HIV ENFEKSİYONUNDA KÜR MÜMKÜN MÜ?

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Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji A.D

Akılcı antiretroviral tedavi
(ART)

HIV enfeksiyonu → Yönetilebilir kronik enfeksiyon

Erken tanı

+

ART ile

hastalarda beklenen yaşam süresi

53 yıl

JL Marcus et al. JAIDS 2016

- ✓ **Standart tedaviler** ile bağışıklık sisteminin fonksiyonu ve sağlık durumu **tamamen iyileştirilemiyor.**
- ✓ Hastalarda **ART'ye rağmen komorbiditeler** gözleniyor.
- ✓ ART kesilmesini takiben geri tepen viremi ve **AIDS'e progresyon** gelişebiliyor.

Towards an HIV cure: a global scientific strategy. Nat Rev Immunol 2012 Jul 20;12(8):607-14.

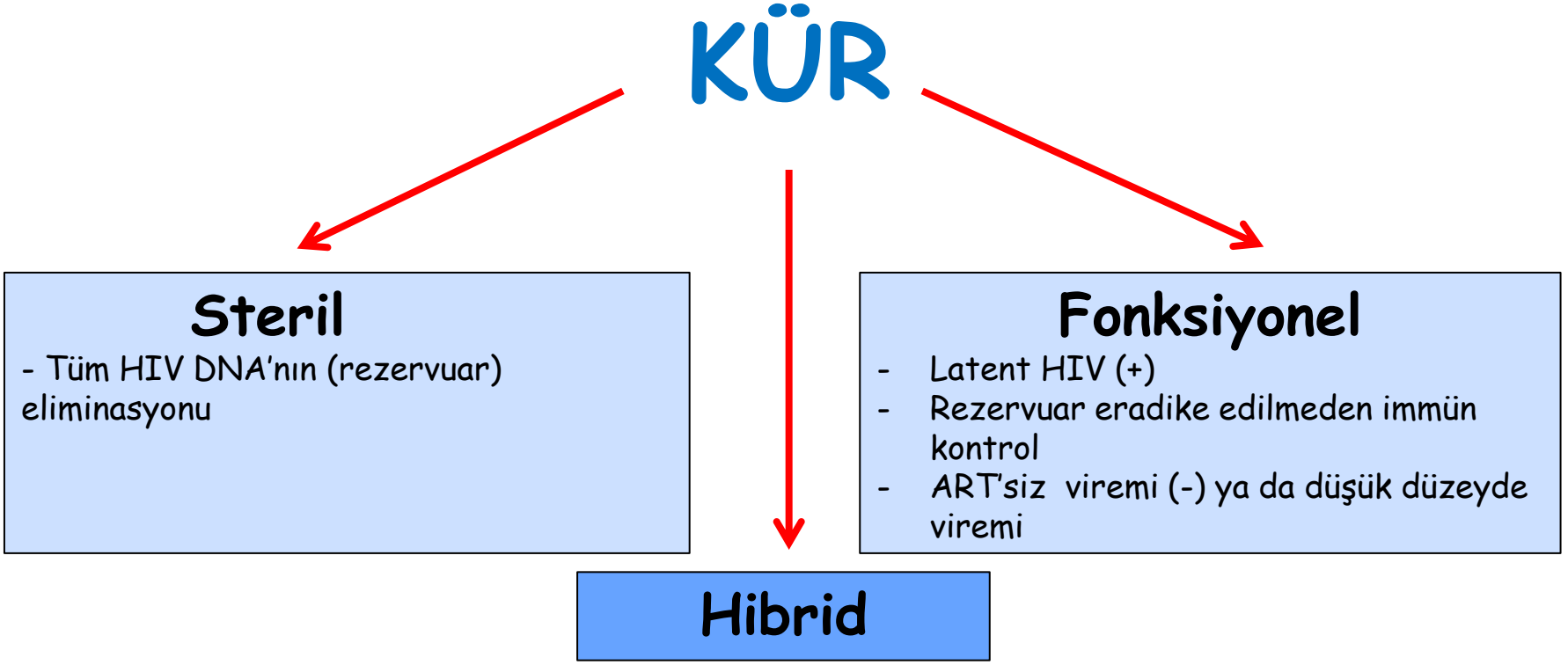
Yeni Tedavi Seçenekleri

- ✓Yeni ilaçlar
- ✓Yeni yaklaşımlar
- ✓Küre yönelik çalışmalar

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

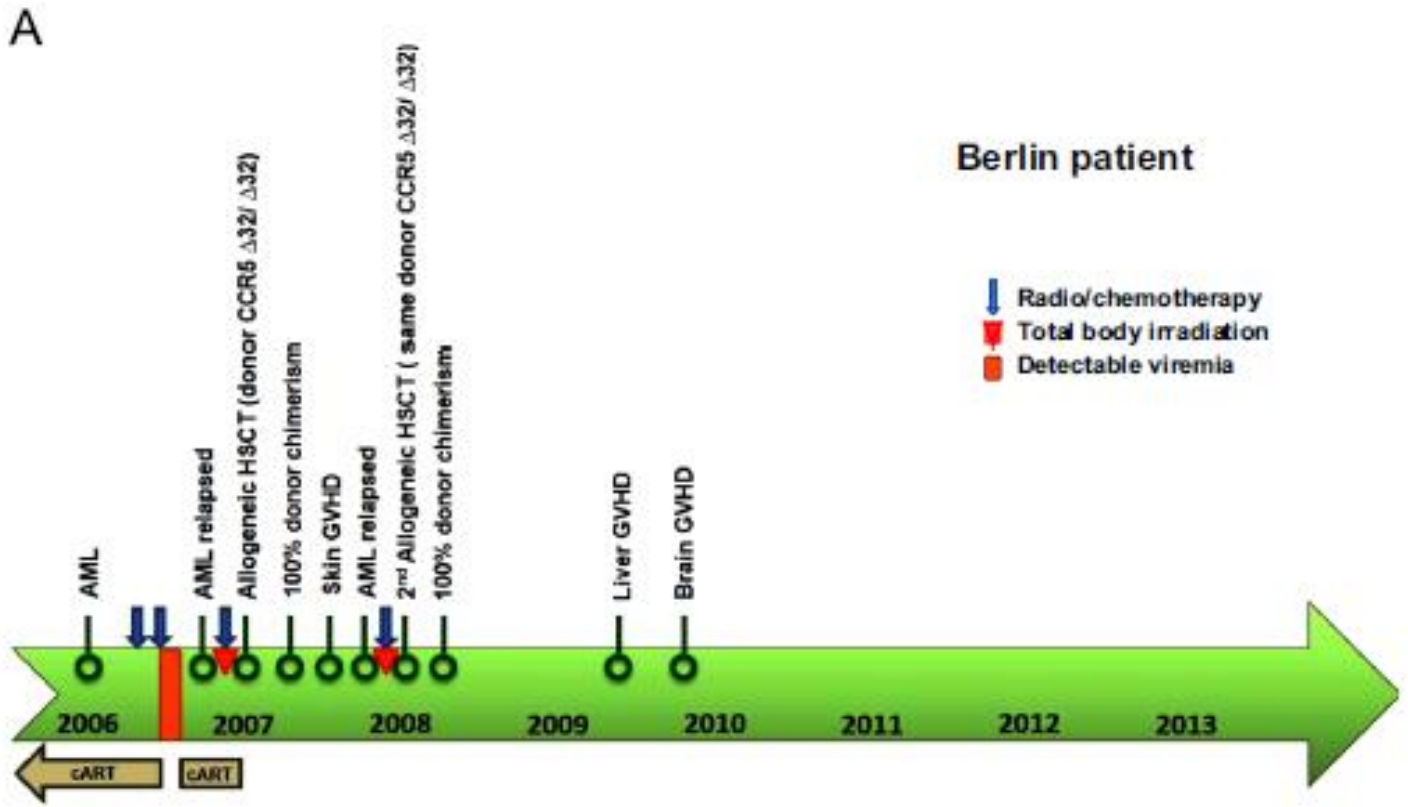
Küre Yönelik Çalışmalar

Birey veya halk sağlığı açısından ve ekonomik perspektiften bakıldığında amaç



Towards an HIV cure: a global scientific strategy. Nat Rev Immunol 2012 Jul 20;12(8):607-14.
Dahabieh MS, et al. Annu Rev Med .2015;66:407-21.
Cillo Ar, et al. Current Opinion in Virology 2016, 18:14–19

Steril kür



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

- ✓Eş zamanlı malignitesi olan 15 HIV enfekte hastaya kemik iliği nakli yapılmış.
- ✓Çoğu hastada işlemler Berlin hastasına benzer
- ✓Etik nedenlerle tüm hastalarda antiretroviral tedaviye devam edilmiş.

IAS; 2016.

- ✓ **6 hastada** ultrasensitif HIV DNA ölçümleri sonucunda HIV rezervuarlarında **viral DNA çok düşük düzeylerde**
- ✓ **2 hastada** ise kanda virüs (-), dokuda ise sadece **eser düzeyde HIV DNA (+)** (vericinin *CCR5* durumundan bağımsız)

IAS; 2016.

HIV enfeksiyonu persistansı

- ✓ **En önemli neden: Latent rezervuar**

  replike olma özelliğini koruyan virüs CD4 yardımcı T hücrelerinde (özellikle hafıza) latent olarak kalması

- ✓ Hedef hücrelerin de novo enfeksiyonu (devam eden replikasyon)

- ✓ İmmün sistemin enfekte hücreleri eradike edememesi

Towards an HIV cure: a global scientific strategy. Nat Rev Immunol 2012 Jul 20;12(8):607-14.
Dahabieh MS, et al. Annu Rev Med 2015;66:407-21.

