HCV&HIV KOENFEKSİYONU

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Hitit Ünversitesi Tıp Fakültesi

SUNUM PLANI

HCV/HIV koenfeksiyonu

- Epidemiyoloji
- Patogenez
- Klinik
- Tedavi

HCV MONOENFEKSİYONDAN FARKLI NE VAR?

OLGU

- 34 Y, Erkek
- Başvuru tarihi:03.01.2017
- Biseksiüel, IVDU, Alkol, esrar, extasy
- 2015:Dış merkezde Anti HIV (+)
- Takip: 1 yıl ilaçsız izlem
- 2016: Elvitegravir/kobisistat/emtrisitabin/TDF(Stribild)
- Düzensiz ilaç kullanımı
- Şikayet: Halsizlik, yorgunluk
  El ve ayaklarda uyuşma
- Anksiyete ve depresyon
- FM: Olağan

OLGU

Laboratuvar:04.01.2017

- WBC:7900 /uL
- Hgb:15,2 g/dL
- Trombosit:221000 /uL
- AKŞ:99 mg/dL
- Kreatinin:1,07 mg/dL
- INR:1,1
- Albumin:4,6gr/dl

- AST:28 U/L ALT:32 U/L
- ALP:98 U/L GGT:196 U/L
- Trigliserid:137 mg/dL Total Kolesterol:121 mg/dL
- HDL:35mg/dL LDL:59 mg/dl
- HbsAg: (-) Anti-HBs: (-) Anti-HBc IgG: (-)
- Anti HCV: (+)

EPİDEMİYOLOJİ

- Benzer bulaş yolları (parenteral-seksüel-vertikal)

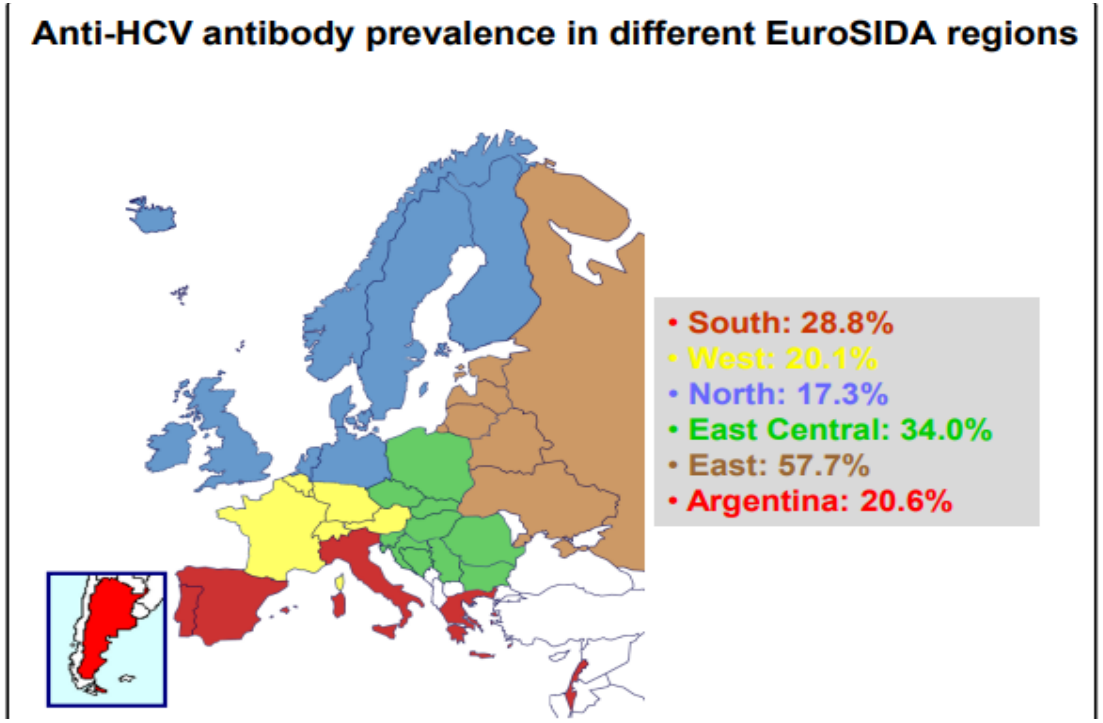
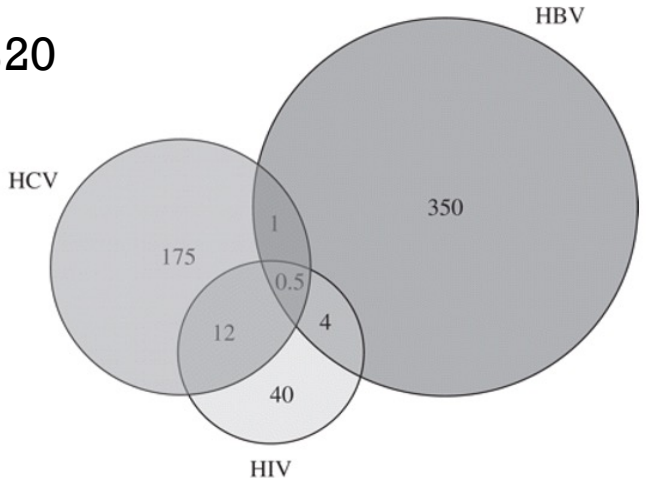


Figure 1. Estimated number (in millions) of subjects infected with HIV, HBV and HCV worldwide.

