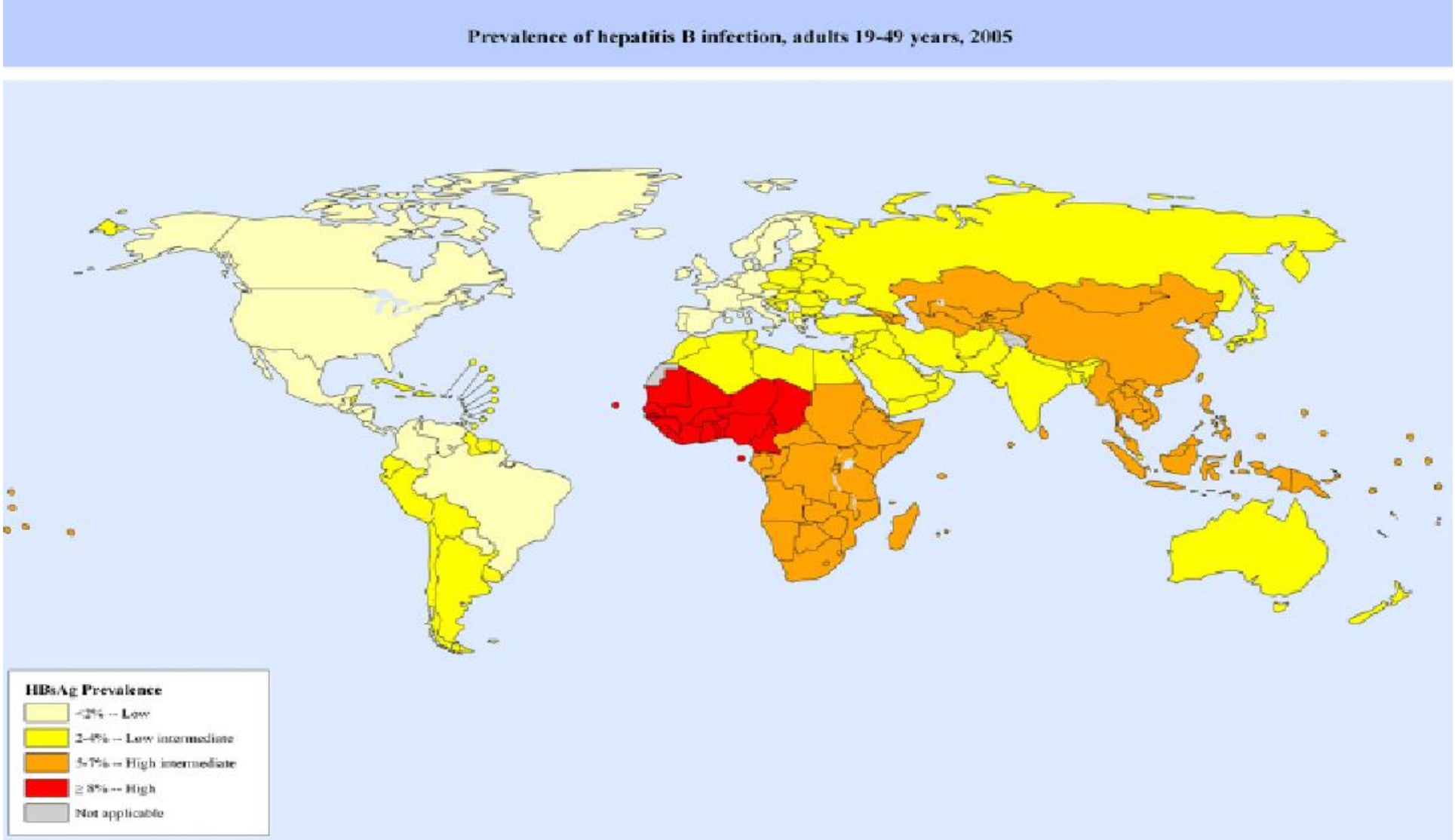
Kronik B ve D Hepatiti Tedavisi

Prof. Dr. Cihan YURDAYDIN
Ankara Üniversitesi Tıp Fakültesi
Gastroenteroloji Bilim Dalı

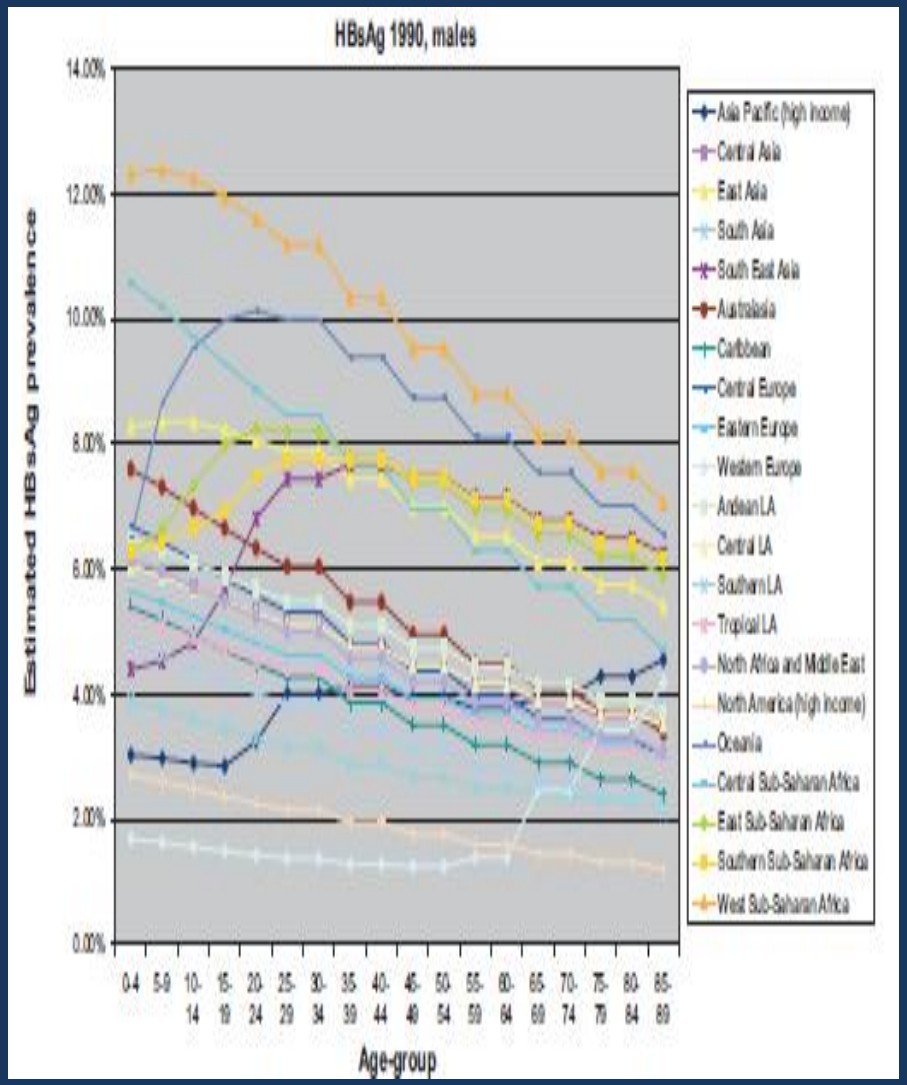
1. Türkiye Azerbeycan
Ortak Hepatoloji Kursu
18-19 Eylül 2015

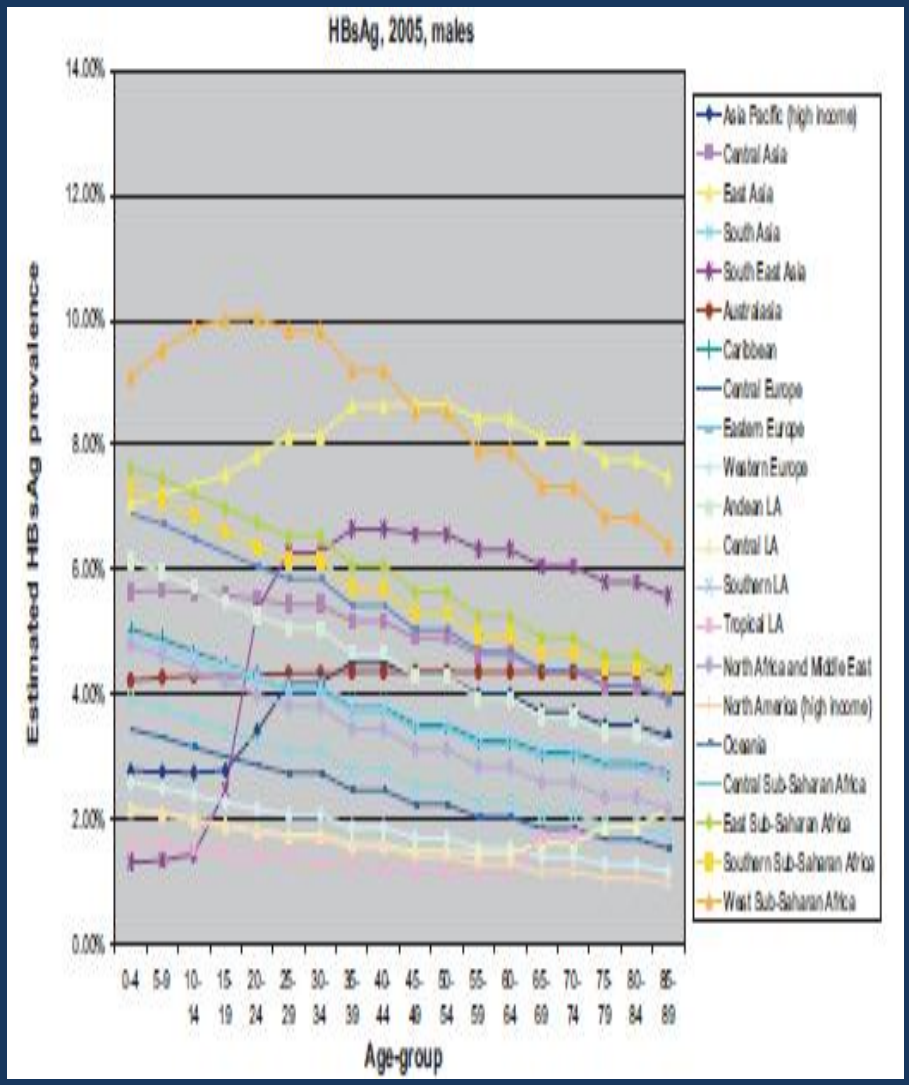
HBV epidemiology as of 2005 based on published 396 articles



Ott JJ et al, Vaccine 2012

HBsAg seroprevalence comparison : 1990 vs. 2005





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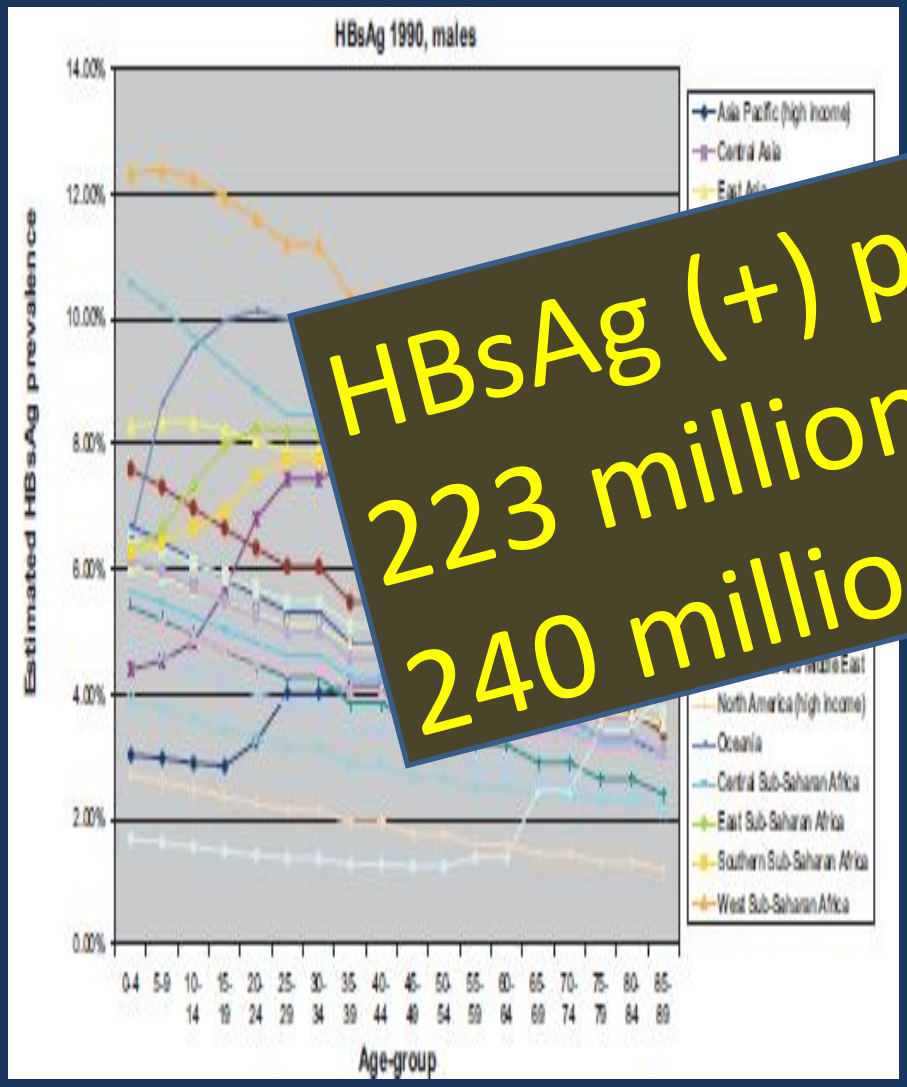

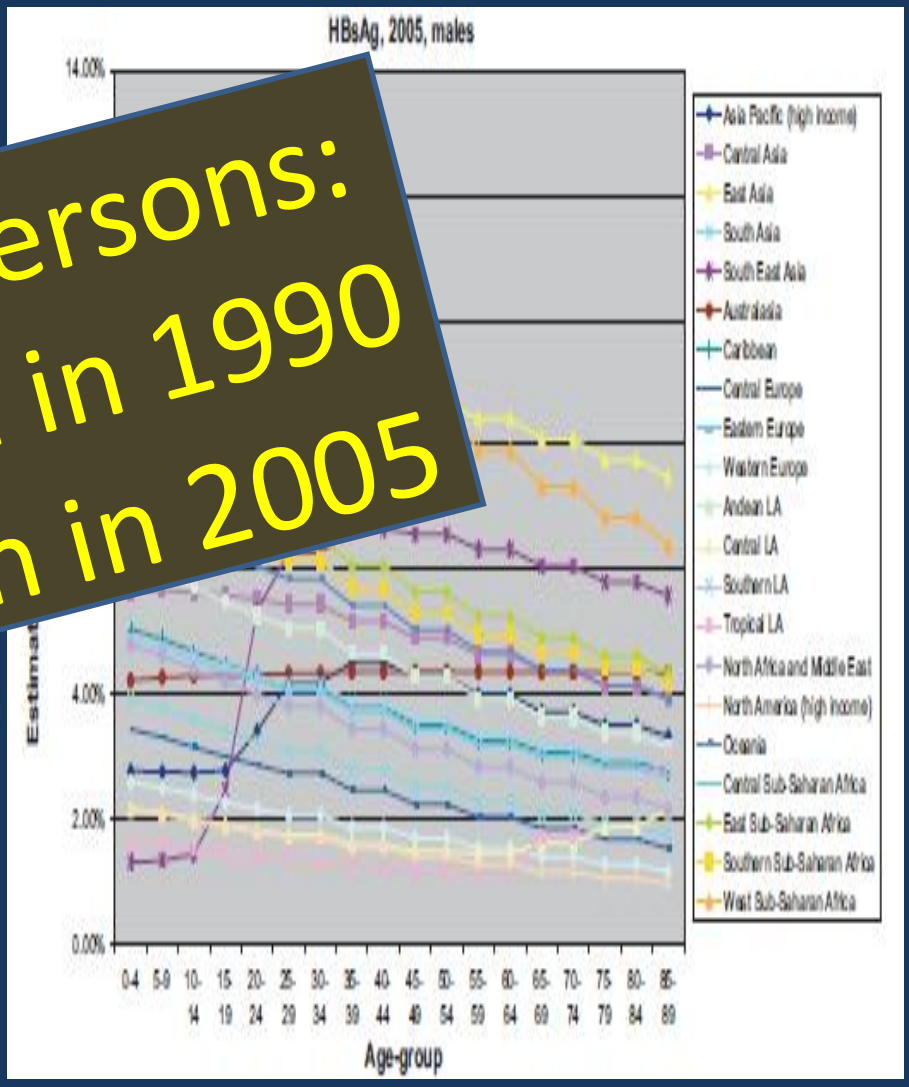

HBsAg (+) persons:
223 million in 1990
240 million in 2005

Ott JJ et al, Vaccine 2012

Review

JOURNAL OF HEPATOLOGY

Strategies to control hepatitis B: Public policy, epidemiology, vaccine and drugs

Stephen Locarnini[1,*], Angelos Hatzakis[2], Ding-Shinn Chen[3], Anna Lok[4]

Key Points

- Fifty years of basic and translational research has resulted in tools for effective surveillance, vaccines and therapies for chronic hepatitis B
- Only a small percentage of persons living with HBV either know they are infected or are able to access treatment
- A number of countries are still yet to implement universal infant immunization
- The WHO has released its Global Hepatitis Program to help countries develop National Action Plans
- Achievement and implementation of these National Action Plans will require the co-operation of the affected community, health care providers and Governments committed to the goal of HBV eradication

Problem overall in HBV Tx

- **HBsAg Prevalence in Turkey: 4,29 %**
  - **West Turkey: 3,54 %**
  - **Central Turkey: 4,55 %**
  - **East Turkey: 6,88 %**
- **Number of HBsAg Positives:**
  - **71.517.100 x 4,29 % = 3.068.083**
  - **If 10 % were to have active chronic hepatitis = 306.808 patients**
  - **Patients under Therapy: 30.000***

***SGK – According to net sold pill tablets in Turkey 02/2008 – 02/ 2009**

Toy et al, Eur J Health Econ 2012

KHB tedavisi

NA’ları HBV tedavisinde bir devrime yol açtı

Bu durumu nasıl okunmak gerekir?

Uzatılmış tedavi endikasyonları

Kompanse Siroz

HBV-DNA ölçülebilir ise tedavi et

Dekompanse siroz

Acil tedavi et

HCC takibi

KC transplantasyonu sonrası re-enfeksiyon

EASL Clinical Practice Guidelines, J Hepatol 2012

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Başlangıçta Sirozu olan 96 Hastada 5 yılda Ishak Fibroz Skorlarında gözlenen Değişim

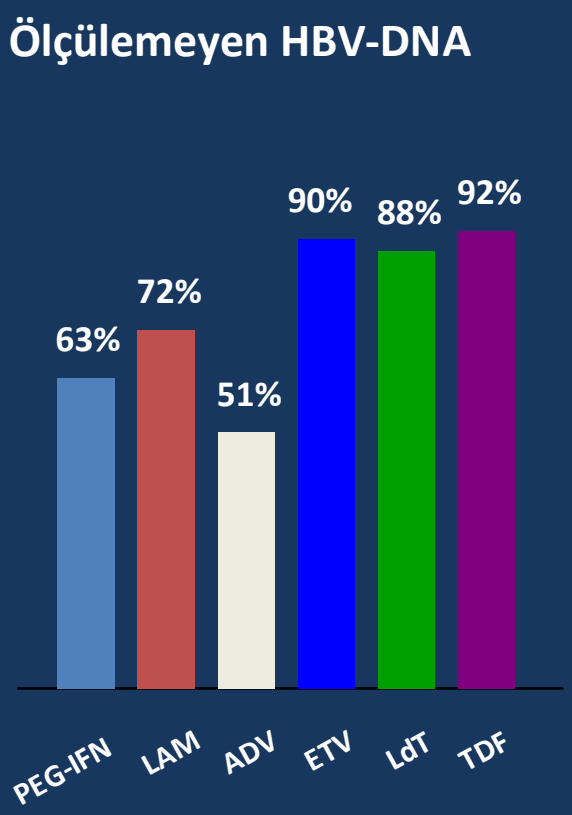
- Sirozlu 96 hastada (Ishak fibroz skoru ≥5) eşlenmiş BL ve 5. yıl biyopsileri vardı
- 5 yılda hastaların %74'ünde siroz (n=71) tersine dönmüş (Ishak fibroz skoru <5) ve %73'ünde (n=70) 5. yılda ≥2 puan azalmalar olmuştur; hastaların %25'inde (n=24) değişiklik olmamıştır

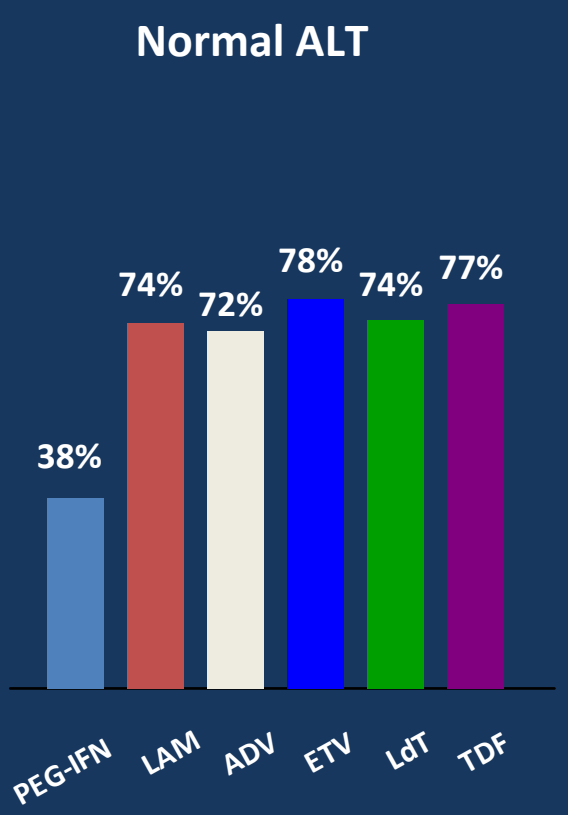
- FTC ilavesi yapılmayan 94 hastadan %73'ünde siroz tersine dönerken, %26'sı değişiklik göstermemiştir.

Marcellin, P, et al. AASLD 2011; Poster #1375.

*Ne Truvada (TVD = TDF + FTC) ne de emtrisitabin (FTC) HBV'de kullanım onayı almamıştır.

HBeAg-negatif hastalar

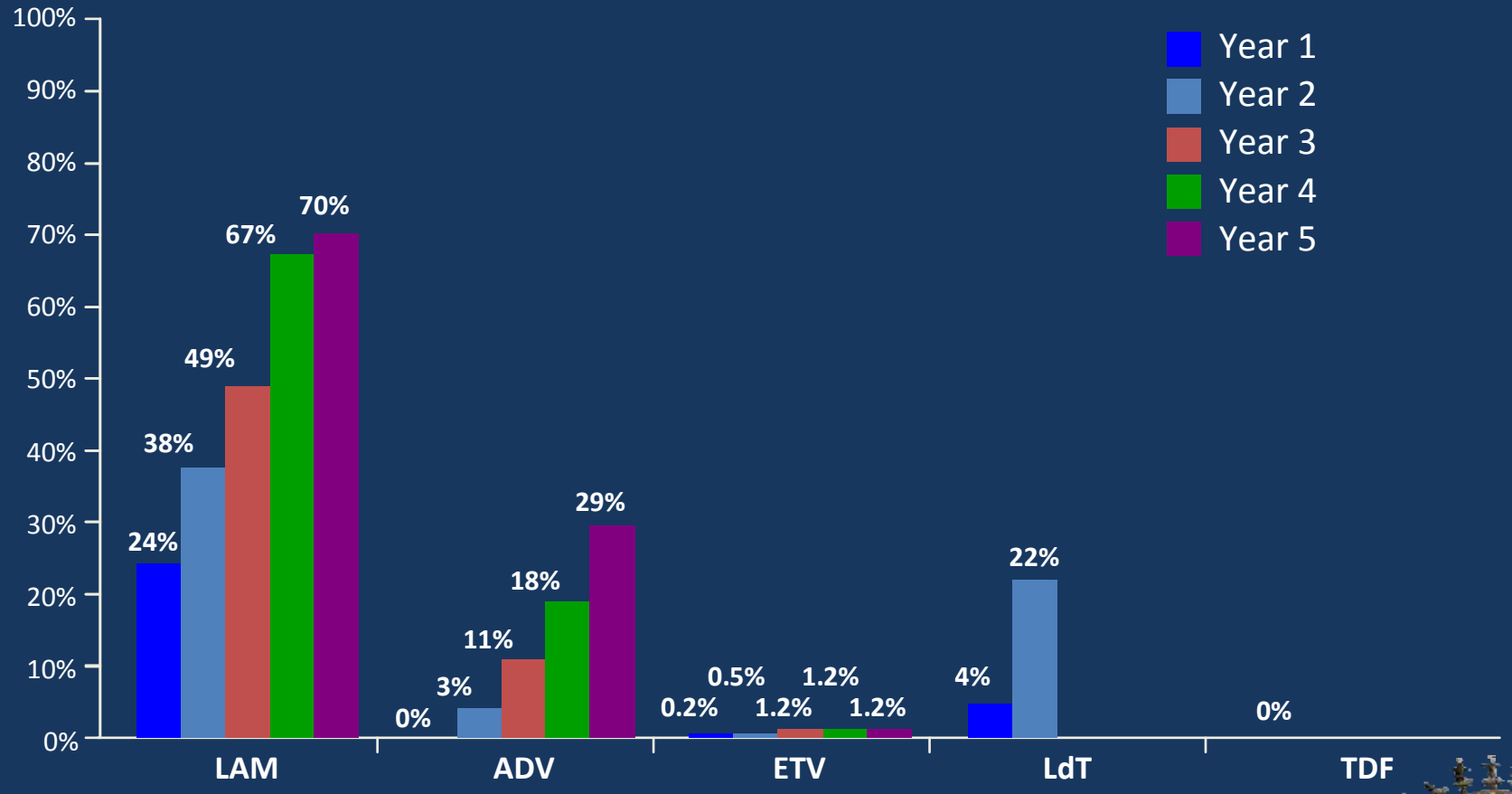




EASL Clinical Practice Guidelines, J Hepatol 2009

Ankara Uni.

