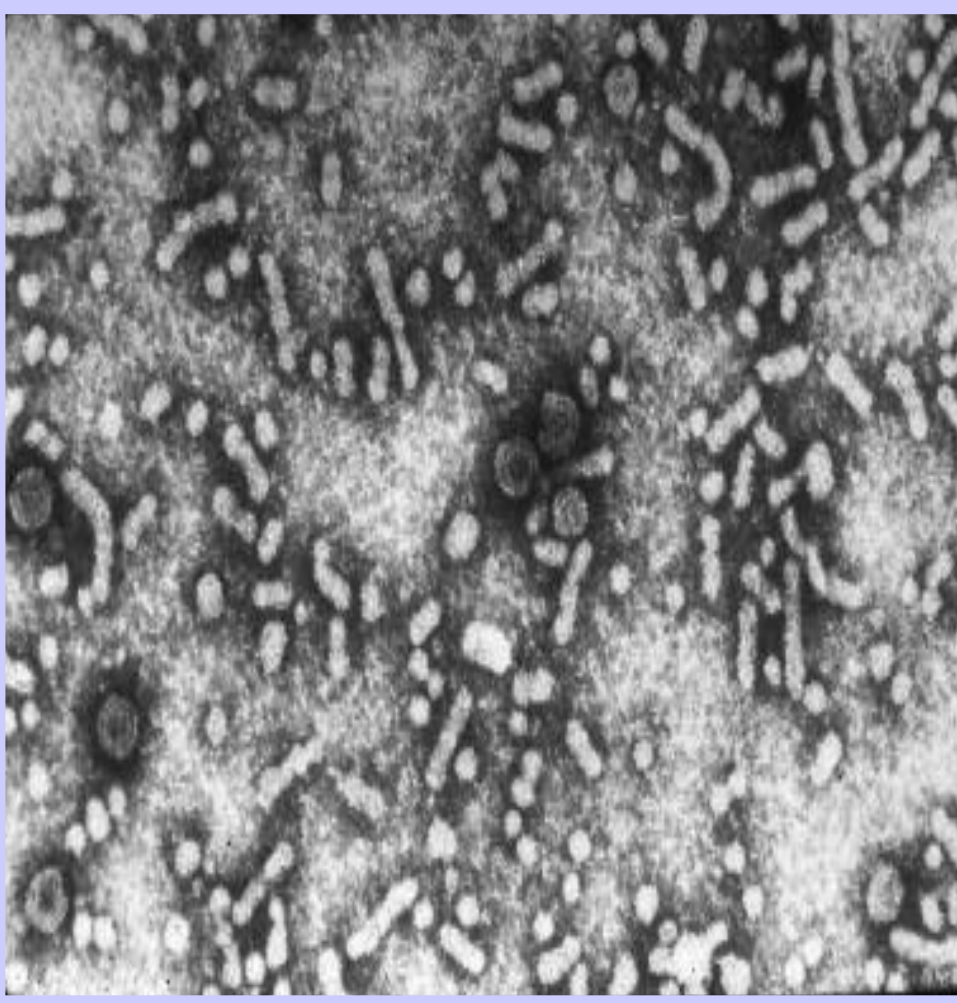


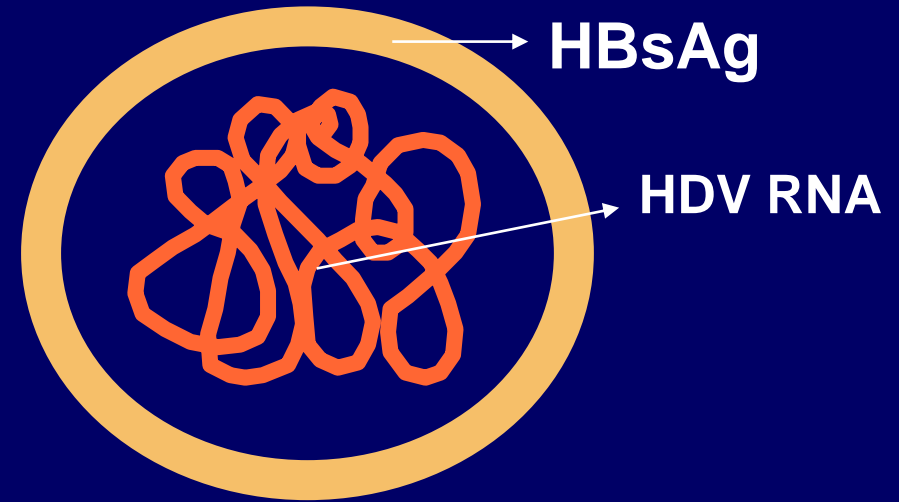
# Kronik Delta (D) Hepatiti

Prof. Dr. Yılmaz akalođlu

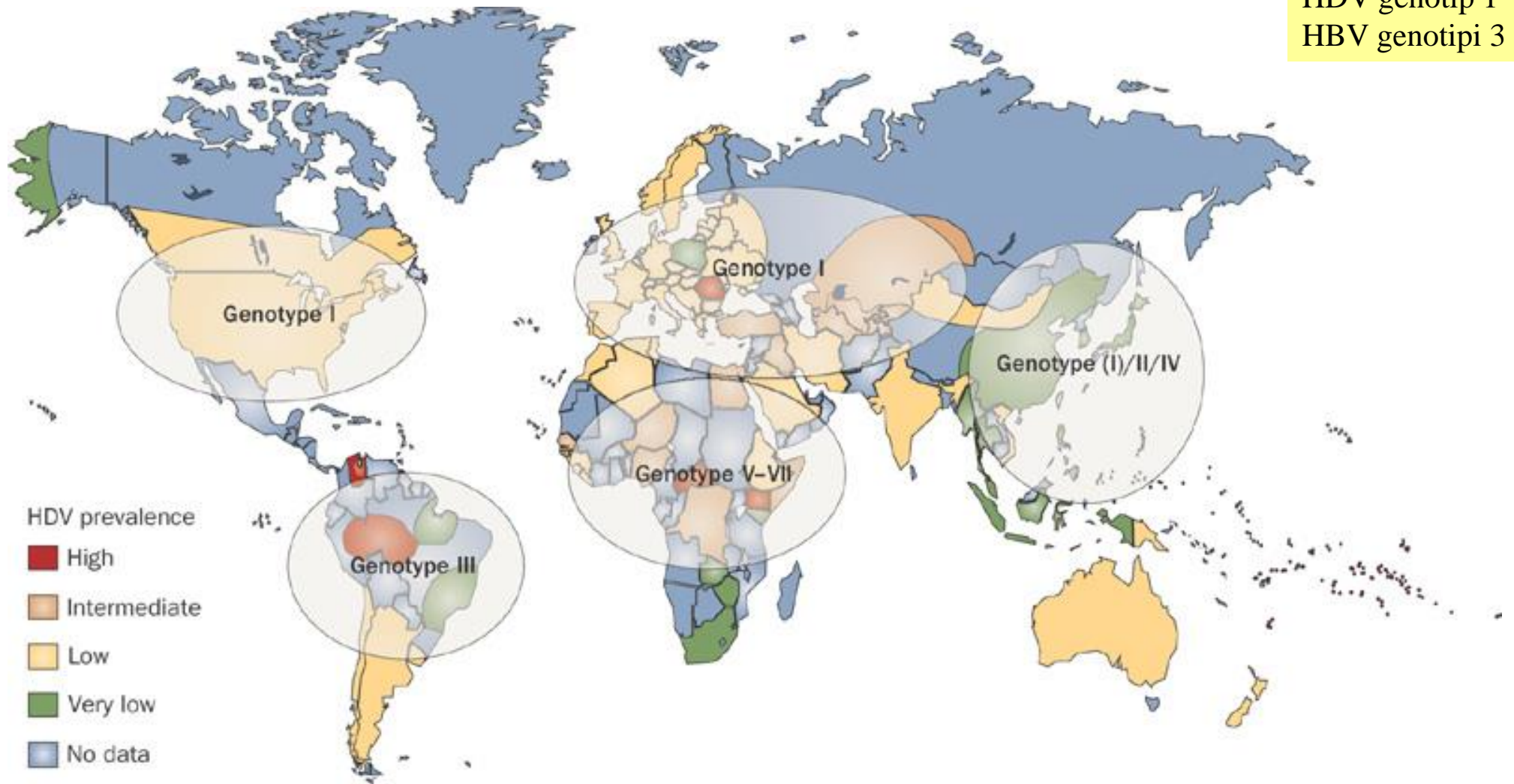
# Hepatitis B Virusu



# Hepatitis Delta Virusu

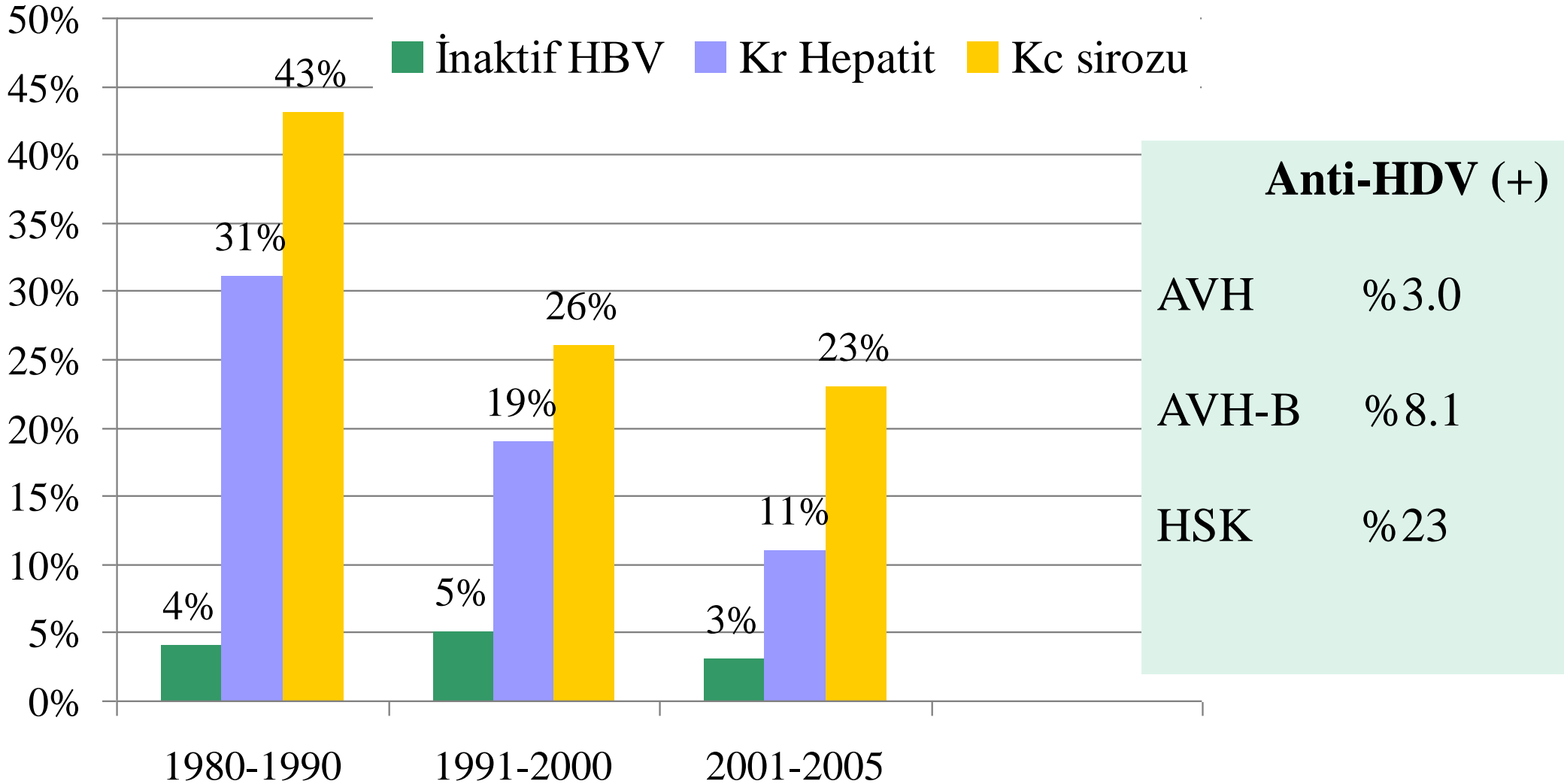


HDV genotip 1  
HBV genotipi 3



Epidemiology, pathogenesis and management of hepatitis D: Update and challenges ahead.  
Wedemeyer H, Manns MP. Nat Rev Gastroenterol Hepatol 2010; 7: 31-40.

# Türkiye’de HBV’ye bağlı akut/kronik karaciğer hastalıklarında Hepatit Delta Virus (HDV) infeksiyonu sıklığı



# TKAD-Ulusal Hepatit Epidemiyolojisi Çalışması (TürkHep 2010)

5471 erişkin kişide

**HBsAg pozitifliği** %4.0 3.000.000 kişi

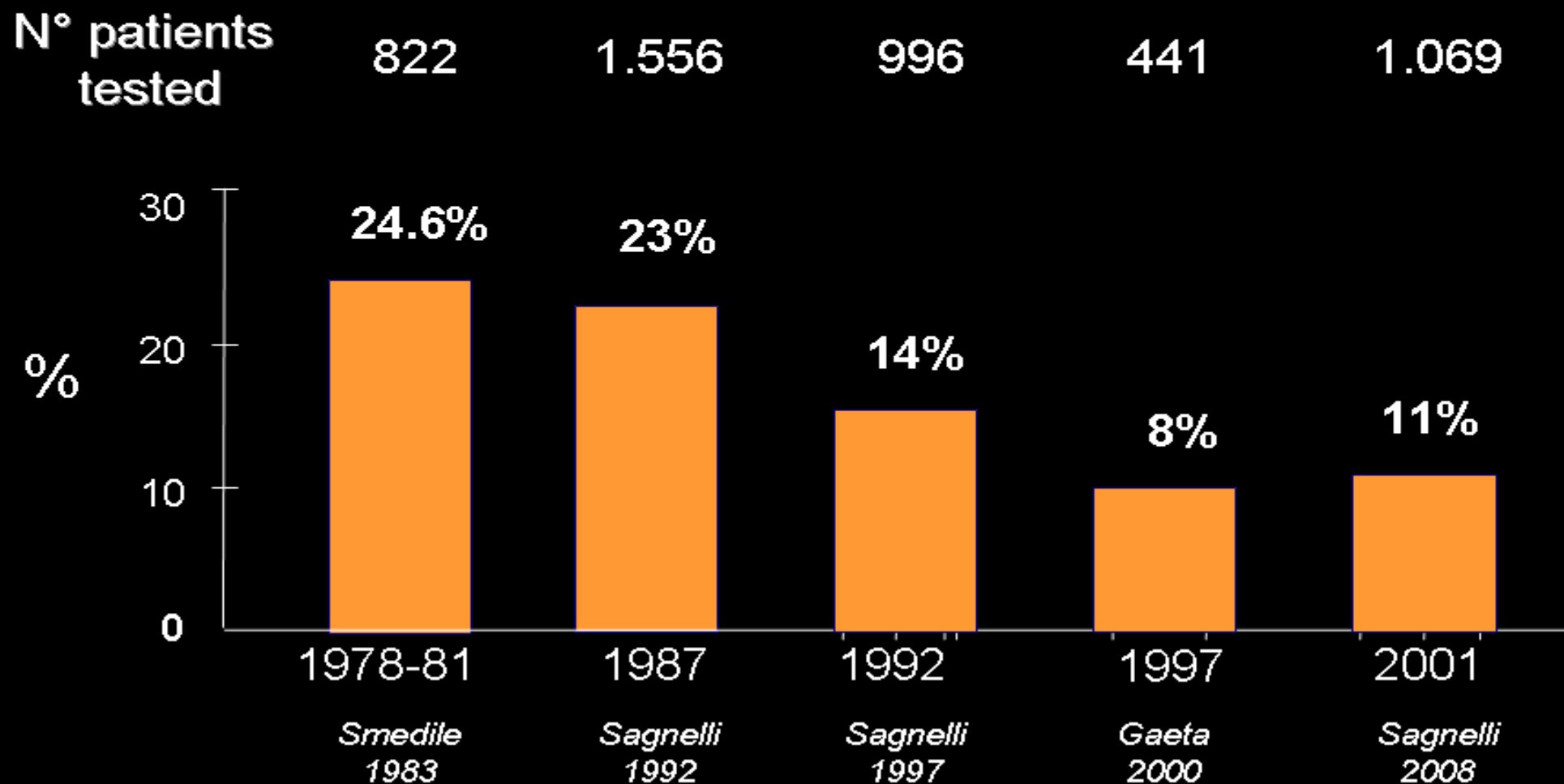
-Anti HDV pozitifliği %2.7

Toplumda anti-HDV pozitifliği %011 81.000 kişi ?