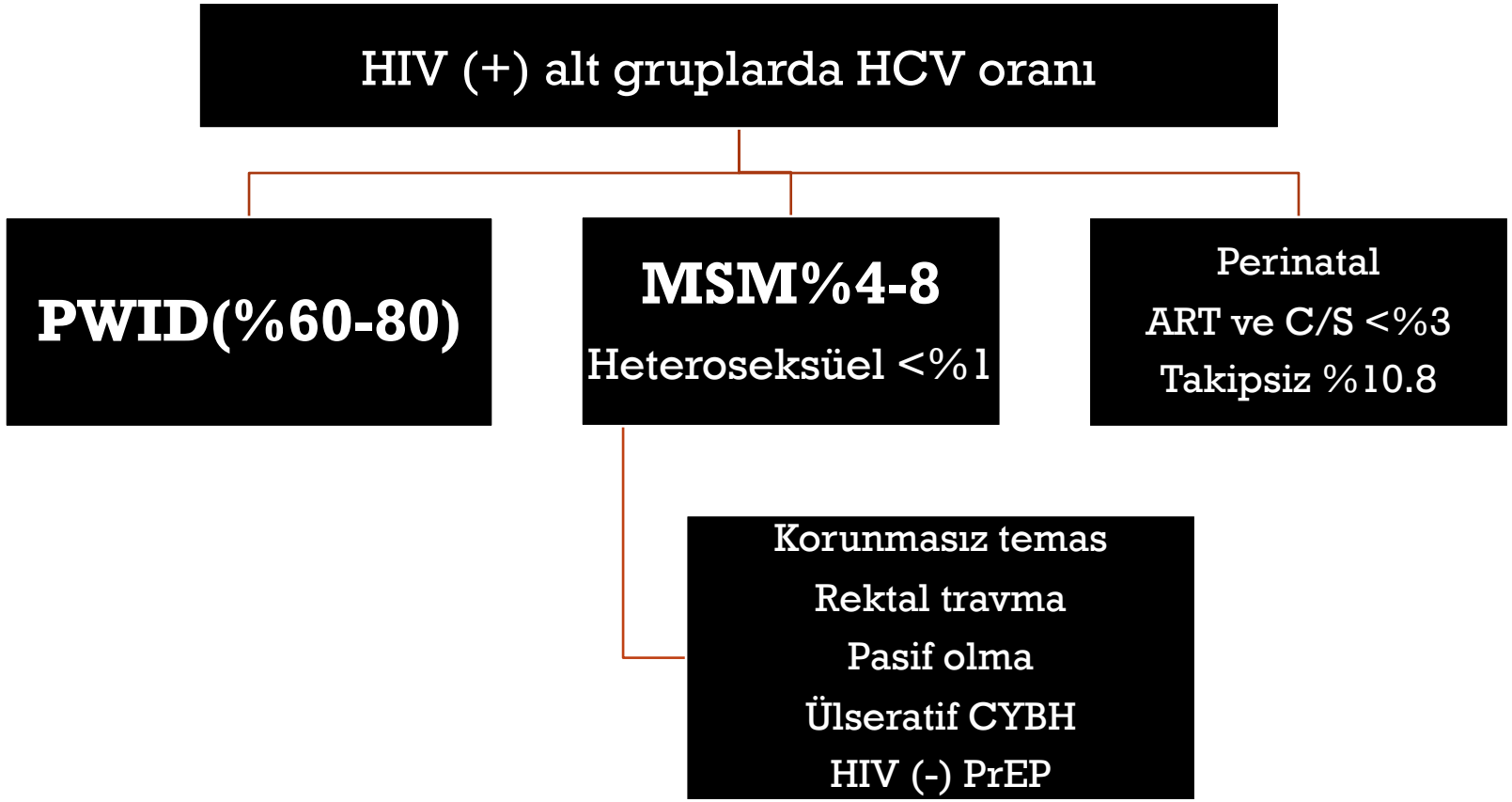
%20



U.S.A.%15-30
Türkiye %1,7

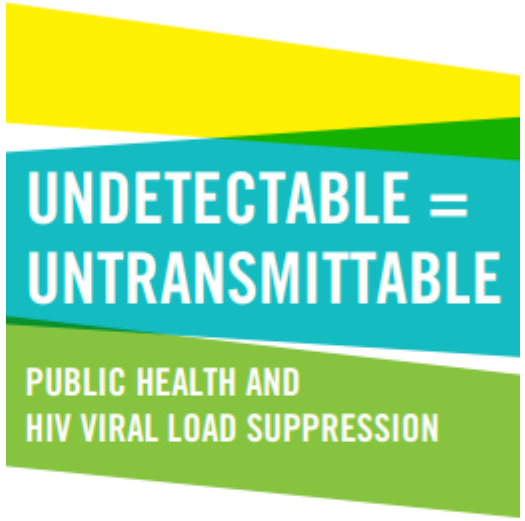
Management of chronic hepatitis B and C in HIV-coinfected patients*Journal of Antimicrobial Chemotherapy*, Volume 57, Issue 5, May 2006, Pages 815–818 Hepatitis C Coinfection Among People Living with HIV in a University Hospital in İstanbulViral Hepatitis Journal 2021;27(2):57-6A2HIV and hepatitis C co-infection in Europe, Israel and Argentina: a EuroSIDA perspective BMC Infectious Diseases volume 14, Article number: S13 (2014)

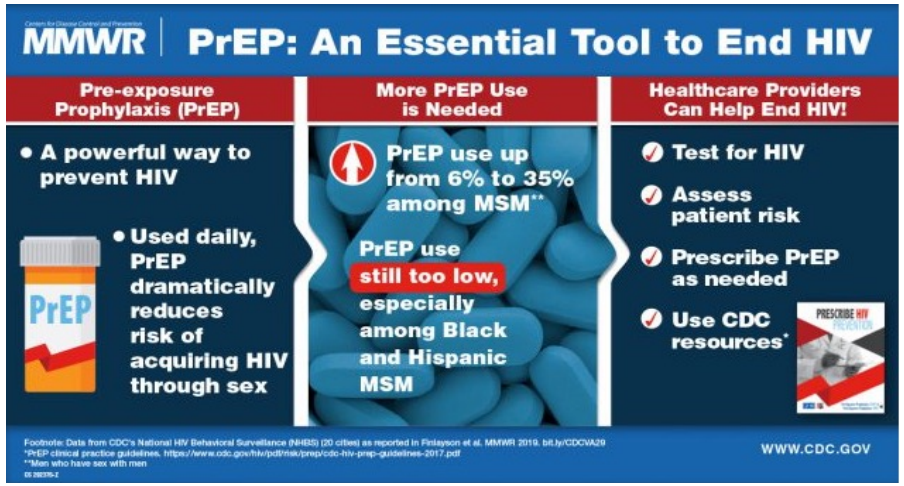
EPİDEMİYOLOJİ



Hepatitis C Coinfection Among People Living with HIV in a University Hospital in İstanbulViral Hepatitis Journal 2021;27(2):57-6A2
ASLD-IDSA Hepatitis C Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. v2021.1
Vertical transmission of hepatitis C virus: systematic review and meta-analysis2014 Sep 15;59(6):765-73. Epub 2014 Jun 13

EPİDEMİYOLOJİ





UNAIDS Explainer

- MSM: HIV insidansı ☺
- Seksüel davranış ve iletişimi değiştirdi
- PrEP alan HIV (-) MSM: HCV olgular☹
- HIV-pozitif MSM ??

Patterns of Hepatitis C Virus Transmission in Human Immunodeficiency Virus (HIV)-infected and HIV-negative Men Who Have Sex With Men Clin. Inf. Dis. 2019 Nov 27;69(12):2127-2135

EPİDEMİYOLOJİ

Clinical Infectious Diseases

MAJOR ARTICLE

Decline in Hepatitis C Virus (HCV) Incidence in Men Who Have Sex With Men Living With Human Immunodeficiency Virus: Progress to HCV Microelimination in the United Kingdom?

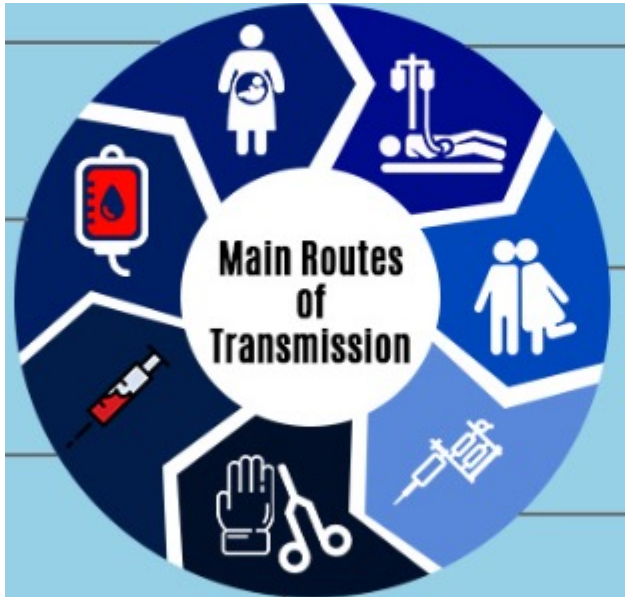
Clinical Trial › Clin Infect Dis. 20 ...174. doi: 10.1093/cid/ciaa1499.

Microelimination of Hepatitis C Among People With Human Immunodeficiency Virus Coinfection: Declining Incidence and Prevalence Accompanying a Multicenter Treatment Scale-up Trial

Last Mile to Microelimination of Hepatitis C Virus Infection Among People Living With Human Immunodeficiency Virus

HCV insidansı HIV (+) bireylerde de azalıyor

TARAMA



HIV (+) bireylerde ne zaman?