HBV direncinin kümülatif direnci



EASL Clinical Practice Guidelines, J Hepatol 2009

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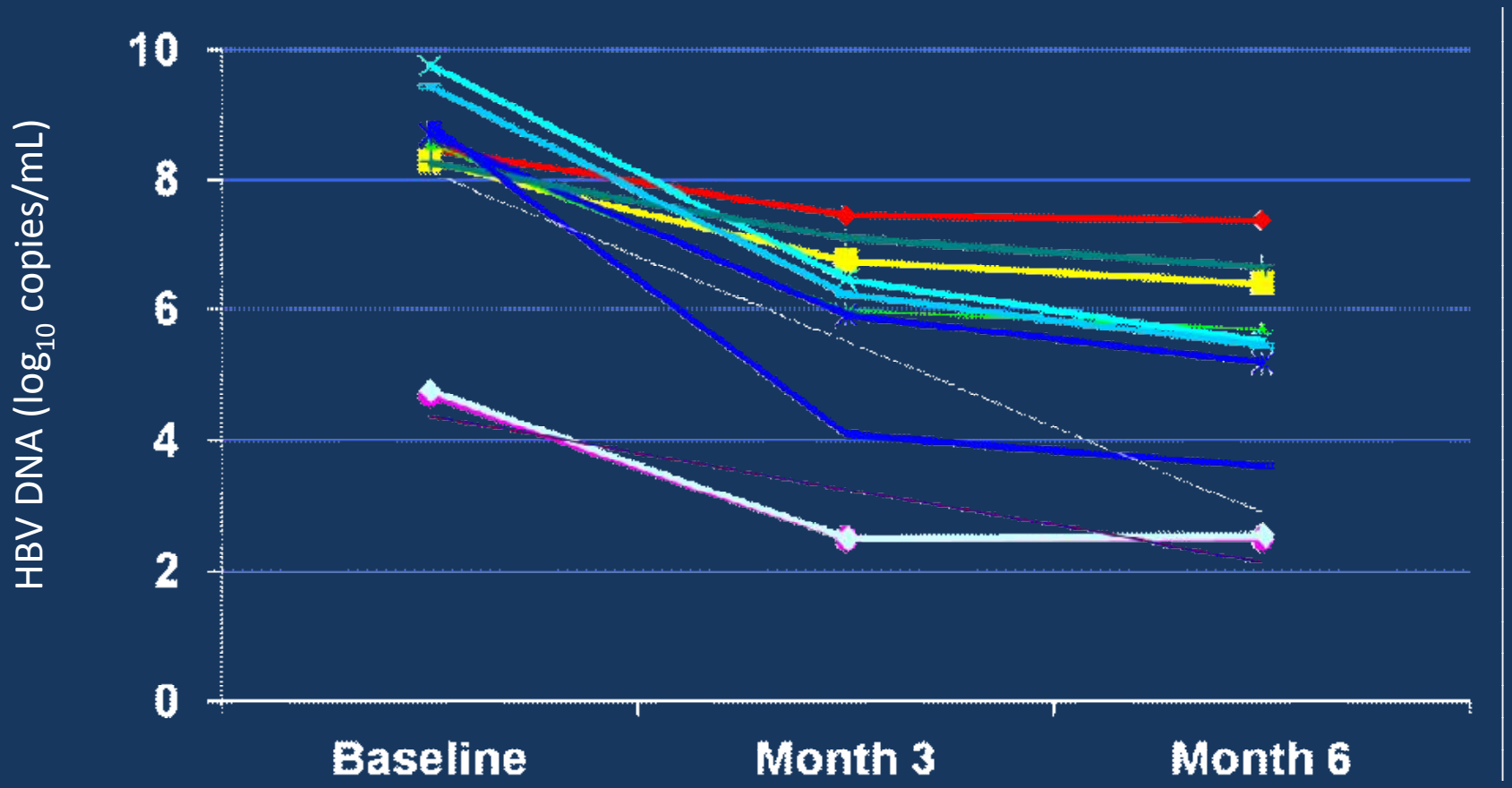
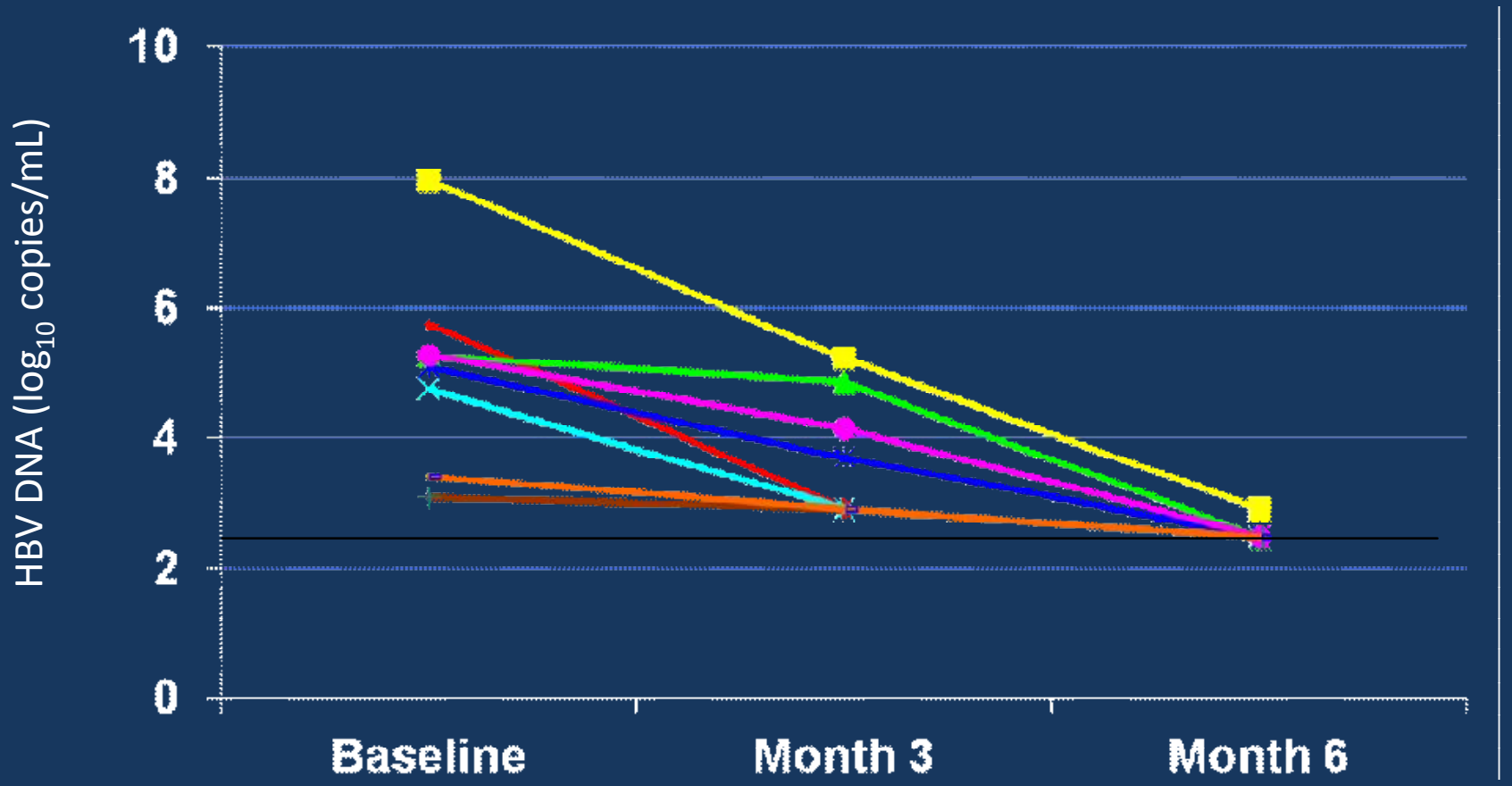
ETV dirençli hastalarda LVD + AD etkisi



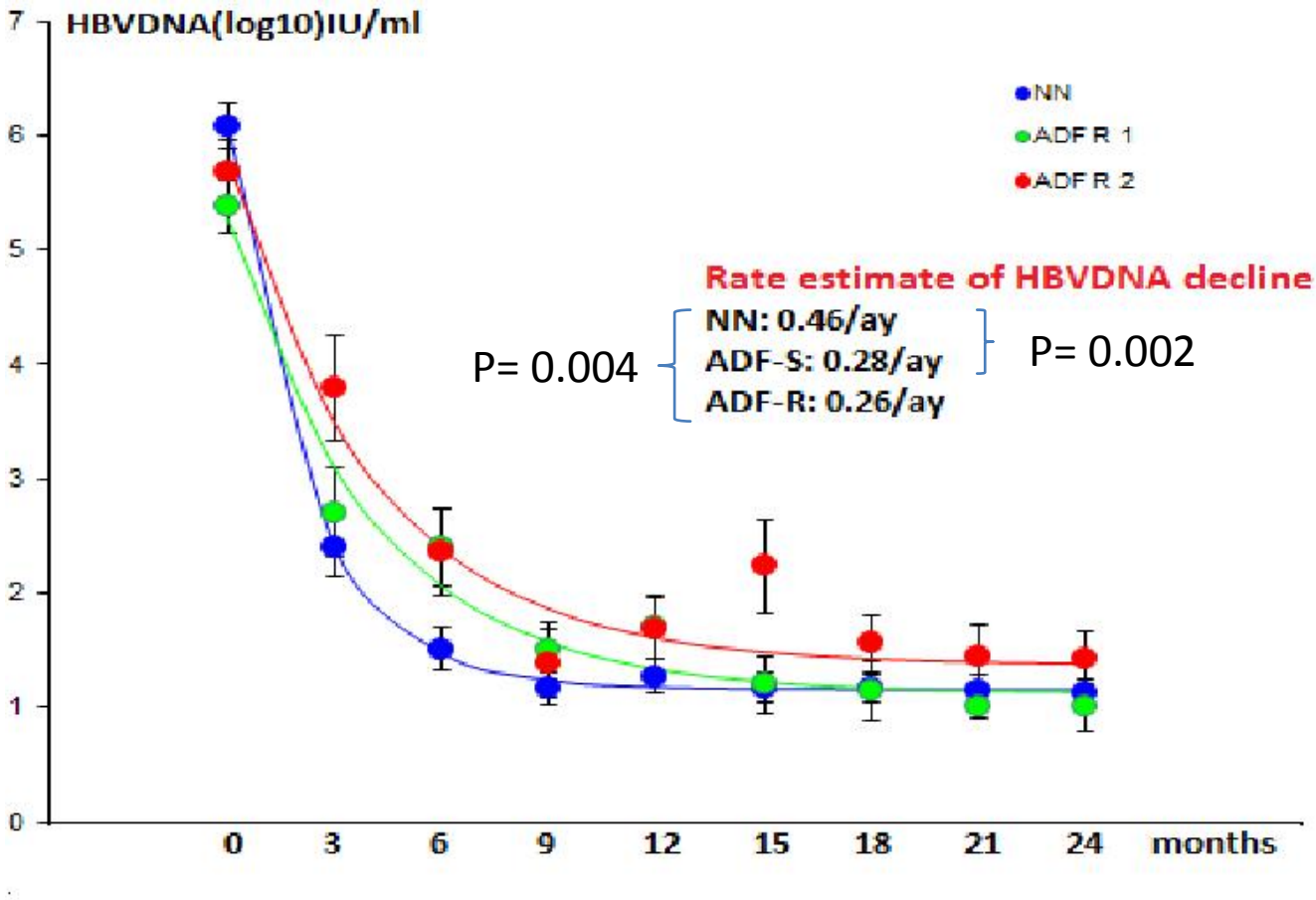
Karataylı et al, AVT 2013

ETV dirençli ve AD'e suboptimal cevaplı hastalarda TVF etkisi



Karataylı et al, AVT 2013

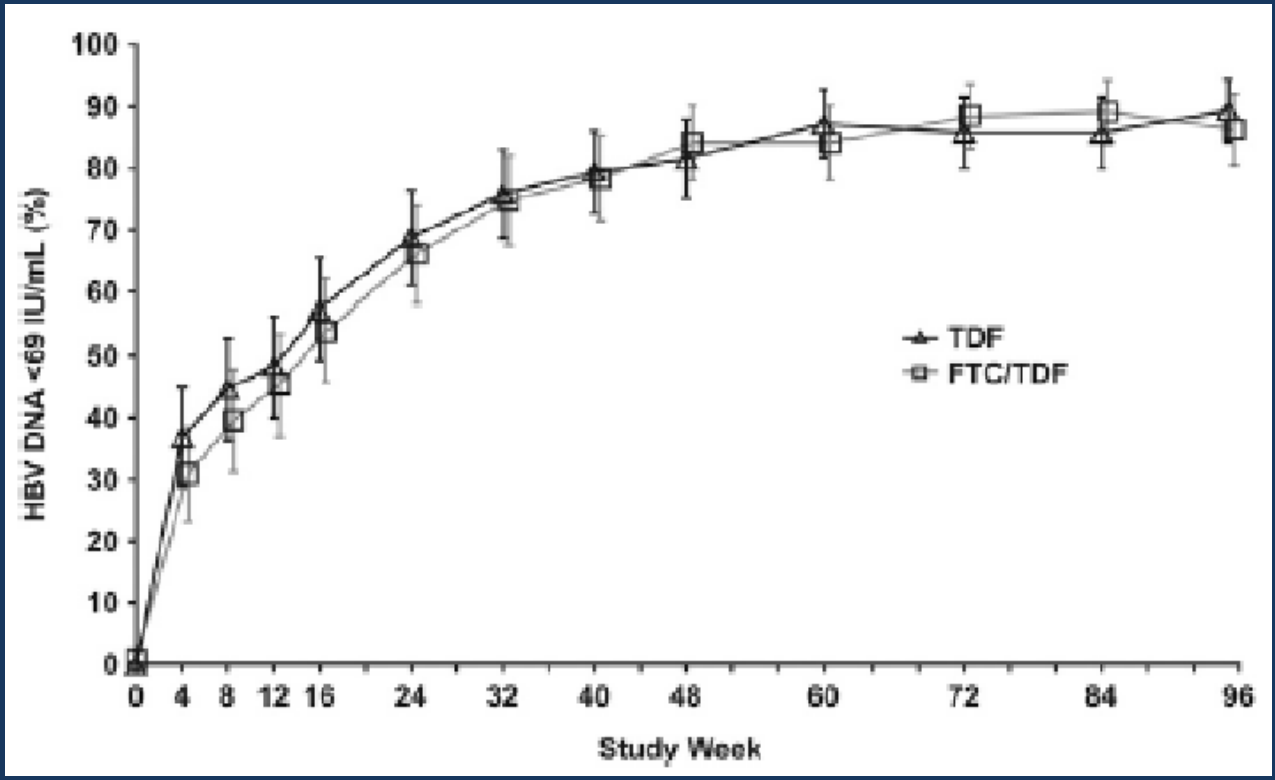
AD dirençli vs NA naiv hastalarda tenofovir etkisi



Keskin et al, AVT 2014

Direnc tedavisinde kombinasyon tedavisi gerekli mi?

Lamivudine dirençli KHB'de Tenofovir vs. Tenofovir + Emtrisitabin etkisi



Fung S et al, Gastroenterology 2014

ZOR DURUMLAR:

DEKOMPANSE SIROZ

AKUT ON KRONIK KC

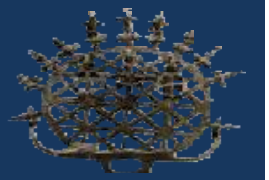
Predictors of survival

- Serum creatinine and bilirubin levels and detectable DNA associated with six month mortality

  Index calculation

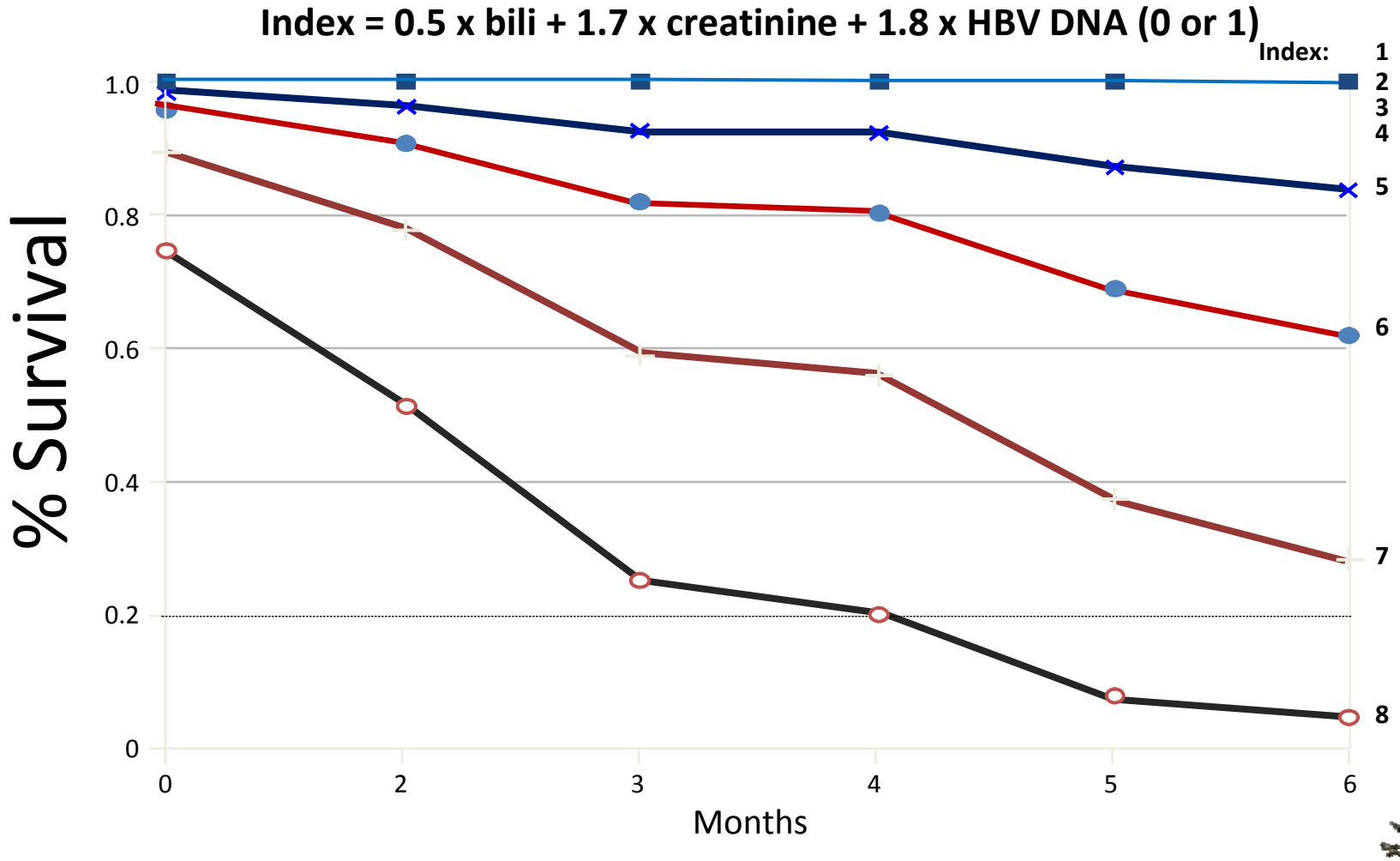
- 0.5 x bilirubin + 1.7 x creatinine + 1.8 x HBV DNA (0 or 1)
- Example 1: serum bilirubin 2 mg/dL creatinine 1.2 mg/dL undetectable DNA
  - index score 3
  - 5% probability 6 months mortality whilst on LAM
- Example 2: serum bilirubin 6.0 mg/dL, creatinine 2 mg/dL, detectable DNA:
  - index score 8.2
  - 95% probability death within 6 months whilst on LAM

Fontana R, *et al. Gastroenterology* 2002;**123**(3):719.



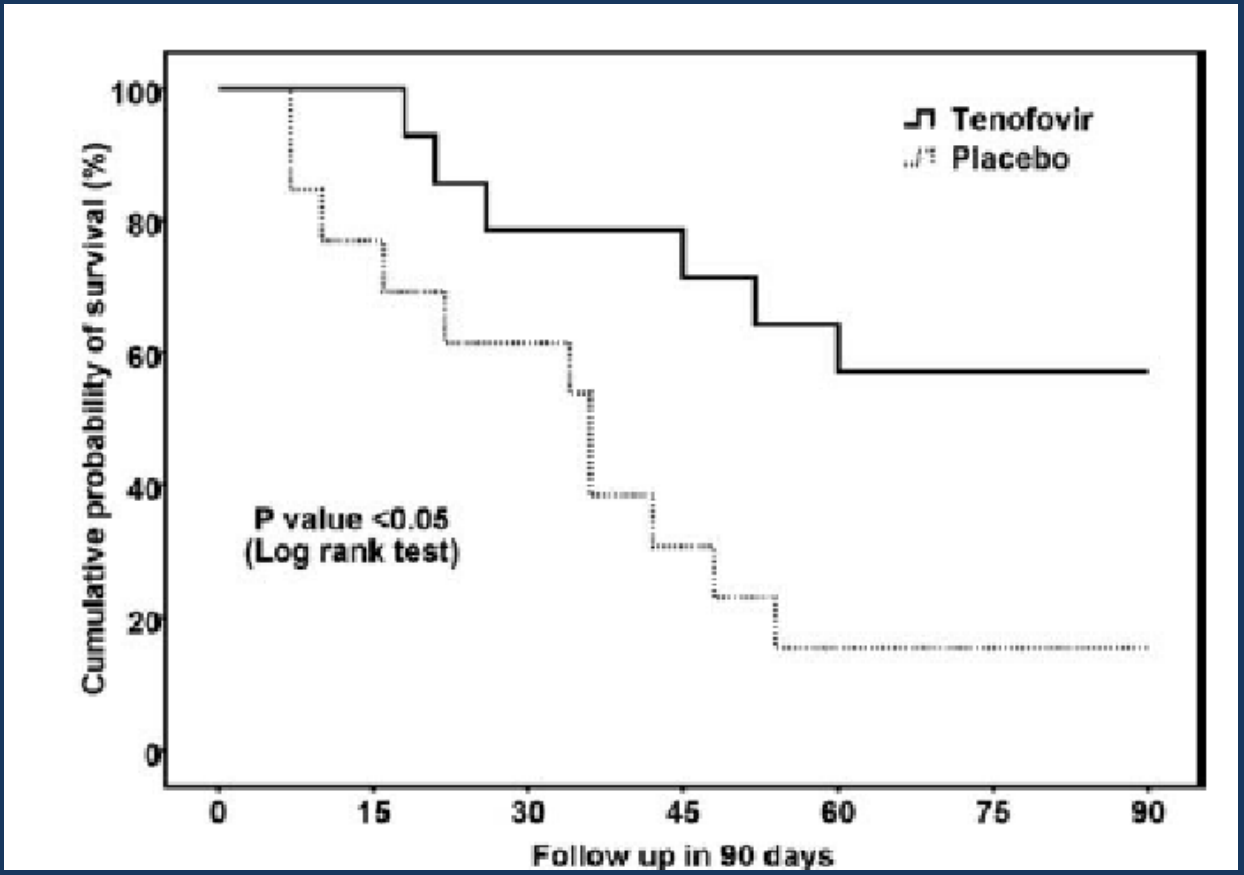
Ankara Uni.

Predicted 6 month survival in patients with HBV cirrhosis receiving lamivudine (modelled)



Fontana R, *et al. Gastroenterology* 2002;**123**(3):719.

HBV'nin spontan reaktivasyonuna bagli 'Acute on Chronic Liver Failure'de TVF



Garg et al, Hepatology 2011

Hayatta kalmanın prediktörleri

TVF

PLB

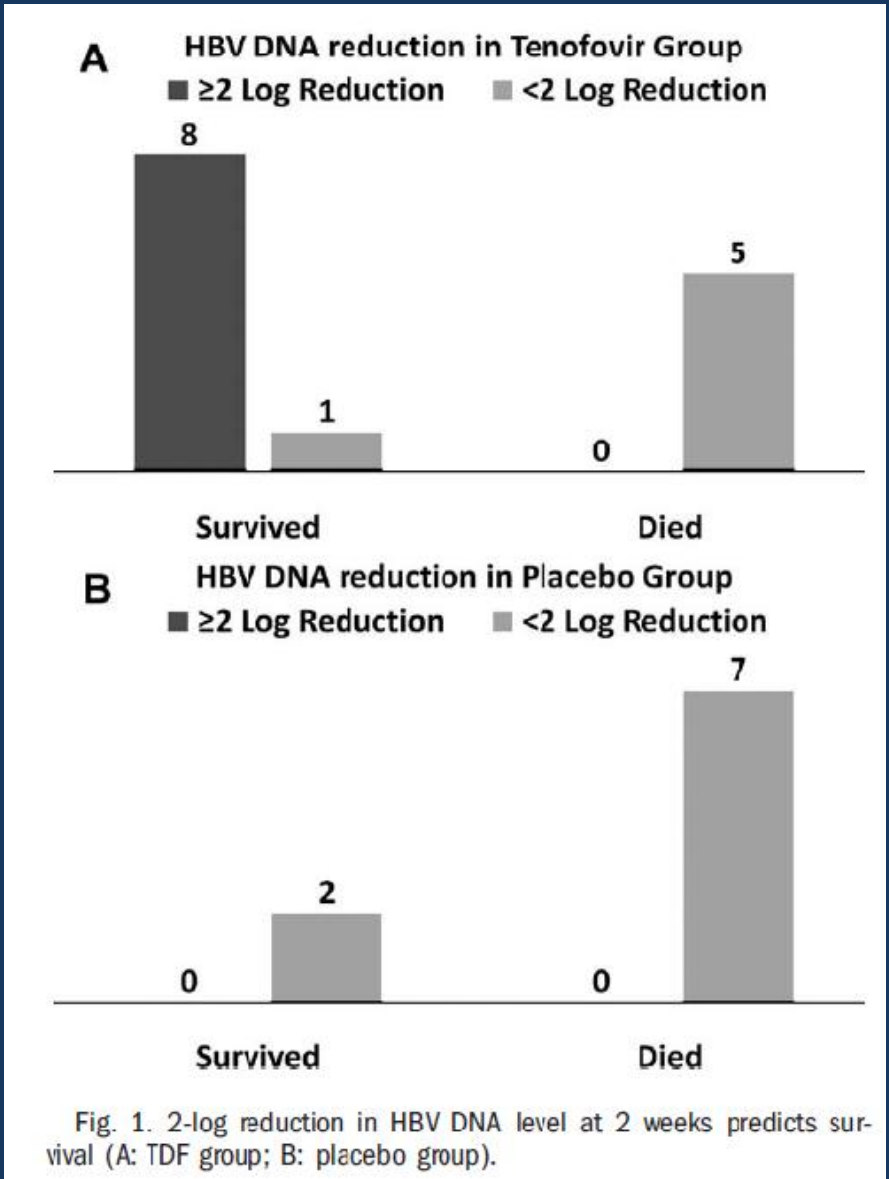


Fig. 1. 2-log reduction in HBV DNA level at 2 weeks predicts survival (A: TDF group; B: placebo group).

