

# HIV - Patogenez

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Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD

# HIV

- Retrovirus ailesi
- Lentivirus cinsi
- HIV-1 ve HIV-2
- HIV-1
  - 100 nm çapında
  - Lipit membran ile çevrili
  - 12-16 adet glikoprotein kompleksi bu membrana gömülmüş durumda

# Molecular epidemiology of HIV-1 genetic forms and its significance for vaccine development and therapy

Michael M Thomson, Lucía Pérez-Álvarez, and Rafael Nájera

*Lancet Infect Dis* 2002; 2: 461–71

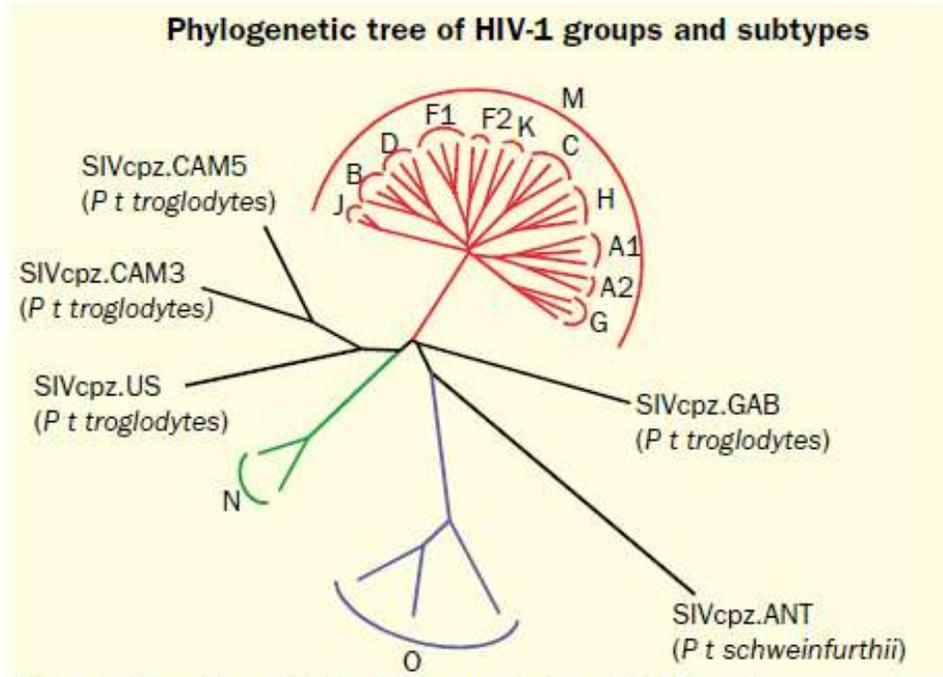


Figure 1. Neighbour-joining phylogenetic tree of full-length genome sequences of representative HIV-1 isolates from group M subtypes, group O and group N. SIV isolates from Pan troglodytes troglodytes (P t troglodytes) and Pan troglodytes schweinfurthii (P t schweinfurthii) chimpanzees are also included in the tree (indicated by SIVcpz followed by the name of the isolate).

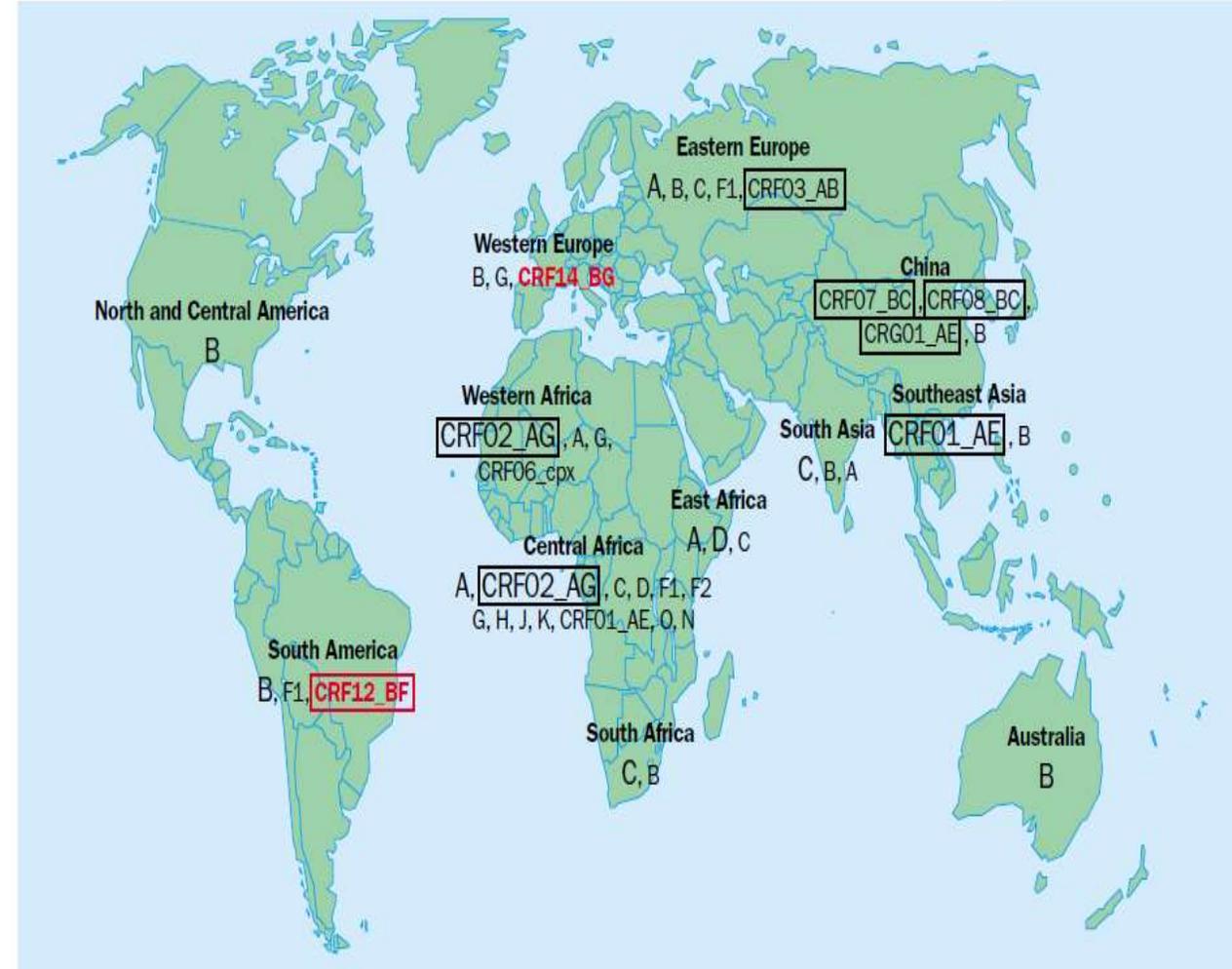


Figure 3. Geographical distribution of HIV-1 genetic forms circulating in different areas of the world. Genetic forms predominant in an area are shown in letters of larger size. The recently identified CRF12\_BF and CRF14\_BG are shown in red, and epidemiologically relevant CRFs are boxed.

# Diversity of HIV-1 Subtypes and Transmitted Drug-resistance Mutations Among Minority HIV-1 Variants in a Turkish Cohort

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Affiliations

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## Abstract

**Background:** The World Health Organization (WHO) recommends the surveillance of transmitted drug resistance mutations (TDRMs) to ensure the effectiveness and sustainability of HIV treatment programs.

**Objective:** Our aim was to determine the TDRMs and evaluate the distribution of HIV-1 subtypes using and compared next-generation sequencing (NGS) and Sanger-based sequencing (SBS) in a cohort of 44 antiretroviral treatment-naïve patients.

**Methods:** All samples that were referred to the microbiology laboratory for HIV drug resistance analysis between December 2016 and February 2018 were included in the study. After exclusions, 44 treatment-naive adult patients with a viral load of > 1000 copies/mL were analyzed. DNA sequencing for reverse transcriptase and protease regions was performed using both DeepChek ABL single round kit and Sanger-based ViroSeq HIV-1 Genotyping System. The mutations and HIV-1 subtypes were analyzed using the Stanford HIVdb version 8.6.1 Genotypic Resistance software, and TDRMs were assessed using the WHO surveillance drug-resistance mutation database. HIV-1 subtypes were confirmed by constructing a maximum-likelihood phylogenetic tree using Los Alamos IQ-Tree software.

**Results:** NGS identified nucleos(t)ide reverse transcriptase inhibitor (NRTI)-TDRMs in 9.1 % of the patients, non-nucleos(t)ide reverse transcriptase inhibitor (NNRTI)-TDRMs in 6.8 % of the patients, and protease inhibitor (PI)-TDRMs in 18.2 % of the patients at a detection threshold of  $\geq 1$  %. Using SBS, 2.3 % and 6.8 % of the patients were found to have NRTI- and NNRTI-TDRMs, respectively, but no major PI mutations were detected. M41L, L74I, K65R, M184V, and M184I related to NRTI, K103N to NNRTI, and N83D, M46I, I84V, V82A, L24I, L90M, I54V to the PI sites were identified using NGS. Most mutations were found in low-abundance (frequency range: 1.0 % - 4.7 %) HIV-1 variants, except M41L and K103N. The subtypes of the isolates were found as follows; 61.4 % subtype B, 18.2 % subtype B/CRF02\_AG recombinant, 13.6 % subtype A, 4.5 % CRF43\_02G, and 2.3 % CRF02\_AG. All TDRMs, except K65R, were detected in HIV-1 subtype B isolates.

**Conclusion:** The high diversity of protease site TDRMs in the minority HIV-1 variants and prevalence of CRFs were remarkable in this study. All minority HIV-1 variants were missed by conventional sequencing. TDRM prevalence among minority variants appears to be decreasing over time at our center.

RESEARCH ARTICLE

# Investigation of drug resistance against protease, reverse transcriptase, and integrase inhibitors by next-generation sequencing in HIV-positive patients

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## Abstract

Our aim was to investigate the mutations in protease (PR), reverse transcriptase (RT), and integrase (IN) gene regions in human immunodeficiency virus (HIV) using a single amplicon via next-generation sequencing (NGS). The study included plasma samples from 49 HIV-1-positive patients, which were referred for HIV-1 drug resistance testing during 2017. A nested polymerase chain reaction (PCR) was performed after the RNA extraction and one-step reverse transcription stages. The sequencing of the HIV genome in the PR, RT, and IN gene regions was carried out using MiSeq NGS technology. Sanger sequencing (SS) was used to analyze resistance mutations in the PR and RT gene regions using a ViroSeq HIV-1 Genotyping System. PCR products were analyzed with an ABI3500 GeneticAnalyzer (Applied Biosystems). Resistance mutations detected with NGS at frequencies above 20% were identical to the SS results. Resistance to at least one antiretroviral (ARV) drug was 22.4% (11 of 49) with NGS and 10.2% (5 of 49) with SS. At least one low-frequency resistance mutation was detected in 18.3% (9 of 49) of the samples. Low-frequency resistance mutations resulted in virological failure in only one patient. The cost of the analyses was reduced by sample pooling and multiplex analysis using the MiSeq system. This is the first study in Turkey to use NGS technologies for the detection of resistance mutations in all three gene (PR, RT, IN) regions using a single amplicon. Our findings suggest that NGS is more sensitive and cost-effective than the SS method.

