Hepatit B Hastalarında Uzun Dönem Tedavi Başarısını Nasıl Sağlayabiliriz ?

Prof. Dr. Bülent Değertekin
Acıbadem Üniversitesi Tıp Fakültesi
Gastroenteroloji BD.

Konuşmamda

- Güncel HBV tedavisi ve
- Gri bölgelerdeki hastalarda tedavi yaklaşımı

- Başarıyı uzun dönemde ne etkiler ?
  - ✓ Direnç gelişimi
  - ✓ Kemik erimesi
  - ✓ Renal sorunlar
  - ✓ Hepatosteatoz
  - ✓ Hiperlipidemi
  - ✓ Kilo alımı

- Gebelerde tedavi
- İmmünsupresif tedavi planlanan hastalar

Doğru Hastaya Tedavi Başlamalayız

EASL ve TKAD Guideline

HBeAg (+/-)

HBV DNA <2,000 IU
ALT < NÜS
Hafif histoloji

↓

Yakın Takip

HBV DNA> 2,000 IU
Ve ALT > NÜS ve/veya
Karaciğerde orta-şiddetli karaciğer hasarı

↓

Tedavi

Orta – Şiddetli Karaciğer Hasarı: Metavire göre > A2 ve F2

EASL Practice Guidelines J Hepatol. 2018

Türkiye de İki Sorun Var

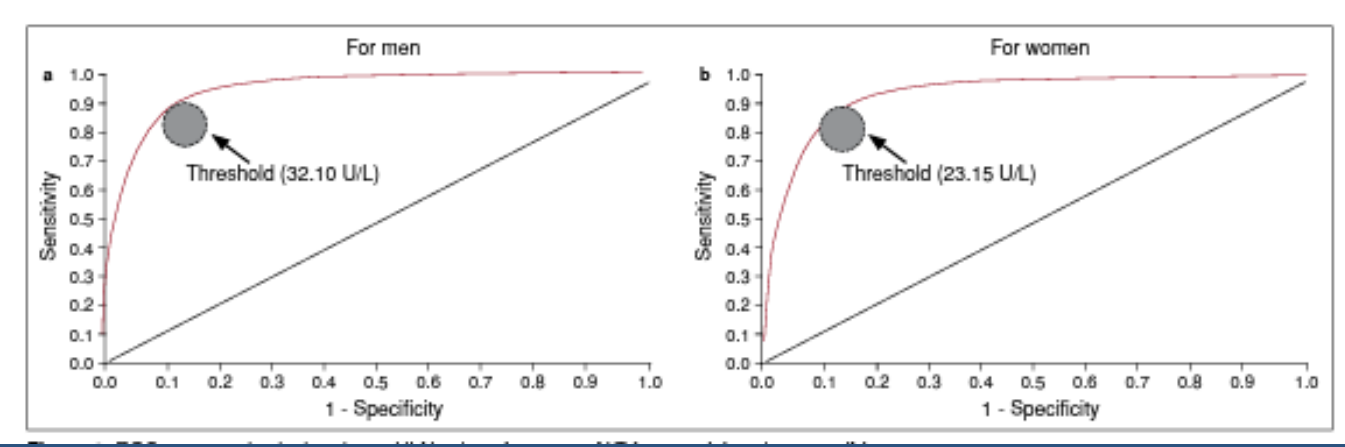
- ✓ Normal Serum ALT Seviyesi Nedir ?
- ✓ Non-invaziv markerları neden kullanmıyoruz ?

Research Article
HEPATOLOGY FORUM
Upper limits for serum alanine aminotransferase
doi: 10.14744/hf.2020.2020.0012

Determination of the upper limits of normal serum alanine aminotransferase (ALT) level in healthy Turkish population

Bulent Degertekin[1], Nurdan Tozun[1], Figen Demir[2], Gizem Soylemez[3], Suna Yapali[1], Ugur Bozkurt[3], Ezgi Gurtay[3], Tolga Hayrettin Seymenoglu[3], Deniz Mutlu[3], Meltem Toraman[3]

[1]Department of Gastroenterology and Hepatology, Acibadem Mehmet Ali Aydinlar University, School of Medicine, Istanbul, Turkey; [2]Department of Social Health, Acibadem Mehmet Ali Aydinlar University, School of Medicine, Istanbul, Turkey; [3]Acibadem Mehmet Ali Aydinlar University, School of Medicine, Practitioner



Degertekin B et al. Hepatology Forum 2020; 2(1): 44-47

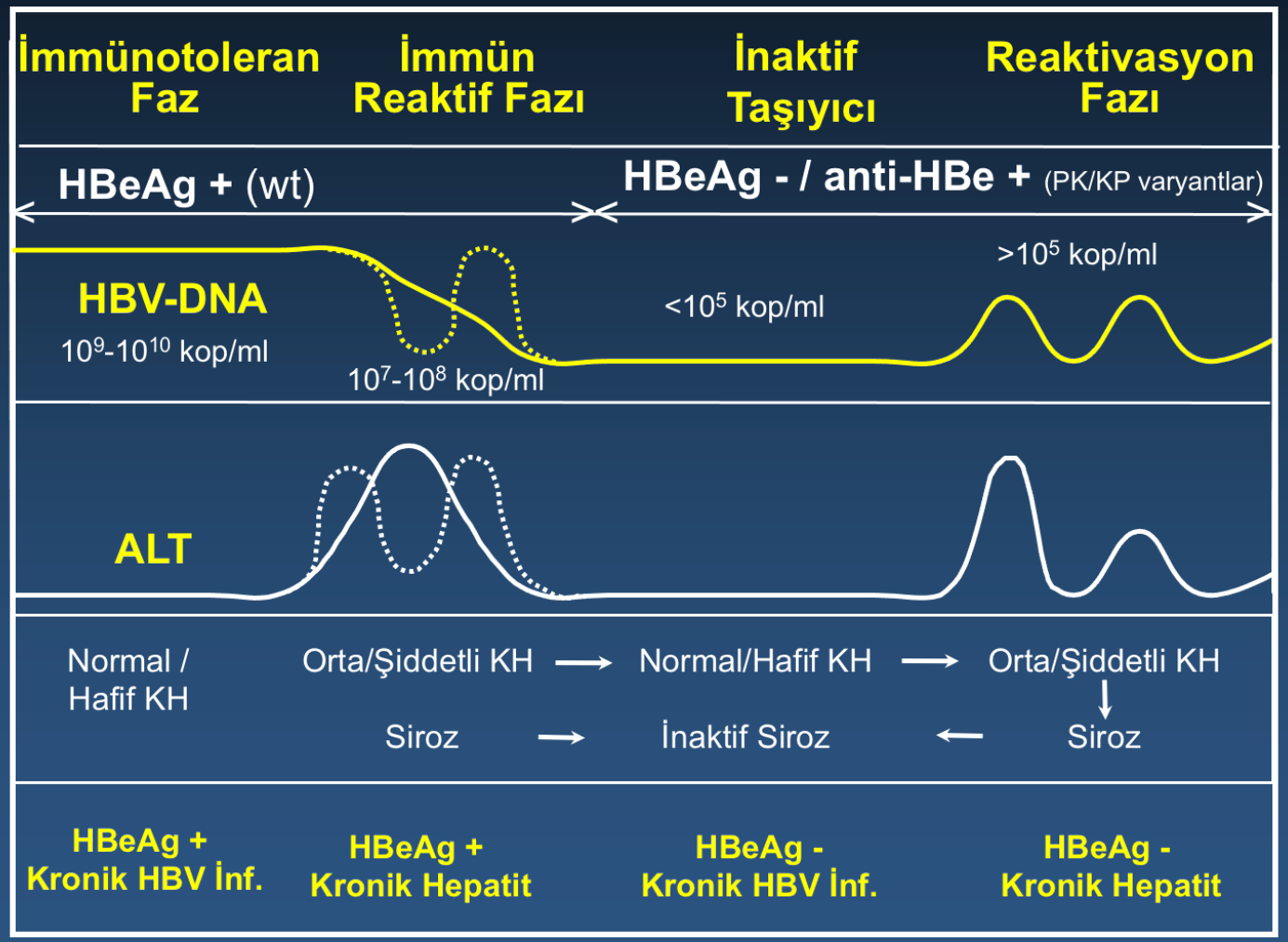
Kompanze ve Dekompanze Sirozlular

- HBV DNA (+) olan her vaka tedavi edilmeli
- Tedavi ile
  - Karaciğer yetmezliğine girmede
  - HCC ve Karaciğere bağlı ölümlerde belirgin bir azalma olmaktadır
  - Transp gidiş ve rekkürens ve post LT HCC azalıyor

Fontana R, Gastro 2002; 123: 719

Villeneuve J, Hepatology 2000; 31: 207 Yao F, Hepatology 2001; 34: 411

Uzun Dönem Başarıda Bir Diğer Önemli Nokta Hastanın Nerede Olduğunu İyi Anlamak Lazım



Tedavi Yaklaşımı Nasıl Olmalı

- ✓ İnaktif HBV Taşıyıcılarında (HBV DNA <2000 ve ALT:N)
- ✓ İmmüntoleran Fazda, <30 yaş

- ✓ İnaktif taşıyıcı >40 yaş
- ✓ İmmüntoleran >30 yaş
- ✓ HCC için kuvvetli aile öyküsü

- ✓ Hepatik dekompanzasyon
- ✓ Şiddetli alevlenmeler
- ✓ Karaciğer Sirozu
- ✓ HBeAg+ kronik hepatit (HBV DNA >2000 ve ALT>N)
- ✓ HBeAg- kronik hepatit (HBV DNA >2000 ve ALT>N)

Elimizde Tedavi için Ne Var ?

- İnterferonlar
- Lamivudine
- Telbivudin
- Adefovir
- Entekavir
- Tenofovir Disoproksil
- Tenofovir Alefolamat

✓ HIV tedavisinde kullanılan ancak HBV de etkili olduğu bilinen ilaçlar

- Emtricitabine
- Tenofovir + Emtricitabine (Truvada)

Tedavi Hedeflerimiz Neler ?

	HEDEF	ZAMAN
Virolojik	HBV DNA' nın supresyonu (negatifleştirilmesi)	KISA DÖNEM
Biyokimyasal	ALT' nin normalleşmesi	
Histolojik	Fibroziste azalma olması veya ilerlememesi	ORTA DÖNEM
	HAI' de ≥ 2 düşme	
	İnflamatuvar aktivitede azalma	
Serolojik	HBeAg kaybı ile beraber Anti-HBe serokonversiyonu	UZUN DÖNEM
	HBsAg kaybı ± Anti-HBs serokonversiyonu	

Günümüz Kılavuzlarına Göre Uzun Dönem Tedavi Hedefleri

- HBV tedavisindeki temel amaç
  - Siroz,
  - Karaciğer yetmezliği ve
  - Hepatoselüler kanser gelişmesini engellemektir

EASL Clinical Practice Guidelines: 2018, Journal of Hepatology

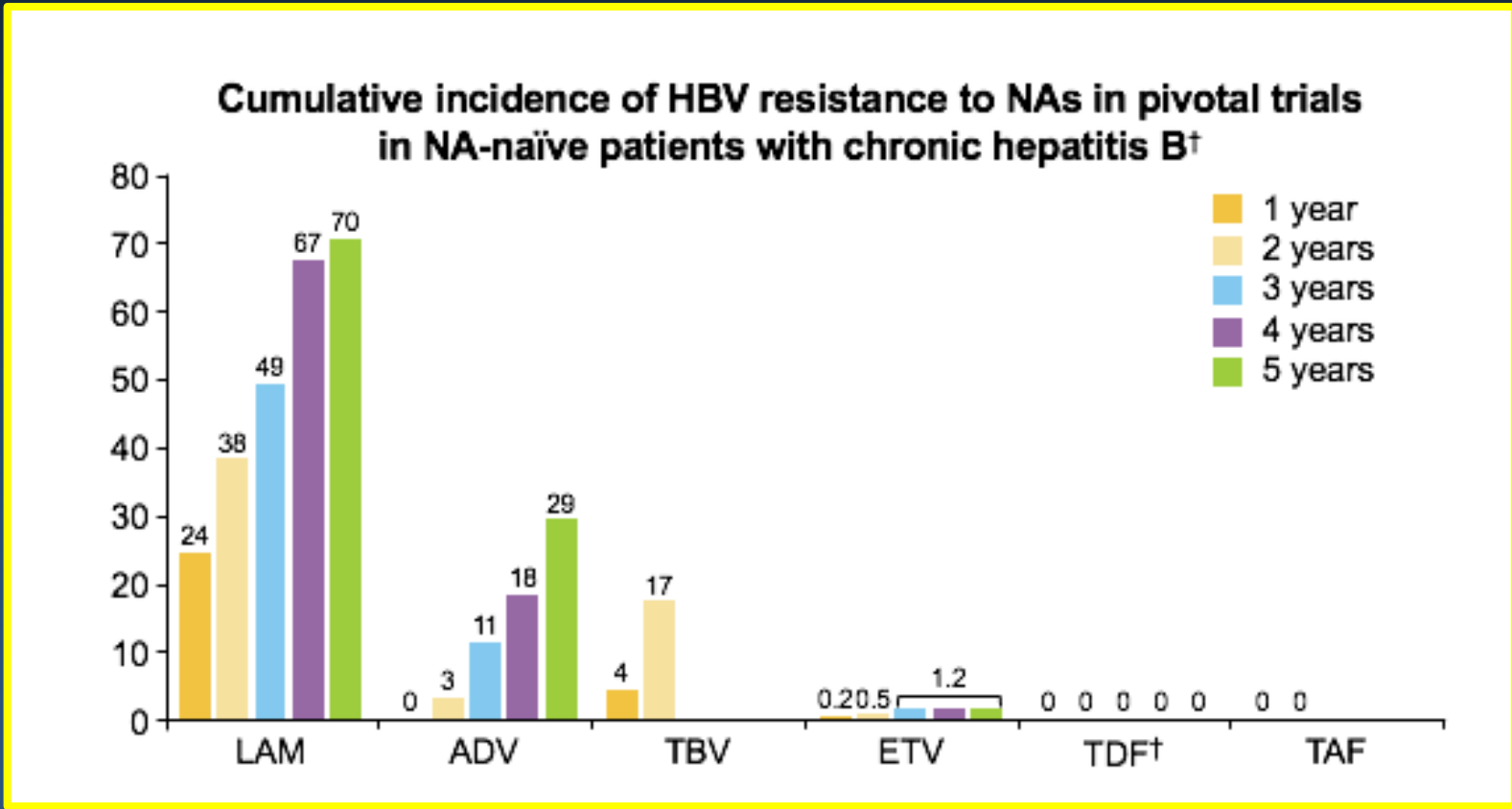
Lok AS ve McMahon BJ. Hepatology 2018;50:661-2

Uzun Dönemde Tedavide Başarıyı Ne Etkileyebilir ?

- Direnç gelişimi
- İlaç yan etkileri
  - ✓ Kemik erimesi
  - ✓ Renal sorunları
  - ✓ Karaciğer Yağlanması
  - ✓ Hiperlipidemi
  - ✓ Kilo alımı
  - ✓ Metabolik sendrom
- Gebelik gelişmesi
- İmmünsupresyon tedavi

I-Antiviral Direnç

✓ Günümüzde antiviral direnç artık çok büyük problem değil



EASL Practice Guidelines J Hepatol. 2018

I-Antiviral Direnç

Cross-resistance data for the most frequent NA-resistant HBV variants:

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

Tan J, Degertekin B et al. J Hepatol. 2008 Mar;48(3):391-8
EASL Practice Guidelines J Hepatol. 2018

LAM, TLb, ETV
Direnci Varsa

TDF veya TAF

EASL Practice Guidelines J Hepatol. 2018

LAM, TLb, ETV Direnci Varsa → TDF veya TAF

TDF veya TAF Direnci Varsa → ETV geç (LAM almamışsa)
ETV ekle (LAM almışsa)

EASL Practice Guidelines J Hepatol. 2018

LAM, TLb, ETV Direnci Varsa → TDF veya TAF

TDF veya TAF Direnci Varsa → ETV geç (LAM almamışsa)
ETV ekle (LAM almışsa)

Multidrug Direnci Varsa → ETV+TDF / ETV+TAF

EASL Practice Guidelines J Hepatol. 2018

II-Renal Sorunlar

- ✓ OAV' ler Böbrek Fonksiyonlarını Bozar mı ?
  Hangi İlacı Tercih Etmeliyim ?