'Multivariate' analizde hayatta kalmanın tek bağımsız prediktörü tedavi başlangıcından 2 hafta sonra HBV DNA'da > 2log azalma

Garg et al, Hepatology 2011

SONUÇ:

Bu zor durumlarda belki kombinasyon tedavisi düşünülebilir

Kronik viral hepatit tedavi hedefleri

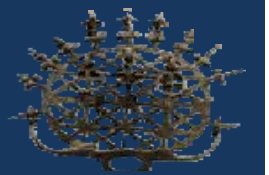
Önlenmesi gerekenler:

Hastalığın progresyonu

Siroz gelişimi

HCC gelişimi

KC hastalığından ölüm



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Kronik hepatit B tedavisi hedefleri

HBsAg serokonversiyonu

(Kronik Hepatit C'de HCV-RNA nın ölçülemeyecek değerlere yakın olması)

→ Virus eredikasyonunu sağlamaktan ziyade immünolojik kontrolü sağlamak

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HBeAg-negatif KHB

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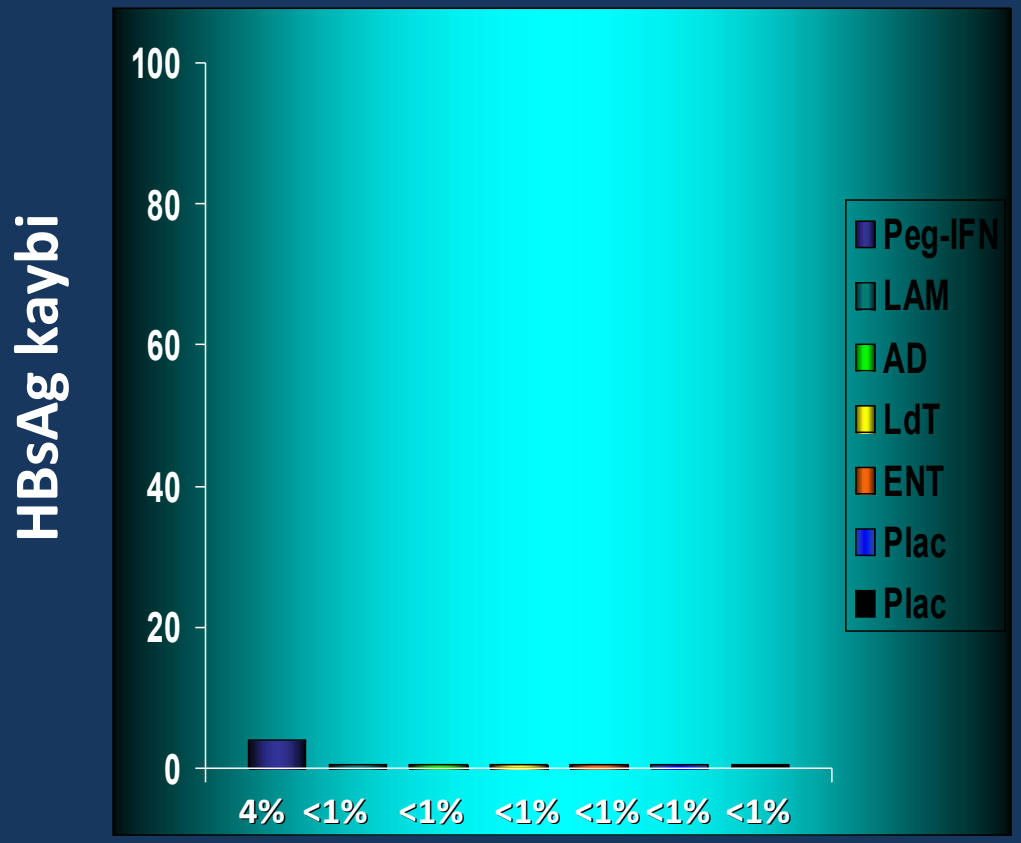
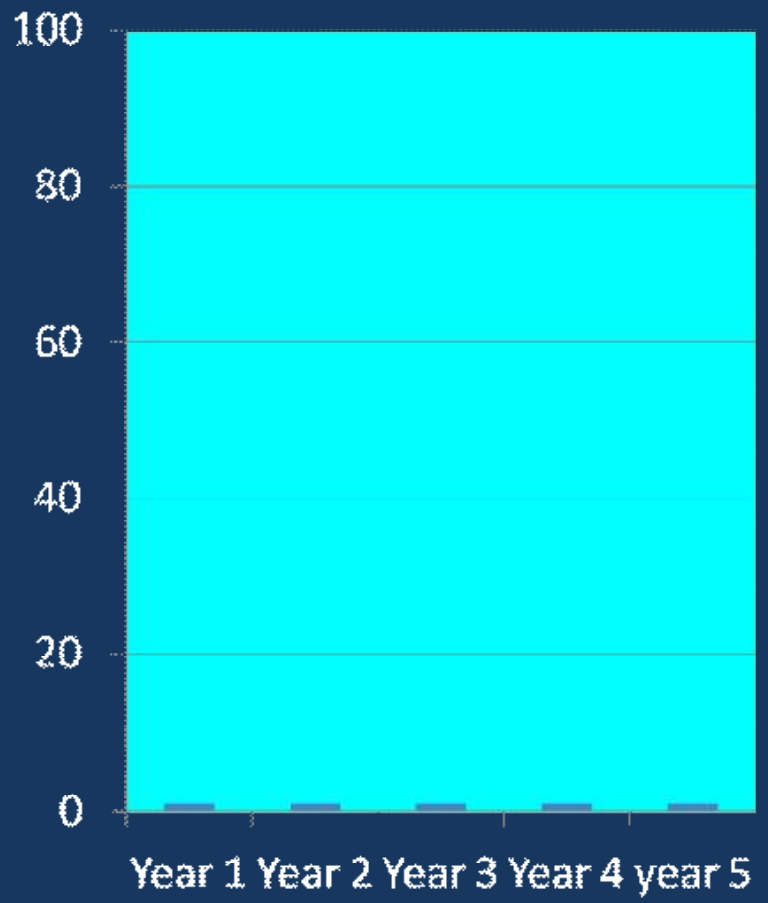
1 yıllık tedavi sonrası HBsAg kaybı

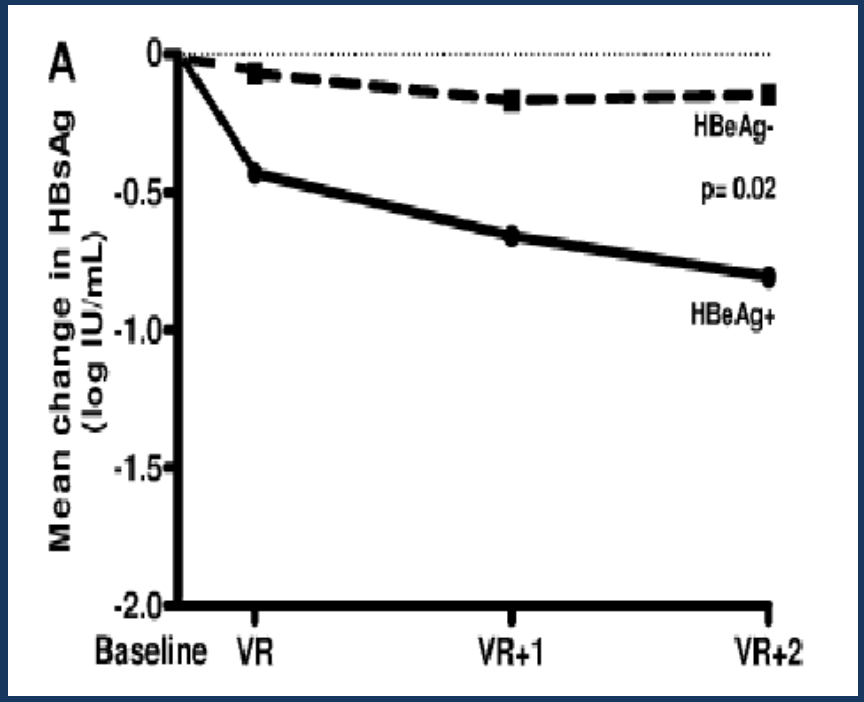


EASL Guidelines, J Hepatol 2009; AASLD 2011

5 yıllık TVF tedavisi sonrası HBsAg kaybı



HBeAg-negatif KHB'de NA tedavisi sırasında kantitatif HBsAg düzeyleri



İyi haber:
36 yılda HBsAg kaybı

Zoutentijk et al, JID 2011

Kişi Başına Düşen Milli Gelir (ABD dolar) ve Hepatit B prevalansı

	Gelir	HBV prevalansı	Geri ödeme
Bangladesh	470	Orta	Hayır
China	2360	Yüksek	Neredeyse yok
India	950	Orta	Hayır
Indonesia	1650	Orta	Hayır
Malaysia	6540	Orta	Hayır
Philippines	1620	Yüksek	Hayır
Singapore	32470	Orta	Sınırlı
S. Korea	19690	Yüksek	Sınırlı
Taiwan	17930	Yüksek	Sınırlı
Thailand	3400	Yüksek	?

Liaw YF, J Hepatol 2009

Ankara U

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Thailand	3400	Yüksek	?

Liaw YF, J Hepatol 2009

Ankara U

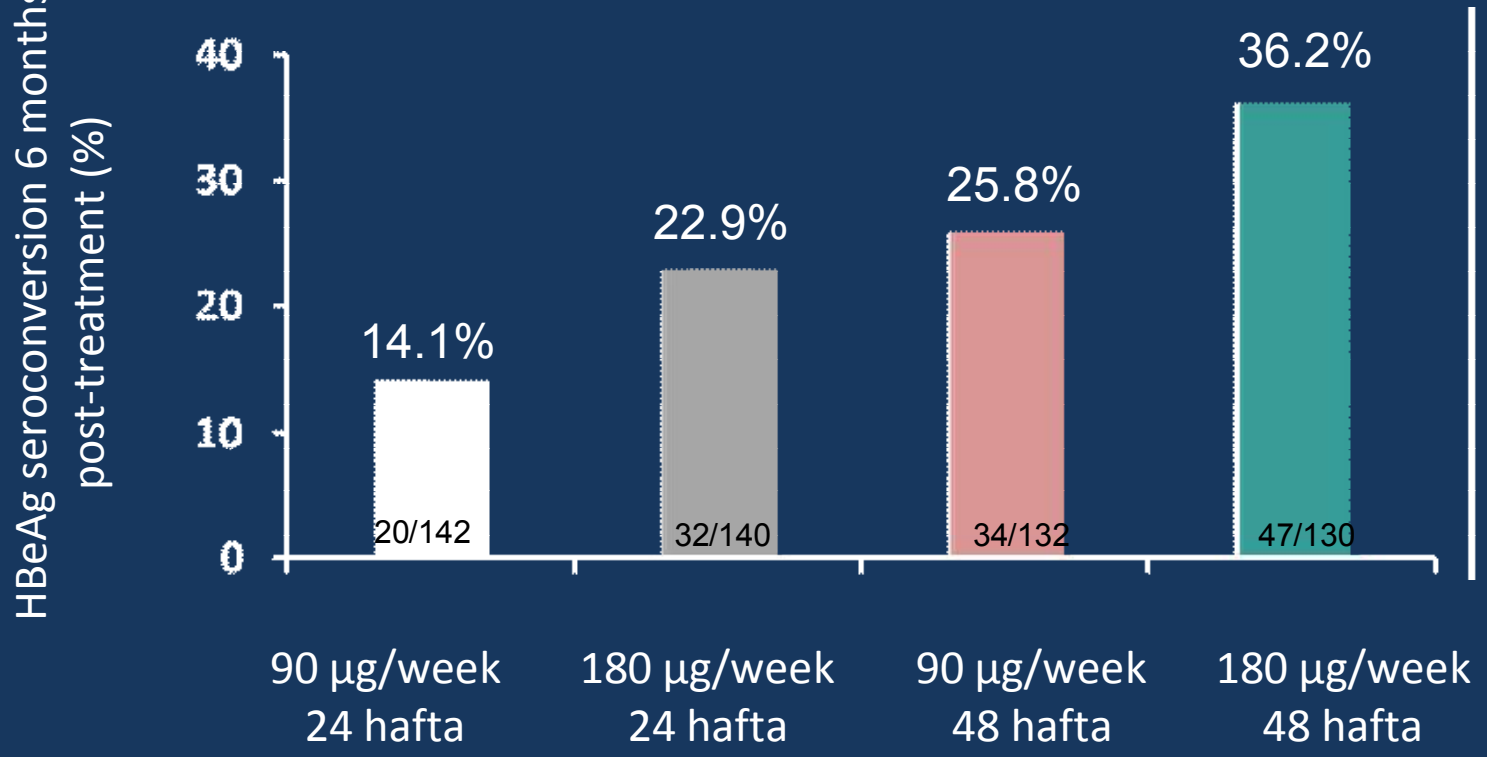
Guideline & HBV Tedavisi

	AASLD 2009	EASL 2012	APASL 2012
Lamivudine	Tercih edilmemiş	Tercih edilmemiş	Tercih edilmemiş
Adefovir	Tercih edilmemiş	Tercih edilmemiş	Tercih edilmemiş
Entecavir	İlk tercih	İlk tercih	İlk tercih
Telbivudine	Tercih edilmemiş	Tercih edilmemiş	Tercih edilmemiş
Tenofovir	İlk tercih	İlk tercih	İlk tercih
PEG-IFN	İlk tercih	İlk tercih	İlk tercih

Lok and McMahon 2009, Liaw et al., 2012, J Hep 2012

Peg IFN tedavisi

NEPTUNE: En yüksek HBeAg serokonversiyon oranı 180 µg/hf - 48 hafta grubunda

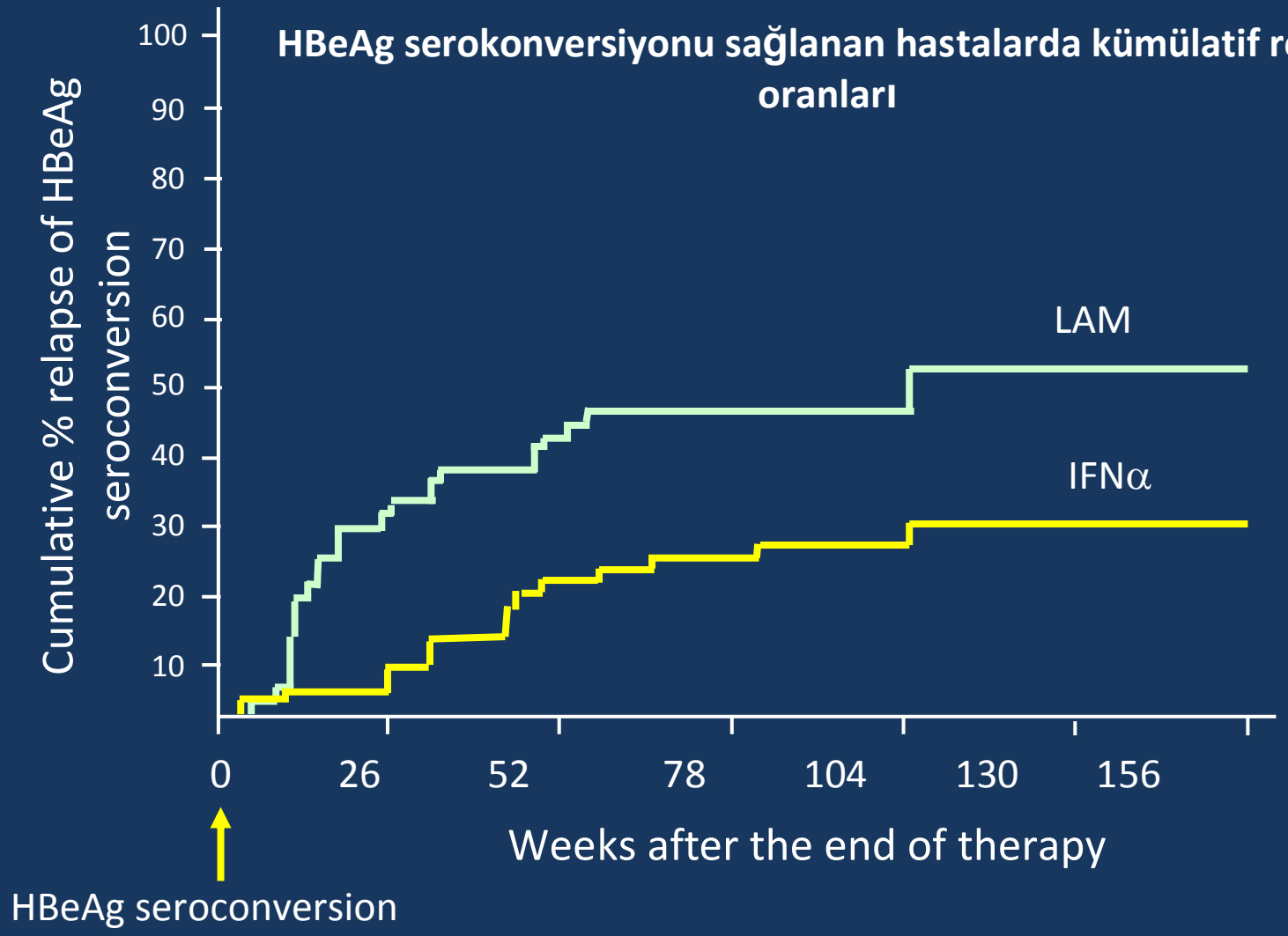


Doz ve süre arasında ilişki yok : P=0.8959

HBeAg: hepatitis B 'e' antigen

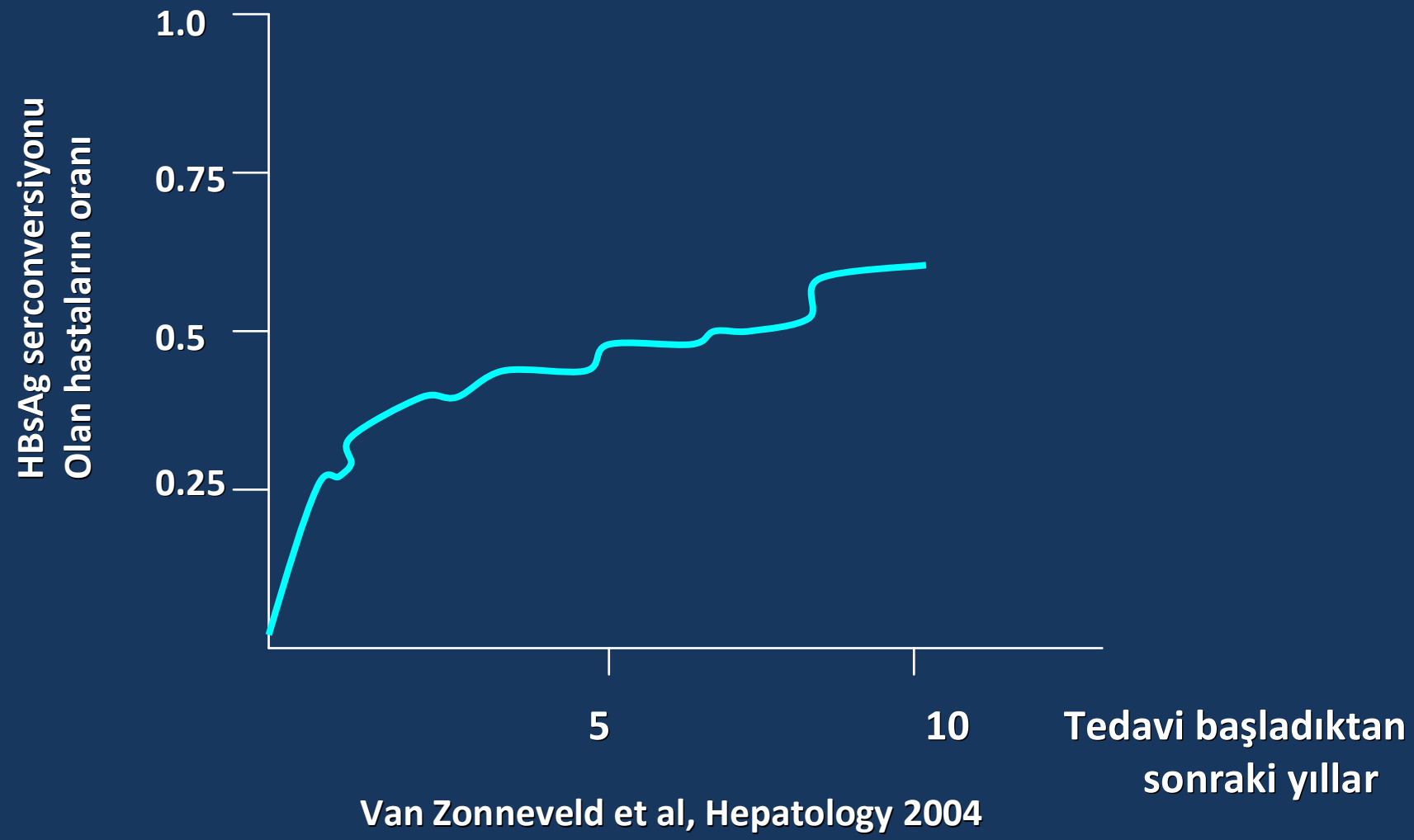
Liaw et al. EASL oral 2010

Lamivudin kaynaklı HBeAg Serokonversiyonu IFNα' a göre daha kısa ömürlü



van Nunen et al. *Gut* 2003

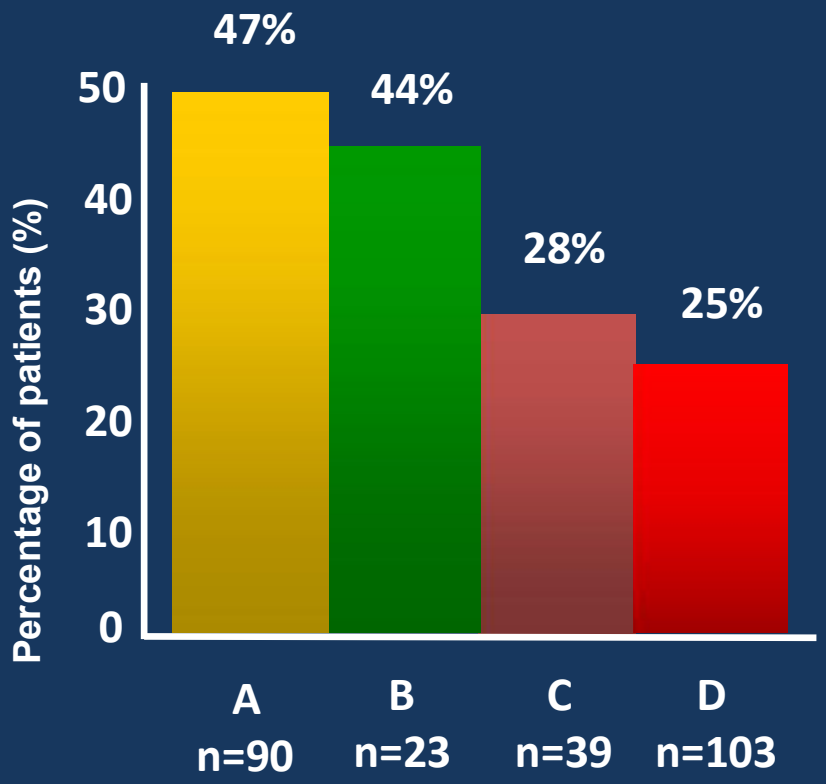
HBsAg serokonversiyonu olan IFN' a Cevap alınan hastalarda ;



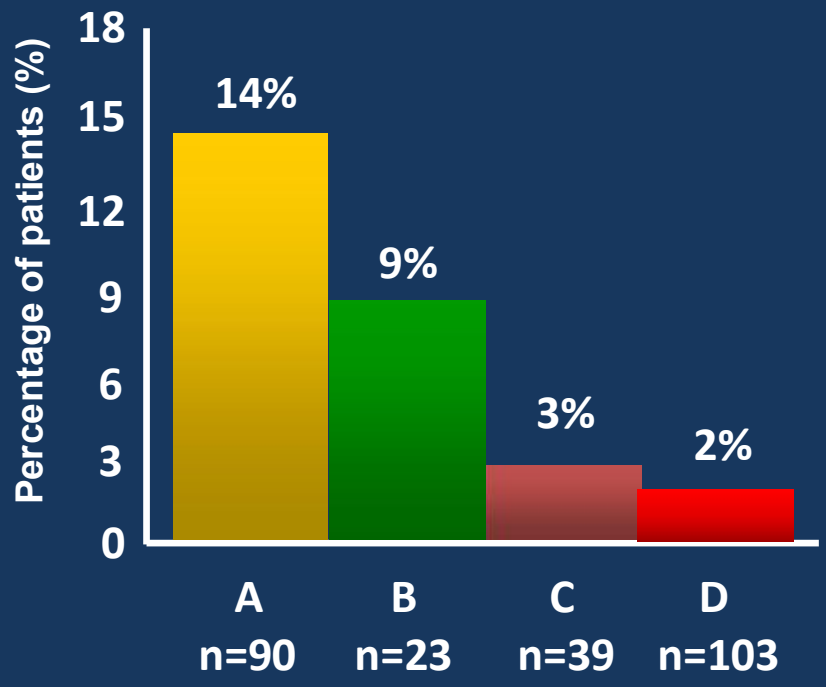
Van Zonneveld et al, Hepatology 2004

HBeAg pozitif KHB'de PEG-IFN'a cevap alınan

PEG-IFN α-2b - HBeAg Kaybı [1]



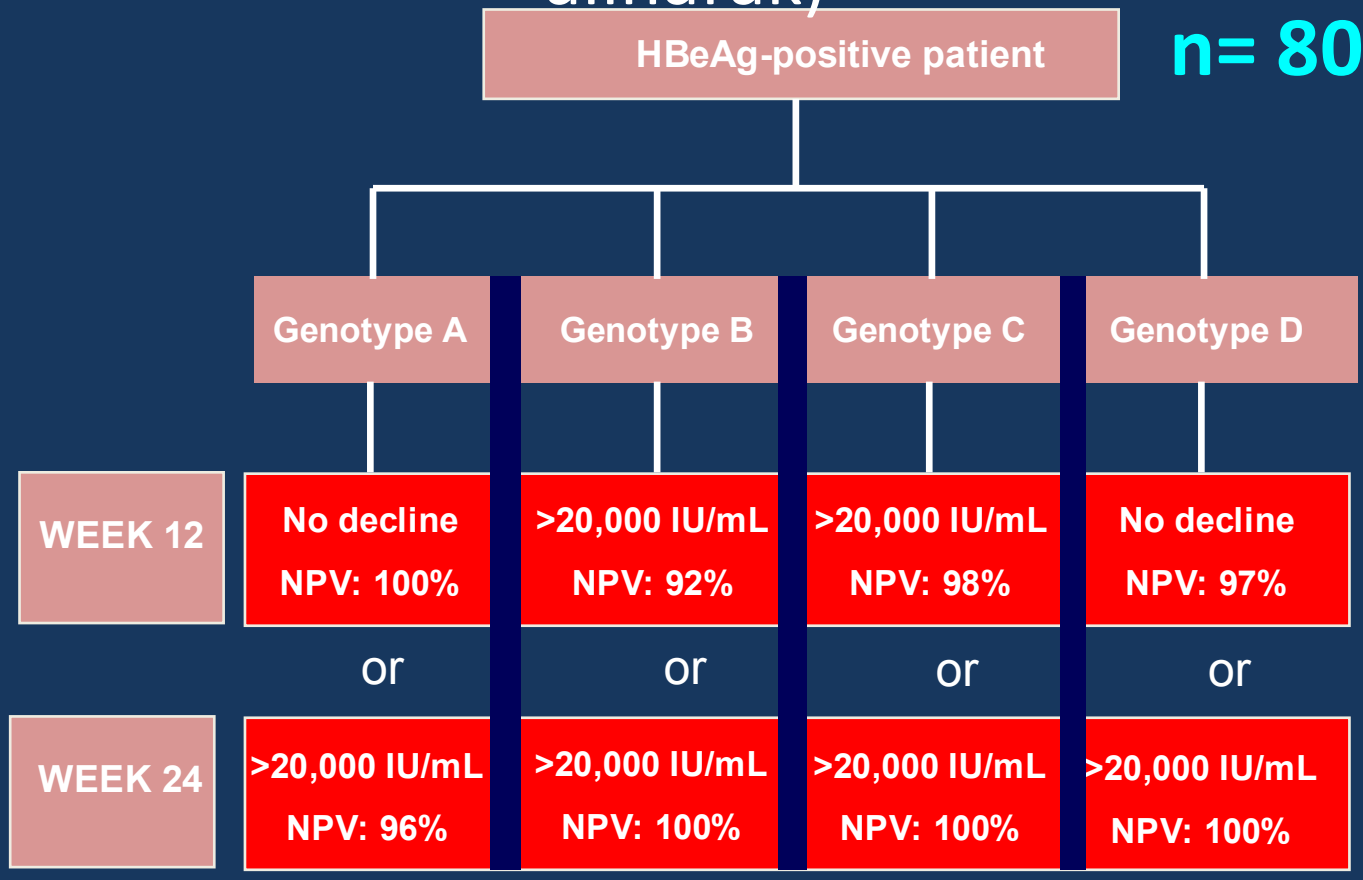
PEG-IFN α-2b - HBsAg Kaybı [2]



[1] Janssen, Lancet 2005; [2] Flink, Am J Gastro 2006

HBeAg (+) hastalarda PEG-IFN tedavisi ile tam yanıt alınan hastalar için HBsAg algoritmi

(HBsAg düzeyleri ile 3 global çalışma temel alınarak)



Sonneveld et al. Hepatology 2013

AISF Study: 558 HBeAg negatif hasta

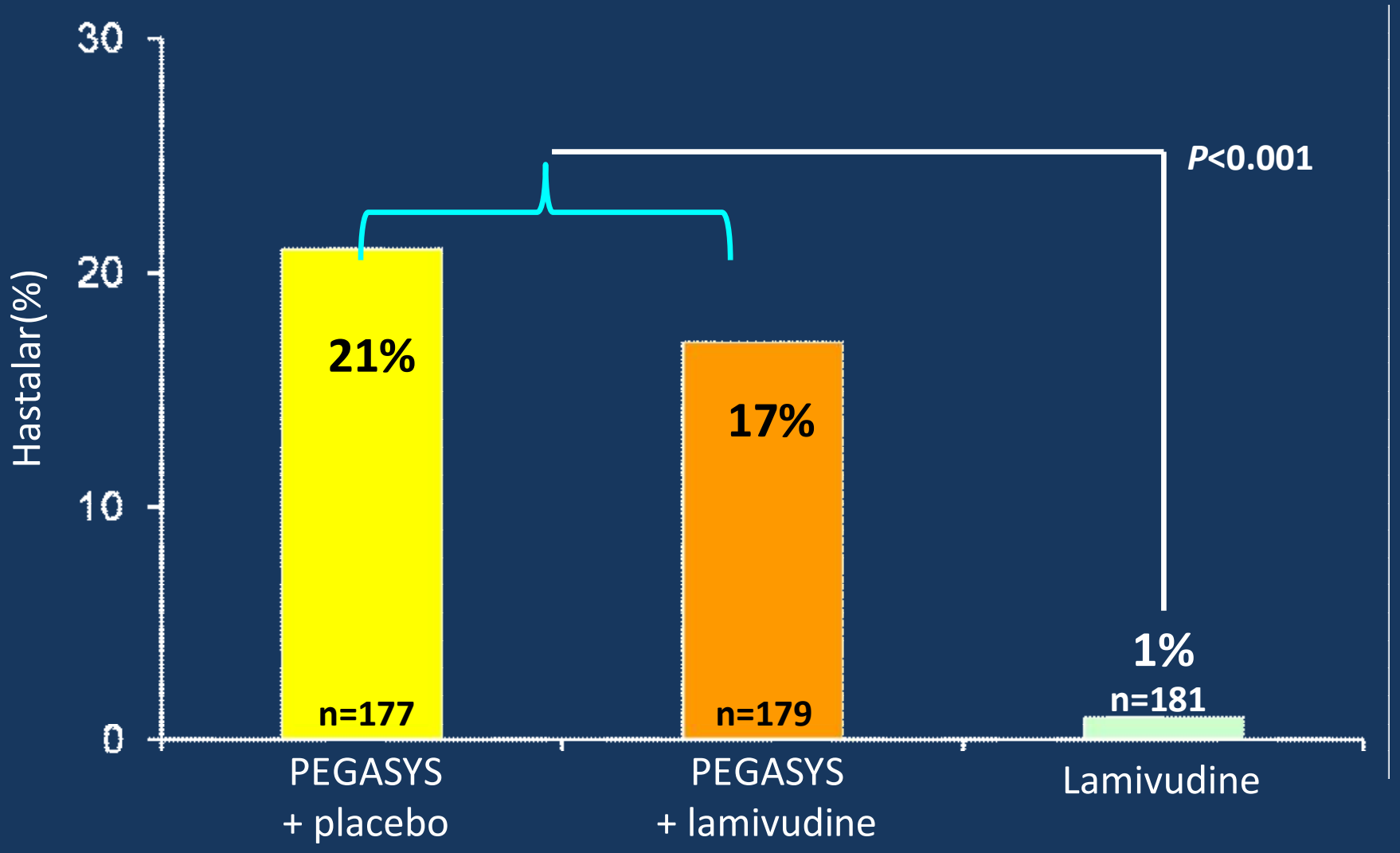
Rate of EoF SR by treatment duration

IFN tedavisi süresince (ay)	End of F.U. Sustained Response hasta (%)	
	Yes	**No**
≤ 6	**10 (5,7%)**	164 (94,3%)
7 –12	**19 (12,8%)**	129 (87,2%)
13 – 18	**26 (22,8%)**	88 (77,2%)
>18 *	**41 (33,6%)**	81 (66,4%)
Overall	***96 (17,2 %)***	*462 (82,8%)*

