İZMİR KÂTİP ÇELEBİ ÜNİVERSİTESİ

ATATÜRK EĞİTİM VE ARAŞTIRMA HASTANESİ İZMİR

HCV-HIV KOİNFEKSİYONU OLGUSU

Dr. Bahar ÖRMEN

OLGU

44 YAŞINDA,

BEKAR ,

ERKEK,

HALSİZLİK

YORGUNLUK

İŞTAHSIZLIK

YURT DIŞINDA YAŞAM
10 YIL ÖNCE HIV TANISI
5 YIL SÜRE İLE ANTİRETROVİRAL TEDAVİ
(Zidovudin, Lamivudin Ritonavir)
SON 6 AYDIR TÜRKİYE'DE BAŞKA BİR MERKEZDE ART
Zidovudin(600mg/gün),
Lamivudin (300mg/gün),
Lopinavir/ ritonavir (200/50mg, 2x2/gün)
PROFİLAKTİK OLARAK Trimetoprim-Sülfametoksazol (TMP/SMX) (80/400mg, 1x1tb/gün)

ÖZ GEÇMİŞ:
HCV TANISI
2 YIL ÖNCESİNE KADAR IV MADDE KULLANIMI
FİZİK BAKI:
PATOLOJİK BULGU YOK

LABORATUVAR TETKİKLERİNDE:

Lökosit:5640/mm^3
Hemoglobin: 13.5gr/dL
Trombosit: 215000/mm^3

BUN:38 mg/dL
Kreatinin: 0.93 mg/dL

Total kolesterol:160 mg/dl
Trigliserid: 84 mg/dL
LDL: 110 mg/dl
HDL : 33 mg/dL

AST: 32 IU/mL
ALT: 66 IU/mL
ALP: 95 IU/mL
GGT:209 IU/mL
LDH: 150 IU/L
T.Bil: 0.64 mg/ dL
D.Bil: 0.18 mg/dL

T.protein: 7.9 gr/dL
Alb: 4.7 gr/dL
AFP: 4.68 IU/mL

Protrombin zamanı:12.3 sn
INR:1.07

ANA
AMA
ASMA
Anti dsDNA
Anti-LKM

negatif

Tiroid fonksiyon testleri
Tiroid otoantikorları

normal

HIV GÖSTERGELERİ:

HIV RNA: <50kopya/mL
CD4+ T lenfosit sayısı: 877 hücre/mm^3

SEROLOJİK GÖSTERGELER:

Toxoplasma IgM / IgG : -/-

Anti CMV IgM / IgG: -/+
Anti Rubella IgM / IgG: -/+

VDRL /PRP: -/-

HEPATİT GÖSTERGELERİ:

HBsAg : (-)
Anti-HBs: (-)
Anti-HBc IgG: (-)

Anti-HAV IgG : (+)

AntiHCV : (+)

HCV RNA: 651 311 IU/mL

HCV genotip: 1b

BATIN USG:
Karaciğerde çok sayıda **hemanjiyom**
Karaciğer biyopsisi kontrendike!!!!

NONİNVAZİV GÖSTERGELER:

ACTİTEST: A1
FİBROTEST: F3

HIV-HCV KOİNFEKSİYONUNDA KVY İLE İLİŞKİLİ FAKTÖRLER

- **Beyaz ırk** √
- **Genç yaş(<40)** √
- Minimal fibroz
- **Düşük vücut kitle indeksi** √
- **İnsülin direncinin olmaması** √
- **Alkolik hepatiti ,Hepatik steatoz eşlik etmemesi,** √
- Madde kulllanımı olmaması
- Psikiatrik bozukluk olmaması
- **Yüksek CD4+ Tlenfosit sayısı** √
- IL28B genotipi (CC polimorfizm)
- Genotip 2,3
- **Düşük HCV viral yükü(<400000IU/mL)** √

Hastaya (2009) SUT gereği

Peg IFN α2a 180µg/hafta ve Ribavirin1000mg/gün

Endikasyon dışı tedavi onayı alındı

~~Zidovudin, lamivudin ve lopinavir/ritonavir~~
~~TMP/SMX~~

CD4>200hücre/mm3 (3 ay süresince) ---TMP-SMX kesildi

İlaç etkileşimi---- ART değişimi

Tenofovir/emtrisitabin (300mg/200mg,1x1) ve
Lopinovir/ritonavir (200/50mg, 2x2)