**ORIGINAL ARTICLE**

# Molecular epidemiological analysis and investigation of antiretroviral drug resistance profile, including capsid inhibitors, among treatment-naïve individuals with HIV-1 in Türkiye

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**Funding information**

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**Abstract**

**Introduction:** Monitoring transmitted drug resistance is crucial for guiding first-line antiretroviral therapy (ART) and controlling the rising HIV epidemic in Türkiye. This study aimed to determine the prevalence of transmitted antiretroviral resistance to protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs) and capsid assembly inhibitors (CAIs). We also assessed the distribution of HIV-1 subtypes and circulating recombinant forms (CRFs) at one of the main national referral centres in Türkiye.

**Methods:** We included 104 consecutive ART-naïve people living with HIV who presented at Hacettepe University Hospital in Ankara between November 2021 and November 2022. Demographic data, probable transmission routes and geographic origins were recorded. HIV-1 genotyping was performed to identify subtypes and resistance-associated mutations using standard methods.

**Results:** Of the 104 individuals, 97 were from 25 different cities in Türkiye, while 7 originated from 5 different countries. The most probable transmission routes were men who have sex with men (MSM) (64.42%), heterosexual contact (30.77%) and unknown (4.81%). Resistance-associated mutations were detected in 14.42% of individuals. Resistance rates were 1.92% for PI, 4.80% for NRTI and 7.69% for NNRTI. No resistance mutations were found against INSTI or CAI.

**Conclusion:** Transmitted resistance to PI, NRTI and NNRTI remains present in Türkiye, though at moderate levels. The absence of resistance to INSTI and CAI supports their potential utility as effective components of treatment regimens in Türkiye.

Article

# Temporal Trends in HIV-1 Subtypes and Antiretroviral Drug Resistance Mutations in Istanbul, Türkiye (2021–2024): A Next-Generation Sequencing Study

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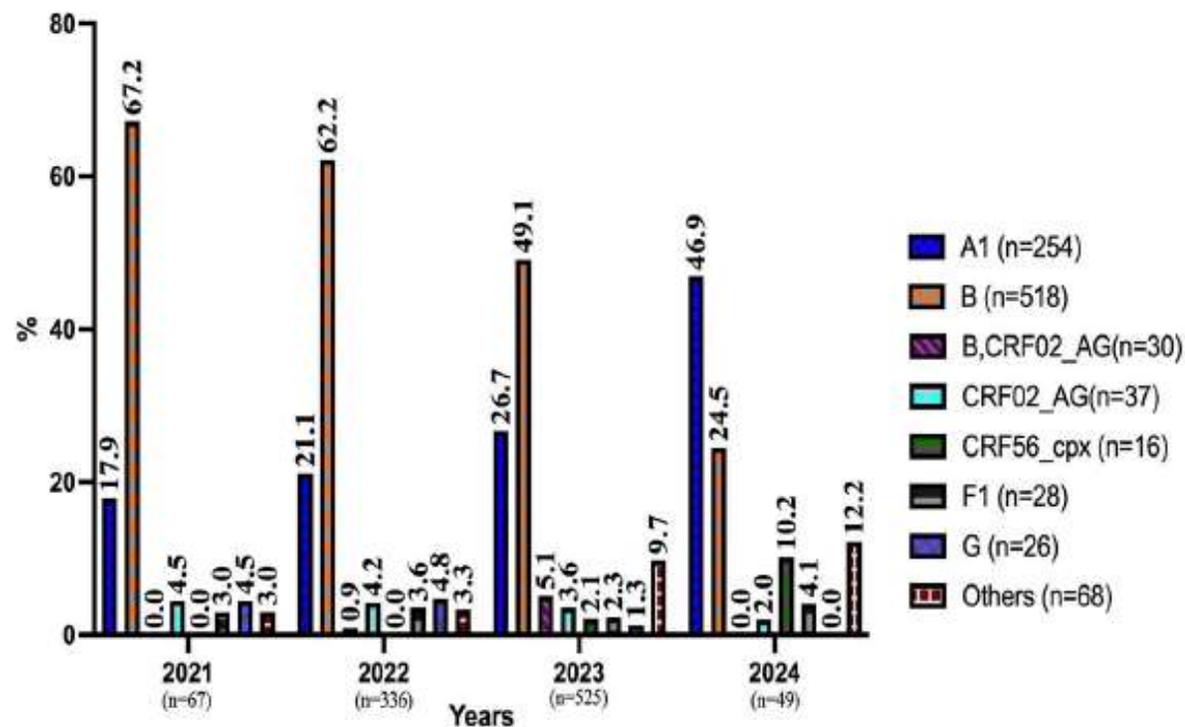


Figure 2. Changes in HIV-1 Subtypes Over The Years.

Subtype B (54.4%, 498/915) was the most frequently detected subtype in Turkish cases, and subtype A1 (43.5%, 27/62) in foreign cases. Subtype G was detected only in males. CRF56-cpx and F1 subtypes were not detected in foreign cases. Among the recombinant forms, CRF02\_AG was detected in 37 cases (3.8%) and CRF56 cpx in 16 cases (1.6%), respectively. In addition, the combination of subtype B and CRF02\_AG was detected in a total of 30 cases (3.1%) (Table 2).

Review

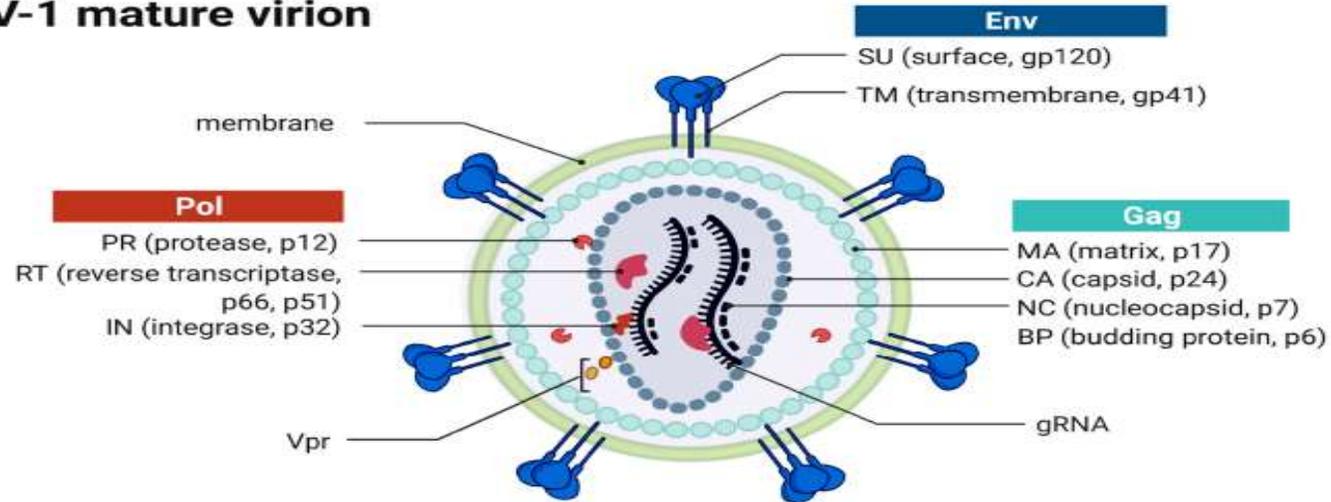
# Infectious RNA: Human Immunodeficiency Virus (HIV) Biology, Therapeutic Intervention, and the Quest for a Vaccine

Yasemin van Heuvel <sup>1,2</sup>, Stefanie Schatz <sup>1,2</sup>, Jamila Franca Rosengarten <sup>1,2</sup> and Jörn Stitz <sup>1,\*</sup>

## HIV-1 genome



## HIV-1 mature virion



**Figure 1.** HIV-1 genome and virion structure. (Top) Schematic overview of the genomic organization of the HIV-1 genome encompassing the open reading frames coding for the different structural, regulatory, and accessory proteins. The dimeric, linear gRNA is ~9 kb long and flanked by the 5'- and 3'-long terminal repeats (LTRs) that contain the viral promoter and sequences required for reverse

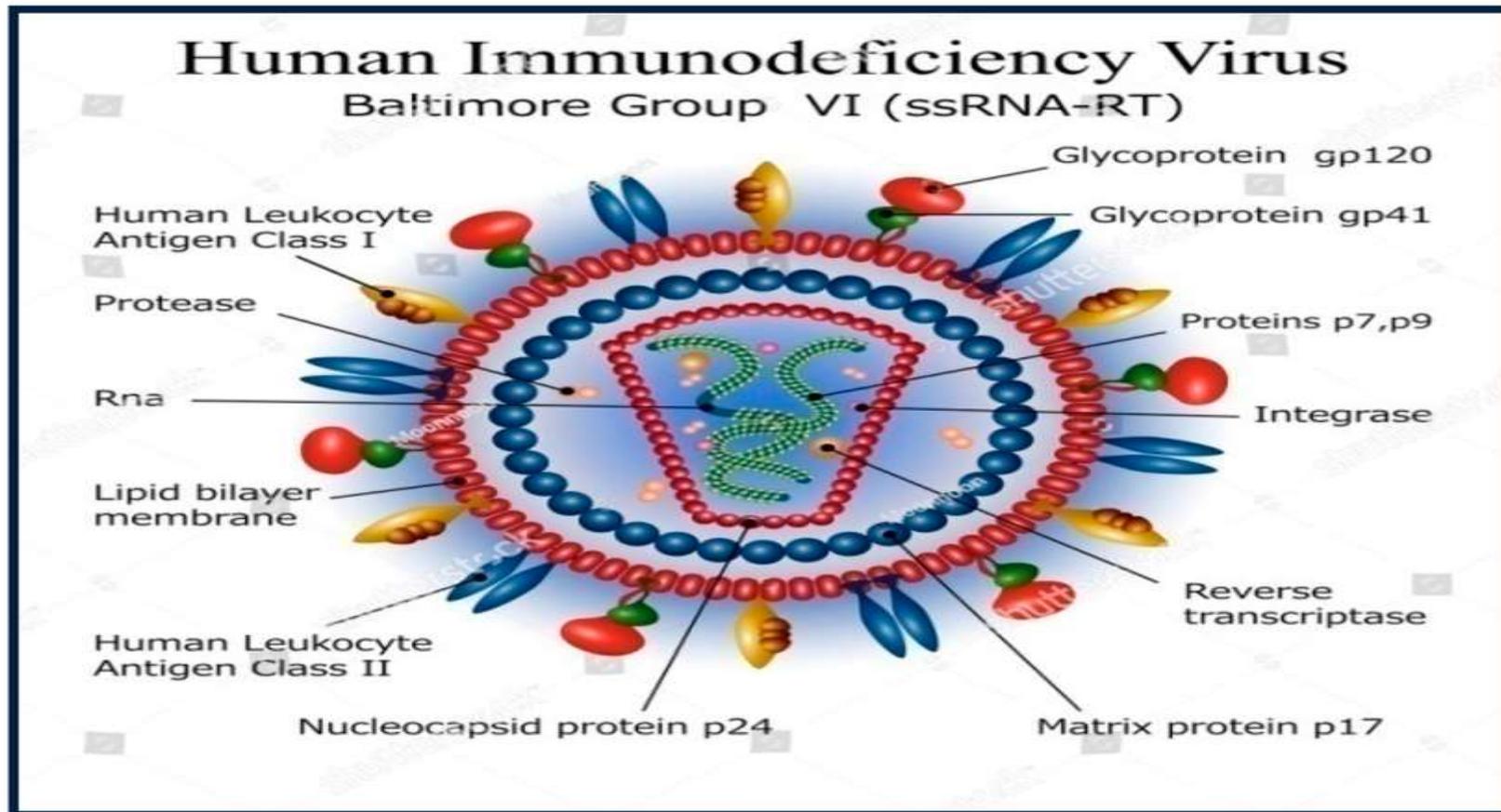
LTR: Transkripsiyonun regülasyonu ve integrasyon