* Median 24 mo, range 19-59

Oliveri F, AISF 2005

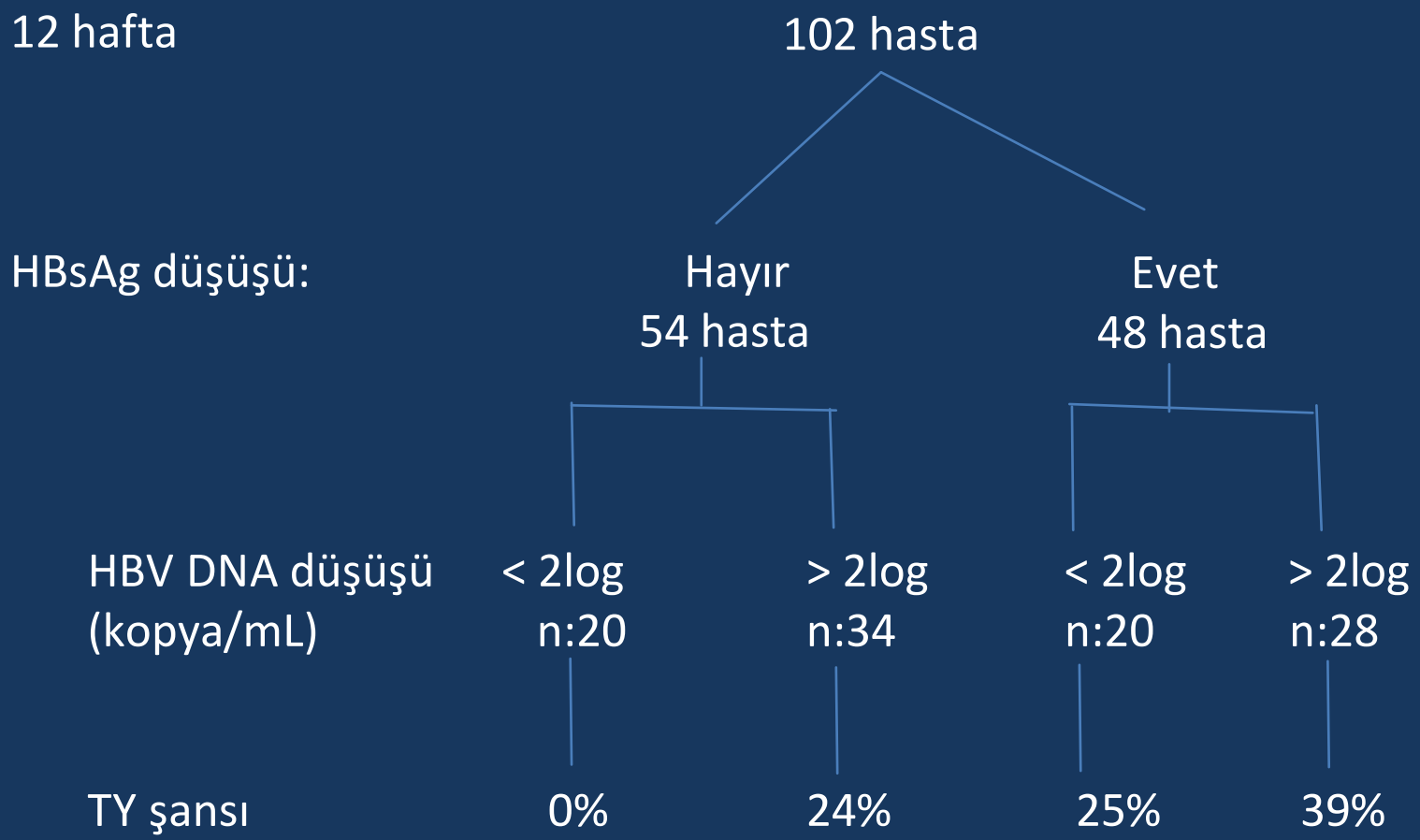
HBsAg <100 IU/mL (Tedavi sonunda)



Brunetto et al, Hepatology 2009

PEG-IFN ile tedavi edilen HBeAg (-) KHB hastalarında Tedaviye yanıtın öngörülebilmesinde HBsAg + HBV-DNA

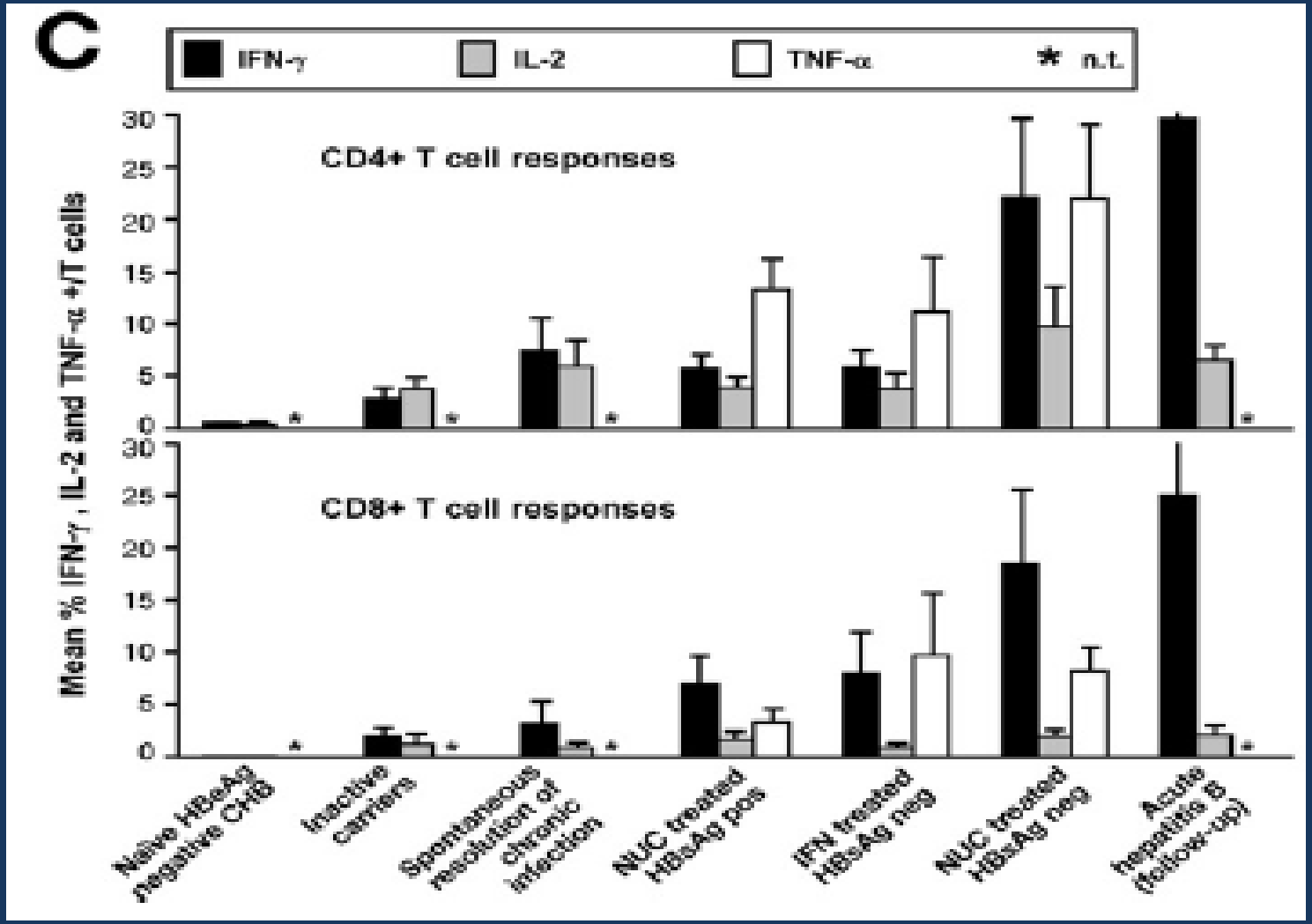
Ricjkborst et al, Hepatology 2010



Uzlaşma

NA ve IFN akılcı yolla kullanılmalı

Uzun süreli NA tedavisi sonrası T hücre fonksiyonlarında düzelme

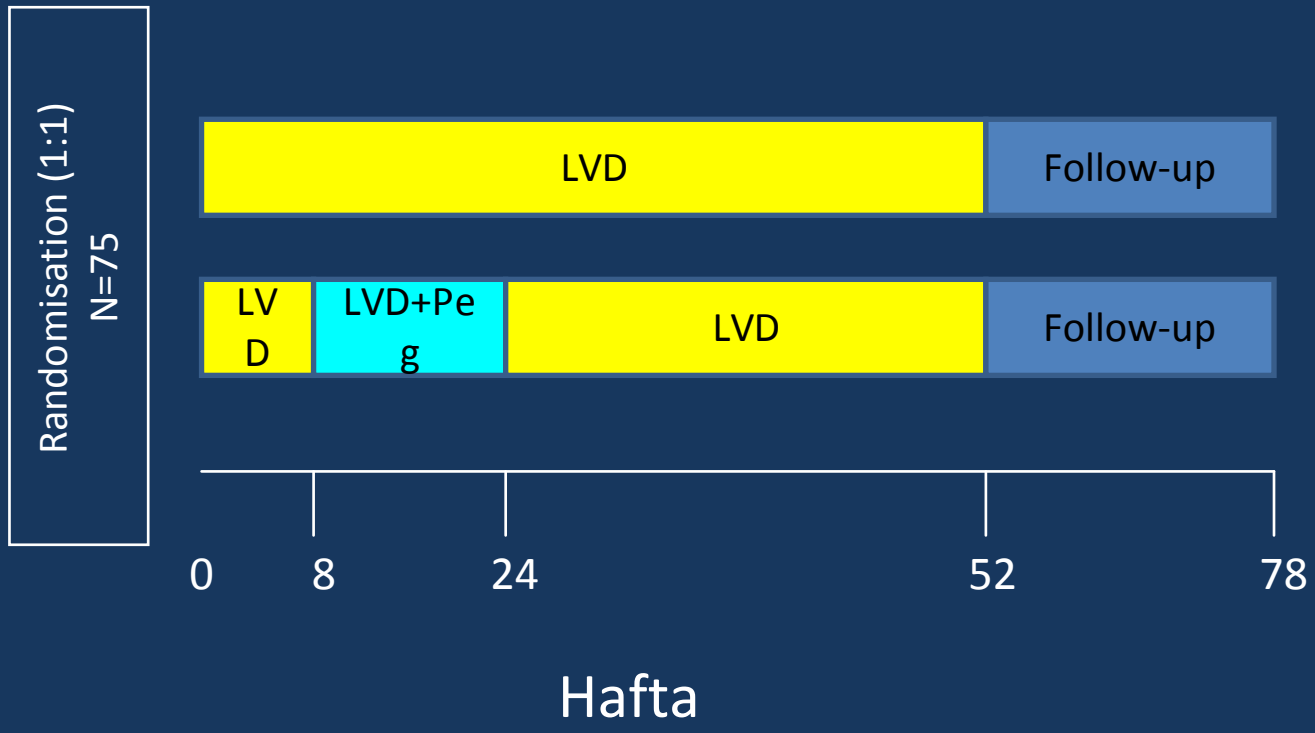


Boni C et al, Gastroenterology 2012

IFN- NA kombinasyonu: ardışık yaklaşım

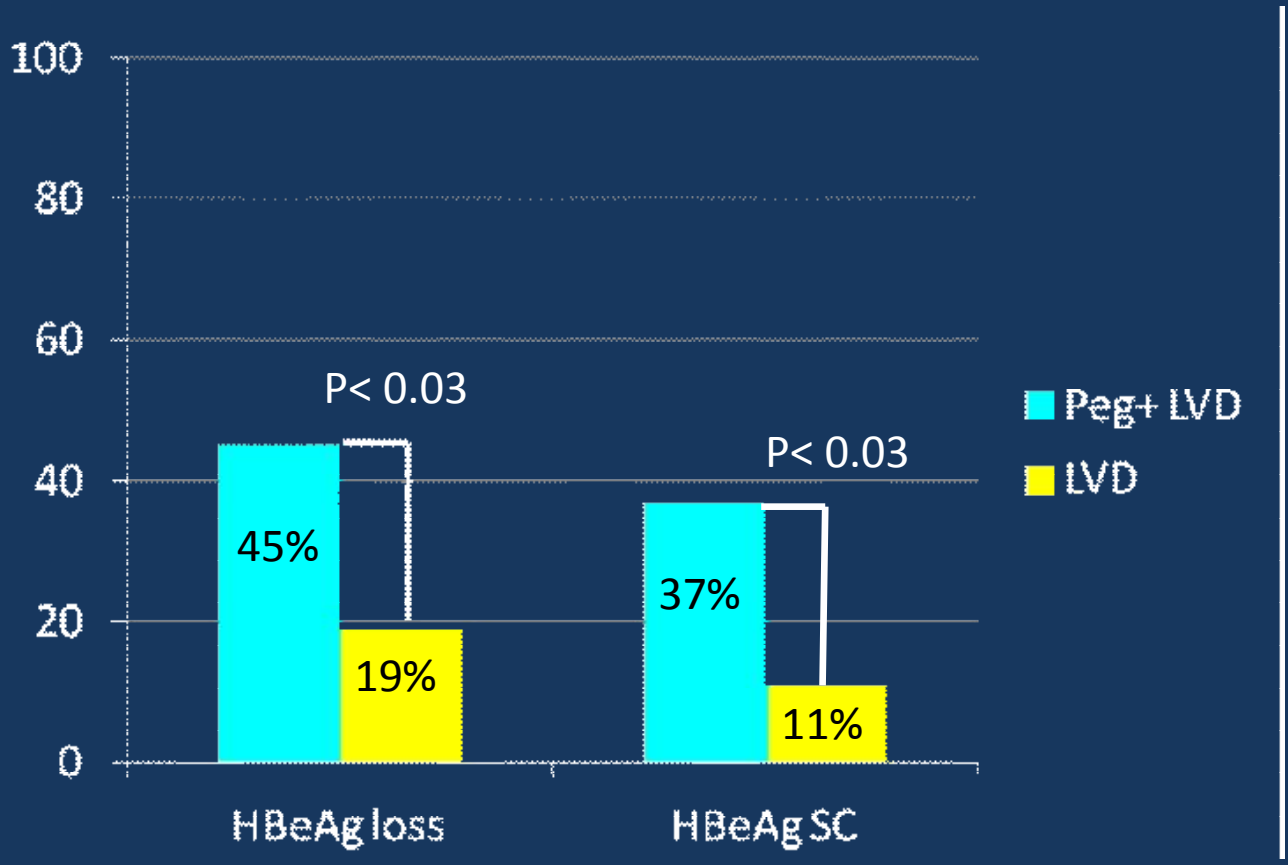
Hastalar:

- HBeAg-pozitif
- ≥18 yaş
- ALT ≥1.5 x ULN



Sarin S et al, AJG 2005

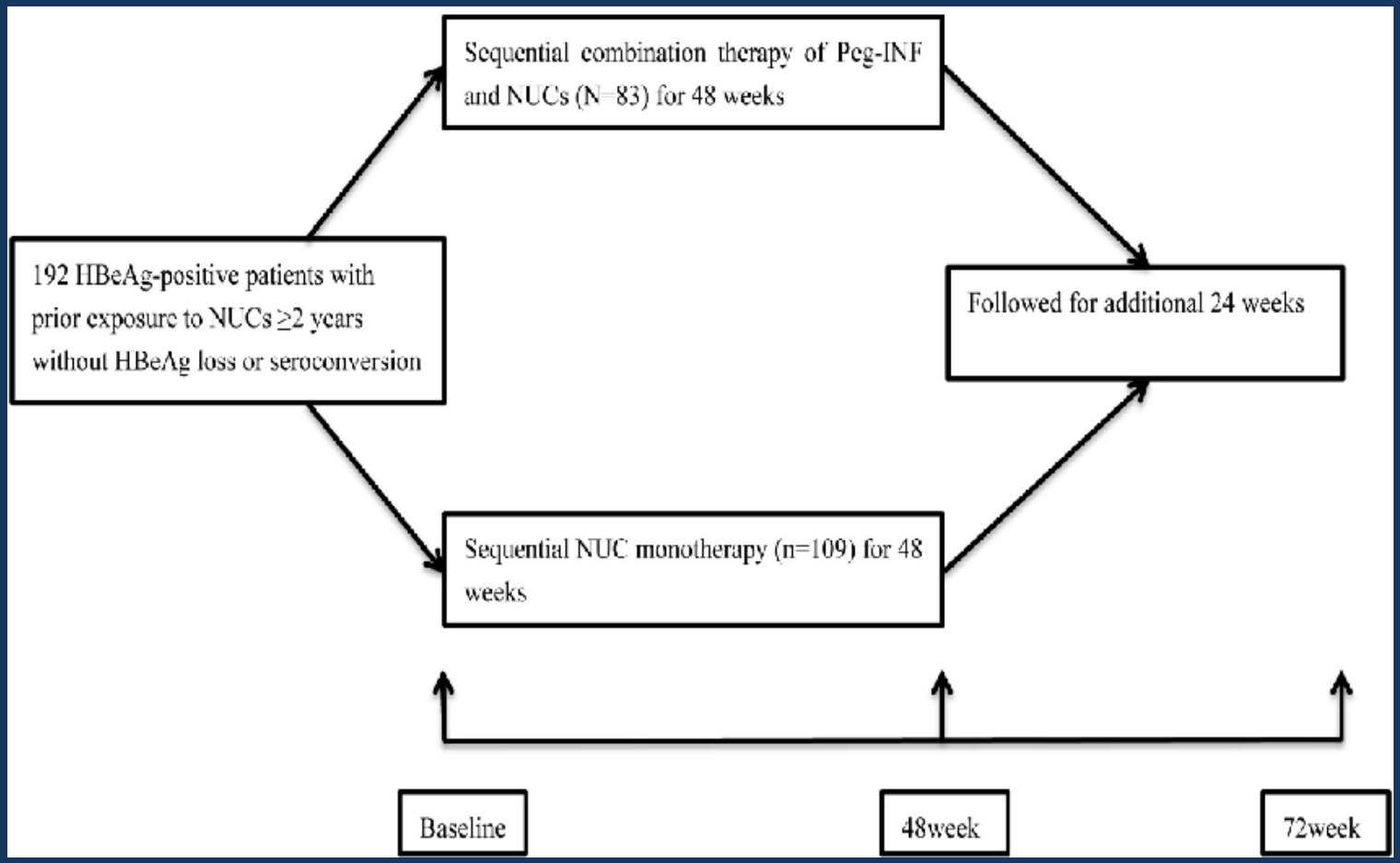
Ardışık LVD – Peg Tedavisi



Sarin S et al, AJG 2005

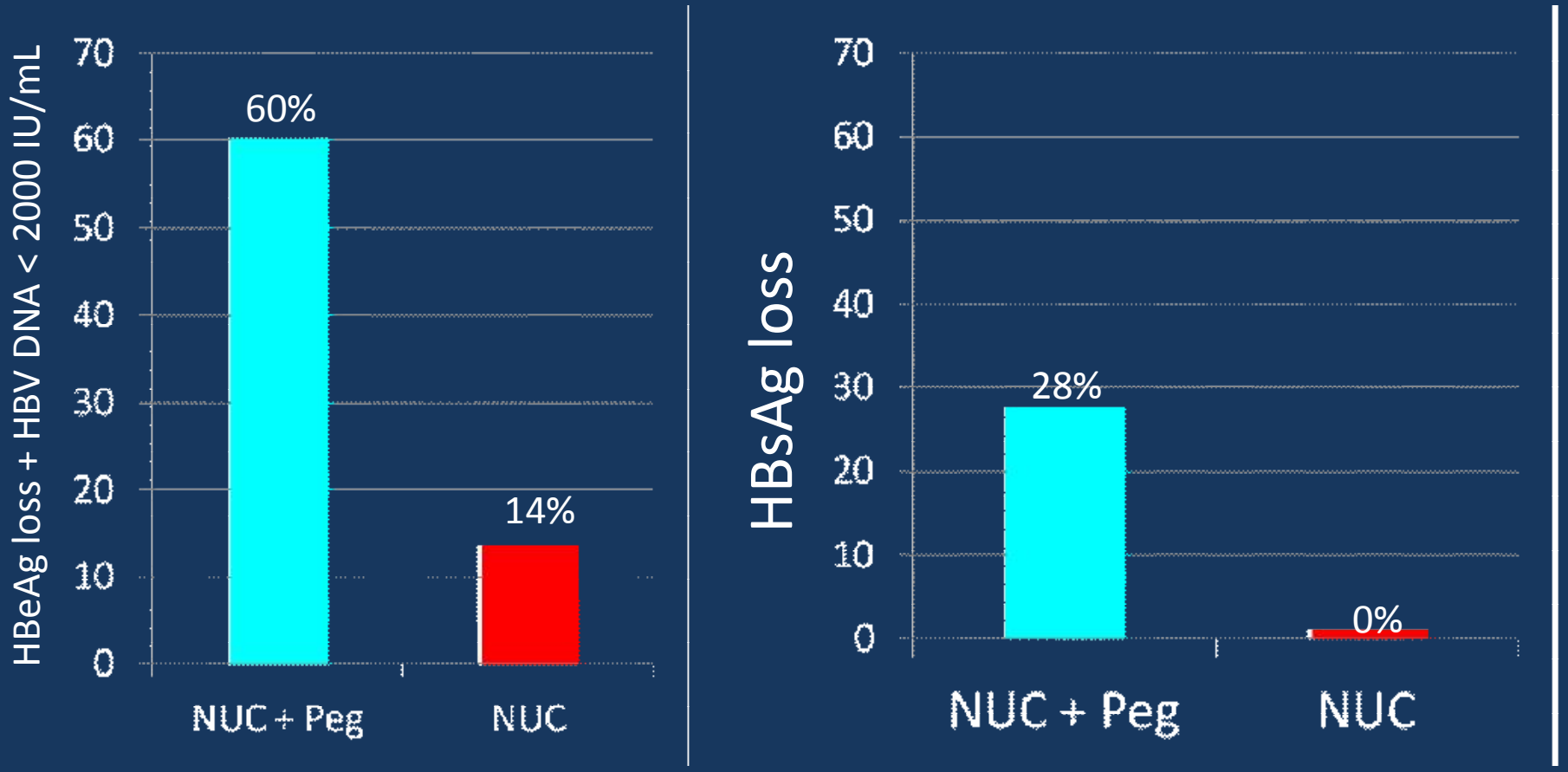
LT NA tedavisi sonrası Peg-IFN

Çalışmaya göre hasta akışı



Li G et al, EASL 2014, Oral #117

Sonuçlar



Li G et al, EASL 2014, Oral #117

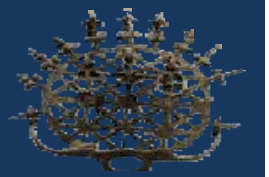
Sonuç

- Çalışma sonuçları NA-PEG ardışık tedavisini önermekte
- Çalışmalar hala tutarsız
- Farklı çalışma dizaynı, farklı coğrafik bölgeler, farklı HBV genotipleri
- NA alan hastalara konsantre olmak makul görülmekte
- KHB'de; HBV guidelineları NA-PEG ardışık tedavisi üzerinde optimize tedavi için durmakta ;
  - KHB'de gerçekçi bir yaklaşım ile kür şansını yakalamak için

Can we discontinue oral antiviral therapy in HBeAg-negative CHB?*

- In decompensated liver cirrhosis? **NO!**
- In compensated cirrhosis? **NO!**
- In others? May be
  - Stage of liver disease important:
    - Mild to moderate liver disease (Ishak score ≤3)
  - Treatment duration important
  - New markers (quantitative HBsAg) may be of use

* Grade of evidence < C2



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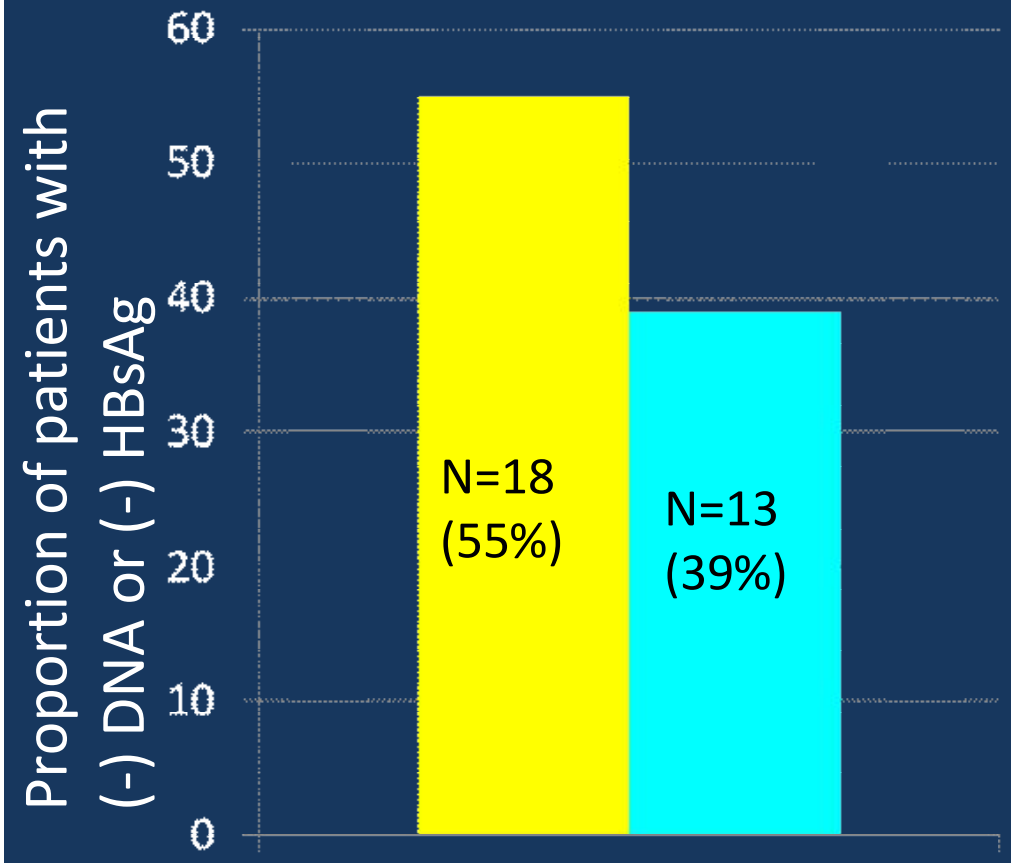
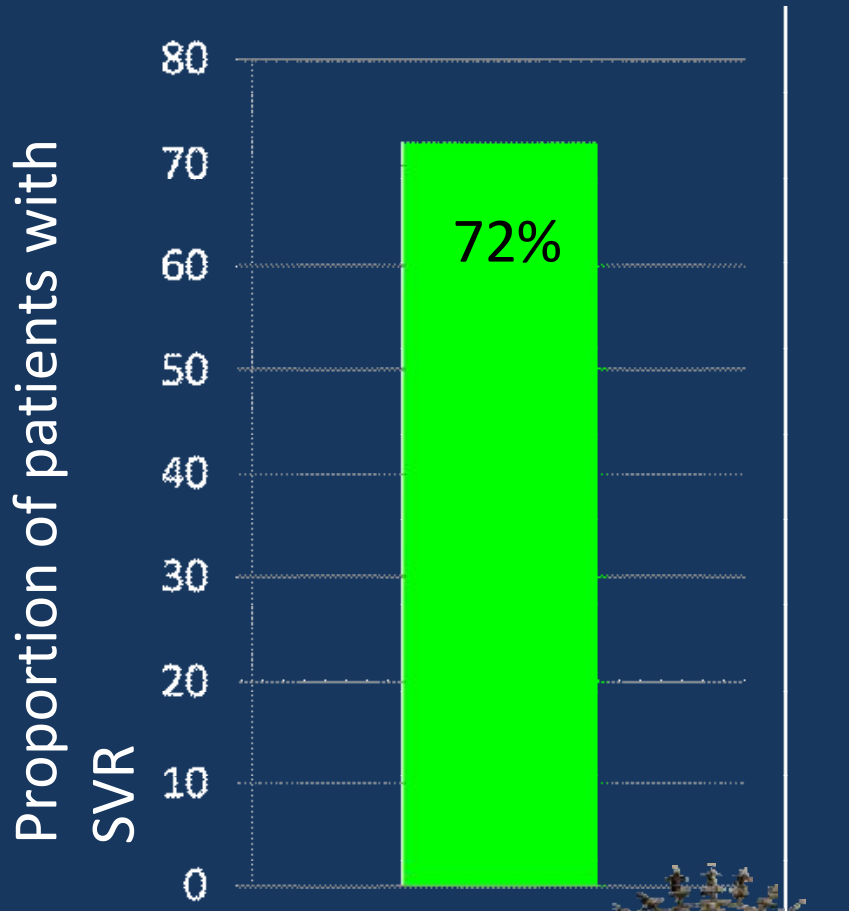
Outcome after discontinuation of 4-5 years of adefovir therapy (n:33)

