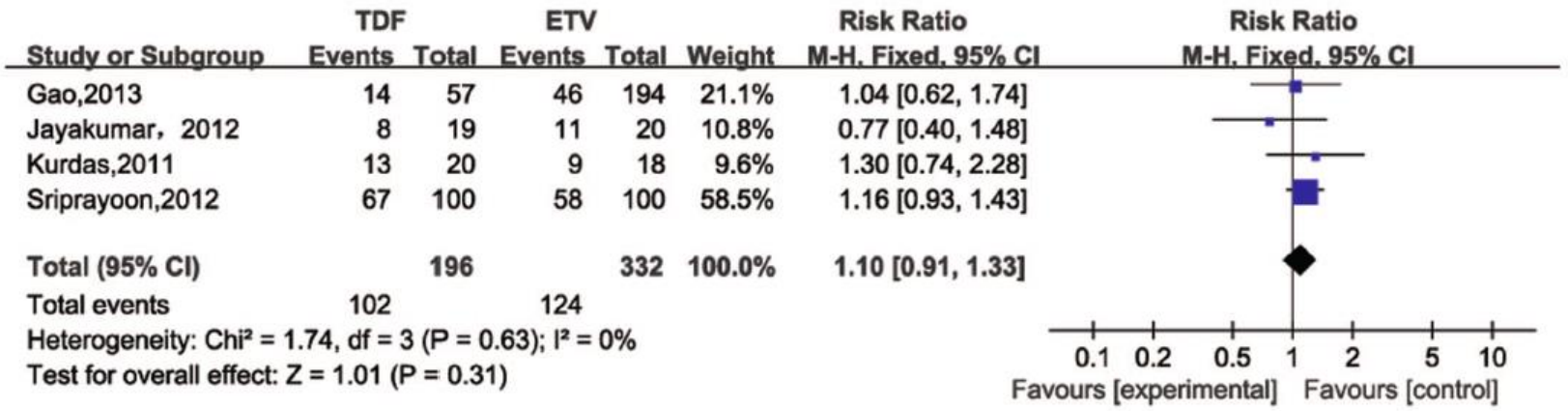

Figure 2. Forest plot for HBV DNA suppression rates 24 weeks post therapy.

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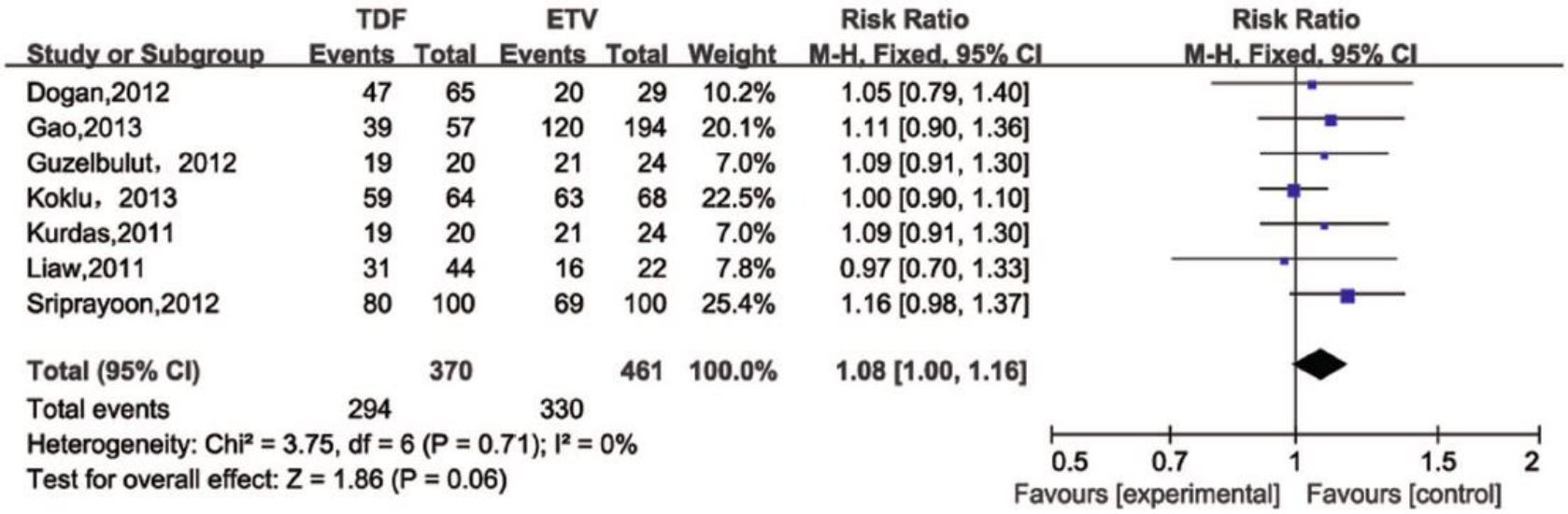

Figure 3. Forest plot for HBV DNA suppression rates 48 weeks post therapy.