-Tanı anında

-Her yıl

-Klinik şüphe varsa (KCFT yüksekliği)

-Riskli cinsel aktivite/IVDU → 3-6 ayda bir

Devam eden riskli davranış
Reinfeksiyon??

Anti HCV: Negatif ve akut enfeksiyon şüphesi → HCV RNA/HCVcAg

Geç (1-6 ay sonra) serokonversiyon

EACS Guidelines 11.0

OLGU

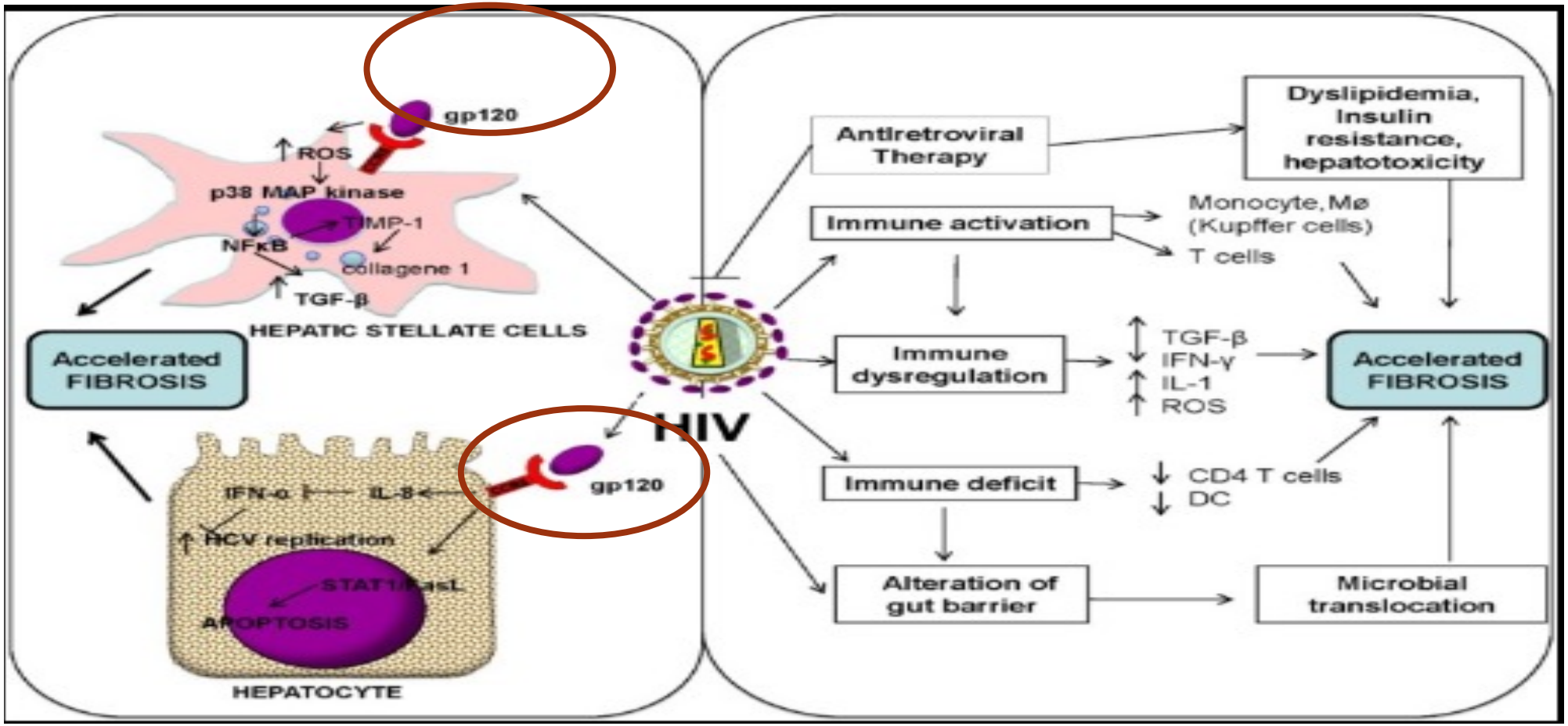
Laboratuvar:04.01.2017

- HCV RNA:5600000 kopya/ml
- HCV genotip:1b
- HIV RNA : Negatif
- CD4:568/mm3 CD8:1693/mm3 CD4/CD8:0,34
- ART: Elvitegravir/kobisistat/emtrisitabin/TDF(Stribild) devam ediliyor
- Spontan klirens için 12 haftalık izlem

Immunkompromize bireylerde
Spontan klirens oranı <%20

Management of acute HCV infection in the era of direct-acting antiviral therapy
Nature Reviews Gastroenterology &Hepatology 15 s412–424 (2018)

