HIV/AIDS: KÜR YAKIN GELECEKTE HAYAL Mİ?

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Akılcı kombine antiretroviral tedavi (ART)

HIV enfeksiyonu → yönetilebilir kronik enfeksiyon

Erken tanı + düzenli izlem + antiretroviral tedavi ile hastalarda beklenen yaşam süresi

33 ila 45,8 yıl

Lohse N, et al. Survival of persons with and without HIV infection in Denmark, 1995–2005, Ann Intern Med 2007;146:87–95.
May M, et al. Impact of late diagnosis and treatment on life expectancy in people with HIV-1: UK Collaborative HIV Cohort (UK CHIC) Study, Brit Med J 2011; 343.

- ✓ **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
- ✓Güçlendirilmiş ART
- ✓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

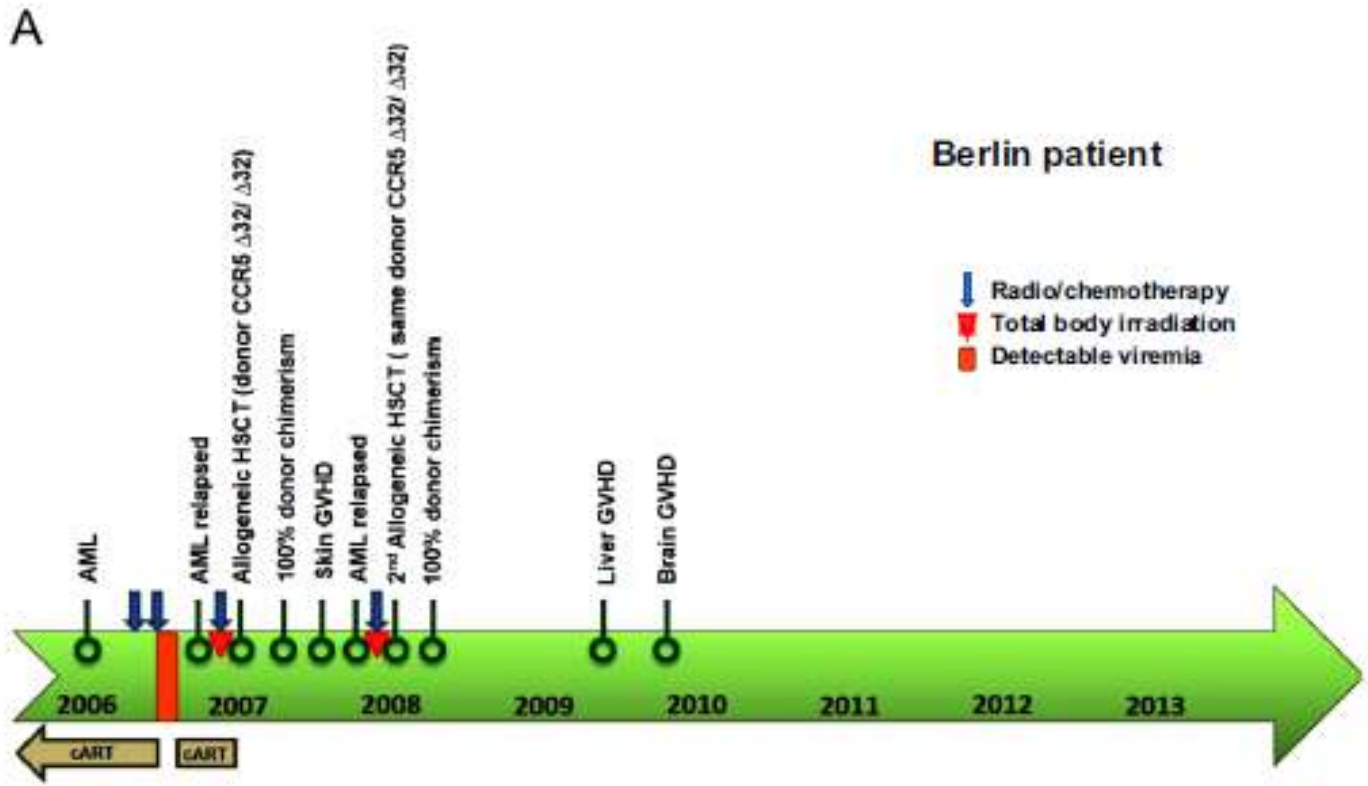
KÜR

Steril
- Tüm HIV DNA'nın (rezervuar) eliminasyonu

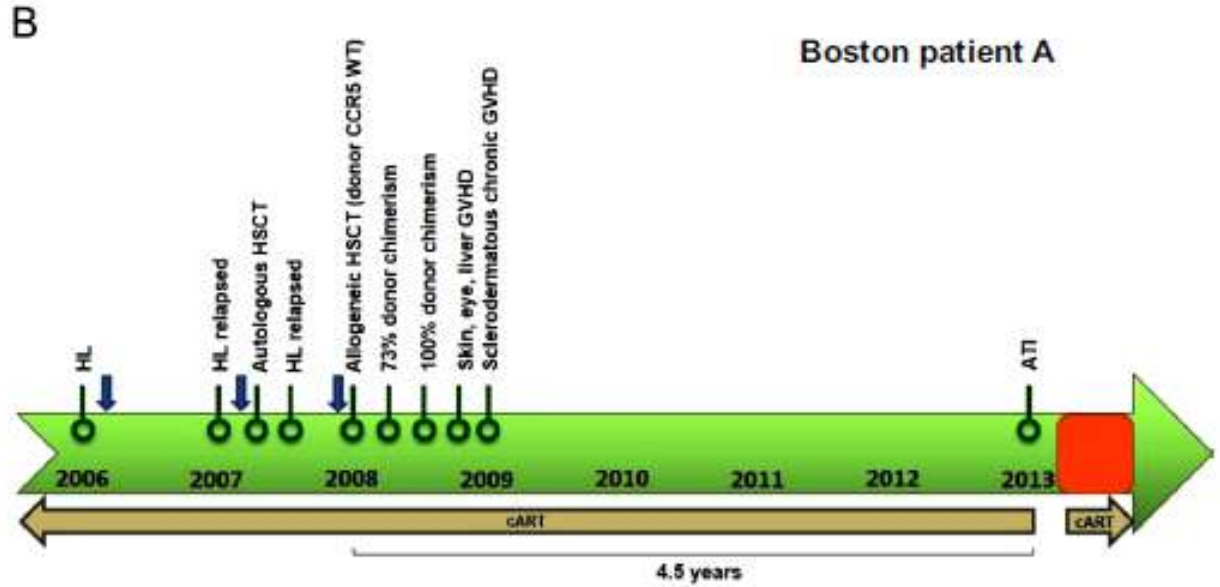
Fonksiyonel
- Rezervuar eradike edilmeden immün kontrol Latent HIV (+)
- ART'siz viremi (-) ya da düşük düzeyde viremi

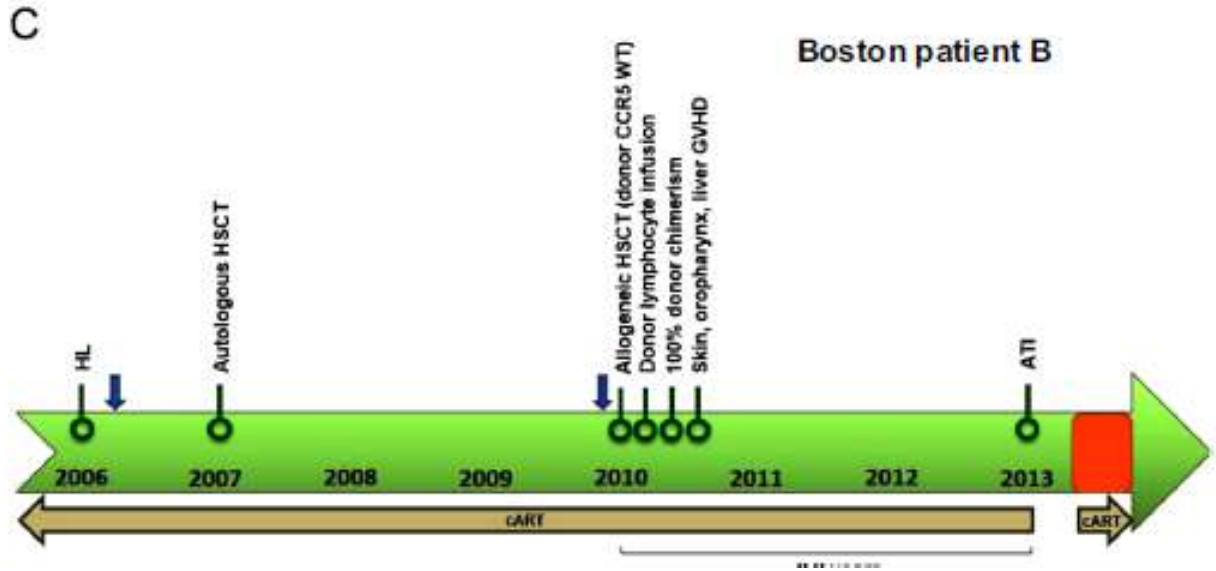
Hibrid

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



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





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

Persistan HIV enfeksiyonu

- ✓ En önemli neden: **replike olma özelliğini koruyan virüs havuzunun CD4 yardımcı T hücrelerinde (özellikle hafıza) latent olarak kalması**

HIV provirüsü transkripsiyon aşamasında sessiz ve immünolojik olarak inaktif olarak kalır.

