Antiretroviral Tedavi ve Kürde Son Durum

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ANTİRETROVİRAL TEDAVİ

Tedaviye başlama zamanı

HIV Prevention Trials Network (HPTN) Study 052

1783 Serodiskordan çift (%97 heteroseksüel)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Initiation of Antiretroviral Therapy in Early

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa

The TEMPRANO ANRS 12136 Study Group*

- ✓ CD4 düzeyi 500/mm^3'ün üzerinde olan hastalarda antiretroviral tedaviye (ART)'ye başlanması tedaviyi ertelemeye üstün

- ✓ Erken tedavi grubunda AIDS ile ilişkili ya da ilişkili olmayan ciddi durumlar anlamlı oranda daha düşük

Test and Start 2015

Rehberler

- ✓ **DHHS**

(Department of Human and Health Services)

- ✓ **EACS**

(European AIDS Clinical Society)

- ✓ **IAS** (International AIDS Society)
- ✓ **WHO** (World Health Organization; DSÖ)
- ✓ **BHIVA** (British HIV Association)
- ✓ **Türkiye HIV/AIDS Tanı Tedavi Rehberi**

Önerilerde Değişiklikler

DHHS/EACS

Tüm HIV ile enfekte viremik bireylerde, **CD4 sayıları dikkate alınmadan** ART'ye en kısa sürede başlanmalıdır

- mortalite ve morbiditede azalmaya yol açar (AI)
- hastalığın ilerlemesini ve bulaşmayı önler (AI)

✓ Antiretroviral tedavi başlanacak hastanın tedaviye **istekli ve hazır olması**, tedavinin yarar ve riskleri ve **ilaç uyumunun** önemi hakkında bilgilendirilmesi ger

✓ H la klin **AR**

ART mümkün olan en kısa sürede **hatta ilk vizitte** başlanır

DHSS;2017

Acil tedavi gerektiren durumlar

- ✓ AIDS tanımlayıcı hastalık öyküsü (HIV ilişkili demans dahil)
- ✓ Gebelik
- ✓ Akut fırsatçı enfeksiyonlar
- ✓ CD4 <200/mm^3
- ✓ HIV-ilişkili nefropatili hasta
- ✓ HIV/HBV ko-enfeksiyonlu hasta
- ✓ HIV/HCV ko-enfeksiyonlu hasta
- ✓ Akut/erken HIV enfeksiyonu

DHHS; 2017

Antiretroviral tedavi

Antiretroviral ilaç grupları

1-Nükleozid veya nükleotid revers transkriptaz inhibitörleri (NRTİ)

2-Non-nükleozid revers transkriptaz inhibitörleri (NNRTİ)

3-Proteaz inhibitörleri (Pİ)

4-Giriş inhibitörleri (ko-reseptör antagonistleri) (Gİ)

5-Füzyon inhibitörleri (Fİ)

6-İntegraz inhibitörleri (İNİ)

Antiretroviral ilaçlar

Nükleozid veya nükleotid revers transkriptaz inhibitörleri (NRTİ)

Tenofovir disoproksil fumarat (TDF)
Tenofovir alafenamid (TAF)
Emtrisitabin (FTC)
Abakavir (ABC)
Lamivudin (3TC)
Zidovudin (AZT)
Zalsitabin (ddC)
Didanozin (ddI)
Stavudin (d4T)

Non-nükleozid revers transkriptaz inhibitörleri (NNRTİ)

Efavirenz (EFV)
Nevirapin (NVP)
Rilpivirin (RPV)
Etravirin (ETV)
Delavirdin (DLV)

Antiretroviral ilaçlar

Proteaz inhibitörleri (Pİ)

Tipranavir (TPV)
İndinavir (IDV)
Sakinavir (SQV)
Darunavir (DRV)
Atazanavir (ATV)
Lopinavir (LPV)
Ritonavir (RTV)
Amprenavir (APV)
Fosamprenavir (FPV)
Nelfinavir (NFV)

Giriş inhibitörleri (Gİ)

Maravirok (MVC)

Füzyon inhibitörleri (Fİ)

Enfuvirtid (T-20)

İntegraz inhibitörleri (İNİ)

Raltegravir (RAL)
Dolutegravir (DTG)
Elvitegravir/kobisistat (EVG/cobi)

Tenofovir alafenamid (TAF)

HHS Panel on Antiretroviral Guidelines for Adults and Adolescents Includes a Fixed-Dose Combination of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Among the Recommended Regimens for Antiretroviral Treatment-Naive Individuals with HIV-1 Infection

Date: November 18, 2015

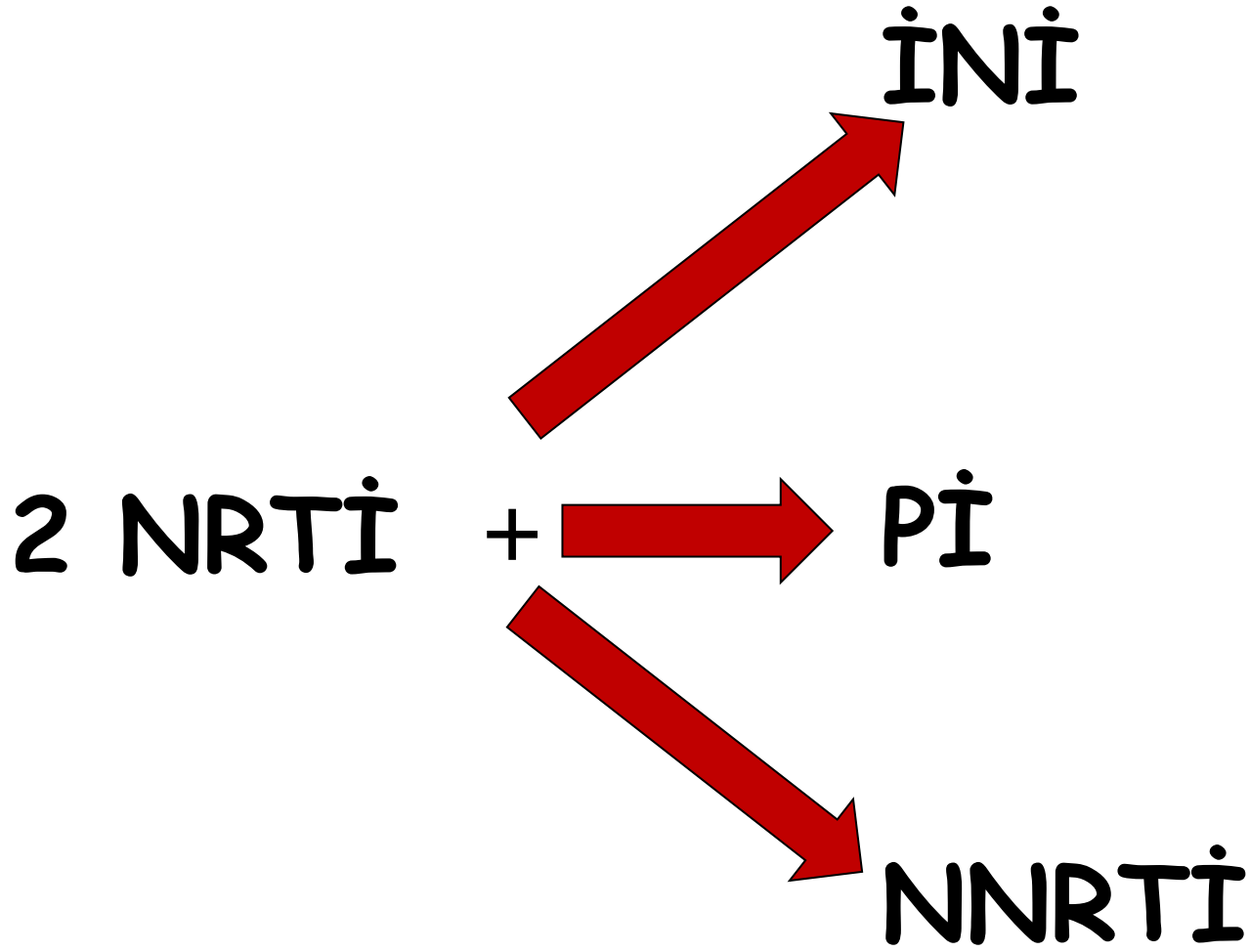
Source: AIDS*info*

Panel's Recommendation

Based on efficacy and safety data from phase 3 randomized clinical trials, EVG/c/FTC/TAF will be added as one of the Recommended Initial Regimens for ART-naive adults and adolescents with estimated creatinine clearance ≥ 30 mL/min (AI).

ART'de temel prensip

Tedavide 2 ya da daha fazla sınıftan en az 2 tercihen 3 ilaçlı kombinasyonlar kullanılmalı


İNİ
2 NRTİ
+
Pİ
NNRTİ

Öneriler

- ✓ **Tercih edilen**
  - Randomize kontrollü çalışmalarda optimal etkisi gösterilmiş
  - Uygun tolerabilite ve toksisite
- ✓ **Alternatif**
  - Etkili fakat potansiyel dezavantajlara sahip
  - Bazı gruplara sınırlı kullanım
  - Veriler kısıtlı
- ✓ **Diğer**
  - Virolojik başarı oranı düşük
  - Veriler kısıtlı
  - Toksisite oranı yüksek, tablet sayısı fazla, yan etki oranı yüksek
  - Bazı gruplara sınırlı kullanım

DHHS; 2016

- **HIV ile enfekte hastaların çoğunda** önerilen tedaviler

- **Bazı klinik durumlarda** önerilen tedaviler

DHHS; 2017

HIV İLE ENFEKTE HASTALARIN ÇOĞUNDA ÖNERİLEN TEDAVİLER

(virolojik etkinlik, tolere edilebilir, düşük yan etki profili ve kolay kullanım)

İNİ+2 NRTİ

- **DTG/ABC/3TC** (AI)

(sadece HLA-B*5701 negatif olan hastalar)

- **DTG + tenofovir/FTC** (TDF ve TAF için AI)
- **EVG/cobi/tenofovir/FTC** (TDF ve TAF için AI)
- **RAL* + tenofovir/FTC** (TDF, AI ve TAF, AII)

* 2x400 mg ya da 1x 1200 mg (600 mg'lık tabletler)

DHHS; 2017

BAZI KLİNİK DURUMLARDA ÖNERİLEN TEDAVİLER
(tolere edilebilir ancak ilk tercih ilaçlarla kıyaslandığında bazı dezavantajları mevcut ya da randomize klinik çalışma verileri yetersiz)

Pİ + 2 NRTİ (DRV ATV'ye tercih edilir)

- **(DRV/c veya DRV/r)+ tenofovir/FTC** (DRV/r, AI ve DRV/c AII)
- **(ATV/c veya ATV/r) + tenofovir/FTC** (BI)
- **(DRV/c veya DRV/r) + ABC/3TC**

(sadece HLA-B*5701 negatif olan hastalar) (BII)

- **(ATVc veya ATV/r) + ABC/3TC**

(sadece HLA-B*5701 negatif olan hastalar) (ATV/r, CI ve ATV/c CIII)