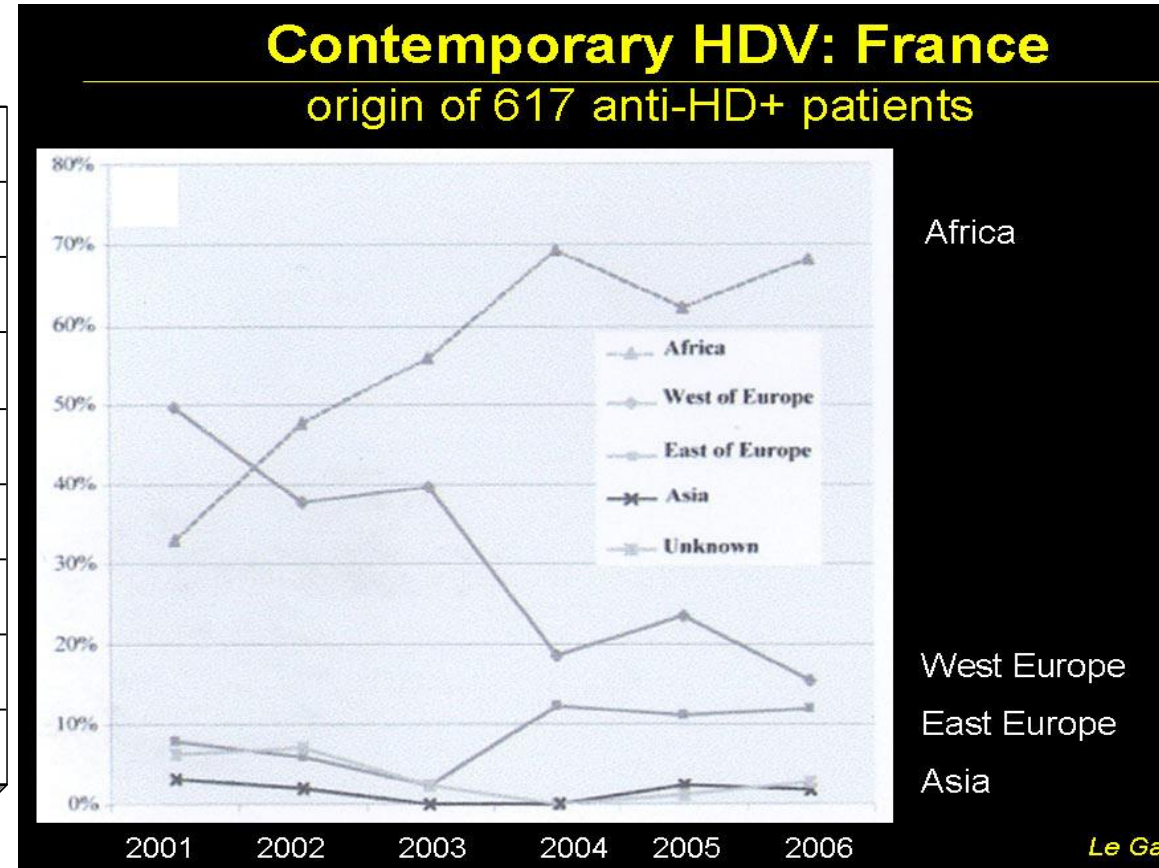
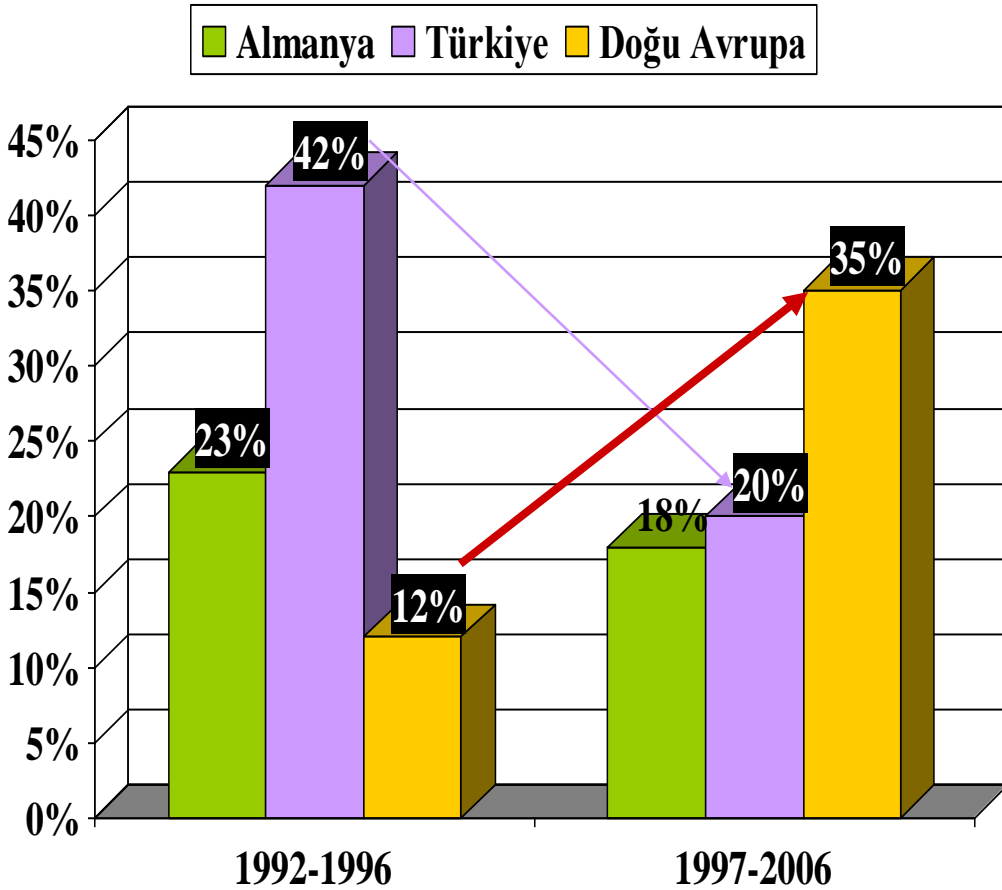
**Anti-HCV pozitifliği** %0.95 712.500 kişi

**Anti-HAV IgG pozitifliği** %93.2

# Prevalence of anti-HD in HBsAg-carriers with liver disease in Italy



# Avrupa'da deęişen HDV epidemiyolojisi



*Wedemeyer et al Hepatology 2007*

# HDV infeksiyonunda azalma sebepleri

UNİVERSAL HBV  
AŞILAMASI

Sosyoekonomik  
düzeyin yükselmesi  
ve daha iyi hijyen

HIV infeksiyonu için  
alınan önlemler

# DELTA HEPATİTİ TANISI

**HBsAg pozitif her hastada;**

HBeAg, anti-HBe, anti-HBc IgM ve

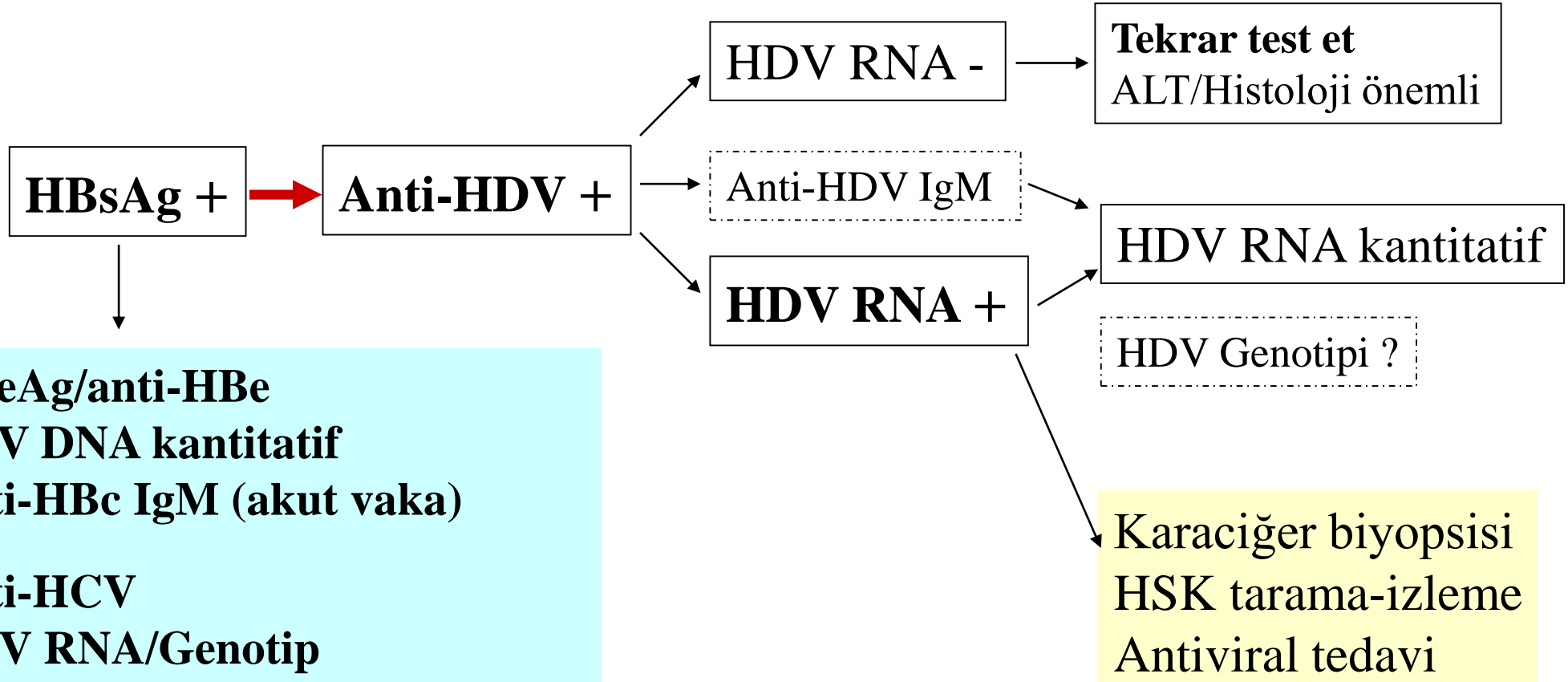
HBV DNA PCR kantitatif tayini ile birlikte

- **Anti-HDV (total veya IgG) testi**
- **HDV RNA PCR kantitatif tayini**
- Anti-HDV IgM testi
- Dokuda HDAg antijeni
- HDV genotipi

HDV infeksiyonu tanısı

Ayrıca tamamlayıcı serolojik testler olarak anti-HAV IgG, anti-HCV testi ve anti-HIV bakılmalıdır.

# DELTA HEPATİTİ TANISI



**HBeAg/anti-HBe**  
**HBV DNA kantitatif**  
**Anti-HBc IgM (akut vaka)**

**Anti-HCV**  
**HCV RNA/Genotip**

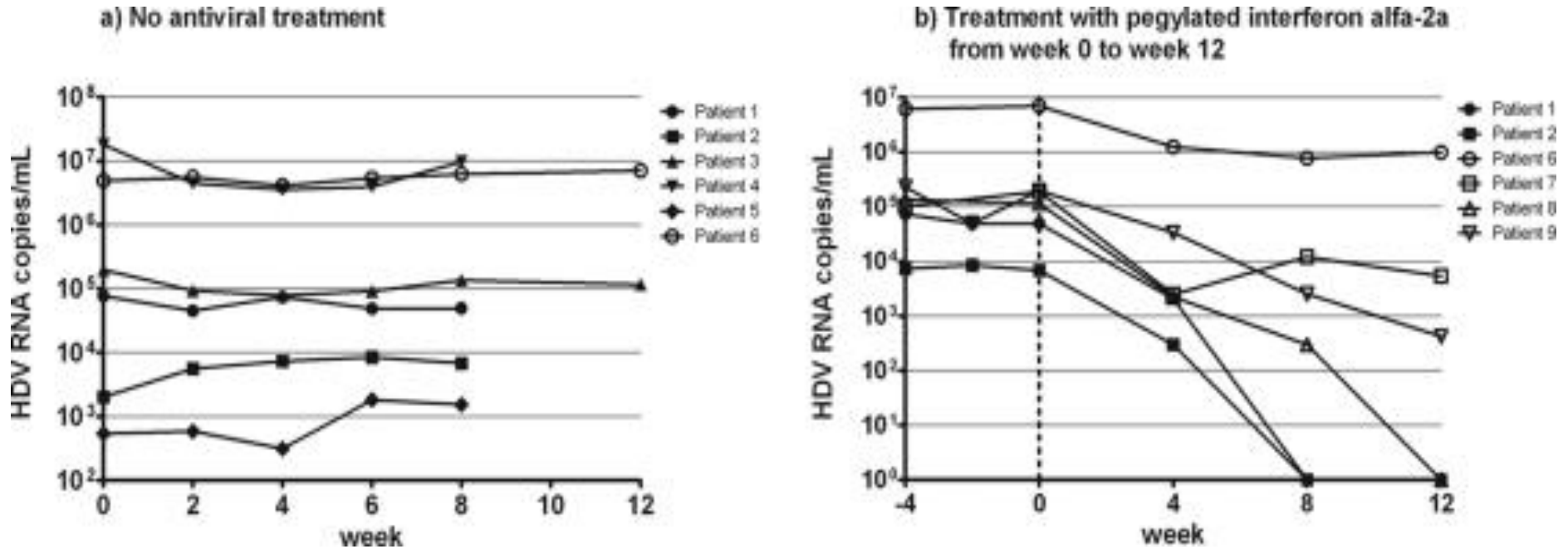
**Anti-HIV**

**Çoklu infeksiyon seyrek değildir**  
**Baskın olan virusa göre davran**

# Kantitatif HDV RNA testi

- HDV infeksiyonu tanısı için altın standart
- Tedavi kararı verilmesi için gerekli
- ALT ve histoloji ile ilişkisi zayıf/yok
- Kantitatif HBsAg düzeyi ile ilişkili
- Tedavinin izlenmesinde çok önemli
  - HDV RNA 24.haftada  $\geq 3$  log<sub>10</sub> azalmış olmalı
- Tedaviye cevap HDV RNA negatifliğidir....

## Tedavisiz izlenen ve pegIFN alfa-2a tedavisi alan kronik D hepatiti hastalarında 0-12 hafta arasında izlenen HDV RNA kinetiği



“Cobas TaqMan assay” ile oldukça duyarlı ve güvenilir bir testtir...