Latent hücreler canlı kaldığı sürece virüs dorman kalır ve tedavinin intensifikasyonundan etkilenmez.

- ✓ 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

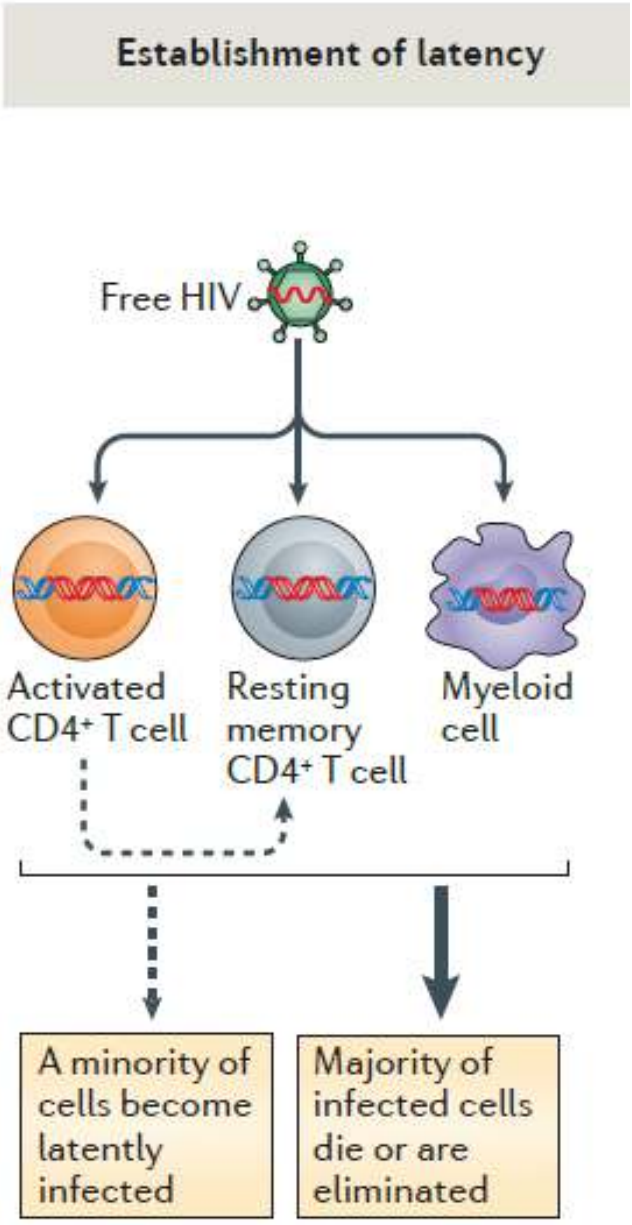
⇩

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

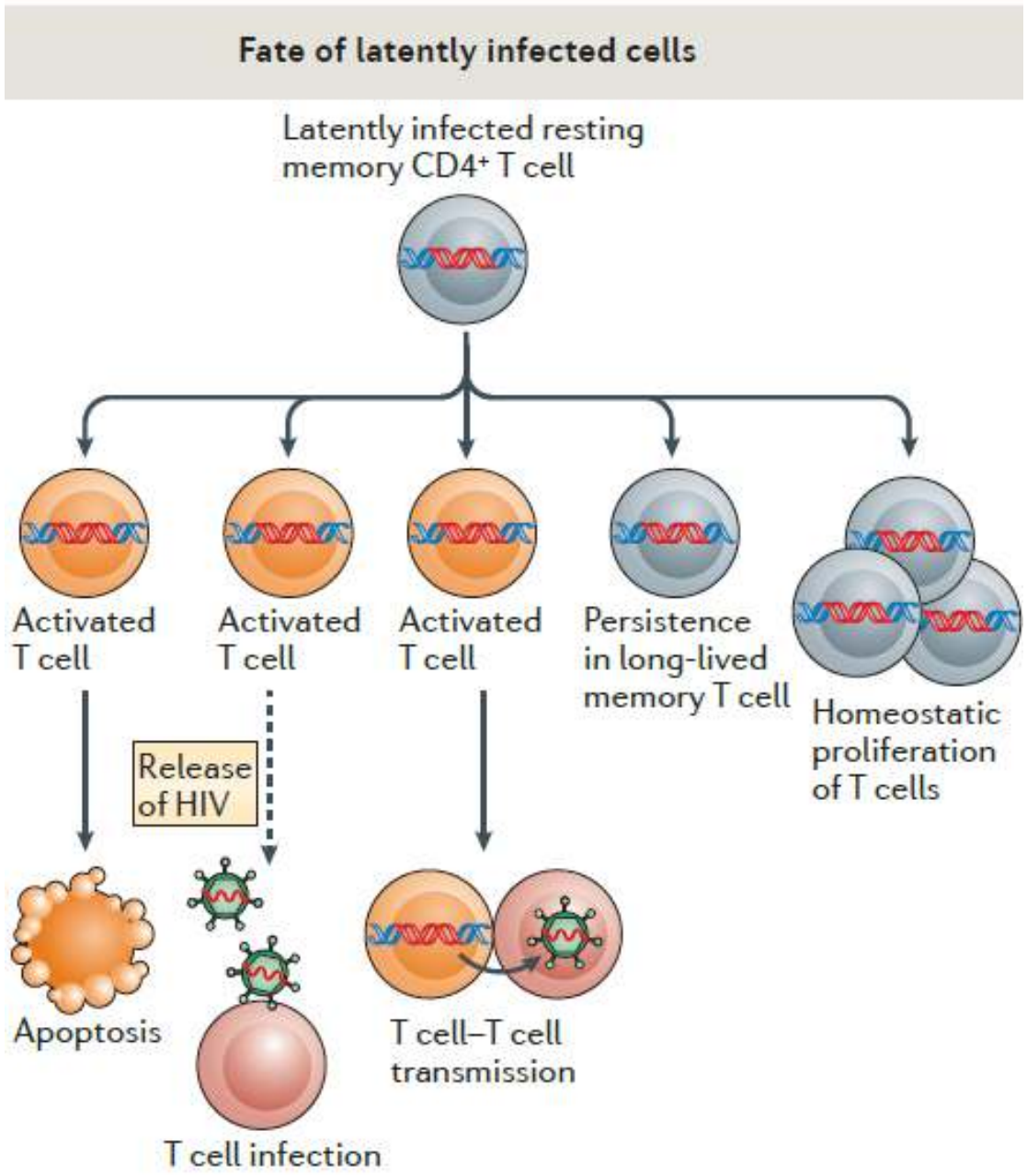
Hücresel uyarı

⇩

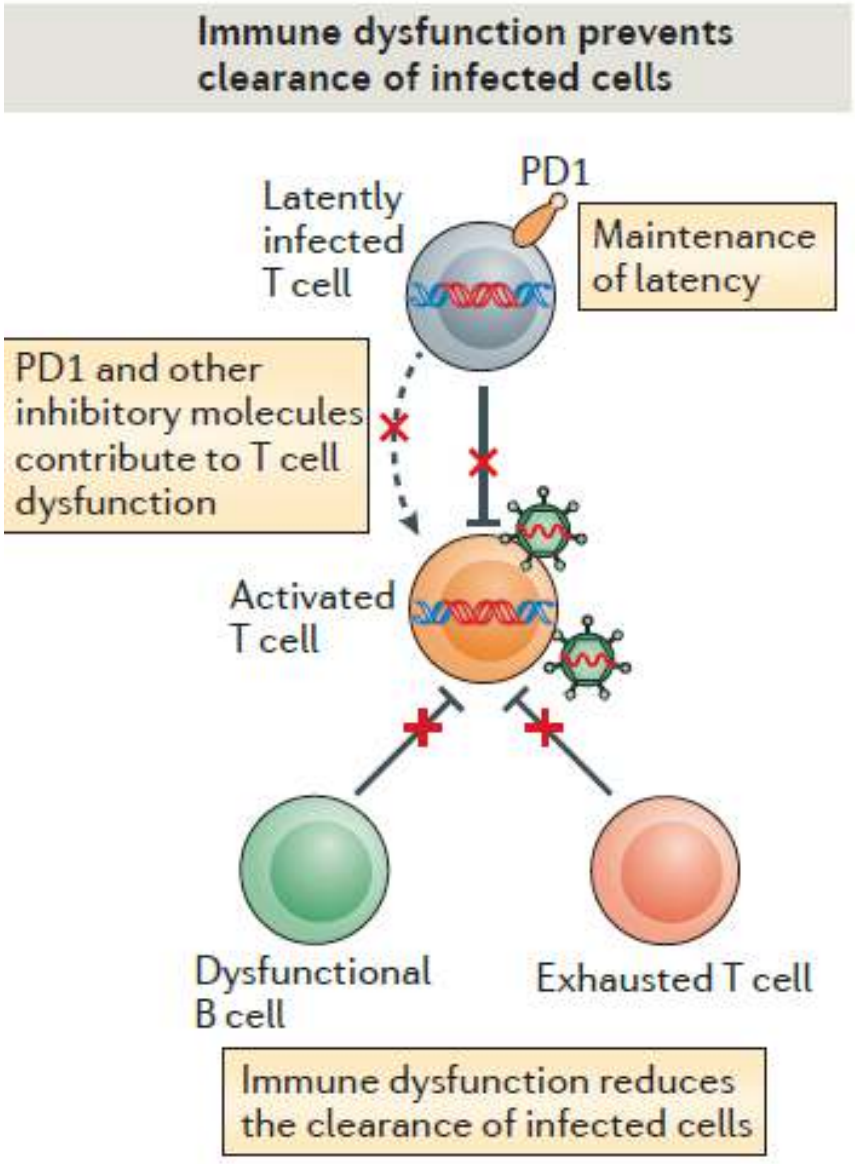
viriyon üretimi



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.