Latent hücre

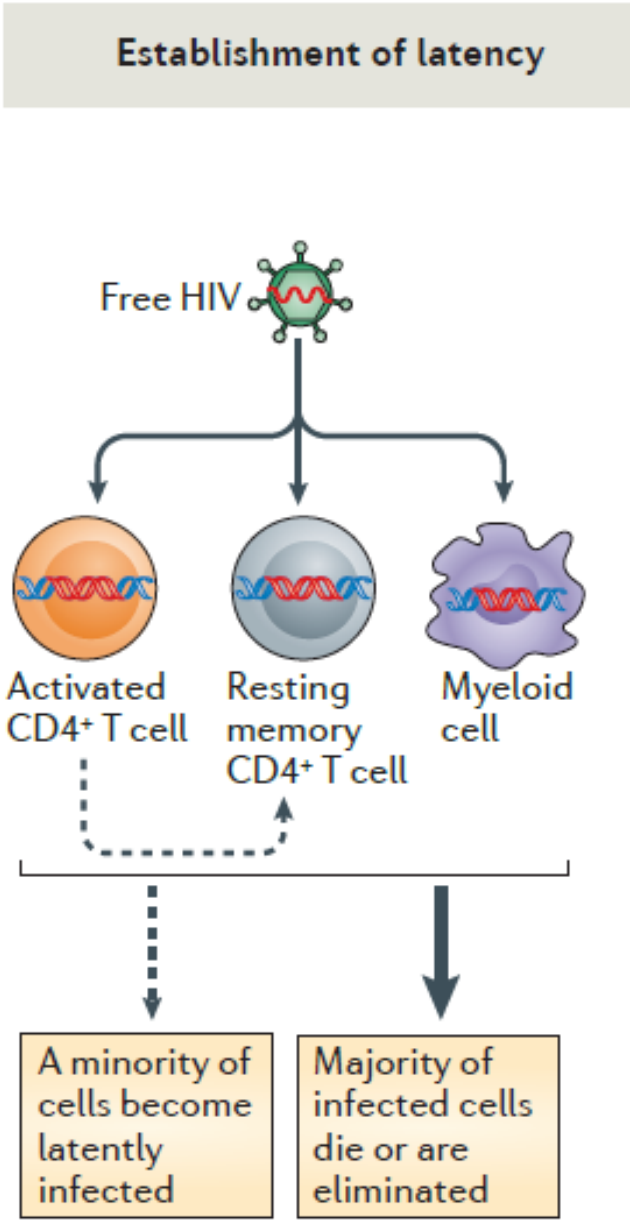
⇩

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

Hücresel uyarı

⇩

Viriyon üretimi



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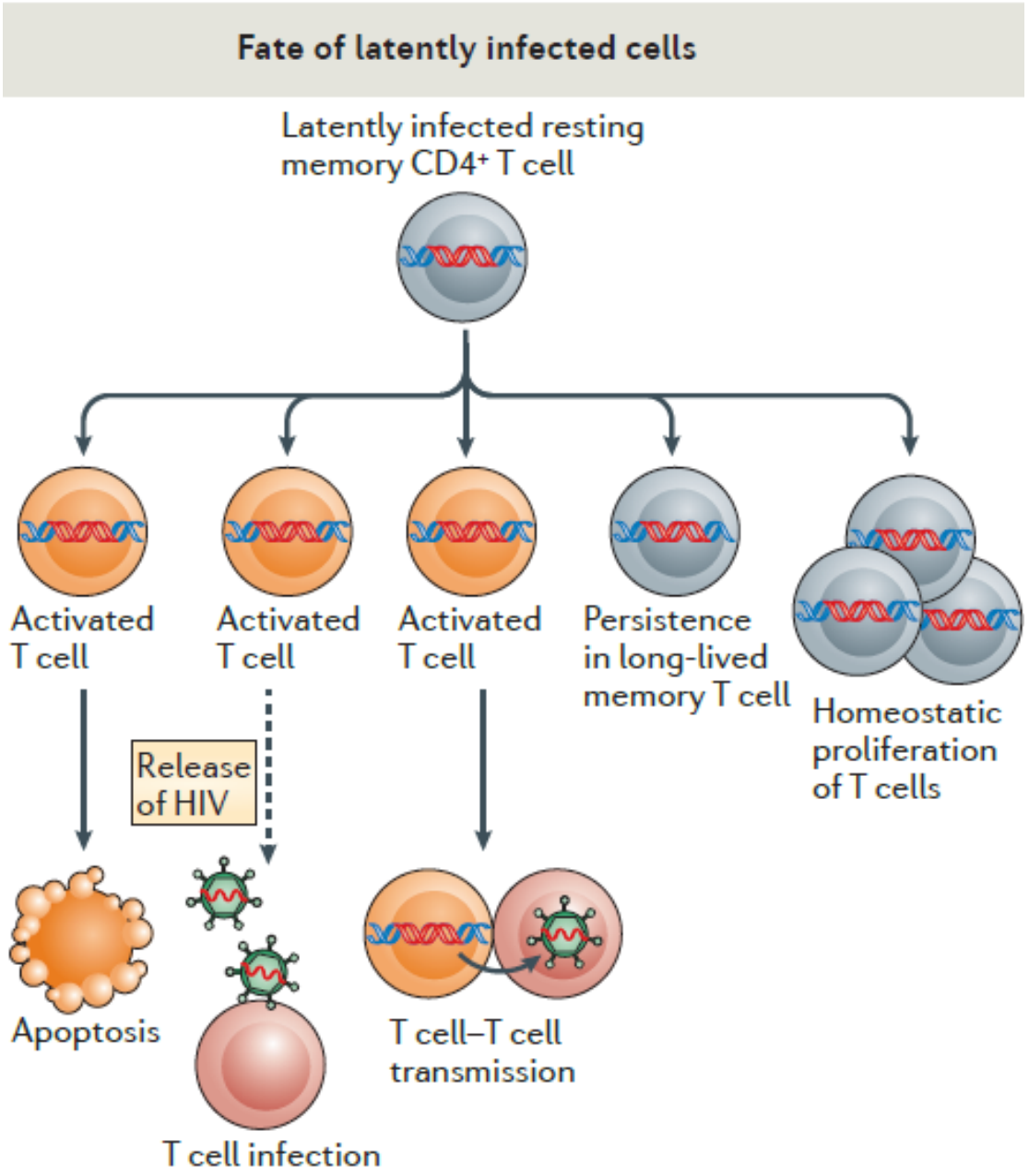
Kumar A, et al. Clin Epigenetics 2015 Sep 24;7(1):103.



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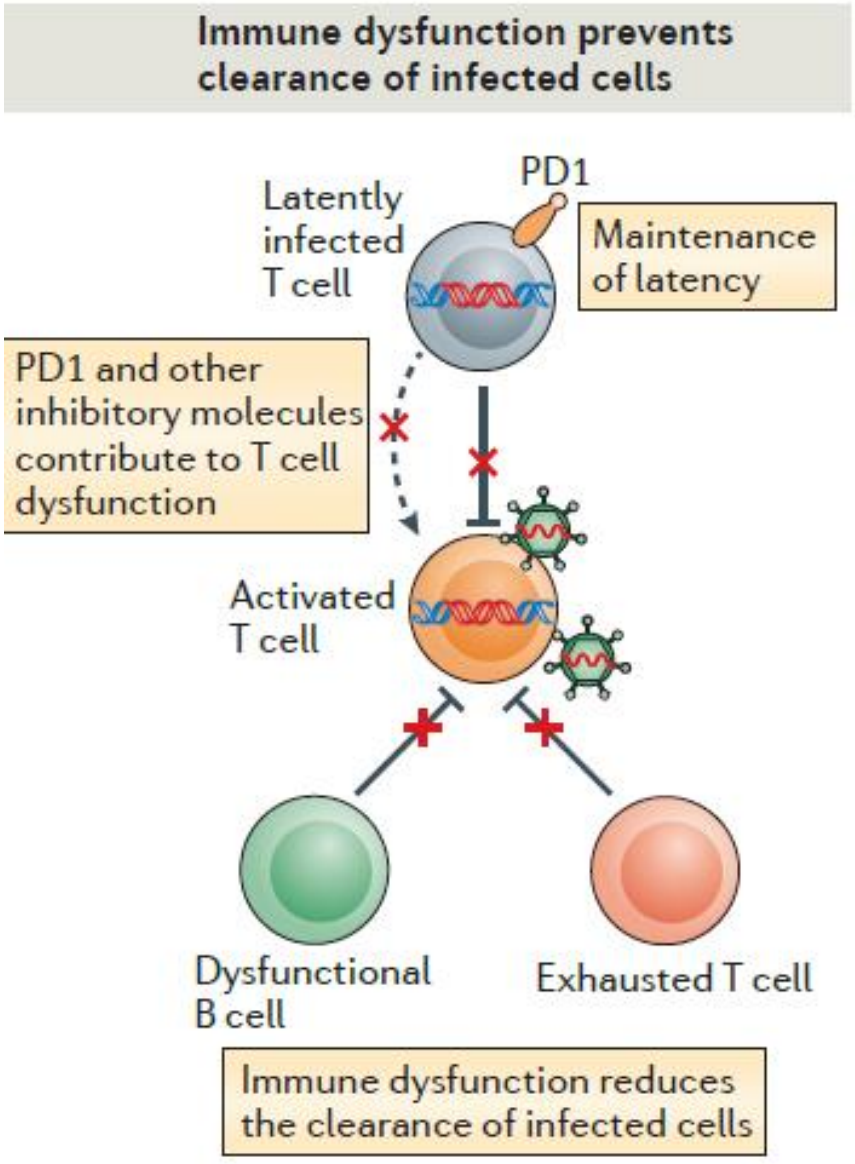

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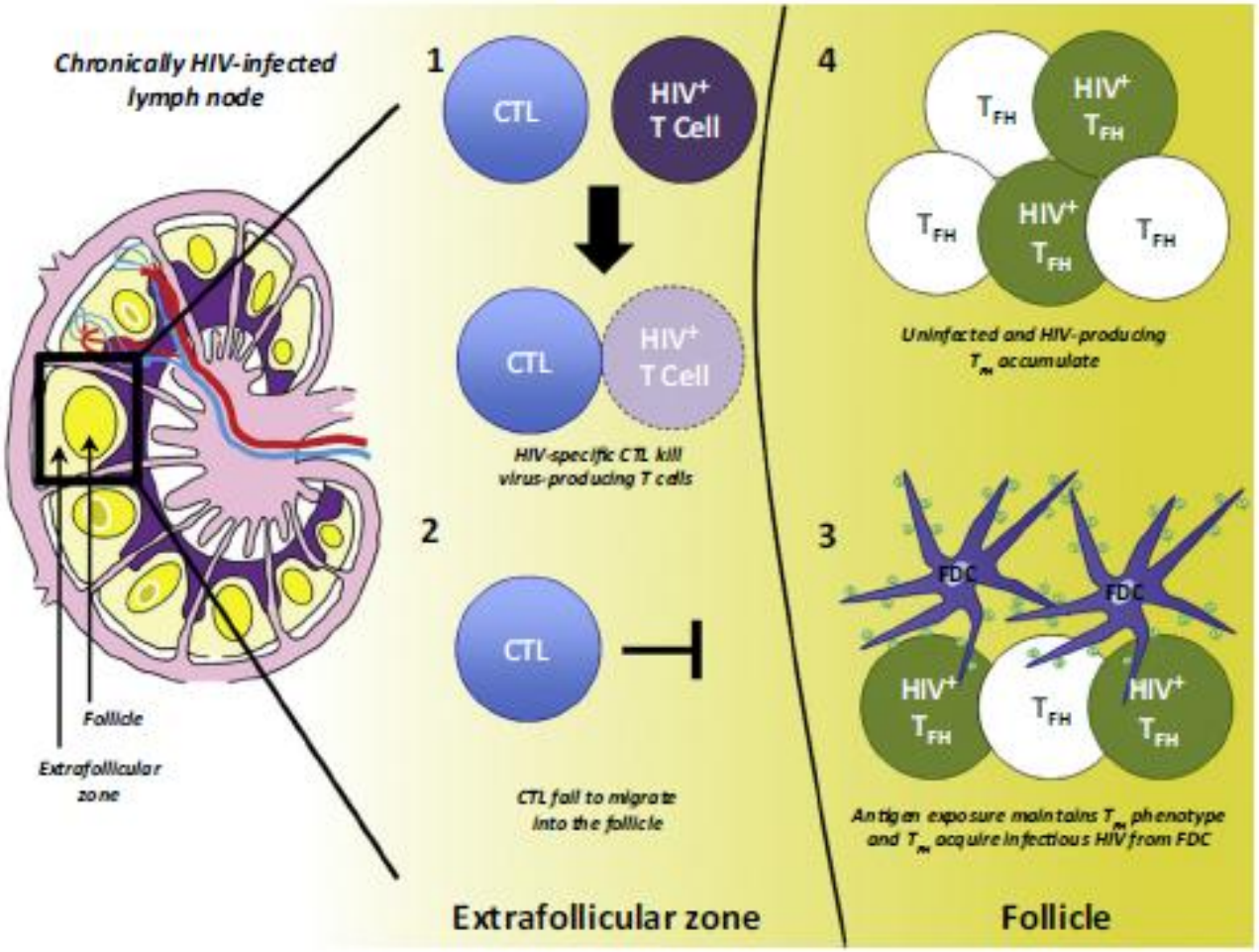


Figure 1. Model of T Follicular Helper Cells (T_{FH}) Accumulation in Chronic, Untreated HIV Infection. HIV-specific cytotoxic T lymphocytes (CTLs) recognize and kill virus-producing T cells (HIV$^+$ T cell) in the extrafollicular zone (1), but are found in low numbers within the follicle due to low CXCR5 expression (2). Within the follicle, T_{FH} receive both activation signals and infectious HIV from interactions with follicular dendritic cells (FDCs) (3). T_{FH}, including HIV-producing T_{FH} (HIV$^+$), accumulate within the follicle (4).