# Viral Genler ve Proteinler

gag: yapısal proteinler(p24, p17, p7, p6)

env: yüzey proteinleri(gp41, gp120)

pol: reverse transkriptaz, proteaz, integraz

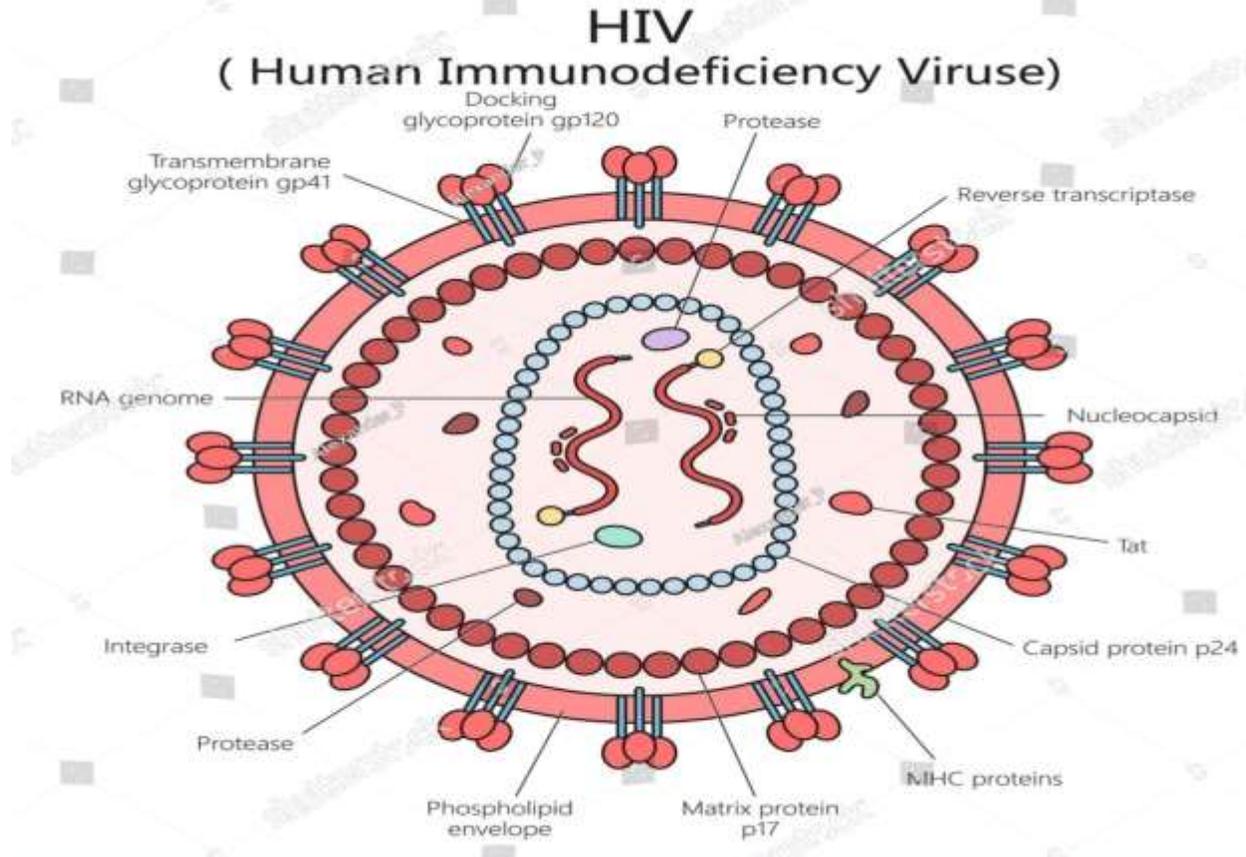


# Viral Genler ve Proteinler

tat, rev(düzenleyici genler) ve nef, vif, vpr, vpu(aksesuar genler)

Viral replikasyonda rol oynarlar

tat: viral replikasyonu başlatır



# Viral Genler ve Proteinler

rev: viral mRNA'nın nükleus'tan sitoplazmaya çıkarılması

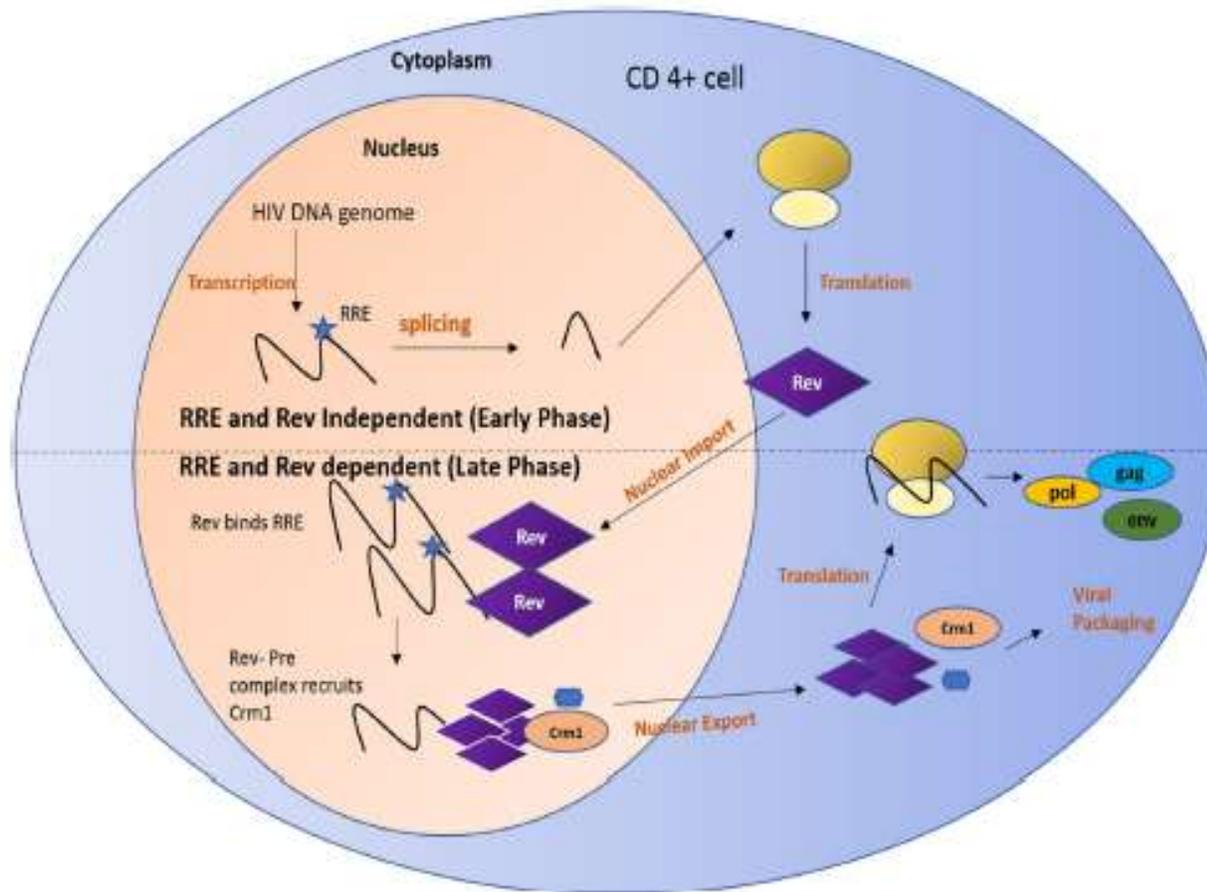


Fig. 1 An overview of the role of Rev protein in the HIV life cycle [22, 23]