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



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

Kür için en büyük engel latent rezervuar

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

Kürde hedeflenen temel prensipler

- ✓**Viral rezervuarın eradikasyonu**
- ✓**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

↓ **Aktivatör**

Virüs tetikli sitopatik etki ve/veya konak bağışıklık sistemine bağlı hücrelerin ölümü

↓ **ART**

Hücrelerden salınan virüslerin yeni hücreleri enfekte etmesinin engellenmesi

Chun TW, et al.Nat Immunol 2015 Jun;16(6):584-9.

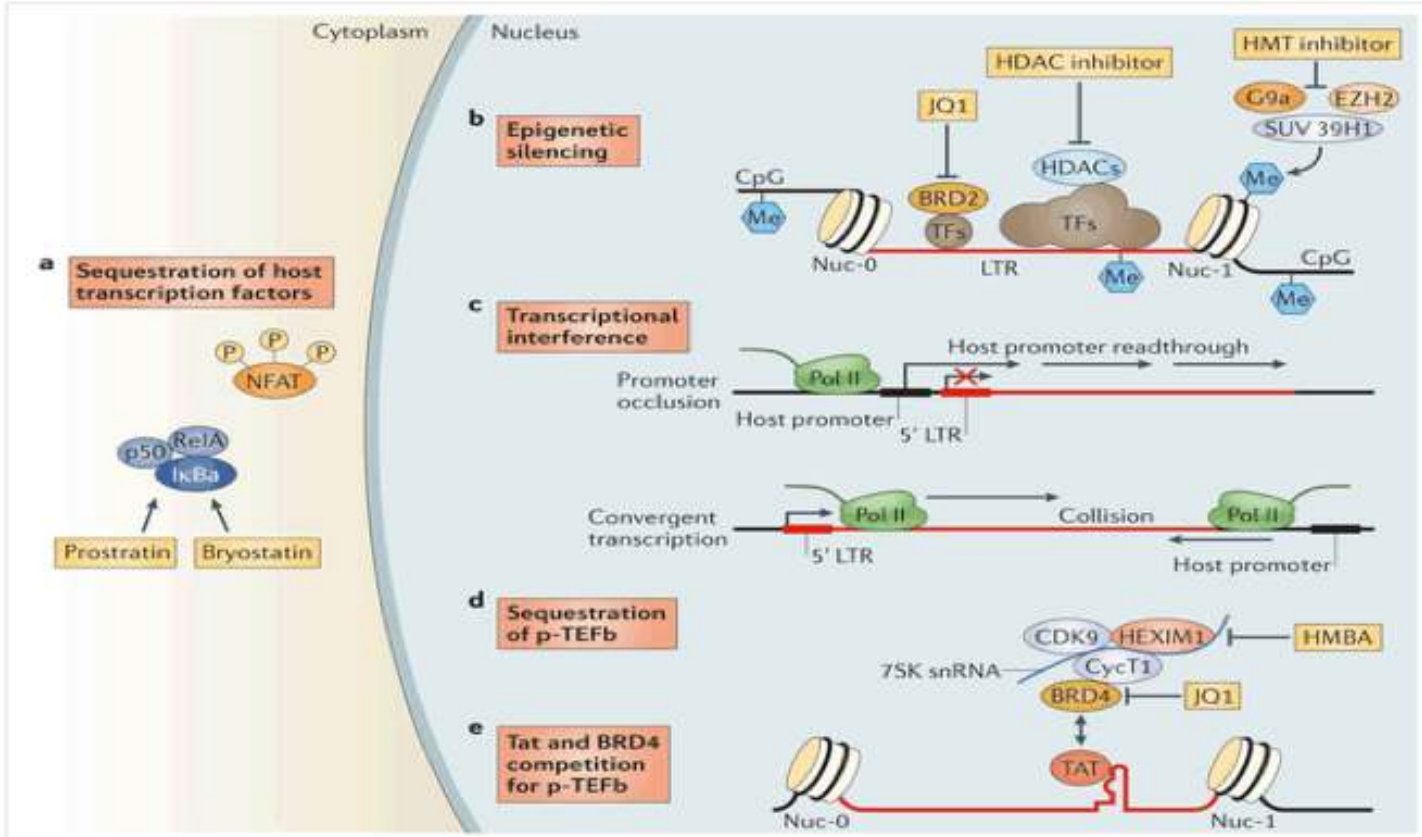
Latent CD4 hücrelerinin aktivasyonu

- ✓ IL-2 ve anti-CD3 ile proviral HIV-1 DNA üreten CD4+ T hücrelerin aktivasyonu
- ✓ ART+ IL-2 ile bazı küçük çaplı çalışmalarda latent rezervuarın azaldığı düşünülse de klinik çalışmalar destekleyici değil
- ✓ Toksik etkiler

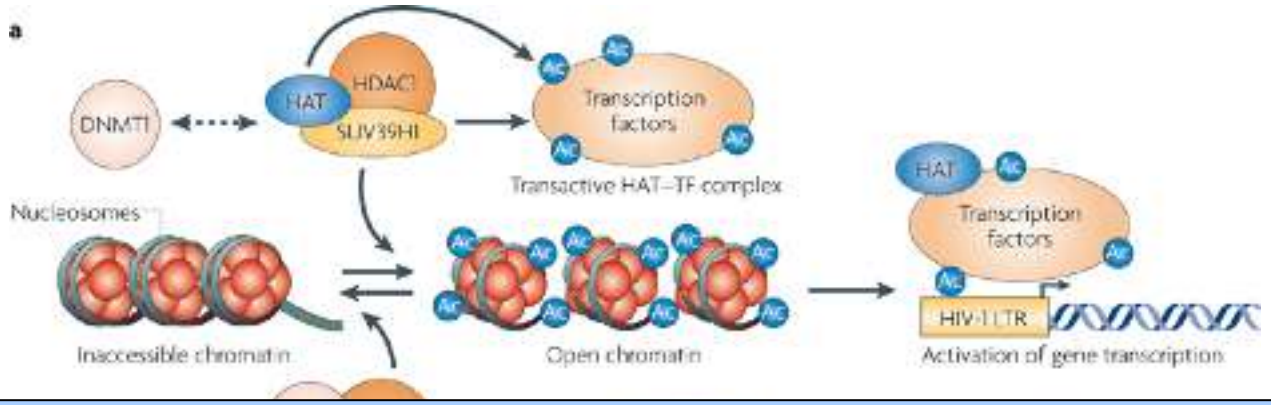
Chun TW, et al. Nat Med 1999; 5: 651–55.
Stellbrink HJ, et al. AIDS 2002;16: 1479–87.

Latent CD4 hücrelerinin aktivasyonu

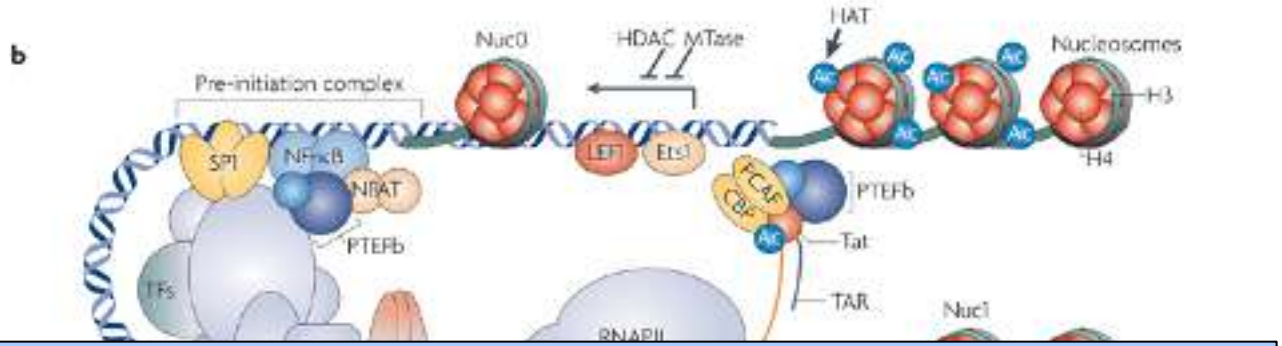
Figure 1: Mechanisms involved in the maintenance of HIV-1 latency and strategies to disrupt latency.