Hadziyannis et al, Gastroenterology 2012





Predictors of HBsAg loss by MVA: High ALT, low EOT HBsAg, no retx

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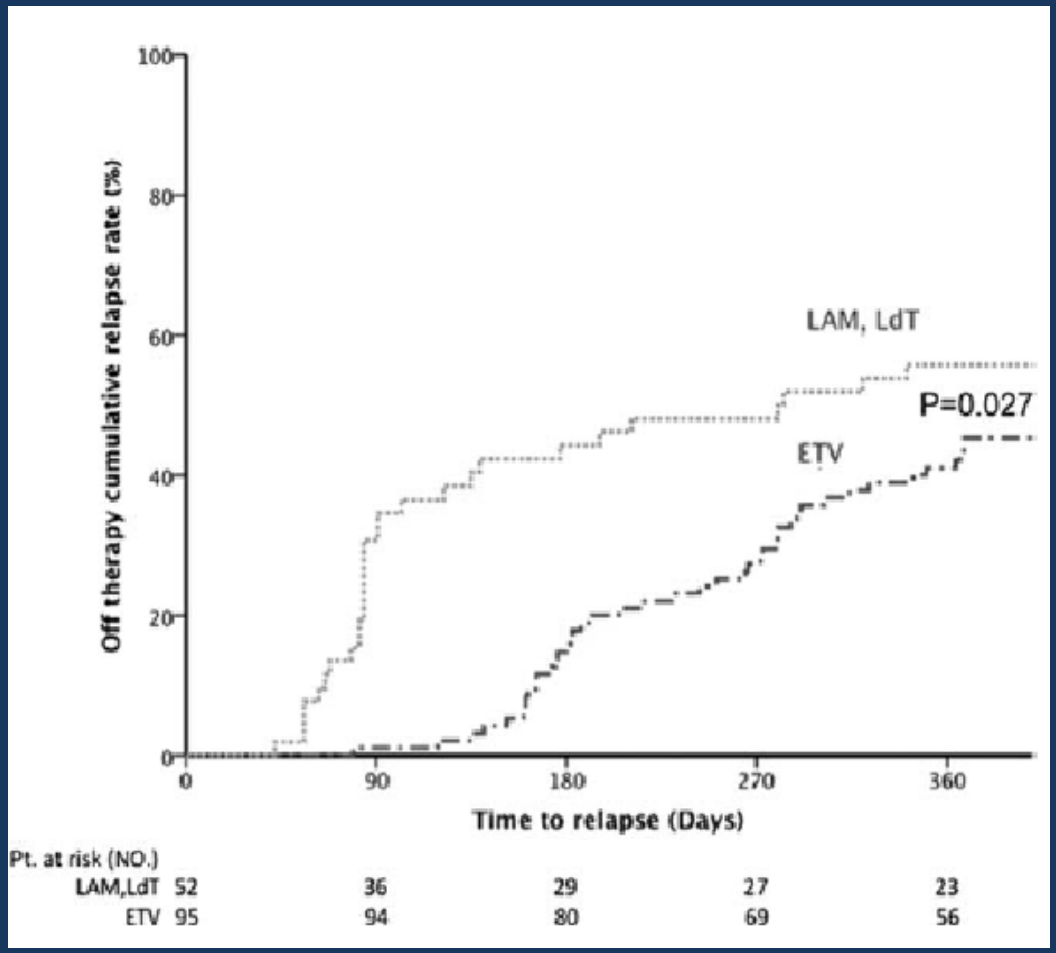
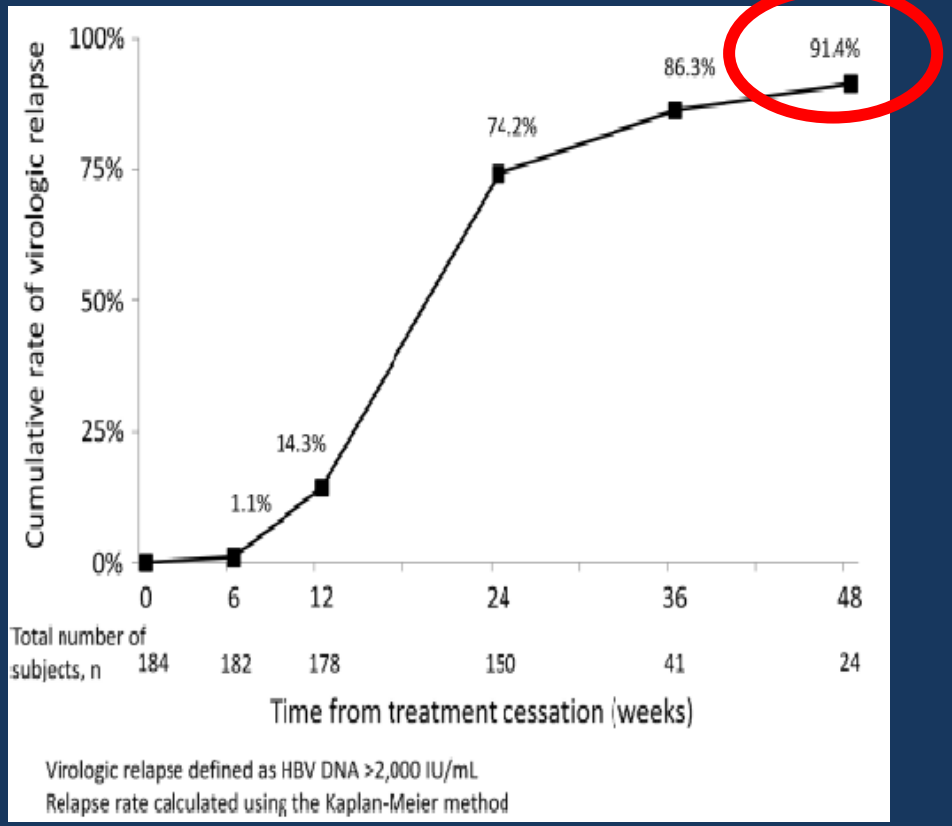
Cumulative relapse rates after tx dc in ETV vs LVD or LdT-treated patients (n=95)



Median tx duration:
2 years (50% > 2 years)
Relapse defined as
ALT >2xULN and
HBV DNA > 2000 IU/mL
Relapse rate: 45%
Median duration until relapse: 230 days
(74% after > 6 months)
HBsAg levels did not predict remission

Jeng WJ et al, Hepatology 2013; 58:1888-96

Cumulative relapse rates after 3 years of ETV treatment (n=184)



Patients had undetectable HBV DNA on 3 occasions 6 months apart

Mean tx duration: 3 ± 0.6 yrs.

Relapse defined as HBV DNA > 2000 IU/mL

Quantitative HBsAg did not predict relapse or remission

Use ETV indefinitely

Seto WK et al, Gut 2014

German Multicenter Study of tx dc in CHB

45 pts on LT TDF tx randomized to tx dc or continuation

19 of 21 of pts who dc tx had viral rebound

At week 48 3 pts restarted TDF

HBsAg levels declined in pts who stopped TDF but not in those who continued

Berg T et al, EASL 2015

Uzun sureli LVD tedavisinde LVD kesilmesi

23 hasta

8 hastada tekrar NA tx baslandi

15 hasta ilacsiz median 5 yildir takipte

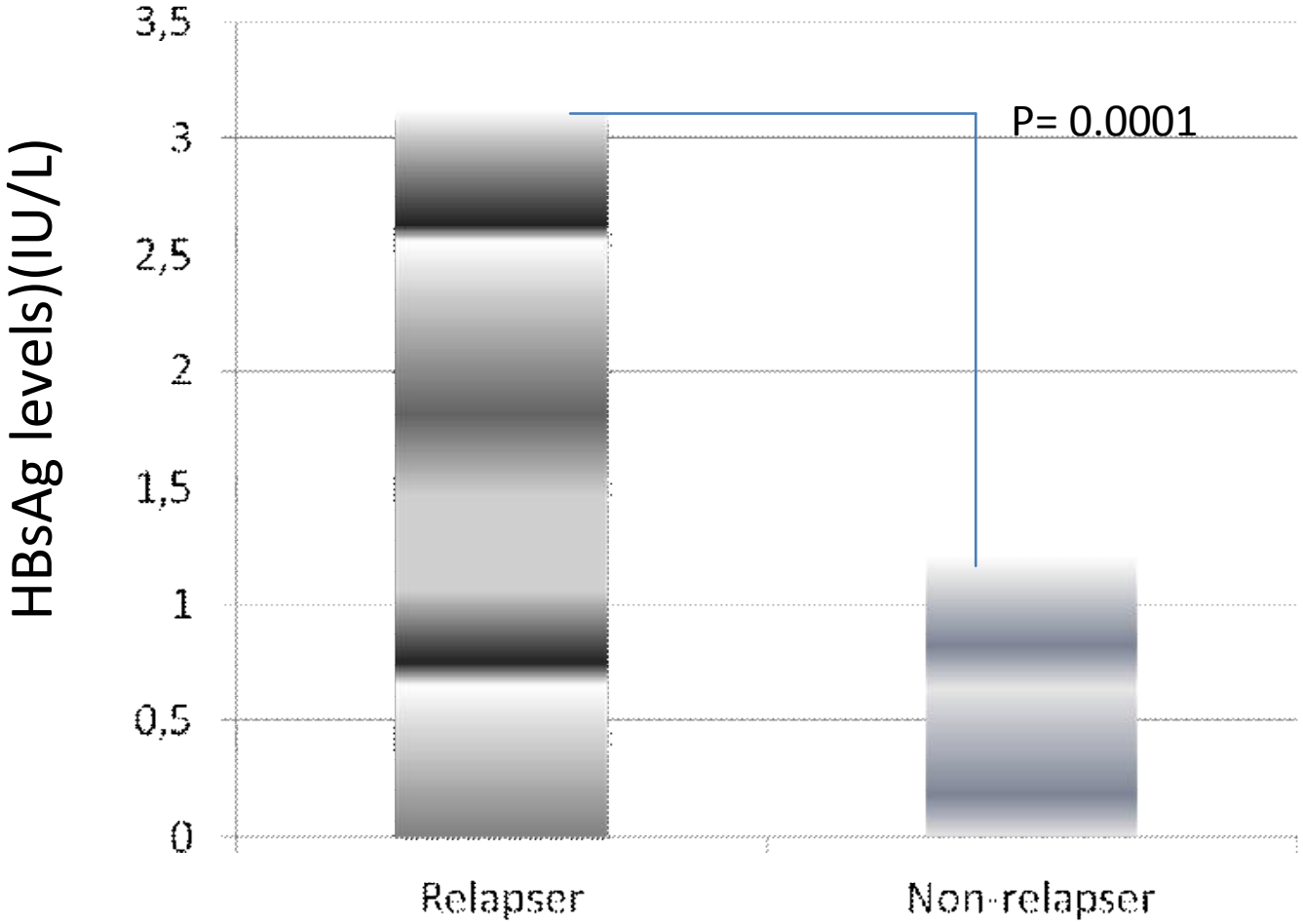


Figure 1A: Quantitative HBsAg levels after 6 years of follow-up of patients who did or did not develop viral relapse after treatment discontinuation

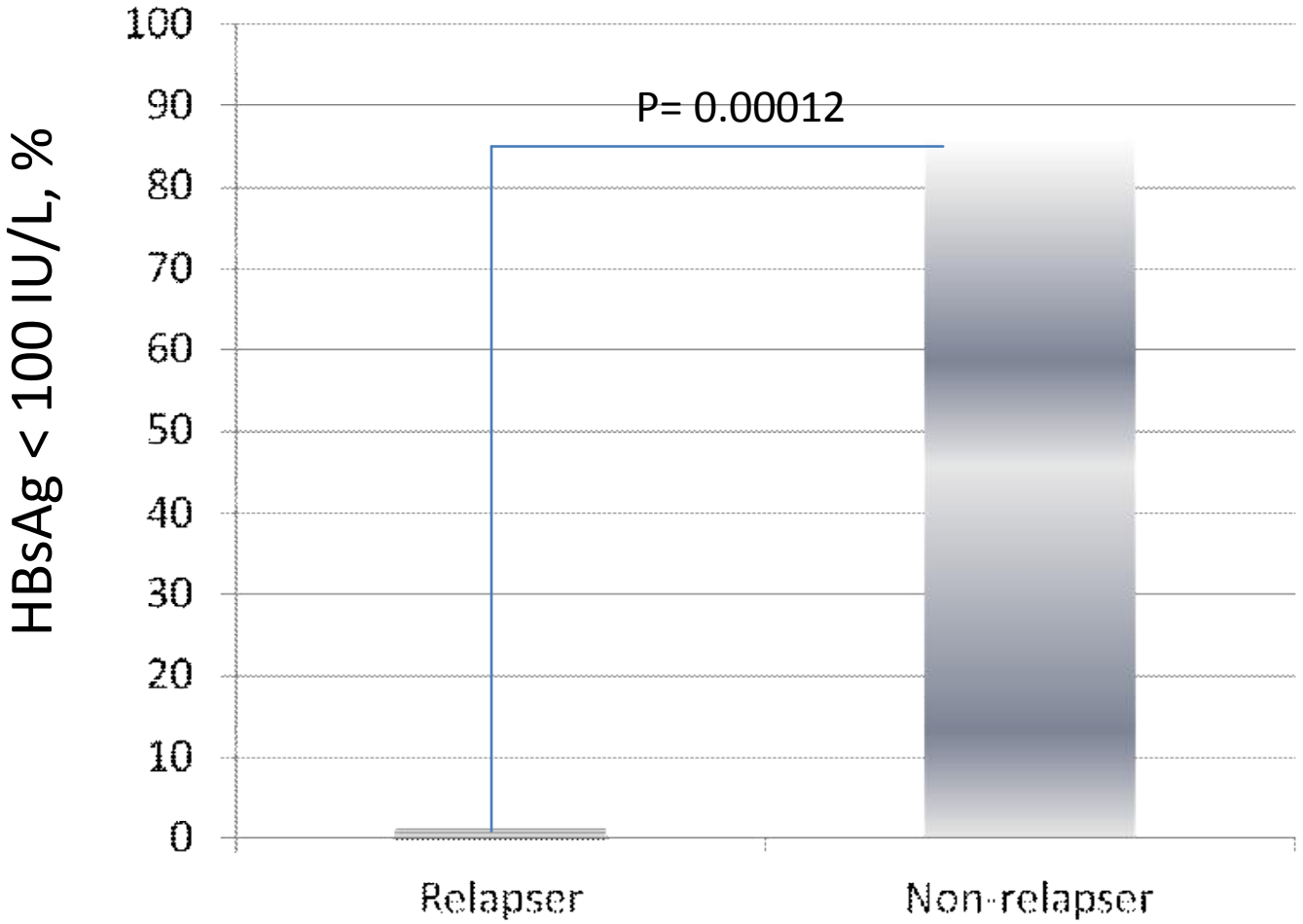
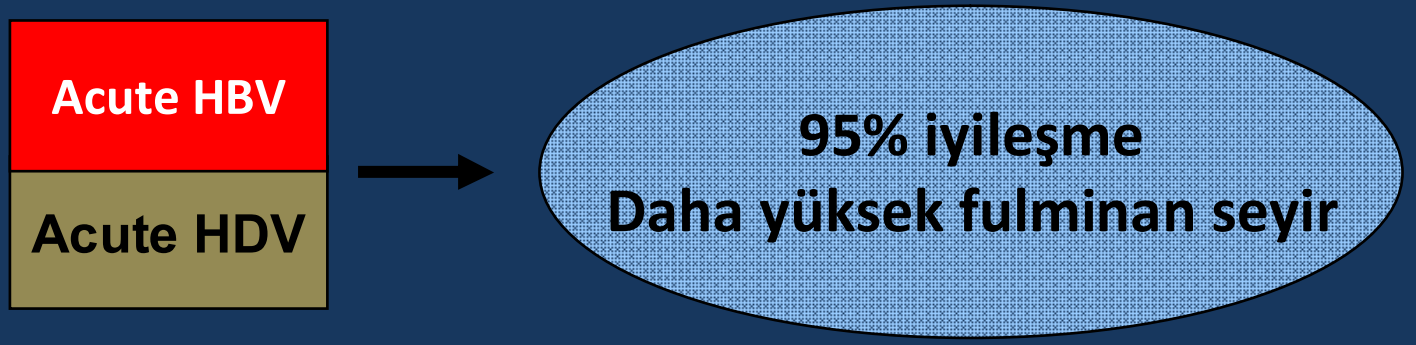


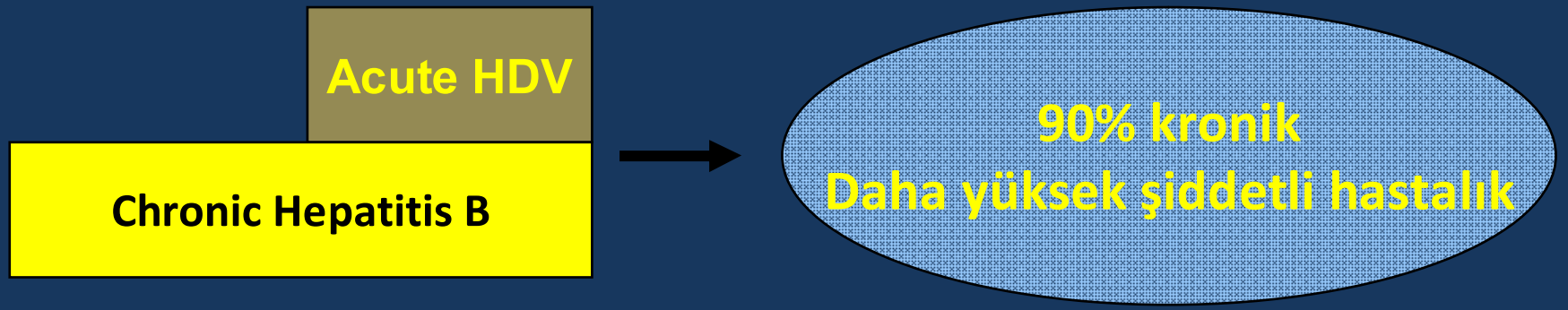
Figure 1A: Patients with low HBsAg levels after 6 years of follow-up of patients who did or did not develop viral relapse after treatment discontinuation

HDV

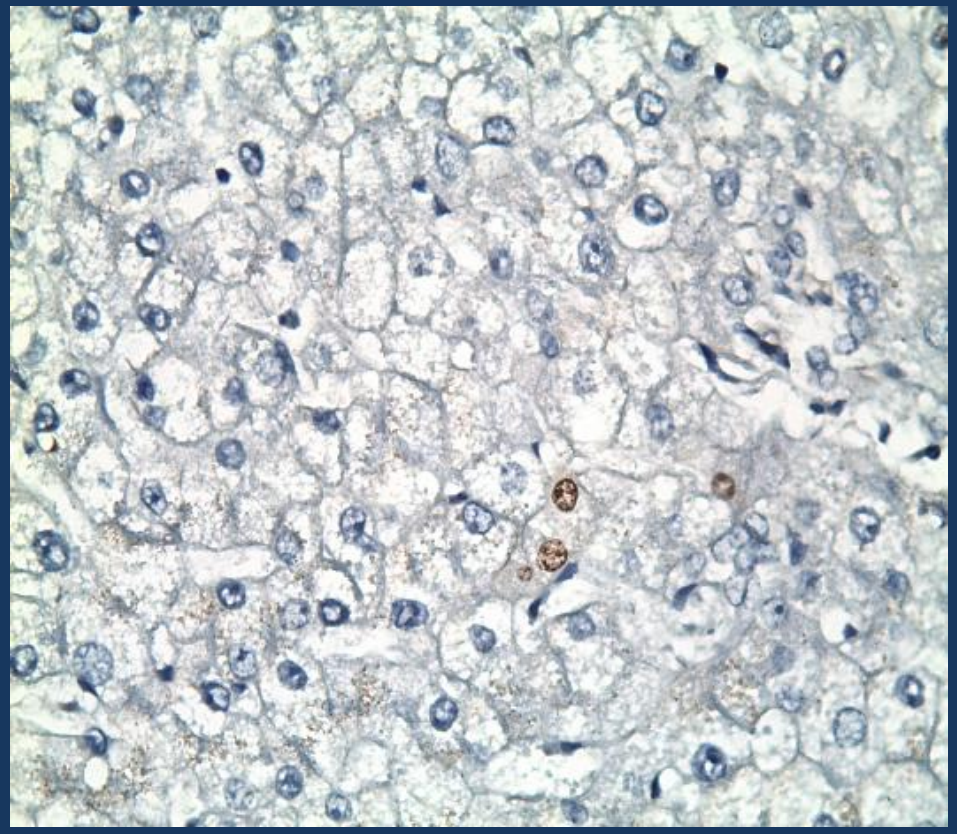
Eşzamanlı Ko-Infeksiyon



HDV Super-Infeksiyon



HBcAg IHC in CDH



Nuclear localization

No correlation with liver injury, even in HBV-HDV co-dominant cases

Kabaçam et al, Liver Int 2013

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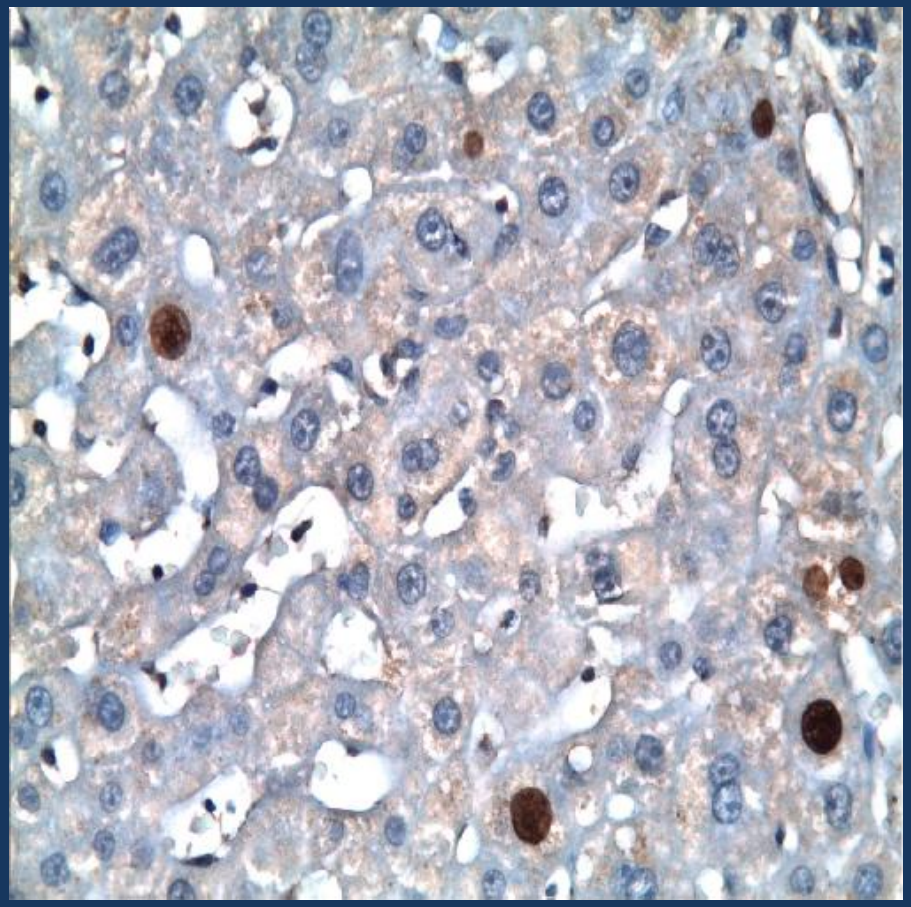
HDAg IHC in CDH



HDAg display (+) correlation with ALT and HBsAg levels

Kabaçam et al, Liver Int 2013

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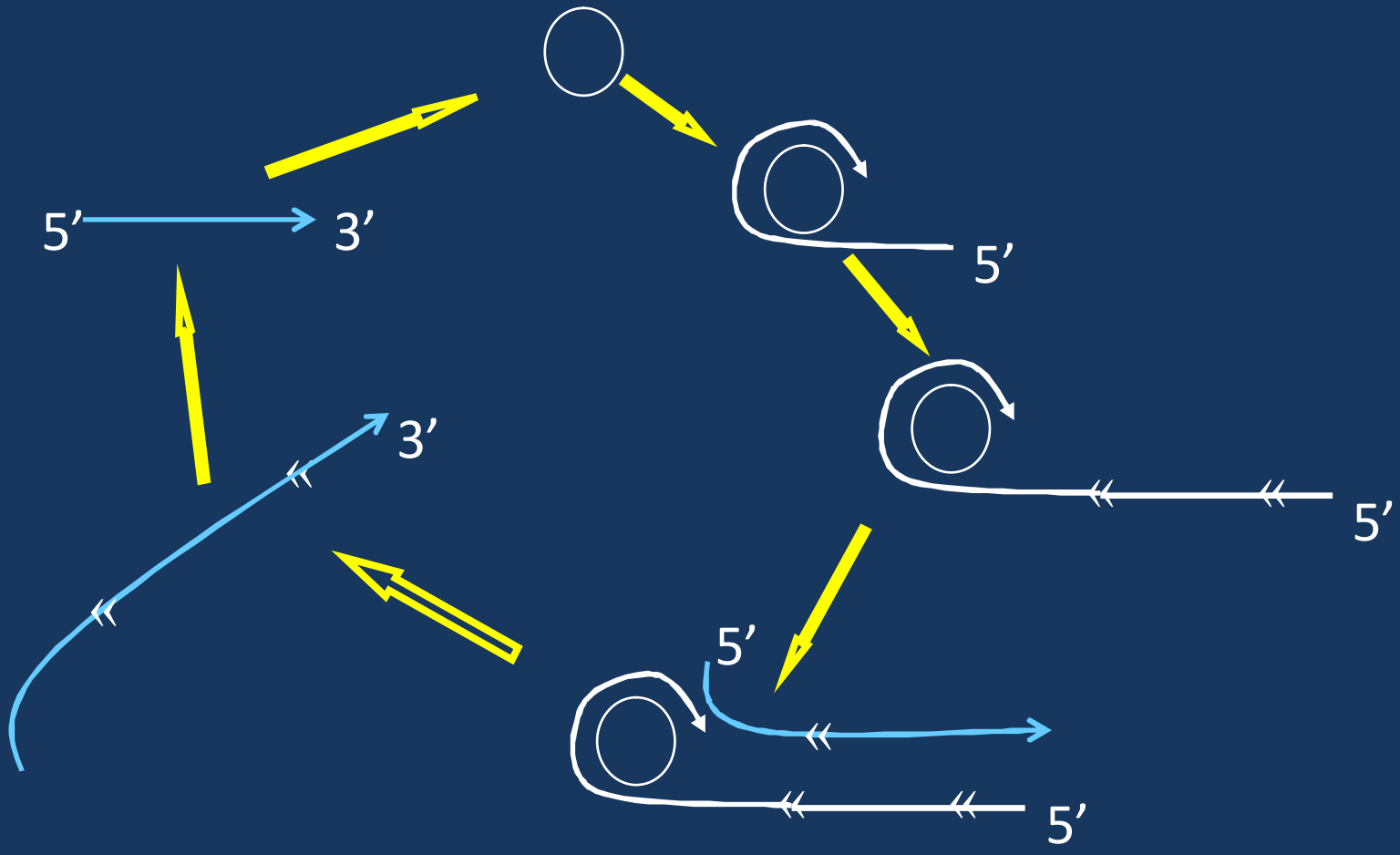
Delta virüs replikasyonu