# HIV-1 latency: From acquaintance to confidant

Chenbo Yang<sup>a,1</sup>, Ling Tong<sup>c,1</sup>, Jing Xue<sup>a,b,\*</sup>

C. Yang et al.

Journal of Virus Eradication 11 (2025) 100597

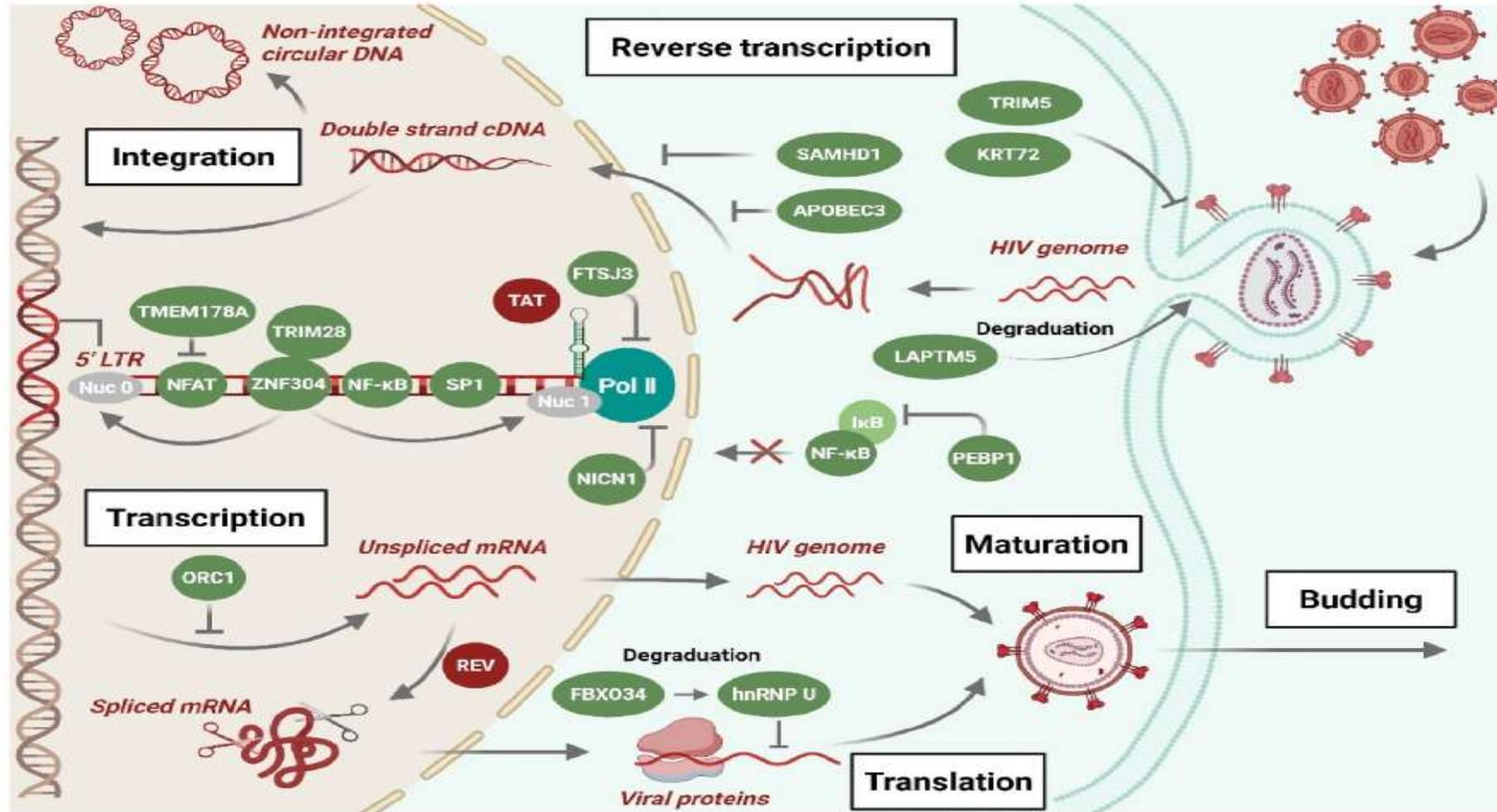
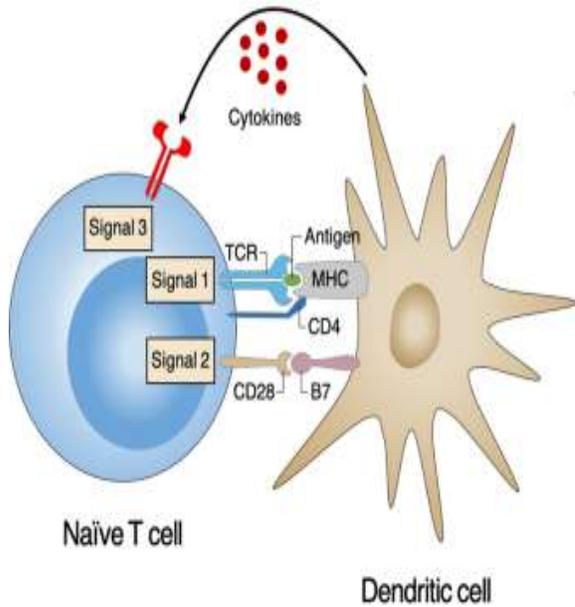


Fig. 2. Factors related to both the virus and the host are implicated in the maintenance and activation of reservoirs. Upon entering host cells, the viral RNA undergoes reverse transcription to form double-stranded complementary DNA (cDNA), referred to as provirus. The HIV provirus can integrate into the host genome and remain in a quiescent state. Upon activation, the viral genome is transcribed, leading to the production of mature viral particles. Various viral and host molecules may play a role at different stages of the HIV life cycle, influencing the maintenance or activation of the reservoirs.

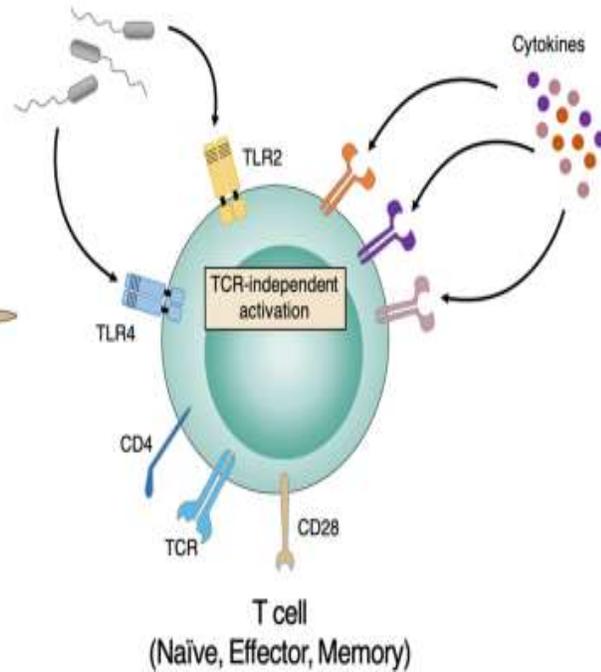
# Akut HIV-1 Enfeksiyonu

- Mukozal HIV-1 enfeksiyonunu takiben, virüs dendritik hücreler ve makrofajlar gibi myeloid hücreler tarafından alınır ve bu hücreler bölgesel lenf nodlarına gider
- Virüsü bölgesel lenf nodlarında CD4+ T hücrelerine transfer ederler
- SIV modellerinde enfekte dendritik hücreler 24 saat içinde lenf nodlarına ulaşmaktadır
- Virüs hızlı bir şekilde sekonder lenfoid organlara yayılır(lenf nodları, dalak, GALT)
- Sekonder lenfoid organlar tüm CD4+ T hücrelerinin %98'ini kapsar ve bu organlar yüksek düzey replikasyon yerleridir
- Bu durum çok sayıda organın(genital traktüs,MSS gibi) invazyonu ile sonuçlanır

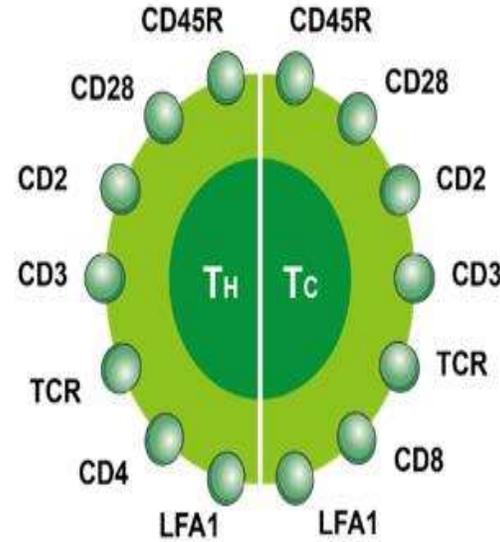
**a. Antigen-specific T cell activation**



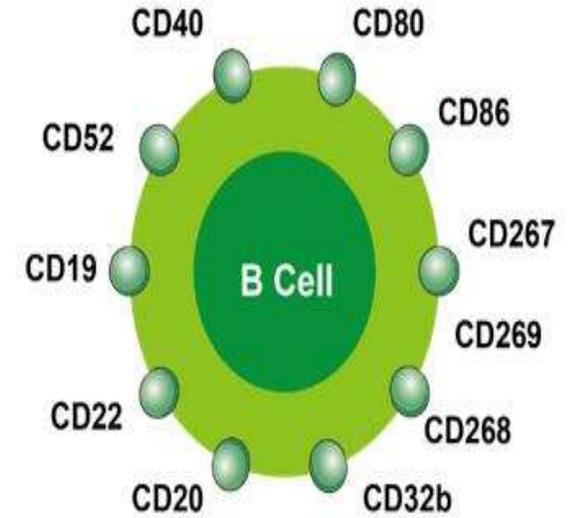
**b. Bystander T cell activation**



T cell CD antigen



B cell CD antigen

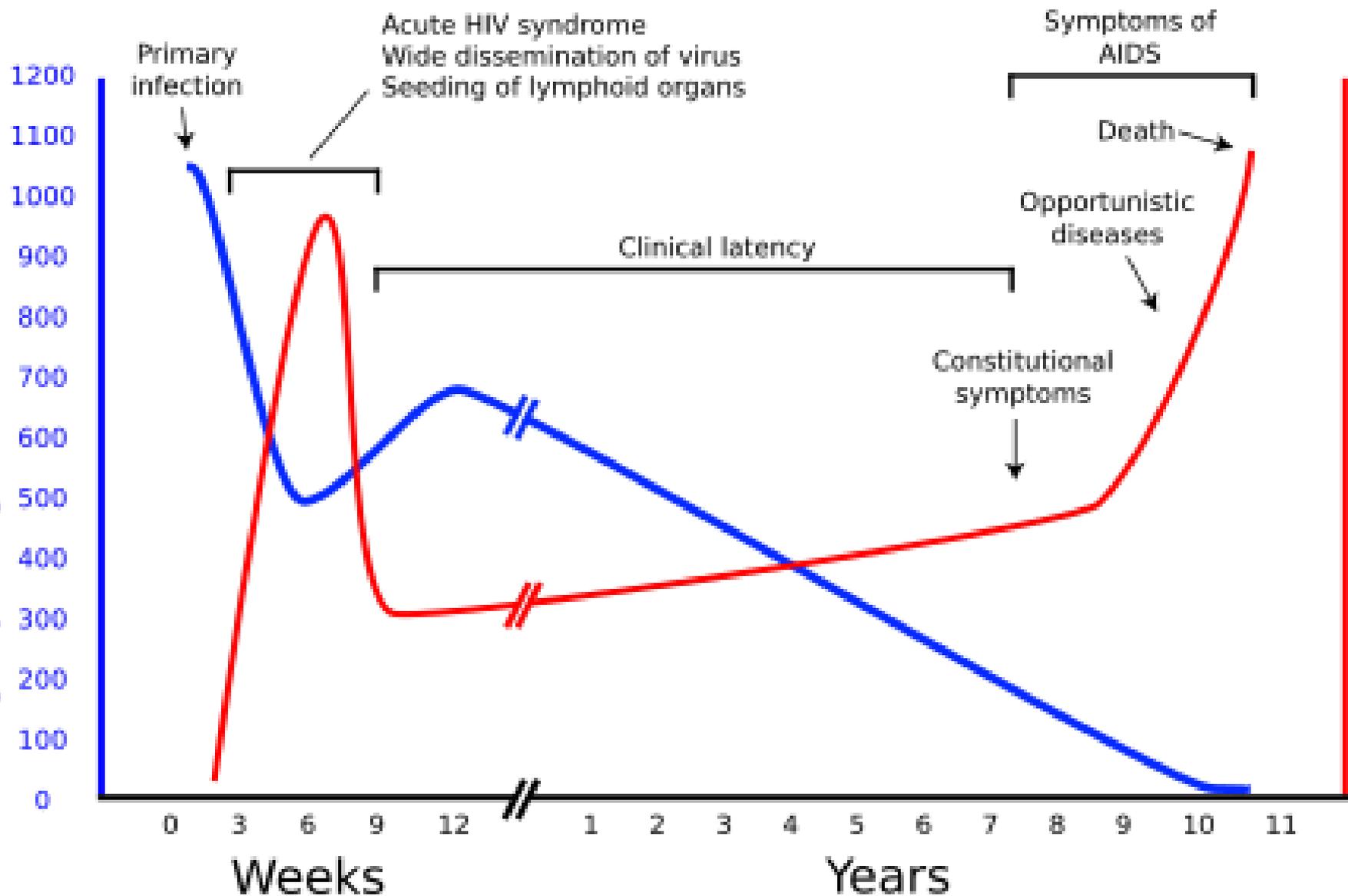


CD4 pozitif hücreler: T helper lenfositler, monositler , makrofajlar, dendritik hücreler ve MSS mikroglial hücreler