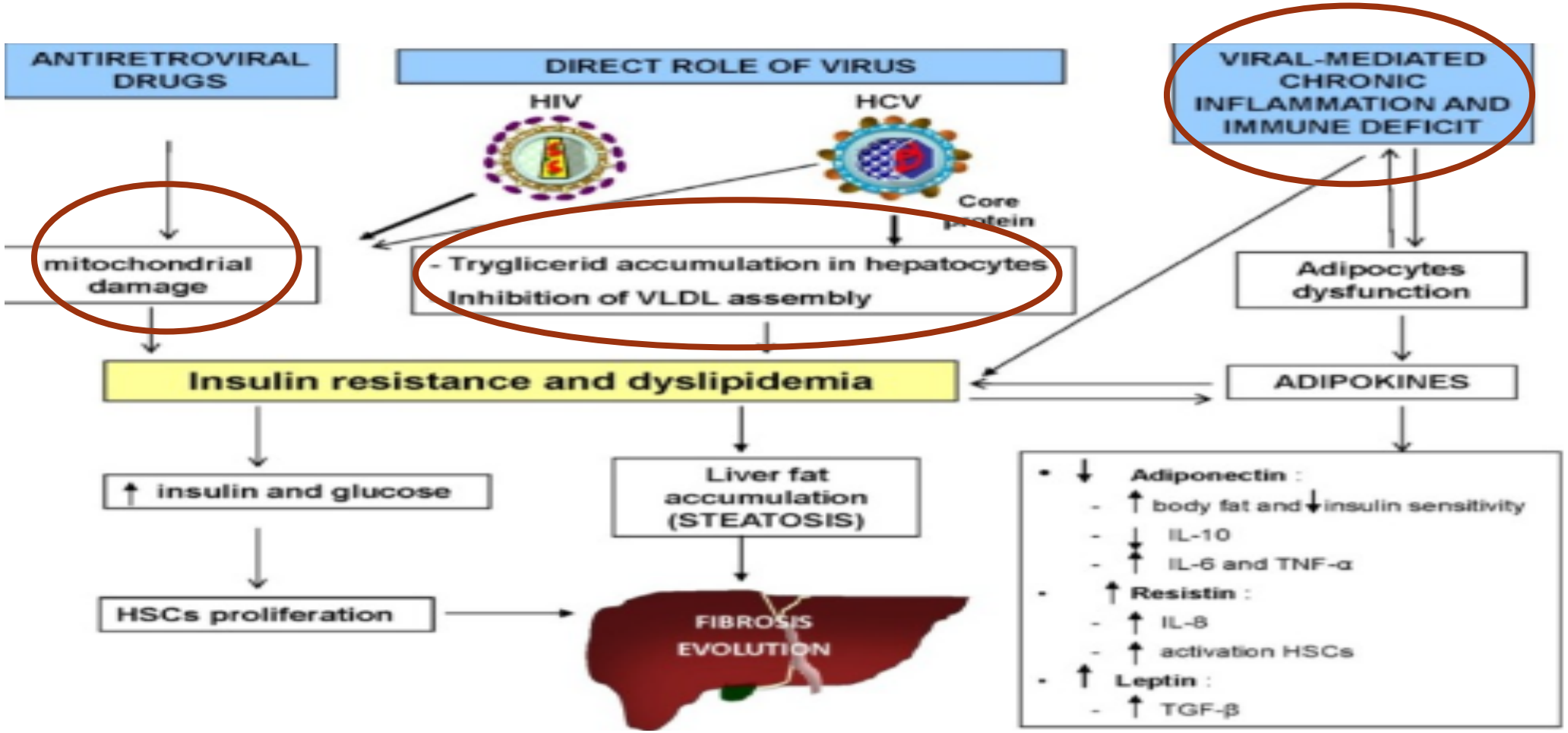
PATOGENEZ



KOENFEKSİYONDA SİROZA PROGRESYON NEDEN DAHA HIZLI?

Molecular Mechanisms of Liver Fibrosis in HIV/HCV Coinfection.Int. J. Mol. Sci. 2014

PATOGENEZ



HEPATOSTETAOZ VE FİBROZİS

Molecular Mechanisms of Liver Fibrosis in HIV/HCV Coinfection.Int. J. Mol. Sci

KOENFEKSİYON KLİNİĞİ NASIL ETKİLEDİ?

HIV

HIV ilişkili immünsüpresyonun derecesi ile HCV ilişkili KC hasarı korele
Progresyon daha hızlı, siroza ilerleme 3 kat daha yüksek
Mortalite ve morbidite riski fazla

ART

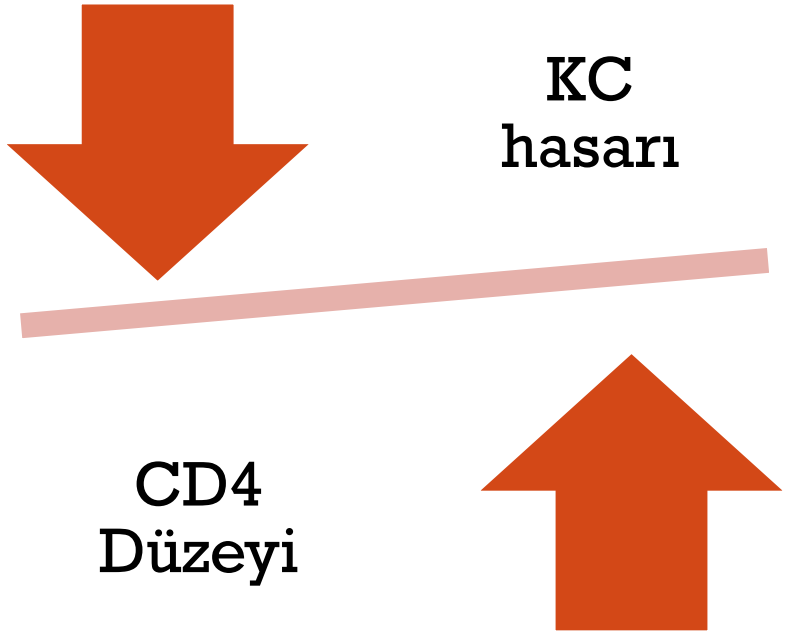
ART, KC hastalığının progresyonunu yavaşlatır
ART seçilirken hepatotoksisite göz önünde bulundurulmalı
İlaç ilişkili KC hasarı(DILI) monoinfekte hastalara göre daha yüksek

HCV

HCV'nin HIV klinik progresyonuna/ART yanıtına etkisi minimal ya da yok

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. Considerations for antiretroviral use in patients with coinfections: hepatitis C (HCV)/HIV coinfection.
Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis. 2001;33(4):562-569

KOENFEKSİYON KLİNİĞİ NASIL ETKİLEDİ?



Ek risk faktörleri:

- İleri yaş
- Alkolizm
- Erkek cinsiyet

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. Considerations for antiretroviral use in patients with coinfections: hepatitis C (HCV)/HIV coinfection.

TEDAVİ ÖNCESİ DEĞERLENDİRME

- Monoenfeksiyon ile aynı
- Tedavi hedefi:Hepatik/extrahepatik komplikasyonların önlenmesi

Bulaş riskini azaltmak

- HCV RNA ve Genotip tayini?

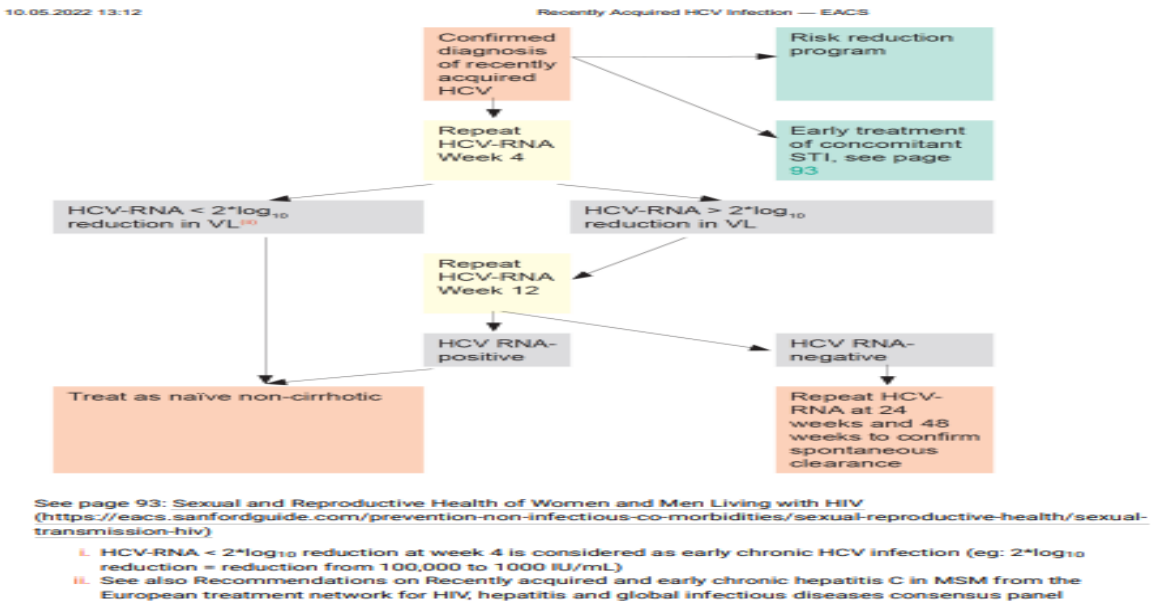
Pangenotipik rejimler için gerekli değil
Devam eden riskli davranış REİNFEKSİYON?

- HBV enfeksiyonu açısından değerlendirme

YENİ TANI HCV

Yeni tanı HCV spontan klirens beklenmeden tedavi edilmeli

AASLD-IDSA Hepatitis C Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. v2021.1



Riskli davranış devam ediyorsa ACİL tedavi endikasyonu !