NNRTİ +2 NRTİ

- **EFV+ tenofovir/FTC** (EFV/TDF/FTC, BI ve EFV+ TAF/FTC BII)
- **RPV/tenofovir/FTC** (BI)

(sadece tedavi öncesi viral yükü <100.000 kopya/ml ve CD4 sayısı > 200/mm^3 olan hastalar)

DHHS; 2017

BAZI KLİNİK DURUMLARDA ÖNERİLEN TEDAVİLER

İNİ+ 2NRTİ

- **RAL*+ ABC/TC** (CII)

(sadece HLA-B*5701 negatif olan hastalar viral yükü <100.000 kopya/ml)

TAF,TDF veya ABC kullanılamadığında diğer seçenekler

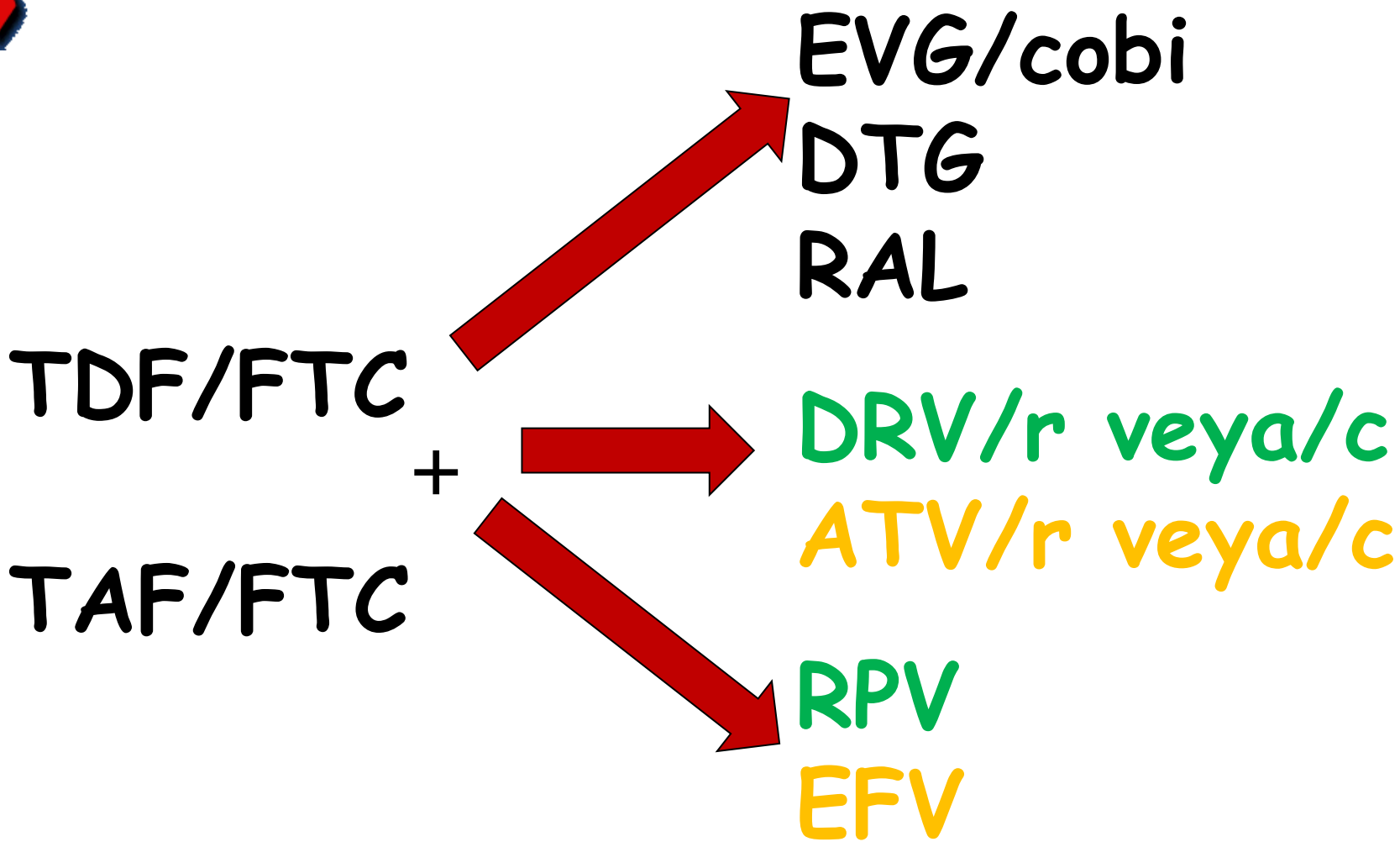
- **DRV/r+RAL (BID)** (CI)

(sadece tedavi öncesi viral yükü <100.000 kopya/ml ve CD4 sayısı >200/mm^3 olan hastalar)

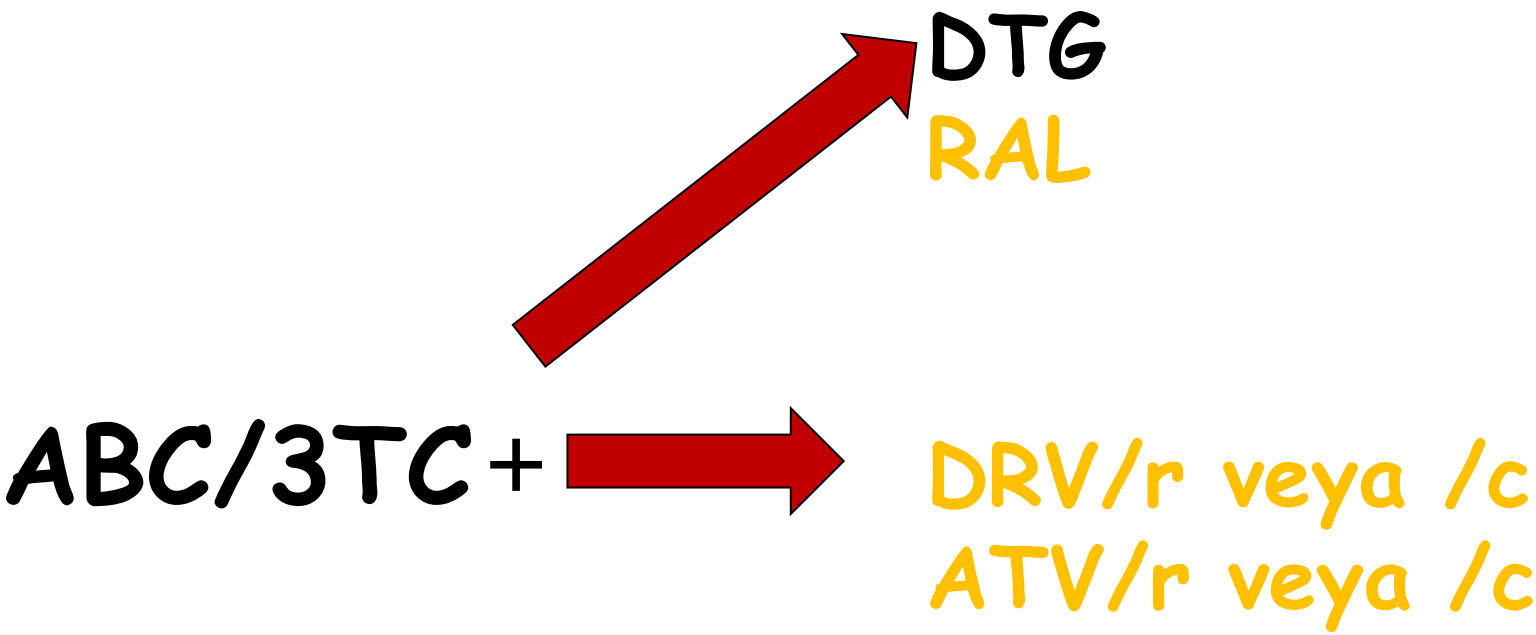
- **LPV/r+3TC (BID)** (CI)

* 2x400 mg ya da 1x 1200 mg (600 mg'lık tabletler)

DHHS; 2017



—: EACS'ta ilk tercih
—: 2. seçenek



—: EACS'ta ilk tercih
—: 2. seçenek

TDF--------sadece KrKl≥ 60 ml/dak

TDF+cobi----sadece KrKl≥ 70 ml/dak

TAF--------sadece KrKl≥ 30 ml/dak

ABC--------sadece HLA-B*5701 negatif hastalar

RPV------sadece tedavi öncesi viral yükü<100.000 kopya/ml ve CD4 sayısı >200/mm^3 olan hastalar

FDA News Release

FDA approves first two-drug regimen for certain patients with HIV

For Immediate Release

Summary

Release

Dolutegravir/rilpivirin

The U.S. Food and Drug Administration today approved Juluca, the first complete treatment regimen containing only two drugs to treat certain adults with human immunodeficiency virus type 1 (HIV-1) instead of three or more drugs included in standard HIV treatment. Juluca is a fixed-dose tablet containing two previously approved drugs (dolutegravir and rilpivirine) to treat adults with HIV-1 infections whose virus is currently suppressed on a stable regimen for at least six months, with no history of treatment failure and no known substitutions associated with resistance to the individual components of Juluca.

"Limiting the number of drugs in any HIV treatment regimen can help reduce toxicity for patients," said Debra Birnkrant, M.D., director of the Division of Antiviral Products in the FDA's Center for Drug Evaluation and Research.