# Akut HIV-1 Enfeksiyonu

- AHI sırasında makrofajlar ve dendritik hücreler gibi myeloid hücreler ilk defans çizgisini oluştururlar
- Bu hücreler IFN- $\alpha/\beta$  ile antiviral yanıt verirler ve adaptif immüniteyi başlatırlar(viral antijenleri T ve B hücrelerine sunarak)
- CD4+ Th(özellikle Th1) ve CD8+ T hücre yanıtları AHI sırasında viral replikasyonun kontrolünde anahtar rol oynarlar
- Sitokin fırtınası HIV-1'e özgü ve özgü olmayan B ve T hücrelerinde apoptozisi indükler
- Bu yanıt T hücrelerinin tükenmesi ve yaşlanmasına, T ve B hücrelerinin GALT'da depleksiyonuna ve sonuçta özellikle kronik enfeksiyon döneminde foliküler hiperplazi, lenfoid dokularda immün tükenme, lenf nodu fibrozu, Treg proliferasyonu ve mikrobiyal translokasyona yol açar
- AHI'de bu immün yanıtlar kısmen viral kontrole(viral set point) neden olur

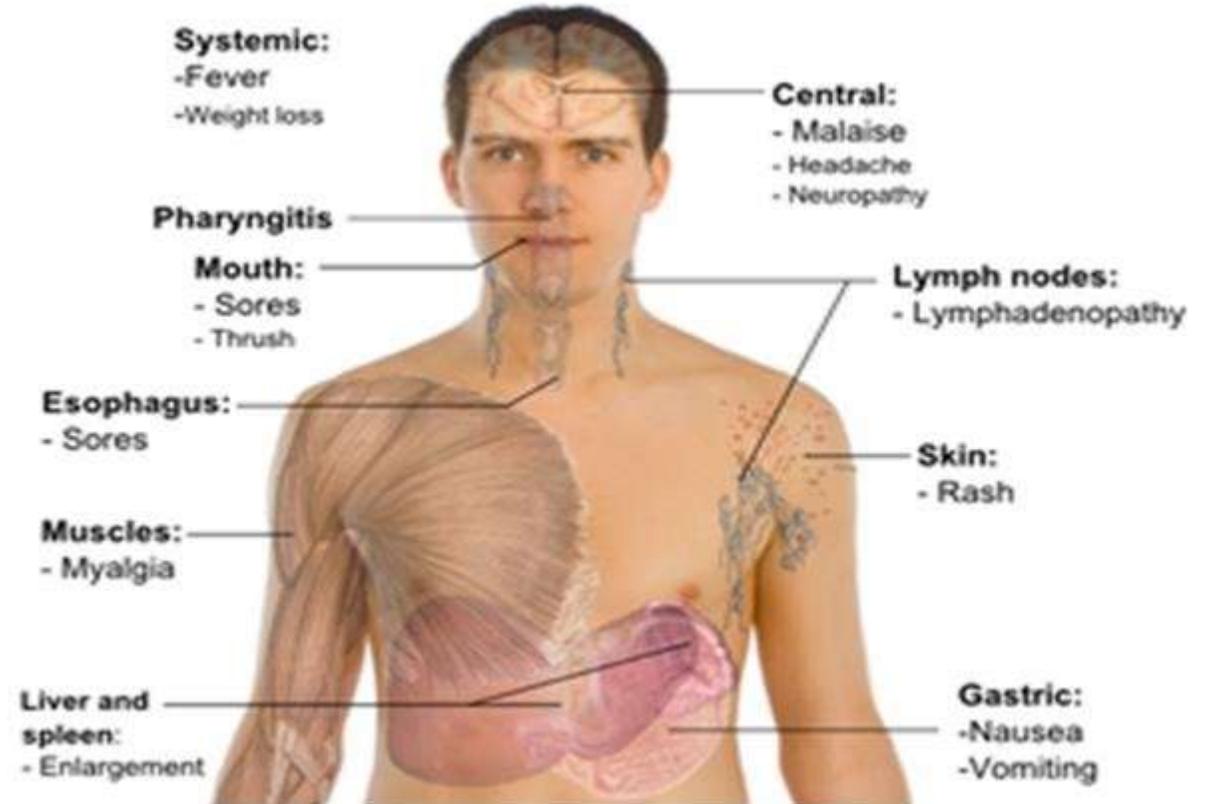
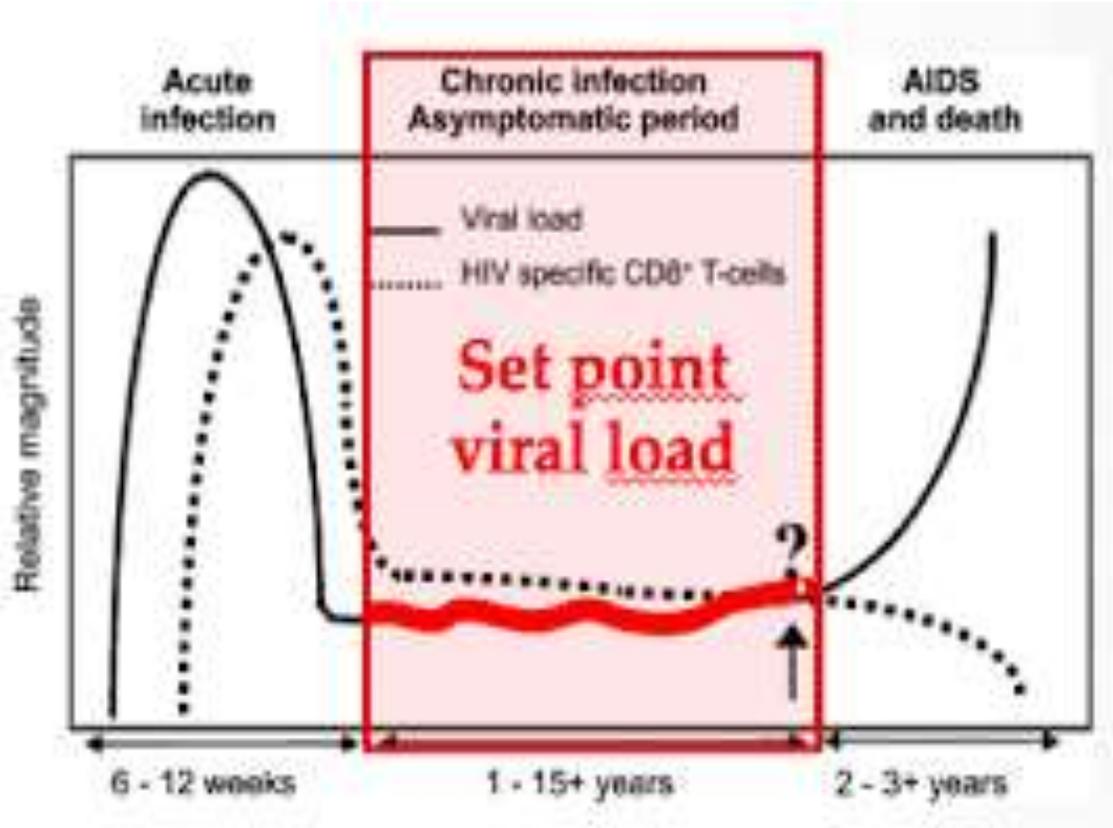
CD4+ Lymphocyte Count (cells/mm<sup>3</sup>)