# AKUT DELTA (D) HEPATİTİ

## 1) KOİNFEKSİYON (BİRLİKTE İNFEKSİYON)

-HBV ve HDV birlikte bulaşır-hastalık yapar

-Önce HDV sonra HBV'ye bağlı hasar ve ikili (bifazik)

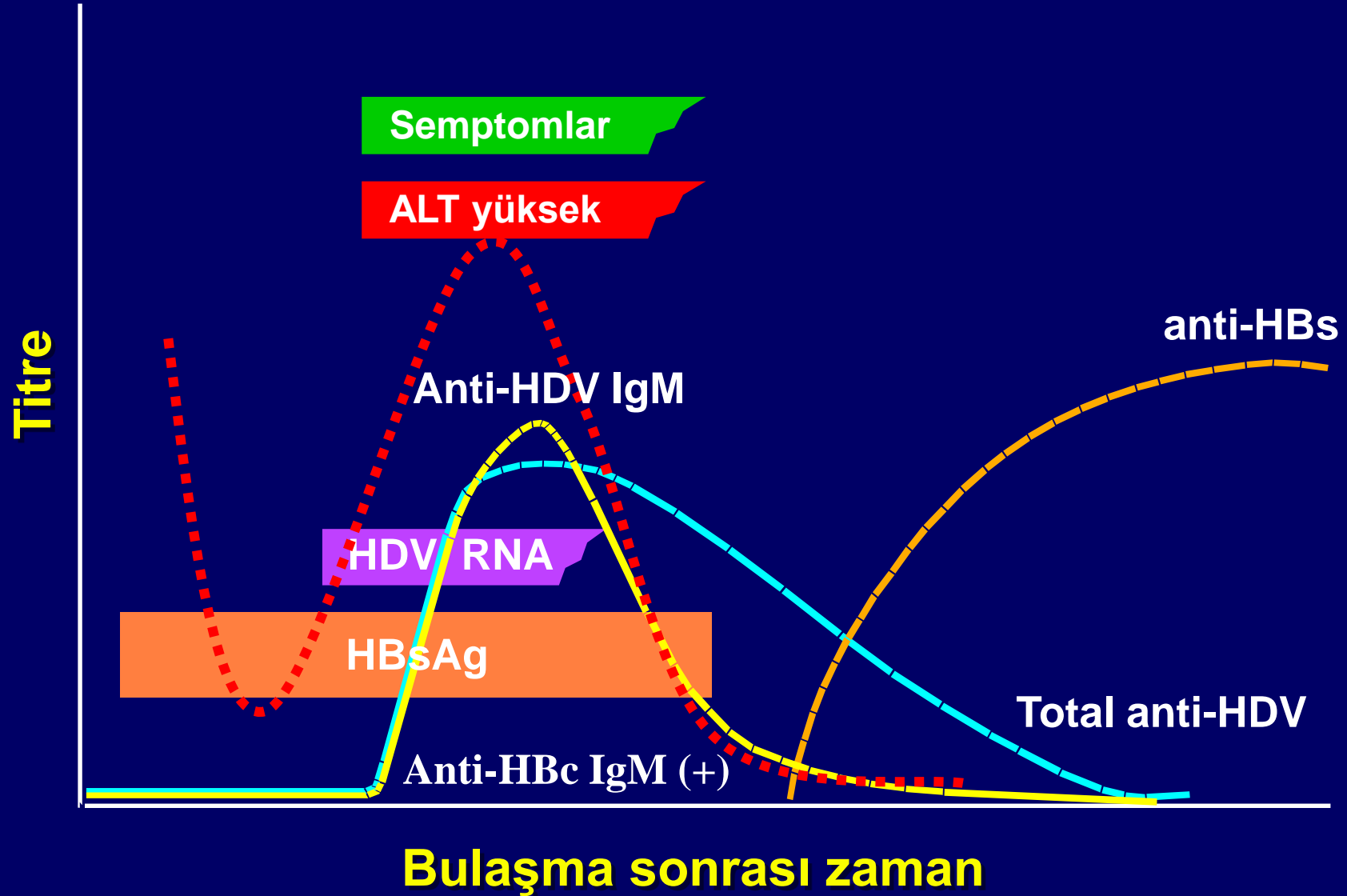
ALT/AST yükselmesi olur

## 1) SÜPERİNFEKSİYON (EKLENEN İNFEKSİYON)

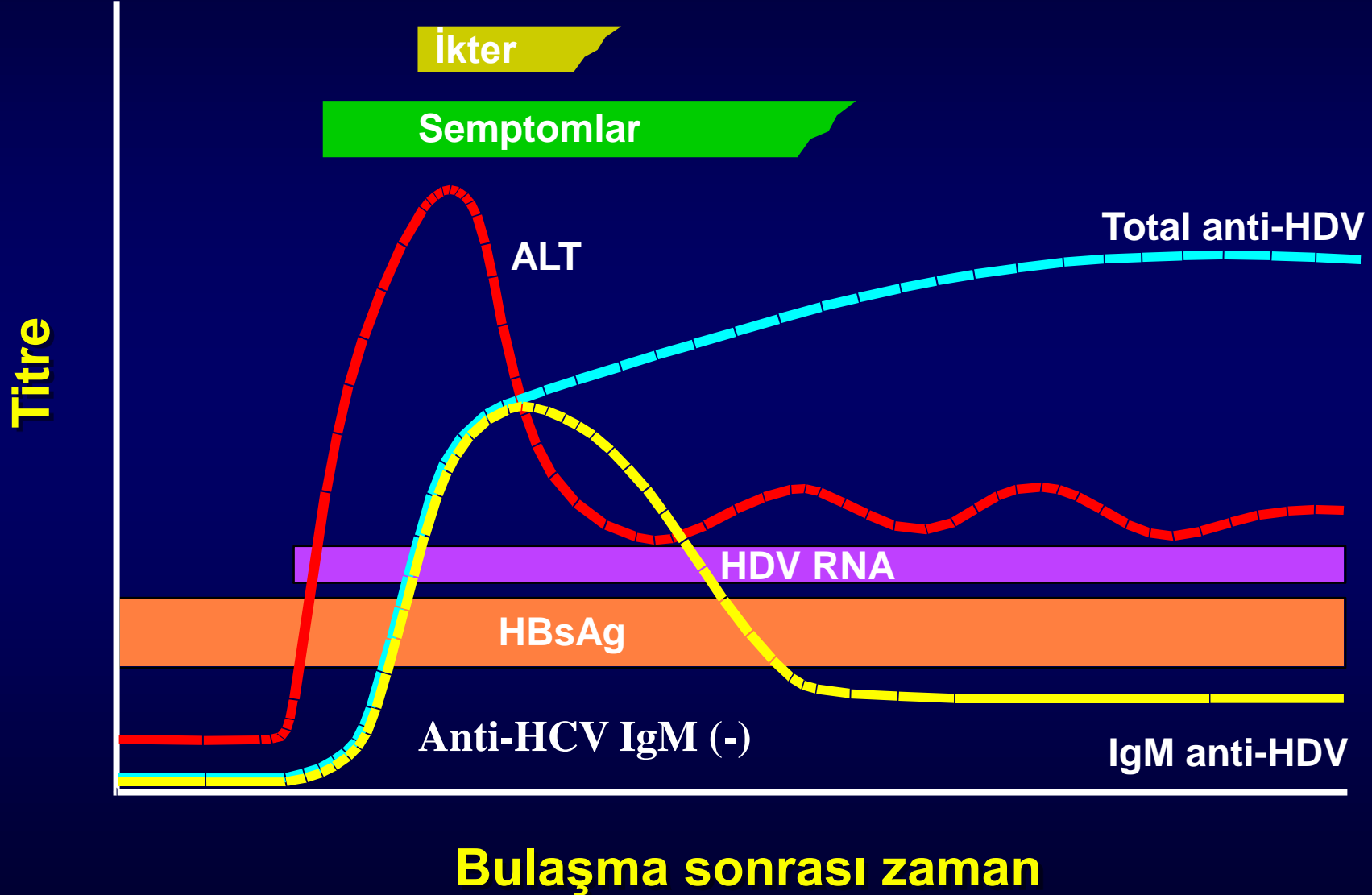
-Kronik HBV enfeksiyonlu kişilerde akut HDV enfeksiyonu

# HBV - HDV Koinfeksiyon

## Tipik Serolojik Seyir

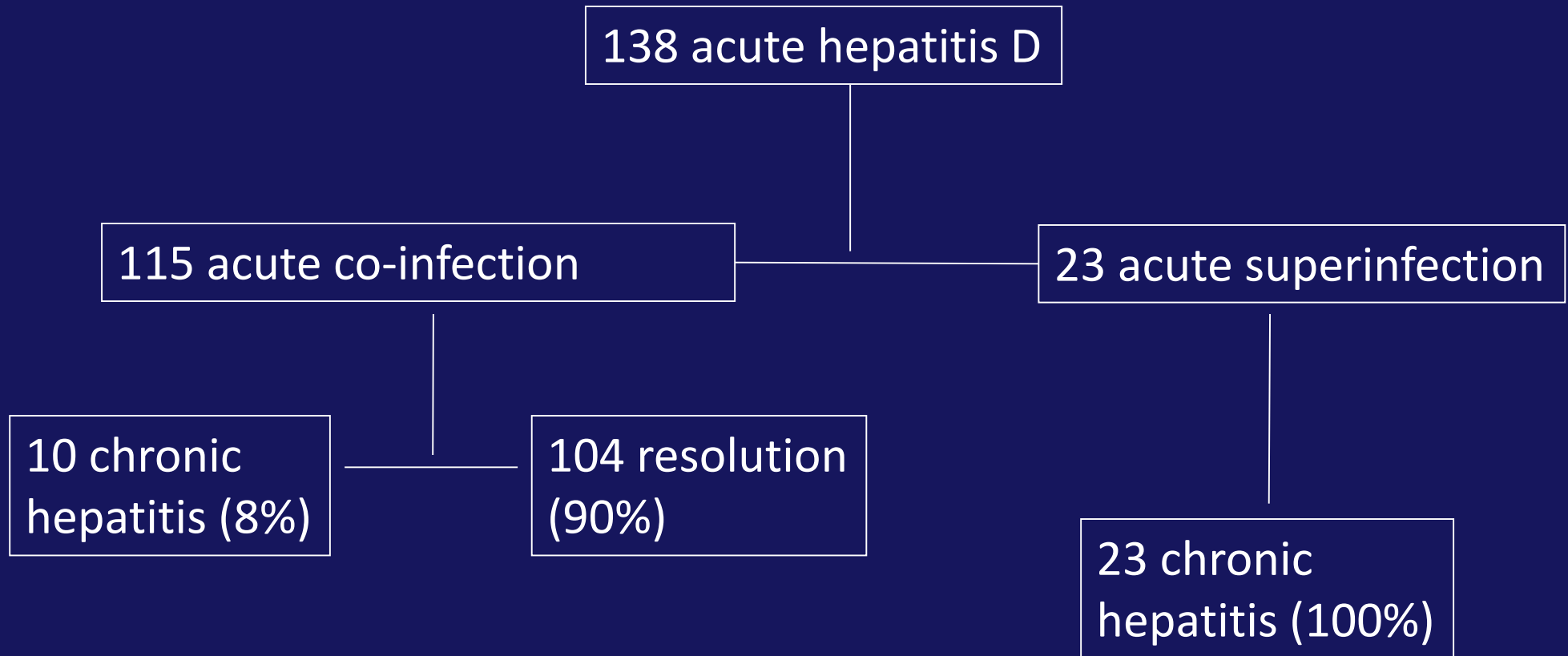


# HBV - HDV Superinfeksiyonu Serolojik Bulgular



# Outcome of Acute Delta Hepatitis

*Buti et al, J Viral Hepat 2010 (in press)*



# DELTA HEPATİTİ

**koinfeksiyon**

**süperinfeksiyon**

**Fulminan**  
%2-20

**İyileşme**  
%80-90

**Kronikleşme**  
%2-10

**Kronikleşme**  
%80-90

**İyileşme**  
%5-10

**Fulminan**  
%10-20

**SİROZ**

**HSK**

HBV'den 10 yıl önce  
10 yılda %80

Risk 2-3 kat yüksek

# HDV İnfeksiyonu-Dođal Seyir

- Kronik HDV dođal seyri, HBV'den kötüdür...
- 10 yılda hastaların %80'inde siroz gelişir...
- Dekompansasyon daha sıktır ...
- HSK daha sıktır....

**GERÇEKTEN BÖYLE Mİ?**

# Toplam 299 kronik HDV İnfeksiyonu Hastasının Uzun Süreli (28 yıl) Takip Sonuçları (İtalya)

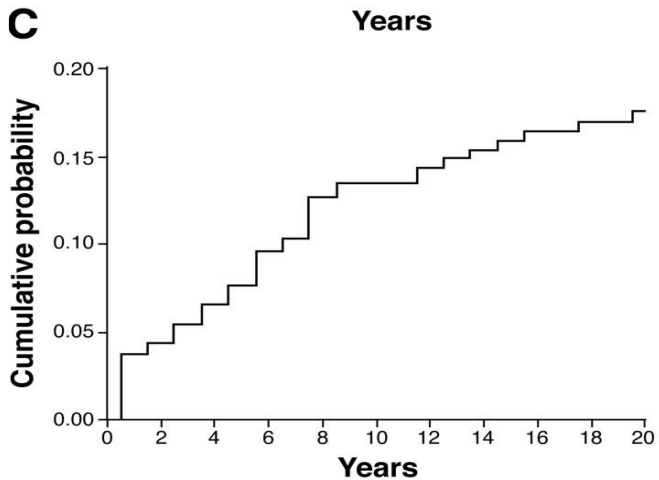
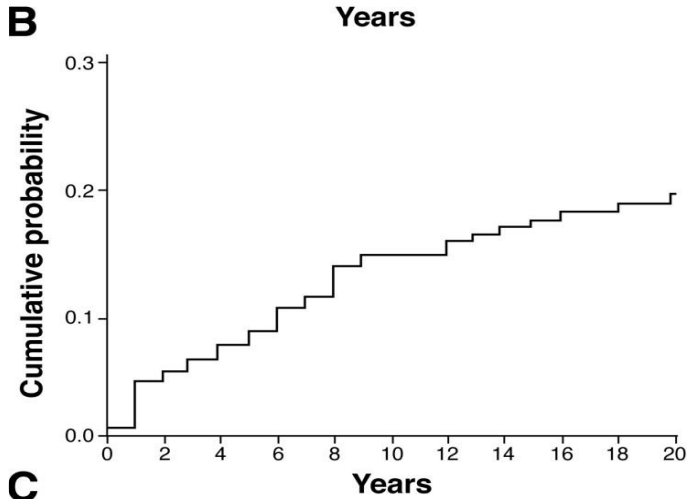
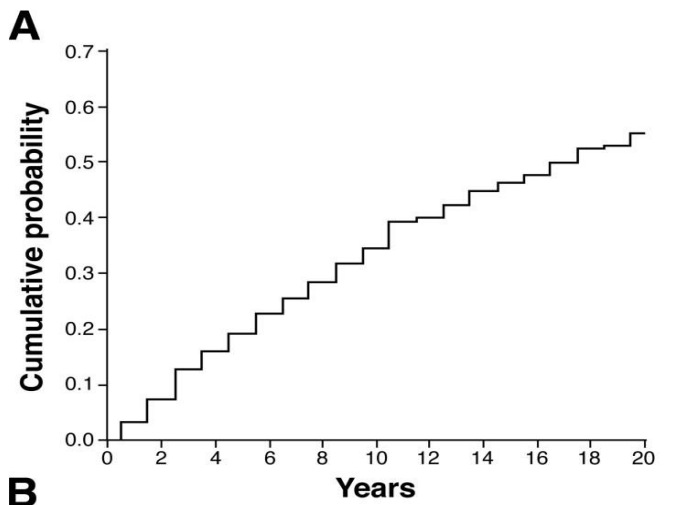
- %77 erkek, ortalama yaş 30 yıl (Ort. 233 ay takip edilmiş hastalar)
- 195 kronik hepatitli hastanın %42'sinde siroz
- 186 sirozlu hasta: %30'unda dekompanseasyon, %25'inde HSK
- 63 (%21) hasta kaybedilmiş, 29 hastaya karaciğer nakli yapılmış  
Yıllık ölüm oranı %1.1 / (Mortalite + Kc nakli - %31)
- Asıl ölüm sebebi 37 hastada karaciğer yetersizliği (%60)
- **Yıllık ve 5 yıllık siroz (%4 - %20) ve HSK insidensi (%3 ve %12)**
- **Kronik HDV inf. tanısından sonra 20 yıl sağkalım %85**
- **HDV replikasyonu-olumsuz prognozun işareti**

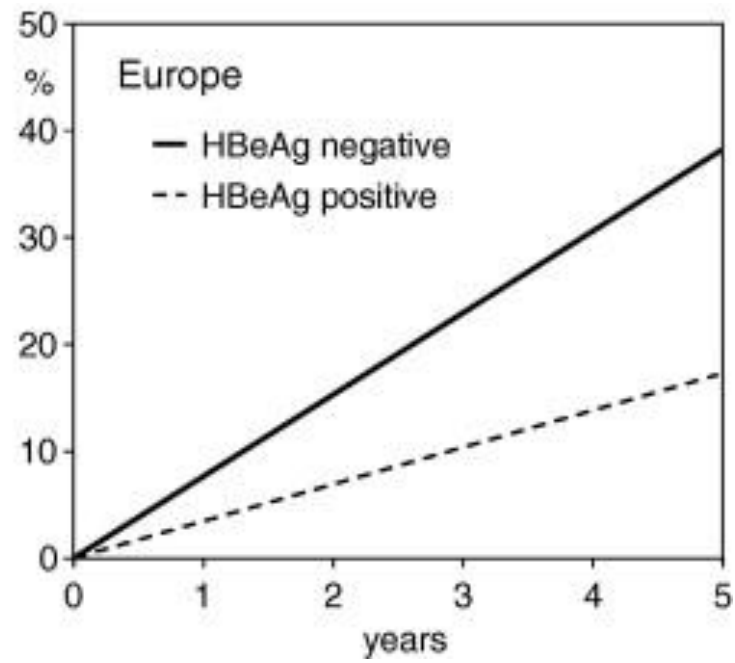
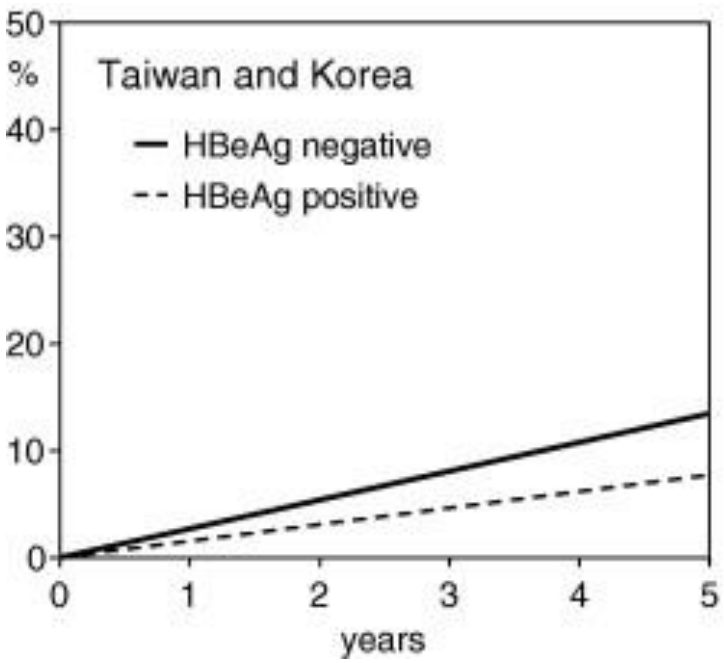
## KÜMÜLATİF RİSK (ort. 233 ay izlem)