II-Renal Sorunlar

✓ OAV' ler Böbrek Fonksiyonlarını Bozar mı ?
Hangi İlacı Tercih Etmeliyim ?

- KBY hastalarında ve renal problemleri olan hastalarda ilk tercih edilecek ajan ETV' dir
- Renal tubullerde toksik etkisi nedeniyle Tenofovir molekülü problemli bir moleküldür

II-Renal Sorunlar

✓ OAV Tedaviler ile Renal Sorunlar (TDF ve TAF)

- ✓ Tubül disfonksiyonu
- ✓ Böbrek fonksiyon bozukluğu (GFR da azalma)
- ✓ Kreatininde yükselme
- ✓ Hipofosfatemi ve proksimal tübülopati (Fanconi sendromu dahil)

II-Renal Sorunlar

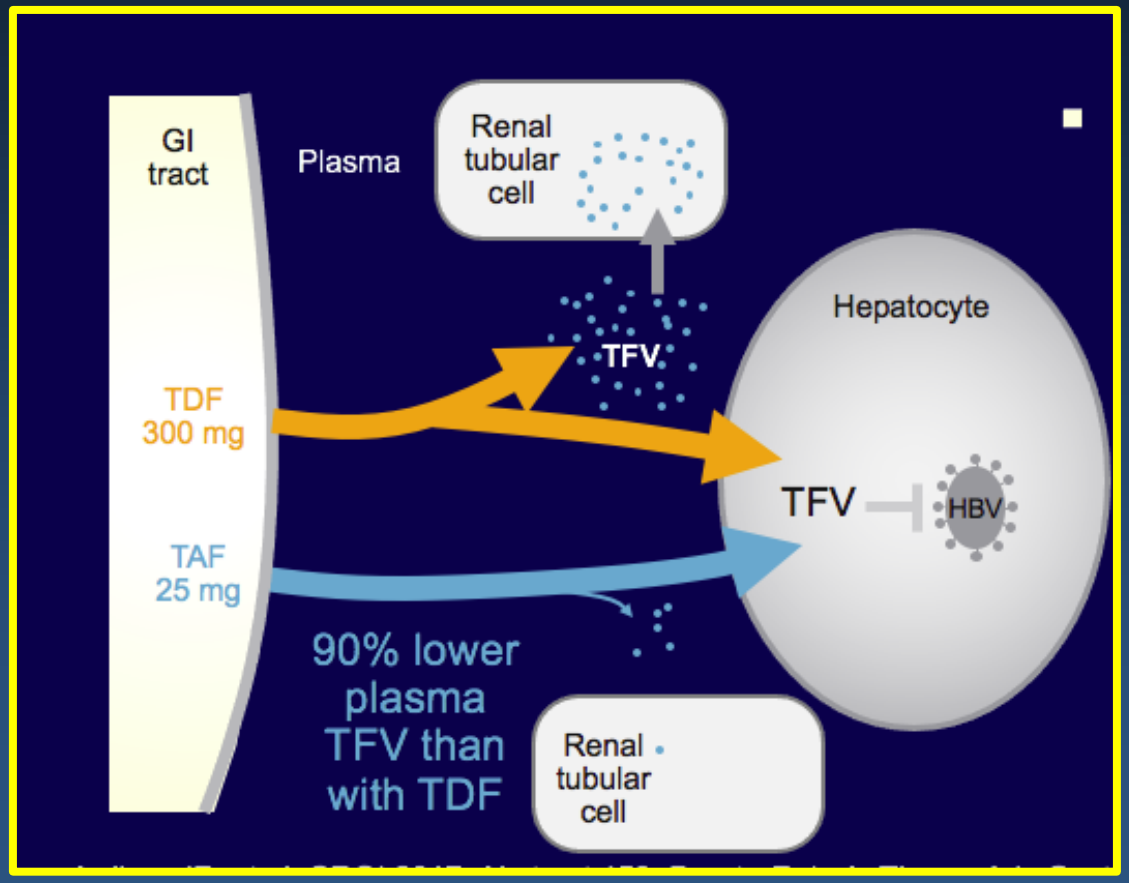
✓ OAV Tedaviler ile Renal Sorunlar (TDF ve TAF)

- ✓ Tubül disfonksiyonu
- ✓ Böbrek fonksiyon bozukluğu (GFR da azalma)
- ✓ Kreatininde yükselme
- ✓ Hipofosfatemi ve proksimal tübülopati (Fanconi sendromu dahil)

ETV de böyle bir sorun yok !!!

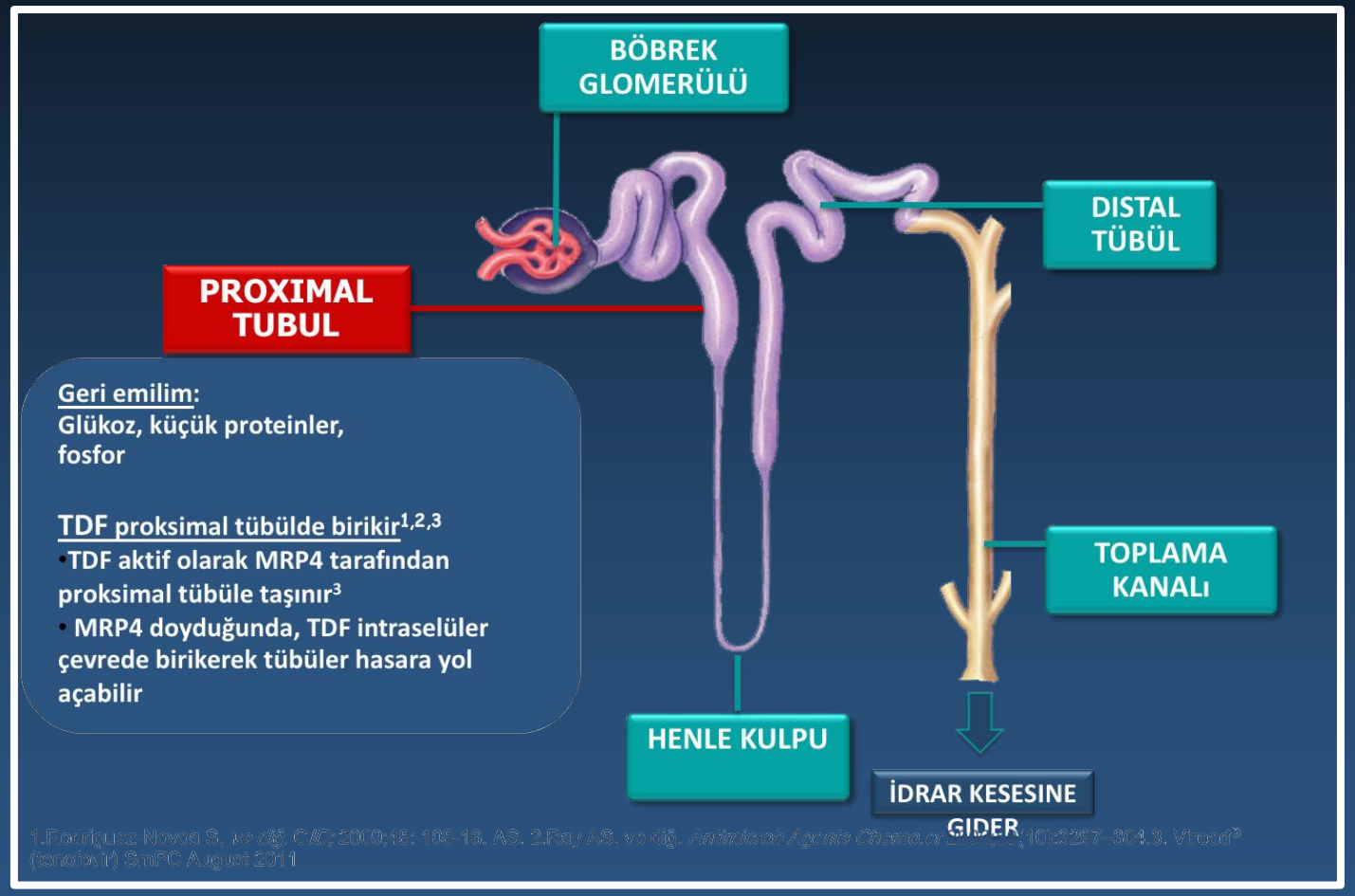
II-Renal Sorunlar

✓ Renal Sorunlar (TDF vs. TAF)



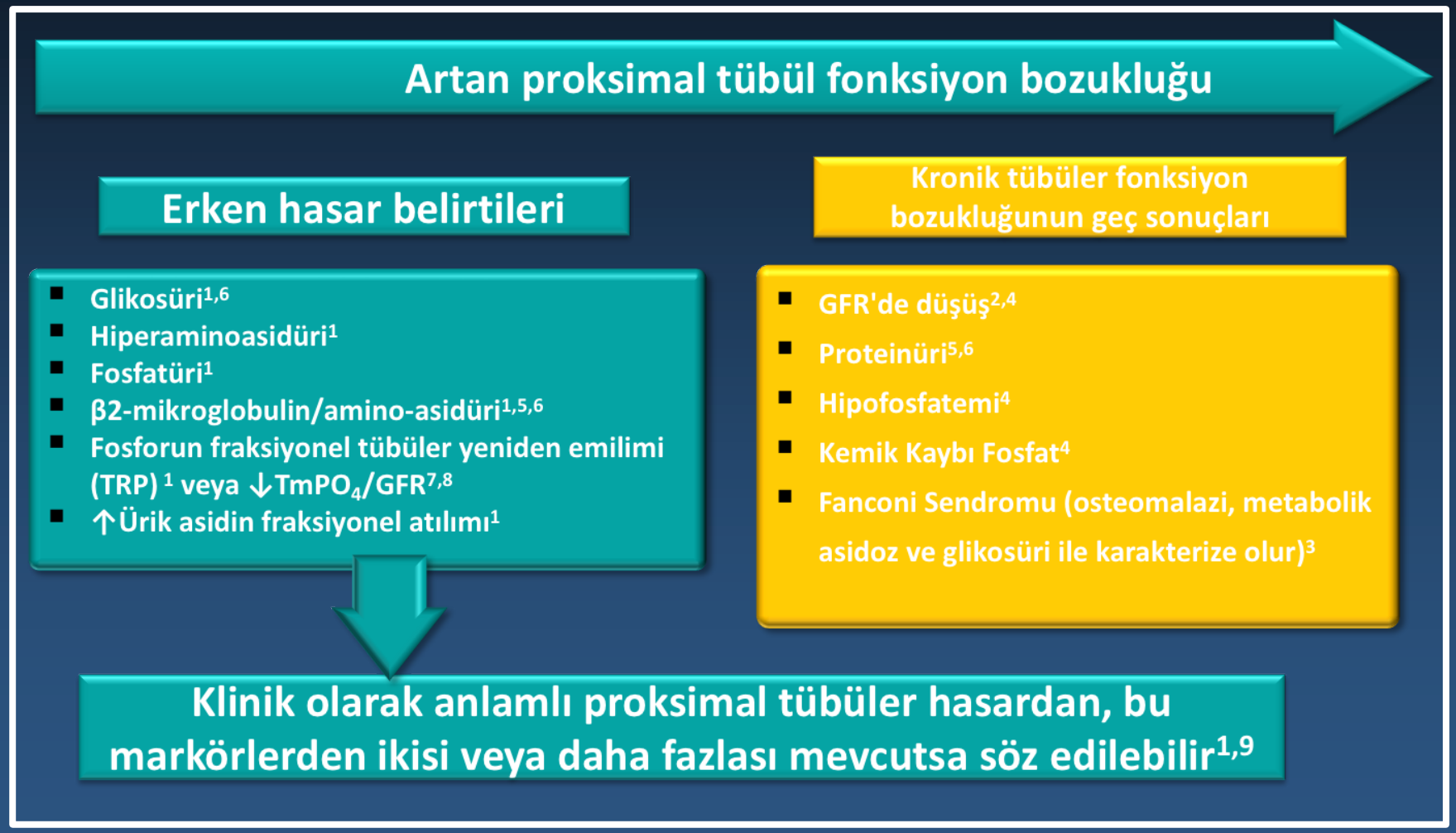
✓ Sorun Tubulde yüksek konsantrasyonda olma

II-Renal Sorunlar



D vitamini de burada yapılıyor

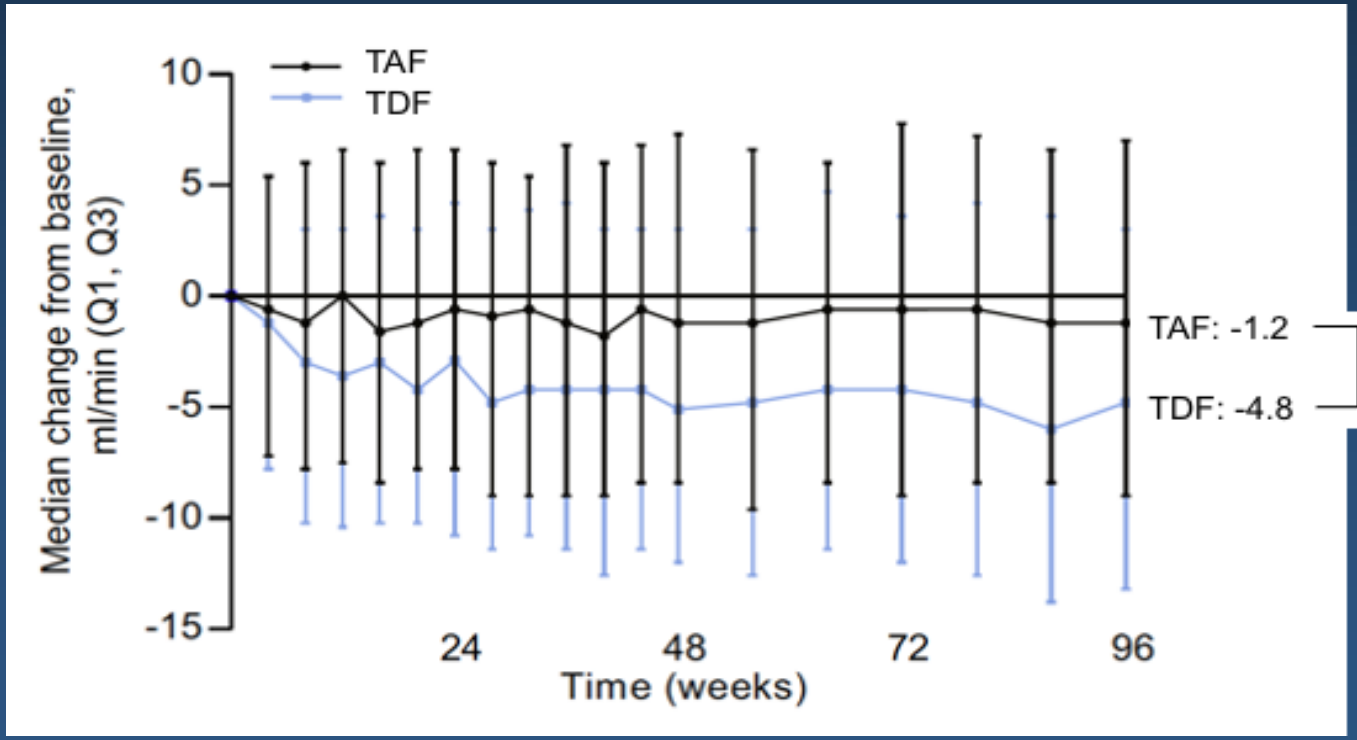
II-Renal Sorunlar



II-Renal Sorunlar

GFR Değişimi:

96 Haftalık tedavi sonunda başlangıca göre median
TAF 25 mg (n=866) vs. TDF 300 mg (n=432)



II-Renal Sorunlar

✓ TDF Molekülü Problemli (TAF çok da masum değil....)

Clinical Case Report

Medicine®

OPEN

Tenofovir alafenamide nephrotoxicity in an HIV-positive patient

A case report

Tessa K. Novick, MD[a,*], Michael J. Choi, MD[a], Avi Z. Rosenberg, MD[b], Blaithin A. McMahon, MD, PhD[a], Derek Fine, MD[a], Mohamed G. Atta, MD, MPH[a,*]

- ✓ TAF a bağlı gelişmiş proksimal tubül mitokondrial disfonksiyon
- ✓ İlk case report

II-Renal Sorunlar

✓ TDF Molekülü Problemli (TAF çok da masum değil....)