HIV RNA Copies per mL plasma

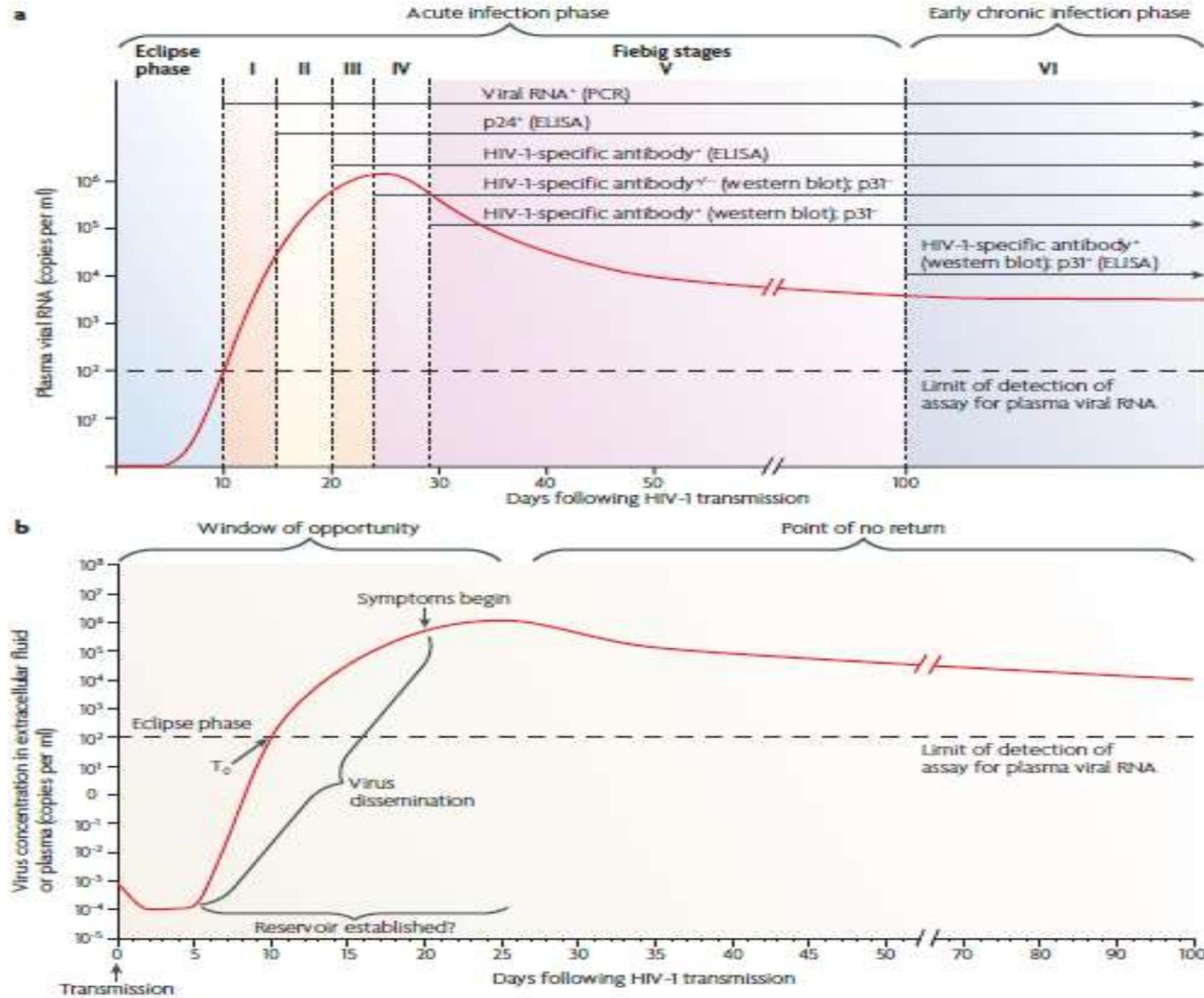
# Akut HIV-1 Enfeksiyonu

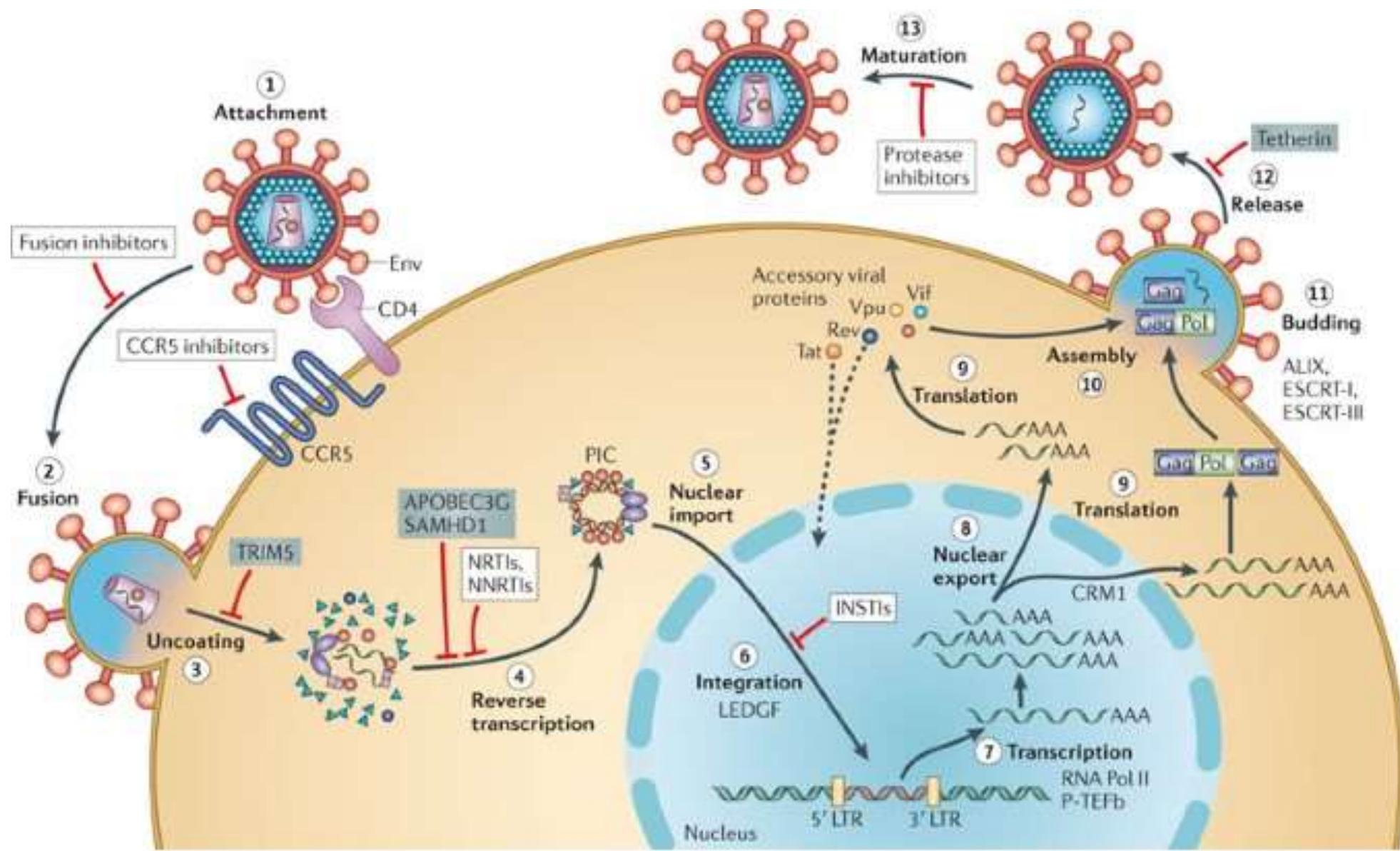
- 2-4 hafta içinde HIV-1 RNA tepe değerine ulaşır
- AHI'da viral replikasyon aktif CD4+ T hücrelerinde gerçekleşir
- PBMC'deki HIV-1 DNA rezervuar büyüklüğü ile ilişkili klinik belirteç

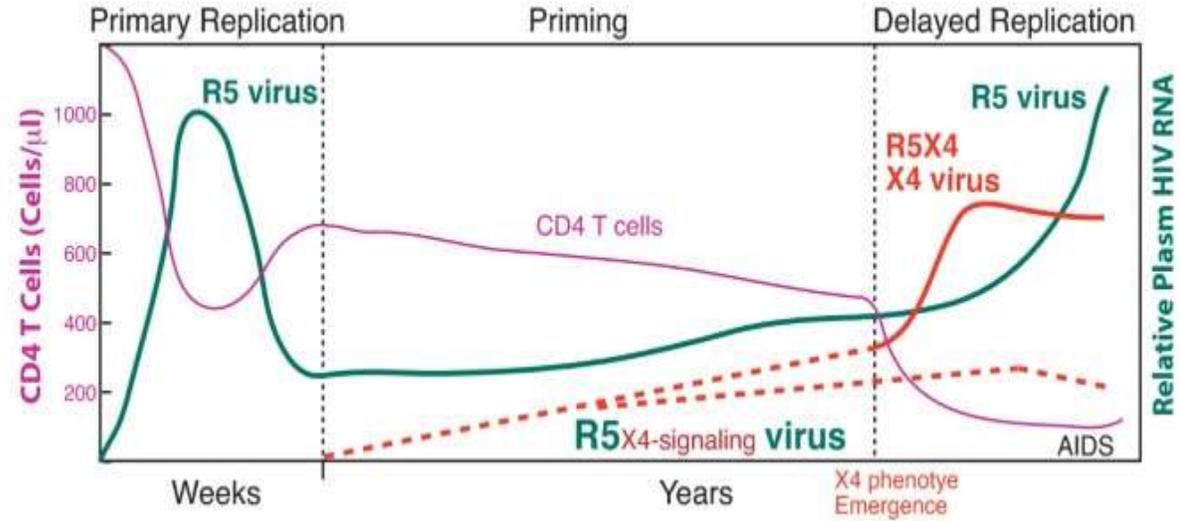
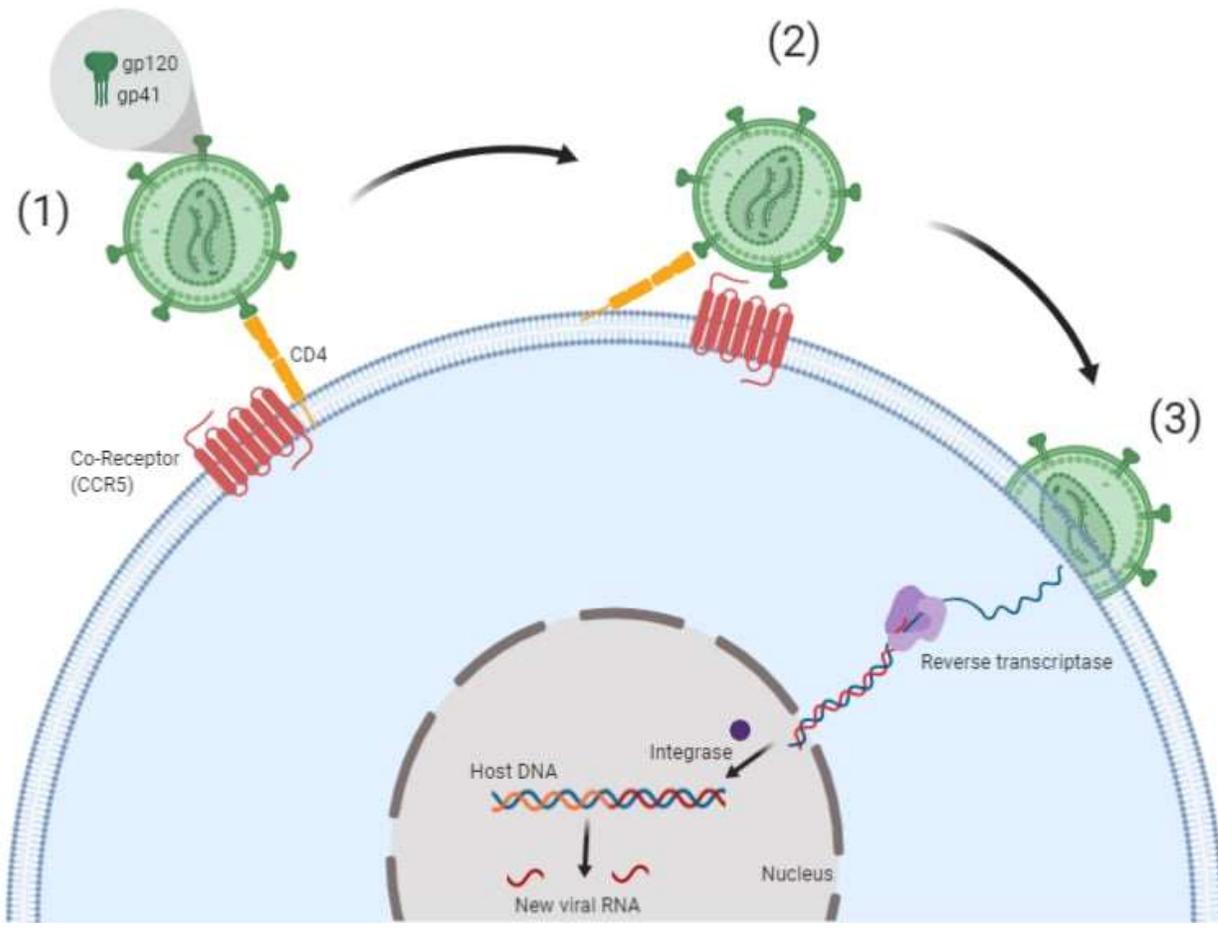


# The immune response during acute HIV-1 infection: clues for vaccine development

Andrew J. McMichael\*, Persephone Borrow<sup>†</sup>, Georgia D. Tomaras<sup>§</sup>,







CCR5: Hafıza T hücreleri, makrofajlar, dendritik hücreler

CXCR4: Naif T hücreleri

CCR5(R5 tropik), CXCR4(X4 tropik), dual tropizm

Primer HIV-1 enfeksiyonu, enfeksiyonun başlangıç fazında R5 tropik virüsler ile oluşur