**SİROZ:** %60  
(Ort. 233 ay izlenen 299 hastada)

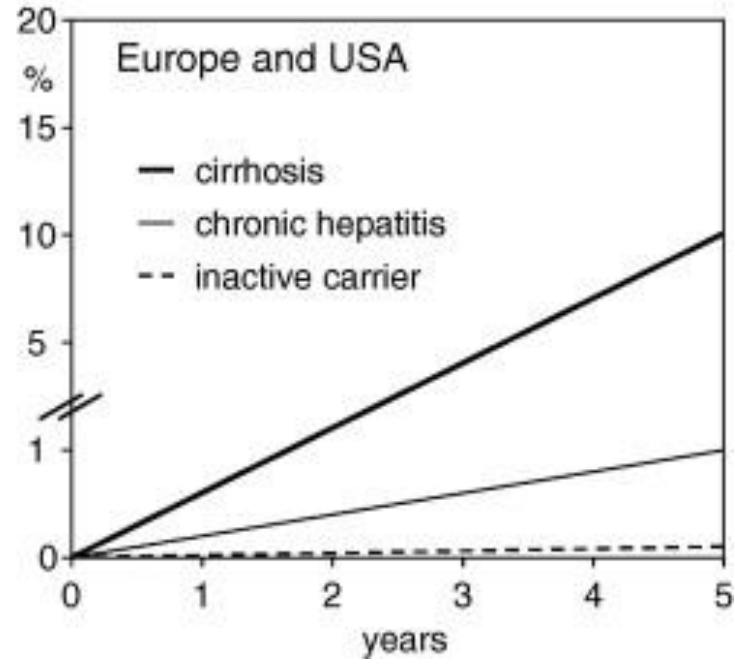
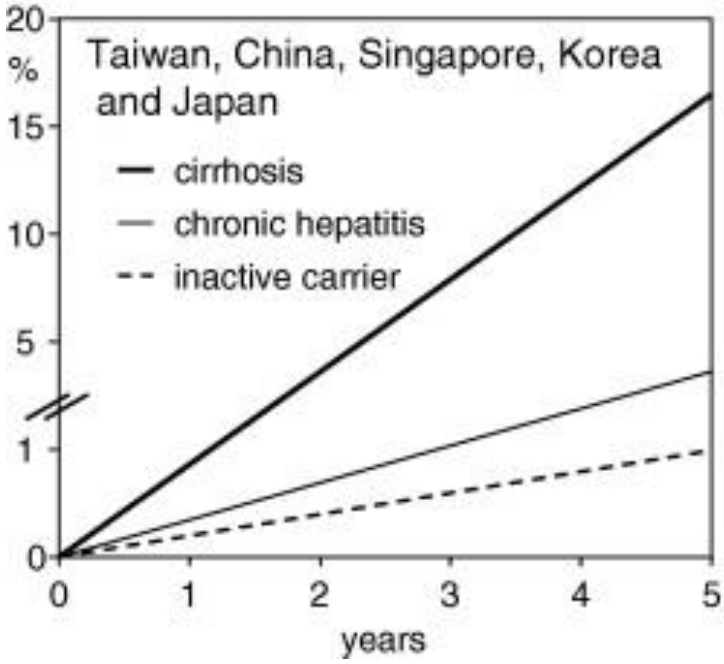
**DEKOMPANSASYON:** %20  
(Ort. 125 ay izlenen 186 sirozlu hastada)

**HSK:** %18  
(Ort. 233 ay izlenen 299 hastada)



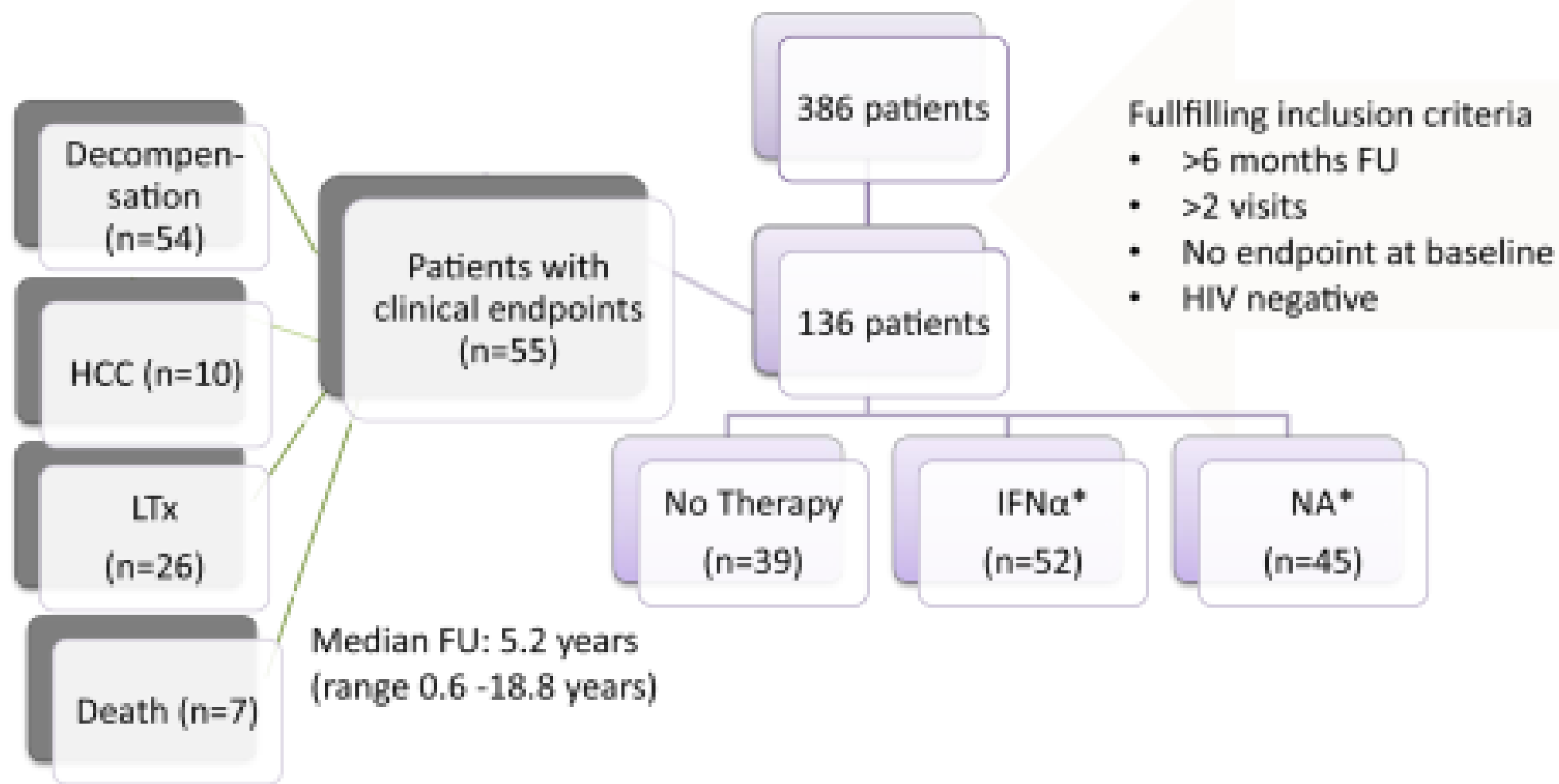


**SİROZ**  
5 yıl kümülatif oran



**HSK**  
5 yıl kümülatif oran

\*



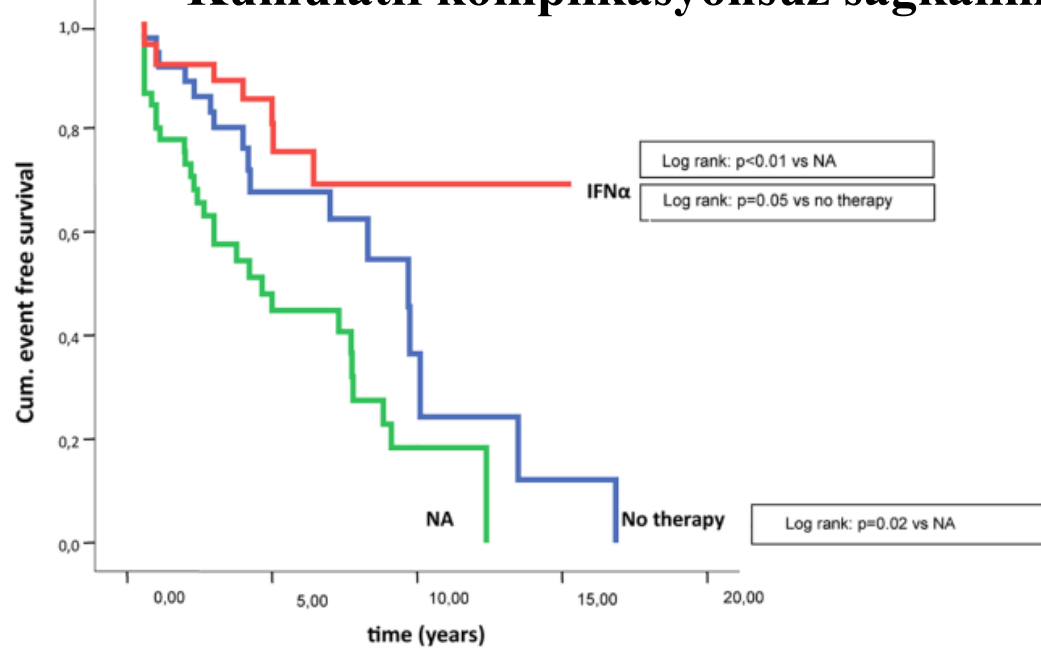
\*development of multiple endpoints were observed

\* IFN  $\alpha$  with or without NA

\* HBV reverse transcriptase inhibitors

A

## Kümülatif komplikasyonsuz sağkalım

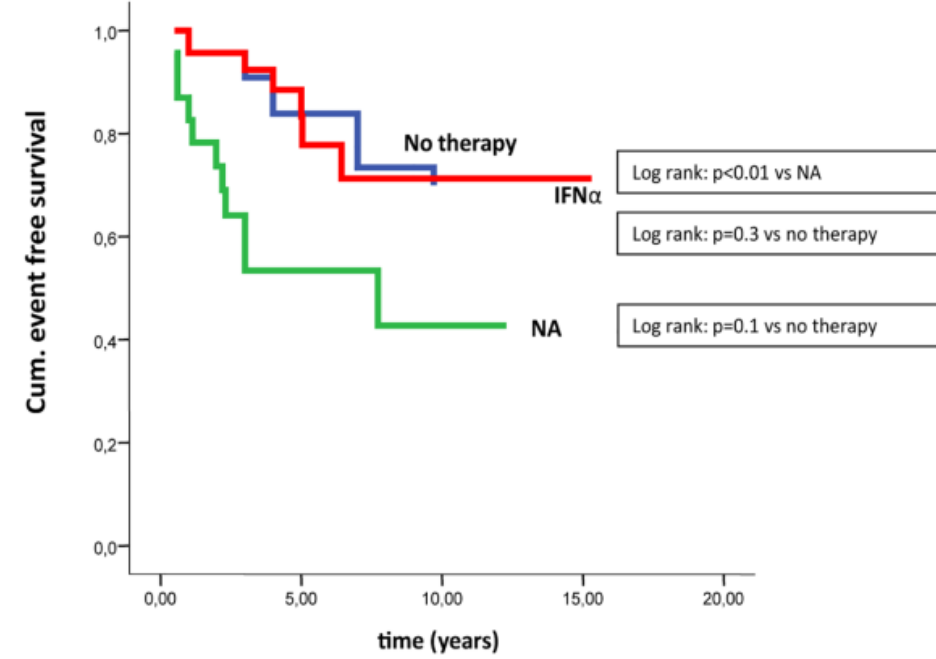


Number at risk

IFN $\alpha$	52	17	7	1
No therapy	45	15	4	1
NA	39	14	4	0

B

## Patients with platelets $>90000/\mu\text{l}$ only



Number at risk

IFN $\alpha$	46	17	7	2
No therapy	25	10	2	
NA	23	7	3	

**Olumlu seyrin en önemli göstergesi kalıcı HDV RNA negatifliğidir.**

Komplikasyonlar (“event”): Dekompansasyon, HSK, transplantasyon ve ölüm

# Kronik Delta Hepatiti Tedavisi

- ORAL ANTİVİRAL İLAÇLAR
- İNTERFERON ALFA
  - Standart IFN alfa, -**Pegile IFN Alfa**
- KARACİĞER NAKLİ ve  
POSTTRANSPLANT PROFİLAKSİ
- YENİ İLAÇLAR ?

# Kronik Delta Hepatiti Tedavisinde Kullanılan İlaçlar

## Etkisiz olduğu gösterilmiş ve kullanılması önerilmeyen ilaçlar

Ribavirin\* (53-56)

Famciclovir (57)

Lamivudine\* (58,59)

Adefovir\* (60)

Entecavir (61)

Tenofovir

## Kısmi başarılı olan/kullanılan veya çalışmaları devam eden ilaçlar

**Standart Interferon alfa** (62-66)

**Pegile İnterferon alfa** (56, 60, 67-69)

Tenofovir/emtricitabine (70)

Clevudine\*\* (71)

Glucosidase inhibitörleri\*\*\* (72)

Prenilasyon inhibitörleri (73-75)

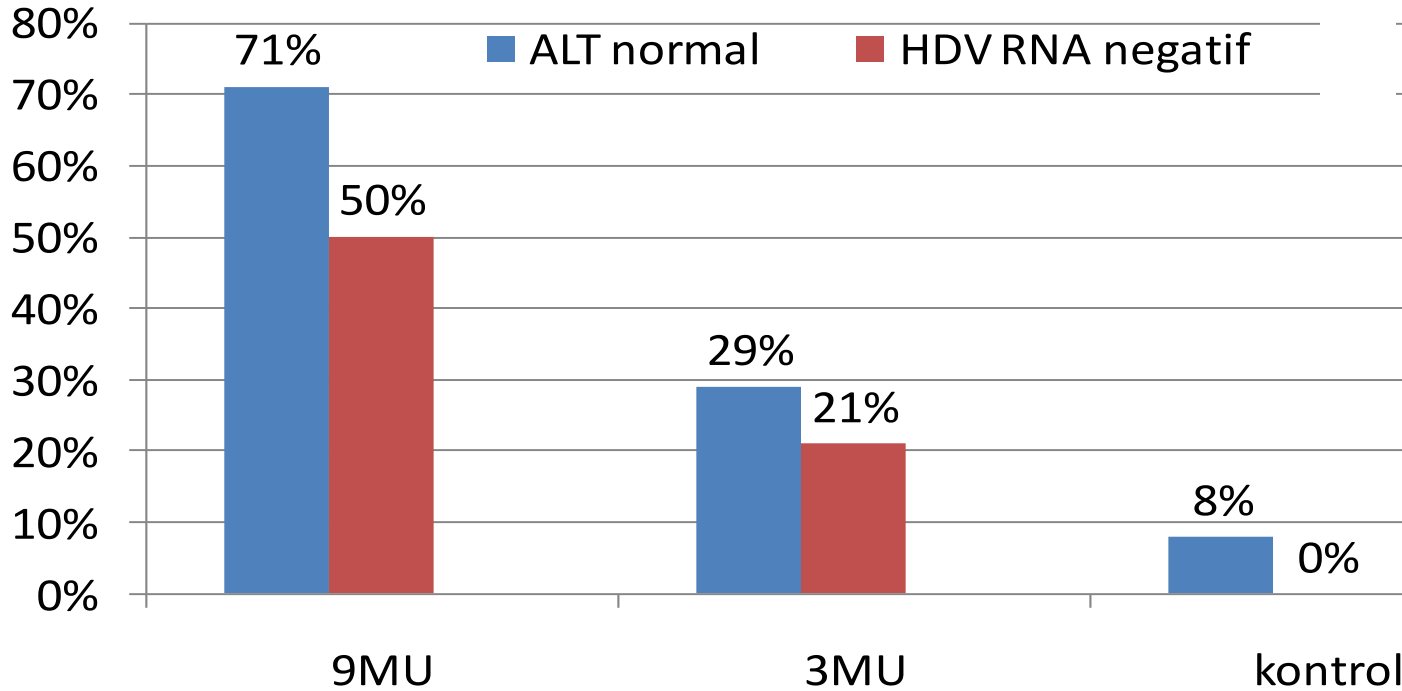
Myrcludex B

*\*IFN alfa ile kombine kullanımları da HDV tedavisinde etkisizdir. \*\*HBV tedavisi çalışması durdurulmuştur.*

*\*\*\*Hepatokarsinogenezise yol açabilir.*

## TREATMENT OF CHRONIC HEPATITIS D WITH INTERFERON ALFA-2a

PATRIZIA FARCI, M.D., ANTONELLA MANDAS, M.D., ALESSANDRA COIANA, PH.D., MARIA ELIANA LAI, M.D.,  
VALEER DESMET, M.D., PETER VAN EYKEN, M.D., YUKIO GIBO, M.D., LUCIANO CARUSO, M.D.,  
SERGIO SCACCABAROZZI, M.D., DOMENICO CRISCUOLO, M.D., JEAN-CHARLES RYFF, M.D.,  
AND ANGELO BALESTRIERI, M.D.