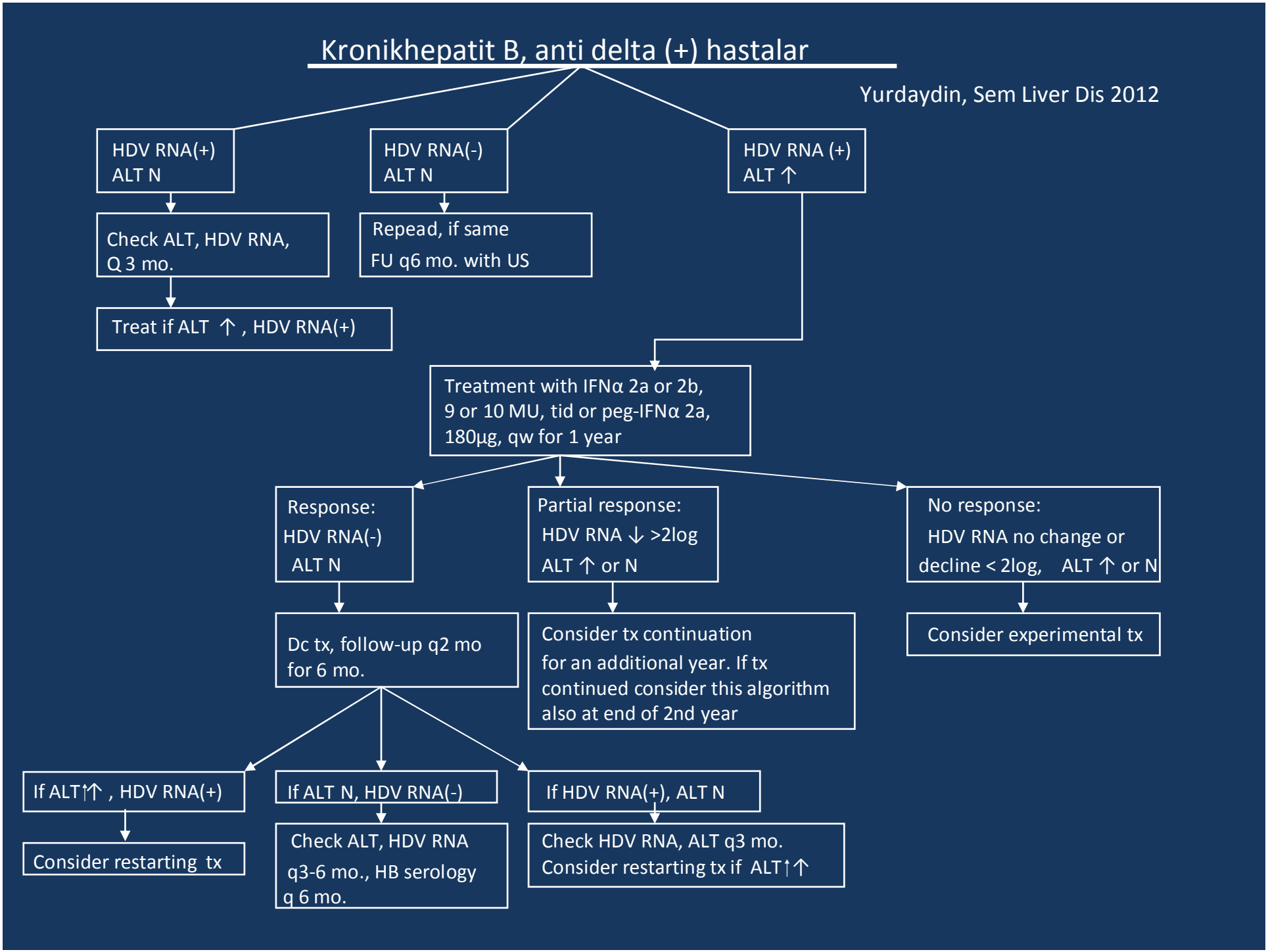
KHD'de Peg-IFN ile yapılan çalışmalar

Author	Treatment Schedule	N	EOT VR	EOFU VR
Niro et al[2006]	Peg-IFNα-2b, 1.5 µg/kg, qw ×18 m.	16	19%	25%
	Peg-IFNα-2b, 1.5 µg/kg, qw ×18 m. + Ribavirin, 1-1.2 g, qd ×12 months	22	9%	18%
Castelnau et al [2006]	Peg-IFNα-2b, 1.5 µg/kg, qw ×12 m.	14	57%	43%*
Erhardt et al [2006]	Peg-IFNα-2b, 1.5 µg/kg, qw ×12 m.	12	17%	17%
Wedemeyer et al[2011]	Peg-IFNα-2a, 180 µg, qw ×12 m.	29	24%	26%
	Peg-IFNα-2b, 180 µg, qw ×12 m. + Adefovir, 10 mg, qd	31	23%	31%
Gheorge et al [2011]	Peg-IFNα-2b, 1.5 µg/kg, qw ×12 m.	48	33%	25%
Örmeci et al [2011]	Peg-IFNα-2b, 1.5 µg/kg, qw ×24 m.	9	56%	44%
	Peg-IFNα-2b, 1.5 µg/kg, qw ×12 m.	7	57%	100%

Yurdaydin C, Sem Liver Dis 2012

Kronikhepatit B, anti delta (+) hastalar

Yurdaydin, Sem Liver Dis 2012



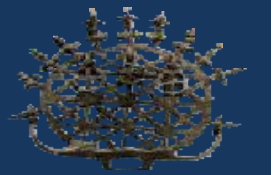
IFN treatment: Problems

- How can treatment efficacy be assessed?

  Best: HBsAg clearance
  Realistic: Posttreatment HDV RNA negative

- How consistent and reliable is a sustained virologic response?

  Not reliable



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DEVELOPMENT OF AN INTERNATIONAL REFERENCE PREPARATION FOR HEPATITIS D VIRUS RNA

Michael Chudy

Paul-Ehrlich-Institut
Federal Institute for Vaccines and Biomedicines

WHO Collaborating Centre for Quality Assurance of Blood Products and *in vitro* Diagnostic Devices

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EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 21 to 25 October 2013

Collaborative Study to Establish a World Health Organization International Standard for Hepatitis D Virus RNA for Nucleic Acid Amplification Technique (NAT)-Based Assays

Michael Chudy[1], Kay-Martin Hanschmann[1], Mithat Bozdayi[2], J. Kreß[1], C. Micha Nübling[1] and the Collaborative Study Group*

Summary

This report describes the World Health Organization (WHO) project to develop an international standard for hepatitis D virus (HDV) RNA for the use with nucleic acid amplification technique (NAT)-based assays. The candidate standard is a lyophilized preparation of HDV genotype 1 strain, obtained from a clinical plasma specimen, diluted in human negative plasma. Fifteen laboratories from nine countries participated in a collaborative study to evaluate the candidate preparation (sample 1 and sample 2) alongside the corresponding liquid-frozen bulk material (sample 3) and a liquid frozen unprocessed HDV RNA positive plasma specimen (sample 4) using their routine HDV NAT. The results of the study indicate the suitability of the candidate material of the HDV genotype 1 (sample1 and sample 2) as the proposed \1st WHO standard for HDV RNA. It is therefore proposed that the candidate material (PEI code 7657/12) is established as the 1st WHO International Standard for HDV RNA for NAT-based assays with an assigned potency of 5.75×10^5 International Units (IU) when reconstituted in 0.5 mL of nuclease-free water. On-going real-time and accelerated stability studies of the proposed International Standard indicate that the preparation is stable and suitable for long-term use at the proposed storage conditions.

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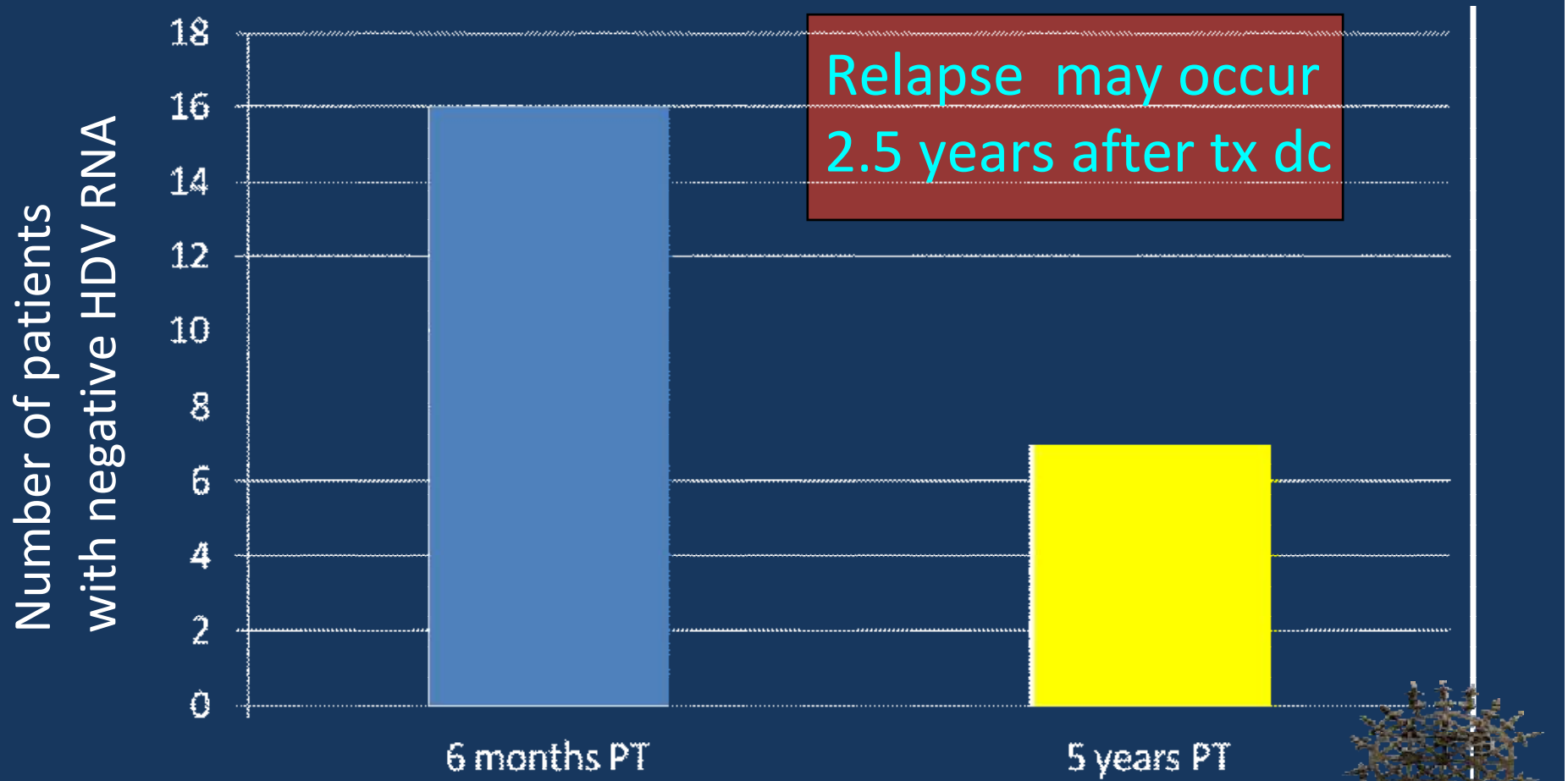
Is 6 months treatment-free follow-up a reliable surrogate marker of tx efficacy?



Heidrich et al, Hepatology 2014, Keskin O et al, manuscript in preperation

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IFN treatment: Problems

What is the optimal duration of tx?

Of note, no published study so far has shown that prolonging treatment is better than one year treatment …

but the quality of those studies were in general poor

Lack of evidence is not equal to lack of efficacy

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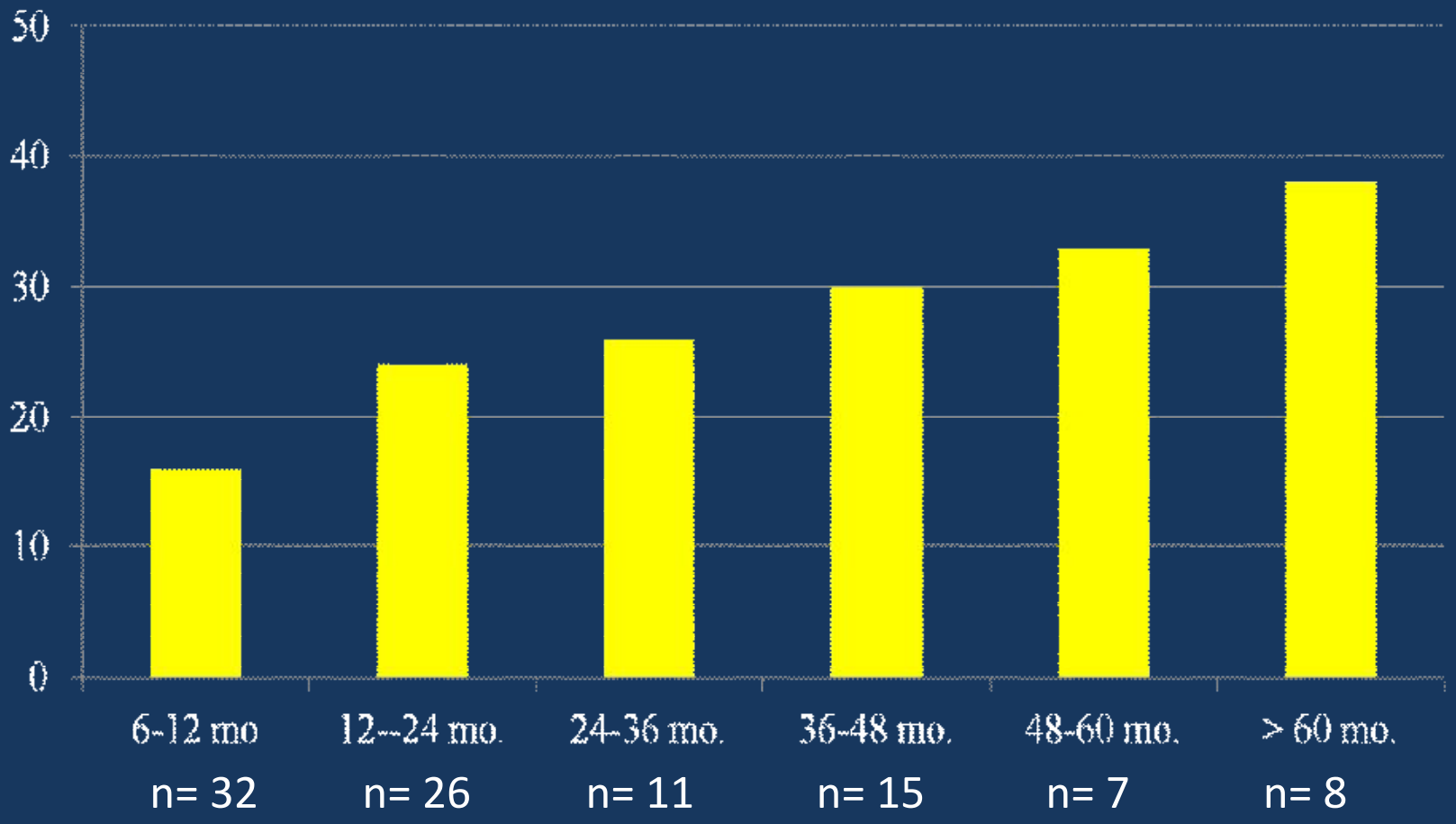
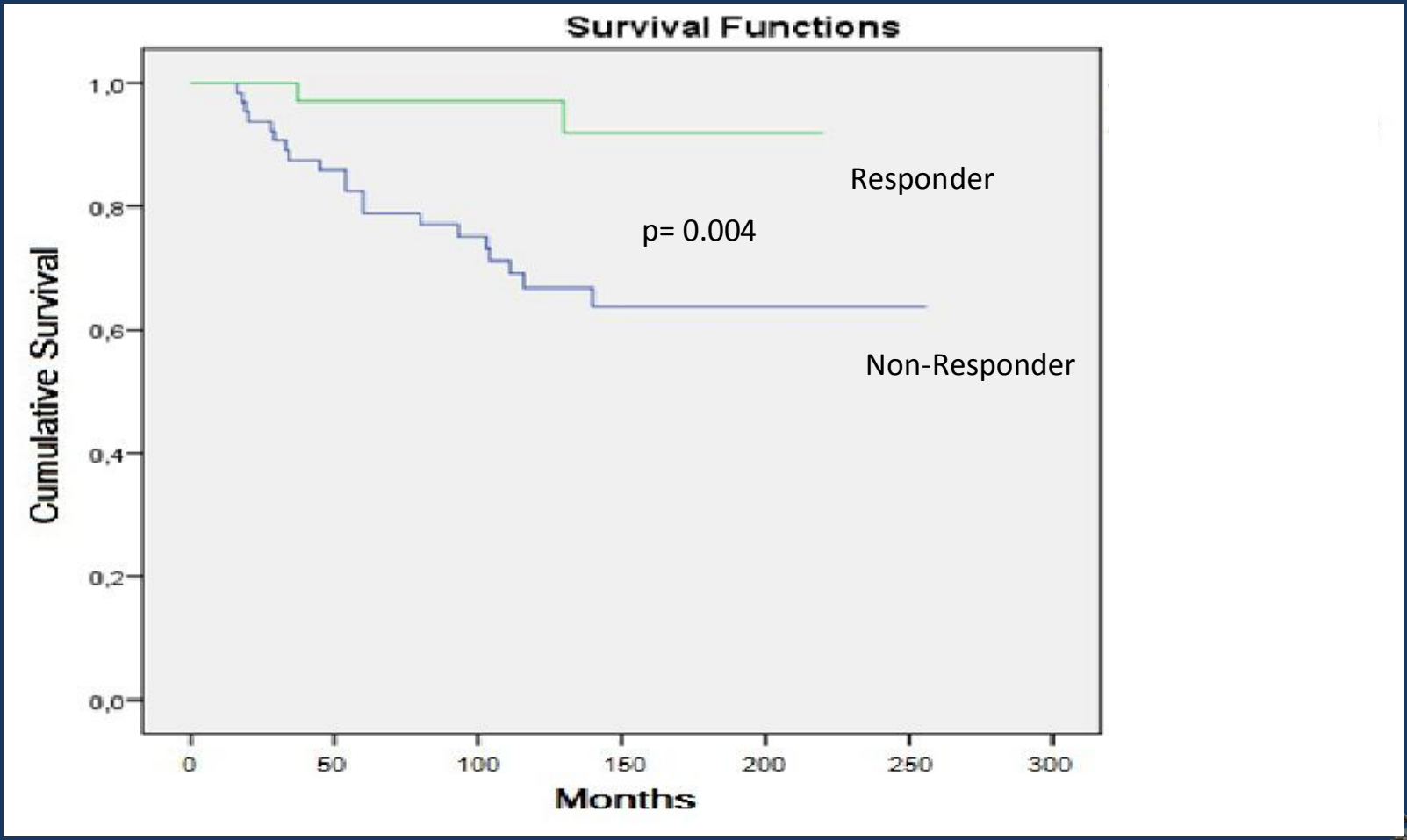
Cumulative probability of maintained virologic response with different durations of IFN tx



Keskin O et al. AASLD 2015

Mortality/ liver transplantation comparison of pts with vs without durable VR



Keskin O et al, manuscript in preperation

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IFN treatment: Problems

Can response to treatment be predicted?

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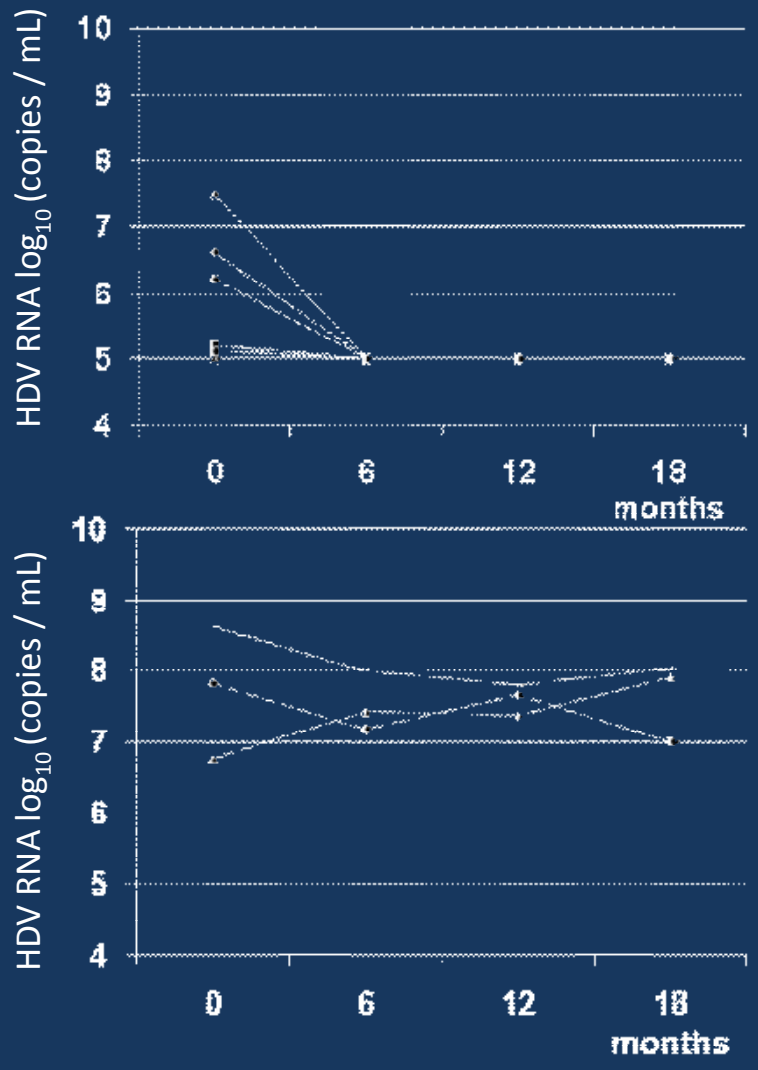
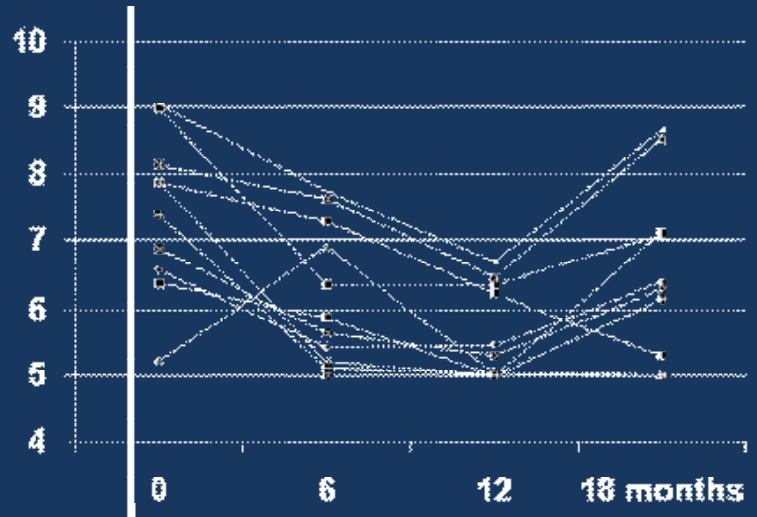
HDV RNA levels in INF early responders

Yurdaydin et al, J Viral Hepat 2008





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Multivariate logistic regression analysis for predicting end of treatment and post- treatment week 24 virologic response

End of treatment response:

	OR	95% CI	p value
HDV RNA week 24	1.627	1.070 – 2.474	0.023
Baseline HAI	0.586	0.366 – 0.937	0.026

Post-treatment week 24 response:

HDV RNA week 24	2.538	1.347 – 4.782	0.004

Keskin O, et al, Clin Gastroenterol Hepatol 2015

Ankara Uni.