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



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



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

Histon deasetilaz inhibitörleri

	Drug	n	Design	Results
Lehrman et al,[37] 2005	Valproic acid	4	Proof of concept study—treatment analysis of infectious units per million cells	Reduced viral reservoir after valproate given in combination with antiretroviral intensification
Siliciano et al,[38] 2007		9	Observational study of patients on combined antiretroviral therapy and valproate	No differences in infectious units per million cells
Sagot-Lerolle et al,[39] 2008		11/13	Case-control study	No effect
Archin et al,[40] 2010		3	Follow-up of Lehrman et al[37] at 48 and 96 weeks	No long-term effect of valproate in initial responders
Routy et al,[41] 2012		56	Randomised study (27 given valproate in weeks 0–16, 29 given valproate in weeks 16–32)	No effect on infectious units per billion cells at 16 or 48 weeks
NCT01319383	Vorinostat	30	400 mg single dose; later investigation to use 400 mg daily for 3 consecutive days per week (maximum 8 weeks)	Initial analysis[35] of single dose in eight patients showed an increase in cell-associated HIV RNA in resting CD4 T cells
NCT01365065		20	400 mg daily for 14 days; initial follow-up to 24 weeks	NA
NCT01680094 (CLEAR study)	Panobinostat	16	20 mg on days 1, 3, and 5, every other week for 8 weeks; viral load, proviral DNA, and infectious units per million cells recorded for 32 weeks	NA
NCT01286259	Disulfiram	20	500 mg daily for 1 month	NA

Table: Clinical studies of drugs to reduce viral latency by activating the latent virus

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

Table 1 HIV-1 latency reversal agents in various phases of HIV-1 therapeutic development

Latency reversal agent	Class of agent	Agent tested on	Mechanism of action	Stage of therapeutic development	Ref
Vorinostat (SAHA)	HDAC inhibitor	J89 cells and Resting CD4$^+$ T cells	Induce acetylation of histone H3K4, H4K4 resulting in remodeling of nuc-1	In vitro, ex vivo and tested in a clinical trial	[81, 87]
Valproic acid	HDAC inhibitor	J-Lat cell lines and U1 cells, patient derived cells	Formation of euchromatin at HIV-1 5'LTR and reactivation of HIV-1 transcription	In vitro, ex vivo, and tested in a clinical trial	[58, 135]
Panobinostat	HDAC inhibitor	CD4$^+$ T cells	Formation of euchromatin at HIV-1 5'LTR and reactivation of HIV-1 transcription	Phase 1/2 clinical trial	[136]
Romidepsin	HDAC inhibitor	CD4$^+$ T cells	Formation of euchromatin at HIV-1 5'LTR and reactivation of HIV-1 transcription	Ex vivo	[137]
Entinostat	HDAC inhibitor	CD4$^+$ T cells, ACH2, and J-lat cell lines	Formation of euchromatin at HIV-1 5'LTR and reactivation of HIV-1 transcription	In vitro, ex vivo	[138, 139]
M344	HDAC inhibitor	J-Lat clones (A7)	Increases histone acetylation and activation of NF-kappaB	In vitro	[140]
Sodium butyrate	HDAC inhibitor	CD4$^+$ T cells, J-Lat cell lines, ACH2 and U1 cells	Increases histone acetylation resulting in transcriptional activation of HIV-1 promoter	In vitro	[58, 141]
Trichostatin A	HDAC inhibitor	CD4$^+$ T cells, ACH2, and J49 cells	Increases histone acetylation resulting in transcriptional activation of HIV-1 promoter	In vitro, ex vivo	[49, 139]
Oxamflatin	HDAC inhibitor	J89GFP and A7 cell	Increases the acetylation level of histone H3 and histone H4 at the nucleosome 1(nuc-1) site	In vitro	[59, 142]
Scriptaid	HDAC inhibitor	J89GFP and A7 cells	Promotes hyperacetylation of histone	In vitro	[59, 143]

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

- ✓ HDAC inhibitörleri özgül olmadığı için tüm hücresel transkripsiyon etkilenebilir
- ✓ HDAC inhibitörleri tek başına latent rezervuarın aktivasyonu için yeterli olamayabilir

HDAC inhibitörleri + HIV transkripsiyon aktivatörleri

(PKC agonistleri: prostratin, bryostatin, ingenol B

bromodomain inhibitörleri

NF-kB aktivasyonuna yol açanTLR 7 ve 9 agonistleri)

Passaes CP, et al. Virology 2014 Apr;454-455:340-52
Thornhill J, et al. Curr Opin Infect Dis. 2015 Feb;28(1):1-9.

Givinostat (ITF2357)	HDAC inhibitor	J89GFP, ACH2 and U1 cells	Induces hyperacetylation of histone	In vitro	[59, 144]
CG05/CG06	HDAC inhibitor	ACH2 cells	Induces hyperacetylation of histone	In vitro	[145]
Chaetocin	HMT inhibitor	Resting $CD4^+$ T cells isolated from HIV infected patients, ACH-2, OM10.1 cells, infected Jurkat-tat cells	A Suv39H1 inhibitor, induces loss of H3K9me3	In vitro, ex vivo	[64, 92, 93]
BIX-01294	HMT inhibitor	ACH-2 and OM10.1 cells	A G9a inhibitor, promotes repressive H3K9me2	Ex vivo	[64, 93]
3-deazaneplanocin A	HMT inhibitor	Latently infected Jurkat E4 and G4 cells	An inhibitor of EZH2, Induces loss of H3K27me3	In vitro	[65]
5-aza-2' deoxycytidine	DNMTI	ACH-2 cells, U1 cells, and J-Lat cell lines	Inhibits of cytosine methylation and prevent the recruitment of MBD2 and HDAC2 to the 5'LTR	In vitro	[97]
Prostratin	PKC agonist	Patient derived CD4 + T cells, J-Lat cell lines	Activates NF-KB	Ex vivo	[146, 147]
Phorbolmyristate acetate (PMA)	PKC agonist	J-Lat cell lines	Activates NF-KB	Ex vivo	[146, 147]
Diterpene ester ingenol-3-angelate	PKC agonist	U1 cells	Activates NF-KB	In vitro	[148]
Bryostatin-2	PKC agonist	$CD4^+$ T-cells, J-Lat cell lines, U1 and OM10.1 cells	Activates NF-KB	In vitro, ex vivo	[149, 150]
JQ1	Unclassified agents	$CD4^+$ T cells derived from patient, J-Lat cell lines, U1, ACH2, and OM10.1 cells	Releases BRD4 from the 5'LTR and allows Tat-mediated recruitment of P-TEFb to the 5'LTR.	In vitro and ex vivo	[109, 111]
I-Bet, I-Bet151 and MS417	Unclassified agents	J-Lat cell lines, primary $CD4^+$ T cells	Releases BRD4 from the 5'LTR and allows Tat-mediated recruitment of P-TEFb to the 5'LTR.	In vitro	[111]
Disulfiram	Unclassified agents	$CD4^+$ T cells	Reactivates latent HIV-1 expression through depletion of the phosphatase and tensin homolog	Ex vivo, clinical trial	[113–115]

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

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

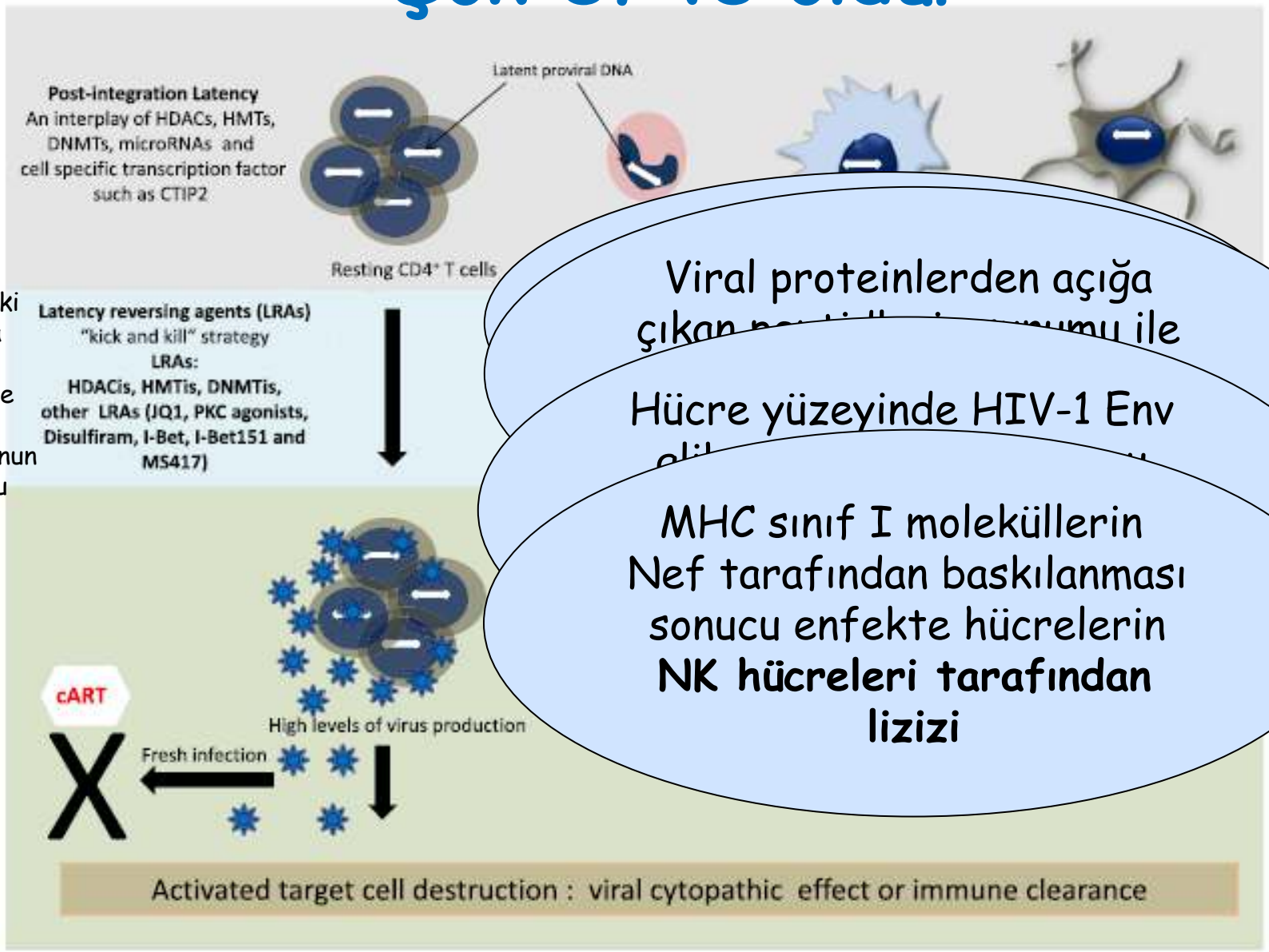
tat bağımlı transkripsiyonun baskılanması

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»

ART altındaki hastalarda hafıza T hücrelerinde HIV transkripsiyonun aktivasyonu



Viral proteinlerden açığa çıkan [illegible] ile

Hücre yüzeyinde HIV-1 Env [illegible]

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.