9MU grubunda  
belirgin histolojik  
düzelme var...

Tedavi sonrası  
viral nüks sık...

**Tedavi Sonunda Cevap Durumu**

Her gupta 14 hasta var (42 hasta)

# Long-term benefit of interferon $\alpha$ therapy of chronic hepatitis D: regression of advanced hepatic fibrosis

Patrizia Farci, Tania Roskams, Luchino Chessa, Giovanna Peddis, Anna Paola Mazzoleni, Rosetta Scioscia, Giancarlo Serra, Maria Eliana Lai, Maurizio Loy, Luciano Caruso, Valeer DeSmet, Robert H. Purcell and Angelo Balestrieri

**Gastroenterology**

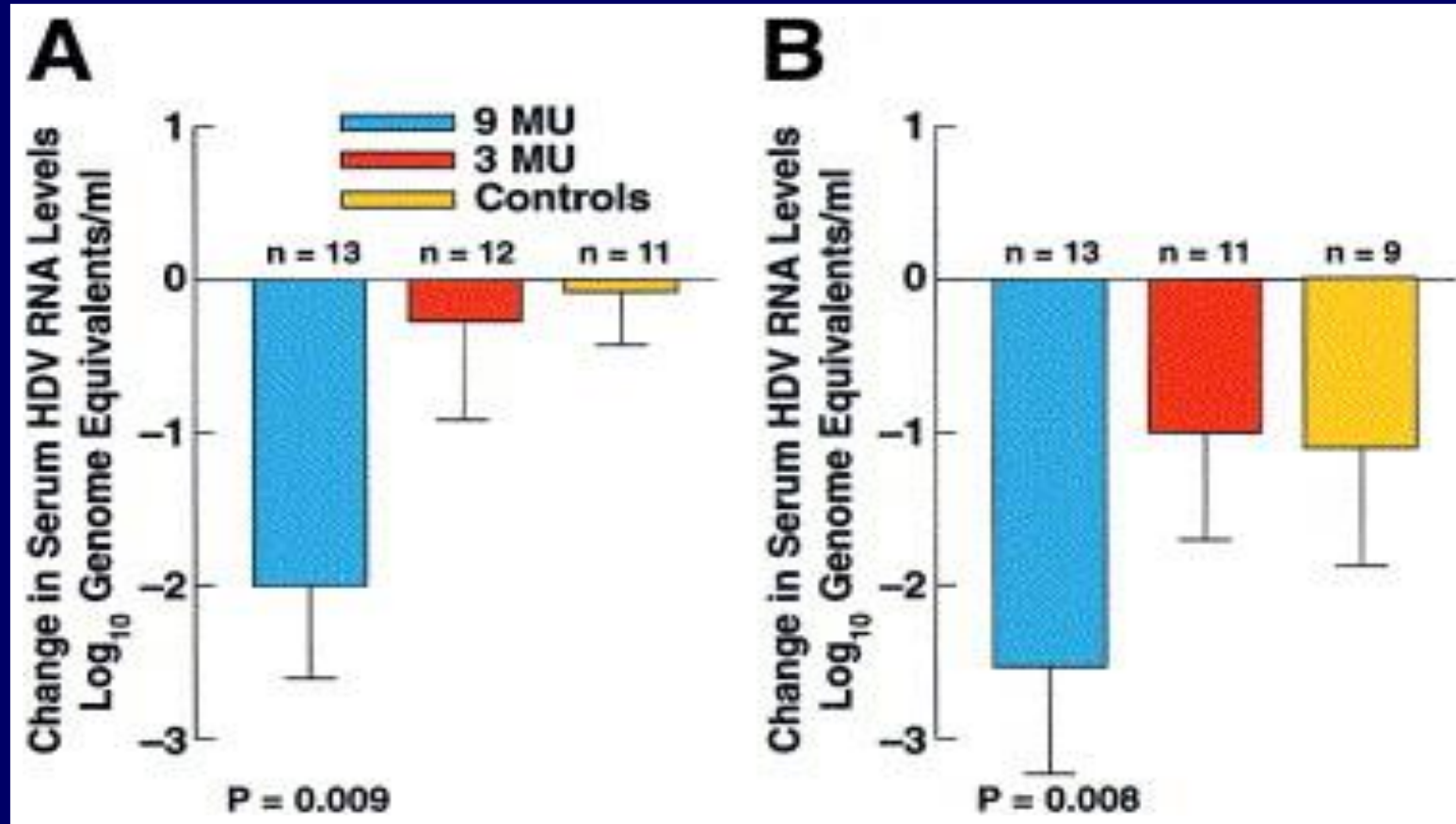
Volume 126, Issue 7, Pages 1740-1749 (June 2004)

DOI: 10.1053/j.gastro.2004.03.017

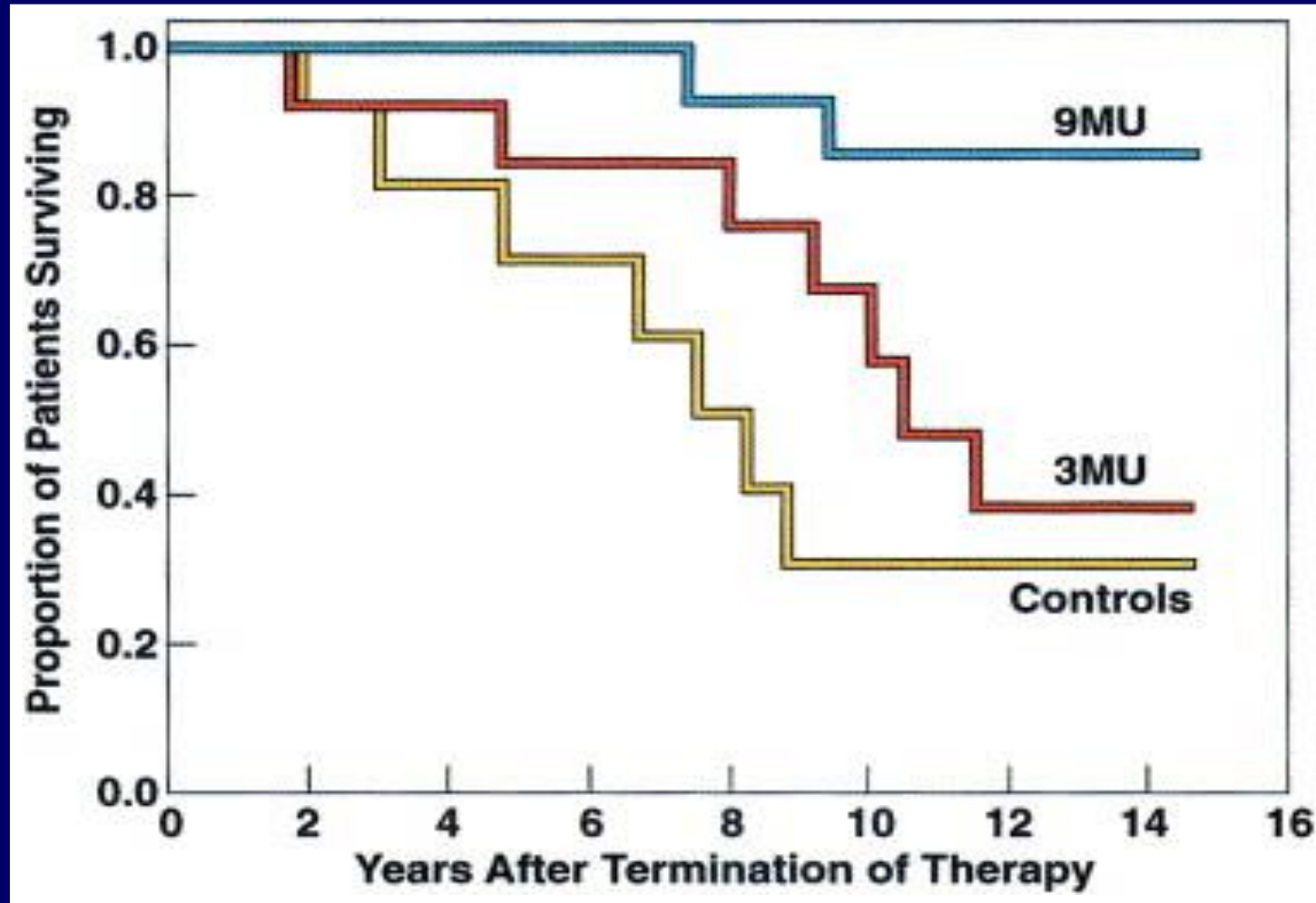
# Serum HDV RNA düzeyinde gözlenen değişiklikler

Tedavi sonu değerlendirme

En son değerlendirme



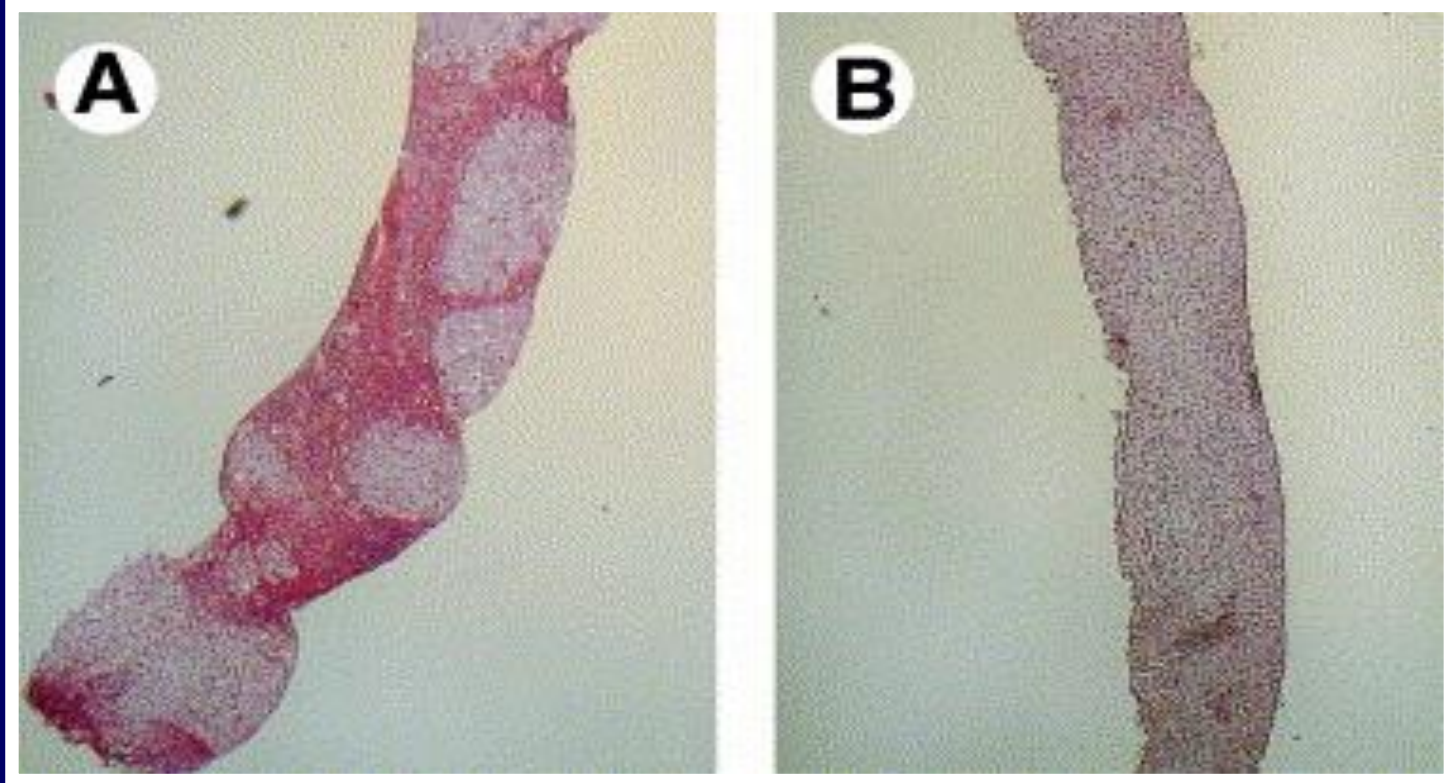
# Kümülatif sağkalım oranları (ölüm veya kc nakli yapılana kadar)



Source: [Gastroenterology 2004; 126:1740-1749 \(DOI:10.1053/j.gastro.2004.03.017\)](https://doi.org/10.1053/j.gastro.2004.03.017)

Figure 5

# HİSTOLOJİK İYİLEŞME

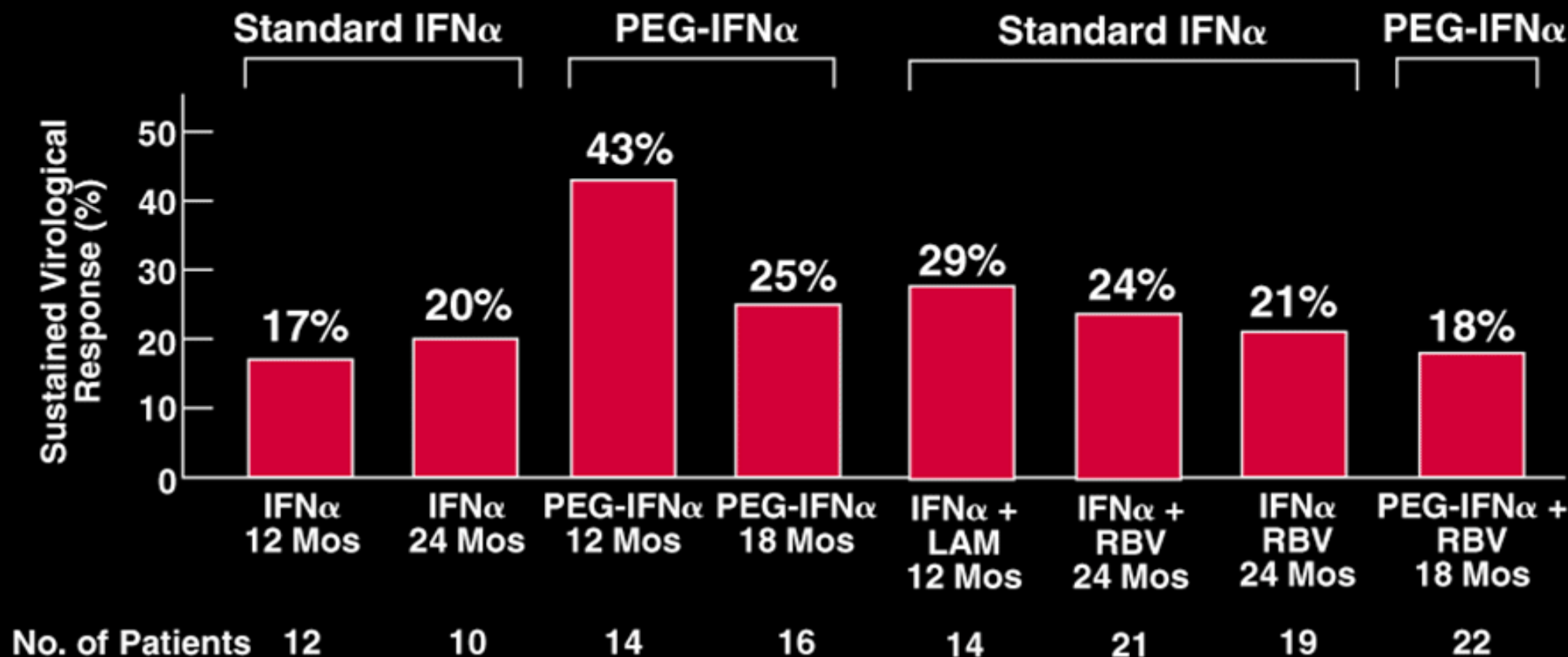


Source: [Gastroenterology](https://doi.org/10.1053/j.gastro.2004.03.017) 2004; 126:1740-1749 (DOI:10.1053/j.gastro.2004.03.017 )

