Klinik HIV/AIDS Sempozyumu 2010

ART Dirençli bir Olgu Tedavi Yönetimi

Dr. Aysel Kocagül Çelikbaş

Ankara Numune Eğitim ve Araştırma Hastanesi

KAÇE71CU

- 39 y
- Erkek
- 1996 “pneumocystis carinii pnömonisi”
- 15 yıl Almanya’da yaşamış
- Heteroseksüel korunmasız cinsel temas
- IV ilaç kullanımı
- Anti HIV ve Anti HCV +
- CD4 210/mm ^{3}

1996 Yılında Ülkemizde Bulunan Antiretroviral Ajanlar

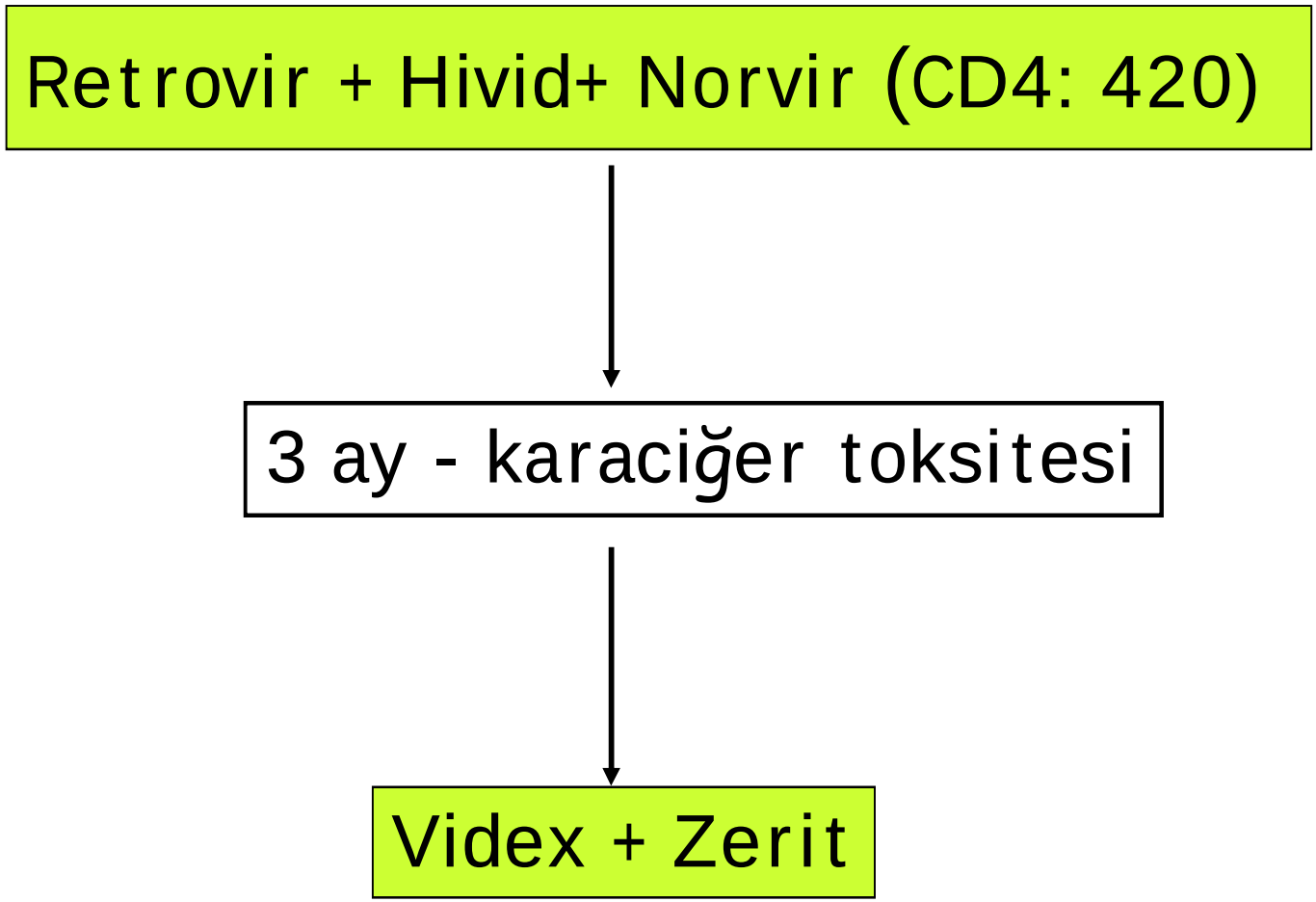
NRTI

- Zidovudin AZT
- Lamivudin 3TC
- Zalcitabin ddC
- Stavudin d4T
- Didanozin ddI

Proteaz inhibitörü

§ Norvir

(CD4: 210) Retrovir + Hivid


Retrovir + Hivid+ Norvir (CD4: 420)
3 ay - karaciğer toksitesi
Videx + Zerit

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Yıl	CD4	Viral yük	Tedavi
1996	210		Retrovir + Hivid
1996	420		Retrovir + Hivid + Norvir(Kc tok)
1997			Videx + Zerit
1999	245	$1.58X10^4$	Retrovir + Epivir
2000	124	$2.14X10^5$	Videx + Zerit+ Crixivan
2002	110	$2.1\ X10^5$	Combivir + Viramun
2004			

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Dtsch Med Wochenschr. 2010 Jun;135(23):1166-70. Epub 2010 May 31.

[Long-term efficacy of second-line treatment of HIV infection after class change following virological failure on protease inhibitor-based therapy]