Heron *et al. BMC Nephrology* (2020) 21:339
https://doi.org/10.1186/s12882-020-01981-9

BMC Nephrology

CASE REPORT Open Access

Renal proximal tubulopathy in an HIV-infected patient treated with tenofovir alafenamide and gentamicin: a case report

Jack E. Heron[1*], Mark Bloch[2,3], Vinay Vanguru[4], John Saunders[1] and David M. Gracey[1,5]

II-Renal Sorunlar

- ✓ TDF den TAF' a geçmek düzeltmedi çünkü yoğun TDF birikimi vardı

Clinical Nephrology, DOI 10.5414/CN110377 – Letter to the editor

clinical nephrology

Letter

ISSN 0301-0430

DOI 10.5414/CN110377
e-pub: March 22, 2021

LETTER TO THE EDITOR

A rare case of acute tubular necrosis tenofovir alafenamide-related

Michela Pontolillo[1], Luca Piscitani[2], Claudio Ucciferri[1,3], Lorenzo Di Liberato[2], Mario Bonomini[2], and Jacopo Vecchiet[1]

renal functi
of 1.6 mg/d
tration rate
urea, electro
After 1 mo
deterioratio
the cART
of ATV/r to
However, d
ther worsen
9 mL/min/1
proteinuria

- ✓ TDF renal sorunları olanlarda ETV daha iyi bir tercih olabilir !!!

II-Renal Sorunlar

- ✓ TAF başlanması sonrası gelişen Akut Böbrek Yetmezliği

Letter to the Editor

Acute Kidney Injury in a Patient Treated with Tenofovir Alafenamide Fumarate for Hepatitis B Virus Infection

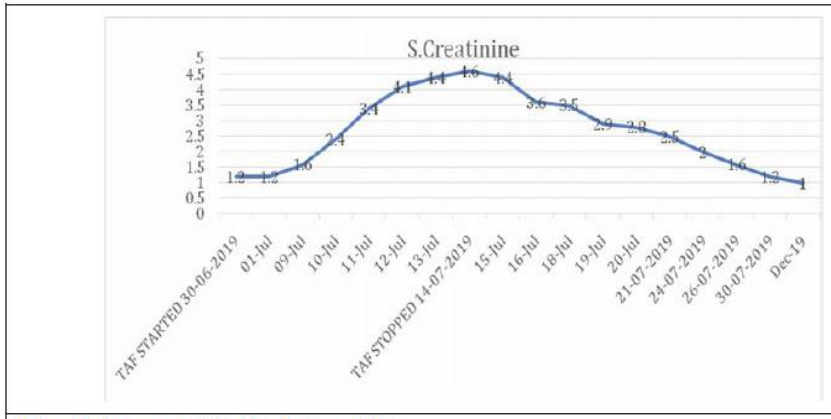


Figure 1. Serum creatinine levels (in mg/dL).

- ✓ TDF renal sorunları olanlarda ETV daha iyi bir tercih olabilir !!!

S J Kidney Dis Transpl 2021;32(2):592-594

II-Renal Sorunlar

✓ Sonuç Olarak

- Tenofovir molekülünün (TDF ve TAF) gerçekten tubullerde birikme ve potansiyel toksik etkileri var
- GFR' da minimal bir düşme etkisi var
- Ciddi bir böbrek yetmezliği gelişimi yok
- TAF ile de tubul hasarı bildiren yayınlar var
- TAF' a geçince düzelmeyen hastalar var

✓ Sonuç olarak ETV burada daha doğru bir ajan gibi görünüyor

III-Kemik Erimesi Bir Sorun mudur ?

✓Kemik Erimesi

✓ **Temel sorunu olan ajan Tenofovir Molekülü**

- ❖ Kemik mineral yoğunluğunda azalma
- ❖ Kemik turn-over markerlarında artma
- ❖ Vitamin D düzeylerine potansiyel etkisi var
- ❖ Kırık oranında artışa neden olmuyor

III-Kemik Erimesi Bir Sorun mudur ?

✓Kemik Erimesi

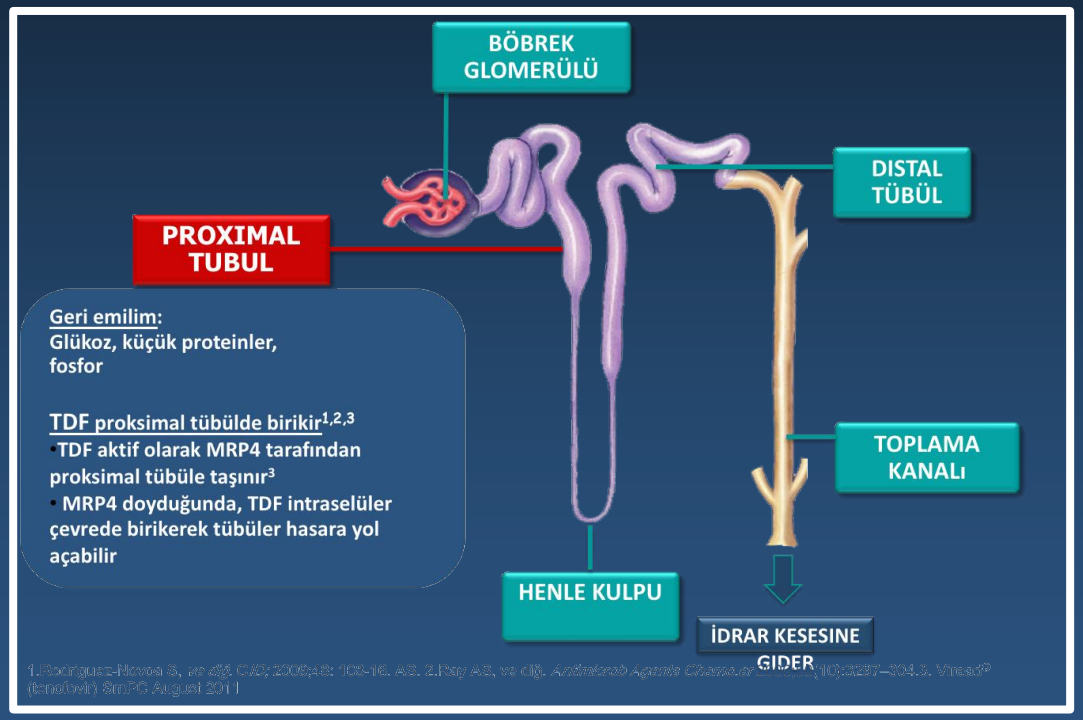
✓**Temel sorunu olan ajan Tenofovir Molekülü**

- ❖ Kemik mineral yoğunluğunda azalma
- ❖ Kemik turn-over markerlarında artma
- ❖ Vitamin D düzeylerine potansiyel etkisi var
- ❖ Kırık oranında artışa neden olmuyor

ETV de böyle bir sorun yok !!!

III-Kemik Erimesi Bir Sorun mudur ?

✓Kemik Erimesi



1.Rodriguez-Nieves JA, ve diğ. CJD; 2009;48: 163-16. AS. 2.Ray AS, ve diğ. *Antimicrob Agents Chemother*. 2006;50:3237–3244. 3. Viread® (tenofovir) SmPC August 2011

Fosfor atılımı artınca

↓

Kemikten kalsiyum ve fosfor mobilize olur

↓

D vitamini üretimi de azalınca

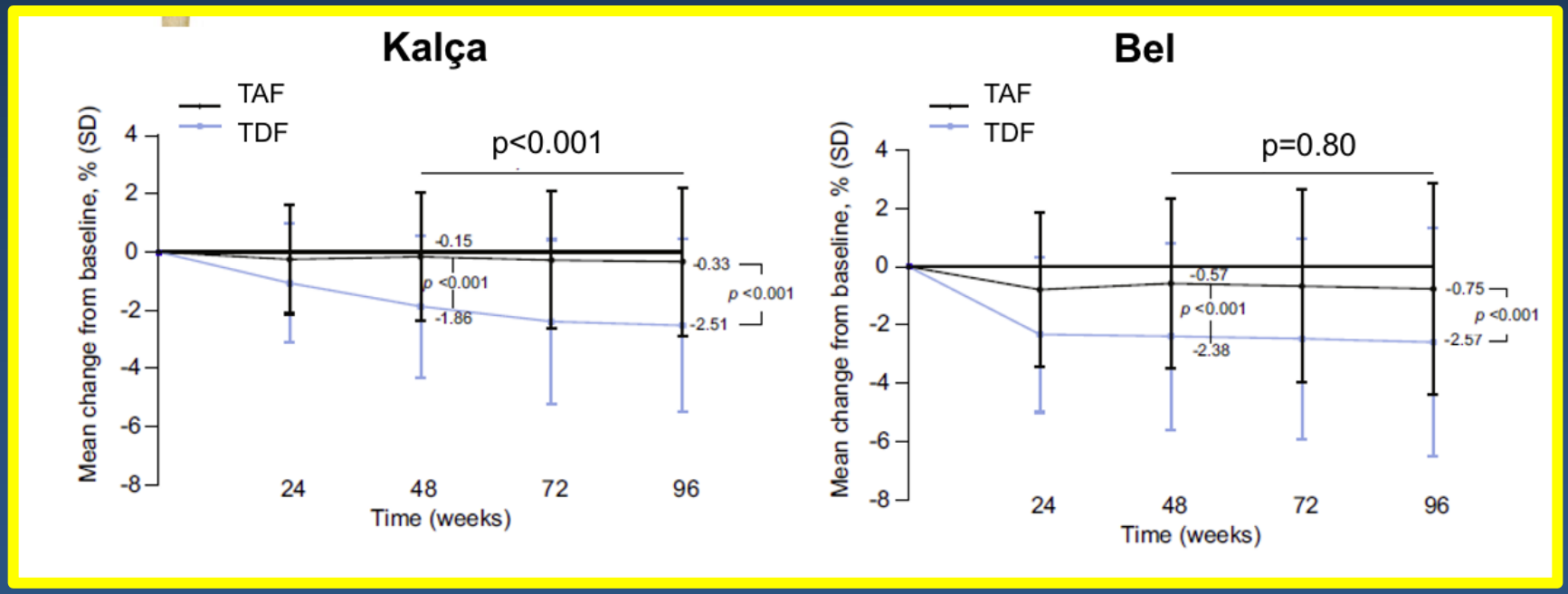
↓

Kemik erimesi Hızlanır

III-Kemik Erimesi Bir Sorun mudur ?

KMY Değişimi:

96 Haftalık tedavi sonunda başlangıca göre median
TAF 25 mg (n=866) vs. TDF 300 mg (n=432)



III-Kemik Erimesi Bir Sorun mudur ?

✓Kemik Erimesi

✓ETV de sorun yok

Hepatology International
https://doi.org/10.1007/s12072-021-10271-x

ORIGINAL ARTICLE

Longitudinal renal changes in chronic hepatitis B patients treated with entecavir versus TDF: a REAL-B study

Lung-Yi Mak[1,2] · Joseph Hoang[3] · Dae Won Jun[4] · Chien-Hung Chen[5] · Cheng-Yuan Peng[6] · Ming-Lun Yeh[7,28] · Sung Eun Kim[8] · Daniel Q. Huang[9,10] · Jae Yoon Jeong[11] · Eileen Yoon[12] · Hyunwoo Oh[4] · Pei-Chien Tsai[7,28] · Chung-Feng Huang[7,28] · Sang Bong Ahn[13] · Huy Trinh[14] · Qing Xie[15] · Grace L. H. Wong[16] · Masaru Enomoto[17] · Jae-Jun Shim[18] · Dong-Hyun Lee[19] · Li Liu[20] · Ritsuzo Kozuka[17] · Yong Kyun Cho[21] · Soung Won Jeong[22] · Hyoung Su Kim[23] · Lindsey Trinh[3] · Allen Dao[3] · Rui Huang[24] · Rex Wan-Hin Hui[1] · Vivien Tsui[1] · Sabrina Quek[9] · Htet Htet toe Wai Khine[9] · Eiichi Ogawa[25] · Chia Yen Dai[7,28] · Jee Fu Huang[7,28] · Ramsey Cheung[3,26] · Chao Wu[24] · Wan-Long Chuang[7,28] · Seng Gee Lim[9,10] · Ming-Lung Yu[7,28] · Man-Fung Yuen[1,2] · Mindie H. Nguyen[3,27]

Abstract

Background and aims We aimed to compare the longitudinal changes in estimated glomerular filtration rate (eGFR) in chronic hepatitis B (CHB) patients treated with entecavir (ETV) vs. tenofovir disoproxil fumarate (TDF).

Methods This is a retrospective study of 6189 adult treatment-naïve CHB patients initiated therapy with TDF ($n=2482$) or ETV ($n=3707$) at 25 international centers using multivariable generalized linear modeling (GLM) to determine mean eGFR (mL/min/1.73 m^2) and Kaplan–Meier method to estimate incidence of renal impairment (≥ 1 chronic kidney disease [CKD] stage worsening). We also examined above renal changes in matched ETV and TDF patients (via propensity score matching [PSM] on age, sex, diabetes mellitus [DM], hypertension [HTN], cirrhosis, baseline eGFR, and follow-up duration).

Results In the overall cohort (mean age 49.7 years, 66.2% male), the baseline eGFR was higher for TDF vs. ETV group (75.9 vs. 74.0, $p=0.009$). PSM yielded 1871 pairs of ETV or TDF patients with baseline eGFR ≥ 60 and 520 pairs for the eGFR < 60 group. GLM analysis of the overall (unmatched) cohort and PSM cohorts revealed lower adjusted mean eGFRs in TDF (vs. ETV) patients (all $p<0.01$) during 10 years of follow-up. Among PSM eGFR ≥ 60 patients, the 5-year cumulative incidences of renal impairment were 42.64% for ETV and 48.03% for TDF ($p=0.0023$). In multivariable Cox regression, TDF vs. ETV (adjusted HR 1.26, 95% CI 1.11–1.43) was associated with higher risk of worsening renal function.

Conclusion Over the 10-year study follow-up, compared to ETV, TDF was associated with a lower mean eGFR and higher incidence of renal impairment.

III-Kemik Erimesi Bir Sorun mudur ?

✓ Sonuç Olarak

- Tenofovir molekülü KMY da azalmaya neden oluyor
- Gerçek hayatta pratik çok bir önemi yok
- Kemik kırık riski olmayanlar TDF başlanabilir
- TDF başlanacaklarda başta Dexa bakıp yılda bir Dexa ile gidilebilir
- Tedaviye mutlaka D vitamini eklenmeli

✓ Sonuç olarak ETV naif hastalarda daha sorunsuz bir ajan gibi görünüyor

IV-Metabolik Sorunlar

- Karaciğer Yağlanması
- Hiperlipidemi gelişmesi
- Kilo alımı
- Metabolik sendrom gelişmesi

V-Hiperlipidemi ve Hepatosteatoz İlaç Seçimimi Etkilemeli mi ?

✓ Hiperlipidemi

- ✓ TDF: T. Kolestrol, LDL, HDL ve TG düşürüyor
- ✓ TAF: Lipidlerde yükselmeye neden oluyor
- ✓ ETV: Etki yok gibi
- ✓ TAF dan TDF ye geçme ile parametreler düzeliyor

HDL/T kol oranı bozulmadığından kardiyak fayda pek yok

V-Hiperlipidemi ve Hepatosteatoz İlaç Seçimimi Etkilemeli mi ?

✓ Hiperlipidemi

- TDF Hepatik CD36 upregülasyonu yaparak PPAR alfa aktivasyonuna neden oluyor

J Gastroenterol (2021) 56:168–180
https://doi.org/10.1007/s00535-020-01750-3

The Japanese Society of Gastroenterology

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Tenofovir–disoproxil–fumarate modulates lipid metabolism via hepatic CD36/PPAR-alpha activation in hepatitis B virus infection

Kazuharu Suzuki[1] · Goki Suda[1] · Yoshiya Yamamoto[2] · Ken Furuya[3] · Masaru Baba[3] · Akinobu Nakamura[4] · Hideaki Miyoshi[5] · Megumi Kimura[1] · Osamu Maehara[2] · Ren Yamada[1] · Takashi Kitagataya[1] · Koji Yamamoto[1] · Taku Shigesawa[1] · Akihisa Nakamura[1] · Masatsugu Ohara[1] · Naoki Kawagishi[1] · Masato Nakai[1] · Takuya Sho[1] · Mitsuteru Natsuizaka[1] · Kenichi Morikawa[1] · Koji Ogawa[1] · Shunsuke Ohnishi[1] · Naoya Sakamoto[1] · for the NORTE Study Group

Received: 20 July 2020 / Accepted: 2 November 2020 / Published online: 19 November 2020

J Gastroenterology 2021

V-Hiperlipidemi ve Hepatosteatoz İlaç Seçimimi Etkilemeli mi ?