# Sustained Virological Response Rate Evaluated by PCR Summary of 5 Recent Trials

## Monotherapy

## Combination Therapy



# Kronik Delta (D) Hepatiti Tedavisi

Arařtirmacı	Sayı	Tedavi	TSC	KVC
Gunsar et al*	10	IFN 9MU 2 yıl	%50	%20
	21	IFN+RBV	%52	%24
Yurdaydın et al**	15	IFN 10MU 2 yıl	%40	%15
Canbakan et al***	12	IFN 10MU	%42	%18
	14	IFN+LMV	%64	%29
Kaymakoglu et al	19	IFN 10MU+RBV	%42	%21

\*8 sirozlu hastanın hepsi cevapsız, \*\* 2 hastada HBsAg kaybı

\*\*\*5 yıl saękalım sırasıyla %65 ve %85 (kombine tedavi daha etkili)

Original Article

# Peginterferon plus Adefovir versus Either Drug Alone for Hepatitis Delta

Heiner Wedemeyer, M.D., Cihan Yurdaydın, M.D., George N. Dalekos, M.D., Andreas Erhardt, M.D., Yılmaz Çakaloğlu, M.D., Halil Değertekin, M.D., Selim Gürel, M.D., Stefan Zeuzem, M.D., Kalliopi Zachou, M.D., Hakan Bozkaya, M.D., Armin Koch, M.D., Thomas Bock, M.D., Hans Peter Dienes, M.D., Michael P. Manns, M.D., for the HIDIT Study Group

N Engl J Med Volume 364(4):322-331 January 27, 2011

<b>PegIFN alfa-2a and Adevfovir</b>	<b>31 hasta</b>
<b>PegIFn alfa-2a</b>	<b>29 hasta</b>
<b>Adefovir</b>	<b>30 hasta</b>



The NEW ENGLAND  
JOURNAL of MEDICINE

**Table 1. Baseline Characteristics of the Study Participants.\***

Characteristic	Peginterferon Alfa-2a plus Adefovir Dipivoxil (N=31)	Peginterferon Alfa-2a plus Placebo (N=29)	Adefovir Dipivoxil (N=30)
Age — yr			
Median	42	38	33
Range	23–59	17–62	21–55
Male sex — no. (%)	20 (65)	17 (59)	19 (63)
HBeAg-positive — no. (%)	5 (16)	5 (17)	4 (13)
HBV DNA			
Median — log <sub>10</sub> IU/ml	1.4‡	2.6	2.1
≥100 IU/ml — no./total no. (%)	13/31 (42)	17/27 (63)	15/28 (54)
HDV RNA			
Median — log <sub>10</sub> copies/ml	6.3	5.9	5.7
Above median — no./total no. (%)	16/28 (57)	12/23 (52)	11/26 (42)
Alanine aminotransferase			
Median — IU/liter	88	73	111
Above median — no./total no. (%)	12/31 (39)	11/27 (41)	19/29 (66)
Cirrhosis — no./total no. (%)	4/29 (14)	5/25 (20)	7/29 (24)
HDV genotype 1 — %	100	100	100
Previous interferon treatment — no. (%)	12 (38)	15 (52)	12 (40)

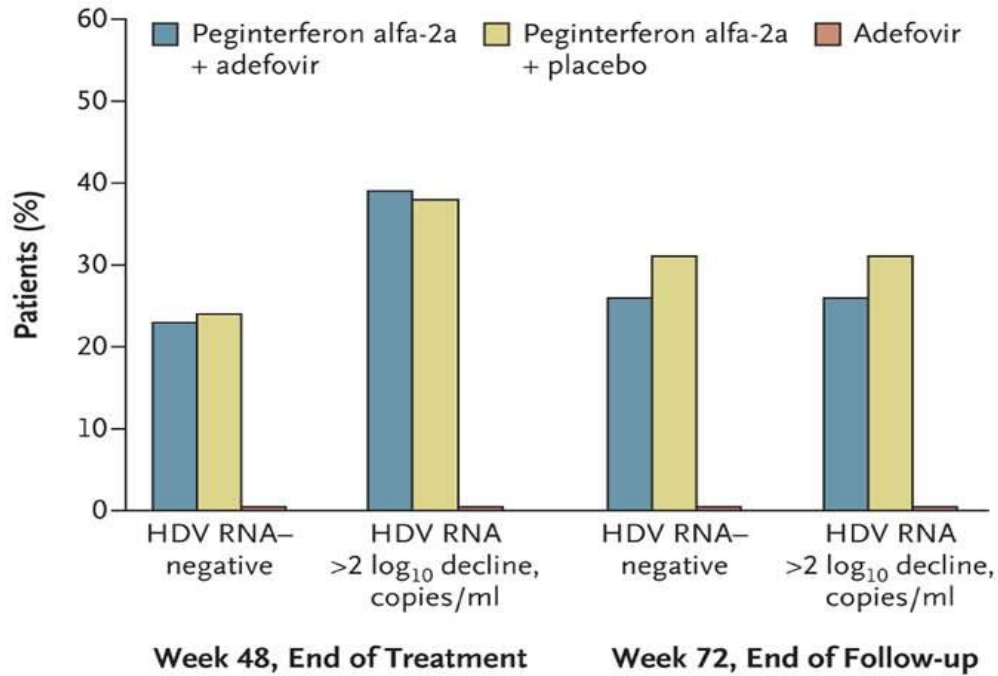
\* HBeAg denotes hepatitis B e antigen, HBV hepatitis B virus, and HDV hepatitis delta virus.

† P=0.01 for the comparison of adefovir dipivoxil with peginterferon alfa-2a plus adefovir, and P=0.04 for the comparison of adefovir with peginterferon alfa-2a plus placebo.

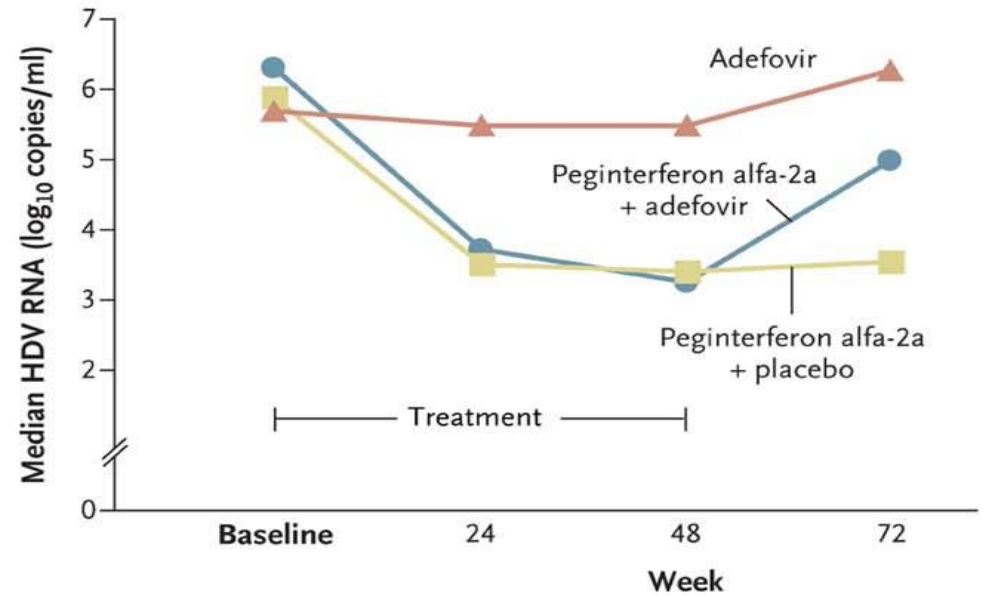
‡ P<0.05 for the comparison of peginterferon alfa-2a plus adefovir with peginterferon alfa-2a plus placebo.

# Virologic Response to Treatment as Determined by Serum Level of HDV RNA, According to Treatment Group.

**A HDV RNA**

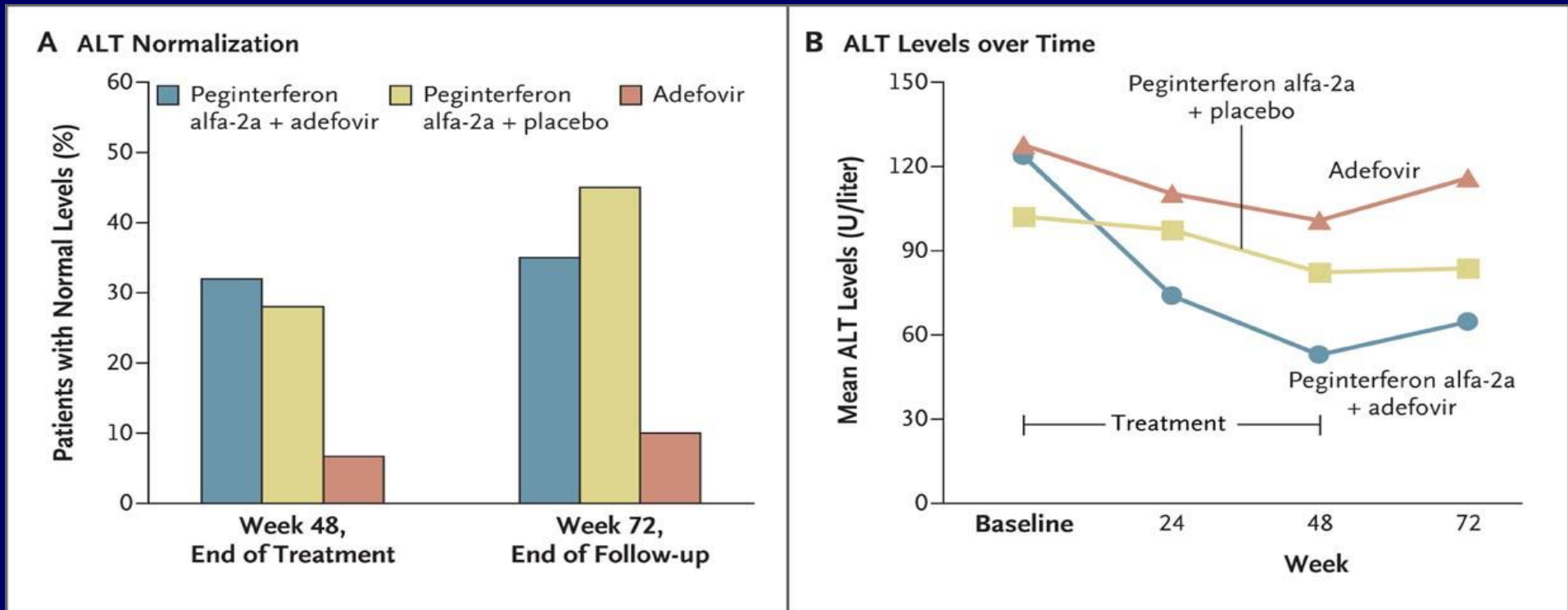


**B Median HDV RNA Levels over Time**



Wedemeyer H et al. N Engl J Med 2011;364:322-331

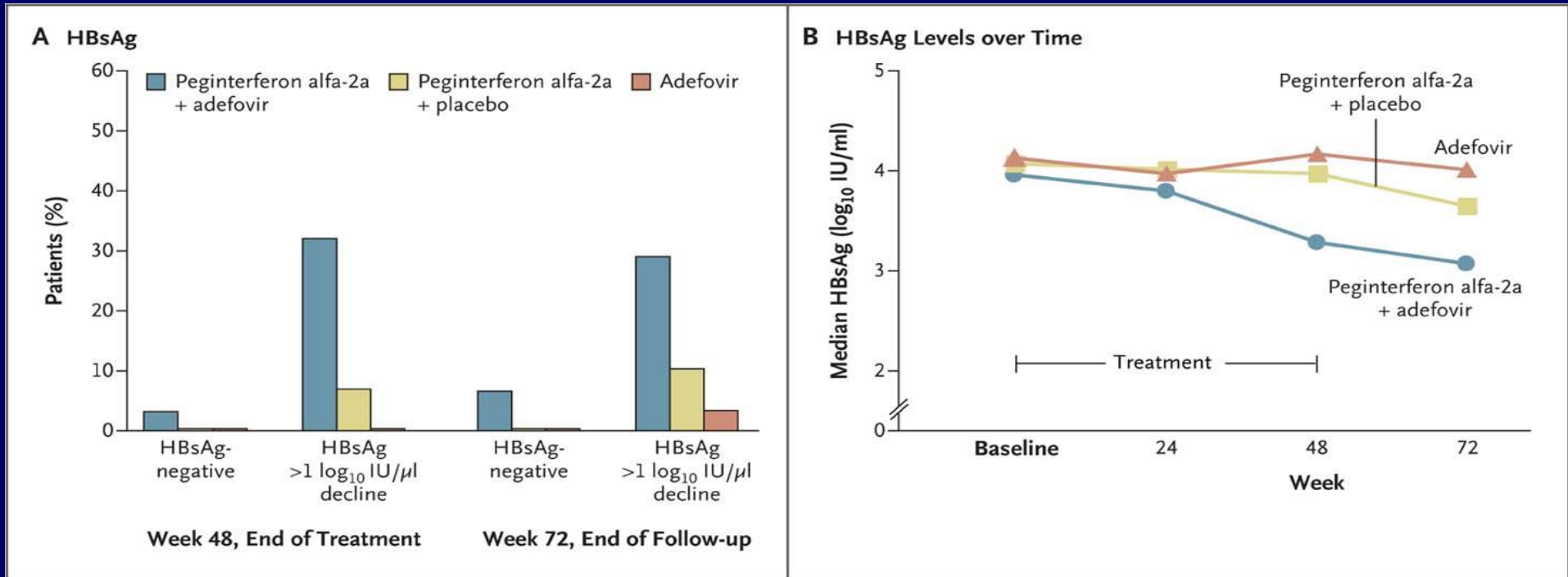
# Biochemical Response to Treatment as Determined by Serum Level of Alanine Aminotransferase, According to Treatment Group.



Wedemeyer H et al. N Engl J Med 2011;364:322-331



# Change in Levels of Hepatitis B Surface Antigen According to Treatment Group.



Wedemeyer H et al. N Engl J Med 2011;364:322-331

# Sirotik kronik D hepatiti tedavisi

- 30 hasta F4-6 ve Plt <130.00 PegIFN±ADV
- 31 hasta F1-3 and Plt>130.000 PegIFN±ADV
- Sirotik hastalar KH ile benzer oranlarda virolojik cevaba sahiptir (HDV RNA negatif: %53 vs %30)
- Ancak rapor edilen bütün ciddi yan etkiler sirozlu hasta grubundadır: 5 kanama, 2 dekompanse, 2 HSK gelişimi ve 1 tüberküloz aktivasyonu

**SONUÇ:** Kompanse sirozlu kronik D hepatiti hastaları tedaviye cevap açısından KH'li hastalar gibidir. Ancak pegIFN alfa tedavisininin ciddi yan etkilerine daha sık maruz kalırlar.

# Özet değerlendirme sonuçları

- Tek başına veya adefovir ile birlikte PegIFN alfa-2a tedavisi hastaların %40'ında belirgin bir antiviral etkinlik sağlamış, **%25'inde kalıcı viral cevap** elde edilmiştir.
- Peginterferon alfa-2a ve adefovir kombine tedavisi, peinterferon alfa-2a monoterapisinden üstün değildir...
- Tek başına adefovir etkili değildir.
- PegIFN alfa-2a ve adefovir kombine tedavisi HBsAg düzeylerinde sağlanan azalmada (ve HBsAg kaybında ?) daha etkilidir.



# Prolonged therapy of hepatitis delta for 96 weeks with PEG-IFNa-2a plus tenofovir or placebo does not prevent HDV RNA relapse: The HIDIT-2 study.