[Article in German]

Brunner J, Seyf

Collaborato

Infektionsabteilun

İlk ART rejiminde PI kullanılan hastaların
2. ART
Olgumuzda başarısız
NNRTI
Farklı bir prot masından
daha etkili

Abstract

BACKGROUND there are no comparative st nd-line strategies after virological on-nucleoside reverse transcr

PATIENTS AND METHODS: This cohort study retrospectively analyzed patient data documented for the Clinical Surveillance of HIV Disease project (ClinSurv) between 1999 and 2008, run by the Robert Koch Institute in Berlin, Germany. Follow-up data for at least three months of a treatment switch after virological failure of the first-line regimen were available for 157 patients out of the 14,377 patients in the ClinSurv cohort. Eighty-four (54%) of these had a PI-based first-line regimen and were therefore included into the

Tedaviye Optimal Virolojik Yanıt:

Maksimal virolojik baskılanma

- Tedavinin

  24. haftasında HIV RNA düzeyi <400 kopya/mL

  48. haftada <50 kopya/mL

İnkomplet Virolojik Yanıt

HIV- RNA

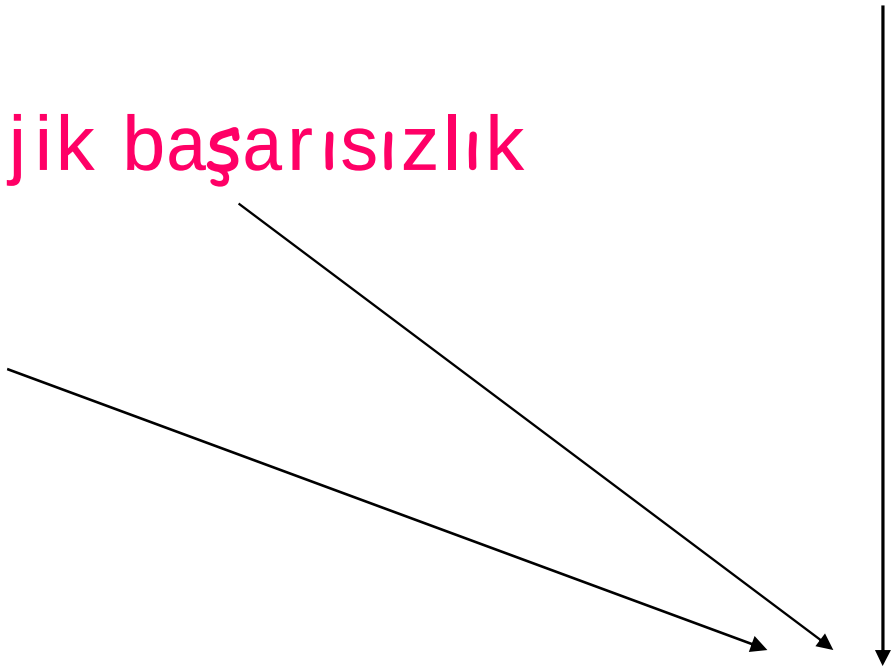
- 12-24 hafta arasında > 1000 kopya/mL
- 24 haftada > 400 kopya/mL
- 48 haftada > 50 kopya/mL