	Tedavi öncesi	4.hf	12.hf	24.hf	48.hf
*HCV RNA (IU/mL)	2820	23	negatif	negatif	negatif
ALT (U/L)	41	27	13	15	10
**HIV RNA (kopya /mL)	387	-	negatif	negatif	negatif
CD4+ T lenfosit (sayı/mm³)	589	-	-	680	864

*HCV RNA: Real-time PCR (saptama alt sınırı: 12IU/mL)
**HIV RNA: Abbot real-time PCR (saptama alt sınırı: <20kopya /mL)

Tedavi İzlemi ve Yan Etkiler

- Hasta uyumu iyi
- Ciddi yan etki yok
- İlaç doz ayarlaması yok
- Tedavi 48 haftaya tama

Tedaviyle ilişkili faktörler:

Hızlı virolojik yanıt,

Yeterli PegIFN dozu √

Kiloya ayarlı Ribavirin dozu √

İyi tedavi uyumu √

Eş zamanlı Zidovudin, didenozin,

abakavir kullanılmaması √

48 HAFTALIK KHC TEDAVİ TAMAMLANDIKTAN

24 HAFTA SONRA

- HCV RNA: NEGATİF---- **KALICI VİROLOJİK YANIT**
- ALT: 15 U/L,
- **Actitest: A0,**
- **Fibrotest: F2,**
- Hastanın takiplerinde HCV RNA negatifliği devam etmekte

HIV/HCV koinfeksiyonu

- HIV pozitif hastalarda KC'e bağlı ölümlerin 2/3'ünü HCV oluşturur.
- Koinfekte bireylerde hastalık hızlı ilerler
- HCV de 10-15 yılda siroza gidiş:

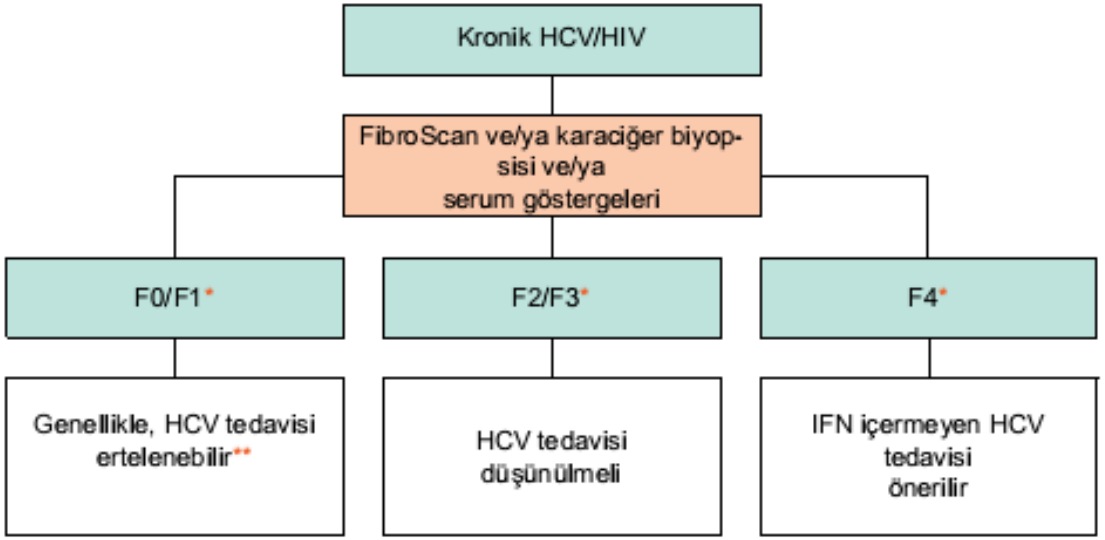
  koinfeksiyon: %10-15, monoinfeksiyon: %2-6
- HIV viral yük yüksek ise HCV ye bağlı karaciğer hasarı daha ileri, mortalite riski yüksek
- Tanı: AntiHCV (+) HIV hastalarının >%80 HCV RNA(+)
- Antiretroviral tedavi (ART) ile HCV de %15 spontan klirens
- ART ile HCV bağlı karaciğer ilişkili mortalite azalmakta
- ART kullanılan ilaçlarla etkileşim nedeni ile tedavi güç

HCV-HIV Koinfeksiyonunda Tedavi Önceliği nedir???