- ✓ Reaktivasyon sonrası virüs güdümlü hücre ölümü gerçekleşmeyebilir.
- ✓ HDAC inhibitörleri CTL'in HIV enfekte hücreleri öldürme yeteneğini baskılayabilir.
- ✓ Elit kontrollülerde gözlenen etkili CD8+T yanıtı normal konakta gözlenmiyor.

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.

T hücreleri aktive olmadan HIV-1'in in vitro aktivasyonu ile latent

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

ART

elimine eder

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

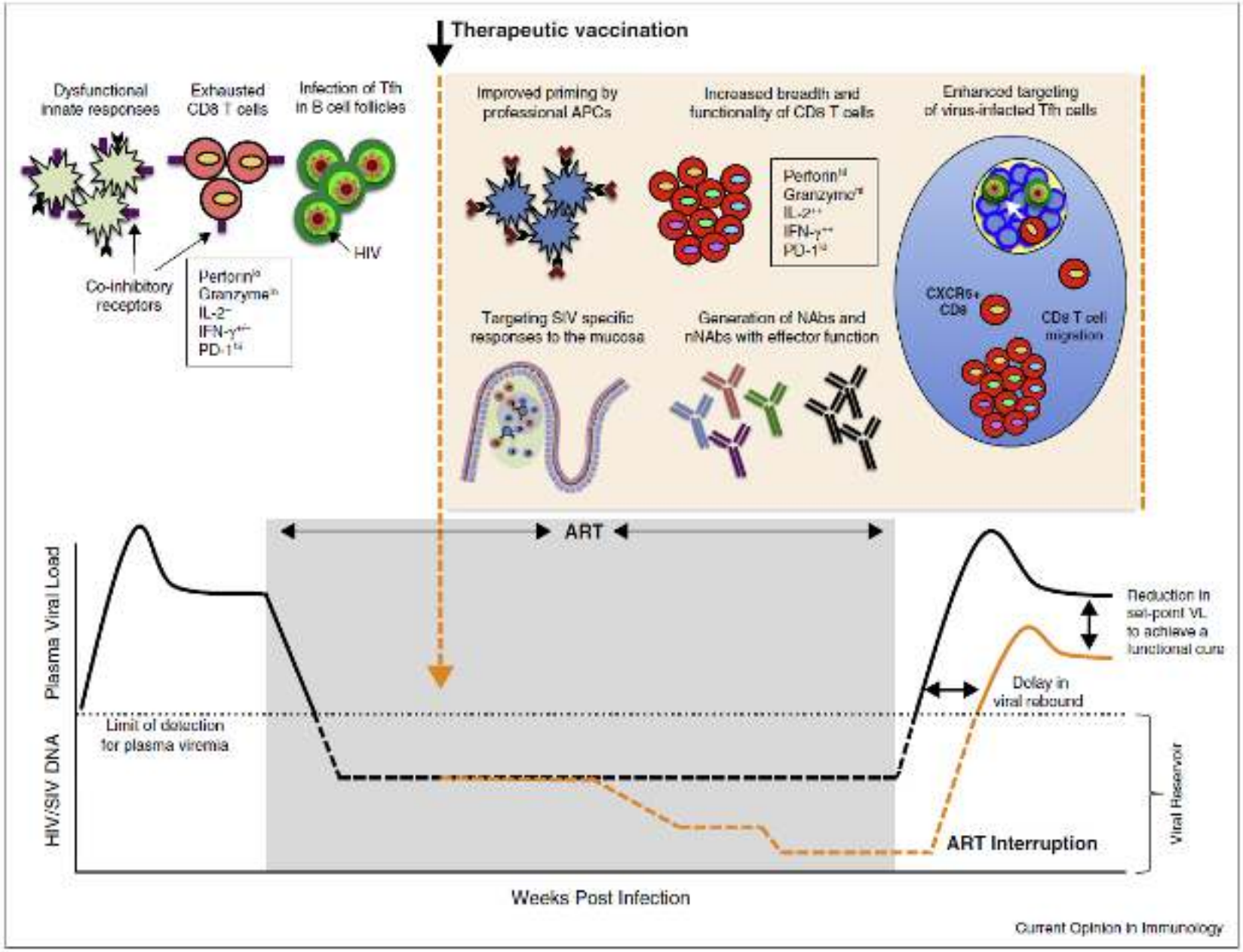
Terapötik aşı hedefleri:

- ✓ 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 T foliküler hücreleri hedef alacak) üretimi

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

Figure 1


Therapeutic vaccination
Dysfunctional innate responses
Exhausted CD8 T cells
Infection of Tfh in B cell follicles
HIV
Co-inhibitory receptors
Perforin^lo
Granzyme^lo
IL-2^-
IFN-γ^+/-
PD-1^hi
Improved priming by professional APCs
Increased breadth and functionality of CD8 T cells
Perforin^hi
Granzyme^hi
IL-2^++
IFN-γ^++
PD-1^lo
Enhanced targeting of virus-infected Tfh cells
CXCR5+ CD8
CD8 T cell migration
Targeting SIV specific responses to the mucosa
Generation of NAbs and nNAbs with effector function
ART
Plasma Viral Load
HIV/SIV DNA
Limit of detection for plasma viremia
Reduction in set-point VL to achieve a functional cure
Delay in viral rebound
ART Interruption
Viral Reservoir
Weeks Post Infection
Current Opinion in Immunology

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

Makak ve insan çalışmalarında

otolog virüs ya da virüsten türetilmiş lipopeptid sunan de pötik aşılar

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

nması

t

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

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 antikor bağımlı hücre aracılıklı 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?

Gen terapileri

Gen terapileri

- ✓Enfeksiyon ilişkili özgül genleri modifiye ederek hücreleri HTV'e c

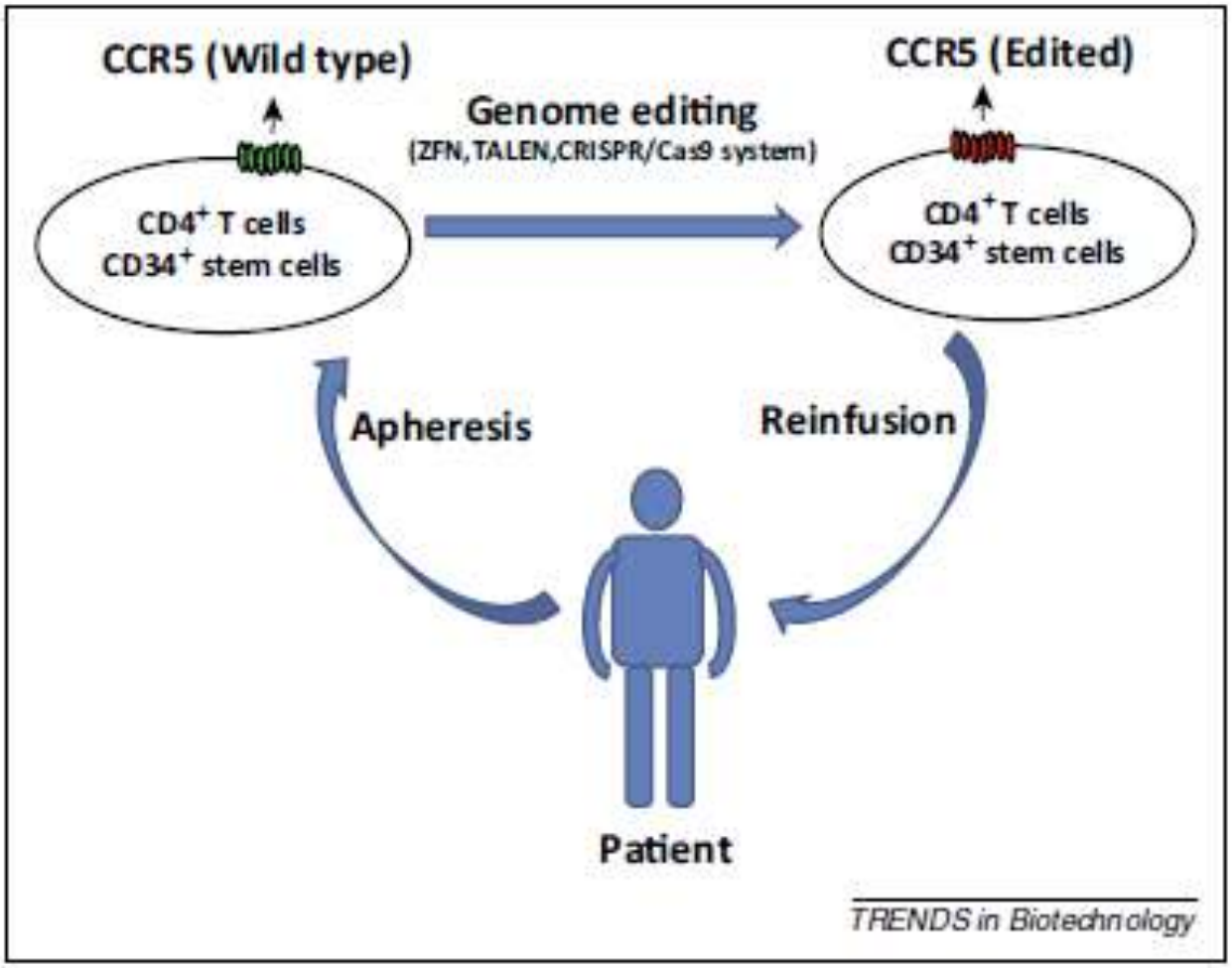
Hedef: Steril ya da fonksiyonel kür

Ken
hüc
düşük düzeylerde virüs varlığında bile)