✓ Hiperlipidemi

Received: 18 April 2017 | First decision: 25 May 2017 | Accepted: 20 June 2017
DOI: 10.1111/apt.14218

WILEY APT Alimentary Pharmacology & Therapeutics

Tenofovir disoproxil fumarate significantly decreases serum lipoprotein levels compared with entecavir nucleos(t)ide analogue therapy in chronic hepatitis B carriers

A. A. Shaheen | M. AlMattooq | S. Yazdanfar | K. W. Burak | M. G. Swain | S. E. Congly | M. A. Borman | S. S. Lee | R. P. Myers | C. S. Coffin

TABLE 3 Impact of tenofovir disoproxil fumarate (TDF) on achieving lower levels of lipid profile components in chronic hepatitis B carriers

Characteristic	Cholesterol	LDL-C	HDL
	Average change (%) by using TDV compared with ETV[a,b,c]		
5% lower than baseline	36% (21%-50%)	24% (11%-38%)	25% (10%-40%)
10% lower than baseline	31% (18%-44%)	21% (8%-34%)	26% (12%-40%)
15% lower than baseline	23% (11%-35%)	17% (4%-30%)	23% (9%-37%)
20% lower than baseline	14% (3%-25%)	13% (1%-25%)	20% (10%-30%)

TABLE 2 Comparison of serum lipoprotein lipid profile pre-treatment in chronic hepatitis B carriers before and after starting at least year of either tenofovir disoproxil fumarate (TDF) or entecavir (ETV) anti-viral therapy

Characteristic	TDF (N=224)		ETV (N=78)		*P* value[a]
	Median (IQR)	*P* value[b]	Median (IQR)	*P* value[b]	
Pre-Rx TC	4.42 (3.97-4.98)	<.01	4.46 (3.87-5.06)	.70	.73
Post-Rx TC	3.92 (3.51-4.50)		4.43 (3.95-5.31)		<.01
Pre-Rx LDL-C	2.51 (2.06-3.00)	<.01	2.54 (2.10-2.99)	.85	.91
Post-Rx LDL-C	2.25 (1.86-2.78)		2.54 (1.96-3.16)		<.01
Pre-Rx HDL-C	1.34 (1.09-1.62)	<.01	1.36 (1.11-1.67)	.07	.50
Post-Rx HDL-C	1.14 (0.96-1.36)		1.28 (1.07-1.59)		<.01
Pre-Rx TGL	1.02 (0.74-1.36)	.77	1.00 (0.80-1.50)	.12	.52
Post-Rx TGL	0.99 (0.74-1.46)		1.19 (0.83-1.56)		.04

[a]Comparing the same variable (either pre- or post-treatment) according to type of treatment.
[b]Comparing the pre- and post-treatment variables (paired) in each treatment type.

V-Hiperlipidemi ve Hepatosteatoz İlaç Seçimimi Etkilemeli mi ?

✓ Hiperlipidemi

✓ TDF den TAF' a geçmek

Drug Design, Development and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

The Effect of Switching from Tenofovir Disoproxil Fumarate (TDF) to Tenofovir Alafenamide (TAF) on Liver Enzymes, Glucose, and Lipid Profile

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy

Nicola Squillace,[1] Elena Ricci,[2] Barbara Menzaghi,[3] Giuseppe Vittorio De Socio,[4] Simone Passerini,[5] Canio Martinelli,[6] Maria Sabrina Mameli,[7] Paolo Maggi,[8] Katia Falasca,[9] Laura Cordier,[5] Benedetto Maurizio Celesia,[10] Elena Salomoni,[11] Antonio Di Biagio,[12] Giovanni Francesco Pellicanò,[13] Paolo Bonfanti[1]

On behalf of the CISAI Study Group

[1]Infectious Diseases Unit ASST-MONZA, San Gerardo Hospital-University of Milano-Bicocca, Monza, Italy; [2]"ASIA" Foundation ONLUS, Milan, Italy; [3]Unit of Infectious Diseases, ASST della Valle Olona, Busto Arsizio, Italy; [4]Department of Internal Medicine 2, Infectious Diseases Unit, "Santa Maria della Misericordia" General Hospital, Perugia, Italy; [5]1st Department of Infectious Diseases, ASST Fatebenefratelli Sacco, Milan, Italy; [6]Infectious Diseases Unit, Careggi Hospital, Florence, Italy; [7]Unit of Infectious Diseases, Department of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy; [8]University of Campania "Luigi Vanvitelli", Napoli

Objective: We aimed to investigate the effect of switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) on the hepatic safety and metabolic profile.
Methods: Consecutive HIV patients, enrolled in the Surveillance Cohort Long-term Toxicity Antiretrovirals/Antivirals (SCOLTA) project, switching from TDF to TAF were included. Changes from baseline (T0) to 6-month follow-up (T1) were evaluated using paired *t*-test and signed rank test.
Results: A total of 190 patients switched from TDF to TAF and had one 6-month follow-up visit. They were 80% male, 74.2% at CDC stage A–B, 93.7% with undetectable HIV-viral load. Mean age was 46.7±10.7 years, body mass index was 25.0±3.9 kg/m^2, median CD4 cell count was 634 cell/μL (interquartile range [IQR]=439–900), aspartate aminotransferase (AST) was 23 (IQR=19–30) IU/L, and alanine aminotransferase (ALT) was 24 (IQR=17–34) IU/L. At T1, both AST (median=−1, IQR=−5–2 IU/L, *P*=0.004) and ALT (median=−2, IQR=−7–3 IU/L, *P*=0.0004) showed a significant decrease. Among 28 patients with ALT >40 at baseline, reduction was significant both clinically (−17, IQR=−32–−1) and statistically (*P*=0.0003). Total cholesterol levels (TC) increased (+13.4±3.8 mg/dL, *P*=0.0006), as well as HDL-cholesterol (HDL-C) (+3.8 ±1.2 mg/dL, *P*=0.02), LDL Cholesterol (LDL-C) (+7.6±3.4, *P*=0.03) and glucose (+4.0 ±1.8 mg/dL, *P*=0.02). D:A:D: and Framingham risk score did not change at 6 months after switch.
Conclusion: A significant reduction of liver enzymes was observed after switching from TDF to TAF, especially in subjects with initial level of ALT >40 IU/L. Glucose, TC, HDL-C, and LDL-C increased, with no effect on cardiovascular risk scores.
Keywords: HIV, TDF, TAF, liver enzymes

V-Hiperlipidemi ve Hepatosteatoz İlaç Seçimimi Etkilemeli mi ?

✓ Hiperlipidemi

% 59 da statin reçete edilmeliydi ama edilmedi

✓ TDF den TAF' a geçmek

Clinical Drug Investigation (2021) 41:955–965
https://doi.org/10.1007/s40261-021-01081-y

ORIGINAL RESEARCH ARTICLE

Switch from Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide in People Living with HIV: Lipid Changes and Statin Underutilization

Laurence Brunet[1] · Patrick Mallon[2] · Jennifer S. Fusco[1] · Michael B. Wohlfeiler[3] · Girish Prajapati[4] · Andrew Beyer[4] · Gregory P. Fusco[1]

Accepted: 2 September 2021 / Published online: 21 September 2021

Abstract

Background and Objective Many people living with HIV (PLWH) on stable tenofovir disoproxil fumarate (TDF)-containing regimens have switched to tenofovir alafenamide (TAF), despite the potential lipid-lowering effect of TDF. We aimed to assess the impact of switching from TDF to TAF on lipids in real-world clinical practice.

Methods PLWH prescribed TDF for ≥ 4 weeks who switched to TAF were identified in the OPERA cohort. Patterns of dyslipidemia were compared before and after switch based on NCEP ATPIII guidelines. Elevated 10-year risk of atherosclerotic cardiovascular disease (ASCVD ≥ 7.5%) and statin use were assessed.

Results Among 6423 PLWH switched from TDF to TAF, the proportion with dyslipidemia/severe dyslipidemia observed after switch from TDF to TAF increased statistically significantly ($p < 0.0001$) with total cholesterol (5–10%), low-density lipoprotein cholesterol (16–23%), and triglycerides (21–27%), but decreased statistically significantly with high-density lipoprotein cholesterol (35–30%, $p < 0.0001$). These patterns of dyslipidemia persisted in sensitivity analyses restricted to PLWH who maintained all other antiretrovirals ($N = 4328$) or stratified by pharmaco-enhancer use before and after switch. An elevated ASCVD risk was detected in 29% before and 31% after switch. As many as 59% of PLWH with an elevated ASCVD risk were not prescribed a statin after switch from TDF to TAF.

Conclusions In this large, diverse population of PLWH in the USA, the switch from TDF to TAF was associated with development of less favorable lipid profiles, regardless of pharmaco-enhancers or third-agent use. Statins remained underutilized after a switch from TDF to TAF.

V-Hiperlipidemi ve Hepatosteatoz İlaç Seçimimi Etkilemeli mi ?

✓ Hiperlipidemi

% 59 da statin reçete edilmeliydi ama edilmedi

✓ TDF den TAF' a geçmek

ETV ye geç

Clinical Drug Investigation (2021) 41:955–965
https://doi.org/10.1007/s40261-021-01081-y

ORIGINAL RESEARCH ARTICLE

Switch from Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide in People Living with HIV: Lipid Changes and Statin Underutilization

Laurence Brunet[1] · Patrick Mallon[2] · Jennifer S. Fusco[1] · Michael B. Wohlfeiler[3] · Girish Prajapati[4] · Andrew Beyer[4] · Gregory P. Fusco[1]

Accepted: 2 September 2021 / Published online: 21 September 2021

Abstract

Background and Objective Many people living with HIV (PLWH) on stable tenofovir disoproxil fumarate (TDF)-containing regimens have switched to tenofovir alafenamide (TAF), despite the potential lipid-lowering effect of TDF. We aimed to assess the impact of switching from TDF to TAF on lipids in real-world clinical practice.

Methods PLWH prescribed TDF for ≥ 4 weeks who switched to TAF were identified in the OPERA cohort. Patterns of dyslipidemia were compared before and after switch based on NCEP ATPIII guidelines. Elevated 10-year risk of atherosclerotic cardiovascular disease (ASCVD ≥ 7.5%) and statin use were assessed.

Results Among 6423 PLWH switched from TDF to TAF, the proportion with dyslipidemia/severe dyslipidemia observed after switch from TDF to TAF increased statistically significantly ($p < 0.0001$) with total cholesterol (5–10%), low-density lipoprotein cholesterol (16–23%), and triglycerides (21–27%), but decreased statistically significantly with high-density lipoprotein cholesterol (35–30%, $p < 0.0001$). These patterns of dyslipidemia persisted in sensitivity analyses restricted to PLWH who maintained all other antiretrovirals ($N = 4328$) or stratified by pharmaco-enhancer use before and after switch. An elevated ASCVD risk was detected in 29% before and 31% after switch. As many as 59% of PLWH with an elevated ASCVD risk were not prescribed a statin after switch from TDF to TAF.

Conclusions In this large, diverse population of PLWH in the USA, the switch from TDF to TAF was associated with development of less favorable lipid profiles, regardless of pharmaco-enhancers or third-agent use. Statins remained underutilized after a switch from TDF to TAF.

V-Hiperlipidemi ve Hepatosteatoz İlaç Seçimimi Etkilemeli mi ?

✓ Karaciğer Yağlanması

EFFECT OF ANTIVIRAL TREATMENT ON NAFLD

Few studies have investigated the incidence of hepatic steatosis during antiviral treatment with pegylated interferon and nucleos(t)ide analogs (NAs). NA therapy reduces HBV replication, suppresses inflammation, and improves fibrosis in CHB[56]. Most studies have shown that NAFLD has no impact on viral suppression and biochemical responses during NAs antiviral treatment[65,66]. Whereas, decreased virological responses were also observed in CHB patients concomitant with steatosis in several studies[43,67,68]. In those cases, the authors speculated that the elevated ALT caused by NAFLD could lead to premature antiviral treatment and a poor response.

- TDF karaciğer yağlanmasını azaltıyor
- Hepatik CD36 upregülasyonu yaparak PPAR alfa aktivasyonuna neden olduğu ve
- Lipidler üzerine olumlu etkisi olması olduğu düşünülüyor

Shaheen AA, Pharmacol Ther 2017; 46: 599-604
Suzuki K, J Gastroenterol 2021; 56: 168-180
Sripongpun P, Clin Gastroenterol Hepatol 2020

V-Hiperlipidemi ve Hepatosteatoz İlaç Seçimimi Etkilemeli mi ?

✓ Kilo Alımı

Mallon PWG et al. *Journal of the International AIDS Society* 2021, **24**:e25702
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25702/full | https://doi.org/10.1002/jia2.25702

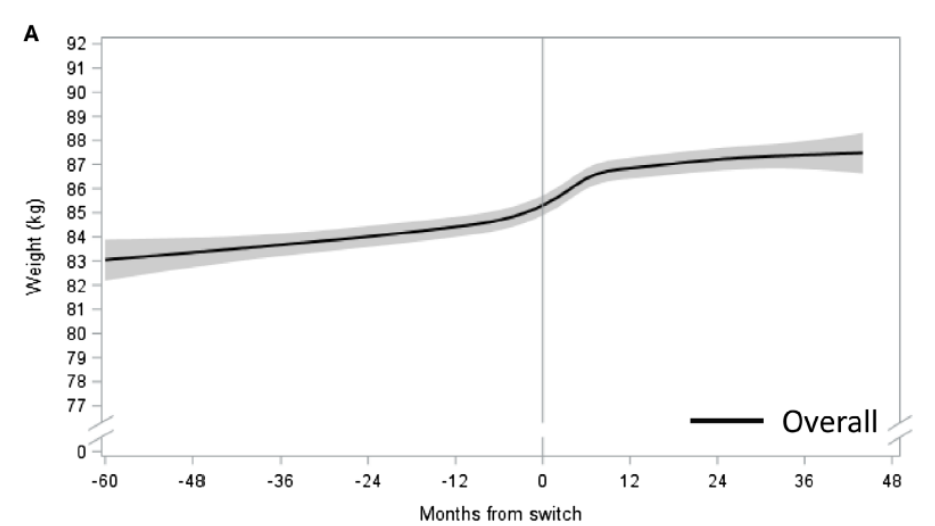
JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Weight gain before and after switch from TDF to TAF in a U.S. cohort study

Patrick WG Mallon[1,2], Laurence Brunet[3,5], Ricky K Hsu[4,5], Jennifer S Fusco[3], Karam C Mounzer[6], Girish Prajapati[7], Andrew P Beyer[7], Michael B Wohlfeiler[8] and Gregory P Fusco[3]