Blip

HIV- RNA düzeyinde her zaman olmayan düşük düzey bir pozitifliğin arada bir görülmesi ("blips") genellikle virolojik başarısızlığı göstermez ve tedavi değişikliği gerektirmez

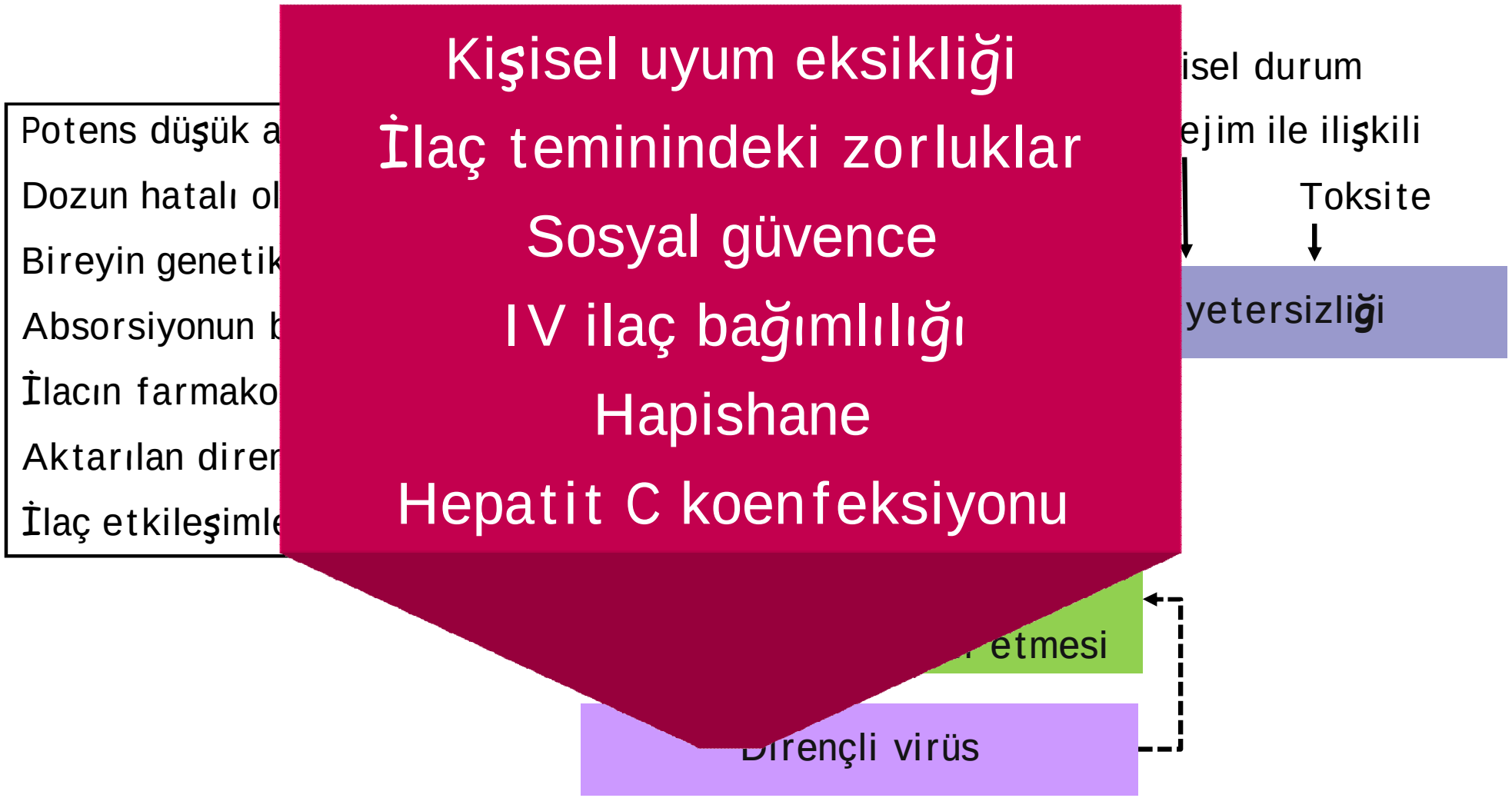
Sunulan Olguda

- (Viral yük: 2.1 X10^5 kopya/ ml): Virolojik başarısızlık
- (CD4 110): İmmünolojik başarısızlık
- Klinik progresyon
  - 2 kez Zona
  - Baziller anjiomatoz
  - Pnömoni



Tedavi başarısızlığı

Tedavi Başarısızlığının Nedenleri



ART resistance testing. AETC National Resource Center.