Inquiries

Media

Theresa Eisenman

FDA onayı bekleyen ilaçlar

- ✓ Darunavir/kobisistat/emtrisitabin/tenofovir alafenamid

- ✓ Bictegravir/emtrisitabin/tenofovir alafenamid

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antiretroviral drug chart

Drugs licensed in the European Union – February 2010

Generic name	Trade name	Formulation	Standard adult dose	Pills/day	Major side-effects	Food restrictions
Nucleoside reverse transcriptase inhibitors (NRTIs)						
3TC, lamivudine	*Epivir*	*150* and 300mg tablets*	150mg twice a day **or** 300mg once a day	2 1	**Common:** Nausea, vomiting, diarrhoea, headache, abdominal pain, insomnia, rash, tiredness	Take with or without food
Abacavir	*Ziagen*	*300mg tablet*	300mg twice a day **or** 600mg once a day	2	**Common:** Rash, nausea, vomiting, diarrhoea, fever, headache, loss of appetite, tiredness **Rare:** Hypersensitivity reaction	Take with or without food
AZT, zidovudine	*Retrovir*	*100 and 250mg* capsules*	250mg twice a day	2	**Common:** Nausea, vomiting, fatigue, headache, dizziness, weakness, muscle pain **Rare:** Blood disorders, lipoatrophy	Take with or without food
d4T, stavudine	*Zerit*	*15, 20, 30 and 40mg* capsules*	**People over 60kg:** 40mg twice a day **People under 60kg:** 30mg twice a day	2	**Common:** Lipoatrophy, peripheral neuropathy, nausea, diarrhoea, abdominal pain, dizziness, tiredness, rash **Rare:** Pancreatitis	Take with food
ddI, didanosine	*Videx*	*25, 50, 100, 150 and 200mg* tablets*	**People over 60kg:** 400mg once a day **or** 200mg twice a day **People under 60kg:** 250mg once a day **or** 125mg twice a day	2 or 4 (chewed or dissolved in water)	**Common:** Peripheral neuropathy, nausea, vomiting, diarrhoea, rash **Rare:** Pancreatitis	Take at least two hours after and 30 minutes before eating
ddI, didanosine (extended release)	*VidexEC*	*125, 200, 250 and 400mg* capsules*	**People over 60kg:** 400mg once a day **or** 200mg twice a day **People under 60kg:** 250mg once a day **or** 125mg twice a day	1 or 2	**Common:** Peripheral neuropathy, nausea, vomiting, diarrhoea, rash **Rare:** Pancreatitis	Take at least two hours after and two hours before eating or drinking anything except water
FTC, emtricitabine	*Emtriva*	*200mg capsule*	200mg once a day	1	**Common:** Nausea, vomiting, diarrhoea, abdominal pain, headache, dizziness, weakness, rash	Take with or without food
Nucleotide reverse transcriptase inhibitors (NtRTIs)						
Tenofovir	*Viread*	*300mg tablet*	300mg once a day	1	**Common:** Nausea, vomiting, diarrhoea, dizziness, low blood phosphate levels **Rare:** Kidney problems	Take with food
NRTI / NtRTI fixed dose combinations						
3TC / AZT	*Combivir*	*Tablet comprising 150mg 3TC and 300mg AZT*	One tablet twice a day	2	See 3TC and AZT	Take with or without food
3TC / abacavir / AZT	*Trizivir*	*Tablet comprising 150mg 3TC, 300mg abacavir and 300mg AZT*	One tablet twice a day	2	See 3TC, abacavir and AZT	Take with or without food
3TC / abacavir	*Kivexa (EU)*	*Tablet comprising 300mg 3TC and 600mg abacavir*	One tablet once a day	1	See 3TC and abacavir	Take with or without food
FTC / tenofovir	*Truvada*	*Tablet comprising 200mg FTC and 300mg tenofovir*	One tablet once a day	1	See FTC and tenofovir	Take with food
NRTI / NRTI / NNRTI fixed dose combinations						
FTC / tenofovir / efavirenz	*Atripla*	*Tablet comprising 600mg efavirenz, 200mg FTC and 300mg tenofovir*	One tablet once a day	1	See FTC, tenofovir and efavirenz	Take without food
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)						
Efavirenz	*Sustiva (EU)*	*600mg tablet* and 200mg capsule*	600mg once a day	1	**Common:** Rash, dizziness, sleep disturbance, abnormal dreams, impaired concentration, nausea, headache, tiredness **Rare:** Depression, psychosis	Take on an empty stomach, preferably at bedtime
Etravirine	*Intelence*	*100mg tablet*	200mg twice daily	4	**Common:** Rash, diarrhoea and nausea **Rare:** Hypersensitivity reaction	Take with food
Nevirapine	*Viramune*	*200mg tablet*	200mg once a day for two weeks **then** 400mg once a day or 200mg twice a day	2	**Common:** Liver toxicity, allergic reaction, rash, nausea, headache **Rare:** Stevens Johnson syndrome	Take with or without food
Protease inhibitors						
Atazanavir	*Reyataz*	*100, 150*, 200 and 300mg capsule*	300mg with 100mg ritonavir once a day	2 §	**Common:** Nausea, diarrhoea, rash, abdominal pain, headache, hyperbilirubinaemia	Take with food
Darunavir	*Prezista*	*300*, 400 and 600mg tablet*	600mg with 100mg ritonavir twice a day	6	**Common:** Diarrhoea, nausea, headache	Take with food
Fosamprenavir	*Telzir*	*700mg tablet*	700mg with 100mg ritonavir twice a day	4 §	**Common:** Lipodystrophy, nausea, vomiting, diarrhoea, rash, abdominal pain, headache, dizziness, tiredness, tingling around the mouth	Take with or without food
Indinavir	*Crixivan*	*200, 333 and 400mg* capsules*	800mg three times a day	6	**Common:** Kidney stones, abdominal pain, liver abnormalities, lipodystrophy, muscle pain, nausea, vomiting, diarrhoea, rash, headache, dry skin and mouth, tiredness	Take one hour before or two hours after food **or** take with a light, low-fat snack
Lopinavir / ritonavir	*Kaletra* *Aluvia* (resource-limited settings)	*Tablet comprising 200mg lopinavir and 50mg ritonavir*	Two tablets twice a day	4	**Common:** Lipodystrophy, raised liver enzymes, nausea, vomiting, diarrhoea, abdominal pain, rash, tiredness, weakness, headache	Take with or without food
Nelfinavir	*Viracept*	*250mg tablet*	1250mg twice a day **or** 750mg three times a day	10 9	**Common:** Lipodystrophy, nausea, vomiting, diarrhoea	Take with food
Ritonavir	*Norvir*	*100mg capsule* and 100mg tablet*	**Full dose:** 600mg twice a day **To 'boost' other PIs:** 100 – 200mg once or twice a day	12 1 – 4	**Common:** Lipodystrophy, nausea, vomiting, diarrhoea, abdominal pain, muscle pain, headache, weakness, numbness around the mouth	Take with food to avoid nausea
Saquinavir	*Invirase*	*200mg capsule and 500mg tablet**	1000mg with 100mg ritonavir twice a day	6 §	**Common:** Lipodystrophy, nausea, vomiting, diarrhoea, abdominal pain, muscle pain, headache, rash, fever, tiredness, dizziness	Take within two hours of food
Tipranavir	*Aptivus*	*250mg capsule*	500mg with 200mg ritonavir twice a day	8 §	**Common:** Lipodystrophy, nausea, diarrhoea, abdominal pain	Take with food
Fusion inhibitor						
T-20, enfuvirtide	*Fuzeon*	*Powder reconstituted in water*	Injection of 90mg under the skin twice a day		**Common:** Injection site reaction, respiratory tract infections	No food restrictions
CCR5 inhibitor						
Maraviroc	*Celsentri*	*150*, 300mg tablets*	300mg twice a day, 150mg twice a day with all ritonavir-boosted PIs except fosamprenavir and tipranavir **or** 600mg twice a day with efavirenz	2 – 4	**Common:** Headache, dizziness, nausea, weakness, flatulence	Take with or without food
Integrase inhibitor						
Raltegravir	*Isentress*	*400mg tablet*	400mg twice a day	2	**Common:** Headache, diarrhoea, nausea	Take with or without food

*Formulation(s) shown. § Includes ritonavir capsule(s).

This drug chart is produced by an organisation called NAM. NAM provides people working in the global fight against HIV & AIDS with up to date and impartial information. Please visit us at our website where you can read the latest HIV news and sign up for free email updates.

NAM, Lincoln House, 1 Brixton Road, London, SW9 6DE. Email info@nam.org.uk **Web** www.aidsmap.com

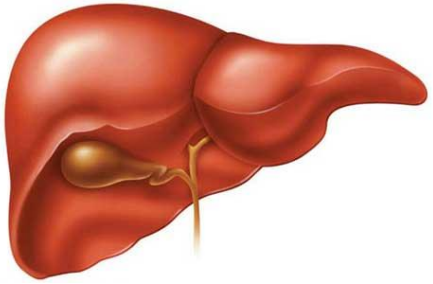
İlaç seçiminde göz önünde bulundurulan faktörler

- Direnç
- Tedavi öncesi HIV RNA ve CD4 düzeyi
- İlaçların genetik bariyer direnci
- Yan etki
- İlaç etkileşimi
- Gebelik ya da gebelik potansiyeli
- HLA-B*5701
- **Komorbidite varlığı** (kardiyovasküler hastalık, hiperlipidemi, kronik hepatit B, kronik hepatit C, karaciğer ya da renal hastalık, tüberküloz, psikiyatrik bozukluk, bağımlılık)
- Hastanın tercihi ve uyum potansiyeli
- Kullanım kolaylığı (ilaç yükü, doz aralığı, tek tablet…)
- Maliyet

KLİNİK DURUM	ÖNERİLER
CD4 <200 hücre/mm^3 veya HIVRNA>100.000 kopya/ml	• RPV temelli rejimler • DRV/r +RAL kullanılmamalı
HIVRNA>100.000 kopya/ml	• ABC/3TC + EFV veya ATV/r veya RAL kullanılmamalı
HLA-B*5701 pozitif	• ABC temelli rejimler kullanılmamalı
HIV direnç sonuçları olmadan ART başlanan durumlar	• NNRTI içeren rejimlerden kaçınılmalı **Önerilen tedaviler:** • DRV/r veya DRV/c +tenofovir/FTC • DTG+tenofovir/FTC

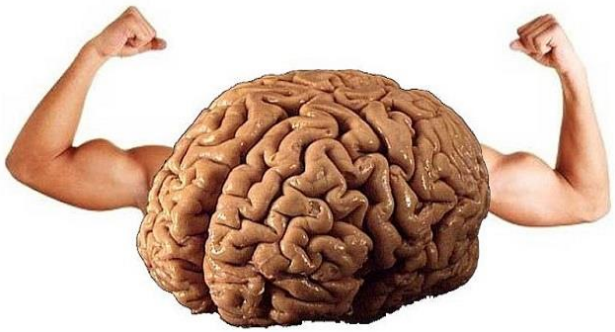
DHHS; 2017

KLİNİK DURUM	ÖNERİLER
 e-GFR<60 ml/dak	• **TDF'den kaçınılmalı (RTV ile birlikte kullanıldığında yüksek risk)** • **ATV'den kaçınma düşünülmeli** • **ABC veya TAF kullanılmalı** • **TAF** KrKl ≥ 30 mL/dak ise kullanılabilir • **KrKl <50 mL/dak, ABC/3TC temelli rejimler kullanılmamalı (3TC doz ayarı)** • **ABC veya TAF kullanılamadığında diğer tercihler:** ❑ **LPV/r + 3TC** veya ❑ **DRV/r + RAL** (HIV RNA<100,000kopya/mL ve CD4 >200/mm^3) DHHS; 2017



KLİNİK DURUM	ÖNERİLER
Karaciğer hastalığı ve siroz	• Bazı ARV'ler kontrendike veya doz ayarı gerekir • **Child B ve C'de ABC kontrendike**
Osteoporoz	• TDF'den kaçınılmalı • **ABC/3TC veya TAF kullanılmalı**

DHHS; 2017



KLİNİK DURUM	ÖNERİLER
Psikiyatrik hastalık	• **EFV ve RPV temelli rejimlerden kaçınılmalı** • Öncesinde psikiyatrik hastalık öyküsü olan **İNİ temelli ART kullanılan hastalar yakından izlenmeli**
HIV ilişkili demans	• EFV temelli rejimlerden kaçınılmalı • **DRV veya DTG temelli rejimler tercih edilmeli**
Narkotik replasman tedavisi	• Hasta metadon kullanıyorsa EFV temelli rejimlerden kaçınılmalı • EFV kullanılıyorsa metadon dozunun arttırılması gerekebilir