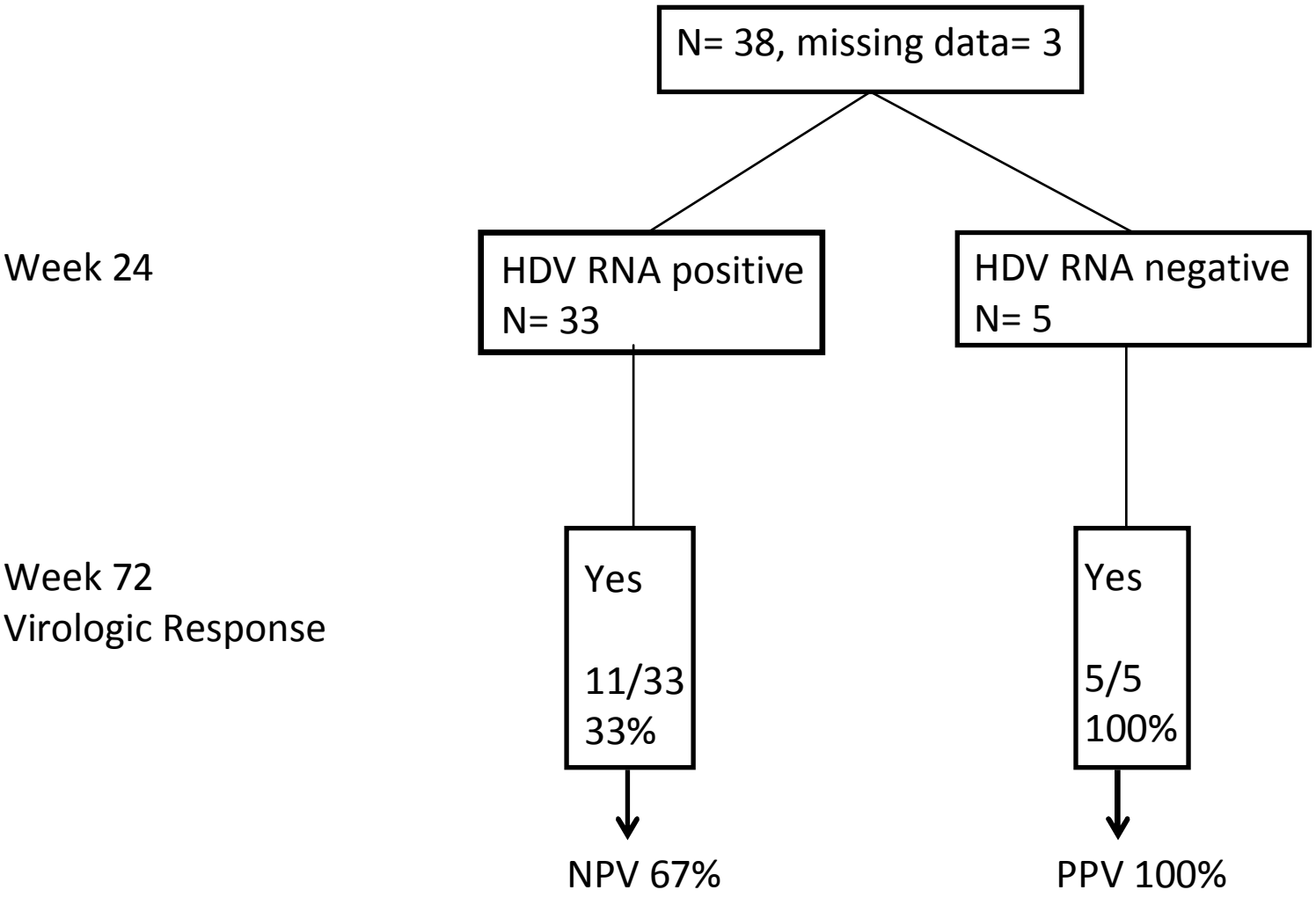


Figure 2: Predictive value of on-treatment week 24 undetectable HDV RNA for post-treatment week 24 virologic response

Keskin O, et al, Clin Gastroenterol Hepatol 2015

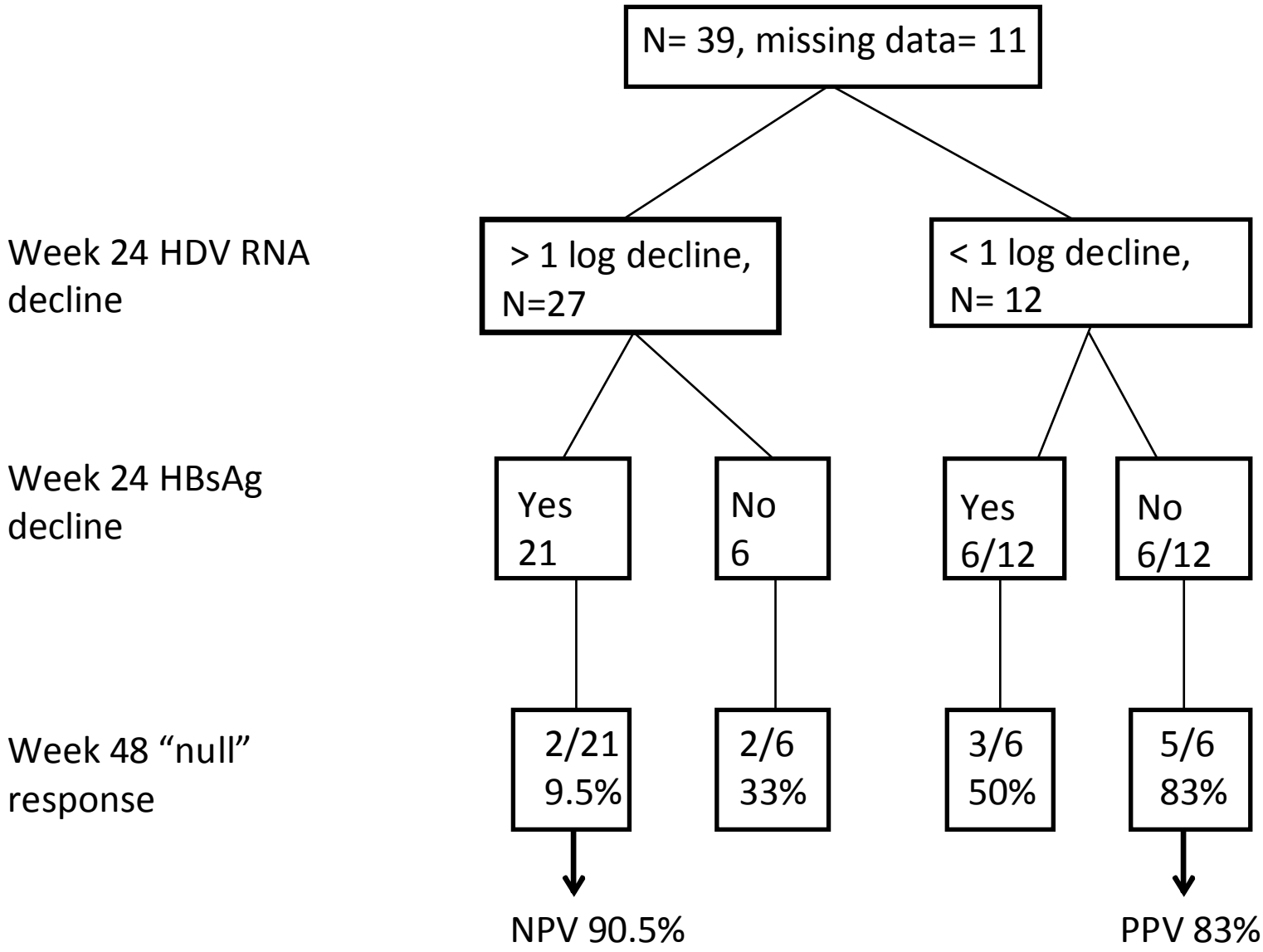
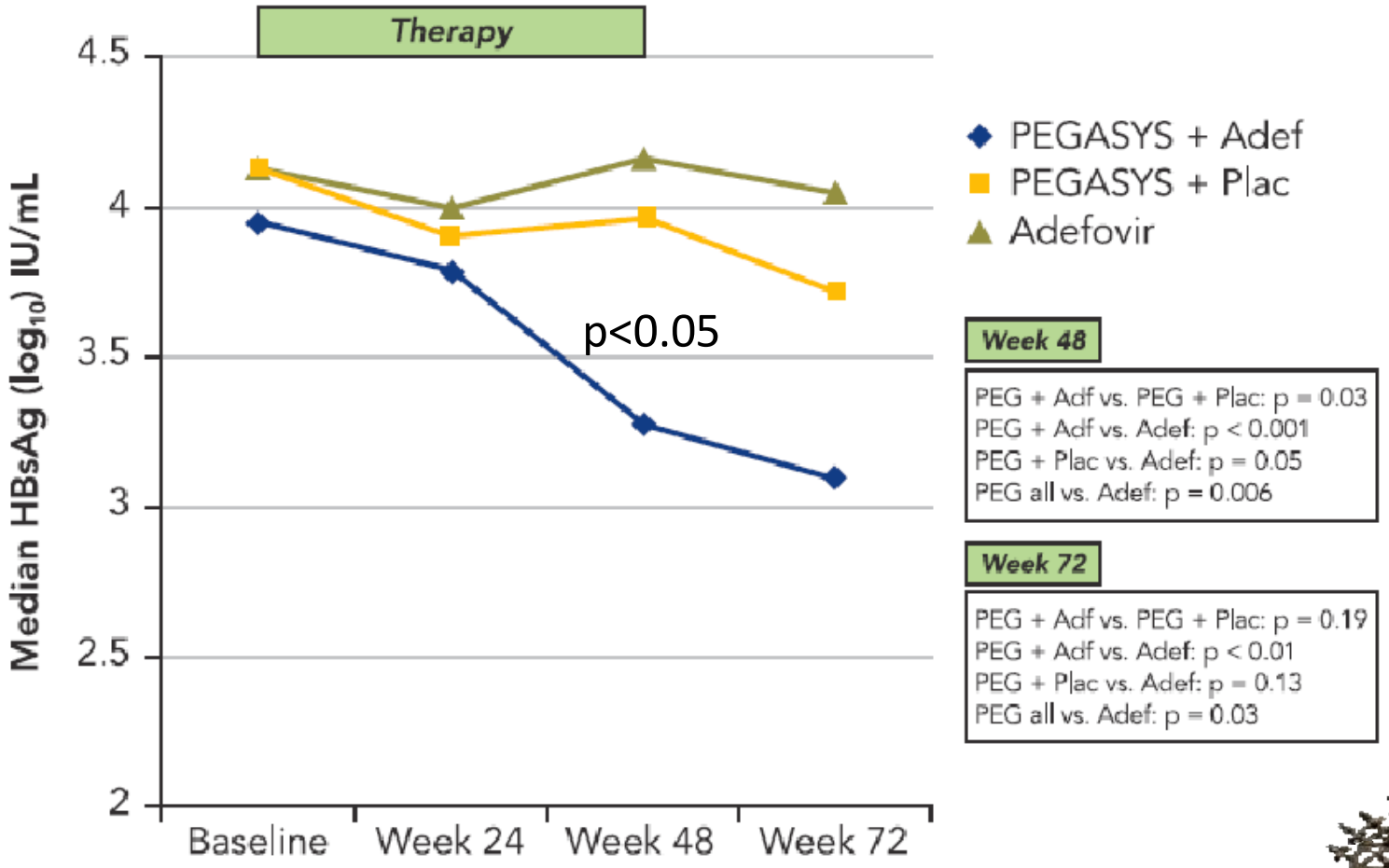


Figure 2D: Predictive value of on-treatment week 24 HDV RNA and HBsAg levels For EOT virologic "null response" (<1 log decline of HDV RNA at EOT)

Keskin O, et al, Clin Gastroenterol Hepatol 2015

HBsAg Levels

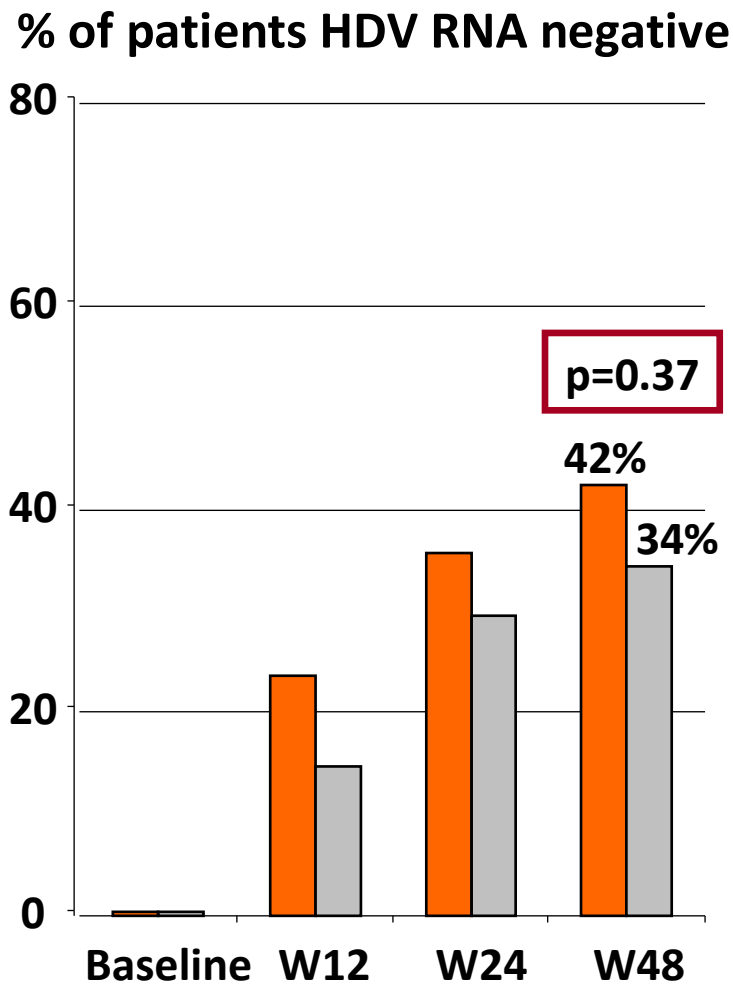


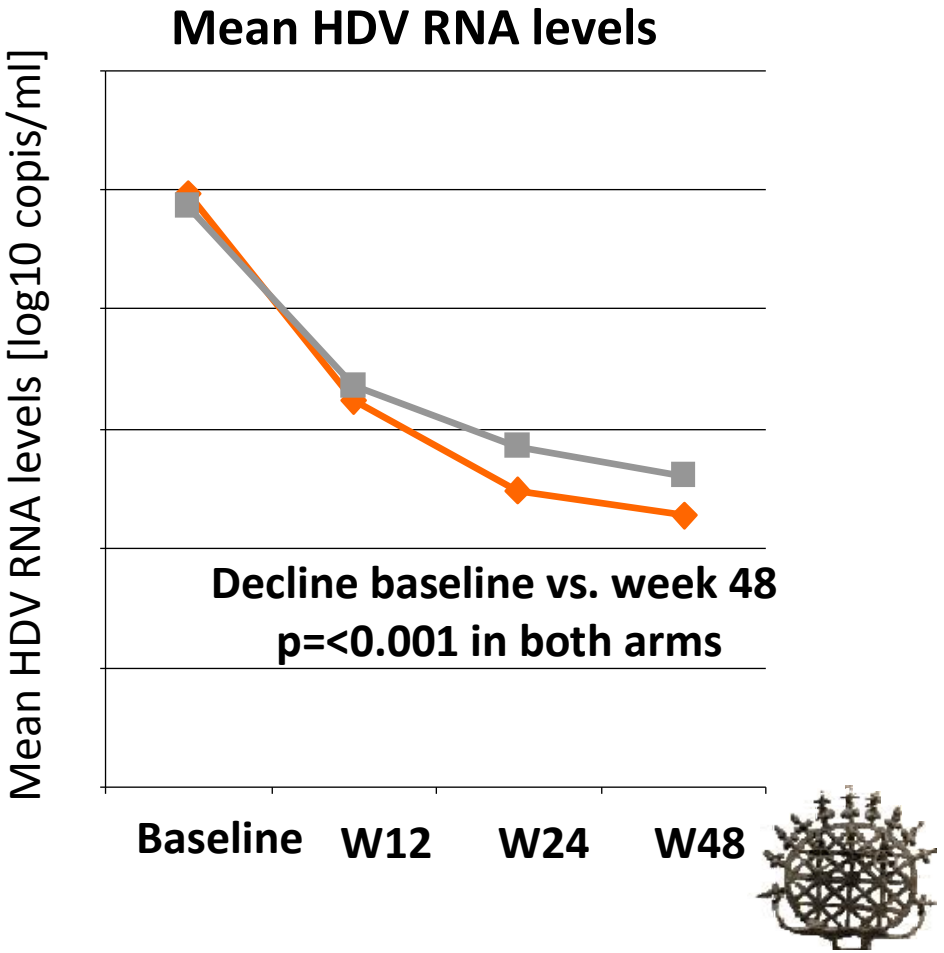
Wedemeyer, Yurdaydin et al, NEJM 2011

HDV RNA response in the HIDIT-2 Study

PEG-IFNa-2a + Tenofovir

PEG-IFNa-2a +Placebo



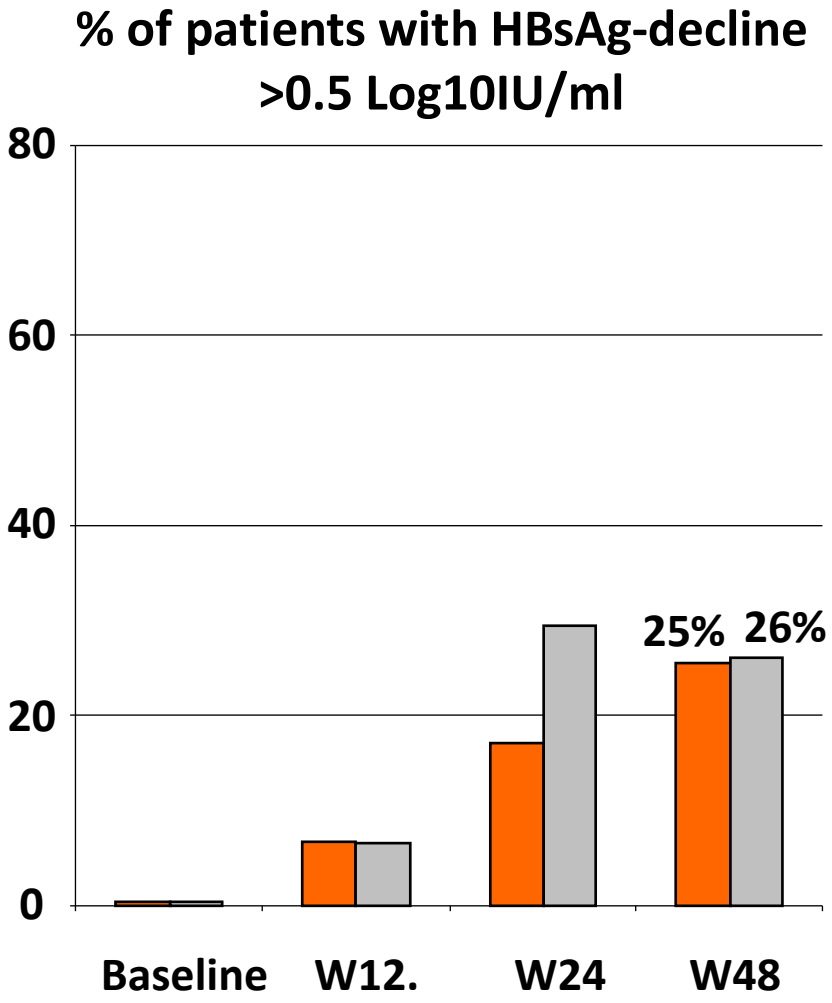


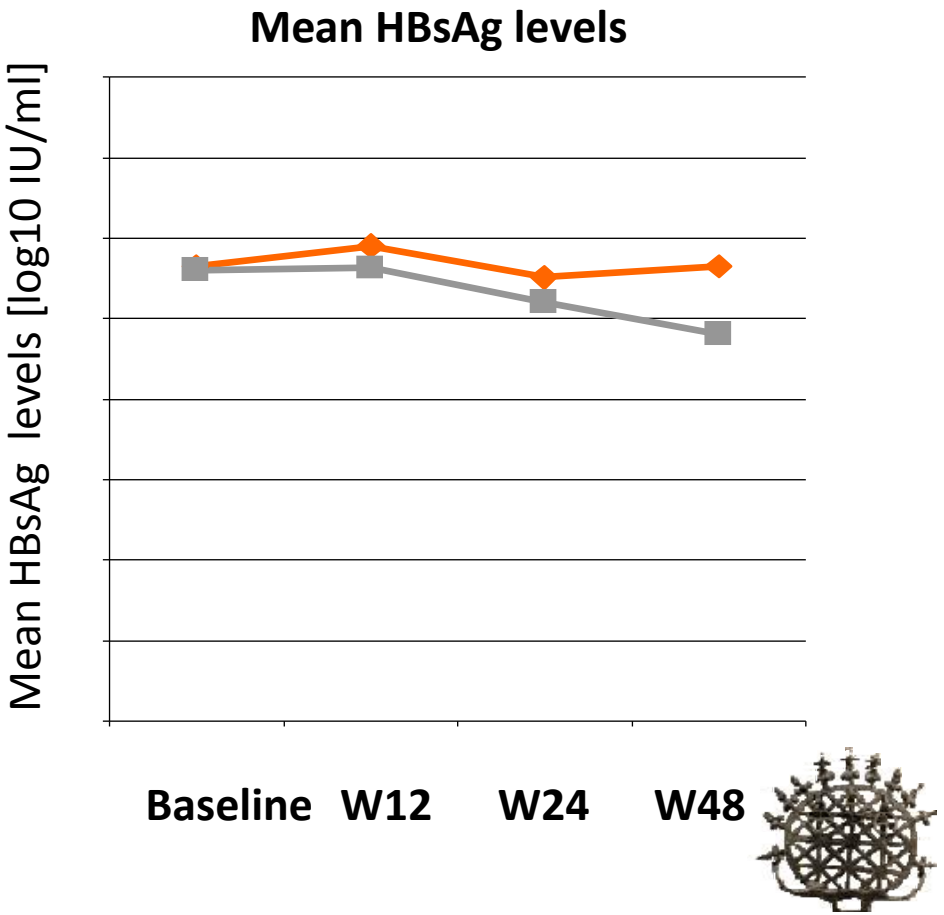
Yurdaydin et al, AASLD 2012

HBsAg response in the HIDIT-2 Study

PEG-IFNa-2a + Tenofovir

PEG-IFNa-2a +Placebo





Yurdaydin et al, AASLD 2012

NUCLEOSIDE ANALOGUES IN CHRONIC DELTA HEPATITIS

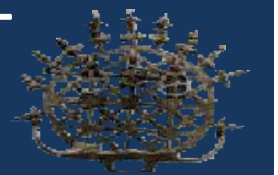
LAMIVUDINE
FAMCICLOVIR
ADEFOVIR DIPIVOXIL
ENTECAVIR
CLEVUDINE

6-12 months
tx data reported
NO EFFECT

TENOFOVIR

Median Tx duration:
6.1 years- EFFECTIVE

Yurdaydin et al, J Hepatol 2002; Yurdaydin et al J Viral Hepat 2008; Wedemeyer et al, NEJM 2011; Kabacam et al Clin Infect Dis 2012; Sheldon et al Antiviral Ther 2008



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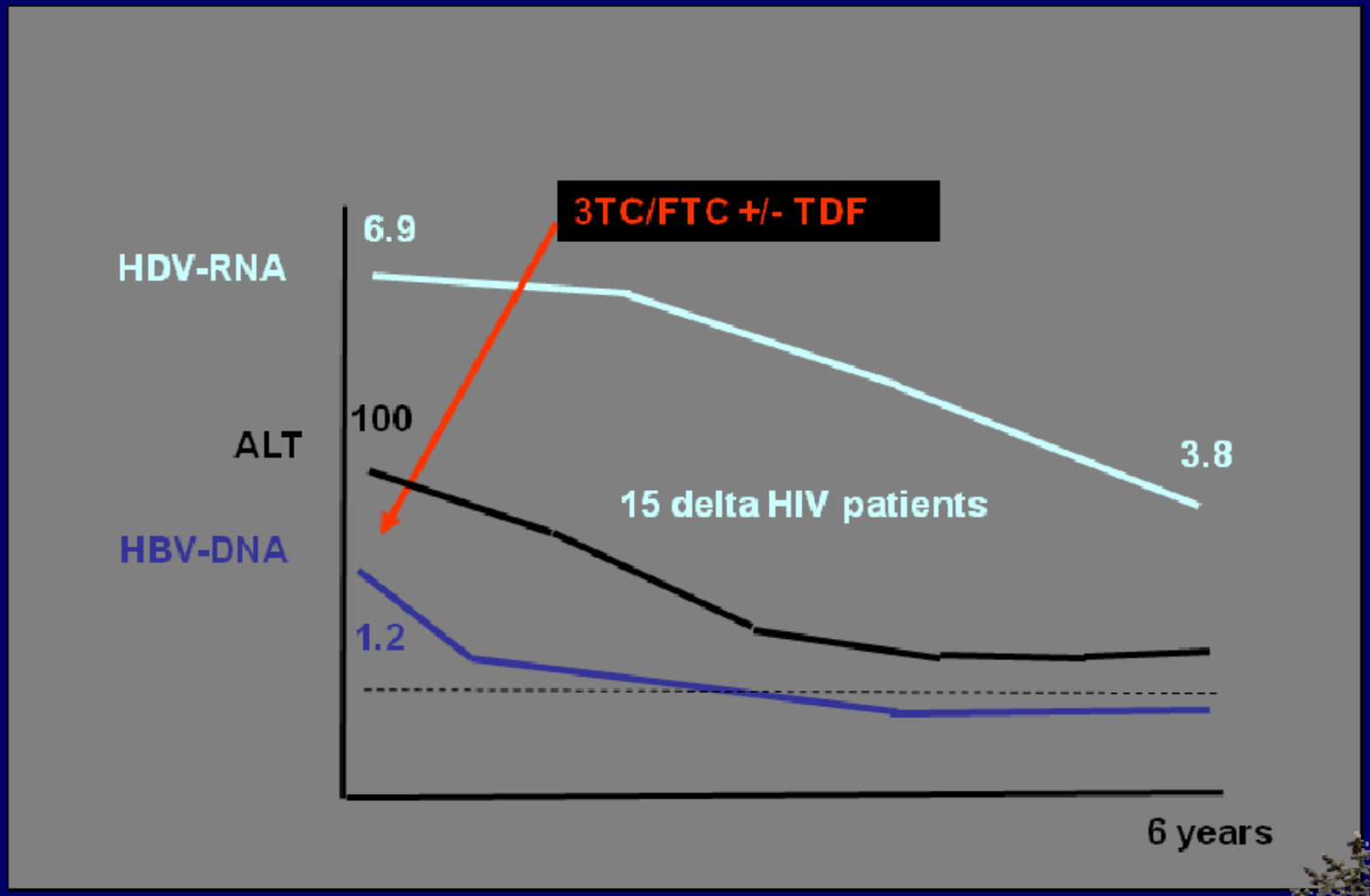
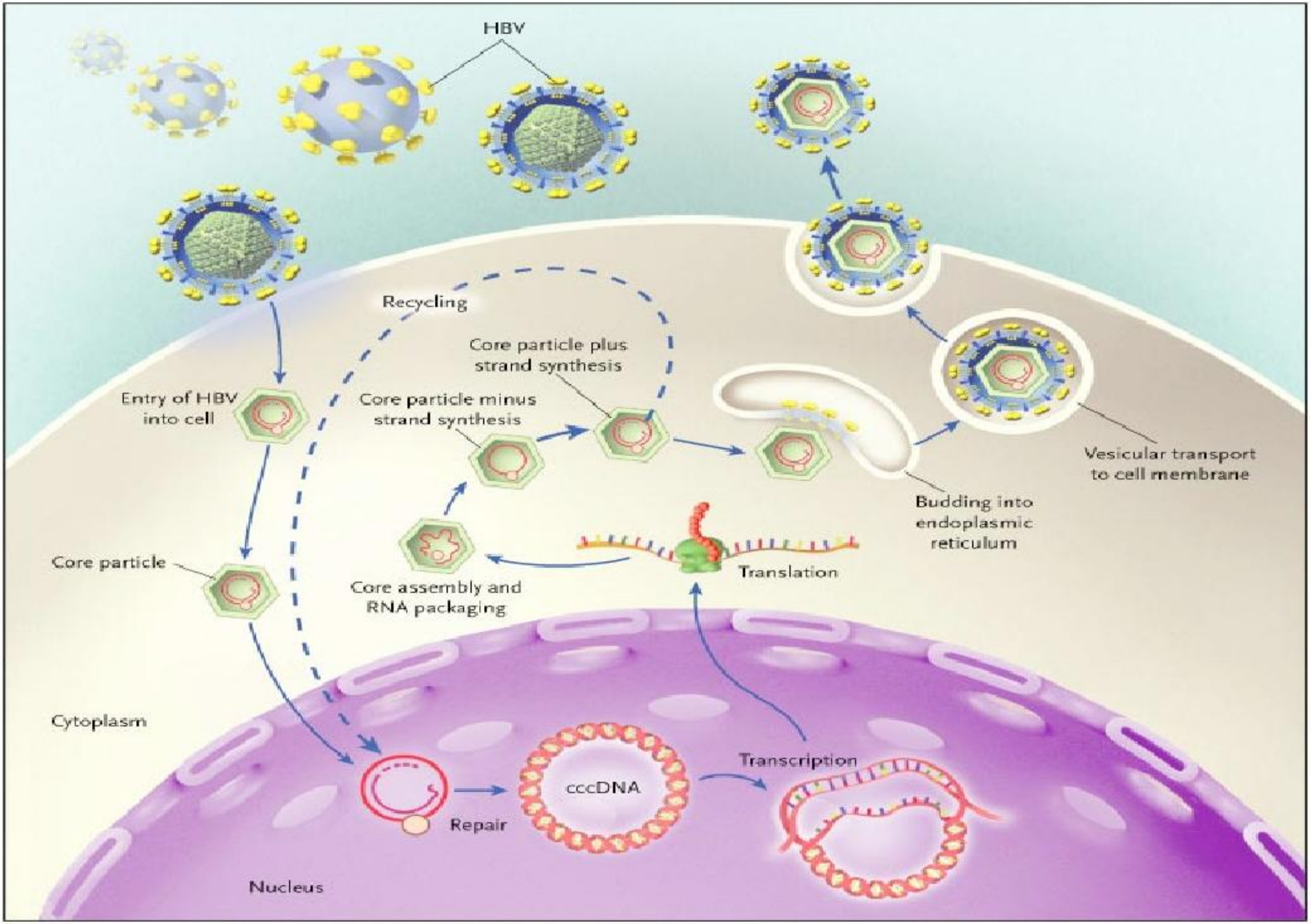
Nucleos(t)ides for HDV in HIV



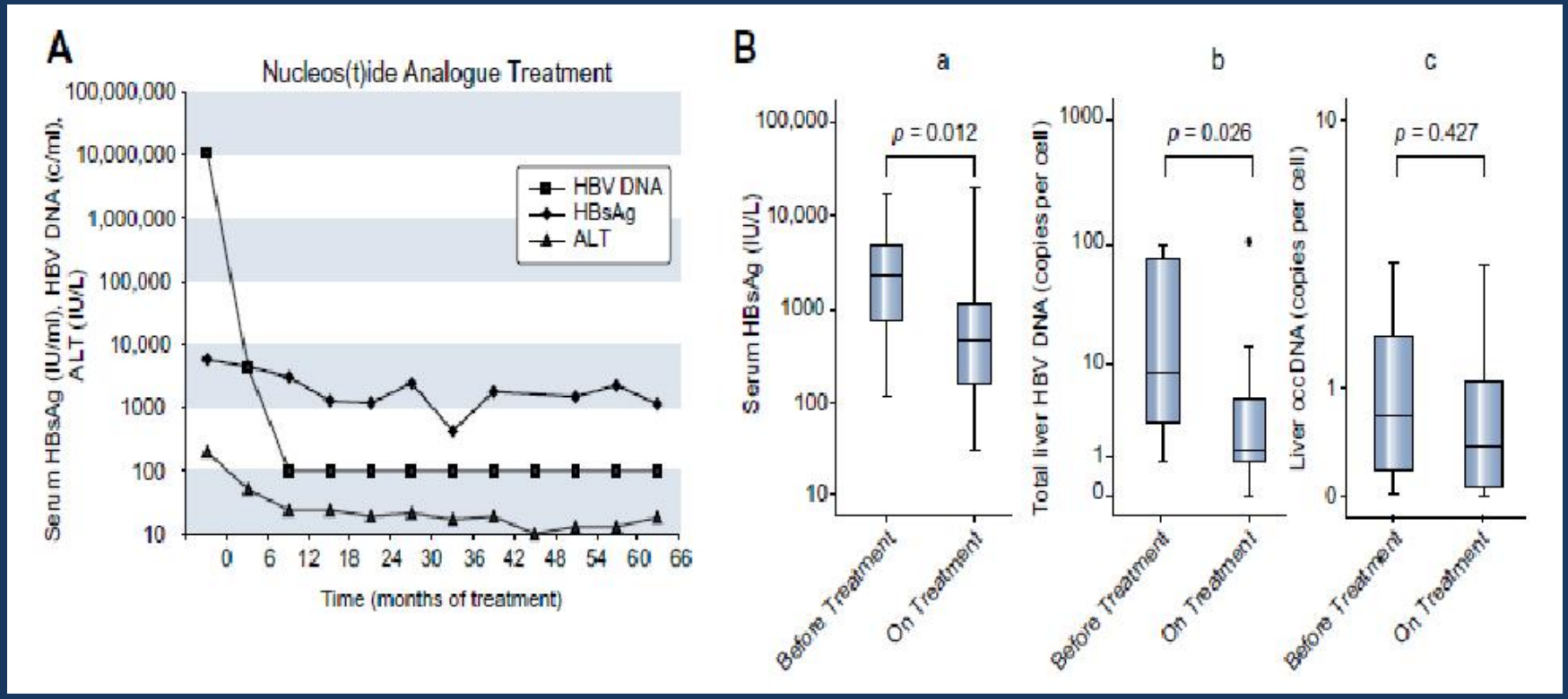
Sheldon et al. Antivir Ther 2008; 13: 97-102.