Miles B, et al. TFH in HIV Latency and as Sources of Replication-Competent Virus. Trends in Microbiology 2016.

Kür için en büyük engel latent rezervuar

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

Kürde hedeflenen temel prensipler

- ✓ **Viral rezervuarın eradikasyonu**

  aktivasyon

  eradikasyon

- ✓ **İmmünoterapi**

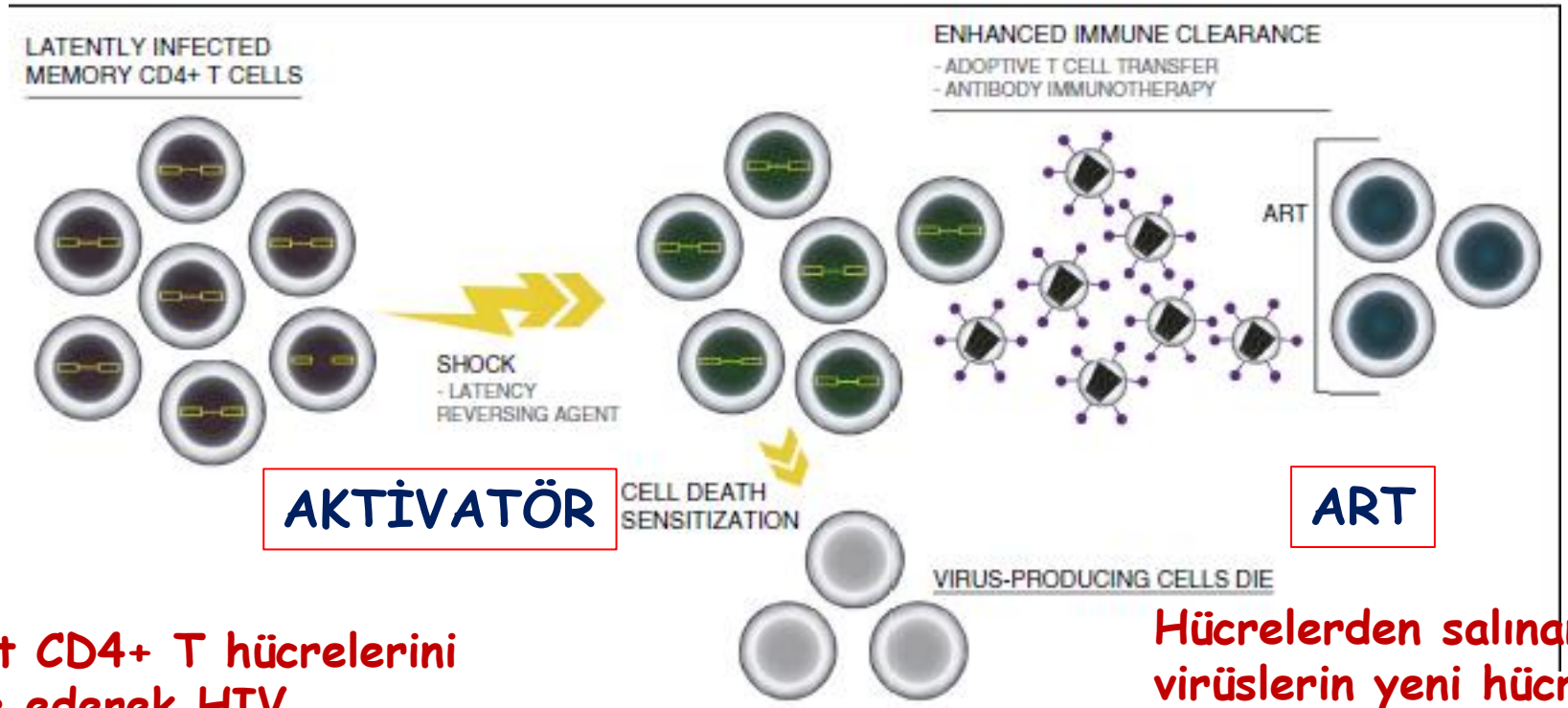
  konağın bağışıklık sistemini HIV'e karşı güçlendirmek

- ✓ **Gen terapileri**

  CD4 + T hücrelerini virüse dirençli hale getirebilmek

Viral Rezervuarın Eradikasyonu

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

Latent CD4 hücreleri aktivatörleri

- ✓ Histon deasetilaz inhibitörleri
- ✓ DNA metiltransferaz inhibitörleri
- ✓ Protein kinaz C agonistleri
- ✓ Bromodomain ekstraterminal motif inhibitörleri
  - ❑ Apoptoz indükleyicileri
  - ❑ BCL-2 inhibitörleri
  - ❑ Retinoik asit-indükleyici gen 1 inhibitörleri
- ✓ Apoptoz protein inhibitörlerinin inhibitörleri
- ✓ İmmün checkpoint inhibitörleri
- ✓ Toll-like reseptör agonistleri

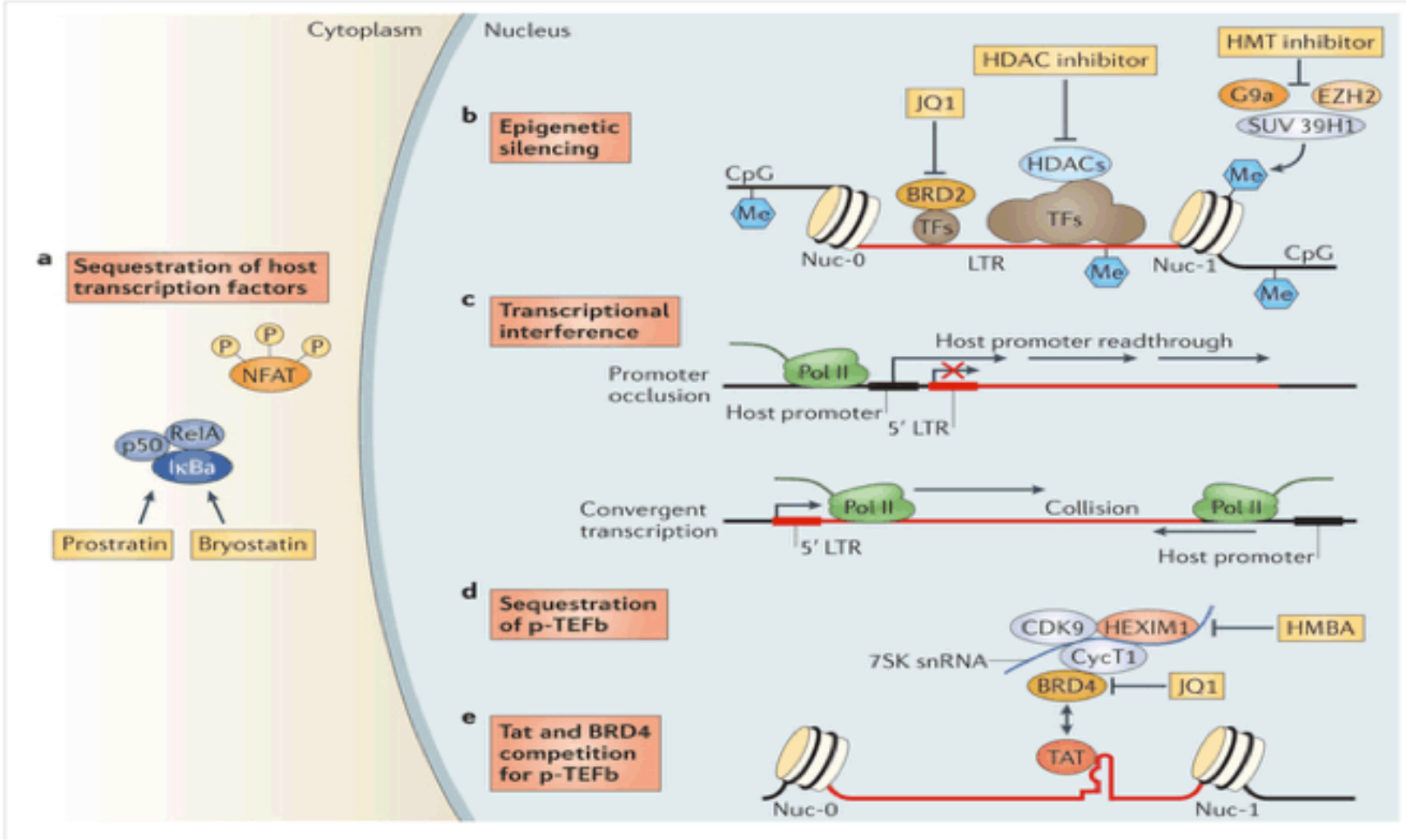
Rasmussen AT, et al. Cancer therapies in HIV cure research. Curr Opin HIV AIDS 2017, 12:96–104

Latentlik

- ✓**Pre-integrasyon**
- ✓**Post-integrasyon**
  - Epigenetik
  - Mikro-RNA

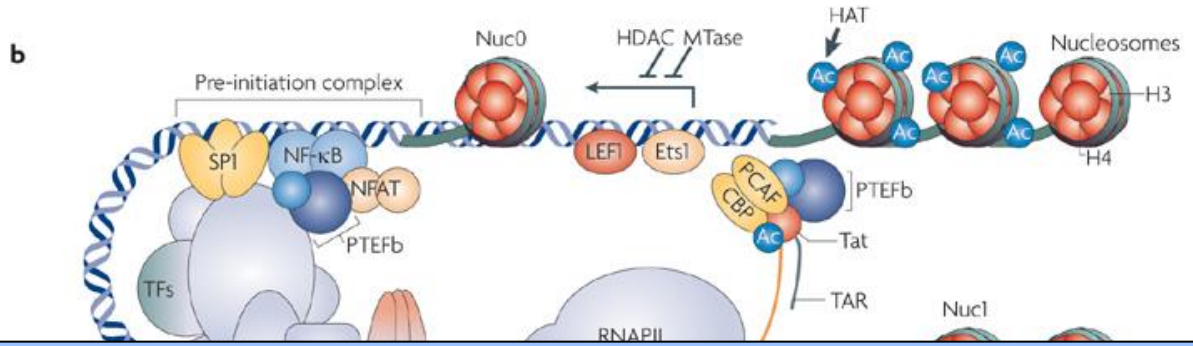
Latentlik

Figure 1: Mechanisms involved in the maintenance of HIV-1 latency and strategies to disrupt latency.