- CD4 T lenfosit sayısı **<200/mm^3** ise önce **ART**
- CD4 T lenfosit sayısı **350-500/mm^3** ise hasta HIV açısından asemptomatik olsa bile **erken ART** önerilir
- CD4 T lenfosit sayısı **> 500/mm^3** ise önce **HCV tedavisi**
- Önceden Antiretroviral tedavi alan hastalarda **kombine tedavi**

EACS2014

Kronik HCV/HIV Koenfeksiyonu Olan Bireylerin Yönetimi



* Metavir fibroz skoru: F0= fibroz yok; F1 = portal fibroz, septa yok; F2= portal fibroz, az sayıda septa, F3=köprüleşme fibrozu, F4=siroz.

** Fibroz evresini yıllık olarak ve tercihen iki ayrı yöntem ile izleyin. Hızlı ilerleme varsa tedavi başlamayı düşünün.

EACS2014

Table 2. Results from randomized clinical trials investigating the efficacy of pegylated interferon plus ribavirin in HIV/HCV-coinfected individuals

Study	Regimen	SVR (%) GT 1 or 4	SVR (%) GT 2 or 3	Key Points of Study
RIBAVIC France (N=412)	PEG-IFN α-2b R 800 mg	17	44	Low-dose RBV Toxicity with ddI + RBV HCV RNA at week 4 >460,0000 IU/mL → 100% NPV
Laguno Spain (N=182)	PE R 1			V → higher rapy for fective
ACTG A5071 USA (N=133)	P R 1			eek 12 e anemia
APRICOT International (N=868)	P R			th advanced CV RNA –
PRESCO Spain (N=389)	PEG-IFN α-2a RBV 1000 – 1200 mg	35	72	Weight-based RBV → higher SVR No increase in anemia Extended (72-week) therapy not well tolerated

Ribavirin dozu: 15mg/kg/gün olmalı

(genotipten bağımsız)

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Genotip 1 KHC-HIV koinfeksiyonu