DHHS; 2017

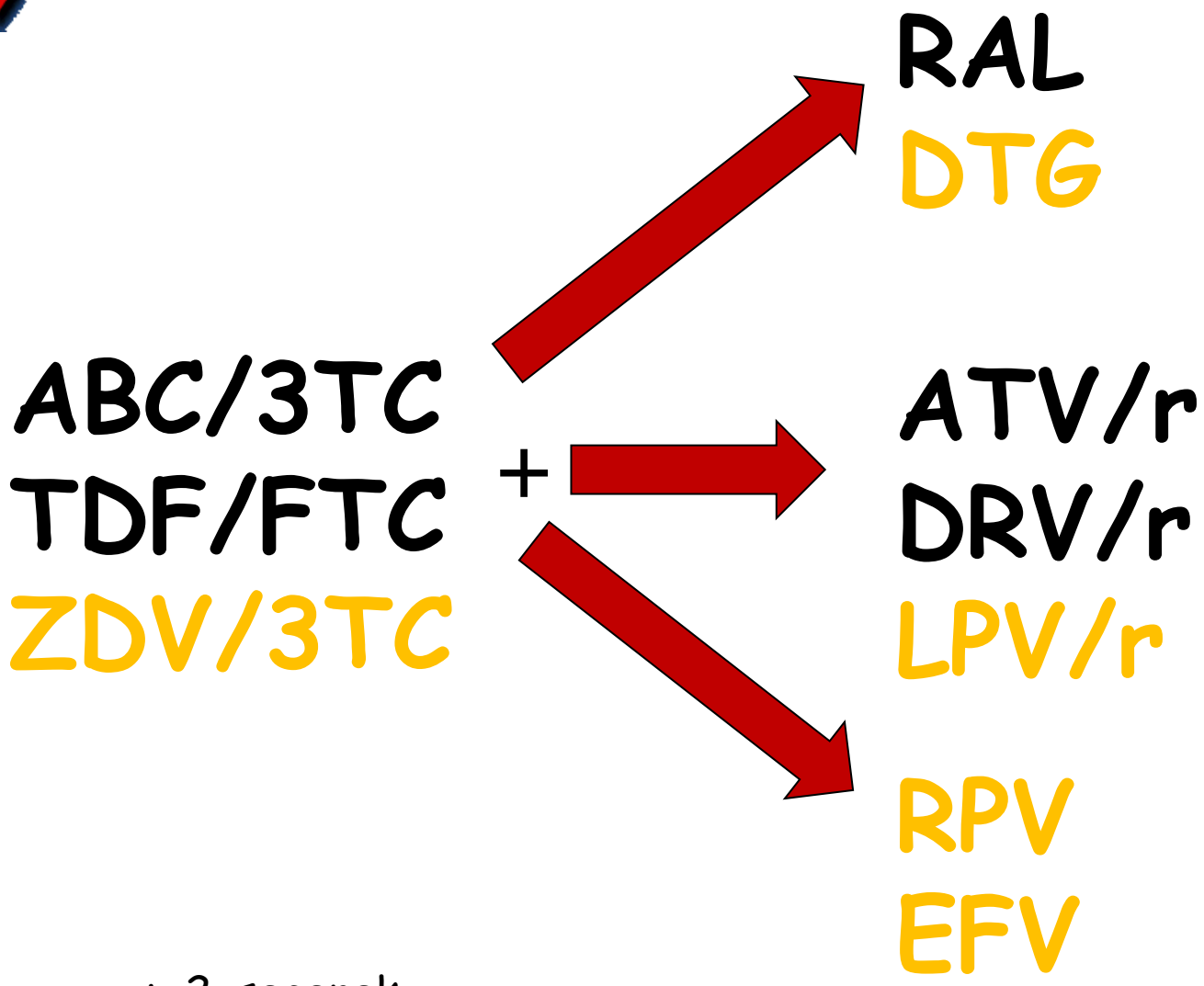
KLİNİK DURUM	ÖNERİLER
Yüksek kardiyak risk	• **ABC veya LPV/r temelli rejimlerden kaçınılmalı** • DTG,RAL veya RPV temelli rejimler tercih edilebilir • PI tercih edilecekse ATV temelli rejimler DRV temelli rejimlere göre daha avantajlı
QT uzaması	• EFV veya RPV temelli rejimlerden kaçınılmalı
Hiperlipidemi	**Lipid düzeyleri üzerine olumsuz etkileri olan rejimler:** • **PI/r veya PI/c** • **EFV** • **EVG/c** DTG, RAL veya RPV 'in lipid profili üzerine yan etkileri daha düşük **(TDF, ABC veya TAF'a kıyasla tercih)**

DHHS; 2017

Gebelik

1. ART altında gebe kalan ya da kalmayı planlayan hasta	1. ART'ye devam, teratojenik ilaçlar değiştirilir.
2. Tedavisiz gebe kalan hasta	2. **Bir an önce ART başlanması önerilir.**
3. 2. ya da 3. trimesterden sonra başvuran hasta	3. Tedaviye hemen başlanır, **viral yük yüksek ise İNİ temelli rejimler seçilir.**
4. 3. trimesterde viral yük saptanamaz düzeyde değil	4. Direnç testi istenir ve mevcut **ART'ye İNİ eklenir veya İNİ içeren rejime geçilir.**

EACS; 2017



—: 2. seçenek

KÜR

Kürde Hedeflenen Temel Prensipler

- ✓ **Viral rezervuarın eradikasyonu**

  aktivasyon

  eradikasyon

- ✓ **İmmünoterapi**

  konağın bağışıklık sistemini HIV'e karşı güçlendirmek

- ✓ **Gen terapileri**

  CD4 + T hücrelerini virüse dirençli hale getirebilmek

Viral Rezervuarın Eradikasyonu

Kür için en büyük engel latent rezervuar

CD4+ T hücreleri
monosit/makrofaj
mikroglia
GİS- ilişkili lenfoid doku makrofajları
dendritik hücreler

Latent hücre

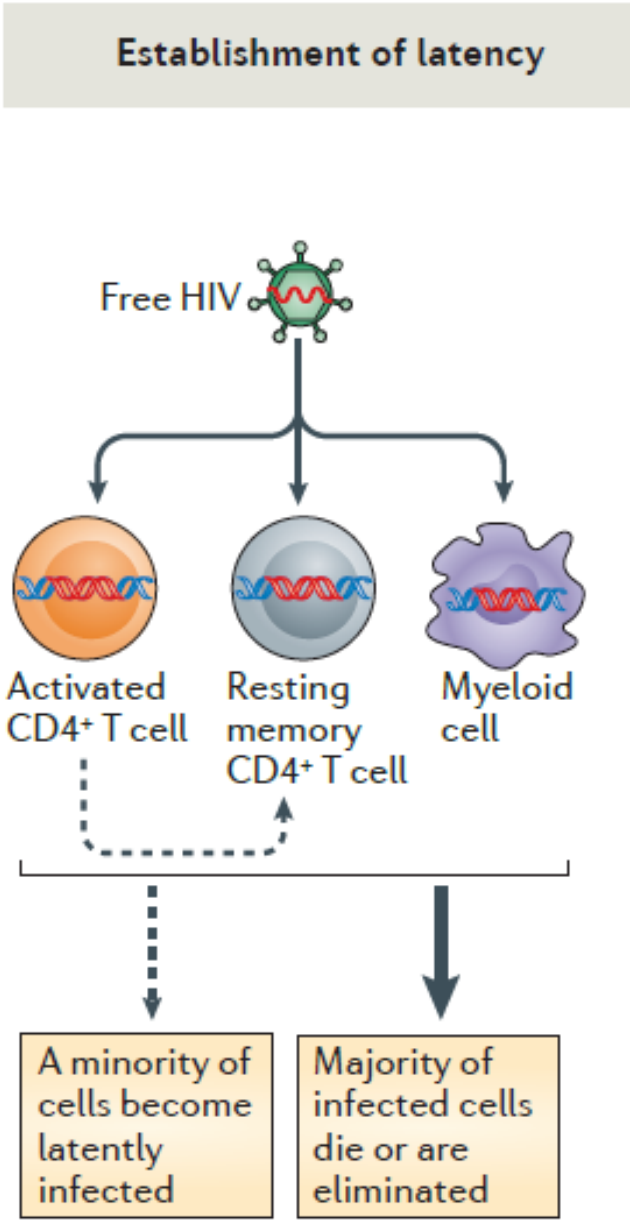
⇩

Replikasyon yeteneği olan
stabil provirüs taşır
Transkripsiyon aşamasında
sesiz
(viral transkript ya da viriyon üretimi yok)

Hücresel uyarı

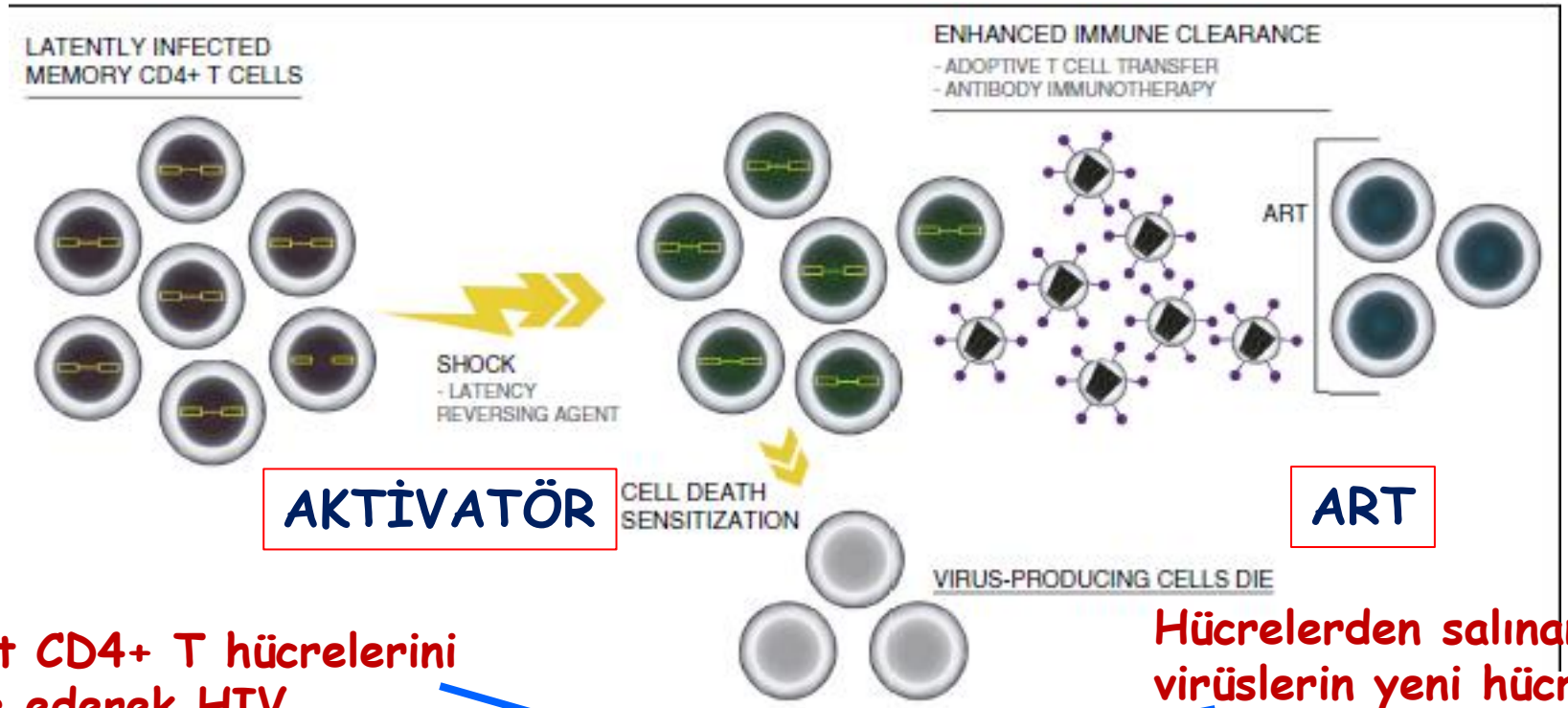
⇩

Viriyon üretimi



Towards an HIV cure: a global scientific strategy.
Nat Rev Immunol 2012 Jul 20;12(8):607-14.
Kumar A, et al. Clin Epigenetics 2015 Sep 24;7(1):103.