Archin NM, et al. Nat Rev Microbiol. 2014 Nov;12(11):750-64

Nükleozomların merkezini oluşturan histonların asetilasyonu-deasetilasyonu ya da metilasyonu veya demetilasyonu kromatin yoğunluğunun belirler



Histon deasetilaz (HDAC), kromatin yapıda kondansasyona yol açar ve transkripsiyon inhibe olur

Latent CD4 hücreleri aktivatörleri

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Table 1. Cancer therapies investigated in HIV

Drug class	Promising compounds in HIV research	Clinical development phase in oncology	Proposed effect in HIV infection	Clinical studies in HIV
(i) Latency reversing agents				
HDAC inhibitors	Vorinostat, romidepsin, panobinostat	Licensed (CTCL, MM)	Reversing HIV latency by chromatin remodelling	Yes, refs [9–13]
BET inhibitors	OTX015, JQ1	Phase 1/2	Reversing HIV latency by promoting recruitment of P-TEFb to the HIV LTR	No
Histone methyltransferase inhibitors	Low doses only of chaetocin, BIX-01294 or DNZep	Not safe at doses tested/preclinical	Prevents histone 3 methylation that represses HIV transcription, thereby reactivating latent HIV	No
DNA methyltransferase inhibitors	Azacitidine, decitabine	Licensed (MDS)	Prevents CpG methylation at the HIV promoter that represses HIV transcription	No
PKC agonists	Bryostatin-1, prostratin	Phase 1/2	Reversing HIV latency by activating NF-κB signalling pathways	Yes, ref. [17▪]

Rasmussen AT, et al. Cancer therapies in HIV cure research. Curr Opin HIV AIDS 2017, 12:96–104

Latent rezervuarı indükleyen ilaçlar in vitro ve klinik çalışmalarda etkin olarak görülse de rezervuarın boyutunu azaltamamaktadır:

- **doz düşüklüğü**
- **tekrarlayan dozlarda etkinin azalması**
- **toksik etkiler**

Kombinasyon tedavi gerekliliği

Table 1. Clinical Trials of Latency Reversing Agents in HIV-1 Infection

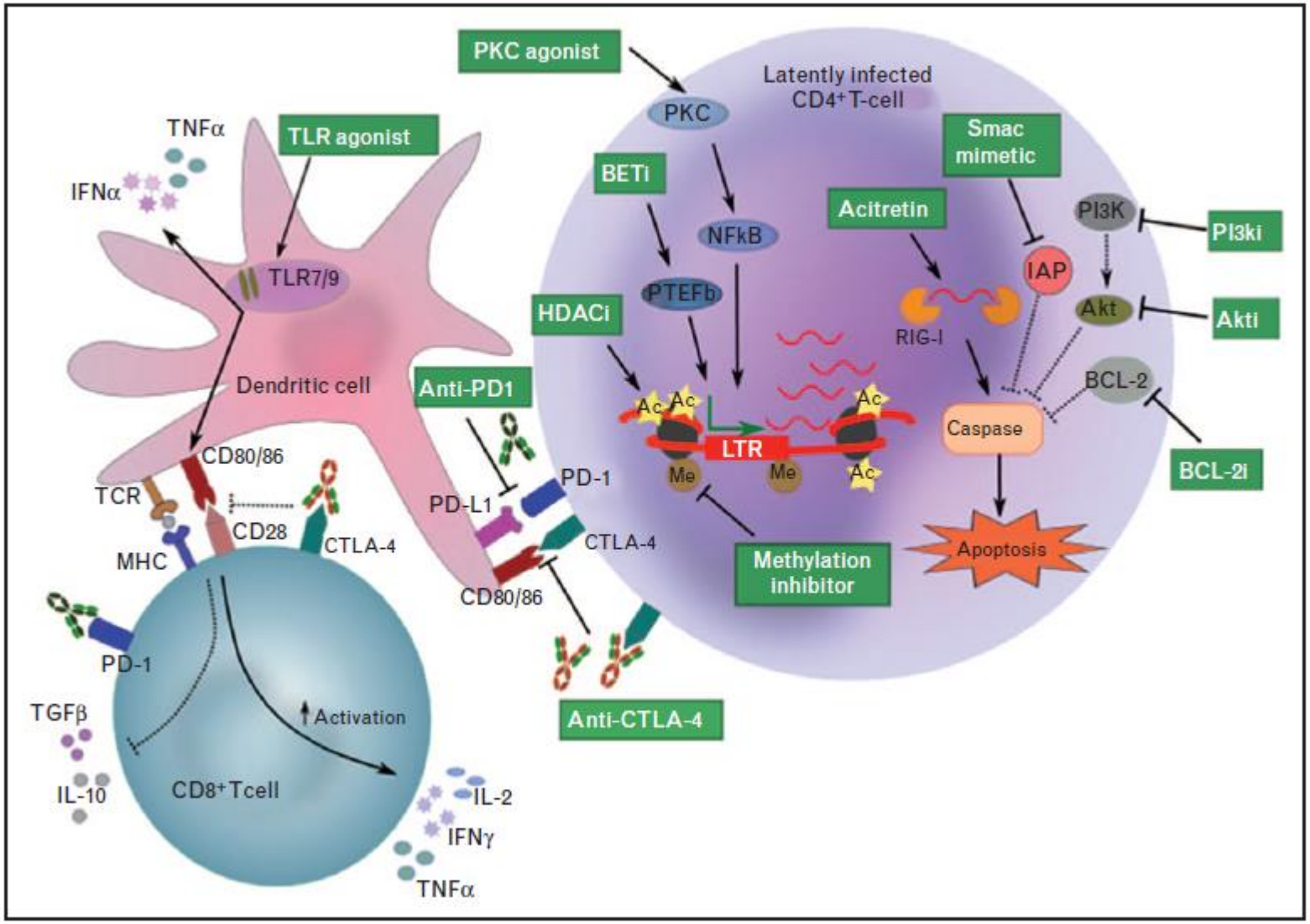
No.	Clinical Trials	Agent 1	Agent 2	Dosing 1	Dosing 2	Inclusion Criteria	N	Arms	Design	Follow-up	ATI	HIV outcome	Status	Completion
1	NCT01319383	Vorinostat	ChAdV63.HIVconsv + MVA.HIVconsv	400 mg/d	—	ART > 18 mo, VL < 50 cp/mL for 24 wks, CD4 > 300/μL	30	1 arm, Step I - VOR single dose twice, Step II - VOR for 3 consecutive days/week (8 wks)	Phase I/II single group open label	15 wks	N	CA-RNA	Recruiting	2016
2	NCT02336074 RIVER	Vorinostat	ChAdV63.HIVconsv + MVA.HIVconsv	10 × 400 mg/d × 28 d starting W32	5×10^{10} vp W24 Boost 2×10^{8} vp W32	PHI (diagnosis < 4 wks) RT naive	52	2 arms: ART only/ART interruption for vaccine-boost and VOR	Phase II multicenter randomized controlled open label	42 wks	N	CA-RNA, CA-DNA, SCA-VL, QVOA	Pre-enrollment	2017
3	VOR VAX	Vorinostat	AGS-004 DC therapy	10 × 400 mg	4 injections×2 cycles	ART > 6 mo, RNA < 50 cp/mL for 2 yrs CD4 > 300/μL	12	1 arm	Phase I single site open label	10 wks	N	QVOA	Recruiting	2020
4	NCT02475915 SEARCH 013	Vorinostat	Hydroxychloroquine + Maraviroc	400 mg/day × 14 d W0, W4, W8	200 mg + 150–600 mg/day × 10 wks	ART > 42 wks (started during PHI) VL < 50 cp/mL for 28 wks CD4 > 450/μL	30	2 arms: ART + VHM/ART only	Phase I/II randomized open label	34 wks	Y	Rebound features, CA-RNA, CA-DNA, 2-LTR	Ongoing	2016
5	NCT02471430 ACTIVATE	Panobinostat	IFN peg alpha2a	5, 10 or 15 mg D0, D2, D4	180 μg SC on D0	ART > 2 yr, VL < 50 cp/mL for 2 yrs CD4 > 400/μL	8	2 arms: Panobinostat + pegIFNα2a/ Panobinostat	Phase I/II, randomized open label	8 wks	N	CA-RNA, CA-DNA, QVOA, 2-LTR, VL	Pre-enrollment	2020
6	NCT02513901 CHARTER	Chidamide	—	10 mg × 2/w for 4 wks or 30 mg × 2/w for 4 wks	—	ART > 18 mo, RNA < 50 for >1 yr CD4 > 350/μL	12	2 arms: Chidamide 10 mg/ Chidamide 30 mg	Phase I/II single site open label dose-finding	8 wks	N	CA-RNA, CA-DNA, VL	Recruiting	2015

Delagrèverie HM, et al. Ongoing Clinical Trials of Human Immunodeficiency Virus Latency-Reversing and Immunomodulatory Agents. Open Forum Infectious Diseases.2016.

7	NCT02092116 REDUC	Romidepsin	Vacc-4x + rhuGM-CSF	5 mg/m^2 IV weekly for 3 wks	1.2 mg/ 0.33 x 10^6 IU x 6 over 12 wks	ART > 1 yr, RNA < 50 cp/mL for >1 yr CD4 > 500/µL	26	2 arms: RMD safety/ RMD + Vacc-4x and ATI	Phase I/II single group open label	10 + 41 wks	Y	Rebound features, CA-RNA, CA-DNA, QVOA, VL, anti-HIV responses	Ongoing	2015
8	NCT01933594 Romidepsin		—	0.5 or 2 or 5 mg/m^2	—	ART (EFV, RAL or DTG) VL < 50 cp/mL for >1 yr, SCA-VL > 0.4 cp/mL at screening, CD4 > 300/µL	45	6 arms: RMD or placebo x 3 dosing	Phase I/II, multicenter placebo- controlled randomized double-blind, dose-finding	4 wks	N	CA-RNA, SCA-VL	Recruiting	2016
9	NCT02616874 BCN02-ROMI	Romidepsin	MVA.HIVconsv vaccine	5 mg/m^2: W3, W4, W5	10^8 pfu: W0 + W9	Subjects from ChAd-MVA. HIVconsv_BCN01 study + BCN01-RO extension study, ART with RAL or DTG, VL < 50 cp/mL for 2 yrs, CD4 > 500/µL	24	1 arm	Phase I single group open label	52 wks	Y	Rebound features, CA-RNA, CA-DNA, SCA-VL, VL	Pre-enrollment	2017
10	RV 438	Romidepsin	3BNC117 Ab	5 mg/m^2: W0, W1, W12, W13	30 mg/kg: W0, W12, W24, W27	ART > 2 yrs started during PHI VL < 50 cp/mL, CD4 > 400/µL	42	4 arms: RMD + 3BNC117/ RMD only/3BNC117 only/no intervention	Phase II randomized open label	78 wks	Y	Control <50 cp/ mL, rebound features, reservoir markers	Pre-enrollment	
11	NCT02269605 BRYOLAT	Bryostatin		—	10 or 20 µg/m^2	—	ART > 2 yrs, VL < LOD, CD4 > 350/ µL	12	3 arms: Bryostatin 10 µg/ m^2 or 20 µg/m^2 or placebo	Phase I randomized placebo-controlled double-blind dose-finding	4 wks	N	CA-RNA, VL, 2-LTR	Completed	2015

Delagrèverie HM, et al. Ongoing Clinical Trials of Human Immunodeficiency Virus Latency-Reversing and Immunomodulatory Agents. Open Forum Infectious Diseases.2016.