HIV RNA >1,000 kopya/ml

- İlaç direnci testi gönder
- Aynı rejime devam edip sonuçları bekle
- Farmakokinetik olarak daha etkin (PI/r) darinovir atazanavir, fosamprenavir gibi bir proteaz inhibitörü ekle

EACS 2009

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Yıl	CD4	Viral yük	Tedavi
1996	210		Retrovir + Hivid
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2000	124	$2.14X10^5$	Videx + Zerit+ Crixivan
2002	110	$2.1\ X10^5$	Combivir + Viramun
2004	Direnç testi		

O Günlerdeki Sorunlarımız

- Direnç çalışan merkez az
- Numunenin gönderilmesi – hastanın gönderilmesi
- Sosyal güvencenin testi karşılamaması
- Sonuçların geç alınması

Clin Microbiol Infect. 2010 Oct;16(10):1511-7. doi: 10.1111/j.1469-0691.2010.03353.x.

The use of human immunodeficiency virus resistance tests in clinical practice.

Ceccherini-Silberstein F, Cento V, Calvez V, Perno CF.

Departmen ', Rome, Italy.

Abstrac

Clin Micr ment of human ir ing HIV-1 to escape fr us; transmitt remains the limiting fa s focus on the importance of tailoring antiretroviral therapy to the individual patient, on the basis onf HIV-1 genetic data, integrated with clinical, laboratory and therapeutic information. The aim of this review is to provide useful information to clinicians and virologists about how and when to use genotypic resistance testing in clinical practice, especially in the management of the first stages of HIV-1 patient care and treatment decisions.

2010

Yeni tesbit edilen olguda direnç testlerini yap

Direnç Testlerinin Klinik Kullanımı (DHHS,2008)

- Akut veya yeni tespit (<12 ay) HIV infeksiyonu
- Bilinen HIV infeksiyonunda antiretroviral tedaviye başlamadan önce
- Tedavi başarısızlığı
- Gebelik (Plazma HIV RNA saptanabilir düzeydeyse)

Disclaimer:

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- All predictions below **aim** at predicting the ***in vitro* resistance phenotype**. Predicting *in vivo* resistance or **clinical utility is not intended**.
- The **atazanavir (ATV) model** has been trained on samples derived from atazanavir-naive patients only. Predictions are thus most reliable for this type of samples.

Phenotype Prediction

At ambiguous sequence positions (due to a mixed virus population) the resistance associated mutation has been assumed if present.

Drug	Cutoff	Decision tree classification[1] [confidence factor]	SVM classification[2]	Predicted fold-resistance (resistance factor, RF)[2]	z-score (number of standard deviations above mean of drug-naive patients) more	Probability score (likelihood of belonging to the resistant subpopulation) more
ZDV	8.5	resistant [0.90]	resistant	108.6	9.9	1
ddC	2.5	resistant [0.74]	resistant	4.3	10.3	1
ddI	2.5	resistant [0.78]	resistant	9.1	12.3	0.99
d4T	2.5	resistant [0.74]	resistant	3.7	8.3	1
3TC	8.5	resistant [0.98]	resistant	262.3	20.0	1
ABC	2.5	resistant [0.89]	resistant	16.3	18.8	1
TDF	2.5	resistant [0.76]	susceptible	3.9	8.1	1
NVP	8.5	resistant [0.94]	resistant	175.7	8.5	1
DLV	8.5	resistant [0.84]	resistant	18.3	6.7	1
EFV	8.5	resistant [0.87]	resistant	25.9	7.5	1
SQV	3.5	resistant [0.66]	resistant	4.8	5.3	1
IDV	3.5	resistant [0.89]	resistant	44.3	11.6	1
RTV	3.5	resistant [0.91]	resistant	60.8	14.0	1
NFV	3.5	resistant [0.91]	resistant	20.4	6.4	1
APV	3.5	resistant [0.84]	resistant	8.3	5.4	1
LPV	3.5	resistant [0.97]	resistant	45.3	12.8	1
ATV	3.5	resistant [0.94]	resistant	22.3	8.5	1