EACS. Management of Recently Acquired HCV Infection in PLWH

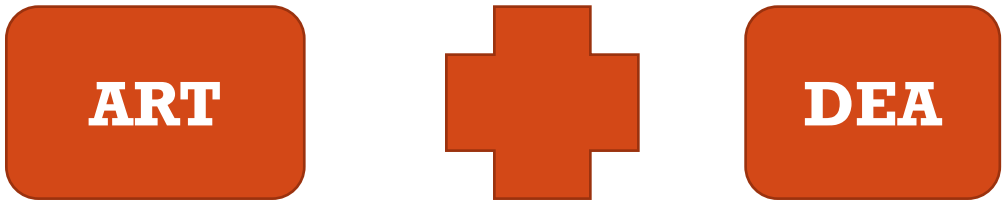
TEDAVİ: NAİV-NON SİROTİK İLE AYNI

OLGU-5 AY SONRA ...

2 Mayıs 2017

- CD4:443/mm3 CD8:1567/mm3 CD4/CD8:0,28
- HIV RNA:negatif
- HCV RNA:33800000kopya/ml Genotip 1b
- Karaciğer biyopsisi; HAİ 3/18 Fibrozis 2/6
- ART: Elvitegravir/kobisistat/emtrisitabin/TDF(Stribild)
- DEA: Sofosbuvir/Ledipasvir başlanması planlanıyor

TEDAVİ



- Eş zamanlı
- Öneriler monoenfeksiyonla aynı
- Potansiyel ilaç-ilaç etkileşimi en önemli nokta
- Virolojik yanıt ve ilaç yan etkileri açısından yakın izlem

CD4<200 hücre /mm^3, ART ile viral supresyon sağlanan kadar ertelenebilir
DEA çalışmalarında hastaların CD4 >200 ve viral supresyonu sağlanmış

AASLD-IDSA Hepatitis C Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. v2021.1

TEDAVİ

- Tedavi deneyimi
- Siroz
- HBV Koenfeksiyonu
- HIV Koenfeksiyonu
- Gebelik
- HCC
- KC tranplantasyonu yapılan

KİMLER BASİTLEŞTİRİLMİŞ HCV TEDAVİSİ İÇİN UYGUN DEĞİL?

AASLD-IDSA Hepatitis C Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. v2021.1

TEDAVİ

Basitleştirilmiş tedavi

Naiv-nonsirotik/kompanse siroz

Glekaprevir (300 mg) / pibrentasvir (120 mg) 8 hafta

Sofosbuvir (400 mg) / velpatasvir (100 mg) 12 hafta

- Genotip 1-4 Glekaprevir (300 mg)/pibrentasvir (120 mg)

  Non sirotik: 8 hafta monoenfeksiyon/koenfeksiyon SVR benzer

  Naiv Child Pugh A(Kompanse siroz):12 hafta

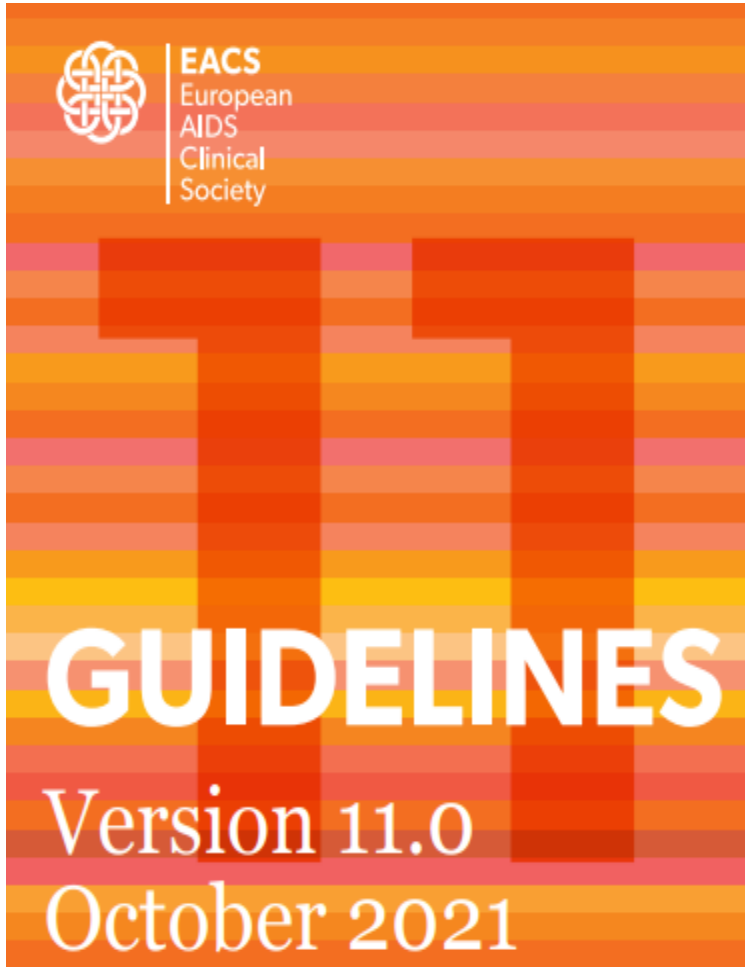
Genotip 1 naiv non sirotik ve HCV RNA <6 million IU/mL:

Sofosbuvir (400 mg)/ Ledipasvir (90 mg) 8 hafta düşünülebilir(I.B) 12 hafta

Genotip 5/6 sirotik /non sirotik :Glecaprevir (300 mg)/pibrentasvir (120 mg) 8 hafta 12 hafta

Brown RS, Buti M, Rodrigues L, et al. J Hepatol. 2020;72(3):441-449.
AASLD-IDSA Hepatitis C Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. v2021.1

HCV TEDAVİ



Preferred DAA HCV treatment options (except for persons pre-treated with Protease or NS5A inhibitors)

HCV GT	Treatment regimen	Treatment duration & RBV usage		
		Non-cirrhotic	Compensated cirrhotic	Decompensated cirrhotics CTP class B/C
1 & 4	EBR/GZR	12 weeks[i]		Not recommended
	GLE/PIB	8 weeks	8-12 weeks[ii]	Not recommended
	SOF/VEL	12 weeks		12 weeks with RBV[ix]
	SOF/LDV +/- RBV	8-12 weeks without RBV[iii]	12 weeks with RBV[iv]	12 weeks with RBV[ix]
2	GLE/PIB	8 weeks	8-12 weeks[ii]	Not recommended
	SOF/VEL	12 weeks		12 weeks with RBV[ix]
3	GLE/PIB	8 weeks[v]	8-12 weeks[ii,v]	Not recommended
	SOF/VEL +/- RBV	12 weeks[vi]	12 weeks with RBV[vii]	12 weeks with RBV[ix]
	SOF/VEL/VOX	-	12 weeks	Not recommended
5 & 6	GLE/PIB	8 weeks	8-12 weeks[ii]	Not recommended
	SOF/LDV +/- RBV	12 weeks +/- RBV[viii]	12 weeks with RBV[iv]	12 weeks with RBV[ix]
	SOF/VEL	12 weeks		12 weeks with RBV[ix]

For HCV treatment options to be used if preferred options are not available, please see version 10.1 of the EACS Guidelines