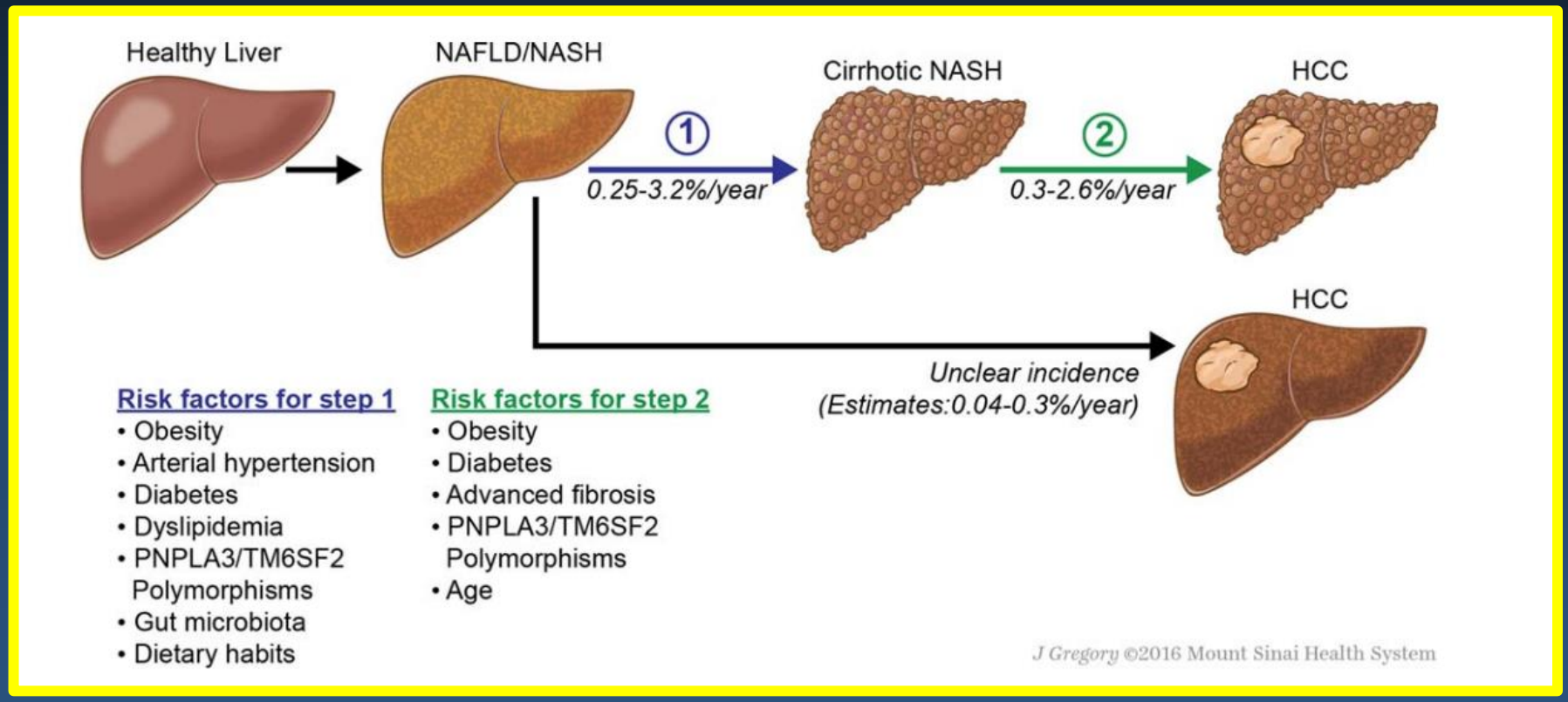
[6]**Corresponding author**: Laurence Brunet, 4819 Emperor Blvd, Suite 400, Durham, North Carolina 27703, USA. Tel: +919-827-0010. (laurence.brunet@epividian.com)



With growing concerns over the risks of weight gain with modern ART, the most recent U.S. HIV treatment guidelines summarize current evidence on weight gain with InSTIs or TAF, but note that "the clinical significance of these findings is still unknown" [32]. It is therefore essential to understand the respective roles of core agents versus TAF on weight gain. The objective of this study was to assess changes in weight before and after switching from TDF to TAF, among virologically suppressed PLWH in the United States, stratified by core agent.

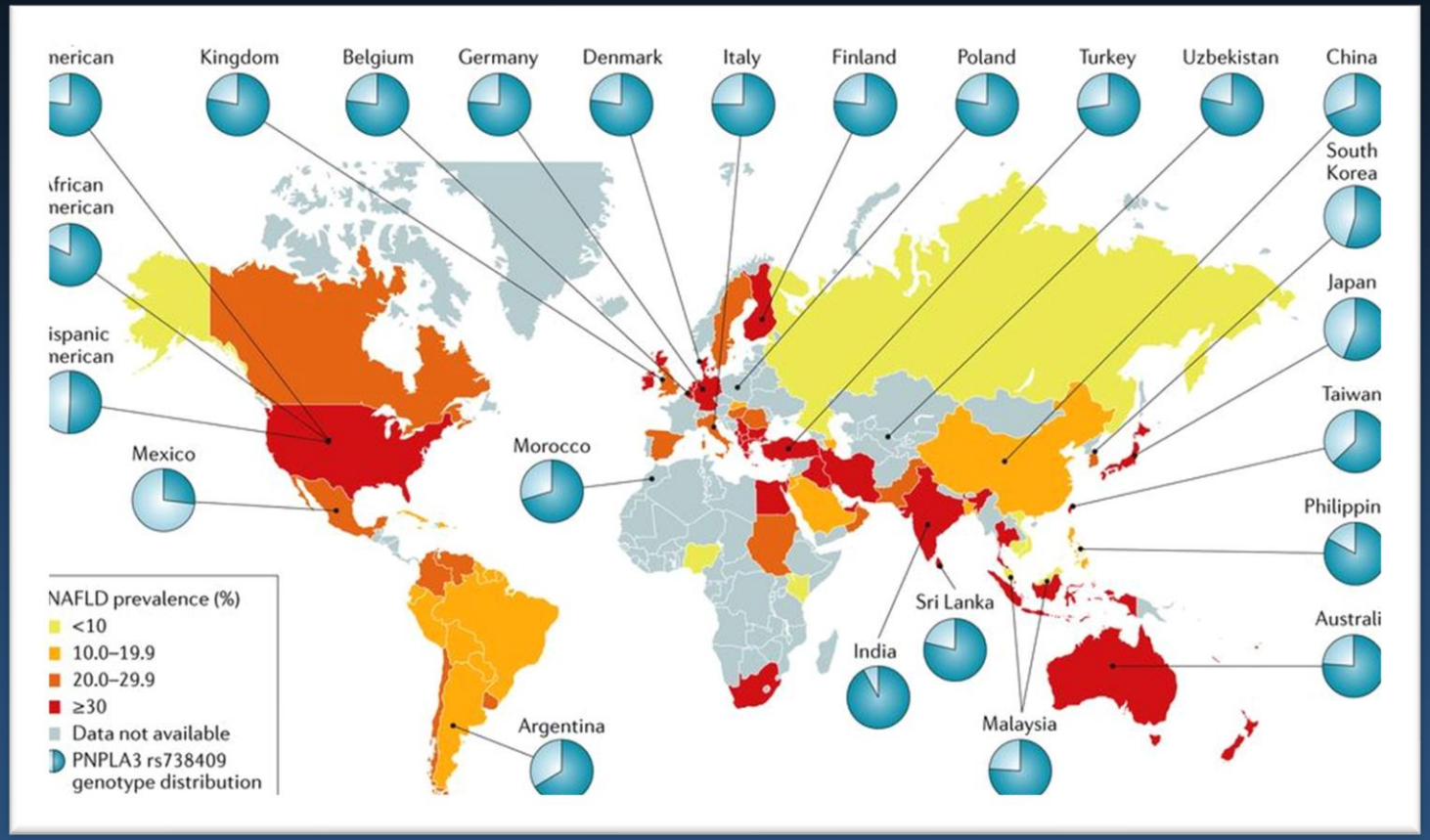
Mallon WP et al. Journal of the International AIDS Society 2021, 24:e25702

Karaciğer Yağlanması Çok Önemli Bir Sağlık Sorunudur



D'Avola D et l.Clin Liver Dis. Vol:8 No:4 Oct 2016

NAFLD-NASH Dünyada Ne Kadar ?



Erişkinlerde: %25…..Çocuklarda: %7-10

Younossi Z, et al. Nat Rev Gastroenterol Hepatol. 2018 Jan;15(1):11-20.

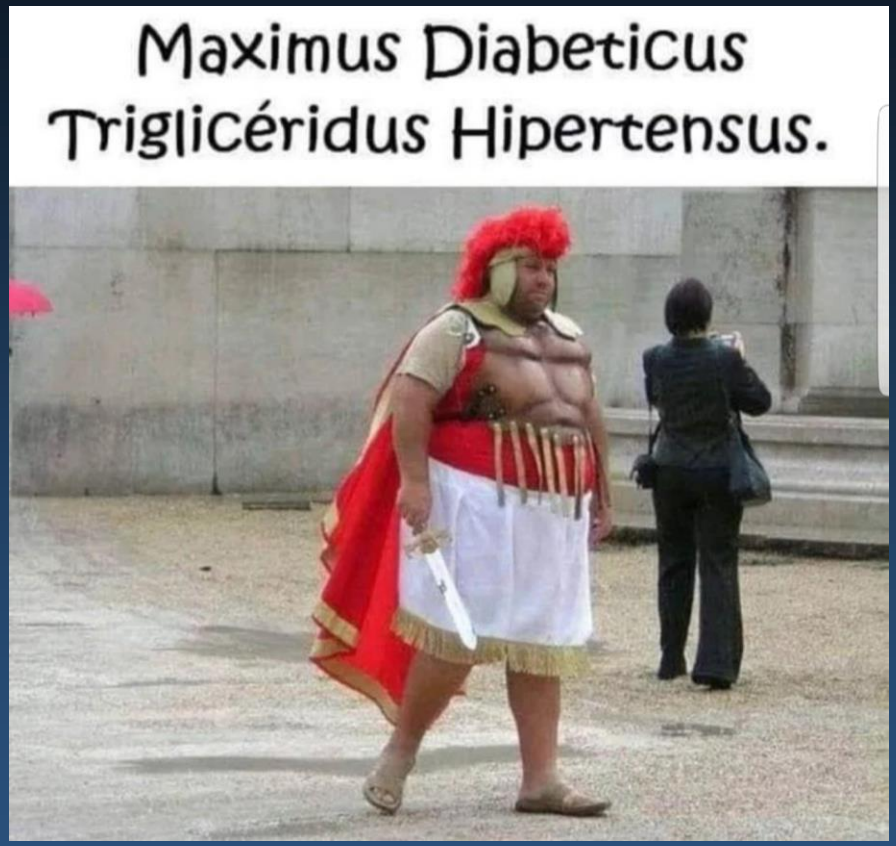
Peki Neden Böyle Artıyor ?

- ✓ Hareket etmiyoruz
- ✓ Kötü besleniyoruz
- ✓ Kilo alıyoruz
- ✓ Diabet oluyoruz
- ✓ Metabolik Sendrom

Karaciğerimiz Yağlanıyor

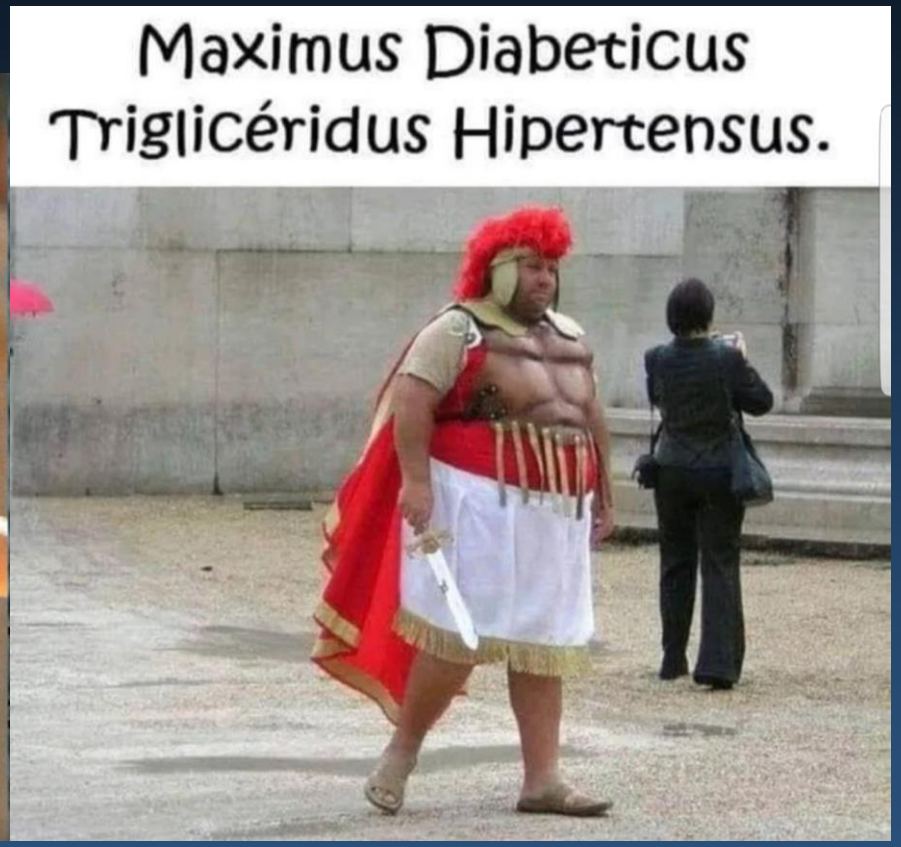
Peki Neden Böyle Artıyor ?

- ✓ Hareket etmiyoruz
- ✓ Kötü besleniyoruz
- ✓ Kilo alıyoruz
- ✓ Diabet oluyoruz
- ✓ Metabolik Sendrom



Karaciğerimiz Yağlanıyor

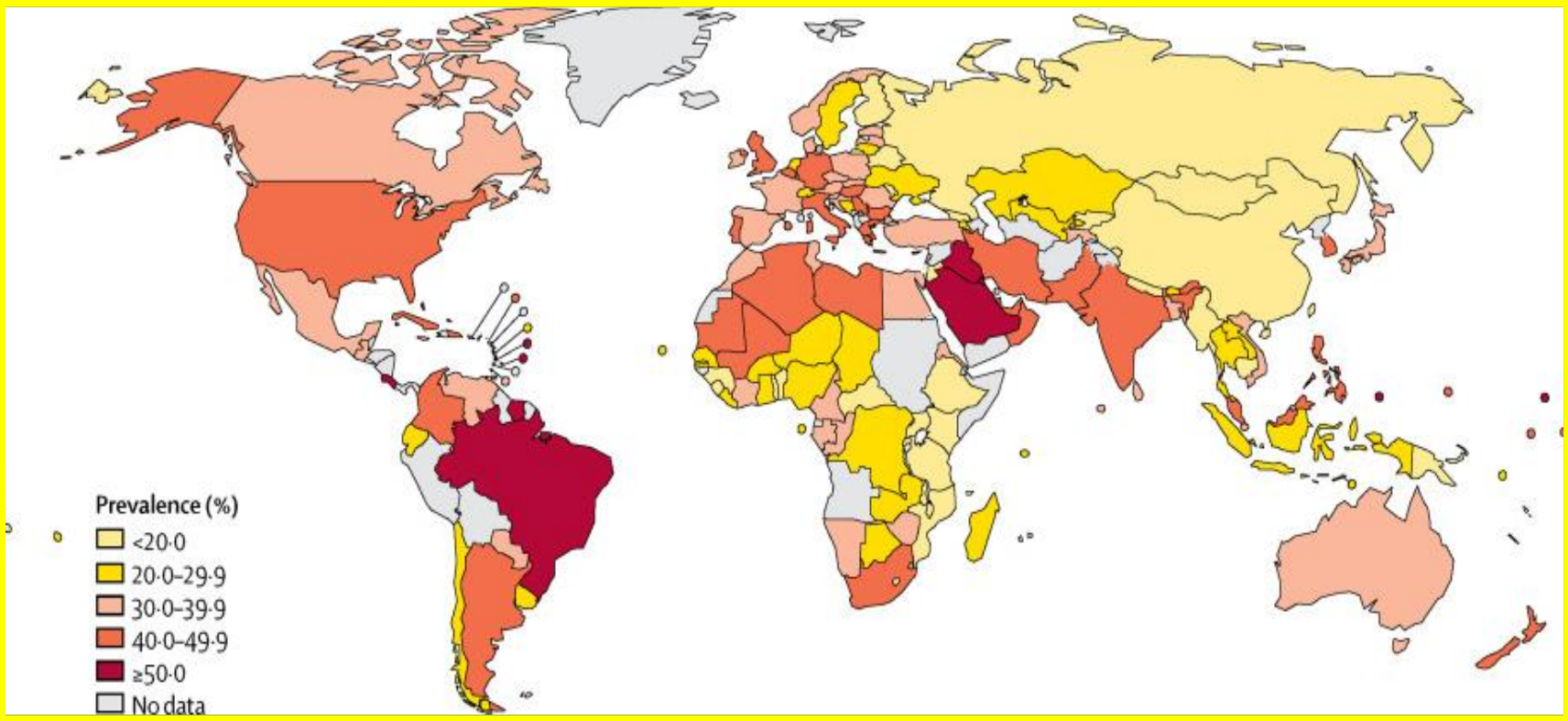
Peki Neden Böyle Artıyor ?



Peki Neden Böyle Artıyor ?

Peki Neden Böyle Artıyor ?