Apoptozu indükleyici ve immün modulatuvar ilaçlar



Rasmussen AT, et al. Cancer therapies in HIV cure research. Curr Opin HIV AIDS 2017, 12:96–104

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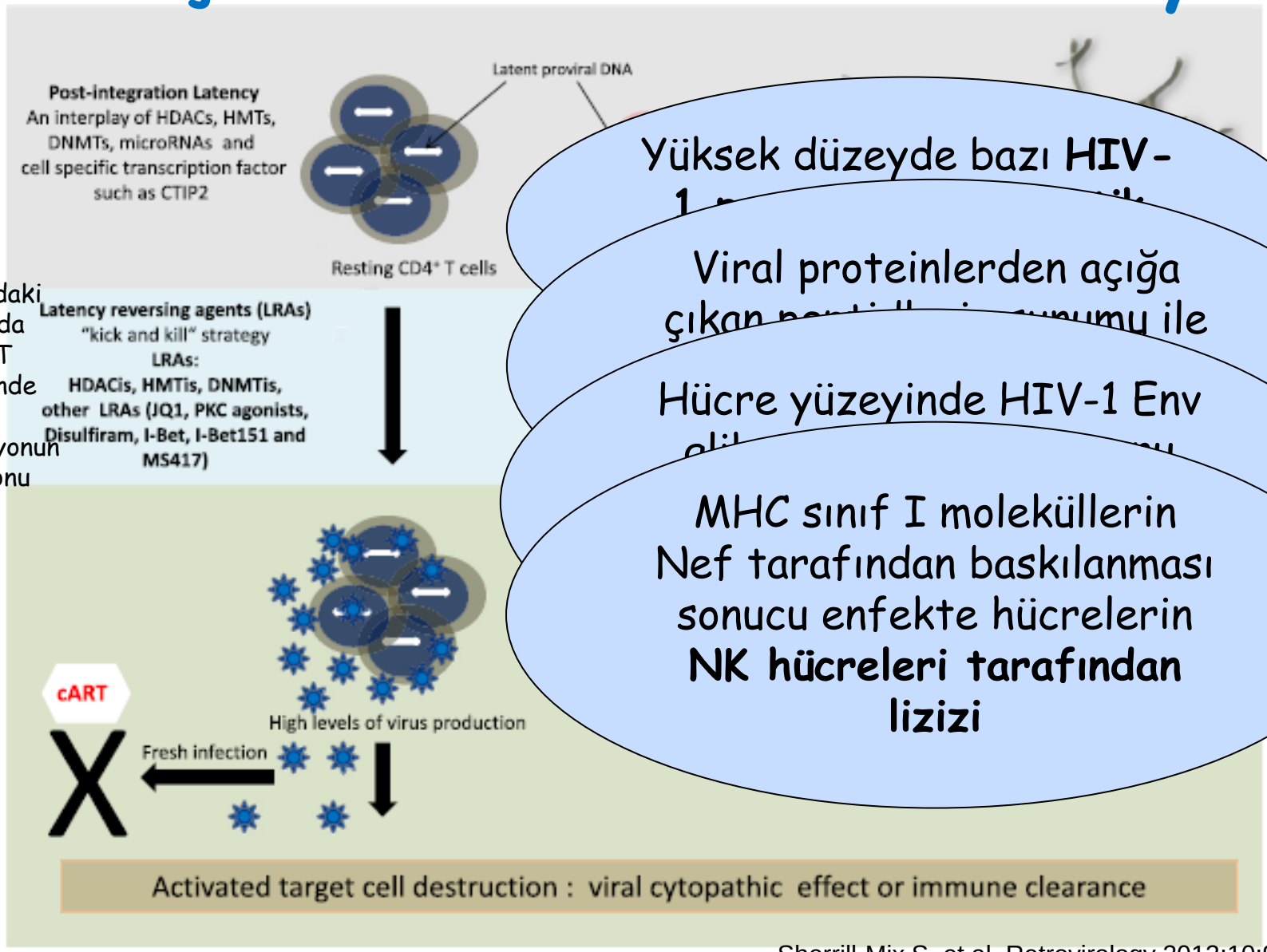
(ii) Apoptosis promoting compounds				
BCL-2 antagonists	Venetoclax	Licensed (CLL), phases 1–3	Inhibits antiapoptotic BCL-2, sensitizing cells to apoptosis. When combined with LRA reactivation, leads to preferential apoptosis of HIV-infected cells	No
RIG-I inducers	Acitretin	Licensed (psoriasis only)	Reactivates HIV transcription and activates RIG-I induced apoptosis, leading to selective apoptosis of HIV-infected cells	No
PI3k/Akt inhibitors	Perifosine, arctigenin	Phase 1/2	Blocks PI3K/Akt pathway signalling, sensitizing HIV-infected cells for apoptosis	No
SMAC mimetics	Birinapant, SBI-0637142, LCL161	Phase 1/2	Inhibits inhibitor of apoptosis proteins (IAPs), sensitizing HIV-infected cells for apoptosis, induces viral replication	No
Tyrosine kinase inhibitors	Ibrutinib	Licensed	Impairs Bruton's tyrosine kinase on the surface of HIV-infected cells, inducing selective depletion of HIV-infected cells	No
(iii) Immune modulation				
Immune checkpoint inhibitors	Ipilimumab, pembrolizumab, nivolumab	Licensed (melanoma, NSCLC)	Enhancing HIV-specific T cell responses; reversing HIV latency	Yes, ref [60]
TLR agonists	GS-9620, MGN1703	Phase 1, 2	Activating DCs and NK cells; reversing HIV latency	Yes, refs [76,78]

Rasmussen AT, et al. Cancer therapies in HIV cure research. Curr Opin HIV AIDS 2017, 12:96–104

«Şok et ve öldür»-eradikasyon

ART altındaki hastalarda hafıza T hücrelerinde HIV transkripsiyonun aktivasyonu



Yüksek düzeyde bazı **HIV-1**

Viral proteinlerden açığa çıkan

Hücre yüzeyinde HIV-1 Env

MHC sınıf I moleküllerin Nef tarafından baskılanması sonucu enfekte hücrelerin **NK hücreleri tarafından lizizi**

Sherrill-Mix S, et al. Retrovirology 2013;10:90.
Spina CA, et al. PLoS Pathog.2013; 9(12).
Kumar A, et al. Clin Epigenetics 2015 Sep 24;7(1):103.

- ✓ Reaktive olan hücreler tarafından salınan **HIV- 1 antijen düzeyleri yetersiz**
- ✓ Reaktivasyon sonrası **virüs güdümlü hücre ölümü** gerçekleşmeyebilir.
- ✓ Elit kontrollülerde gözlenen etkili **CD8+T yanıtı** normal konakta gözlenmiyor.
- ✓ Reaktive olan hücreler **B hücre folliküllerinde** korunur.
- ✓ **HDAC inhibitörleri CTL'in HIV enfekte hücreleri öldürme yeteneğini baskılayabilir.**

Passaes CP, et al. Virology. 2014 Apr;454-455:340-52
Velu V, et al. 2009.Nature 458, 206–210.Amancha P.K, at al. 2013. J. Immunol.191,6060–6070.

Published in final edited form as:
Immunity. 2012 March 23; 36(3): 491–501. doi:10.1016/j.immuni.2012.01.014.

Latent rezervuarın reaktivasyonu öncesi sitotoksik hücrelerin terapötik aşılama ile güçlendirilmesi eradikasyon için gerekli olabilir

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stimulating HIV-1-specific CTLs prior to reactivating latent HIV-1 may be essential for successful eradication efforts and should be considered in future clinical trials.

İmmünoterapi

İmmünoterapi

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

  Anti-HIV immünitesinin işlev ve yaygınlığını arttıracak aşılar

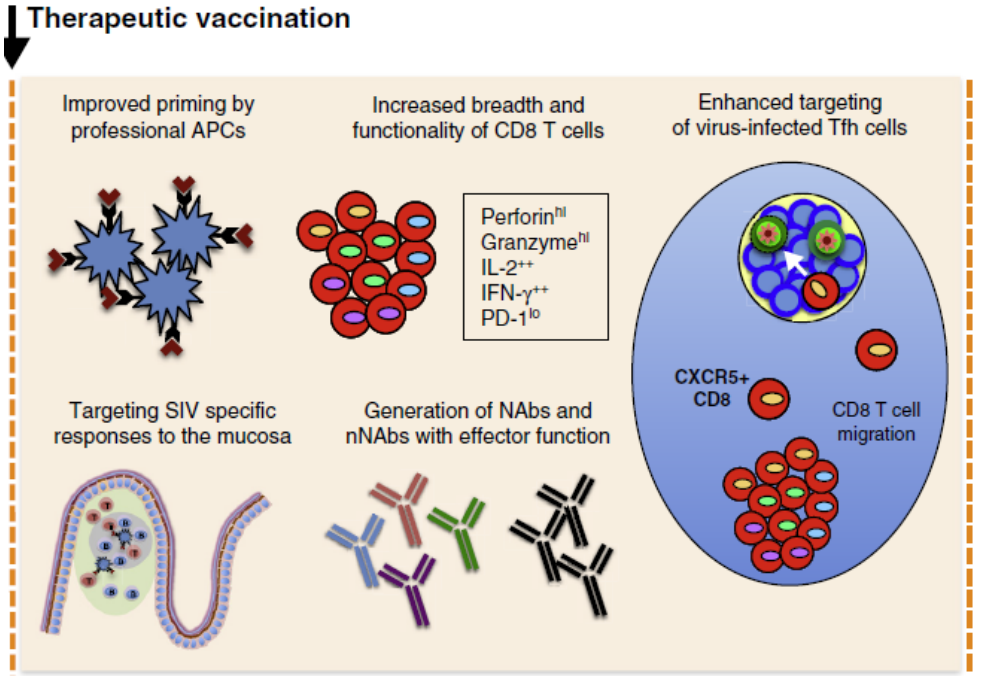
- ✓**Pasif bağışıklama**

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

Terapötik aşılar

Terapötik aşı hedefleri:

- ✓ Anti-viral CD8+ T hücreleri (CTL)
- ✓ CD4+ T hücreleri
- ✓ Nötralizan antikorlar
- ✓ multi-fonksiyonel T hücre (uzun süreli progresse olmayanlarla ilişkili) üretimi
- ✓ CD8 T hücre (B hücre foliküllerindeki foliküler T hücreleri hedef alacak) üretimi



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

Makak ve insan çalışmalarında

otolog inaktive virüs ya da virüsten türetilmiş lipopeptid su lli terapötik

ART altındaki hastalarda dendritik hücre temelli terapötik aşı ile fonksiyonel kür?

masi

Garcia F, et al.:Sci Transl Med 2013; 5:166ra162
Levy Y, et al. Eur J Immunol 2014; 44:2802-2810.