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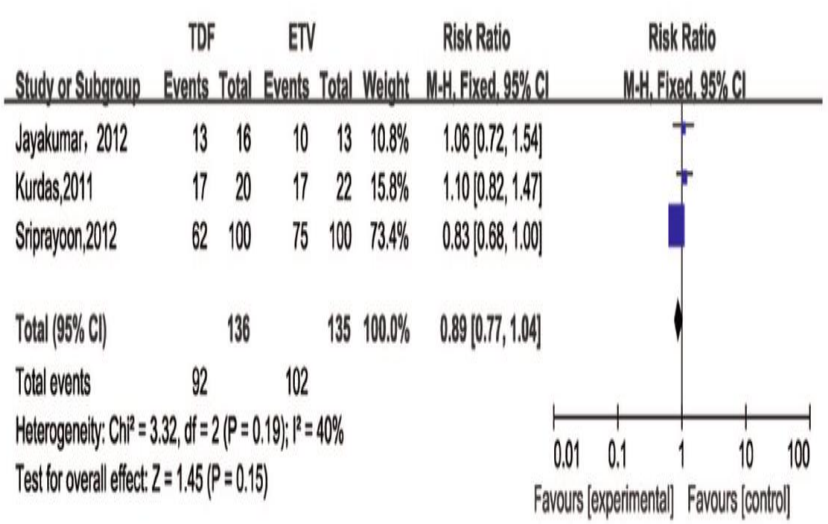


Figure 4. Forest plot for ALT normalization rates 24 weeks post therapy.

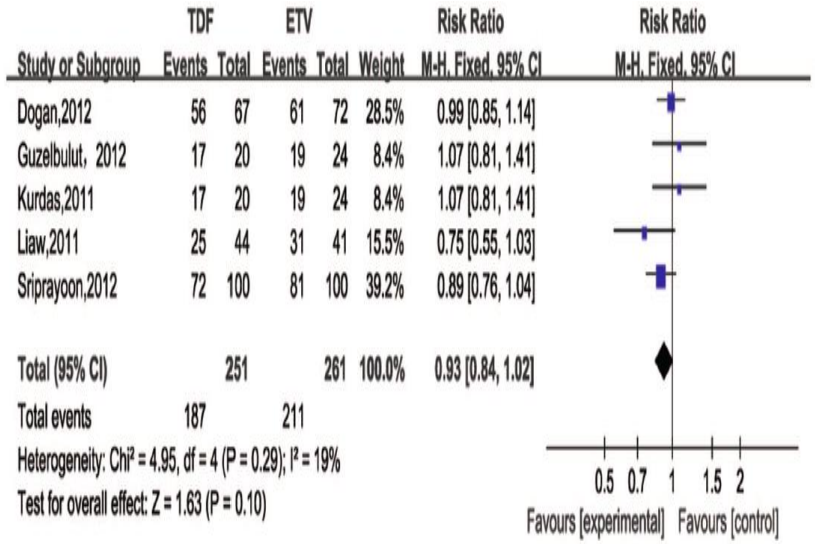


Figure 5. Forest plot for ALT normalization rates 48 weeks post therapy.

Efficacy of tenofovir disoproxil fumarate therapy in Chinese chronic hepatitis B patients after multiple anti-viral failures

Yingxia Liu,[1] Ying Zhang,[1] Jing Yuan,[1] Wen Zeng,[1] Guoliang Zhang,[1] Simin Yao,[1] Huijuan Li,[1] Min Yang,[1] Yong Deng,[1] Rongrong Zou,[1] Shaxi Li,[1] Jia Xiao[1,2,3]

Table 3. Effect of HBV genotypic resistance and baseline HBV DNA on virological and biochemical response after TDF treatment