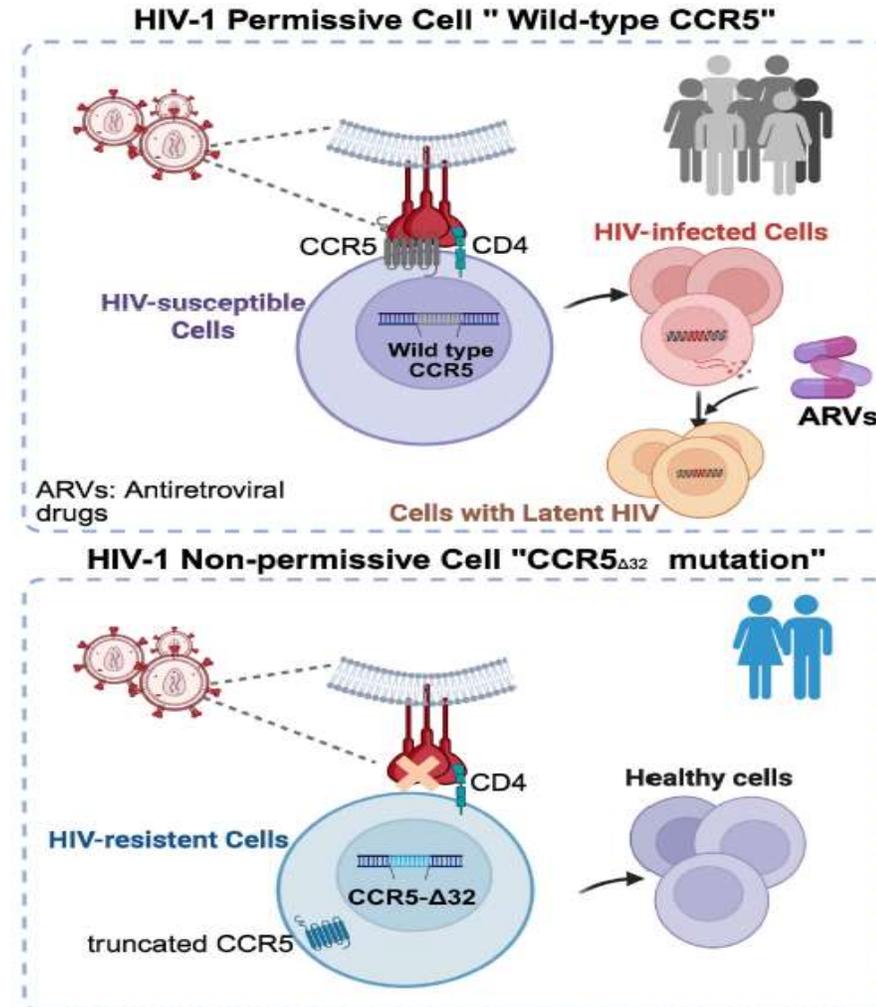
Enfeksiyonun gidişi sırasında hastalık progresyonu ile birlikte tropizm X4 tropik virüslere döner

# CCR5

- CCR5 genindeki delesyon (CCR5  $\Delta$ 32) CCR5 molekülünün fonksiyonunu kaybetmesine neden olur
- Homozigot CCR5  $\Delta$ 32(beyaz ırkta %1): Dirençli
- Heterozigot CCR5  $\Delta$ 32(%10 - Avrupa): Düşük düzey viremi ve yavaş hastalık progresyonu

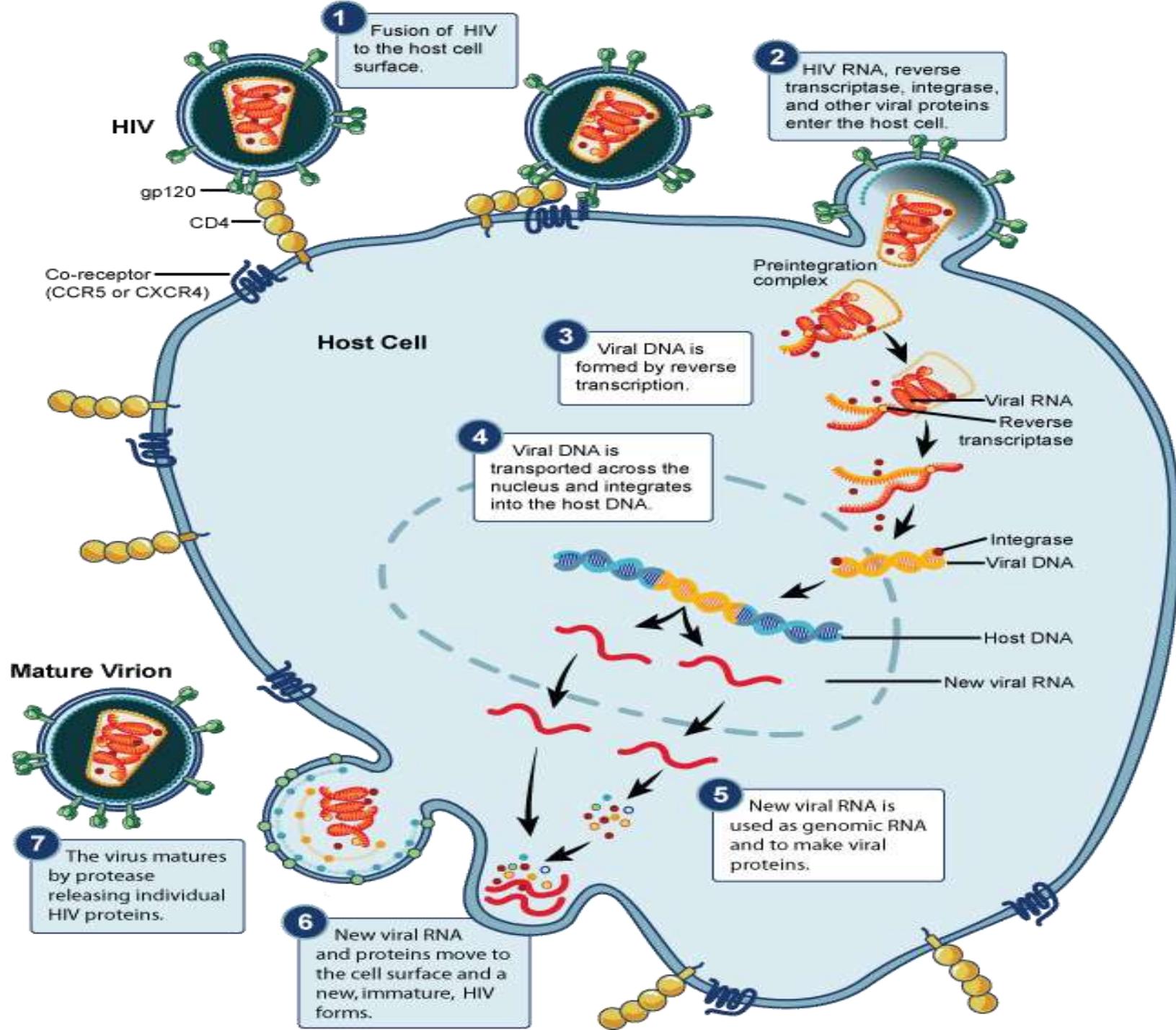
## Searching for a HIV-1 Cure

Chen Zhang<sup>#</sup>, Bharat N. Chaudhary<sup>#</sup>, Mohammad Uzair Ali<sup>#</sup>, Mary G. Hesar, Swara S. Patel, Xiaoqing Du, Soumya S. Dey, R. Lee Mosley, Sudipta Panja<sup>✉</sup>, Howard E. Gendelman<sup>✉</sup>

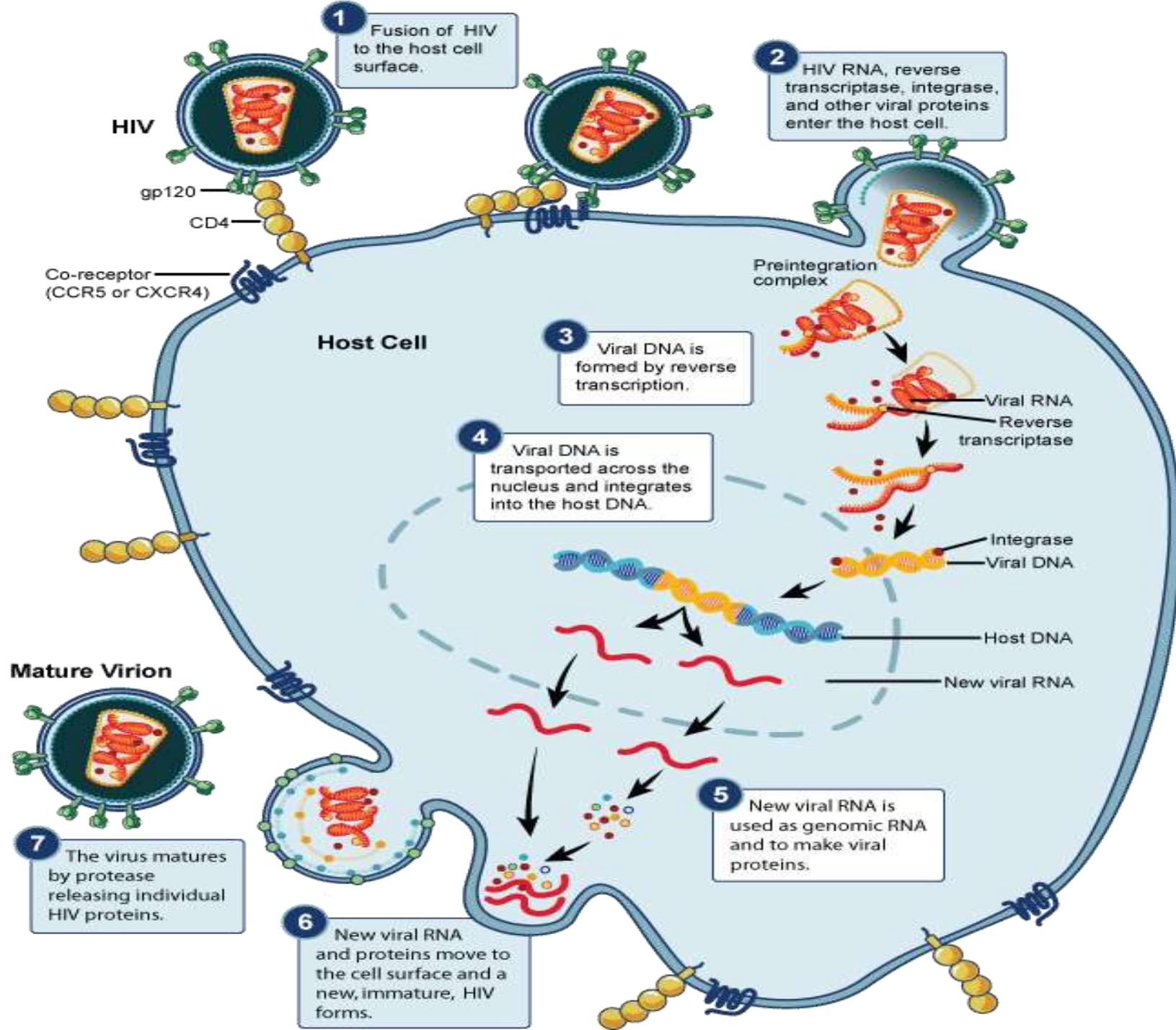


**Figure 3. CCR5- $\Delta$ 32 mutation confers resistance to HIV-1 infection.** Wild-type CCR5 (top panel): CCR5 is one of two co-receptors required for HIV entry. The HIV envelope protein, gp120, first binds to the CD4 receptor on the surface of susceptible T cells and macrophages. This binding induces a conformational change in gp120, exposing a binding site for CCR5. Subsequent interaction with CCR5 triggers gp120 to unfold and expose its hydrophobic fusion peptide, which inserts into the host membrane. This facilitates fusion of viral and host membranes, allowing viral entry. CCR5- $\Delta$ 32 mutation (bottom panel): This 32-base-pair deletion leads to a frameshift that produces a non-functional CCR5 protein that is retained in the endoplasmic reticulum, preventing its expression on the cell surface. As a result, R5-tropic HIV strains cannot infect CD4<sup>+</sup> T cells and myeloid cells. Individuals with homozygous CCR5- $\Delta$ 32/ $\Delta$ 32 genotypes exhibit near-complete protection from HIV-1 infection, whereas heterozygous individuals show reduced viral susceptibility. The discovery of the CCR5- $\Delta$ 32 mutation has inspired gene-editing and therapeutic strategies aimed at blocking or mutating the CCR5 receptor to achieve viral elimination. Created with BioRender.com.