Ankara Uni.



Ganem & Prince, NEJM 2004

Effect of prolonged NA tx on HBsAg levels



Manesis et al, J Hepatol 2011

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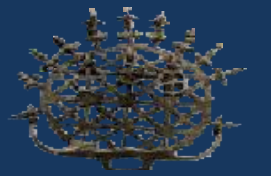
Effect of the immune status on HBsAg levels in patients with HIV-HBV co-infection

	All (n=51)	*HBsAg decrease[a] (n=25)*	*No HBsAg decrease (n=16)*	p *Value[b]*
Age, years	49.0±1.40	49.4±1.88	48.3±3.09	0.74
HBsAg, $\log_{10}$ IU/mL	3.57±0.17	3.49±0.20	3.87±0.17	0.34
Follow-up, months	43.3±3.84	44.1±5.70	43.5±6.30	0.76
HIV-RNA, copies/mL	2.55±0.18	2.67±0.27	2.25±0.27	0.58
Baseline CD4 count (cells/μL)	326±31	401±42	265±50	0.03
Baseline CD8 count (cells/μL)	1097±84	1130±106	1046±187	0.44
Last follow-up CD4 count (cells/μL)	411±32	506±39	310±51	0.01
Last follow-up CD8 count (cells/μL)	972±77	920±89	992±170	0.66
ART, n (%)	43 (84)	25 (100)	16 (100)	-
TDF, n (%)	36	22 (88)	12 (75)	0.28
AIDS, n (%)	19 (37)	9 (36)	6 (37)	0.92
HBeAg-positive, n (%)	17 (33)	8 (32)	6 (37)	0.90
HBV-DNA $\log_{10}$ IU/mL	3.64±0.60	4.08±0.92	4.44±1.13	0.86
ALT U/mL	58±10	63±13	46±11	0.26

Arendt et al, Viral Immunol 2012



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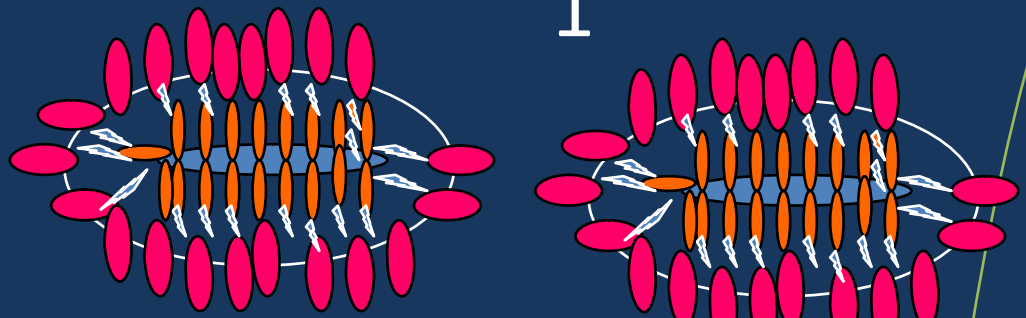
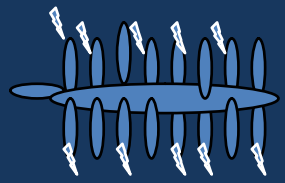
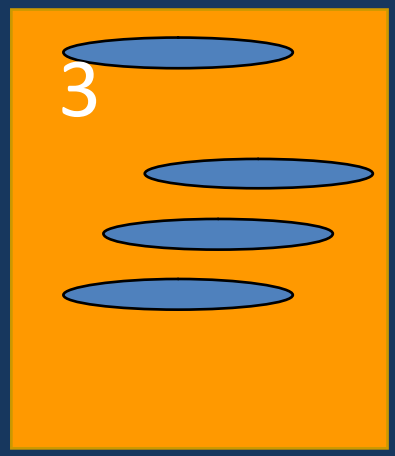
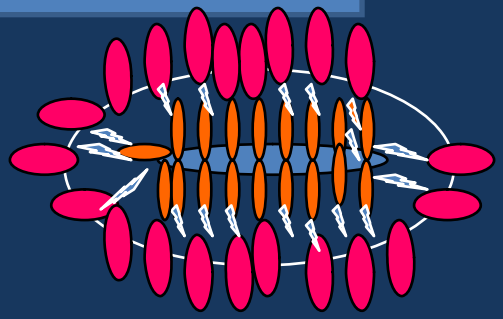
THE HDV LIFE CYCLE



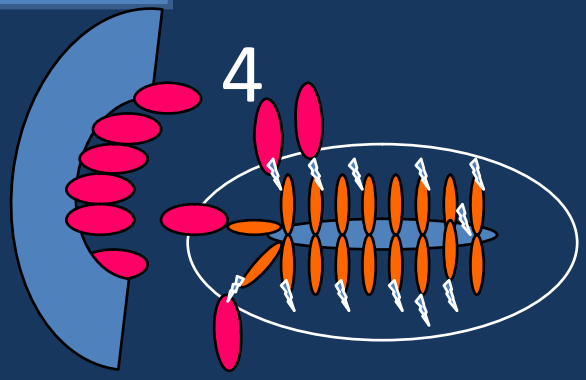


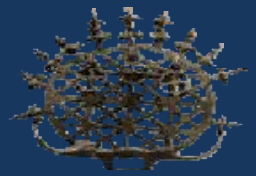


Hepatocyte entry inhibitors
TLR-9 agonists



Prenylation inhibitors





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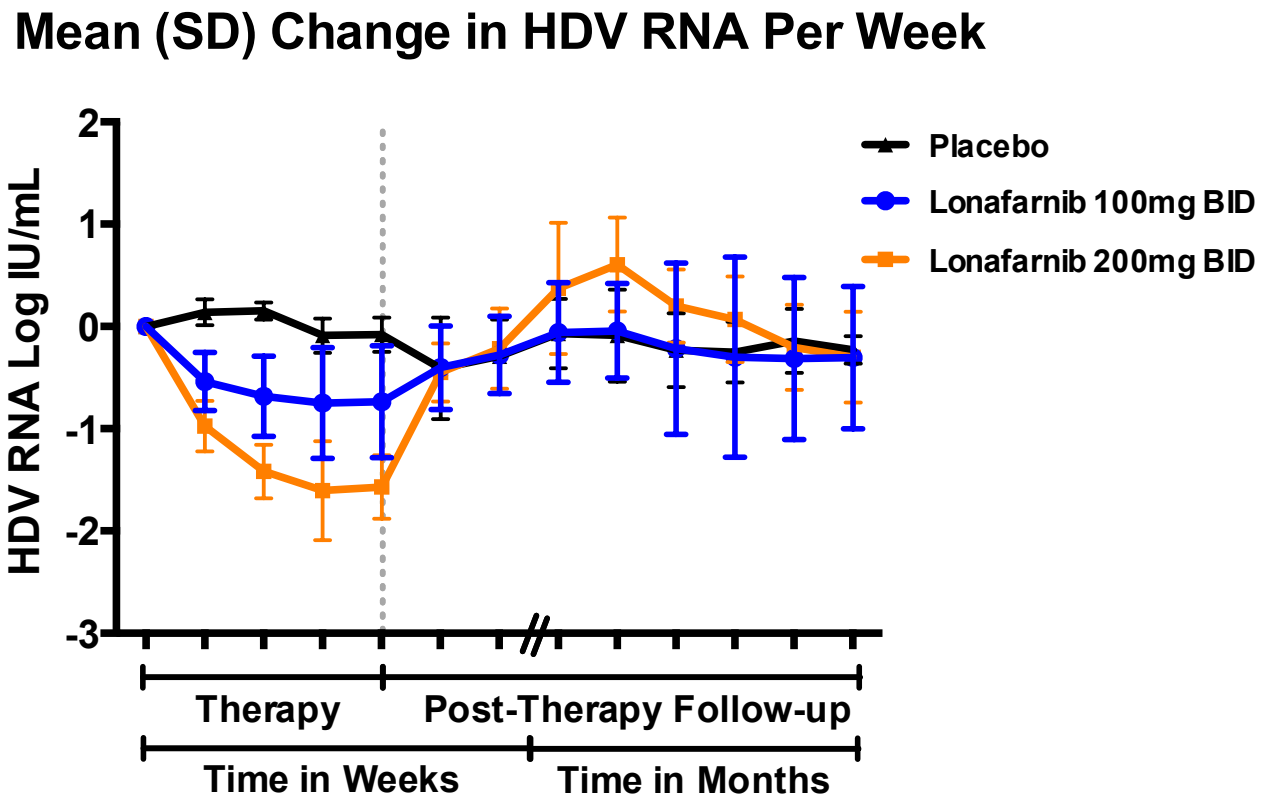
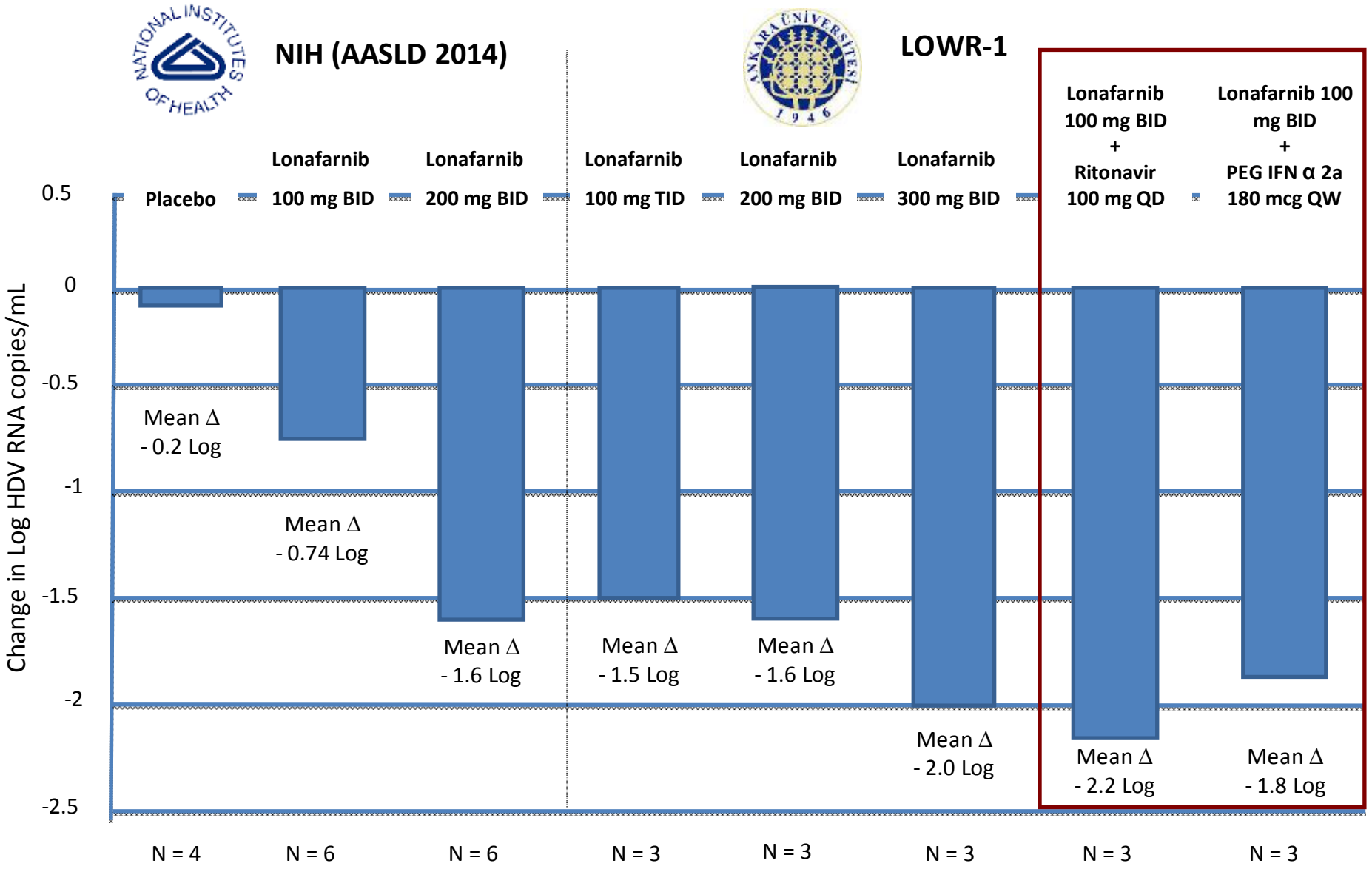
d1


Mean (SD) Change in HDV RNA Per Week
HDV RNA Log IU/mL
2
1
0
-1
-2
-3
Placebo
Lonafarnib 100mg BID
Lonafarnib 200mg BID
Therapy
Post-Therapy Follow-up
Time in Weeks
Time in Months

d1 Chris/Theo, Do we need also to show the median viral load post treatment ?
daharih; 02.02.2015

Day 28 Reduction in Serum HDV RNA



Yurdaydin C et al, EASL 2015 # 118

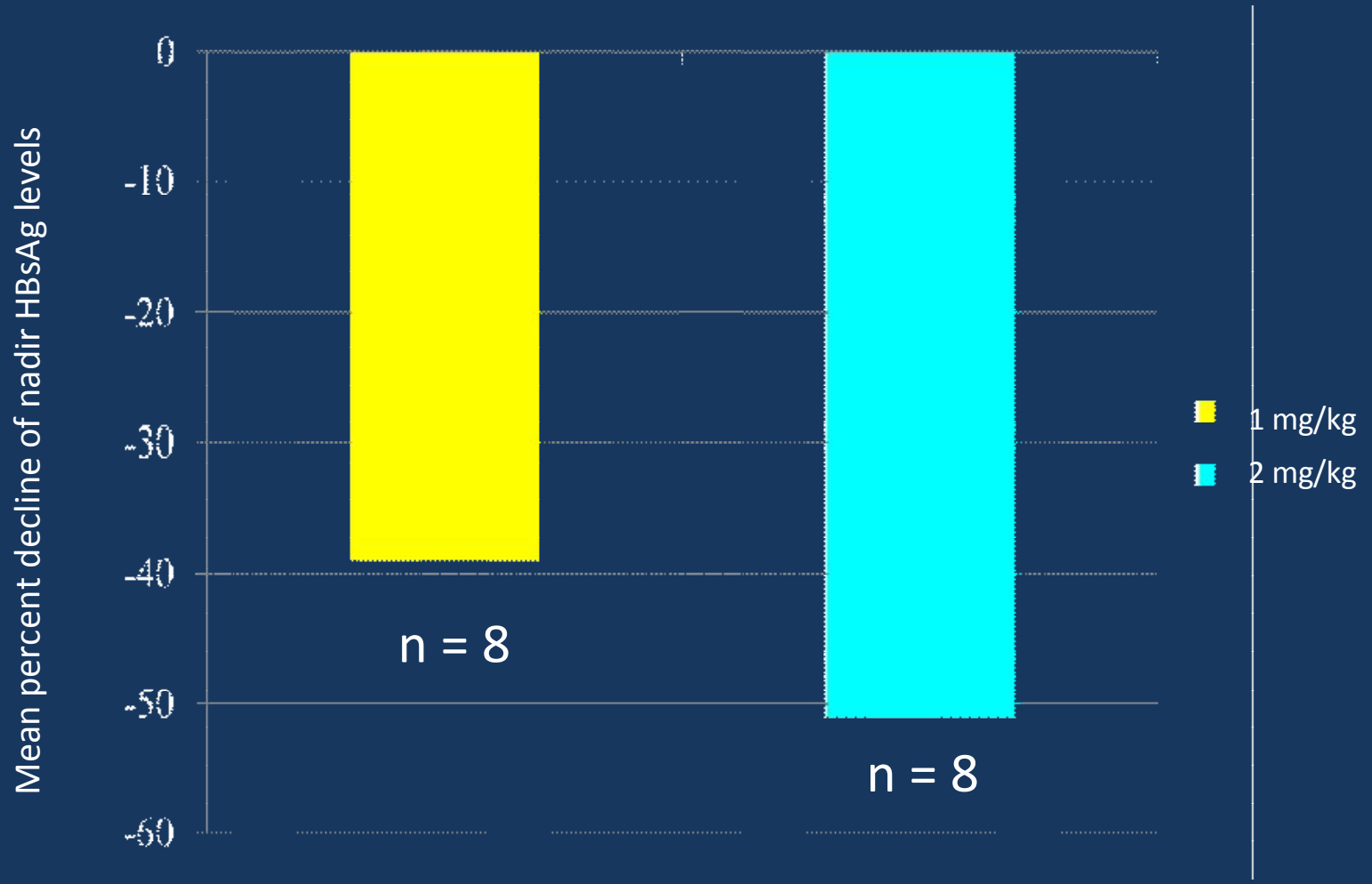
Side effects Improved with LNF Combos

- Mainly GI side effects

	N=3				N=3				N=3				N=3			
	LNF 200 mg BID				LNF 300 mg BID				LNF 100 mg BID RTN 100 mg QD				LNF 100 mg BID PEG IFN 180 mcg QW			
Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Nausea		√				√			√					√		
Diarrhea		√				√				√			√			
Fatigue		√				√				√				√		
Wt Loss		√				√			√				√			
Anorexia		√				√				√				√		

- Graded according to **C**ommon **T**erminology **C**riteria for **A**dverse **E**vents
- Lonafarnib chronically dosed in Progeria for 2 years (PNAS, *2012*, 16666)

Effect of ARC-520, a siRNA based tx as single injection on HBsAg levels in HBeAg (-) CHB



Yuen MF et al, AASLD 2014, LB 21

Effect of the hepatocyte entry inhibitor, Myrcludex in CDH

8 pts receive Myrcludex, 2mg/kg for 6 months
8 pts receive Myrcludex, 2mg/kg + Peg IFN for 6 months
Daily sc injections

Results:

Monotherapy: 2/7 HDV RNA negative and ALT declined In 6/7 at mo. 6

Combo group: 5/7 HDV RNA negative and ALT declined in 4/7 at mo. 6

Urban S et al, AASLD 2014, LB 20

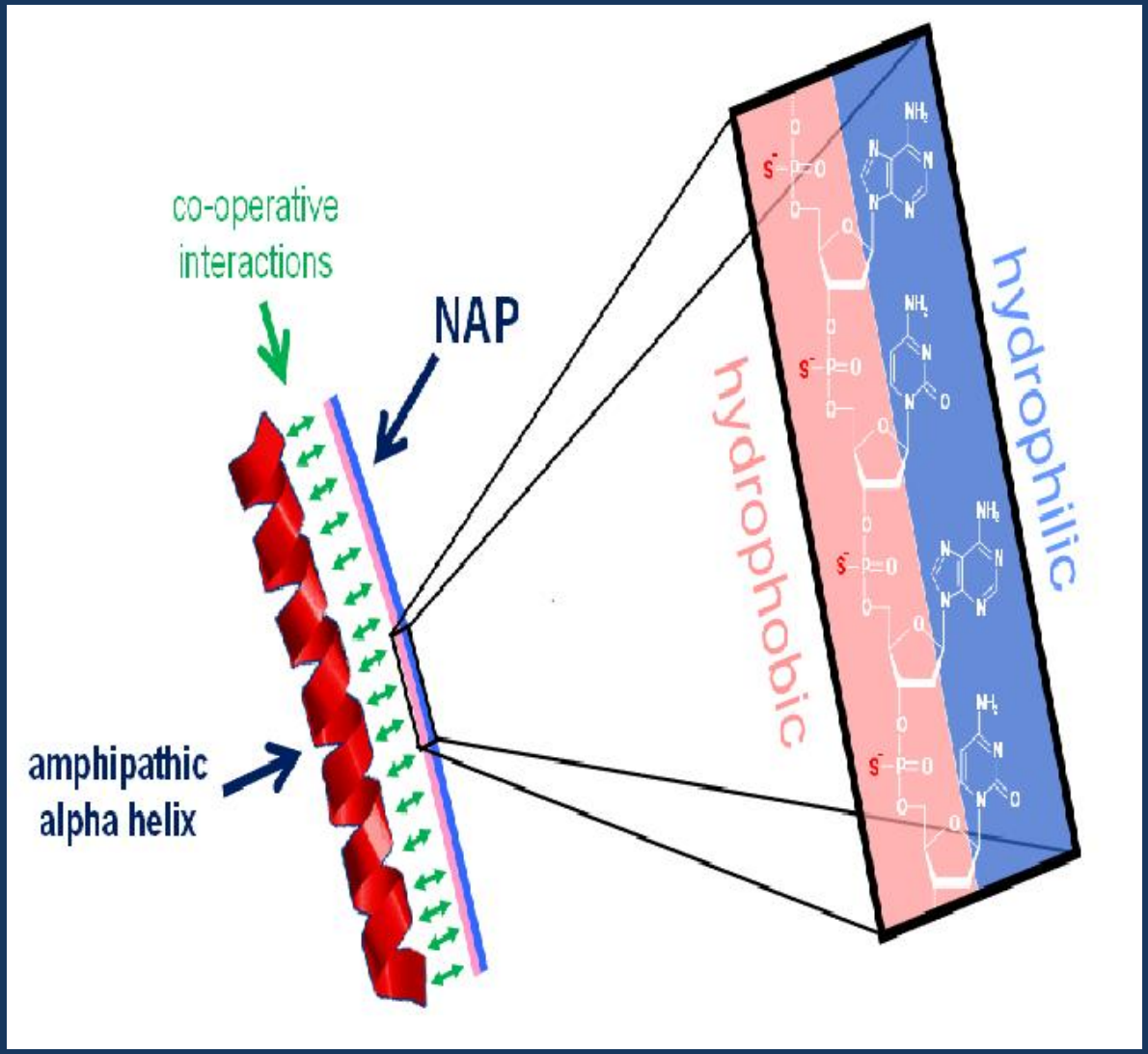
Nucleic acid polymers for treating HBV

They bind with high affinity to amphipathic protein structures

These amphipathic protein structures are very rare in normal human biology (already complexed with each other inside proteins where they help stabilize the protein structure).

However amphipathic targets are required for various stages of viral replication. NAPs effectively block the functions of these proteins, providing an effective, broad-spectrum antiviral activity.

Nucleic acid polymers for treating HBV



Human CHB data presented at EASL 2013 & 2015:
3-4 Log ↓in HBsAg;
4-5 log ↓in HDV RNA after 8- 12 weeks

Jansen L et al EASL #114; Bazinet M et al, LB02; Poutay D et al # LB26; GuillotC et al, # 556; Steima F et al, #659

Definition of Cure in HBV

French ANRS* Workshop 'HBV Cure' Program initiative
June 2014, Paris

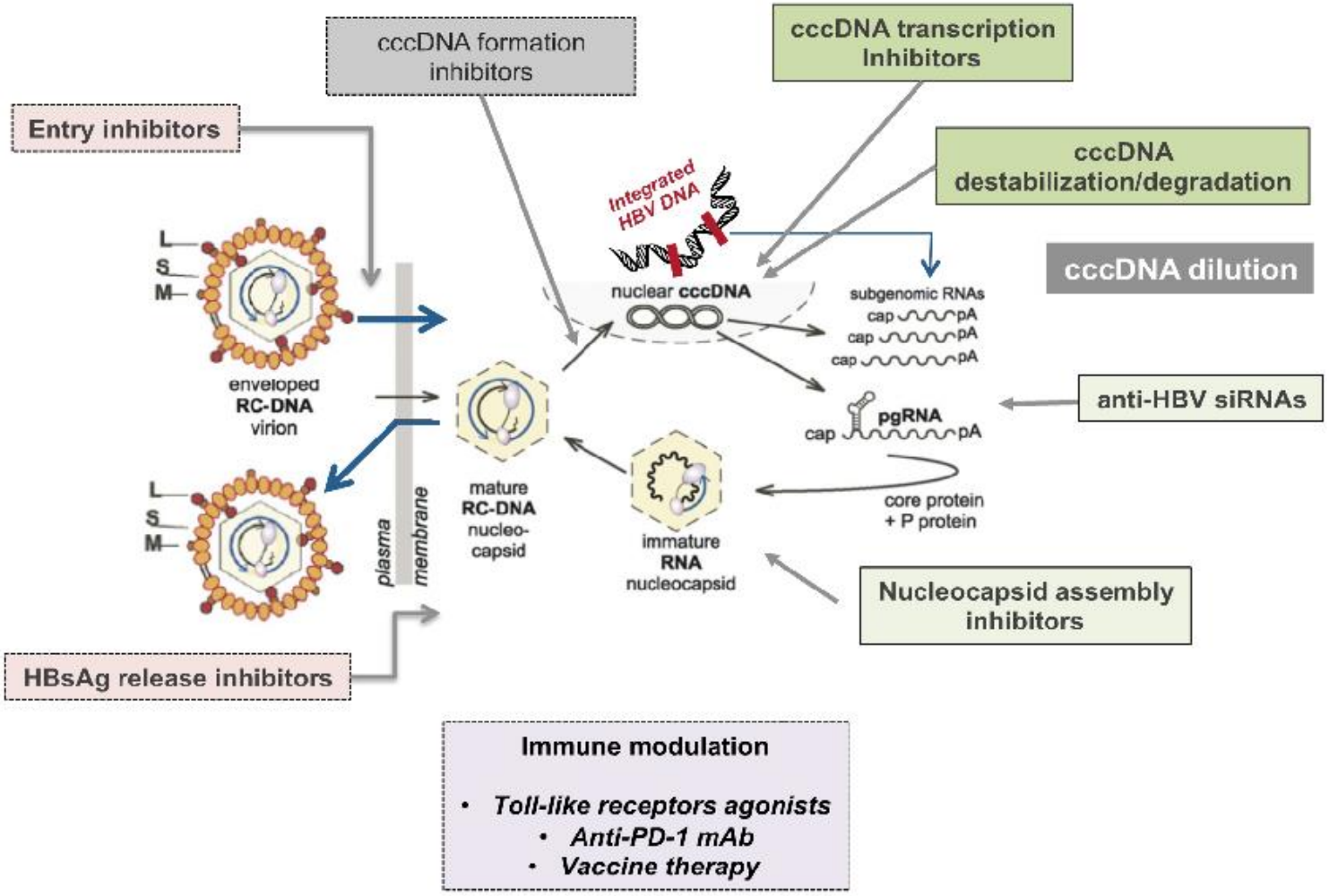
	HBsAg	HBsAb	HBV Viremia	ccc DNA
Functional Cure	(-)	(+)	(-)	(+)
Complete Cure	(-)	(+)	(-)	(-)

Realistic goal: Off-therapy maintained HBV DNA supression

Convert patients to 'inactive carriers'

*ANRS: National Agency for Research on AIDS and Viral Hepatitis

Emerging antiviral approaches



Adapted from Nassal M et al. Virus Res 2008;134:235–249

Summary and Conclusion- 1

The only effective treatment is with interferons

Treatment beyond 1 year needed in a sizeable proportion of patients

Post-treatment week 24 ≠ SVR in CDH

HDV RNA standard now avialable

Summary and Conclusion- 2

The future:

There is now hope:

- Hepatocyte entry inhibitors
- Prenylation inhibitors
- Nucleic acid polymers
- siRNAs

Teşekkürler