- ✓Entegre olan provirüsün eksizyonu

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

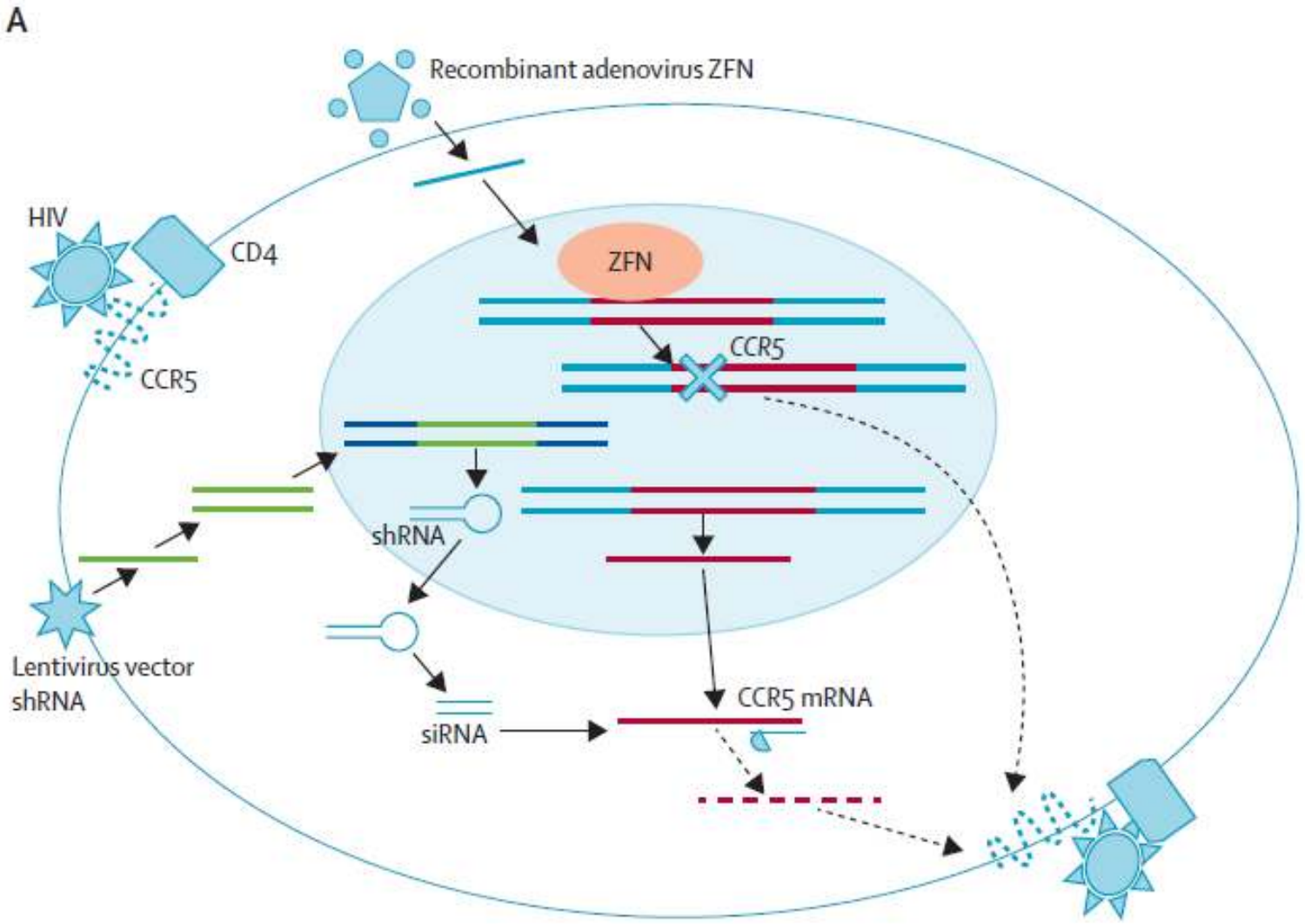
HIV enfeksiyonuna ya da replikasyona dirençli hücre üretimi



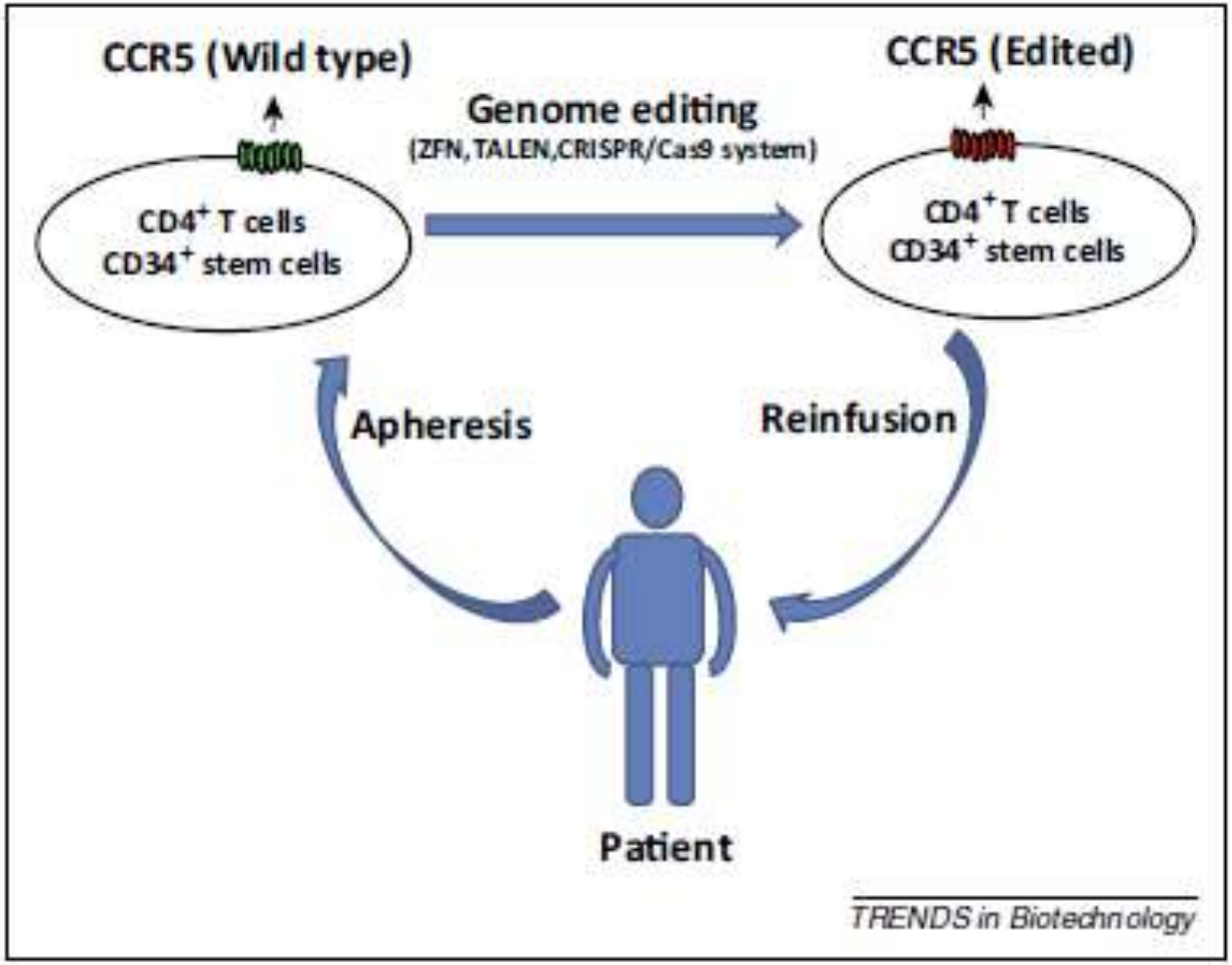
CCR5 geninde
32 bp'lik delesyon
⇩
doğal direnç

Orijinal HIV'e duyarlı hücrelerin eradikasyonu için kemoterapi gerekli

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



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


CCR5 (Wild type)
CCR5 (Edited)
Genome editing
(ZFN, TALEN, CRISPR/Cas9 system)
CD4+ T cells
CD34+ stem cells
CD4+ T cells
CD34+ stem cells
Apheresis
Reinfusion
Patient
TRENDS in Biotechnology

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

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ART altındaki aviremik 12 hastaya ZFN ile modifiye otolog CD4 hücre infüzyonu

BACKGROUND

CCR5 is the major coreceptor for human immunodeficiency virus (HIV). We investigated 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.