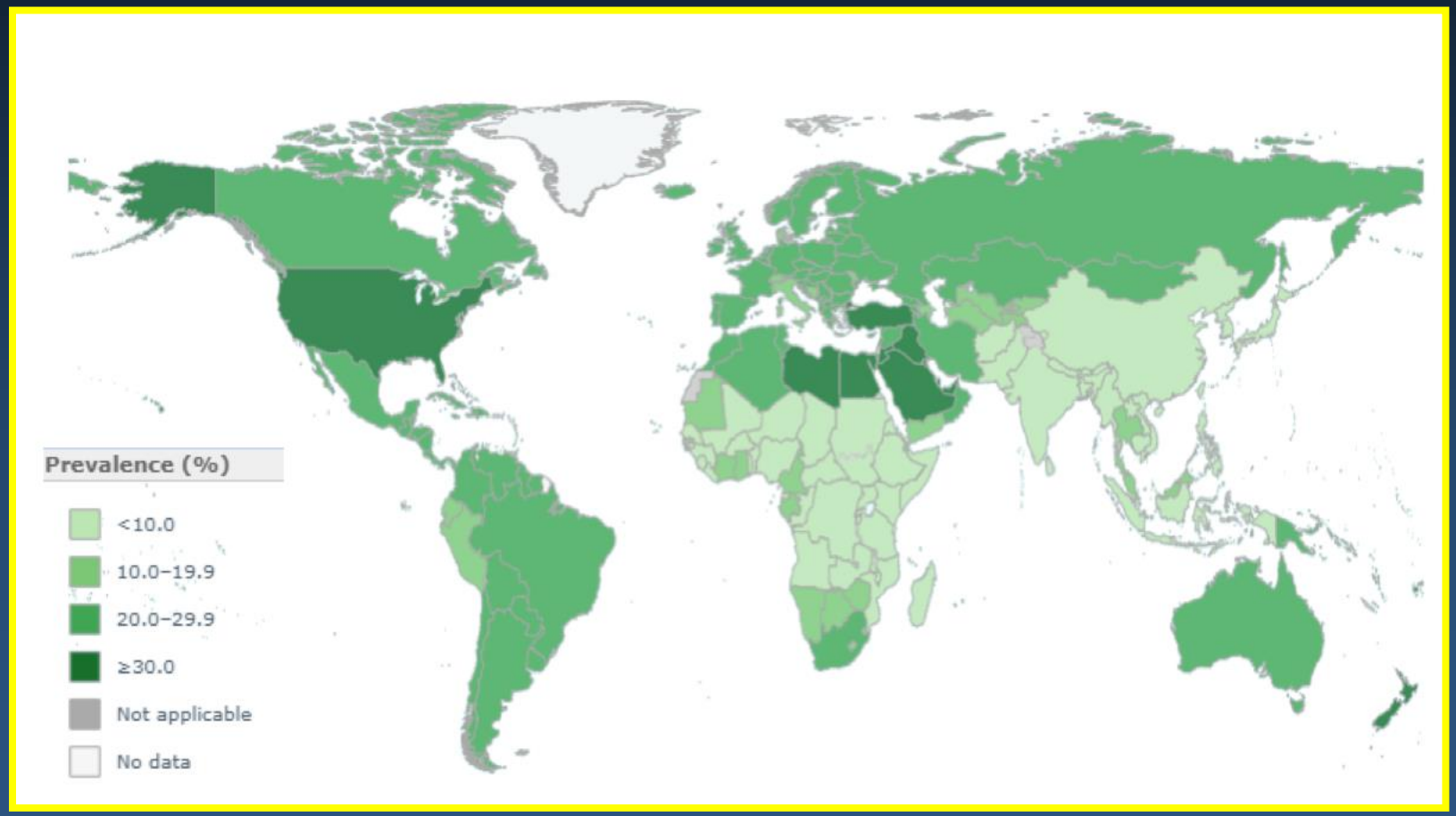
Yetersiz fiziksel aktivite %27,5



Guthold R et al. Lancet Glob Health. 2018 Oct;6(10):e1077-e1086.

Peki Neden Böyle Artıyor ?

Dünyada kilo fazlası olanlar %39



WHO 2016. Global Health Observatory Data. http://www.who.int/gho/ncd/risk_factors/overweight_obesity/obesity_adults/en/ Nov 1, 2018

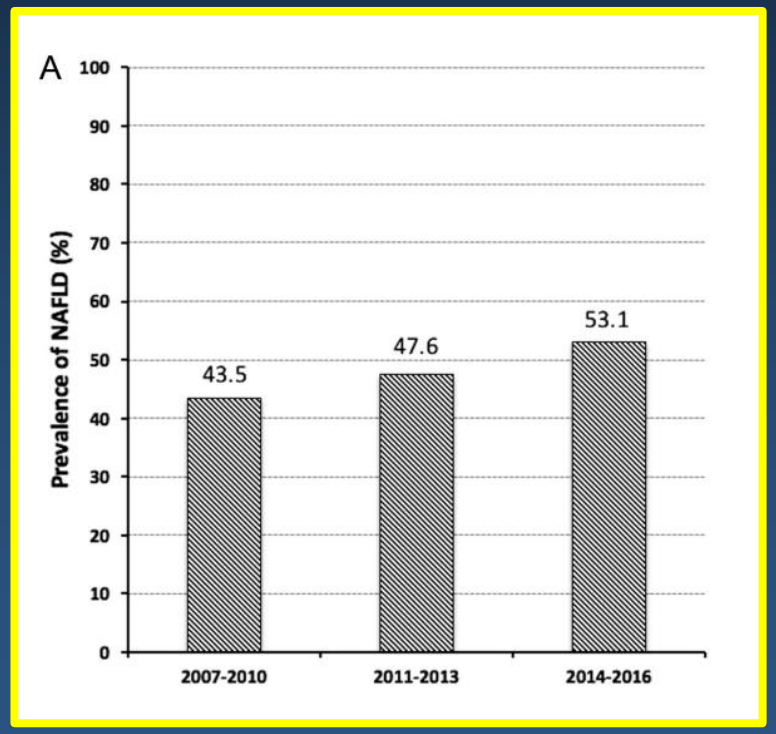
Türkiye'de NAFLD Sıklığı

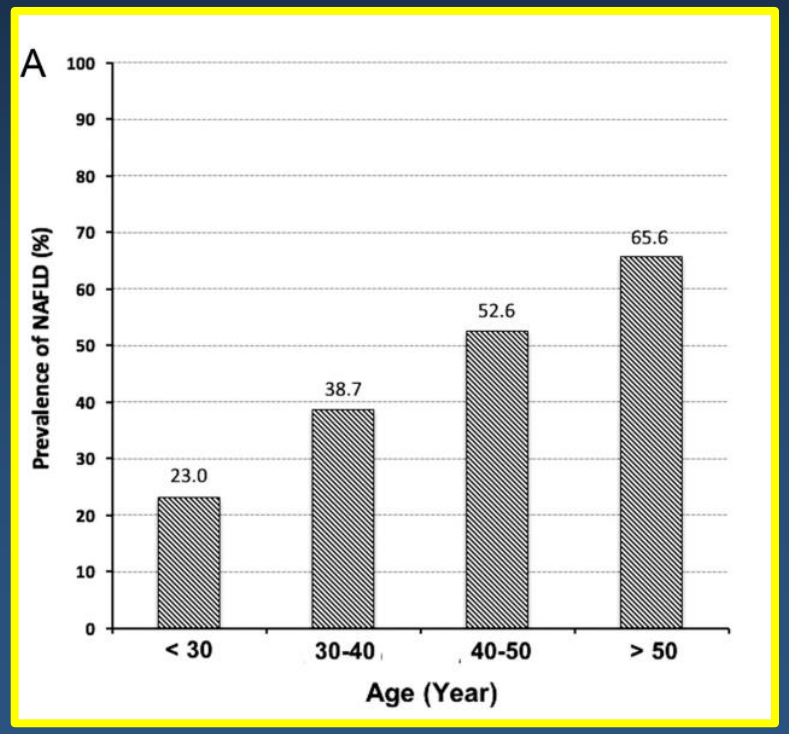
The Changing Prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) in Turkey in the Last Decade

Bülent Değertekin[1], Nurdan Tözün[1], Figen Demir[2], Gizem Söylemez[3], Şirin Parkan[4], Ezgi Gürtay[3], Deniz Mutlu[3], Meltem Toraman[3], Tolga Hayrettin Seymenoğlu[3]

[1]Division of Gastroenterology and Hepatology, Acibadem Mehmet Ali Aydinlar University, School of Medicine, Istanbul, Turkey
[2]Division of Social Health, Acibadem Mehmet Ali Aydinlar University, School of Medicine, Istanbul, Turkey
[3]Acibadem Mehmet Ali Aydinlar University, School of Medicine, Istanbul, Turkey
[4]Check-up Unit of Acibadem Kadikoy Hospital, Acibadem Mehmet Ali Aydinlar University, School of Medicine, Istanbul, Turkey

- n=6567 hasta (15 merkez)
- NAFLD sıklığı %48,3

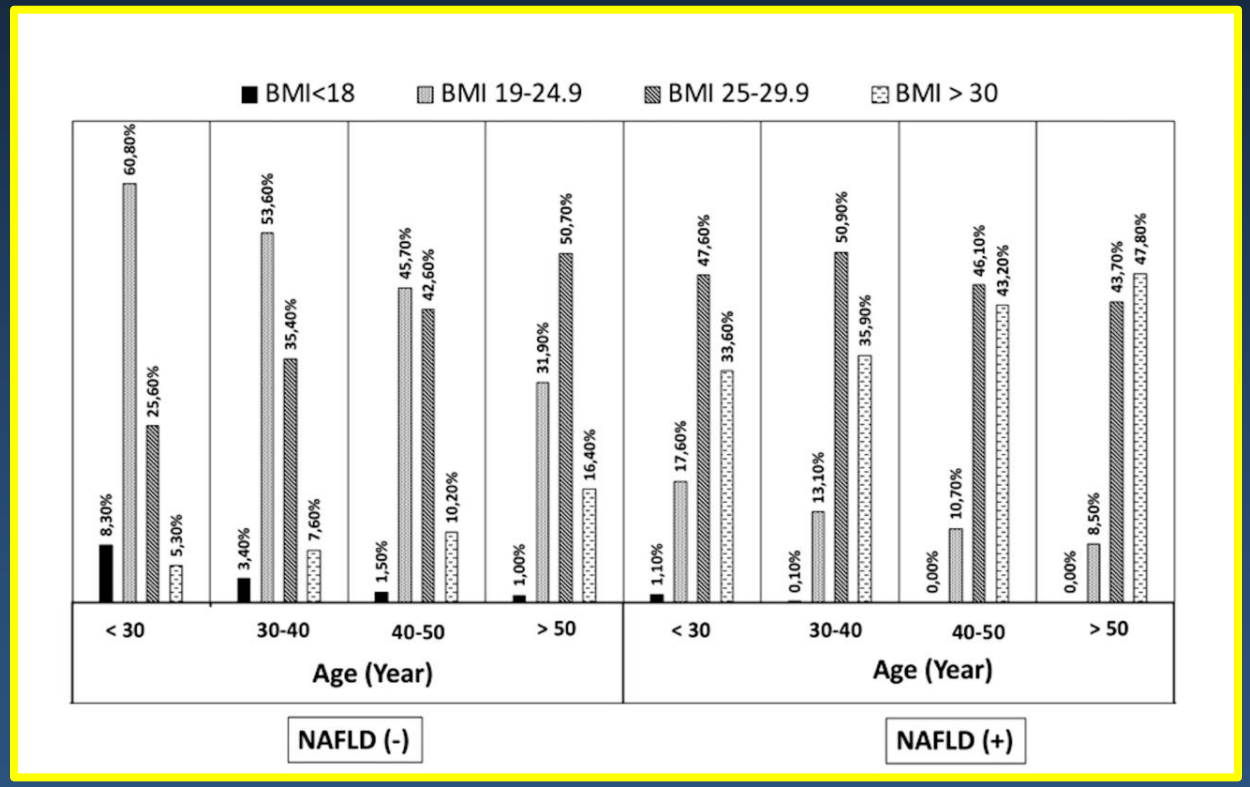




Degertekin B et al. Turk J Gastroenterol. 2021; 32(3): 302-312

Türkiye'de NAFLD Sıklığı

- n=6567 hasta (15 merkez)
- NAFLD sıklığı %48,3



Degertekin B et al. Turk J Gastroenterol. 2021; 32(3): 302-312

Türkiye'de NAFLD ve MAFLD Sıklığı

Research Article
MAFLD in Turkish population

HEPATOLOGY FORUM
doi: 10.14744/hf.2021.2020.0033

The prevalence of metabolic-associated fatty liver disease in the Turkish population: A multicenter study

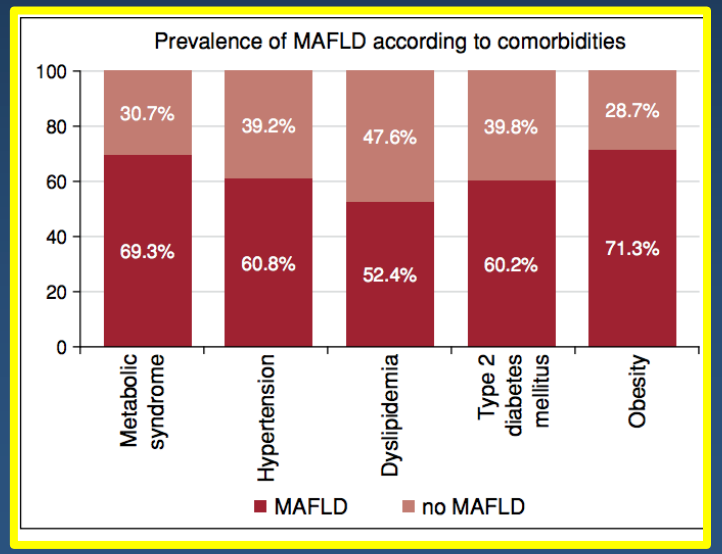
Yusuf Yilmaz[1], Nimet Yilmaz[2], Fehmi Ates[3], Fatih Karakaya[4], Hale Gokcan[5], Eda Kaya[6], Gupse Adali[7], Aysun Caliskan Kartal[8], Ilker Sen[9], Emel Ahishali[10], Seren Ozenirler[11], Mehmet Koruk[12], Ahmet Uygun[4], Ramazan Idilman[8], Turkish Association for the Study of the Liver (TASL), Fatty Liver Diseases Special Interest Groups

- n=909 hasta (8 merkez)
- MAFLD sıklığı %45,5

Table 3. Comparison of comorbidity prevalence between patients with MAFLD and NAFLD