1: based on C5.0, RuleQuest Research Pty Ltd
2: based on LIBSVM, Copyright (c) 2000, Chih-Chung Chang and Chih-Jen Lin

[Protease | Reverse transcriptase | Subtype | Predicted phenotype | New sequence]

TDF

Virolojik Başarısızlığın Yönetimi

Yeni antiviral rejim için ideal olan daha önce kullanılan grupla cihen 3 aktif ilacın başlanm

- Hastan amnezi
- Direnç testi

Tenofovir

DHHS 2009
EASC 2009

Virolojik Başarısızlığın Yönetimi

<2 duyarlı ilaç varsa

Hastayı değerlendir

- CD4 >100/mm3
- Klinik tablo ağır değil

Değişikliği ertele

- CD4 <100/mm3
- Klinik tablo ağır

Mekanizması farklı veya deneysel ilaçlar

Bu durumda ne yaparsınız?

- Hastanın kullanmakta olduğu ilaçlarla tedaviye devam ederim
- Tenofovir temin eder, tedaviye eklerim
- Tedaviyi keserim

Geçmişte çok ilaç deneyimli ve yüksek ilaç direnci olan HIV.

- Tedaviye aktif olan tek bir ajanın eklenmesi önerilmez
- CD4 sayısı <100/mm3

Klinik progresyonu hızlı olan olgularda

Tedaviye eklenen tek aktif ajan HIV -RNA yı düşürüp CD4 sayısını geçici olsada yükselterek hastalığın klinik olarak hızlı ilerlemesini durdurmak gibi bir faydası olabilir. Ancak hızla direnç gelişme riski yüksek


Peki biz ne yaptık?

KAÇE71CU

- ART kesildi

Tedaviyi kesmek önerilmiyor

§6 ay süreyle CD 4 – VY stabil
§2. direnç testi

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ZDV	8.5	resistant [0.90]	resistant	132.3	10.4	1
ddC	2.5	susceptible [0.81]	susceptible	2.2	5.0	1
ddI	2.5	resistant [0.78]	resistant	5.7	9.4	0.93
d4T	2.5	resistant [0.74]	resistant	5.1	10.6	1
3TC	8.5	susceptible [0.80]	susceptible	5.7	5.2	5.5e-05
ABC	2.5	resistant [0.89]	resistant	8.2	13.7	1
TDF	2.5	resistant [0.76]	susceptible	3.6	7.6	1
NVP	8.5	resistant [0.94]	resistant	248.5	9.1	1
DLV	8.5	resistant [0.84]	resistant	12.3	5.6	1
EFV	8.5	resistant [0.87]	resistant	23.7	7.3	1
SQV	3.5	susceptible [0.89]	susceptible	0.6	-2.5	9e-06
IDV	3.5	susceptible [0.90]	susceptible	1.7	0.4	0.0048
RTV	3.5	susceptible [0.91]	susceptible	1.3	-0.2	0.0011

ddC

3TC

SQV

IDV

RTV

Bu duyarlılık paternine göre hangi kombinasyonu tercih edersiniz?

Başlanacak Yeni Tedavinin Hedefi

- HIV RNA
- 3 ayda < 400 kopya /mL
- 6 ayda < 50 kopya/mL

Geçmişte Çok Sayıda İlacı Kullanmış ve İlaç Direnci Olan Olgular

- Hedef HIV RNA nın maksimum düzeyde baskılanması (<50 kopya/mL)
- Pek çok yeni antiretroviral ilaç ve, farklı etki mekanizması olan ilaçlarla bu hedefe ulaşmak mümkün
- Viral baskılanma sağlamanın zor olduğu durumda hedef immunolojik fonksiyonların korunması ve klinik ilerlemenin önlenmesi

Yeni Başlanacak Tedavi Rejiminin Seçimi

Yeni başlanacak rejimlerde

- Ritonovir ile güçlendirilmiş bir proteaz inhibitörü (PI/r)
- NNRTI, genotipik testi yapılarak (etravirine)
- Füzyon/integraz inhibitörü/CCR inhibitörü

Enferm Infecc Microbiol Clin. 2009 Dec;27 Suppl 2:6-11.