Viral rezervuarın eradikasyonu --şok et ve öldür--



Latent CD4+ T hücrelerini aktive ederek HIV ekspresyonunu sağlamak

~~Virüs tetikli sitopatik etki ve/veya konak bağışıklık sistemi etkisiyle hücrelerin ölümü~~

Hücrelerden salınan virüslerin yeni hücreleri enfekte etmesinin engellenmesi

Kimata JT. Challenges and strategies for the eradication of the HIV reservoir . Current Opinion in Immunology 2016, 42:65–70.
Chun TW, et al.Nat Immunol 2015 Jun;16(6):584-9

İmmünoterapi

İmmünoterapi

- ✓**Latent rezervuarı eradike edecek ya da baskılayacak terapötik aşılar**

  Anti-HIV immünitesinin işlev ve yaygınlığını arttıracak aşılar

- ✓**Pasif bağışıklama**

Mylvaganam GH, et al. Curr Opin Immunol. 2015 Aug;35:1-8.

NEWS RELEASES

Wednesday, February 15, 2017

NIH research helps explain how antibody treatment led to sustained remission of HIV-like virus

Scientists at the National Institutes of Health have found that the presence of the protein alpha-4 beta-7 integrin on the surface of HIV and its monkey equivalent — simian immunodeficiency virus, or SIV — may help explain why an antibody protected monkeys from SIV in previous experiments.

"...our team found that anti-alpha-4 beta-7 antibody binds not only to cells but also to HIV and SIV."

Institute/Center

National Institute of Allergy and Infectious Diseases (NIAID)

Contact

Laura S. Leifman
301-402-1663

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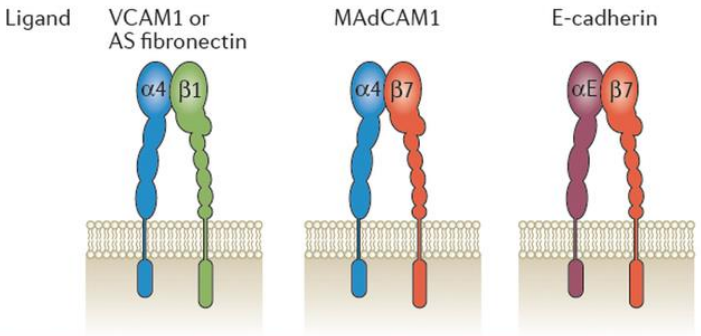
- ✓ **alpha-4 beta-7 integrin** immün sistem hücreleri üzerinde yoğun olarak bulunan bir reseptör
- ✓ HIV ve SIV bu reseptörleri taşıyan hücreleri enfekte ediyor.



				PML
Natalizumab	Yes	Yes	No	Yes
Vedolizumab	No	Yes	No	Not observed
Etrolizumab	No	Yes	Yes	Unknown

Nature Reviews | Drug Discovery

Fauci ve ark.'nın 2014-2016 yılları arasında laboratuvarlarında yürüttükleri çalışma sonuçları:

alpha-4 beta-7 integrine karşı laboratuvar ortamında oluşturulan antikorlar

- ✓ SIV'in enfekte olmayan maymunlara bulaşını azaltıyor
- ✓ enfekte maymunlarda SIV remisyonuna yol açıyor

HIV ve SIV yüzeyinde de alpha-4 beta-7 integrin mevcut mu??

- ✓ HIV ve SIV konak hücrelerden tomurcuklanarak salınırken alpha-4 beta-7 integrinin yoğun olduğu bölgeden ayrıldığı için bu reseptörleri de zarf yüzeyine alıyor
- ✓ HIV ve SIV yüzeyinde yer alan protein alpha-4 beta-7 integrin eşdeğer

18 rhesus makak maymunun SIV ile enfeksiyonu

5 hafta

ART (plan: 90 gün)

9 hafta

9 hafta

11 maymun
23 hafta boyunca
3 haftada 1 kez alpha-4 beta-7 integrin antikor infüzyonu

7 maymun
23 hafta boyunca
3 haftada bir kez **plasebo antikor** infüzyonu

32 haftanın sonunda tüm tedaviler kesildi.

3 maymunda antikor gelişimi
8 maymunda ART kesildikten sonra 23 ay boyunca SIV kan ve GİS'te saptanamaz düzeyde

ART kesildikten
2 ay sonra viral rebound

Scientists at NIH and Emory | CT Vedolizumab (Anti-alpha4bet

https://clinicaltrials.gov/ct2/show/NCT02788175

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Try our beta test site

Example: "Heart attack" AND "Los Angeles"

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Home > Find Studies > Study Record Detail

Text Size

Vedolizumab (Anti-alpha4beta7) in Subjects With HIV Infection Undergoing Analytical Treatment Interruption

This study is currently recruiting participants. (see Contacts and Locations)

Verified December 1, 2016 by National Institutes of Health Clinical Center (CC)

Sponsor:
National Institute of Allergy and Infectious Diseases (NIAID)

Information provided by (Responsible Party):
National Institutes of Health Clinical Center (CC) (National Institute of Allergy and Infectious Diseases (NIAID))

ClinicalTrials.gov Identifier:
NCT02788175

First received: May 28, 2016
Last updated: January 24, 2017
Last verified: December 1, 2016
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

Background:

In most people infected with human immunodeficiency virus (HIV), their immune system cannot control HIV infection. They need drugs called combination antiretroviral therapy (cART) to control the HIV. When people stop cART treatment, their immune system cannot control the infection again. They can also become resistant to cART and have lasting side effects. Researchers want to test if the drug vedolizumab is effective at

Gen terapileri

Gen terapileri

- ✓**Enfeksiyon ilişkili özgül genleri modifiye ederek hücreleri HIV'e dirençli hale getirmek**

  CCR5-defektif hematopoetik hücrelerle repopülasyon sağlamak

- ✓**Entegre olan provirüsün eksizyonu**

Passaes CP, et al. Virology. 2014 Apr;454-455:340-52

Gen terapileri

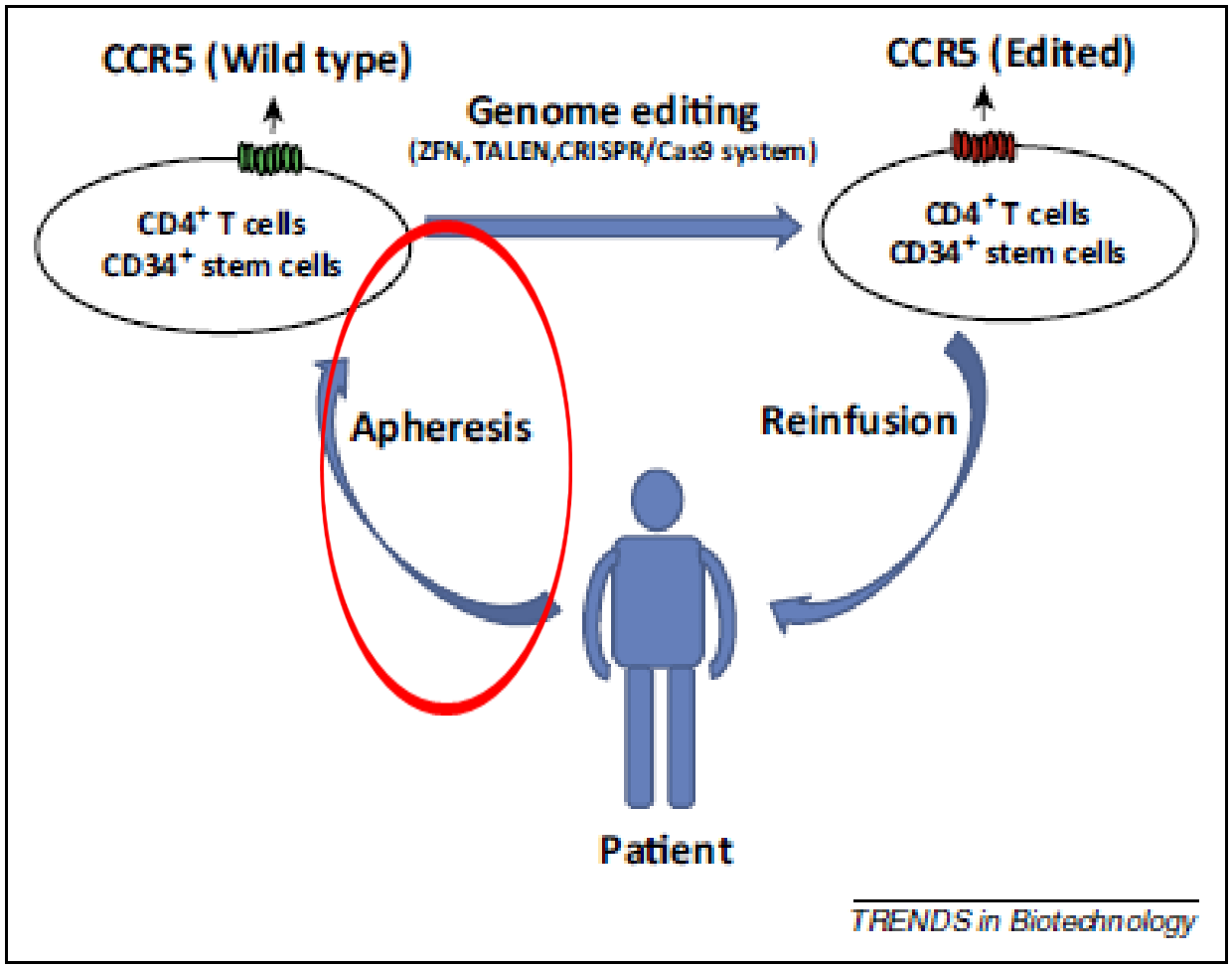
Nükleazlar, rekombinazlar, RNAiler….