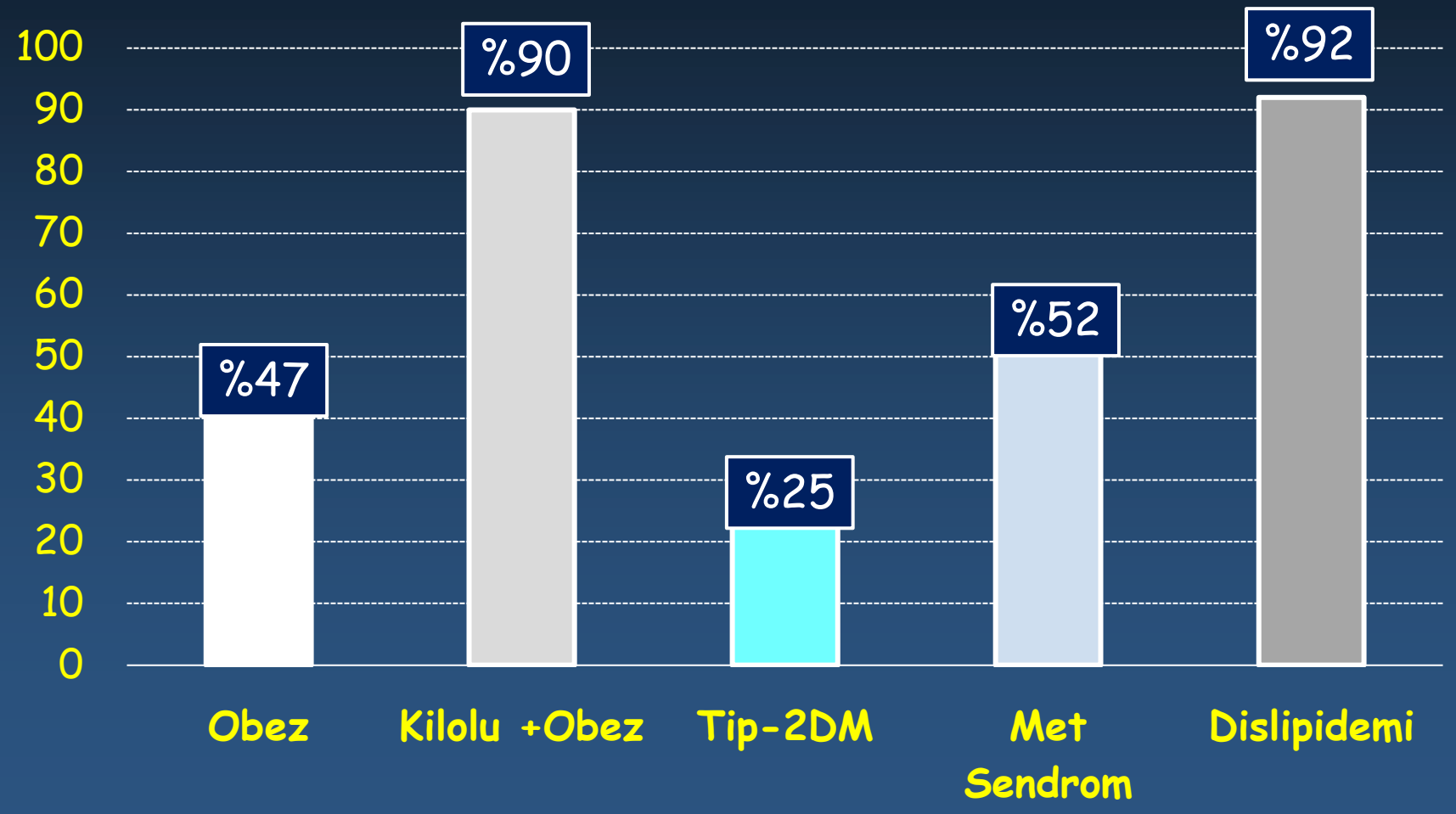
Comorbidity	MAFLD (n=414)	NAFLD (n=467)
Obesity	159/366 (43.4%)	159/386 (41.2%)
Type 2 diabetes mellitus	103/414 (24.9%)	103/467 (22.1%)
Metabolic syndrome	217/413 (52.5%)	217/466 (46.6%)
Dyslipidemia	360/390 (92.3%)	386/430 (89.8%)
Hypertension	132/414 (31.9%)	134/467 (28.7%)

MAFLD: Metabolic-associated fatty liver disease; NAFLD: Non-alcoholic fatty liver disease.



Yılmaz Y et al. Hepatology Forum 2021 Vol. 2 37-42

Poliklinikte Karşımıza Yağlı Karaciğer ile Gelen Hastaların



Ülkemizin Rakamları Neler Söylüyor ?

60 milyon erişkin var

- 30 milyon →NAFLD……. (NAFLD %50)
- 6 milyon →NASH…… (NAFLD hastalarının %20'si)
- 1,5 milyon →İleri fibrozisi (≥ F2) NASH……(NASH hast %25'i)
- 210.00 →NASH ilişkili siroz……(NASH hast %3,5'u)

Peki Bu İleri Fibrozis Hastalarını Nasıl Yakalayabiliriz ?

Aile Hekimlerine, Dahiliyecilere ve Endokrinologlara Öneriler

Obezite, Tip 2 DM, metabolik sendrom tanısı olan hastalar karaciğer yağlanması için ultrasonografi ile taranmalıdır. Yağlanma saptananlarda FIB-4 skoru hesaplanmalıdır.

Herhangi bir görüntüleme yöntemi ile karaciğerde yağlanması olduğu bilinen hastalarda eşlik eden metabolik risk faktörlerinden bağımsız olarak FIB-4 skoru hesaplanmalıdır.

Persistan AST- ALT yüksekliği olan hastalar Gastroenteroloji'ye doğrudan yönlendirilmelidir.

↓

NAFLD

↓

FIB-4 Skoru Hesapla

https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis

↓ *FIB-4 <1.3*

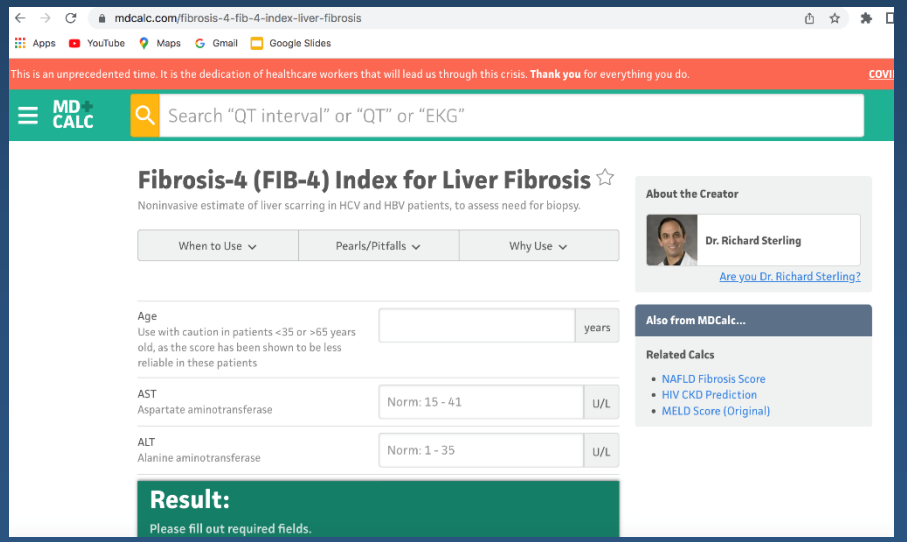
- Yönlendirme ihtiyacı yok
- Kardiyovasküler risk faktörlerinin uygun medikal tedavisi
- Yaşam tarzı değişikliği
- Yılda bir FIB-4 ile yeniden değerlendir

↓ *FIB-4 ≥1.3*

- Hasta Gastroenteroloji'ye yönlendirilmelidir.
- Gastroenteroloji'de öncelikle NAFLD tanısı kesinleştirilmelidir.
- Fibrozis değerlendirilmesi için ek değerlendirmeler gerekir.
- Elastografik yöntemler
  - Fibroscan, ARFI, SSI, MRE
- Biyobelirteç paneller
  - ELF, Pro-C3, ADAPT, FIBC3/ABC3D

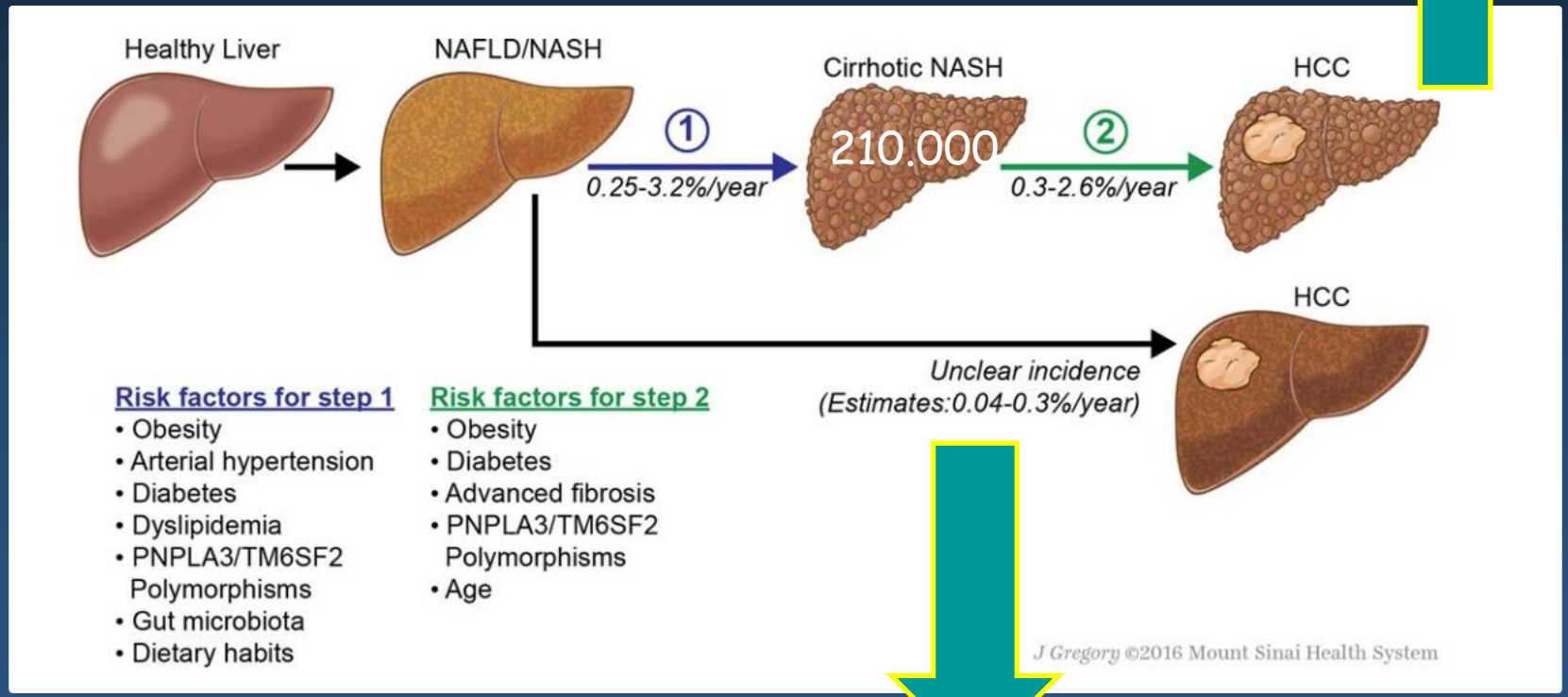
Fibroscan (Vibration controlled transient elastography)
ARFI (Acoustic Radiation Force Impulse)
SSI (Supersonic Shear Imaging)
MRE (Magnetic Resonance Elastography)

Şekil 2. İleri evre fibrozisi olan yüksek riskli hastaları belirleme ve yönlendirme şeması.



Ülkemizin Rakamları Neler Söylüyor ?

630-5469

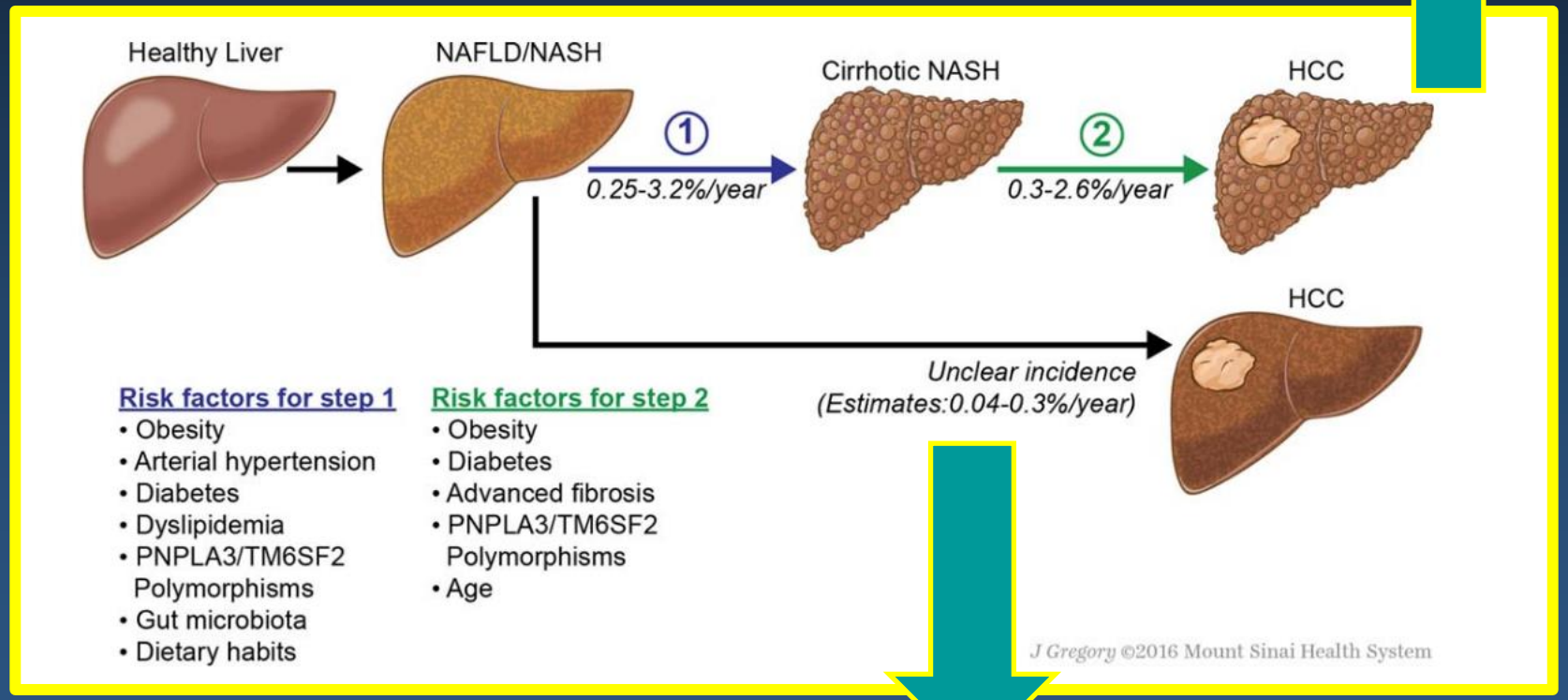


600-4500

Ülkemizin Rakamları Neler Söylüyor ?

1230-9969 hasta/yıllık HCC gelişimi

630-5469



600-4500

HCC' nin Etiyolojisinde NASH Giderek Önem Kazanıyor

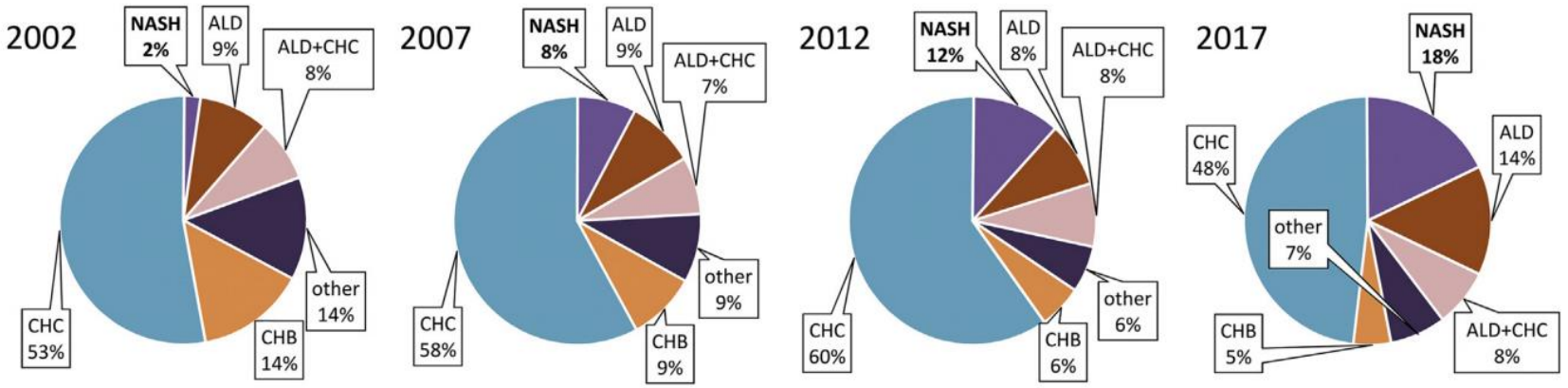


Figure 3. Etiologies of HCC in waitlisted candidates (with available HCC etiology).