HCV TEDAVİ

Glekaprevir /pibrentasvir + **Elvitegravir/cobicistat**

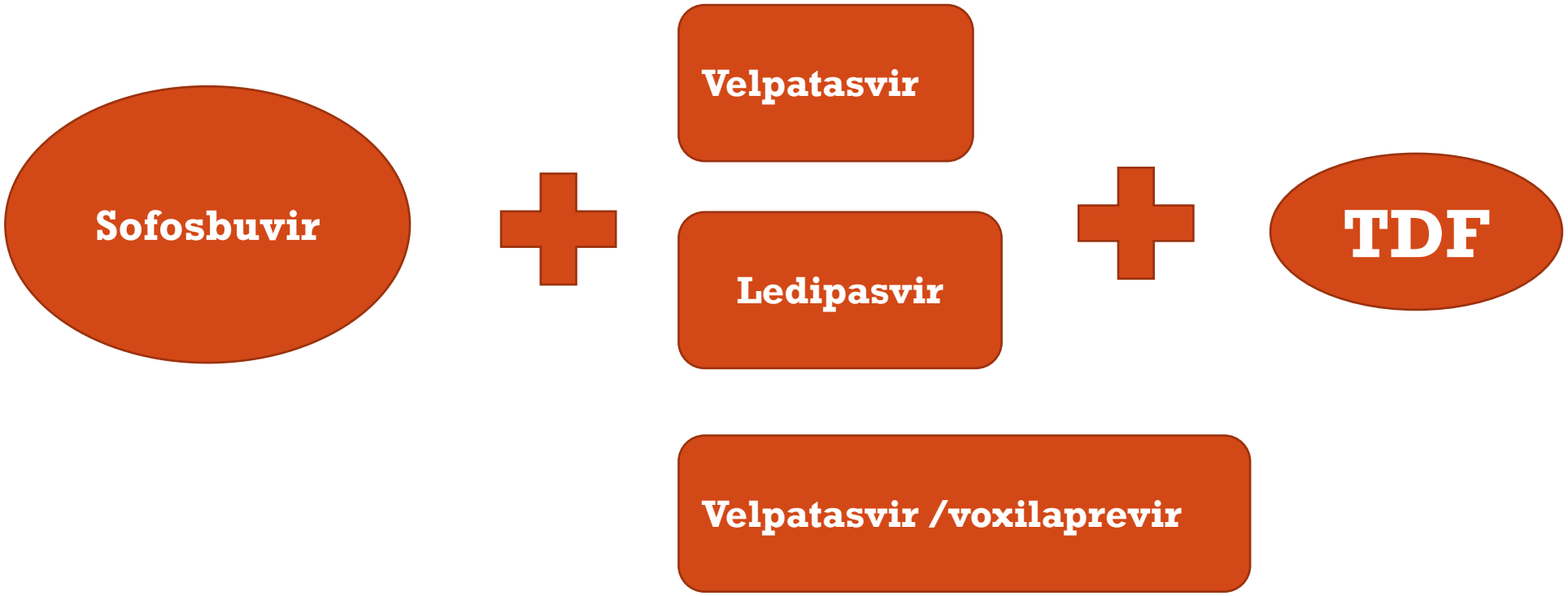
Glecaprevir x3, pibrentasvir x1,5 kat artış
Hepatotoksisite açısından monitorize edilmeli(FDA: klinik önemi yok ancak yine de aylık KCFT takibi)

Sofosbuvir/velpatasvir /voxilaprevir + Darunavir/ritonavir
Elvitegravir/cobicistat

Hepatotoksisite izlemi

Kosloski MP, Oberoi R, Wang S, et al. Drug-drug interactions of glecaprevir and pibrentasvir coadministered with human immunodeficiency virus antiretrovirals. J Infect Dis. 2020;221(2):223-231.
AASLD-IDSA Hepatitis C Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. v2021.1

HCV TEDAVİ



TDF düzeyini yükseltebilir, renal fonksiyonlar izlenmeli
GFR<60 mL/min TAF tercih edilmeli
TDF ve cobistat ya da ritonavir kombinasyonu varsa aylık renal izlem(Ledipasvir ile ART değişimi)

Kosloski MP, Oberoi R, Wang S, et al. Drug-drug interactions of glecaprevir and pibrentasvir coadministered with human immunodeficiency virus antiretrovirals. J Infect Dis. 2020;221(2):223-231.
AASLD-IDSA Hepatitis C Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. v2021.1

HIV TEDAVİ

ART tedavisi altındaki hastalar
ART ara verilmesi/kesilmesi önerilmez!!
Viral supresyon sağlandıysa ART değişimi yapılabilir

2-8. haftalar içinde HIV RNA
DEA tedavi >2 hafta ertelenmeli
1. 2. 6. ve 12. aylar KCFT izlemi
Semptomatik olmayan <x5 NÜS Takip
Semptomatik ve >x5 NÜS ART kesilmesi

Eski ART :DEA tedavisi sonrası
>2 hafta beklenmeli

HIV viroloik kırılma
ART deneyimi
Direnç
Yan etki

İlaçların uzamış yarı ömürleri
ilaç-ilaç etkileşimi

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. Considerations for antiretroviral use in patients with coinfections: hepatitis C (HCV)/HIV coinfection.

AASLD IDSA

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

AASLD AMERICAN ASSOCIATION FOR

IDSA Infectious Diseases Society of America

Table. Drug Interactions Between Direct-Acting Antivirals and Antiretroviral Drugs—Recommended Regimens

		Ledipasvir/ Sofosbuvir (LDV/SOF)	Sofosbuvir/ Velpatasvir (SOF/VEL)	Elbasvir/ Grazoprevir (ELB/GRZ)	Glecaprevir/ Pibrentasvir (GLE/PIB)	Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VOX)
Protease Inhibitors	Boosted Atazanavir	A	A			
	Boosted Darunavir	A	A			
	Boosted Lopinavir	ND, A	A			ND
NNRTIs	Doravirine		ND		ND	ND
	Efavirenz				ND	ND
	Rilpivirine					
	Etravirine	ND	ND	ND	ND	ND
Integrase Inhibitors	Bictegravir			ND	ND	
	Cabotegravir	ND	ND	ND	ND	ND
	Cobicistat-boosted elvitegravir	C	C			C
	Dolutegravir					ND
	Raltegravir					ND
	Dolutegravir					ND
	Raltegravir					ND
Entry Inhibitors	Fostemsavir	ND	ND	ND	ND	ND
	Ibalizumab-uiyk	ND	ND	ND	ND	ND
	Maraviroc	ND	ND	ND	ND	ND
NRTIs	Abacavir		ND	ND		ND
	Emtricitabine					
	Lamivudine		ND	ND		ND
	Tenofovir disoproxil fumarate	B, C	B, C			C
	Tenofovir alafenamide	D	D	ND		D

Green indicates coadministration is safe; yellow indicates a dose change or additional monitoring is warranted; and red indicates the combination should be avoided.

ND: No data

A: Caution only with tenofovir disoproxil fumarate

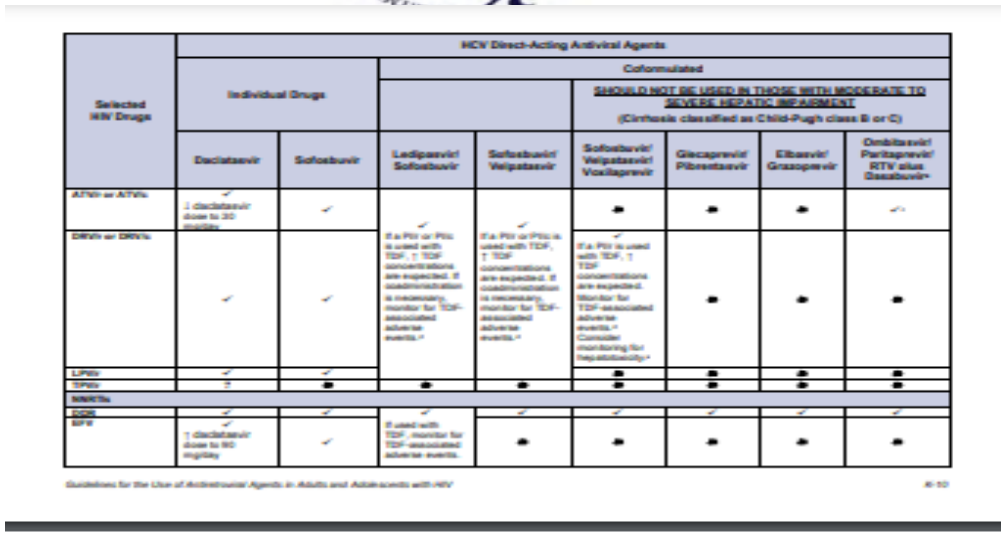
B: Increase in tenofovir depends on which additional concomitant antiretroviral agents are administered.