İnsan çalışmaları

Var olan immüniteyi güçlendiren

- DNA ± adjuvan
- Virüs ± adjuvan
- Dendritik hücre kökenli aşı çalışmaları

ART kesilmesi sonrası viral geri tepmede gecikme, viral yükte 0,5-1 log düşüş

Klinik yarar belirsiz

Latent rezervuar üzerine minimal etki

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

SIV-protein ekspresse eden RhCMV vektör kökenli aşı ile aşılanan rhesus makaklar SIVmac239 ile (intrarektal, intravajinal, IV) enfekte ediliyor

Hafıza T hücrelerini hedef alan aşı +/- antikor temelli yaklaşım ile HIV enfeksiyonunda kür??

future management of millions of HIV-infected individuals. We recently reported that ~50% of

69-172 hafta sonra yapılan nekropsilerde perifer ya da dokuda SIV RNA veya SIV DNA saptanamadı (ultrasensitif PZR)

of measurable plasma or tissue-associated virus using ultrasensitive assays, and loss of T cell reactivity to SIV determinants not in the vaccine. Extensive ultrasensitive RT-PCR and PCR analysis of tissues from RhCMV/SIV vector-protected RM necropsied 69–172 weeks after challenge did not detect SIV RNA or DNA over background, and replication-competent SIV was not detected in these RM by extensive co-culture analysis of tissues or by adoptive transfer of 60 million hematolymphoid cells to naïve RM. These data provide compelling evidence for progressive clearance of a pathogenic lentiviral infection, and suggest that some lentiviral

VIRAL CONTROL INDUCED BY HIVCONSV VACCINES & ROMIDEPSIN IN EARLY TREATED INDIVIDUALS

Author(s):
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Abstract Body:
The combined use of therapeutic vaccination and specific drugs that can reactivate latent reservoir virus (Kick and kill strategies) hold the promise to achieve a functional cure for HIV infection. The recently completed BCN01 vaccine trial (NCT01712425) consisted in a ChAd.HIVconsv and MVA.HIVconsv prime/boost vaccination in early treated individuals (

BCN02-Romi (NCT02616874) is an ongoing single-arm proof-of-concept study enrolling 15 individuals rolled-over from BCN01 trial. After 3 years under viral suppression, all participants were immunized with MVA.HIVconsv (2x10E8 pfu), followed by three weekly-doses of romidepsin (RMD, 5 mg/m2 BSA), and by a second MVA.HIVconsv vaccination. Participants underwent a monitored antiretroviral pause (MAP) and treatment was resumed if plasma viral load (pVL) increased >2,000 copies/ml.

15 participants completed all immunizations and RMD infusions, with pVL >20 copies/ml being detected during the intervention in all of them. After the first MVA.HIVconsv vaccination, HIVconsv-specific T cell responses raised to a median peak magnitude of 965 IFNg SFC/10E6 (range 400-3,340, in cryopreserved-and-thawed PBMC), which was significantly higher (p=0.0353) than peak responses during BCN01. Responses transiently decreased by 35% in magnitude after RMD in 10 individuals. However, all but two participants were able to maintain or increase HIV-consv specific responses after the 2nd vaccination relative to pre-RMD, and were therefore invited to start the MAP. To date, 11 patients have interrupted treatment: 7 had to resume cART within the first 4 wk of MAP while 4 participants remain off cART after 7, 12, 14 and 22 weeks (36% of viremic controllers)

Therapeutic vaccination targeting conserved regions of HIV-1 combined with HIV latency reactivation strategies may facilitate clearance of the viral reservoir in early-treated individuals. This is the first reported immune intervention demonstrating a manipulation of the CTL immunodominance pattern and a durable viremic control of HIV-1 infection in a large proportion of participants.

Mothe B et al. *Viral control induced by HIVconsv vaccines & romidepsin in early treated individuals*. Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 119LB, 2017.

- ✓15 hasta (14 kadın, 1 erkek)
- ✓Ortalama yaş: 40 yıl
- ✓**Hastaların tümüne erken ART başlandı** (ortalama 3 ay, maksimum: 5,5 ay).
- ✓**>3 - <4 yıl ART** (INSTI içeren)
- ✓Ortalama CD4: 728 hücre/mm^3(minimum 416)

Curr HIV/AIDS Rep
DOI 10.1007/s11904-016-0296-x

HIV PATHOGENESIS AND TREATMENT (AL LANDAY, SECTION EDITOR)

Post-Treatment Controllers: Role in HIV "Cure" Research

Leslie R. Cockerham[1] · Hiroyu Hatano[2] · Steven G. Deeks[2]

Abstract Descriptions of individuals who are able to control viral replication in the absence of antiretroviral therapy after receiving short-term therapy early in infection ("post-treatment controllers") has generated excitement and controversy within the field. As with natural or "elite" controllers, these cases provide hope that a long-term remission or "functional cure" might one day be possible. Here, we review what is known and not known about these cases and discuss the immunologic factors that may allow these unique individuals to be maintain viral control and may be important for future curative strategies.

Keywords HIV infection · HIV latency · HIV viral rebound · T cell activation · Post-treatment controllers · Antiretroviral therapy

Introduction

Individuals who naturally control HIV replication in the absence of therapy provide the strongest evidence that a remission may one day be achievable. Approximately, 1 % of individuals who acquire HIV are able to control the virus to below the level of detection for years to decades [1]. These so-called "elite" controllers have been extensively studied and reviewed elsewhere [1–3]. Here, we discuss a possible new clinical phenotype that has generated both excitement and controversy: individuals who presented with early HIV infection, who appeared unlikely to be heading toward a state of "elite" control, who started and remained on ART for several years, and who stopped therapy and failed to exhibit the expected viral rebound. These "post-treatment controllers" (PTCs) may indeed be a newly described phenomenon or they may simply be elite controllers whose natural history was interrupted by a

MVA.HIVconsv
(2x10E8 pfu) aşı

3 kür romidepsin/hafta
(RMD, 5 mg/m2 BSA)

MVA.HIVconsv
(2x10E8 pfu) aşı

17. haftada ART kesildi

- ✓ 13 hastanın tedavisi kesildi.
- ✓ 8 hastada ilk 4 haftada viral yük eski düzeylere yükseldi.
- ✓ **5 hastada (%38) viral yük düşük düzeylerde kaldı (<200 kopya/ml)**

  Proviral DNA düzeyleri daha düşük

  Yüksek düzeyde korunmuş bölgelere karşı artmış immünite

1. hasta	6 hafta ART'siz
2. hasta	12 hafta ART'siz
3. hasta	19 hafta ART'siz
4. hasta	20 hafta ART'siz
5. hasta	28 hafta ART'siz

Pasif bağışıklama

- ✓Rhesus makaklarda **monoklonal HIV'e özgül nötralizan antikorlar** (gp120 ve gp41)

---**Hücreler arası HIV yayılımını engellemek**

---**Antikor bağımlı hücre aracılıklı sitotoksiste** ve/veya viral inhibisyon ile **enfekte hücreleri eradike etmek**

Chun TW, et al. Nat Med 1999; 5: 651–55.

Pasif bağışıklama

Makaklarda monoklonal antikor kokteyli

viral yük saptanamayacak düzeyde

kan, lenf nodu ve GİS'te proviral DNA'da azalma

Barouch DH, et al. Nature 2013; 503:224-228.

Rhesus makaklarda

- ✓ **eCD4-Ig** (CD4-Ig ve CCR5- benzeri sulfopeptid) ekspresse eden AAV (adeno-ilişkili virus vektör) ile immünizasyon
- ✓ **Tekrarlayan intra-rektal SHIV uygulamalarına karşı süreğen koruma** (>40 hafta)
- ✓ Nötralizasyona dirençli HIV-1, HIV-2 ve SIV'e karşı nötralizasyon

Gardner MR, et al. Nature 2015; 519:87-91.

Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117

Marina Caskey[1]*, Florian Klein[1]*, Julio C. C. Lorenzi[1], Michael S. Seaman[2], Anthony P. West Jr[3], Noreen Buckley[1], Gisela Kremer[4,5], Lilian Nogueira[1], Malte Braunschweig[1,6], Johannes F. Scheid[1], Joshua A. Horwitz[1], Irina Shimeliovich[1], Sivan Ben-Avraham[1], Maggi Witmer-Pack[1], Martin Platten[4,7], Clara Lehmann[4,7], Leah A. Burke[1,8], Thomas Hawthorne[9], Robert J. Gorelick[10], Bruce D. Walker[11], Tibor Keler[9], Roy M. Gulick[8], Gerd Fätkenheuer[4,7], Sarah J. Schlesinger[1] & Michel C. Nussenzweig[1,12]

Açık etiketli, faz-1 çalışma
Viremik kontrollülerden klonlanan anti-CD4 bağlanma bölgesi antikoru (3BNC117)

12 HIV (-), 17 HIV(+) hasta (2'si ART altında)
1, 3,10,30 mg IV infüzyon
güvenli ve iyi tolere edildi

30 mg tek doz infüzyon ile viral yükte 0.8–2.5 $\log_{10}$ azalma ve 28 gün boyunca sebat
Direnç gelişimi sorunu

3BNC117 monoterapisi etkili değil
3BNC117+ART veya antikor etkili olabilir
Latent rezervuar aktivasyonu+ 3BNC117 ile kür?

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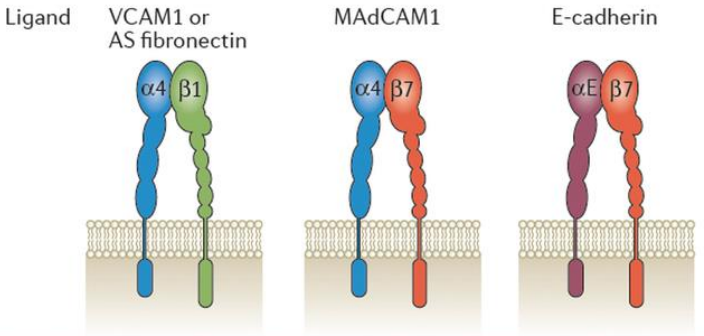
- ✓ **alpha-4 beta-7 integrin** immün sistem hücreleri üzerinde yoğun olarak bulunan bir reseptör
- ✓ HIV ve SIV bu reseptörleri taşıyan hücreleri enfekte ediyor.