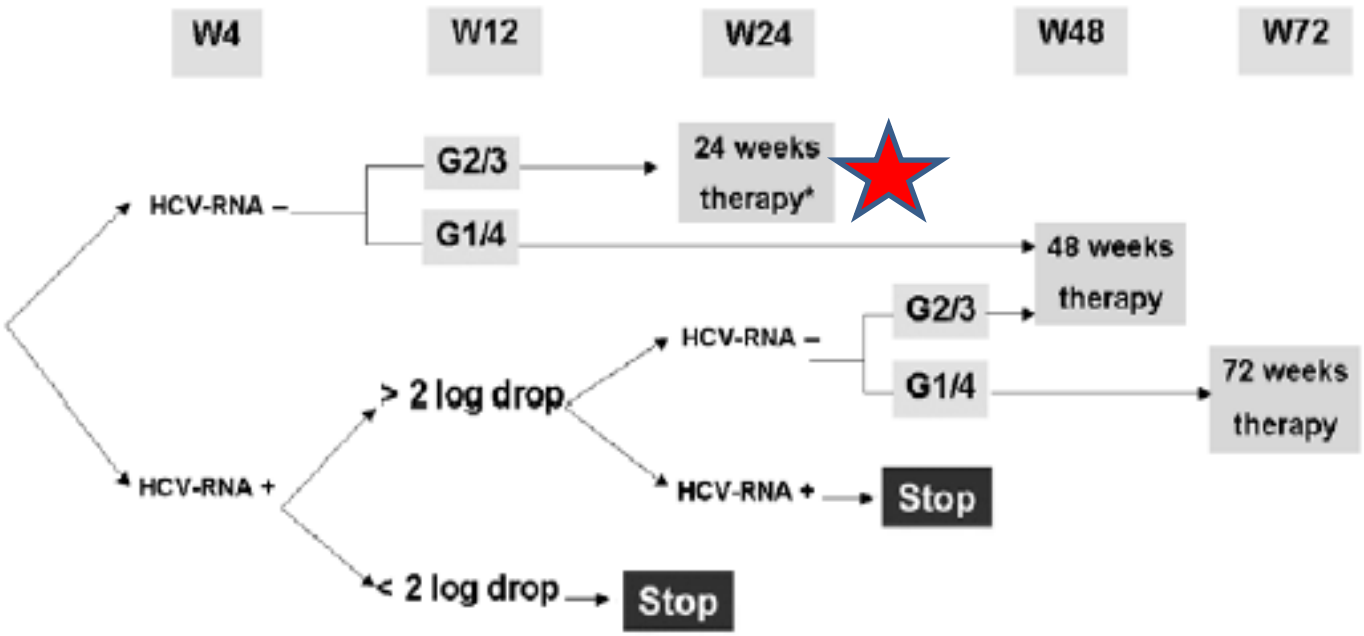

Figure 1. Proposed optimal duration of hepatitis C virus (HCV) therapy in HIV/HCV-coinfected patients treated with pegylated interferon and ribavirin, for GT1 infection only where HCV PIs are not available (w: week; G: genotype) (modified according to Rockstroh 2009). *In patients with low baseline viral load (<400,000 IU/l) and minimal liver fibrosis

HEPATOLOGY 2014: Management of HCV/HIV coinfection

JULY 2015

EASL JOURNAL OF HEPATOLOGY

EASL Recommendations on Treatment of Hepatitis C 2015

SUMMARY

Table 2. Indications for treatment of chronic hepatitis C in 2015: Who should be treated and when?

Treatment priority	Patient group
Treatment is indicated	• All treatment-naïve and treatment-experienced patients with compensated and decompensated liver disease
Treatment should be prioritized	• Patients with significant fibrosis (F3) or cirrhosis (F4), including decompensated cirrhosis • Patients with HIV coinfection • Patients with HBV coinfection • Patients with an indication for liver transplantation • Patients with HCV recurrence after liver transplantation • Patients with clinically significant extra-hepatic manifestations • Patients with debilitating fatigue • Individuals at risk of transmitting HCV (active injection drug users, men who have sex with men with high-risk sexual practices, women of child-bearing age who wish to get pregnant, haemodialysis patients, incarcerated individuals)
Treatment is justified	• Patients with moderate fibrosis (F2)
Treatment can be deferred	• Patients with no or mild disease (F0-F1) and none of the above-mentioned extra-hepatic manifestations
Treatment is not recommended	• Patients with limited life expectancy due to non-liver related comorbidities

Table 3. Approved HCV drugs in the European Union in 2015.

Product	Presentation	Posology
PegIFN-α2a	Solution for injection containing 180, 135 or 90 µg of PegIFN-α2a	Once weekly subcutaneous injection of 180 µg (or less if dose reduction needed)
PegIFN-α2b	Solution for injection containing 50 µg per 0.5 ml of PegIFN-α2b	Once weekly subcutaneous injection of 1.5 µg/kg (or less if dose reduction needed)
Ribavirin	Capsules containing 200 mg of ribavirin	Two capsules in the morning and 3 in the evening if body weight <75 kg or Three capsules in the morning and 3 in the evening if body weight ≥75 kg
Sofosbuvir	Tablets containing 400 mg of sofosbuvir	One tablet once daily (morning)
Simeprevir	Capsules containing 150 mg of simeprevir	One capsule once daily (morning)
Daclatasvir	Tablets containing 30 or 60 mg of daclatasvir	One tablet once daily (morning)
Sofosbuvir/ledipasvir	Tablets containing 400 mg of sofosbuvir and 90 mg of ledipasvir	One tablet once daily (morning)
Paritaprevir/ombitasvir/ritonavir viekirax	Tablets containing 75 mg of paritaprevir, 12.5 mg of ombitasvir and 50 mg of ritonavir	Two tablets once daily (morning)
Dasabuvir exviea	Tablets containing 250 mg of dasabuvir	One tablet twice daily (morning and evening)

Table 6. Treatment recommendations for HCV-monoinfected or HCV/HIV coinfected patients with chronic hepatitis C with compensated (Child-Pugh A) cirrhosis, including treatment-naïve patients and patients who failed on a treatment based on PegIFN-α and ribavirin (RBV)