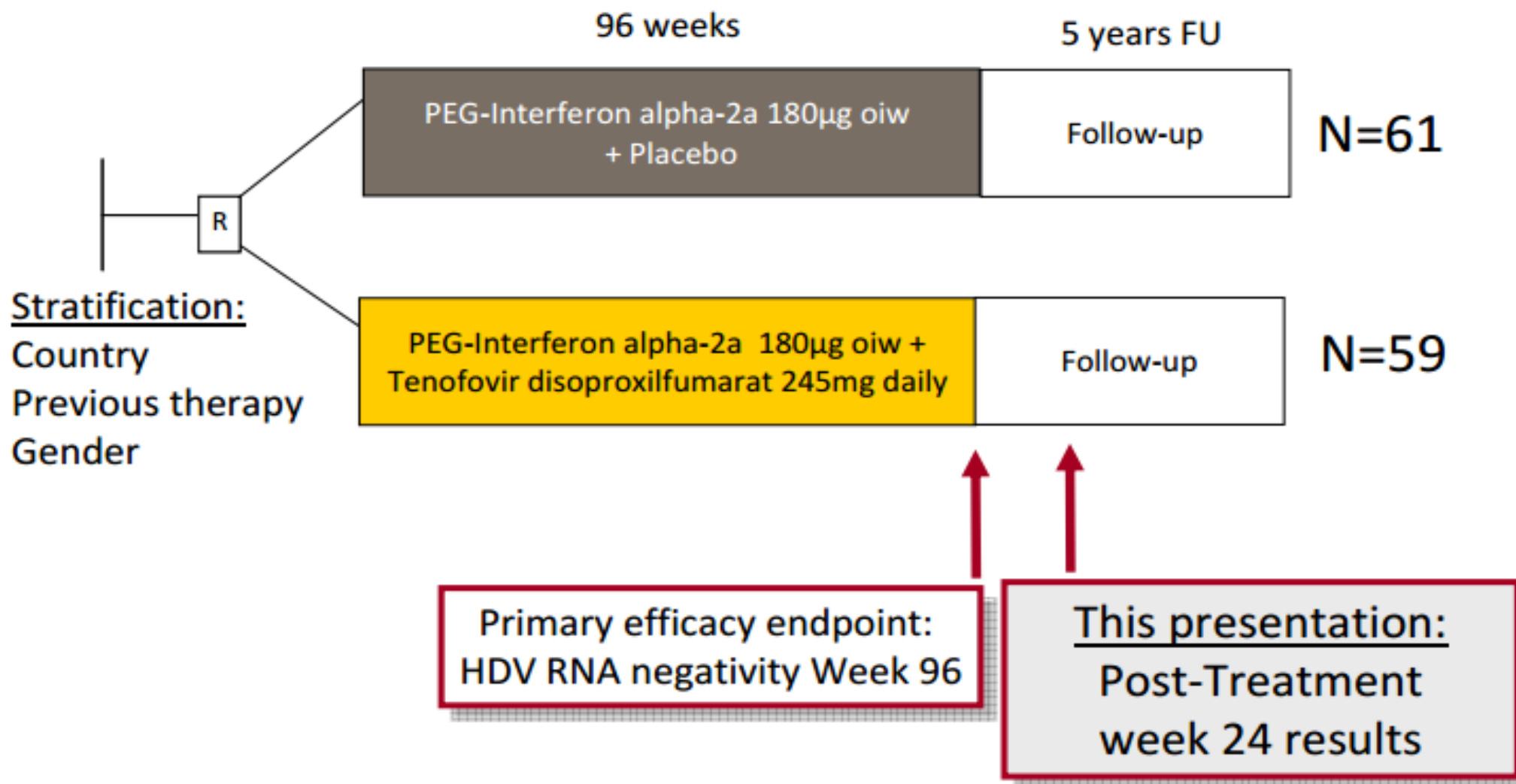
Heiner Wedemeyer\*, Cihan Yurdaydın\*,

Stefanie Ernst, Florin Alexandru Caruntu; Manuela G.Curescu, Kendal Yalçın, Ulus S. Akarca, Selim Gürel, Stefan Zeuzem, Andreas Erhardt, Stefan Lüth, George V. Papatheodoridis, Onur Keskin, Kerstin Port, Monica Radu, Mustafa K. Celen, Ramazan İdilman, Judith Stift, Benjamin Heidrich, Ingmar Mederacke, Svenja Hardtke, Armin Koch, Hans Peter Dienes, Michael P.Manns

for the HIDIT-2 Study Group

*\* Cihan Yurdaydın and Heiner Wedemeyer contributed equally*

# The Hep-Net-International Delta-Hepatitis Intervention Trial 2: **HIDIT-2**



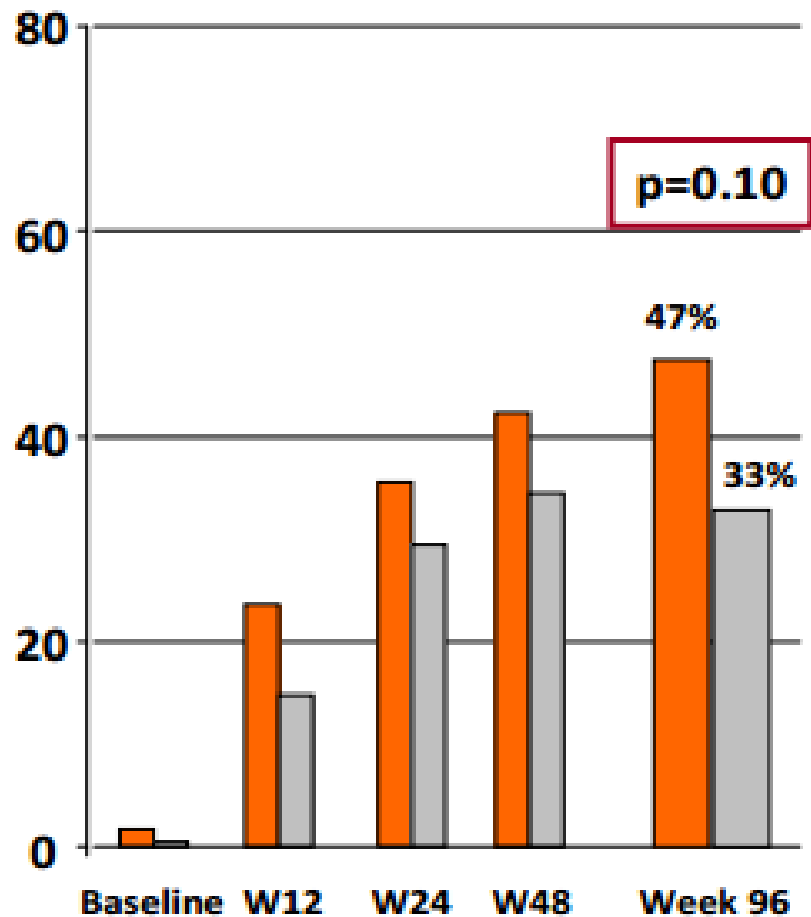
# Baseline Characteristics

	PEG-IFN a Tenofovir (n=59)	PEG-IFNa Placebo (n=61)	p-value
Age [ mean years]	38	42	0.06
Sex [female/male]	21/38	20/41	0.75
cirrhosis at screening	24 (41%)	25 (41%)	0.84
Previous IFN-Therapy	29 (49%)	31 (51%)	0.98
ALT [mean IU/l]	110	122	0.45
Patients with ALT >5xULN	7 (12%)	4 (6.8%)	0.31
HBeAg positive	12 (20%)	8 (13%)	0.50
HDV RNA [median log <sub>10</sub> cop/ml]	5.26	5.18	0.60
HBV DNA [median log <sub>10</sub> IU/ml]	2.65	2.70	0.81
HBsAg [median log <sub>10</sub> IU/ml]	3.94	3.91	0.87

# HDV RNA response (Intent-to-treat analysis)

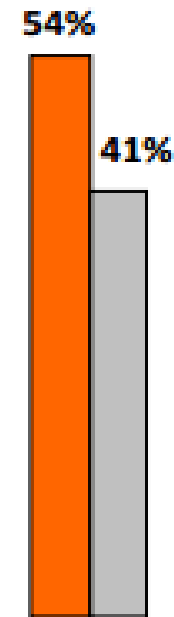
PEG-IFNa-2a + Tenofovir  
PEG-IFNa-2a + Placebo

% of patients HDV RNA negative



## Per-Protocol Analysis (n=99)

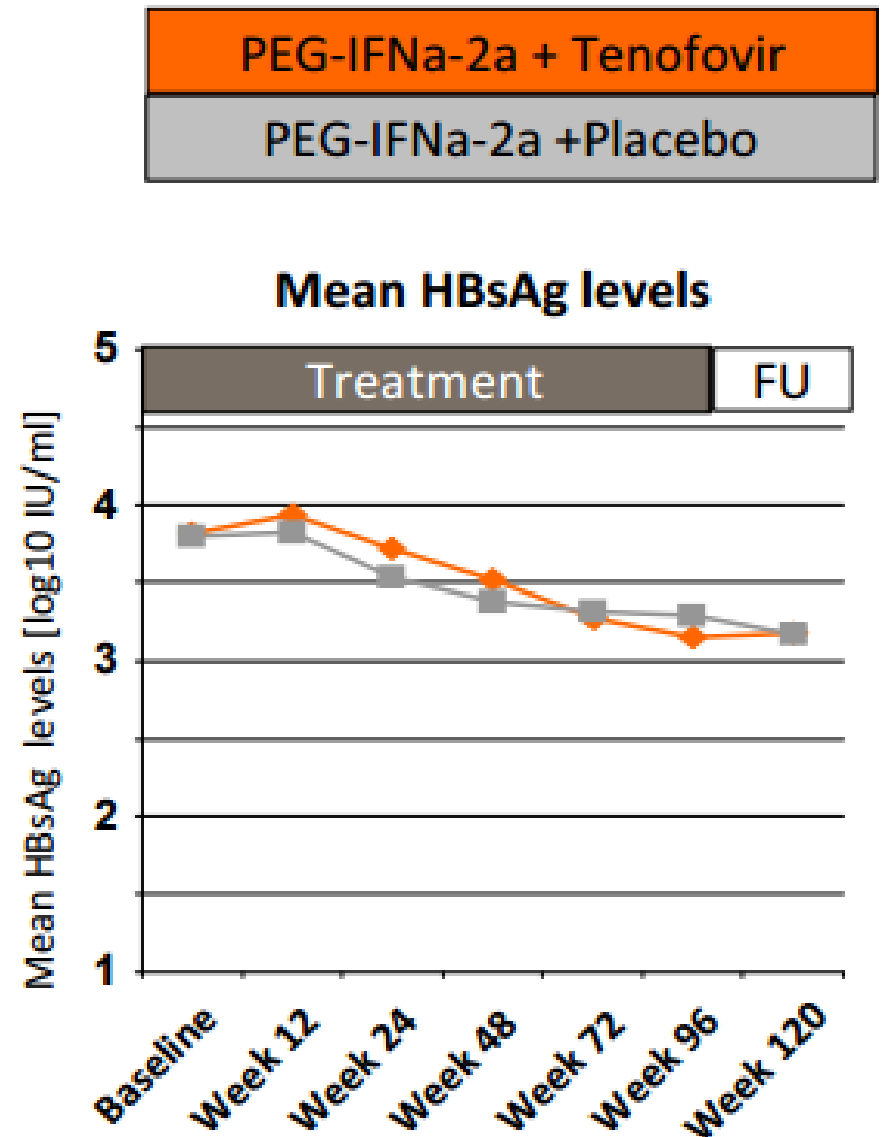
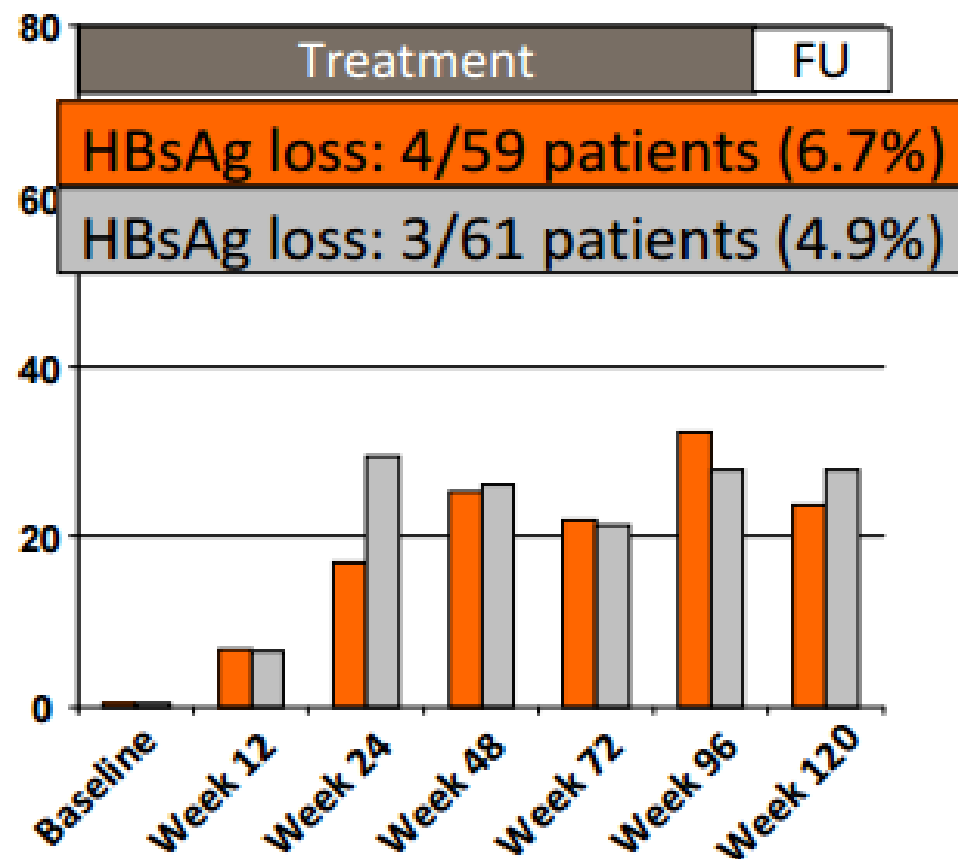
p=0.19



Week 96

# HBsAg response until week 120 (Intent-to-treat analysis)

% of patients with HBsAg-decline  
>0.5 Log<sub>10</sub>IU/ml



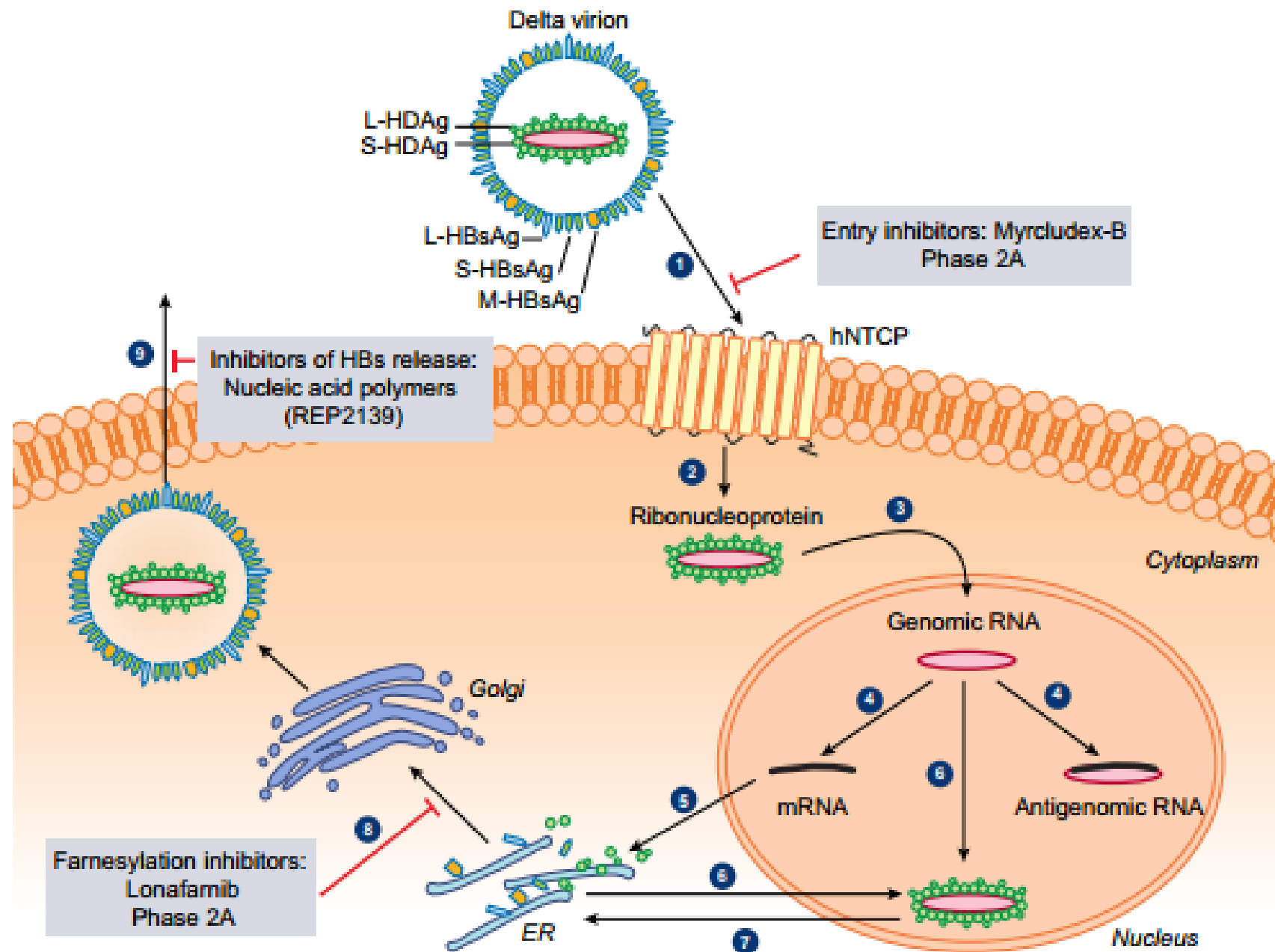
# HIDIT -2 TRIAL: PegIFN alfa-2a + TDF vs PLACEBO