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

Nature Reviews | Drug Discovery

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

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

18 rhesus makak maymunun SIV ile enfeksiyonu

5 hafta

ART (plan: 90 gün)

9 hafta

9 hafta

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

7 maymuna 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"

Search for studies: Search

Advanced Search | Help | Studies by Topic | Glossary

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

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**

Hedef: Steril ya da fonksiyonel kür

- ✓ **Entegre olan provirüsün eksizyonu**

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

Gen terapileri

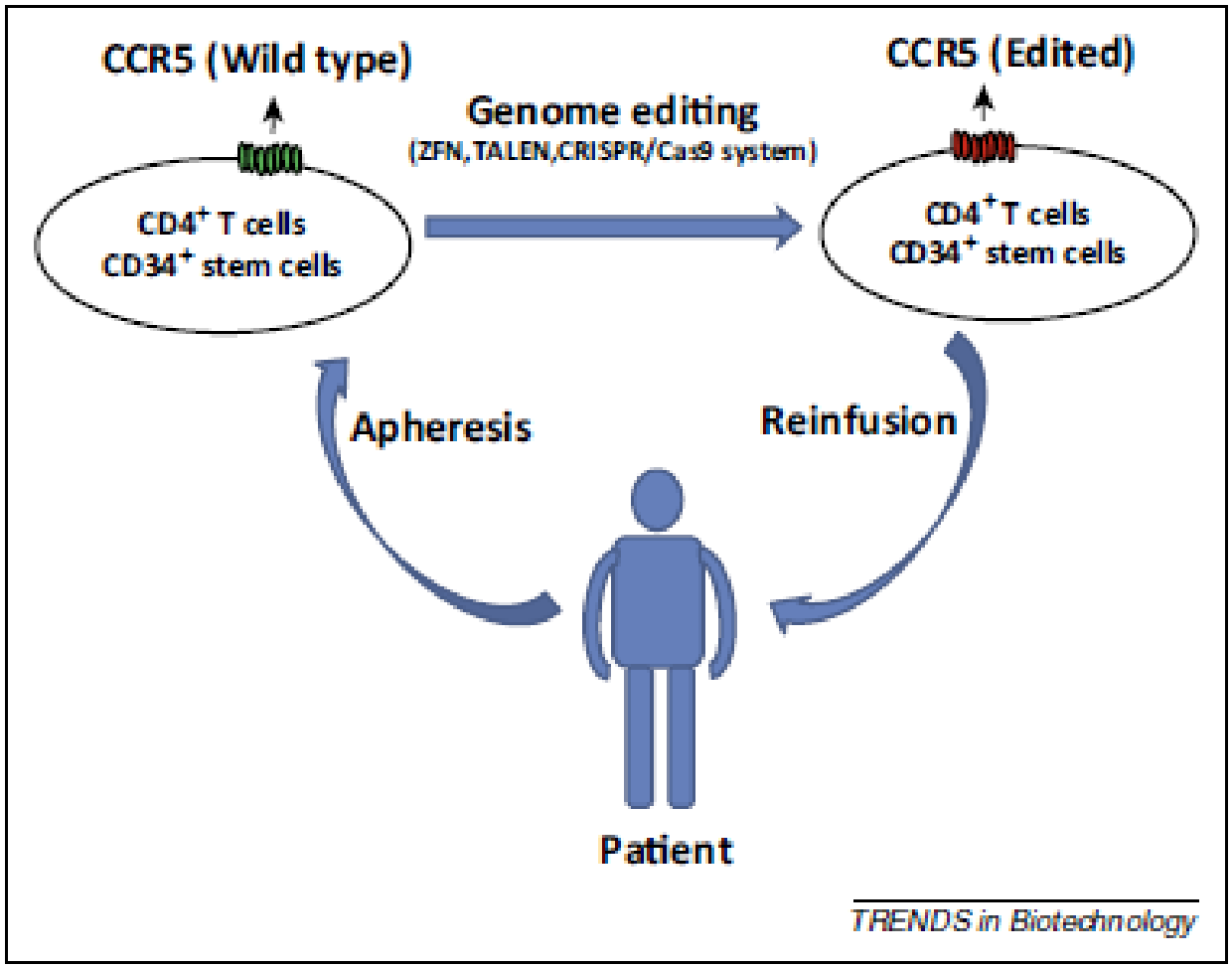
Nükleazlar, rekombinazlar, RNAiler….

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

Genetik materyalde

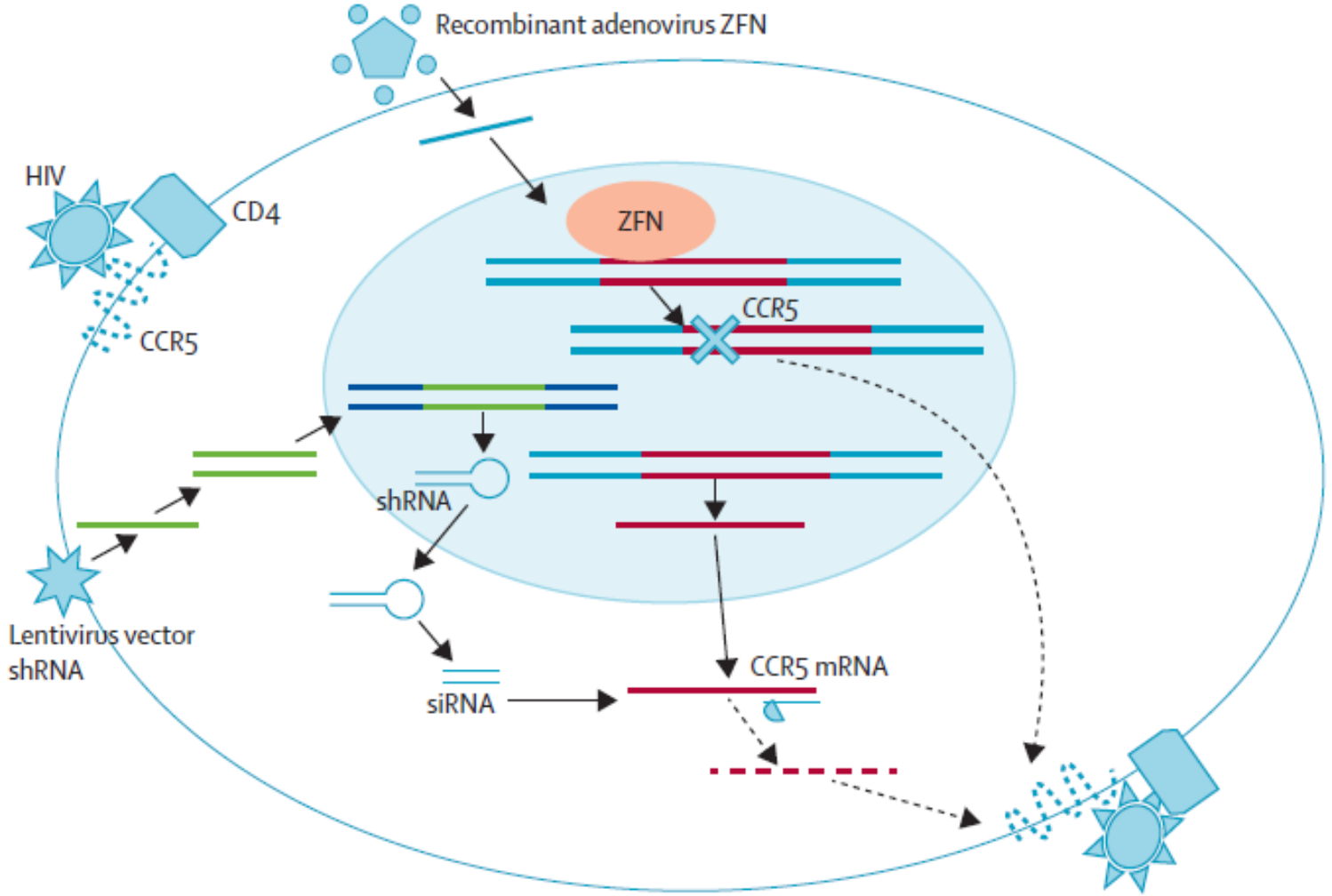
- modifikasyon
- parçalanma
- eklemeler..

HIV enfeksiyonuna ya da replikasyona dirençli hücre üretimi

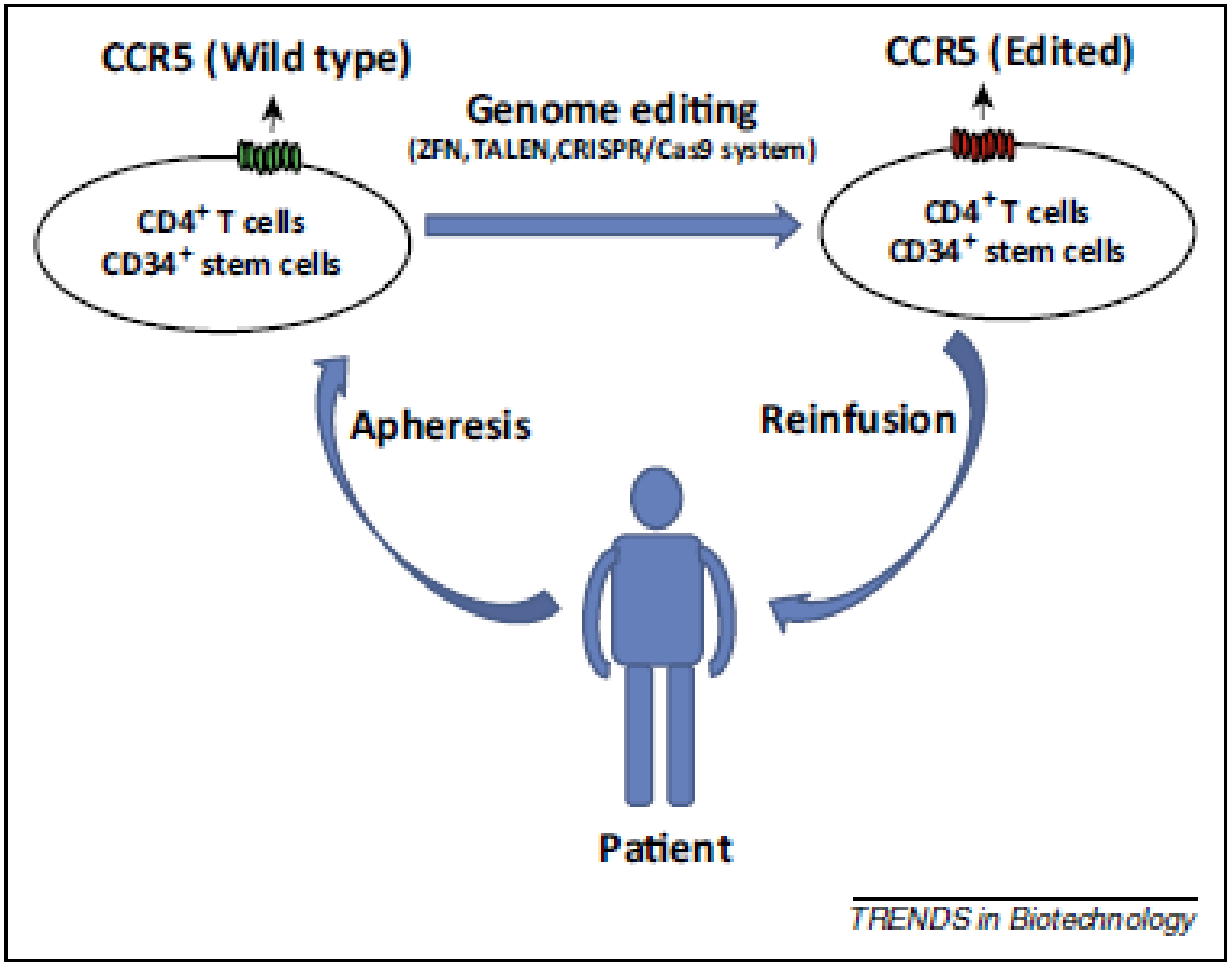


Gu WG.Trends Biotechnol 2015 Mar;33(3):172-9.