Transcription activator-like effector nucleases (TALENs)
Zinc-finger nucleases (ZFNs)
Clustered regularly interspaced palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9)

Genetik materyalde

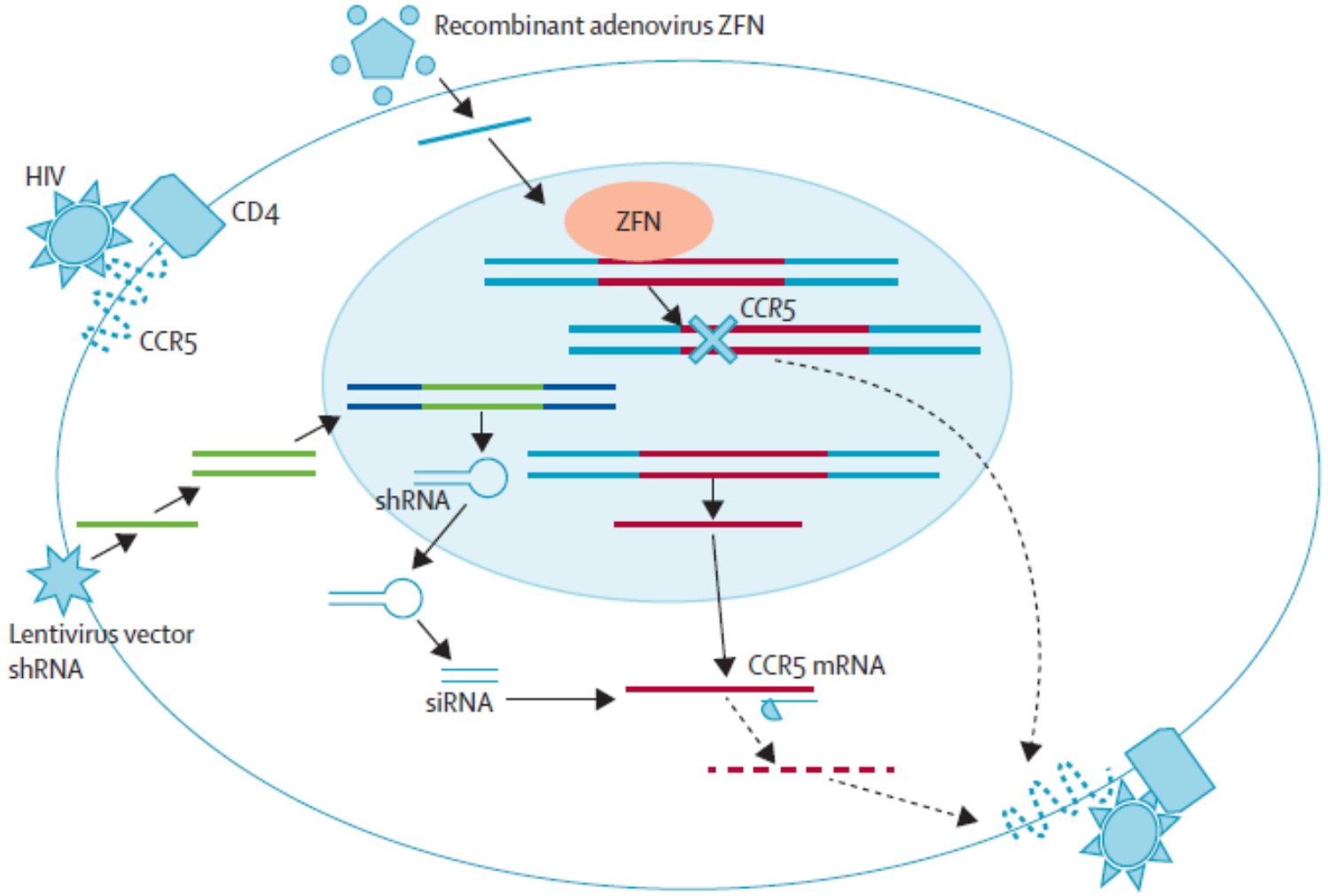
- modifikasyon
- parçalanma
- eklemeler..

HIV enfeksiyonuna ya da replikasyona dirençli hücre üretimi

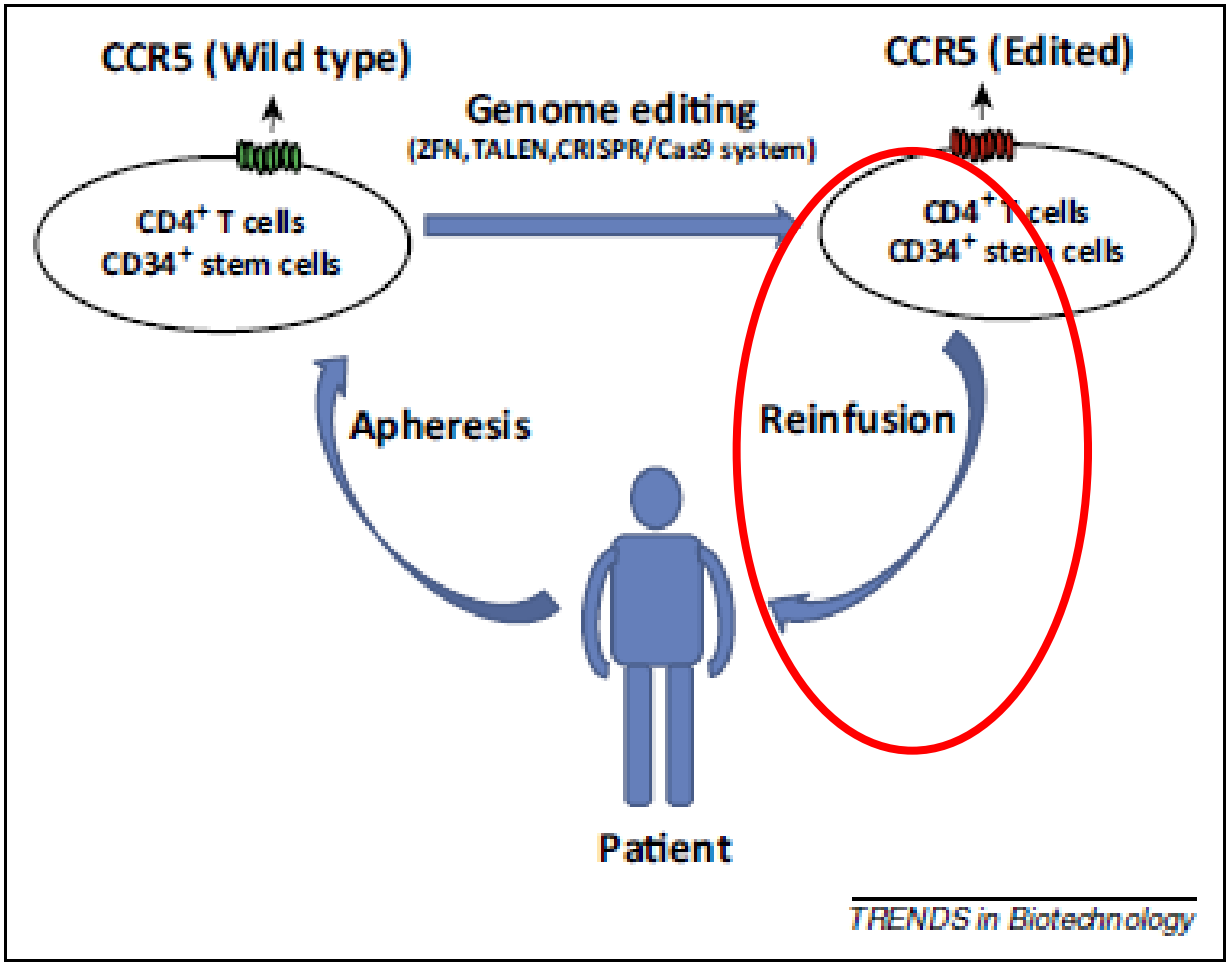


Gu WG.Trends Biotechnol 2015 Mar;33(3):172-9.

A



Kent SJ,et al. Lancet Infect Dis 2013 Jul;13(7):614-21.



Orijinal HIV'e duyarlı hücrelerin eradikasyonu için kemoterapi gerekli Olabilir

CXCR4??

Liu et al. Cell Biosci (2017) 7:47
DOI 10.1186/s13578-017-0174-2

Cell & Bioscience

RESEARCH Open Access

Genome editing of the HIV co-receptors CCR5 and CXCR4 by CRISPR-Cas9 protects CD4$^+$ T cells from HIV-1 infection

Zhepeng Liu[1‡], Shuliang Chen[1,2*‡], Xu Jin[3], Qiankun Wang[1], Kongxiang Yang[4], Chenlin Li[1], Qiaoqiao Xiao[1], Panpan Hou[4], Shuai Liu[1], Shaoshuai Wu[1], Wei Hou[1], Yong Xiong[5], Chunyan Kong[1], Xixian Zhao[1], Li Wu[2], Chunmei Li[1,6], Guihong Sun[1] and Deyin Guo[1,6*]