## Conclusions

- Patients with hepatitis delta and compensated liver cirrhosis should be treated with PEG-IFNa
- Combination therapy with tenofovir does not provide obvious benefits in hepatitis delta patients with low baseline HBV-DNA levels
- 96 weeks of PEG-IFNa treatment does not provide higher off-treatment HDV RNA responses (compared to 48 weeks in the HIDIT-1 study)
- HBsAg levels may be used to individualize treatment duration
- Alternative treatment options are urgently needed for HDV-infected patients

# Delta Hepatiti: Yeni Tedaviler

- “Hepatocyte Entry Inhibitors: **Myrcludex B**”
- “Farnesyltransferase Inhibitors: **Lonafarnib**”  
 (“Prenylation Inhibitor”)
- “Nucleic Acid Polymers”
- “Small Interfering RNAs”
- “Immunologic Approaches;
  - Toll-like Receptor Agonists
  - Checkpoint Inhibitors
  - Hepatitis B Virus Vaccines



**Fig. 2. Schematic representation of the delta virion and its replication cycle.** (1) Virion attachment to the hepatocyte via interaction between large-HBsAg and an uncharacterised membrane receptor in the host cell; (2) Virion enters the cell and is

**Table 2.** Characteristics of novel drug treatment for chronic hepatitis D.

Drug	Mode of action	Administration route	Phase of study
Myrcludex B	Interferes with hepatitis D virus entry into hepatocyte through sodium taurocholate co-transporting polypeptide inhibition	Subcutaneous, daily for 6 months, ± pegylated interferon (peg-IFN)	Ib, IIa
Lonafarnib	Farnesyltransferase inhibitor, inhibits virion assembly	Oral, 2 to 12 months, ± ritonavir ± peg-IFN	II
Rep-2139-Ca	Nucleic acid polymer, binds with high affinity to amphipathic proteins, which are required at various stages of the viral life cycle	Intravenous infusion, once weekly for 4–6 months ± peg-IFN	II

**Table 3.** Side effects of the hepatocyte entry inhibitor myrcludex B, the farnesyltransferase inhibitor lonafarnib, and nucleic acid polymers.**Myrcludex B**

- Lipase and amylase elevation in phase I but not in phase II study
- Elevation of taurine- and glycine-conjugated bile acids without apparent clinical consequences
- Thrombocytopenia, neutropenia, lymphopenia, and eosinophilia: generally mild, transient

**Lonafarnib**

- Gastrointestinal toxicity (anorexia, nausea with or without vomiting, diarrhea, weight loss): dose dependent and in lower dose cohorts generally mild and well tolerated

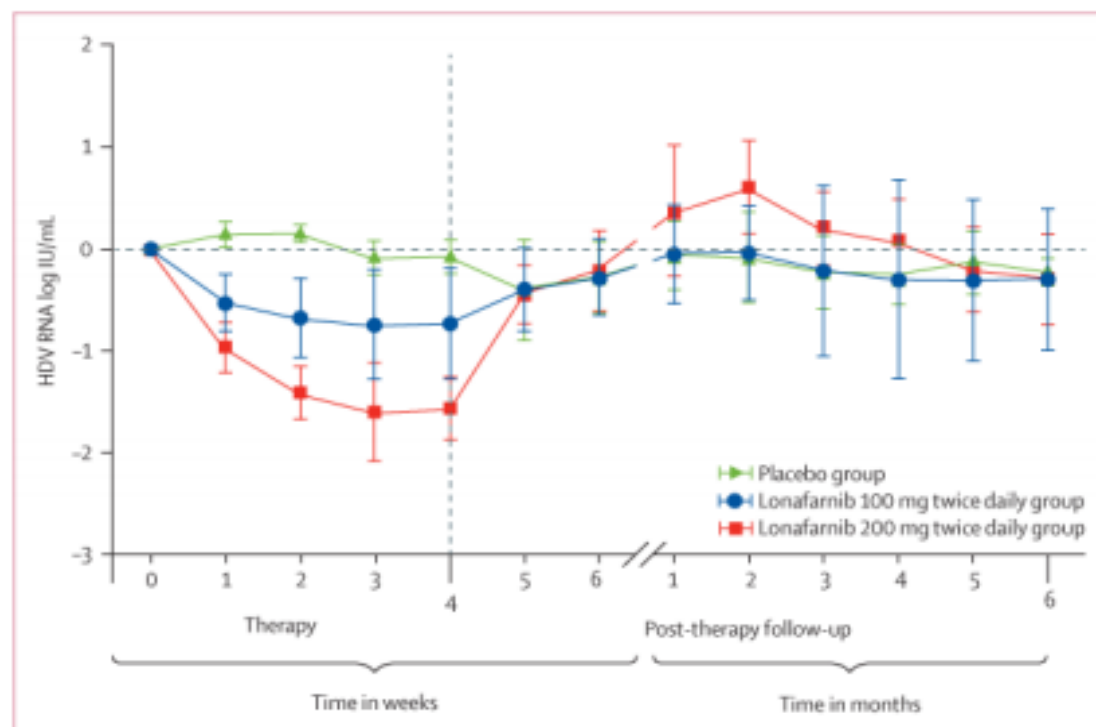
**Nucleic acid polymers**

- Hair loss, dysphagia, anorexia, dysgeusia, in hepatitis B study: related to heavy metal exposure at the trial site?
- Administration route-related side effects: peripheral grade 1 hyperemia, fever, chills, and headache

# Oral prenylation inhibition with lonafarnib in chronic hepatitis D infection: a proof-of-concept randomised, double-blind, placebocontrolled phase 2A trial

Christopher Koh\* , Laetitia Canini, Harel Dahari, Xiongce Zhao, Susan L Uprichard, Vanessa Haynes-Williams, Mark A Winters, Gitanjali Subramanya, Stewart L Cooper, Peter Pinto, Erin F Wolff, Rachel Bishop, Ma Ai Thanda Han, Scott J Cotler, David E Kleiner, **Onur Keskin, Ramazan Idilman, Cihan Yurdaydin**, Jeffrey S Glenn\* , and Theo Heller\*

*Lancet Infect Dis.* 2015 October ; 15(10): 1167–1174. doi:10.1016/S1473-3099(15)00074-2.



**Figure 2.**

Mean serum hepatitis delta virus RNA (SD) change during therapy with lonafarnib

# LONAFARNIB (LNF) / Ritonavir/ PEgIFNalfa-2a LOWR HDV 2-Study.

- 1) LNF (75mg bid) +RTV\* (100mg bid) 12 ve 24 hafta
  - 2) LNF (25-50mg bid) + RTV (100mg bid) 12 hafta
  - 3) LNF (**25**-50mg bid) + RTV (100mg bid) + PegIFN 180 ug qw (24 hafta)
- 24 hafta tedavi sonunda;

- Rejim 1/2 ile HDV RNA'da 1.74 ( $\pm$ 1.2) log 10 azalma
- **Rejim 3 ile HDV RNA'da 5.57 ( $\pm$ 1.9) log 10 azalma**
  - 3/5 (%60) hastada HDV RNA negatif (“undetectable”)
  - 5/5 (% 100) hastada HDV RNA <BLOQ

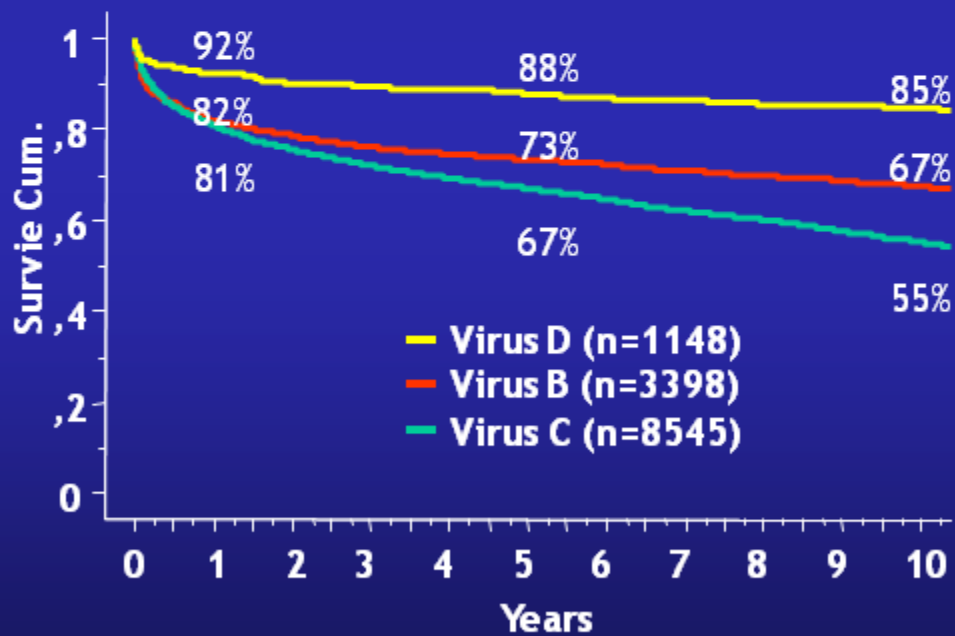
**HDV KÜRÜ MÜMKÜN OLABİLİR!... Mİ ?**

*Ritonavir (RTV) LNH metabolizmasını inhibe ederek, düşük dozlarda yüksek kan düzeyi sağlar. Düşük doz LNF daha iyi tolere edilir ve uzun süre alınabilir.*

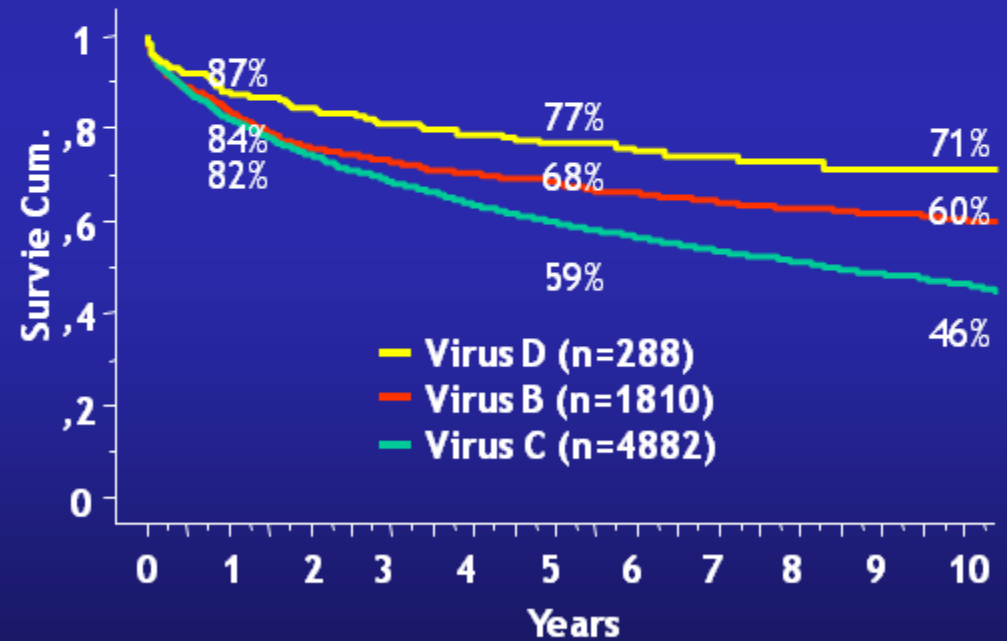
*Yurdaydin C et al J Hepatol 2017; 66: S33 (GS-008)*

# Patient Survival after Liver Transplantation For Viral Cirrhosis in Europe From 13/11/1973 to 30/06/2009

## Without HCC

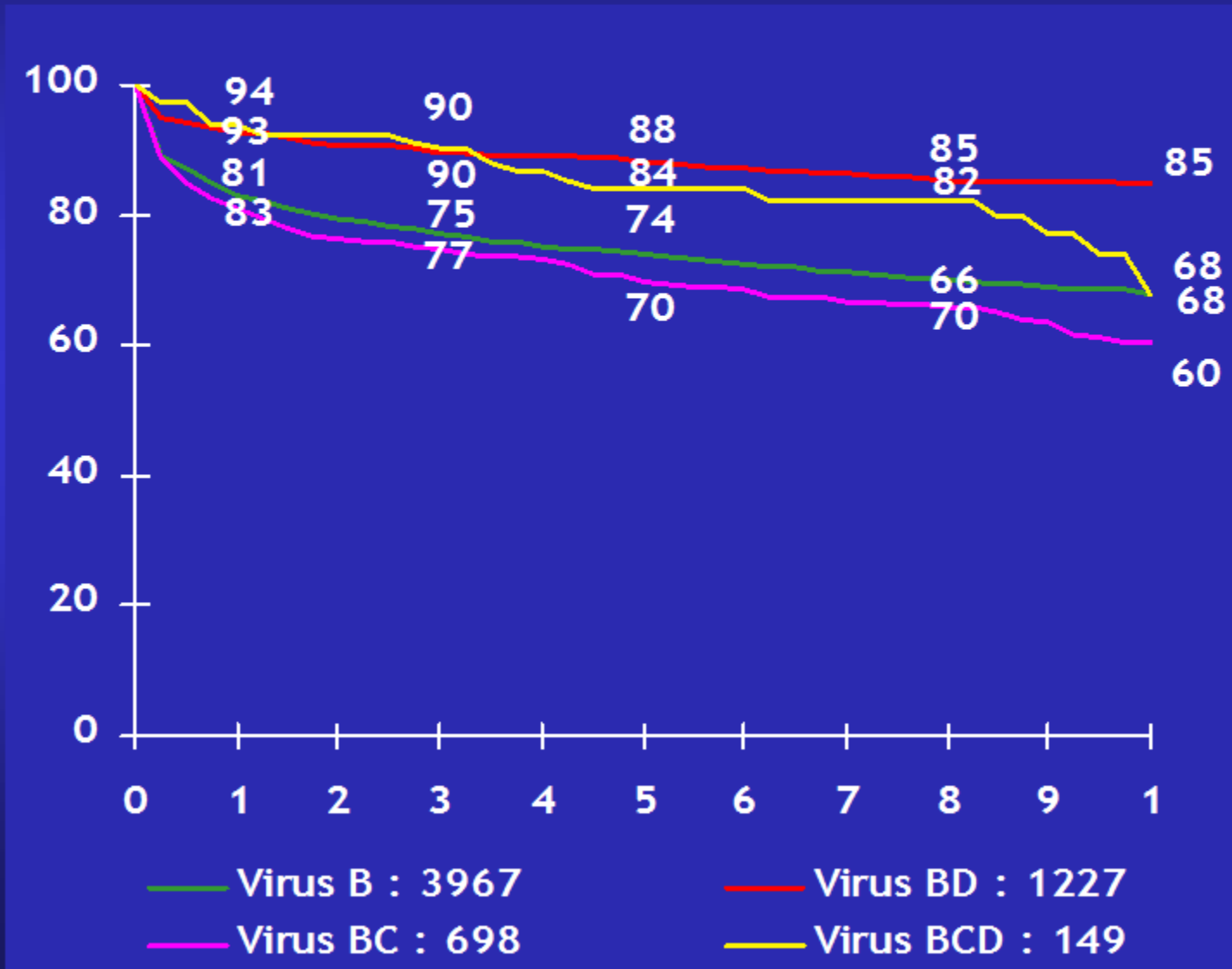


## With HCC



# Survival of Patients with Virus related Cirrhosis as the First Indication

ELTR 01/1988 - 06/2009



# Kronik Delta (D) Hepatiti - Sonuç

- Azalan, ancak hala klinik açıdan önemli bir patoloji
- Uygun hastalarda pegIFN alfa tedavisi yararlı
- Tanıda ve tedavinin değerlendirilmesinde standart hale gelmiş kantitatif HDV RNA testi önemli
- Şiddetle yeni ilaçlara ihtiyaç var
- Karaciğer nakli sonuçları yüzgüldürücü

# BENİM HASTALARIM

HIDIT 1 alıřmasına toplam 7 hasta verdim;

1 hasta tedavi sırasında dekompanse oldu - EX

2 hasta karacięer nakli oldu / saęlıklı normal yařam

3 hasta tedavisiz izleniyor (2'si remisyonunda, dięeri  
dekompanse karacięer sirozu-nakil bekliyor)

Son hasta İstanbul dıřına tařındı. Arıyorum...



**KOİNFEKSİYON MU?**

**SÜPERİNFEKSİYON MU?**

Bu birliktelik  
her halükarda  
riskli bir durum...  
İkisini de almayayım!...