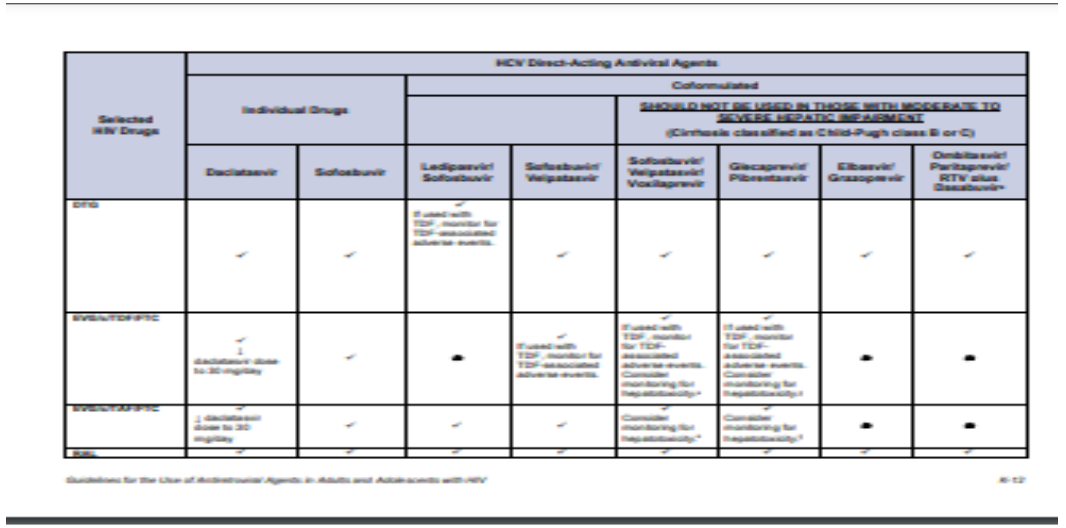
C: Avoid tenofovir disoproxil fumarate in patients with an eGFR <60 mL/min; tenofovir concentrations may exceed those with established renal safety data in individuals on ritonavir- or cobicistat-containing regimens.

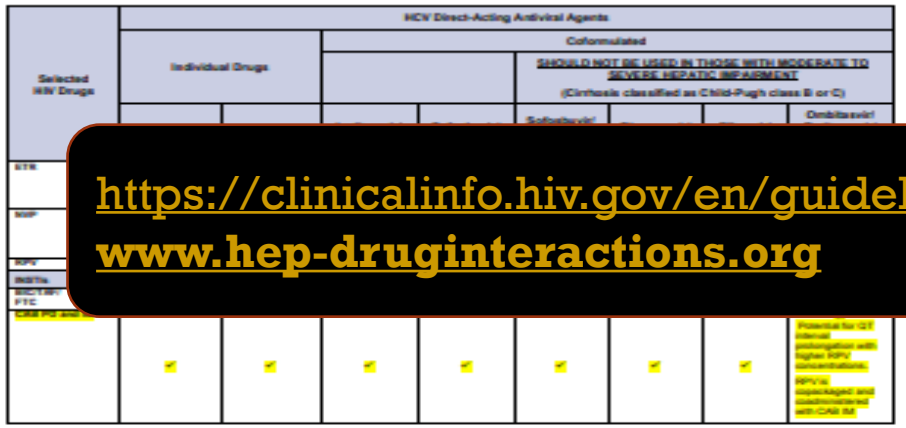
D: Studied as part of fixed-dose combinations with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir plus TAF, emtricitabine, elvitegravir, and cobicistat.

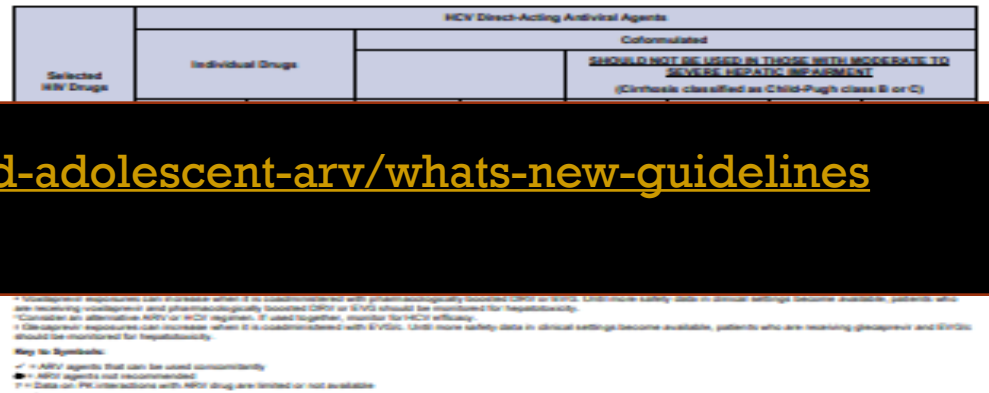
Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)









https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines

www.hep-druginteractions.org

OLGU-5 AY SONRA ...

ART DEĞİŞİMİ:

Elvitegravir/kobisistat/emtrisitabin/TDF(Stribild)

ZDV+3TC(Combivir) + Dolutegravir(Tivicay)

DEA: Sofosbuvir /Ledipasvir 12 hafta

- 4.hafta HCV RNA : Negatif, 12. hafta SVR
- HIV RNA :Negatif
- 1 yıl sonra Mart 2018:HCV RNA negatif
- ART:Elvitegravir/kobisistat/emtrisitabin/TAF(Genvoya)

OLGU-5 YIL SONRA …

- 2019 yılında kadar herşey yolunda…(KCFT normal, HIV RNA negatif olarak takip ediliyor)
- ART:Elvitegravir/kobisistat/emtrisitabin/TAF(Genvoya)
- 11.10.2021 AST: 23 ALT :16
- 19.01.2022 AST:59 ALT :72 HIV RNA: negatif

OLGU-5 YIL SONRA ...

- 29.03.2022
- WBC: 5620/uL
- Trombosit:208000/uL
- Kreatinin: 0,8 mg/dL GFR:106
- **AST: 112 U/L ALT:162 U/L**
- ALP:47 U/L GGT:75 U/L
- Albumin:4,5 gr/dl
- Total/Direk bilirubin:0,84/0,23
- HIV RNA:negatif
- **HCV RNA: 2653000 kopya/ml**
- Trigliserid:47 mg/dL Total Kolesterol:81 mg/dL
- HDL:38 mg/dL LDL:34 mg/dl

RELAPS DEĞİL RE-ENFEKSİYON?