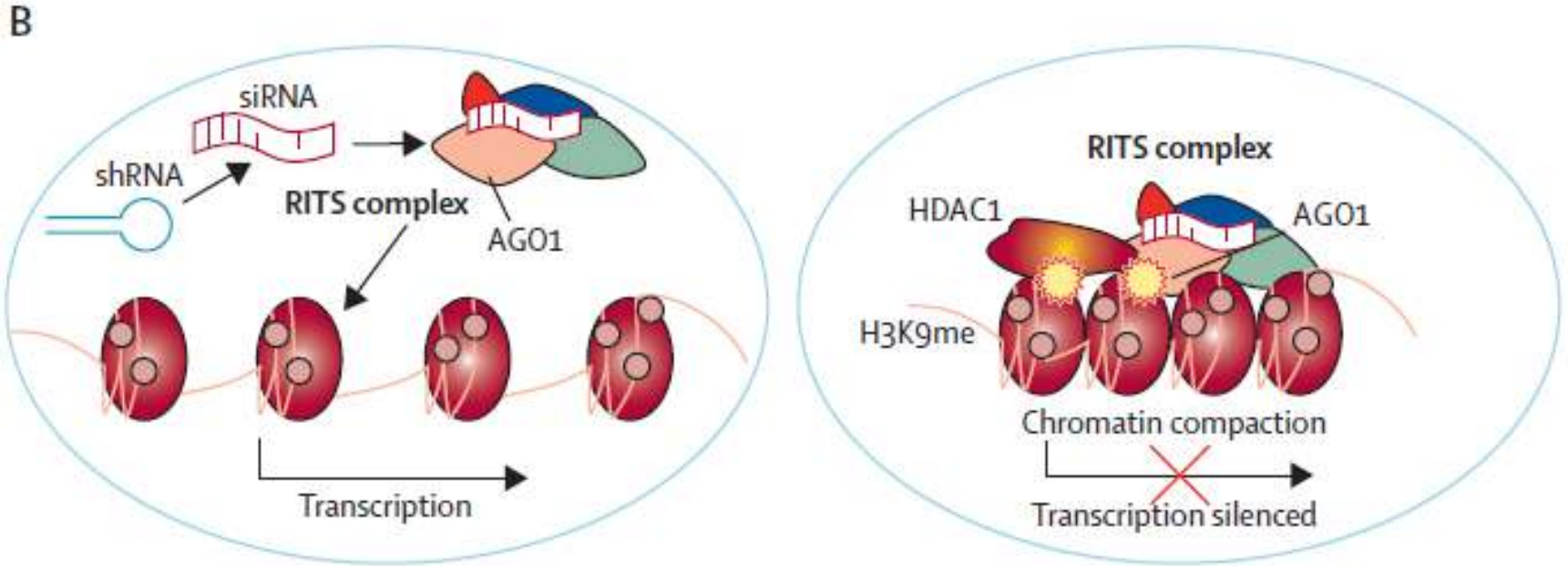
ART kesilmesinden sonra HIV DNA ⇩
CD4 hücre sayısı ⇧
1 hastada HIV RNA saptanamadı

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.)

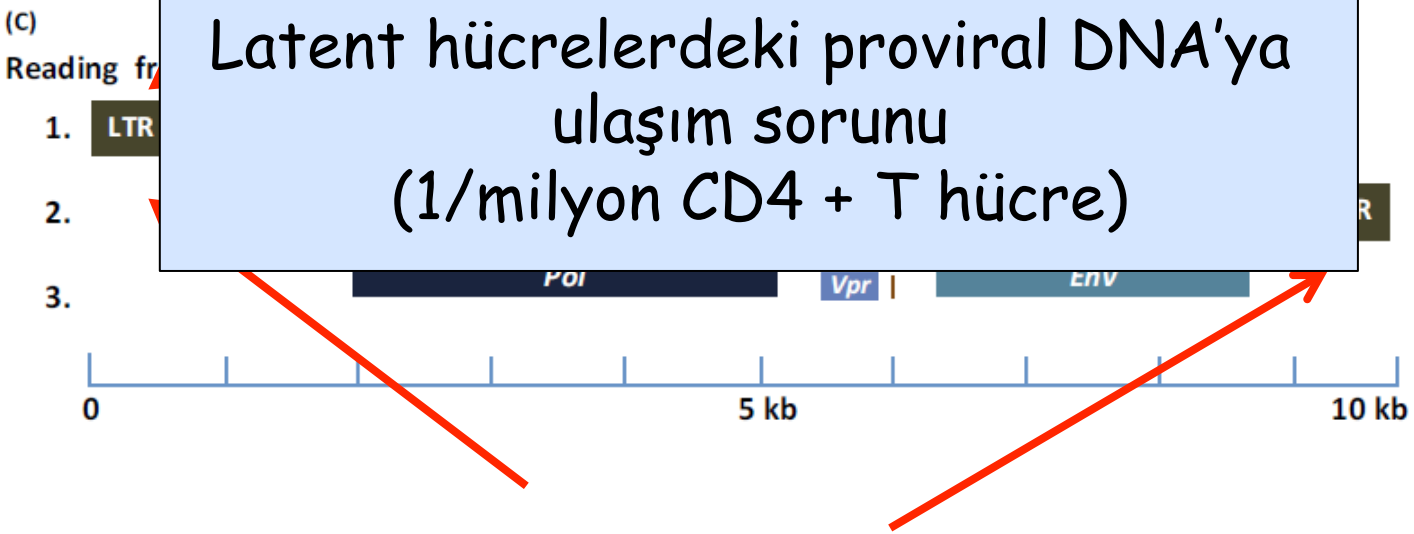
Alternatif gen terapisi:latentliği sağlamak
siRNA ve shRNA'nın entegre viral genomda epigenetik değişikliklere yol açması



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

Proviral DNA eliminasyonu

ZFN



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

CRISPR/Cas9

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

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...

Table 1. Current clinical trials in the field of HIV cure research

Trial (Clinicaltrials.gov identifier)	Location	Phase	Intervention
Chronic HIV infection[a]			
Towards HIV functional cure – ULTRASTOP (NCT01876862)	France	NA	A pilot study evaluating the maintenance of viral suppression after 24 weeks of therapeutic interruption in chronic HIV-1 infected patients with a low circulating HIV-DNA reservoir
ACTG A5308 (NCT01777997)	USA	IV	Single-arm, open-label study to evaluate the effect of fixed-dose TDF/FTC/RPV on T-cell activation, absolute $CD4^+$ count, inflammatory biomarkers and viral reservoir in treatment-naïve HIV-1 controllers
[a]New era study: treatment with multidrug class (MDC) HAART in HIV-infected patients	Germany	III	A multicentre, open-label, nonrandomized trial to evaluate treatment with MDC HAART and its impact on the decay of latently infected $CD4^+$ T cells
Effect of a CCR5 co-receptor antagonist on the latency and reservoir of HIV-1 (NCT00795444)	Spain	II	Pilot study of the effect of maraviroc on the latency and reservoir of HIV-1 in patients taking highly active antiretroviral therapy
Acute HIV			
Antiretroviral therapy for acute HIV infection (NCT00796626)	Thailand	III	This is a protocol designed to randomize subjects with acute HIV infection to receive standard HAART (TDF/FTC/EFV) or mega-HAART (TDF/FTC/EFV and MVC and RAL) for participants who are enrolled in SEARCH 010 study
Early cART and cART in combination with autologous HIV-1-specific CTL infusion in the treatment of acute HIV-1 (NCT02231281)	China	III	The purpose of this study is to assess the ability of the early initiation of cART or cART in combination with autologous HIV-1-specific cytotoxic T lymphocyte (CTL) infusion achieve a posttreatment control amongst treatment-naïve acute HIV-1

Thornhill J, et al. Curr Opin Infect Dis 2015 Feb;28(1):1-9.

Those with [a]below also have an acute infection arm

Antibody trials[a]			
3BNC117 – broadly neutralizing monoclonal antibody (NCT02018510)	USA	I	A phase 1, open-label, dose-escalation study of the safety, pharmacokinetics and antiretroviral activity of 3BNC117 (broadly neutralizing) monoclonal antibody in HIV-infected and HIV-uninfected volunteers
BMS-936559 – anti-PD L1 (NCT02028403)	USA	I	This study will evaluate the safety, PK data, and immune response to BMS-936559 (administered by intravenous infusion), in HIV-infected people receiving cART viral load less than 50
VRC 601 – broadly neutralizing monoclonal antibody (NCT01950325)	USA	I	This is the first clinical trial of the VRC-HIVMAB060-00-AB (VRC01) monoclonal antibody. This is a dose-escalation study to examine safety, tolerability, dose and pharmacokinetics of VRC01
[a]CHERUB 001 – intravenous immunoglobulin	UK	I	A proof-of-concept study examining the effect of high dosage IVIG in ART-treated acute infection on the $CD4^+$ T-cell HIV reservoir
Latency reserving agents			
Vorinostat: HDACi (NCT01365065)	Australia	II	To assess safety and effect on HIV transcription of vorinostat in patients receiving suppressive cART
Vorinostat: HDACi (NCT01319383)	USA	I/II	A study of the effect of vorinostat on HIV RNA expression in resting $CD4^+$ T cells of HIV-infected patients receiving stable antiretroviral therapy
Disulfiram (NCT01944371)	USA	I/II	To determine the safety, pharmacology and bioactivity of disulfiram in treated HIV-infected adults. The primary hypothesis is that 3 days of disulfiram will result in an increase in HIV transcription in $CD4^+$ T-cells
Poly-ICLC: TLR-3 agonist (NCT02071095)	USA	I/II	Investigating the adjuvant, Poly-ICLC to establish if it is safe and well tolerated in HIV-1-infected patients on combination antiretroviral therapy
ALT-803: recombinant human super agonist interleukin-15 complex (NCT02191098)	USA	I	Proof-of-principle study of pulse dosing of IL-15 to deplete the reservoir in HIV-infected people on optimized ART with undetectable plasma HIV RNA
Romidepsin: HDACi (NCT01933594)	USA	I/II	A study of single-dose romidepsin in HIV-infected adults with suppressed viraemia on cART to assess safety, tolerability, and activation of HIV-1 expression

Thornhill J, et al. Curr Opin Infect Dis 2015 Feb;28(1):1-9.