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk (treatment-naïve or relapsers) or 24 wk (partial or null responders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	24 wk with RBV	No	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 1b					12 wk with RBV			
Genotype 2	12 wk	No	16-20 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	No	No	No	No	No	24 wk with RBV
Genotype 4	12 wk	12 wk (treatment-naïve or relapsers) or 24 wk (partial or null responders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	24 wk with RBV	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	No	No	12 wk with RBV, or 24 wk without RBV

Table 7. Treatment recommendations for retreatment of HCV-monoinfected or HCV/HIV coinfected patients with chronic hepatitis C who failed to achieve an SVR on prior antiviral therapy containing one or several DAA(s).

Failed treatment	Genotype	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
PegIFN-α, RBV and either telaprevir or boceprevir	Genotype 1	12 wk with RBV	No	No	No	12 wk with RBV
Sofosbuvir alone, in combination with RBV or in combination with PegIFN-α and RBV	Genotype 1	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
	Genotype 2 or 3	No	No	No	No	12 weeks with RBV or 24 weeks with RBV if F3 or cirrhosis
	Genotype 4	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
	Genotype 5 or 6	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
PegIFN-α, RBV and simeprevir	Genotype 1 or 4	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
PegIFN-α, RBV and daclatasvir	Genotype 1	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 2 or 3	No	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
	Genotype 4	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 5 or 6	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
Sofosbuvir and simeprevir	Genotype 1 or 4	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis

Failed treatment	Genotype	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Sofosbuvir and daclatasvir or Sofosbuvir and ledipasvir	Genotype 1	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 2 or 3	No	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
	Genotype 4	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 5 or 6	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Genotype 1	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
Ritonavir-boosted paritaprevir and ombitasvir	Genotype 4	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis

http://www.hiv-druginteractions.org/Interactions.aspx

Table 4A. Drug-drug interactions between HCV DAAs and HIV antiretrovirals.

		SIM	DCV	SOF	SOF/ LDV	3D
NRTIs	Abacavir	•	•	•	•	•
	Didanosine	•	•	•	•	•
	Emtricitabine	•	•	•	•	•
	Lamivudine	•	•	•	•	•
	Stavudine	•	•	•	•	•
	Tenofovir	•	•	•	•	•
	Zidovudine	•	•	•	•	•
NNRTIs	Efavirenz	•	•	•	•*	•
	Etravirine	•	•	•	•	•
	Nevirapine	•	•	•	•	•
	Rilpivirine	•	•	•	•*	•
Protease inhibitors	Atazanavir; atazanavir/ritonavir	•	•	•	•*	•
	Darunavir/ritonavir; darunavir/cobicistat	•	•	•	•*	•
	Fosamprenavir	•	•	•	•*	•
	Lopinavir	•	•	•	•*	•
	Saquinavir	•	•	•	•*	•
Entry/ Integrase inhibitors	Dolutegravir	•	•	•	•	•
	Elvitegravir/cobicistat	•	•	•	•*	•
	Maraviroc	•	•	•	•	•
	Raltegravir	•	•	•	•	•

SIM, simeprevir; DCV, daclatasvir; SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir.

*Known or anticipated increase in tenofovir concentrations with boosted regimens and with efavirenz and rilpivirine when given sofosbuvir plus ledipasvir: caution and frequent renal monitoring needed.

Colour legend. Green: No clinically significant interaction expected. Amber: Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring. Red: These drugs should not be co-administered.

HIV-HCV KOİNFEKTE HASTA KHC TEDAVİSİ

- HCV monoinfekte hasta ile aynı tedavi yaklaşımı
- **SOF ile ART ajanlar arasında etkileşim yok**

SMP li tdv alan hastada önerilmez:
Cobicistatlı rejimler,
efavirenz,
delavirdin,
etravirin,
nevirapin,
ritonavir
proteaz inh

SMP li tdv alan hastada önerilir
Raltegravir
Rilpivirin
Maraviroc
Enfuvirtide
Tenofovir
Emtrisitabin
Lamivudin

ATZ/r li ART alan hastada
DAC dozu 30mg/gün,
EFV li ART alan hastada
DAC dozu 90mg/gün