[Etravirine in highly treatment-experienced patients]

[Article in Spanish]

Palter DP, Corbera EF, Tiraboschi JM.

Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona, España. dpodzamczer@bellvitgehospital.cat

Abstract

Etravirine (E[illegible]etroviral drugs. Mos[illegible]dentical designs tha[illegible]of hospita admission[illegible]on in only 2%. There [illegible]egimens are now av[illegible]unavir/r) with excelle[illegible]olerated and is the f[illegible]with firstgeneration NNRTI. Moreover, its long half-life allows once daily administration in patients requiring a QD regimen.

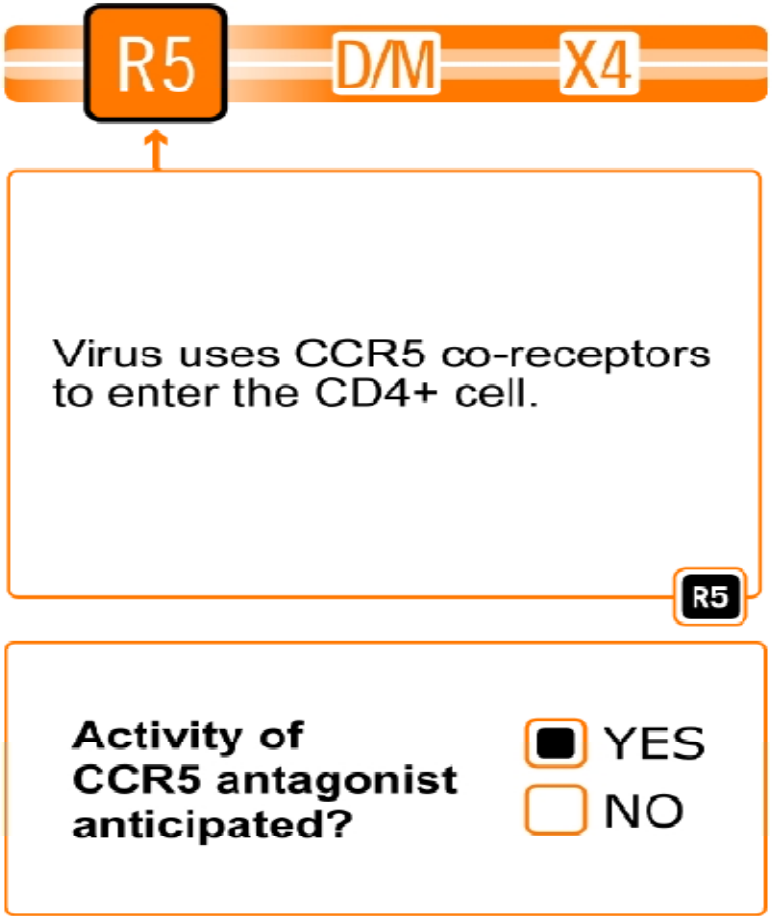
ETR çalışmalarda placebo grubuna göre daha etkin virolojik ve immunolojik cevap sağlamış

Hastaneye başvuru sıklığı ve HIV e bağlı mortaliteyi azaltmış

PMID: 20116622 [PubMed - indexed for MEDLINE]

Yeni Başlanacak Tedavi Rejiminin Seçimi

- Integraz inhi inhibitörü (ENF) daha ö ilerde aktif kabul edilir
- CCR5 antagor ini değerlendiril Tropism Assay)



DHHS. http://www.aidsinfo.nih.gov.

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ddC	2.5	susceptible [0.81]	susceptible	2.2	5.0	1
ddI	2.5					
d4T	2.5					
3TC	8.5					
ABC	2.5	resistant [0.89]	resistant	8.2	13.7	1
TDF	2.5	resistant [0.76]	susceptible	3.6	7.6	1
NVP	8.5	resistant [0.94]	resistant	248.5	9.1	1
DLV	8.5	resistant [0.84]	resistant	12.3	5.6	1
EFV	8.5	resistant [0.87]	resistant	23.7	7.3	1
SQV	3.5	susceptible [0.89]	susceptible	0.6	-2.5	9e-06
IDV	3.5	susceptible [0.90]	susceptible	1.7	0.4	0.0048
RTV	3.5	susceptible [0.91]	susceptible	1.3	-0.2	0.0011

Retrovir + Hivid+ Kaletra

ddC

IDV

RTV

KAÇE71CU

- 2005 Retrovir + Hivid + Kaletra

CD4 76/mm^3 HIV-RNA 1.52X 10^4

Karaciğer enzim yüksekliği

Laktik asidoz

Lökopeni

Tedavi kesildi

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National Institutes of Health

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National Institutes of Health

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Lancet Infect Dis. 2004 Jul;4(7):437-44.