Younossi Z et al. Clinical Gastroenterology and Hepatology 2019;17:748–755

Kronik HBV Hastalarında Metabolik Bozukluklar Önemlidir

- Poliklinikte karşımıza gelen kronik HBV hastasında ciddi yağlı karaciğer sorunu olabileceği unutulmamalı
- Bu hastalarının çoğu karaciğer dışı nedenlerden ölüyorlar
- Bu nedenle hastaların yağlanma dışındaki obezite, dislipidemi, DM ve hipertansiyonu ile de ilgilenmeliyiz
- TDF TAF ve ETV ye oranla avantajlı bir tercih gibi gözüküyor

V-Uzun Dönem Başarıda Gebelik

✓ Gebeler

❖ Gebede HBsAg (+) görüldüğünde

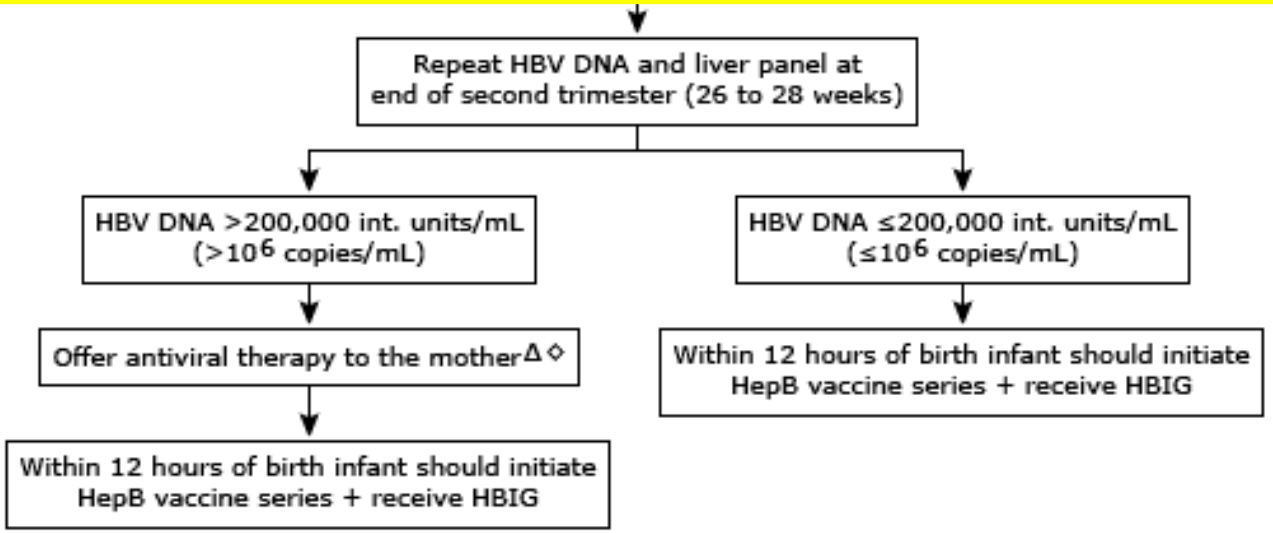
- ✓ Tedaviyi hak ediyor mu ?
  (HBV DNA>2000 ve ALT>NÜS)
- ✓ Bebeğe geçme riski ne kadar ?
  (26-28.hafta HBV DNA düzeyi)

V-Uzun Dönem Başarıda Gebelik

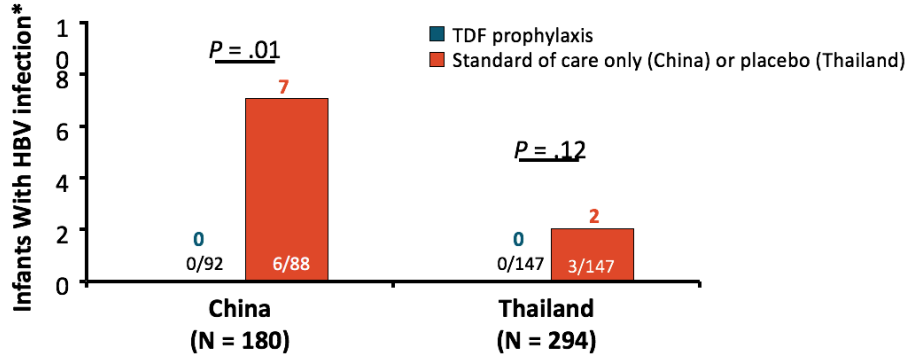
✓ Gebeler

- İlaç kullanmıyorsa 26-28 haftadaki HBV DNA >200000 IU/mL olmasına bakılır
- Tenofovir tercih edilecek ajandır (Kategori B)
- Gebelik sonrası 12 hafta daha verilmeli
- Doğumda HBIG ve aşı verilmeli ilk 12 saatte
- Hasta süt verebilir (HBIG ve aşı olanlar özellikle)

V-Uzun Dönem Başarıda Gebelik



- No cases of transmission with TDF prophylaxis during third trimester of gestation in randomised controlled trials in Asia[1,2]



*At Wk 28 following delivery in China and 6 mos following delivery in Thailand.

VI-Uzun Dönem Başarıda İmmünsupresyonun Etkisi

Hastanın Reaktivasyon Riski

Verilen İmmünosupresyonunun Şiddeti

- HBsAg (+)
- HBsAg (-) AntiHBc (+) Anti-HBs (-)
- HBsAg (-) AntiHBc (+) Anti-HBs (+)

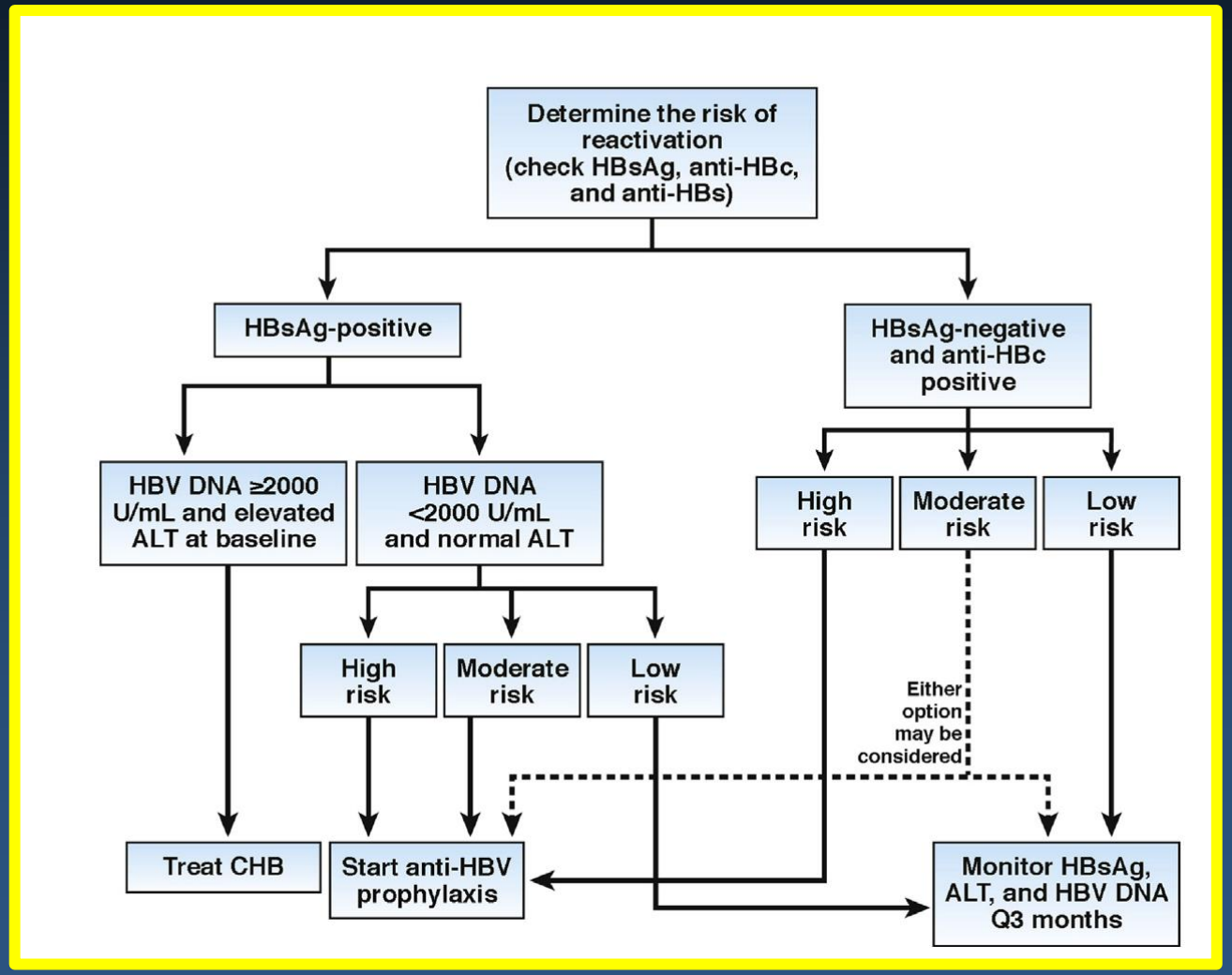
VI-Uzun Dönem Başarıda İmmünsupresyonun Etkisi

HBsAg(+)

HBsAg(-)

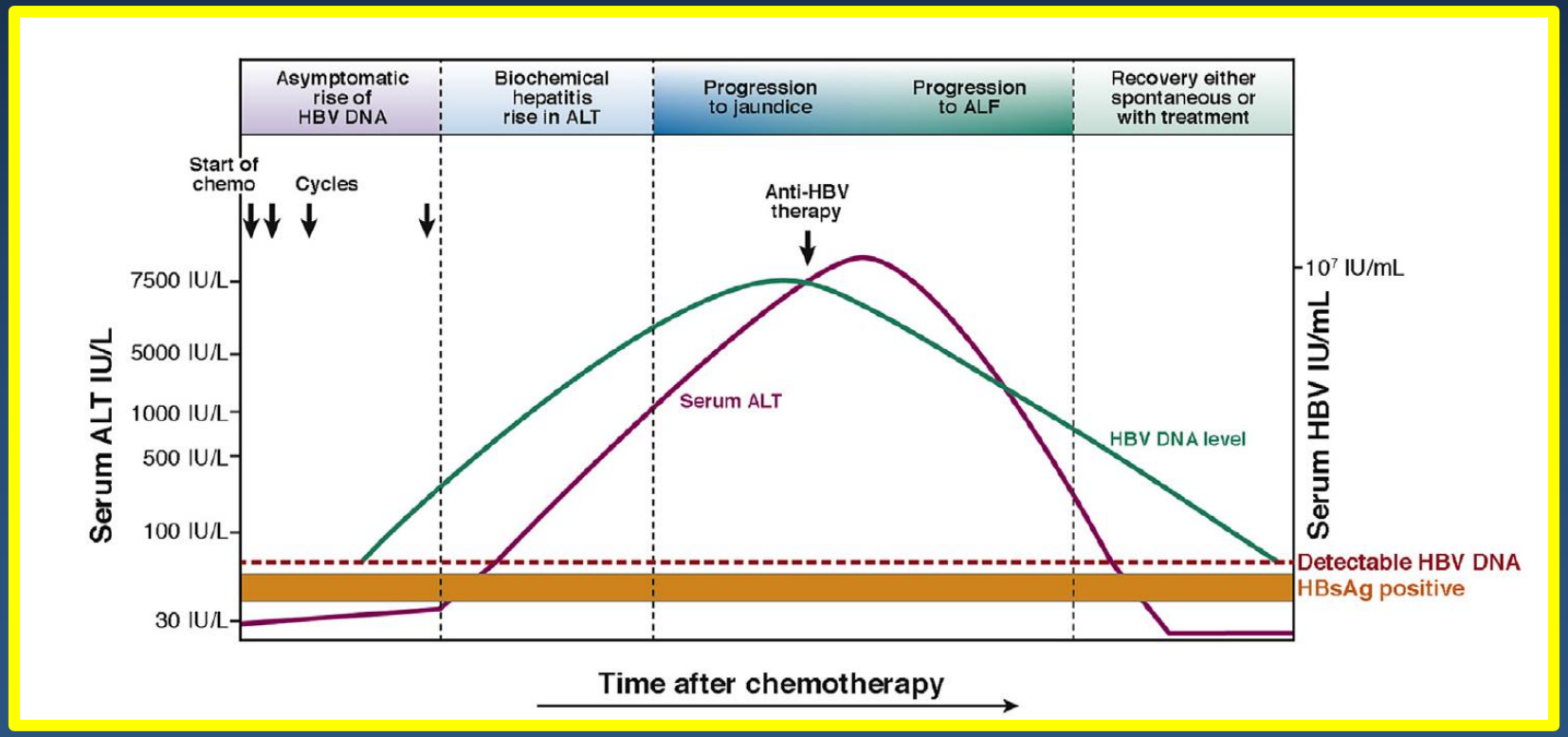
	Immunosuppressive therapies
Risk of reactivation in HBsAg-positive patients	
High risk of reactivation (>%10)	B-cell–depleting agents including rituximab, ofatumumab, natalizumab, alemtuzumab, and ibritumomab
	High-dose corticosteroids — >4 Hafta (>20mg Prednizolon)
	Anthracyclines including doxorubicin and epirubicin
	More potent TNF-α inhibitors including infliximab, adalimumab, certolizumab, and golimumab
	Local therapy for HCC including TACE
Moderate risk of reactivation (%1-10)	Systemic chemotherapy
	Less potent TNF-α inhibitors including etanercept
	Cytokine-based therapies including abatacept, ustekinumab, mogamulizumab, natalizumab, and vedolizumab
	Immunophilin inhibitors including cyclosporine
	Tyrosine-kinase inhibitors including imatinib and nilotinib
	Proteasome inhibitors such as bortezomib
	HDIs
	Moderate-dose corticosteroids — >4 Hafta (>10-20 mg Prednizolon)
Low risk of reactivation	Antimetabolites, azathioprine, 6-mercaptopurine, and methotrexate
	Short-term low-dose corticosteroids
	Intra-articular steroid injections (extremely low risk)
Risk of reactivation in HBsAg-negative and anti-HBc positive patients[a]	
High risk of reactivation	B-cell–depleting agents including rituximab, ofatumumab, natalizumab, alemtuzumab, ibritumomab
Moderate risk of reactivation	High-dose corticosteroids
	Anthracyclines including doxorubicin and epirubicin
	More potent TNF-α inhibitors including infliximab, adalimumab, certolizumab, and golimumab
	Systemic cancer chemotherapy including HCC
	Cytokine-based therapies including abatacept, ustekinumab, mogamulizumab, natalizumab, and vedolizumab
	Immunophilin inhibitors including cyclosporine
	Tyrosine-kinase inhibitors including imatinib and nilotinib
	Proteasome inhibitors such as bortezomib
	HDIs
Low risk of reactivation	Moderate- and low-dose prednisone
	Antimetabolites, azathioprine, 6-mercaptopurine, and methotrexate

VI-Uzun Dönem Başarıda İmmünsupresyonun Etkisi



VI-Uzun Dönem Başarıda İmmünsupresyonun Etkisi

ALT ye güvenmeyin… Önce HBV DNA yükselir



VI-Uzun Dönem Başarıda İmmünsupresyonun Etkisi

- Kemoterapiden 1-3 hafta önce başlanmalı
- ETV, TAF ve TDF eşit düzeyde önerilmektedir
- Supresyon sonrası 6-12 ay devam edilir ve kesilir

Sonuç Olarak.. Uzun Dönem Başarı İçin

- Doğru hastaya tedavi başlamak lazım (Standart tedavi)
  - ✓ ALT > NÜS ve HBV DNA>2000 olması ve/veya F2 hasar

- Bazı Hastalara yakın dikkat lazım (Verilse İyi Olur)
  - ✓ Ailede HCC olanlar
  - ✓ 40 yaş üstü inaktif taşıyıcılar ve
  - ✓ 30 yaş üstü immüntoleran vakalarda

Sonuç Olarak Uzun Dönem Başarı İçin

✓ Doğru OAV Verilmeli

- Naivlerde ETV, TDF ve TAF
- LAM deneyimlilerde… TDF ve TAF tercih edilmeli
- Kemik ve böbrek sorunu olanlarda ETV (deneyimli. TAF)
- TDF veya TAF ile sorun olduğunu düşündüğümüz hastalarda LAM kullanım öyküsü yoksa kesinlikle ETV
- Karaciğer yağlanması ve metabolik sorunlar uzun dönem de hastaların mortalitesinin en büyük sorumlusudur

Uzun Dönem Başarı İçin…

- Renal sorunları → ETV >TAF
- Kemik Erimesi → Naif vakada ETV… Deneyimli TAF
- Gebeler → TDF
- Hiperlipidemi → TDF>ETV
- Hepatosteatoz → TDF>ETV
- Kilo Alımı → TDF>ETV
- ACLF → TDF=ETV=TAF
- KC-Transp. → TDF=ETV=TAF
- İmm. supresyon → TDF=ETV=TAF