Abstract

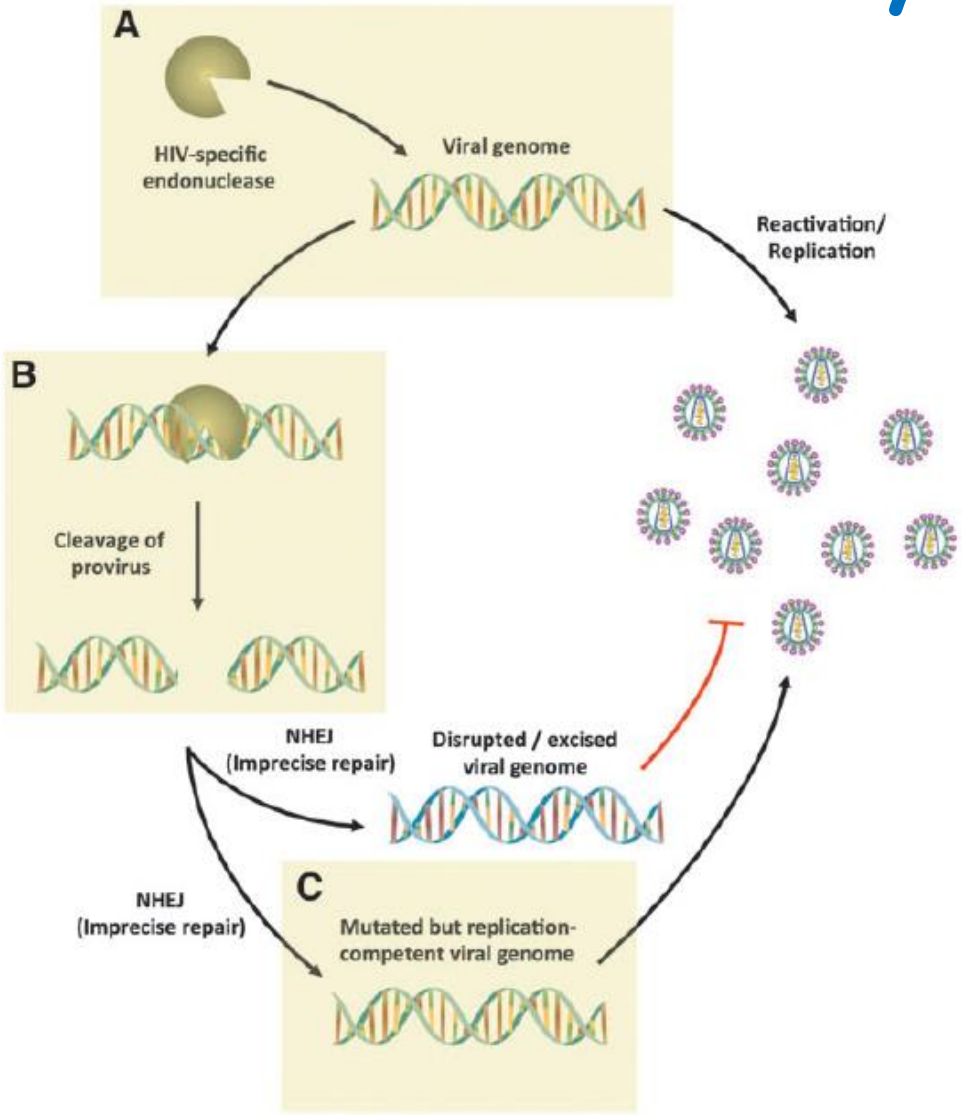
Background: The main approach to treat HIV-1 infection is combination antiretroviral therapy (cART). Although cART is effective in reducing HIV-1 viral load and controlling disease progression, it has many side effects, and is expensive for HIV-1 infected patients who must remain on lifetime treatment. HIV-1 gene therapy has drawn much attention as studies of genome editing tools have progressed. For example, zinc finger nucleases (ZFN), transcription activator like effector nucleases (TALEN) and clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 have been utilized to successfully disrupt the HIV-1 co-receptors CCR5 or CXCR4, thereby restricting HIV-1 infection. However, the effects of simultaneous genome editing of CXCR4 and CCR5 by CRISPR-Cas9 in blocking HIV-1 infection in primary CD4$^+$ T cells has been rarely reported. Furthermore, combination of different target sites of CXCR4 and CCR5 for disruption also need investigation.

Results: In this report, we designed two different gRNA combinations targeting both CXCR4 and CCR5, in a single vector. The CRISPR-sgRNAs-Cas9 could successfully induce editing of CXCR4 and CCR5 genes in various cell lines and primary CD4$^+$ T cells. Using HIV-1 challenge assays, we demonstrated that CXCR4-tropic or CCR5-tropic HIV-1 infections were significantly reduced in *CXCR4*- and *CCR5*-modified cells, and the modified cells exhibited a selective advantage over unmodified cells during HIV-1 infection. The off-target analysis showed that no non-specific editing was identified in all predicted sites. In addition, apoptosis assays indicated that simultaneous disruption of CXCR4 and CCR5 in primary CD4$^+$ T cells by CRISPR-Cas9 had no obvious cytotoxic effects on cell viability.

Conclusions: Our results suggest that simultaneous genome editing of CXCR4 and CCR5 by CRISPR-Cas9 can potentially provide an effective and safe strategy towards a functional cure for HIV-1 infection.

Keywords: CRISPR-Cas9, CCR5 and CXCR4 simultaneous, HIV-1, AIDS

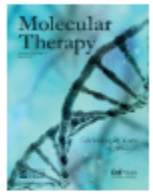
Proviral DNA eliminasyonu



Jerome Kr, et al. Disruption or Excision of Provirus as an Approach to HIV Cure. AIDS PATIENT CARE and STDs Volume 30, Number 12, 2016

Export

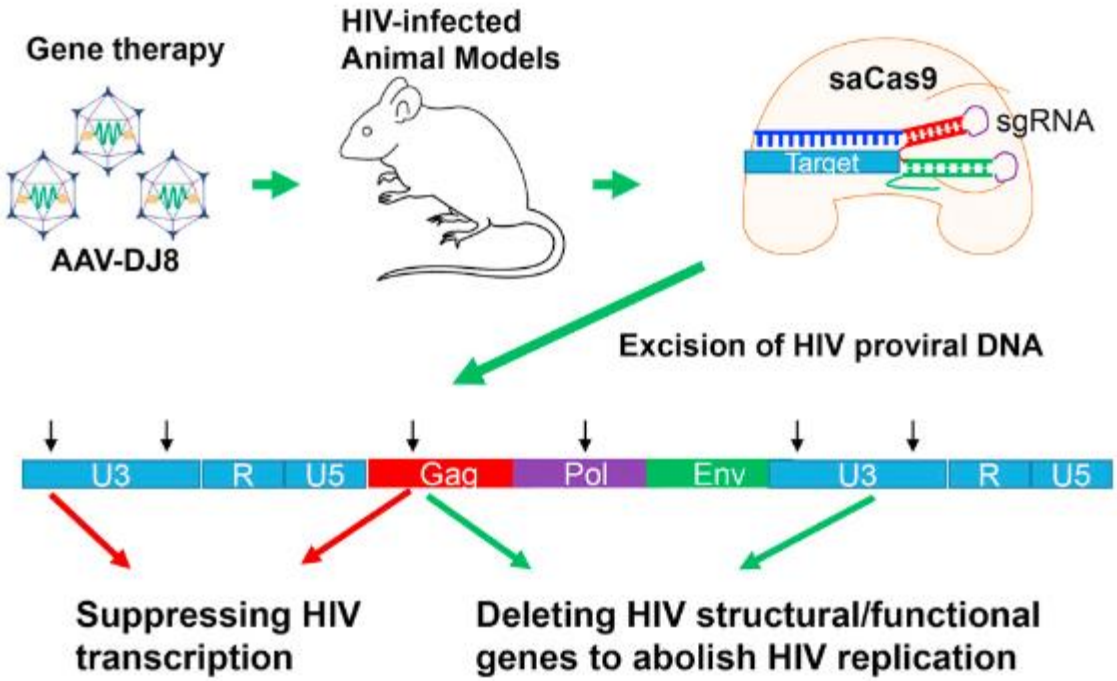
Molecular Therapy



Volume 25, Issue 5, 3 May 2017, Pages 1168-1186

Original Article

In Vivo Excision of HIV-1 Provirus by saCas9 and



Yeni Buluşlar ve Stratejiler

nature International weekly journal of science

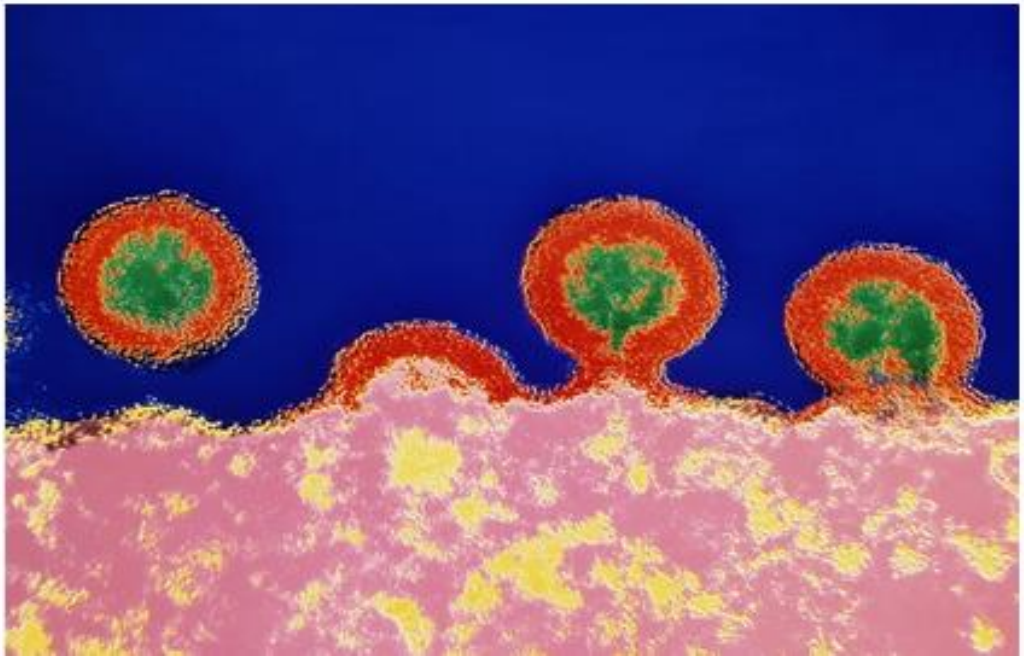
NATURE | NEWS

Hidden HIV reservoirs exposed by telltale protein

The discovery helps to identify dormant infected cells and could one day lead to a cure.

Amy Maxmen

15 March 2017



Virologists lack even basic knowledge of the reservoir, because latently infected cells are exceedingly hard to find in the body. It was Benkirane's quest to solve that problem that led him and his team to the CD32a protein marker. The researchers exposed resting T cells to fluorescently tagged HIV in the lab, and searched for differences in gene expression between cells infected by the marked virus, and those that weren't. A subset of the quiescent infected cells turned on a gene, which coded for CD32a, that was almost undetectable in uninfected cells. The researchers also determined that the protein is not expressed at significant levels in cells actively producing HIV.

Using an antibody that sticks to CD32a, the researchers then pulled cells expressing the protein out of human blood samples from HIV-infected people. As expected, these were quiescent T cells harbouring HIV. "You absolutely could not have done that before now," Benkirane says.

Exposure

Deeks hopes that the new protein target, or biomarker, accelerates research on a cure, in the same way that tests to measure the amount of virus in a sample helped to develop antiretroviral therapy in the late 1990s.

The next steps will be to replicate the findings by screening blood from patients of different genders, ethnicities, ages and stages of the disease, says Tony Fauci, director of the US National Insitute of Allergies and Infectious Disease in Bethesda, Maryland. Scientists will also test tissues

Dekaban and Dikeakos *AIDS Res Ther (2017) 14:53*
DOI 10.1186/s12981-017-0175-6

AIDS Research and Therapy

REVIEW Open Access

HIV-I Nef inhibitors: a novel class of HIV-specific immune adjuvants in support of a cure

Gregory A. Dekaban[1,2*] and Jimmy D. Dikeakos[1*]

Abstract

The success of many current vaccines relies on a formulation that incorporates an immune activating adjuvant. This will hold true for the design of a successful therapeutic HIV vaccine targeted at controlling reactivated virus following cessation of combined antiretroviral therapy (cART). The HIV accessory protein Nef functions by interfering with HIV antigen presentation through the major histocompatibility complex I (MHC-I) pathway thereby suppressing $CD8^+$ cytotoxic T cell (CTL)-mediated killing of HIV infected cells. Thus, this important impediment to HIV vaccine success must be circumvented. This review covers our current knowledge of Nef inhibitors that may serve as immune adjuvants that will specifically restore and enhance CTL-mediated killing of reactivated HIV infected cells as part of an overall vaccine strategy to affect a cure for HIV infection.