HIV and hepatitis C virus co-infection.

Rockstroh JK, Spengler U.

HIV Outpatient Cl

Comment in:

Lancet I

HCV koenfeksiyonunda HAART tedavisi ile karaciğer toksisitesi artıyor

Abstract

Since the decline in HIV-related morbidity and mortality after introduction of highly active antiretroviral therapy (HAART) in 1996, liver disease caused by chronic infection with hepatitis C virus (HCV) has become an increasingly important cause of morbidity and mortality among HIV-infected patients infected parenterally with HCV in more developed countries. A third of HIV-infected individuals in Europe and the USA have HCV co-infection. HIV accelerates HCV liver disease especially when HIV-associated immunodeficiency progresses. With the introduction of pegylated interferon in combination with ribavirin, greatly improved treatment options for patients with HIV and HCV co-infection have become available and have led to sustained virological response rates of up to 40%. Furthermore, recent cohort analyses have shown that immune reconstitution induced by HAART can improve the course of hepatitis C leading to a decline in liver-related mortality. However, patients with HCV co-infection are at increased risk of hepatotoxicity from HAART. Owing to the high rates of HIV and HCV co-infection worldwide, new improved treatment strategies and guidelines for the management of co-infection remain a major future goal.

Curr Opin Infect Dis. 2005 Dec;18(6):550-60.

New paradigms in the management of HIV and hepatitis C virus coinfection.

Soriano V, Martin-Carbonero L, Maida I, Garcia-Samaniego J, Nuñez M.

Department of Inf

Didanozin stavudin ve zidovudinin ribavirin ile etkileşimiyle ilaç yan etkileri artıyor

Abstract

PURPOSE OF R ...emophiliacs and intravenous drug users. The bidirectional interferences between hepatitis C virus and HIV have clinical consequences and complicate the management of coinfected individuals.

RECENT FINDINGS: There is an increased rate of liver complications among coinfected patients due to the decrease in opportunistic infections resulting from the use of potent antiretroviral therapy and accelerated progression to liver cirrhosis in the HIV setting. Conversely, the risk of hepatotoxicity of antiretrovirals is higher in the presence of chronic hepatitis C. While the standard therapy for hepatitis C in HIV is the combination of pegylated interferon plus ribavirin, overall treatment responses are lower in HIV-coinfected than in hepatitis C virus-monoinfected patients. Moreover, interactions between ribavirin and HIV drugs (i.e. didanosine, zidovudine) are associated with higher risks of side effects.

SUMMARY: Given the accelerated progression to end-stage liver disease in coinfected patients, treatment of hepatitis C should be a priority. While hepatitis C therapy should not be denied in the absence of contraindication, it should be re-assessed at week 12 and therapy continued only in patients showing more than 2 log drops in viremia, to avoid side effects. Most recent data suggest that adequate selection of candidates, expert management of side effects, and prescription of appropriate ribavirin doses (in

Semin Liver Dis. 2005 Feb;25(1):33-51.

Treatment of chronic hepatitis C in human immunodeficiency virus/hepatitis C virus-coinfected patients in the era of pegylated interferon and ribavirin.

Bräu N.

Mount Sinai School of Medicine, Bronx Veterans Affairs Medical Center, Infectious Diseases Section (111F), 130 West Kingsbridge Road, New York, NY 0468, USA. norbert.brau@med.va.gov