A



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



Orijinal HIV'e duyarlı hücrelerin eradikasyonu için kemoterapi gerekli olabilir

Gen terapilerinde asıl hedeflenen molekül CCR5

- ✓ CCR5 δ32 HIV enfeksiyonuna direnç sağlar ve kök hücre transplantasyonu ile kür olgusu mevcut
- ✓ HLA uyumlu CCR5 δ32 homozigot donör bulma olasılığı (1/100), transplant zorluğu
- ✓ Yapay CCR5 mutasyonu ve hücrelerin hastaya reinfüzyonu ile HIV direnci sağlanabiliyor

- ✓ **Uzun vadede etkinlik ve güvenlik kaygısı??**
- ✓ **Seçilecek genetik teknoloji, hücre tipi, veriliş şekli??**
- ✓ **Hücre topluluğunda CXCR4 varlığında CCR5 mutasyonu yeterli olabilir mi?**
- ✓ **Virüsün CCR5 ve CXCR4 arası switch göstermesi**
- ✓ **Transfüzyon sırasında ciddi reaksiyon gelişen 1 olgu**

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

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 6, 2014 VOL. 370 NO. 10

ART altındaki aviremik 12 hastaya ZFN ile modifiye otolog CD4 hücre infüzyonu (%11-28'i ZFN ile modifiye)

ART kesilmesinden sonra HIV DNA ⇩
CD4 hücre sayısı ⇧
1 hastada HIV RNA saptanamadı

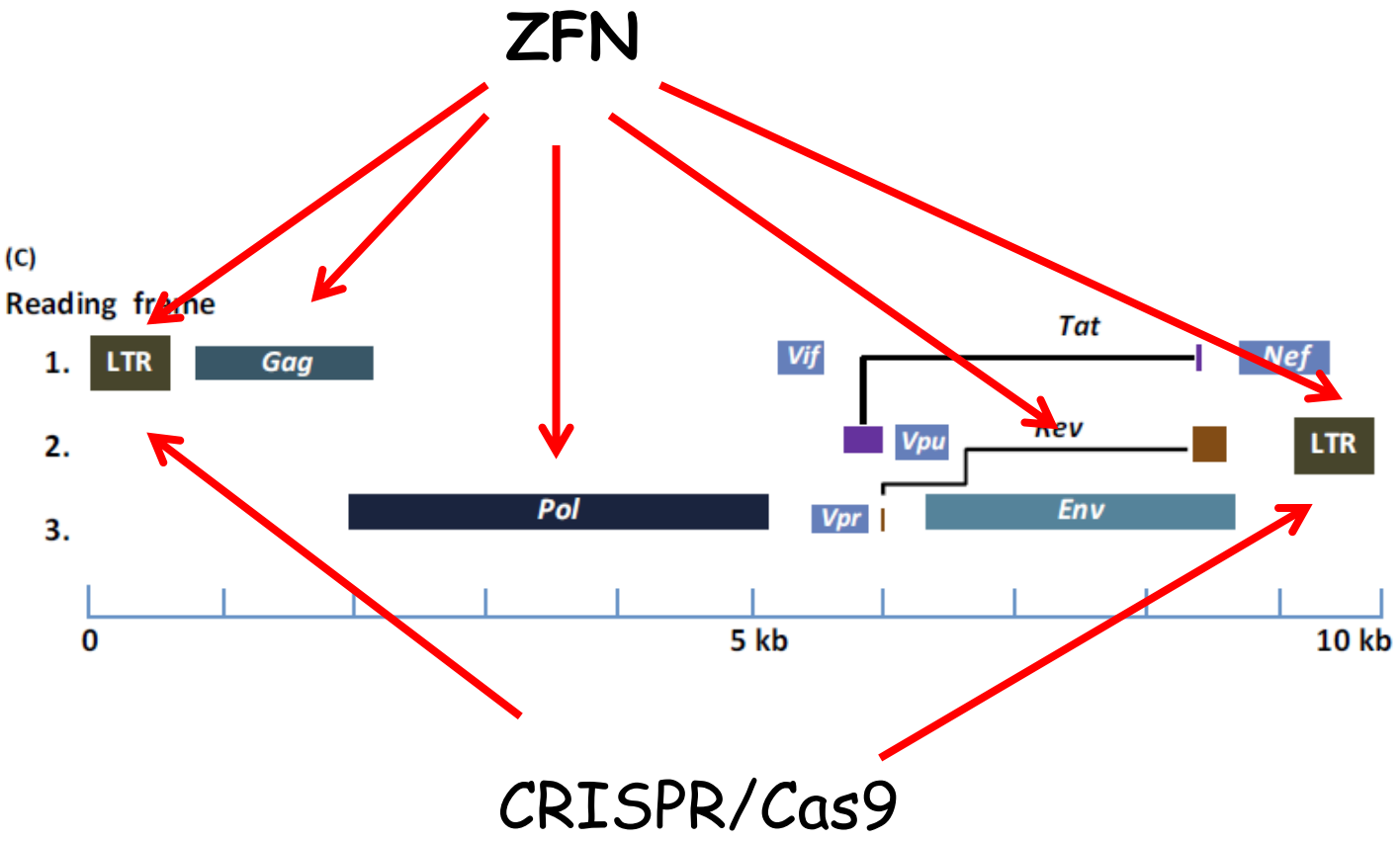
tigated whether site-specific modification of the gene (gene editing) — in this case, the infusion of autologous CD4 T cells in which the *CCR5* gene was rendered permanently dysfunctional by a zinc-finger nuclease (ZFN) — is safe.

One serious adverse event was associated with infusion of the ZFN-modified autologous CD4 T cells and was attributed to a transfusion reaction. The median CD4 T-cell count was 1517 per cubic millimeter at week 1, a significant increase from the preinfusion count of 448 per cubic millimeter ($P<0.001$). The median concentration of *CCR5*-modified CD4 T cells at 1 week was 250 cells per cubic millimeter. This constituted 8.8% of circulating peripheral-blood mononuclear cells and 13.9% of circulating CD4 T cells. Modified cells had an estimated mean half-life of 48 weeks. During treatment interruption and the resultant viremia, the decline in circulating *CCR5*-modified cells (−1.81 cells per day) was significantly less than the decline in unmodified cells (−7.25 cells per day) ($P=0.02$). HIV RNA became undetectable in one of four patients who could be evaluated. The blood level of HIV DNA decreased in most patients.

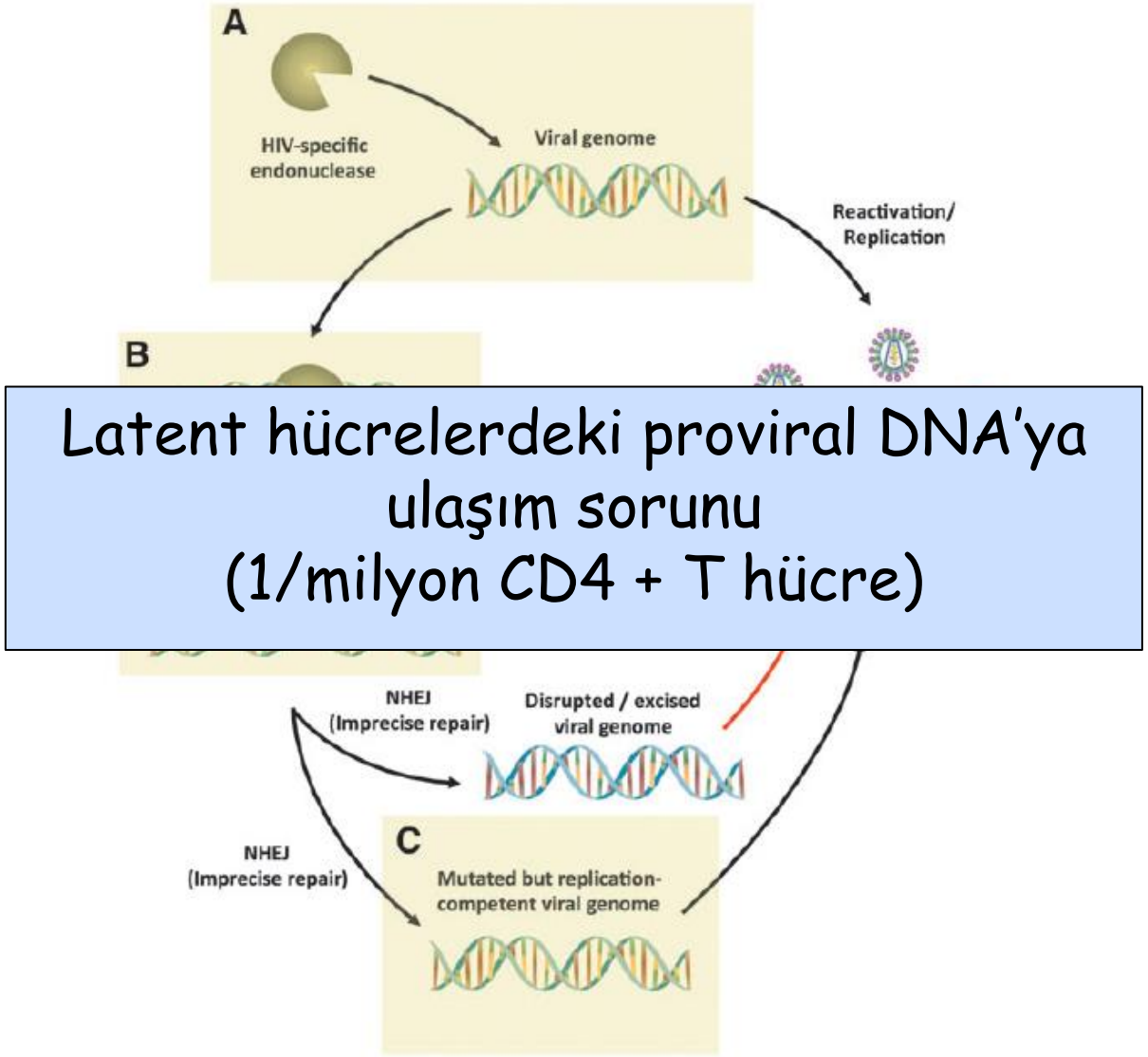
CONCLUSIONS

CCR5-modified autologous CD4 T-cell infusions are safe within the limits of this study. (Funded by the National Institute of Allergy and Infectious Diseases and others; ClinicalTrials.gov number, NCT00842634.)

Proviral DNA eliminasyonu



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



Latent hücrelerdeki proviral DNA'ya ulaşım sorunu
(1/milyon CD4 + T hücre)

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

Genoterapi için diğer hedefler

- ✓ CXCR4 (fizyolojik önemli)
- ✓ Lens epiteli-kökenli büyüme faktörü (LEDGF)/p75 (proviral DNA integrasyonu)
- ✓ Mitokondriyal translokatör protein (TSPO)
- ✓ …
- ✓ …

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

Gelecek…

- ✓ Terapötik aşı+/-HDAC inhibitörleri
- ✓ İmmunomodülatuvar moleküller:

  TLR agonistleri, anti-PD-1/PD-L1 antikorları
- ✓ Kronik enflamasyonu baskılayıcı tedaviler

Yeni stratejiler

- ✓**Heterodimerik interlökin-15** ile tedavi

CD8+ T ve NK hücrelerin sayısının artmasına yol açarak aktive olmuş enfekte hücreler yok edilebilir

- ✓**Regulatuvar T hücre (Tregs) deplesyonu + dendritik hücre temelli aşı**

Pavlakis GN, et al. Heterodimeric IL-15 induces effector cell activation and trafficking to the germinal centers of SIV infected macaques. J VirusErad 2016; 2(Suppl 2): 6. Abstract OA4-1.
He T, et al. T regulatory cell depletion in controller macaques reactivates SIV and boosts CTLs. J Virus Erad 2016; 2(Suppl 2): 16. Poster21.

Sonuç

- ✓ **HIV enfeksiyonu akılcı ART ile yönetilebilir kronik enfeksiyon**

- ✓ **Küre yönelik çalışmalar:**

  Viral rezervuarın aktivasyonu

  İmmünoterapi

  Gen terapileri

  Kombine tedaviler

TEŞEKKÜR EDERİM