Gene therapy			
Cal-1: Safety study of a dual anti-HIV gene transfer construct Cal-1 to treat HIV-1 infection (NCT01734850)	USA	I/II	A study looking at whether an experimental gene transfer agent, LVsh5/C46 (also known as Cal-1), can inhibit HIV infection by removing CCR5 from bone marrow and WBCs, and producing a protein named C46.
VRX496: Tolerability and therapeutic effects of repeated doses of autologous T cells with VRX496 in HIV (NCT00295477)	USA	I/II	An open-label study to evaluate the tolerability, trafficking and therapeutic effects of repeated doses of autologous T cells transduced with VRX496 in HIV-infected individuals.
MazF-T: Redirected MazF CD4 autologous T cells for HIV gene therapy (NCT01787994)	USA	I	Evaluate the safety and immunogenicity of autologous CD4 T cells modified with a retroviral vector expressing the MazF endoribonuclease gene in HIV^+ patients.
SB-728-T: Dose-escalation study of autologous T-cells genetically modified at the CCR5 gene by zinc finger nucleases (NCT01044654)	USA	I	Dose-escalation study of autologous T-cells genetically modified at the CCR5 gene by zinc finger nucleases SB-278 in HIV-infected patients who have exhibited suboptimal $CD4^+$ T-cell gains during long-term cART.

Thornhill J, et al. Curr Opin Infect Dis 2015 Feb;28(1):1-9.

Novel combination therapies[a]			
[a]RIVER: Research In Viral Eradication of HIV Reservoirs. Safety and efficacy of the HDACi vorinostat and a prime boost vaccine	UK	II	An study to evaluate the safety and effect of therapeutic HIV-1 immunization using a prime boost vaccine (ChAdV63.HIVconsv and MVA.HIVconsv, and vorinostat on viral reservoir in suppressed HIV-1 infected adults on 4 drug cART)
REDUC: Safety and efficacy of the HDACi romidepsin and vaccine Vacc-4x for reduction of latent HIV reservoir (NCT02092116)	Denmark	I/II	A study to evaluate the safety and effect of therapeutic HIV-1 immunization using Vacc-4x and rhuGM-CSF, and HIV-1 reactivation using romidepsin, on the viral reservoir in suppressed HIV-1-infected adults on cART
Repeat doses of SB-728mR-T (zinc finger nucleases) after cyclophosphamide conditioning (NCT02225665)	USA	I/II	The purpose of this study is to evaluate the safety and tolerability of repeat doses of autologous T-cells genetically modified at the CCR5 gene by zinc finger nucleases following cyclophosphamide conditioning.
Vacc-4x and lenalidomide vs. vacc-4x and placebo in HIV-1-infected ART (NCT01704781)	Germany	I/II	Vacc-4x is a peptide-based HIV immunotherapy aimed to strengthen the immune response to HIV p24. By adding lenalidomide, an immunomodulator, it is anticipated that the effect of Vacc-4x might be enhanced.
CD4-ZETA gene-modified T cells with and without exogenous IL-2 in HIV patients	USA	I/II	To determine the safety and activity of an experimental anti-HIV treatment using autologous CD4-zeta gene-changed T cells and IL-2

Thornhill J, et al. Curr Opin Infect Dis 2015 Feb;28(1):1-9.

2015 TOWARDS AN HIV CURE SYMPOSIUM

Abstract Book

18 & 19 July 2015
Vancouver, Canada

towards an HIV cure
people focused science driven

PE24

MG1 and VSVΔ51 viruses target and kill latently HIV-infected myeloid cells

Ranganath N.[1], Côté S.[2], Sandstrom T.[1], Angel J.[2,3]

[1]University of Ottawa, Biochemistry, Microbiology, Immunology, Ottawa, Canada, [2]Ottawa Hospital Research Institute, Infectious Disease, Ottawa, Canada, [3]The Ottawa Hospital, Infectious Disease, Ottawa, Canada

PE28

Universal Tre-recombinase (uTre) specifically targets the majority of primary HIV-1 isolates

Hauber I.[1], Karpinski J.[2], Schäfer C.[1,3], Chemnitz J.[1], Hofmann-Sieber H.[1], van Lunzen J.[3,4], Buchholz F.[2], Hauber J.[1,3]

[1]Heinrich Pette Institute, Antiviral Strategies, Hamburg, Germany, [2]TU Dresden, Medical Systems Biology, Dresden, Germany, [3]German Center for Infection Research (DZIF), Hamburg, Germany, [4]University Medical Center Hamburg-Eppendorf, Section Infectious Diseases, Hamburg, Germany

PE40

A novel TLR-9 agonist (MGN1703) activates NK-cells and enhances NK-cell mediated viral killing of HIV-1 infected CD4+ T-cells ex vivo

Offersen R., Tolstrup M., Nissen S.K., Rasmussen T., Østergaard L., Denton P.W., Søgaard O.S.
Aarhus University Hospital, Dept. of Infectious Diseases, Aarhus, Denmark

A first-in-human phase I/II trial demonstrates the safety and the immunogenicity of a lentiviralbased therapeutic HIV vaccine eliciting potent polyfunctional multispecific CD8 and CD4 Tcell responses in HIV-infected individuals

H. Toussaint, E. Sarry, A. Bejanariu, S. Agaugué, M. Rodriguez, E. Sabbah-Petrover, C. Bauche
Theravectys, Villejuif, France

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

Lancet HIV. 2016 Jan;3(1):e49-54. doi: 10.1016/S2352-3018(15)00232-5. Epub 2015 Dec 9.

HIV-1 virological remission lasting more than 12 years after interruption of early antiretroviral therapy in a perinatally infected teenager enrolled in the French ANRS EPF-CO10 paediatric cohort: a case report.

Frange P[1], Faye A[2], Avettand-Fenoël V[3], Bellaton E[4], Descamps D[5], Angin M[6], David A[6], Caillat-Zucman S[7], Peytavin G[8], Dollfus C[9], Le Chenadec J[10], Warszawski J[11], Rouzioux C[3], Sáez-Cirión A[12]; ANRS EPF-CO10 Pediatric Cohort and the ANRS EP47 VISCONTI study group.

Author information

Abstract

BACKGROUND: Durable HIV-1 remission after interruption of combined antiretroviral therapy (ART) has been reported in some adults who started treatment during primary infection; however, whether long-term remission in vertically infected children is possible was unknown. We report a case of a young adult perinatally infected with HIV-1 with viral remission despite long-term treatment interruption.

METHODS: The patient was identified in the ANRS EPF-CO10 paediatric cohort among 100 children infected with HIV perinatally who started ART before 6 months of age. HIV RNA viral load and CD4 cell counts were monitored from birth. Ultrasensitive HIV RNA, peripheral blood mononuclear cell (PBMC)-associated HIV DNA, HIV-specific T-cell responses (ie, production of cytokines and capacity to suppress HIV infection), reactivation of the CD4 cell reservoir (measured by p24 ELISA and HIV RNA in supernatants upon phytohaemagglutinin activation of purified CD4 cells), and plasma concentrations of antiretroviral drugs were assessed after 10 years of documented control off therapy.

FINDINGS: The infant was born in 1996 to a woman with uncontrolled HIV-1 viraemia and received zidovudine-based prophylaxis for 6 weeks. HIV RNA and DNA were not detected 3 days and 14 days after birth. HIV DNA was detected at 4 weeks of age. HIV RNA reached 2·17× 10(6) copies per mL at 3 months of age and ART was started. HIV RNA was undetectable 1 month later. ART was discontinued by the family at some point between 5·8 and 6·8 years of age. HIV RNA was undetectable at 6·8 years of age and ART was not resumed. HIV RNA has remained below 50 copies per mL and CD4 cell counts stable through to 18·6 years of age. After 11·5 years of control off treatment, HIV RNA was below 4 copies per mL and HIV DNA was 2·2 log10 copies per 10(6) PBMCs. The HLA genotype showed homozygosity at several loci (A*2301-, B*1503/4101, C*0210/0802, DRB1*1101-, and DQB1*0602-). HIV-specific CD8 T-cell responses and T-cell activation were weak.

INTERPRETATION: Findings from this case suggest that long-term HIV-1 remission is possible in perinatally infected children who receive treatment early, with characteristics similar to those reported in adult HIV post-treatment controllers. Further studies are needed to understand the mechanisms associated with HIV remission and whether early treatment of infected children might favour the conditions needed to achieve HIV control after treatment discontinuation.

FUNDING: Agence de recherche ANRS (France Recherche Nord & Sud Sida-HIV Hépatites).

Sonuç

- ✓ **HIV enfeksiyonu akılcı ART ile yönetilebilir kronik enfeksiyon**
- ✓ **Yeni ilaçlar**
- ✓ **Küre yönelik çalışmalar:**
  - Viral rezervuarın eradikasyonu
  - İmmünoterapi
  - Gen terapileri
  - Kombine tedaviler

TEŞEKKÜR EDERİM