Variables		HBV genotypic resistance type				HBV DNA (IU/ml)	
		ADV related R^+	LMV R^+	R^-	Total[a]	$\geq 10^6$	$< 10^6$
	n	27	49	39	115	35	80
CVR, n (%)	Week 12	13(48.1)	31(63.3)	22(56.4)	66(57.4)	10(28.6)[b]	56(70)[b]
	Week 24	16(59.3)	38(77.6)	26(66.7)	80(69.6)	15(42.9)[c]	65(81.3)[c]
	Week 48	16(59.3)	41(83.7)	29(74.4)	86(74.8)	20(57.1)[d]	66(82.5)[d]
	Week 72	22(81.5)	46(93.9)	31(79.5)	99(86.1)	28(80)[e]	71(88.8)[e]
HBeAg clearance, n (%)	*B HBeAg+	22[f]	41[f]	36[f]	99	29(82.9)[g]	70(87.5)[g]
	Week 24	3(13.6)	3(7.3)	3(8.3)	9(9)	2(6.9)	7(10)
	Week 48	5(22.7)	6(14.6)	4(11.1)	15(15.2)	5(17.2)	10(14.3)
	Week 72	6(27.3)	10(24.4)	7(19.4)	23(23.2)	5(17.2)	18(25.7)
ALT normalization, n (%)	#BA ALT	16[h]	34[h]	16	66	30(85.7)	36(45)
	Week 12	9(56.3)	9(26.5)[i]	10(62.5)[i]	28(42.4)	9(30)	19(52.8)
	Week 24	10(62.5)	15(44.1)	10(62.5)	35(53)	14(46.7)	21(58.3)
	Week 48	10(62.5)	23(67.6)	13(81.3)	46(69.7)	19(63.3)	27(75)
	Week 72	13(81.3)	23(67.6)[j]	15(93.8)[j]	51(77.3)	20(66.7)	31(86.1)

Takip

- Fibrozis skoru ileri olmayan (düşük HBV DNA) olan hasta
  - Başlangıç, 3.ay, sonra 6 ayda bir HBV DNA

- Fibrozis skoru ileri (yüksek HBV DNA)
  - Başlangıç, 3. ay, sonra 3 ayda bir HBV DNA

Clin Gastroenterol Hepatol. 2006;4(6):666-76..

Takip

- Lamivudin 3 ayda bir
- Entecavir-Tenofovir 6 ayda bir

- Bir antivirale direnç saptanıp tedavi yeniden düzenlendikten sonra, izleyen yıllarda direnç saptanmasa bile kullanılmamalı.

Takip

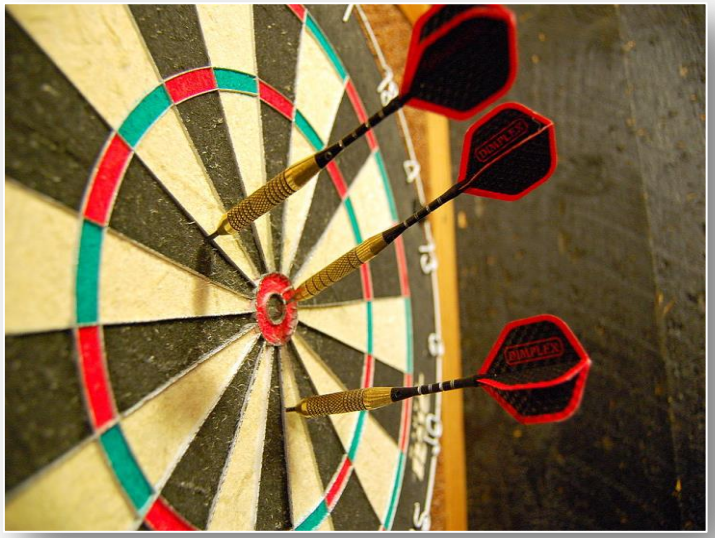
- Serum HBV DNA düzeyi antiviral etkinlik takibi için uygun (Real-time PCR) [1]

- Çalışma aşamasında olan takip kriterleri:
  - cccDNA kantifikasyonu[2]
  - HBsAg boyama ve kantifikasyonu[3,4]
  - HBeAg boyama ve kantifikasyonu[5,6]

1. Pawlotsky JM et al., *Gastroenterology* 2008;134:405. 2. Wursthorn K, et al., *Hepatology* 2006;44:675-84. 3H, et al., *Hepatology* 1988;8:749-54. 4. Chan HL, et al., *Clin Gatroenterol Hepatol* 2007; 5:1462-8. 5. Lindh M, et al., *Liver* 1999;19:294-8. 6. Fried MW, et al., *Hepatology* 2008;47:428-34.

Sonuç

- Uygun hasta
- Uygun ilaç
- Uygun izlem



Teşekkürler…

ENTECAVİR direnci için birden çok mütasyon gerekir
= Direnç karşı yüksek genetik bariyer[1]