Keywords: HIV-1, Nef, Latency, Vaccines

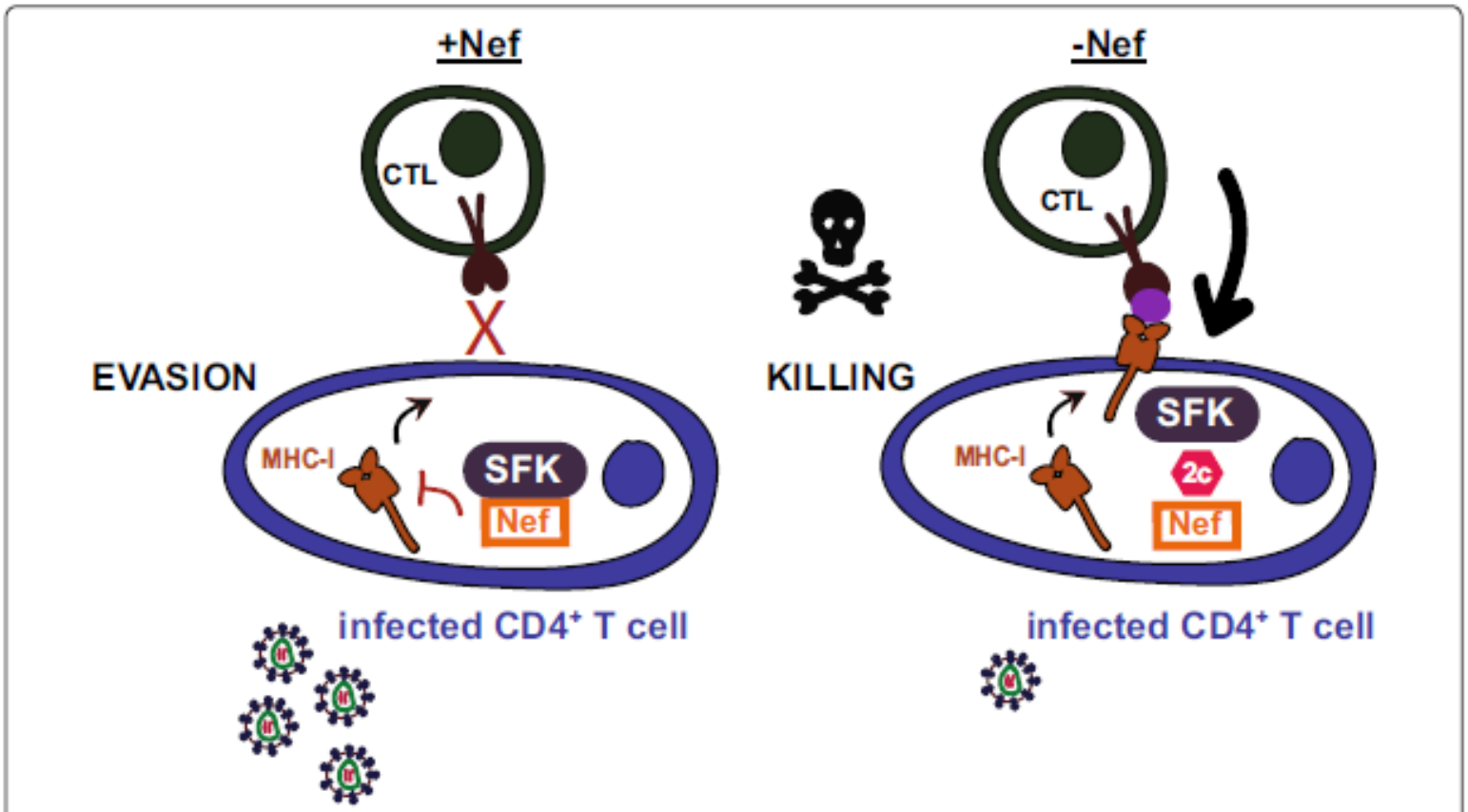


Fig. 1 Shock and kill therapies to cure HIV infection require the inhibition of Nef activity. Shock therapies aim to reactivate latent HIV (shock and to eliminate virus-producing cells (kill). Viral reactivation will enhance Nef activity to evade the immune surveillance system by decreasing cell surface levels of MHC-I on $CD4^+$ T cells (+Nef). Evasion: the interaction between Nef and a Src Family Kinase (SFK) results in the intracellular retention of MHC-I. Subsequently, a $CD8^+$T lymphocyte (CTL) will fail to recognize an HIV infected cell. Killing: conversely, the inhibition of Nef's activity using molecular adjuvants, such as 2c-like compounds (*red hexagon*) that block the interaction between Nef and SFKs (−Nef) will restore cell surface levels of MHC-I which in turn will promote HIV antigen presentation (*purple dot*) and enhance susceptibility to HIV specific $CD8^+$-CTL

SCIENTIFIC REPORTS

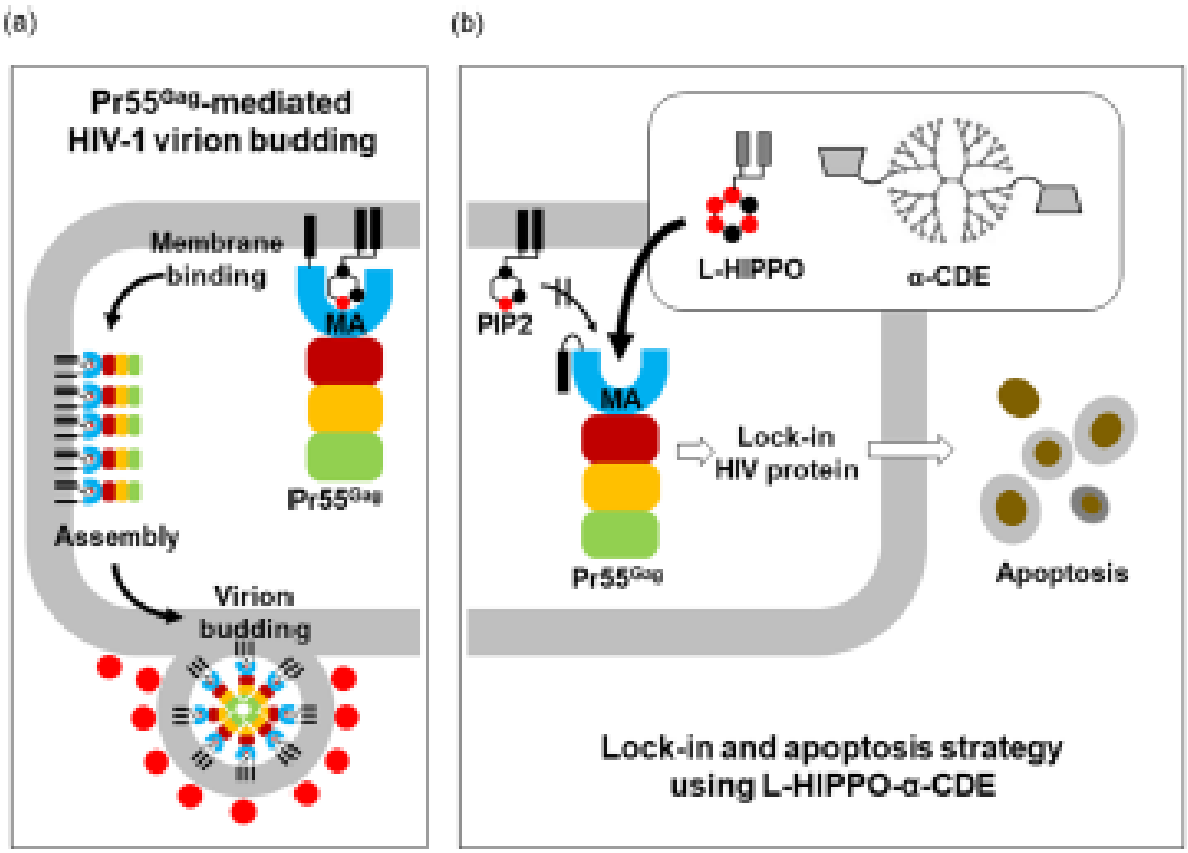
OPEN

A clue to unprecedented strategy to HIV eradication: "Lock-in and apoptosis"

Received: 10 January 2017
Accepted: 24 July 2017
Published online: 21 August 2017

Hiroshi Tateishi, Kazuaki Monde[2], Kensaku Anraku[3], Ryoko Koga[1], Yuya Hayashi[4], Halil Ibrahim Ciftci[1], Hasan DeMirci[5,6], Taishi Higashi[4], Keiichi Motoyama[4], Hidetoshi Arima[4], Masami Otsuka[1] & Mikako Fujita[7]

Despite the development of antiretroviral therapy against HIV, eradication of the virus from the body, as a means to a cure, remains in progress. A "kick and kill" strategy proposes "kick" of the latent HIV to an active HIV to eventually be "killed". Latency-reverting agents that can perform the "kick" function are under development and have shown promise. Management of the infected cells not to produce virions after the "kick" step is important to this strategy. Here we show that a newly synthesized compound, L-HIPPO, captures the HIV-1 protein $Pr55^{Gag}$ and intercepts its function to translocate the virus from the cytoplasm to the plasma membrane leading to virion budding. The infecting virus thus "locked-in" subsequently induces apoptosis of the host cells. This "lock-in and apoptosis" approach performed by our novel compound in HIV-infected cells provides a means to bridge the gap between the "kick" and "kill" steps of this eradication strategy. By building upon previous progress in latency reverting agents, our compound appears to provide a promising step toward the goal of HIV eradication from the body.


(a)
(b)
Pr55Gag-mediated
HIV-1 virion budding
Membrane
binding
MA
Pr55Gag
Assembly
Virion
budding
L-HIPPO
α-CDE
PIP2
MA
Lock-in
HIV protein
Pr55Gag
Apoptosis
Lock-in and apoptosis strategy
using L-HIPPO-α-CDE

- ✓ Tüm viral rezervuarı reaktive etmek sorunlu
- ✓ **Yakın vadede latent viral rezervuarı kontrol altında tutmak daha gerçekçi bir hedef??**

tat bağımlı transkripsiyonun baskılanması

HAT inhibitörleri: garcinol türevleri, curcumin, celastrol (tat blokeri), **cortistatin A analoğu**

Passaes CP, et al. Virology 2014 Apr;454-455:340-52

~~Şok et ve öldür?~~
Bloke et ve kilitle?

At IAS 2017, Valente presented the results of experiments **in mice** adapted so they can be infected with human HIV. Adding dCA to standard ART resulted in a significant **1.5 to 10.5-fold reduction in viral expression from reservoir cells and showed a degree of persistence when ART was withdrawn.**
However, Valente warned that even adapted mice were not the same as humans, and the tricks HIV uses to co-opt the human immune system into making more HIV could in theory neutralise the effect of dCA. Human studies are planned.

Sonuç

Akılcı kombine antiretroviral tedavi

HIV enfeksiyonu → yönetilebilir kronik enfeksiyon

CD4 sayısından bağımsız herkese ART

TEŞEKKÜR EDERİM...