REİNFEKSİYON

Table 3 | **HCV reinfection after treatment for acute and recent HCV infection**

Author, year	Study population (% total study population)	Location, study design	n	Reinfection (n)	PYFU	Reinfection incidence per 100 person-years (95% CI)
Meta-analyses						
Hagan, 2015 (REF.[65])	HIV-positive MSM (100%)	NA, meta-analysis (pooled results of two studies)	170	38	NA	11.4 (7.4–17.7)
Primary studies						
Lambers[a], 2011 (REF.[185])	HIV-positive MSM (100%)	Netherlands, retrospective	56	11	72	15.2 (8.0–26.5)
Martin[a], 2013 (REF.[186])	HIV-positive MSM (100%)	England, retrospective	114	27	NA	9.6 (6.6–14.1)
Vanhommerig, 2014 (REF.[232])	HIV-positive MSM (100%)	Netherlands, prospective	35	16	NA	NA
Martinello, 2017 (REF.[187])	HIV-positive MSM (53%) and recent PWID (49%)	Australia, prospective	120	10	135	7.4 (4.0–13.8)

MSM, men who have sex with men; NA, not available; PWID, people who inject drugs; PY, person-years; PYFU, person-years follow-up. [a]Studies included in the meta-analysis performed by Hagan et al.[65].

Management of acute HCV infection in the era of direct-acting antiviral therapy
Nature Reviews Gastroenterology &Hepatology 15 s412–424 (2018)

REİNFEKSİYON

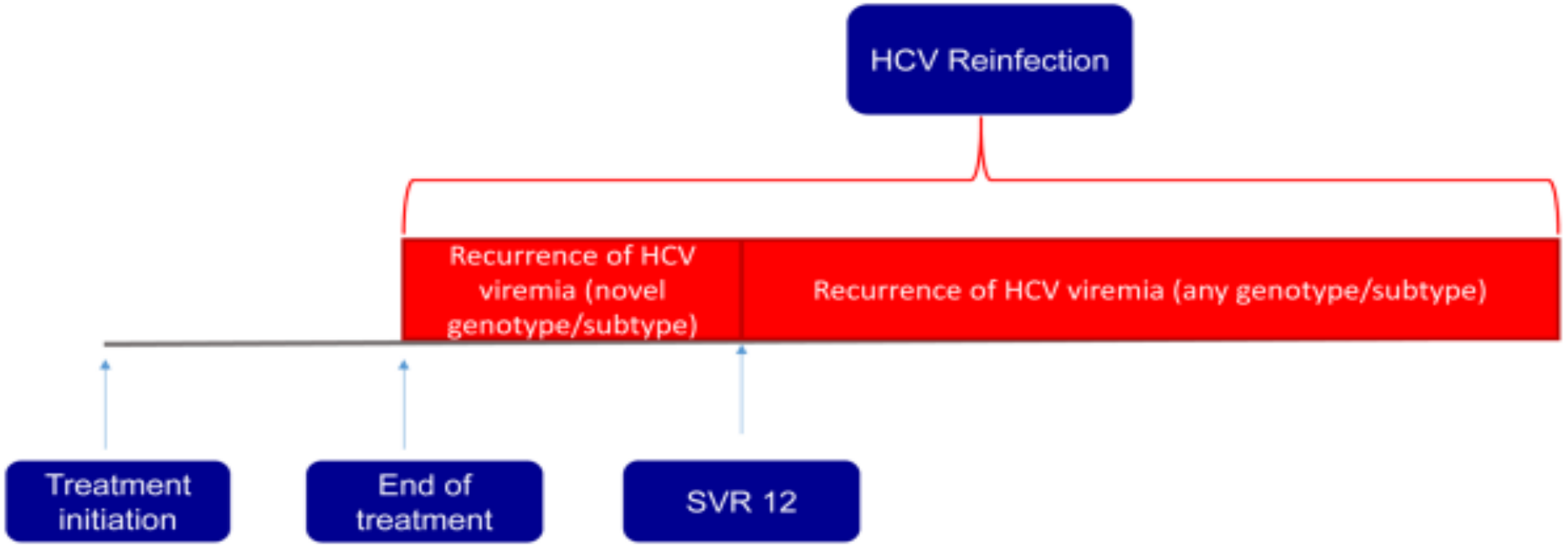


Figure 2.
Algorithm for defining HCV reinfection in clinical practice
A proposed clinical definition for HCV reinfection when the gold standard of phylogenetic analysis of pre- and post-treatment HCV sequences are not available

Understanding and addressing hepatitis C reinfection in the oral direct acting antiviral era
J Viral Hepat. 2018 March ; 25(3): 220–227

Effectiveness of treatment for hepatitis C virus reinfection following direct acting antiviral therapy in the REACH-C cohort

- Glecaprevir/pibrentasvir (50%)
- Sofosbuvir ve velpatasvir /ledipasvir/daclatasvir

  Grazoprevir/elbasvir

  Sofosbuvir/velpatasvir/voxilaprevir (1%)
- SVR12 oranı başlangıç tedavisiyle benzer
- 8 hasta başlangıçtaki rejimle aynı tedavi, etkinlik aynı (100%; 8/8).

AASLD IDSA

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

AASLD AMERICAN ASSOCIATION FOR

IDSA Infectious Diseases Society of America

Table. Drug Interactions Between Direct-Acting Antivirals and Antiretroviral Drugs—Recommended Regimens

Reinfeksiyon DEA:Glekaprevir/pibrentasvir 12 hafta

		Ledipasvir/ Sofosbuvir (LDV/SOF)	Sofosbuvir/ Velpatasvir (SOF/VEL)	Elbasvir/ Grazoprevir (ELB/GRZ)	Glecaprevir/ Pibrentasvir (GLE/PIB)	Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VOX)
Protease Inhibitors	Boosted Atazanavir	A	A			
	Boosted Darunavir	A	A			
	Boosted Lopinavir	ND, A	A			ND
NNRTIs	Doravirine		ND		ND	ND
	Efavirenz				ND	ND
	Rilpivirine					
	Etravirine	ND	ND	ND	ND	ND
Integrase Inhibitors	Bictegravir			ND	ND	
	Cabotegravir	ND	ND	ND	ND	ND
	Cobicistat-boosted elvitegravir	C	C			C
	Dolutegravir					ND
	Raltegravir					ND
	Dolutegravir					ND
	Raltegravir					ND
Entry Inhibitors	Fostemsavir	ND	ND	ND	ND	ND
	Ibalizumab-uiyk	ND	ND	ND	ND	ND
	Maraviroc	ND	ND	ND	ND	ND
NRTIs	Abacavir		ND	ND		ND
	Emtricitabine					
	Lamivudine		ND	ND		ND
	Tenofovir disoproxil fumarate	B, C	B, C			C
	Tenofovir alafenamide	D	D	ND		D

Green indicates coadministration is safe; yellow indicates a dose change or additional monitoring is warranted; and red indicates the combination should be avoided.

ND: No data

A: Caution only with tenofovir disoproxil fumarate

B: Increase in tenofovir depends on which additional concomitant antiretroviral agents are administered.

C: Avoid tenofovir disoproxil fumarate in patients with an eGFR <60 mL/min; tenofovir concentrations may exceed those with established renal safety data in individuals on ritonavir- or cobicistat-containing regimens.

D: Studied as part of fixed-dose combinations with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir plus TAF, emtricitabine, elvitegravir, and cobicistat.

RİSK DEVAM EDİYOR...

TEŞEKKÜR EDERİM.