Pegile interferon ve ribavirin ile
HCV Kalıcı Virolojik Yanıt elde edilebiliyor

Abstr

A sign of HIV-infecte d surviva d progression to liver failure or hepatocellular carcinoma than HCV-monoinfected persons. In contrast to the deleterious effect of HIV on HCV-related liver disease, most studies have shown that HCV does not influence progression of HIV infection to AIDS or death. HCV therapy with peginterferon alfa (2a or 2b) plus ribavirin can achieve a sustained viral response in HIV/HCV-coinfected patients of up to 38% in HCV genotype 1 and up to 73% in genotypes 2 and 3. The safety profile is largely similar to therapy in HIV-monoinfected patients, but there is a higher incidence of mitochondrial toxicity in patients taking didanosine or stavudine and of anemia in patients taking zidovudine. There is no proven anti-HCV therapy for HIV/HCV-coinfected patients with end-stage liver disease (ESLD). Liver transplantation is being investigated as a potential therapeutic option for HIV-infected individuals with ESLD, and initial reports are encouraging. Given that pegylated interferon and ribavirin have been shown to be safe and effective for HIV/HCV coinfection as well as HCV monoinfection, all HIV/HCV-coinfected patients should be evaluated for therapy.

HIV/Hepatit C

- Karaciğer biyopsisi

HAİ 3/18, Fibrozis 3/6 (18.08.2005)

HCV RNA:10^7

Pegile interferon + ribavirin (Lökopeni- trombositopeni)

Genotip bakılamıyor (Enfeksiyon orijini Almanya)

Tedavi süresi 6 ay

Kalıcı viral yanıt

KAÇE71CU

- Combivir+ Crixivan (2007)
- CD 61/mm^3
- HIV RNA 7.8X 10^4

Mekanizması Farklı veya Deneysel İlaçlar

2008 TMC 114

26.03.2008 COMBİVİR+ CRİXİVAN +DARUNOVİR/r

CD4 10/mm^3 - VY 7.8x 10^4

28.09.2008 CD4 109- VY <450 kopya/mL

Vücut kıllarında dökülme
İştahsızlık
Cilt altı yağ dokusunda erime

24.06.2009 Crixivan kesildi

Drugs. 2008;68(16):2257-67. doi: 10.2165/0003495-200868160-00001.

Double-boosted protease inhibitor antiretroviral regimens: what role?

Ribera E, Curran A.

Infectious Diseases D

Lopinavir/ritonavir+ atazanavir

Lopinavir/ritonavir +saquinavir

Lopinavir/ritonavir + diğerleri

Abstract

Despite the clinical ly available drugs to failing regimens me e-boosted protease inhibitors (PIs) to bu HIV; (ii) to achieve higher plasma con reverse transcriptase inhibi e and the availability of more convenient d PI regimens; however, the publis itonavir plus saquinavir and othe ses that are better tolerated and have l trials, even in patients with extens tive drugs, achieving success rates similar to those obtained in treatment-naive patients with recommended regimens. In this context, it is unthinkable that double-boosted PIs could play any role.Double-boosted PIs may be an alternative for those patients with limited therapeutic options in resource-poor settings, where new expensive drugs are not currently available. The fixed combination of lopinavir/ritonavir tablets makes it easier to boost with another PI at the same time, without requiring ritonavir refrigeration, and this may be particularly useful in this setting.

PMID: 18973392 [PubMed - indexed for MEDLINE]

Darunavir: a review of its use in the management of HIV infection in adults.

- Oral HIV-1 proteaz inhibitörü
- Düşük doz ritonavir ile güçlendirilmiş
- Dirence karşı genetik bariyeri yüksek
- Çok ilaca-dirençli HIV isolatlarına etkili
- Darunavir 600 mg/ritonavir 100mg günde iki kez

Drugs. 2009;69(4):477-503

TMC 114

COMBİVİR
CRİXİVAN
DARUNOVİR/r

COMBİVİR →
DARUNOVİR/r

Tarih	CD4	HIV-RNA
12.2008	189	negatif
03.2009	134	131 k/mL
08.2009	182	negatif
11.2009	204	negatif
06.2010	121	negatif
09.2010	98	negatif

Sonuç Olarak

- ART naiv hastaların %10' unda primer dirençli viral varyantlar görülebilmekte bu nedenle tedavi başlanmadan önce viral direnç testi yapılmalı
- Farmakoekonomi çalışmaları ART naiv ve deneyimli olgularda fenotipik testlerin yapılmasının "cost effective" olduğunu göstermiş
- Tüm rehberler bu testlerin yapılmasını öneriyor
- HIV/HCV birlikteliğinde HCV tedavisi gerekli
- Çoklu ilaç deneyimi ve ilaç direnci olan olgularda tedaviye yeni grup ajanların eklenmesi etkili olabilir

İlaç Seçenekleri Artıyor