- Füzyon sonrası viral kapsid sitozole girer
- Sitozolde viral RNA RT enzimi aracılığı ile çift iplikli DNA'ya dönüşür
- Bu dönüşüm sürecinde sekans mutasyonları oluşur(replikasyon başına HIV-1 genomu için 5-10 arası hata) ve viral genomda defektler meydana gelir
- Bunun sonucunda yakın olarak ilişkili farklı viral varyantlar oluşur(**quasispecies**) ve bunlar ART direncine veya immün yanıtı karşı dirence neden olabilir
- Kapsid nükleusa ulaşmadan hemen önce soyulur ve integras enzimi ile konak genomuna integre olur
- İntegrasyon sonrası viral genom **provirüs** olarak tanımlanır

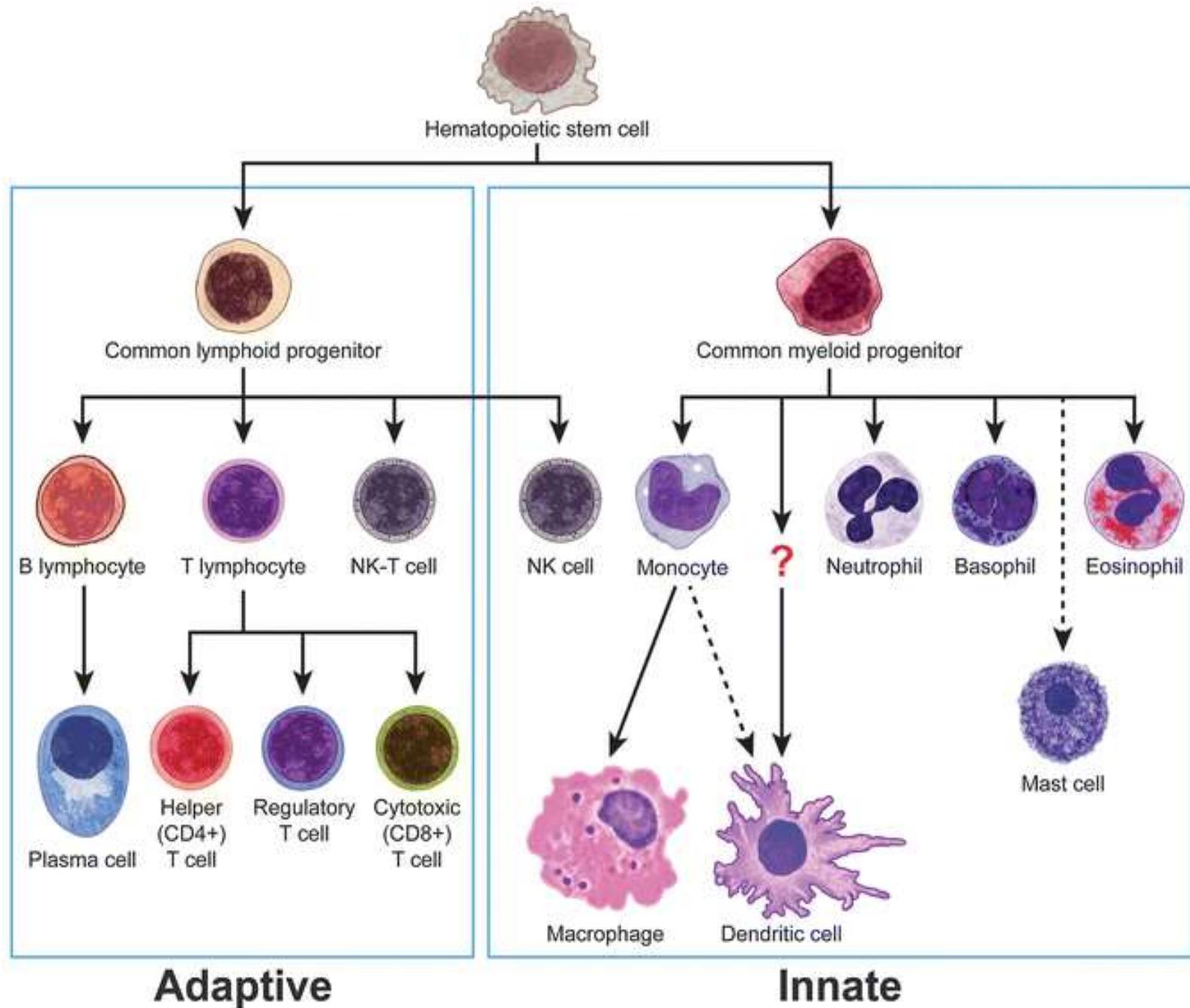


- Proviral DNA'nın transkripsiyonu ve daha sonra viral partiküllerin üretimi enfekte hücrenin hızlı ölümü ile sonuçlanır
- Ayrıca latent enfeksiyon gelişir. Bu durumda viral partiküller üretilemez ve bu hücrelerin immün sistem tarafından tanınması zayıflar



# HIV-1 ve İmmün Sistem

- HIV-1, doğrudan ve dolaylı olarak immün sistemi hasarlar
- İmmün yanıt HIV-1 enfeksiyonu geliştikten sonra eliminasyonda başarısız olmasına karşın, immünolojik antiviral aktivite hastalığın gidişini anlamlı olarak etkileyebilir
  - Uzun dönem progresyon göstermeyenler(LTNPs): Sıklık %10 ve HIV-1 RNA < 2000 c/mL(tedavisiz)
  - Elit kontrol(EC): Sıklık <%1 ve HIV-1 RNA negatif(tedavisiz)



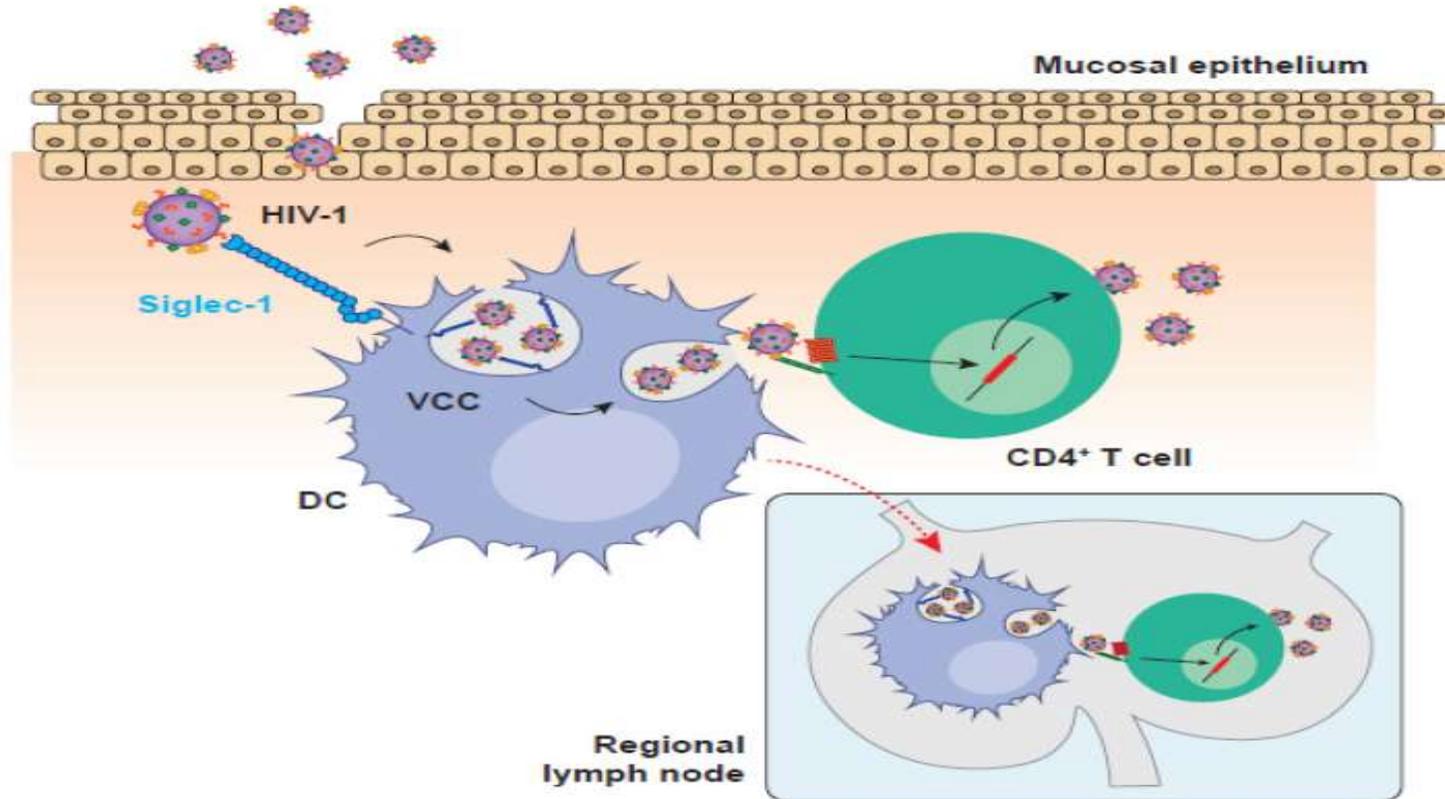
# Doğal İmmün Sistem - Dendritik hücreler(DCs)

- Dendritik hücreler myeloid veya lenfoid hücrelerden oluşan, temel fonksiyonları Th hücreleri gibi diğer immün hücrelere antijenleri HLA-klas-II aracılı sunan heterojen bir gruptur
- HIV-1 ile enfekte olmaları düşük olasılık olmasına karşın, bu hücrelerden zengin mukoza aracılığı ile bulaşta rol oynayabilir
- Enfekte olmadan veziküller içinde virüsü taşırlar
- T hücrelerden zengin lenfoid dokulara göçerler ve veziküllerin saçılmasıyla CD4+ T hücrelerini enfekte edebilirler

Review

## HIV-1 *trans*-Infection Mediated by DCs: The Tip of the Iceberg of Cell-to-Cell Viral Transmission

Daniel Perez-Zsolt <sup>1,†</sup>, Dàlia Raïch-Regué <sup>1,†</sup> , Jordana Muñoz-Basagoiti <sup>1,†</sup>, Carmen Aguilar-Gurrieri <sup>1</sup>, Bonaventura Clotet <sup>1,2</sup>, Julià Blanco <sup>1,2,3</sup>  and Nuria Izquierdo-Useros <sup>1,3,\*</sup> 



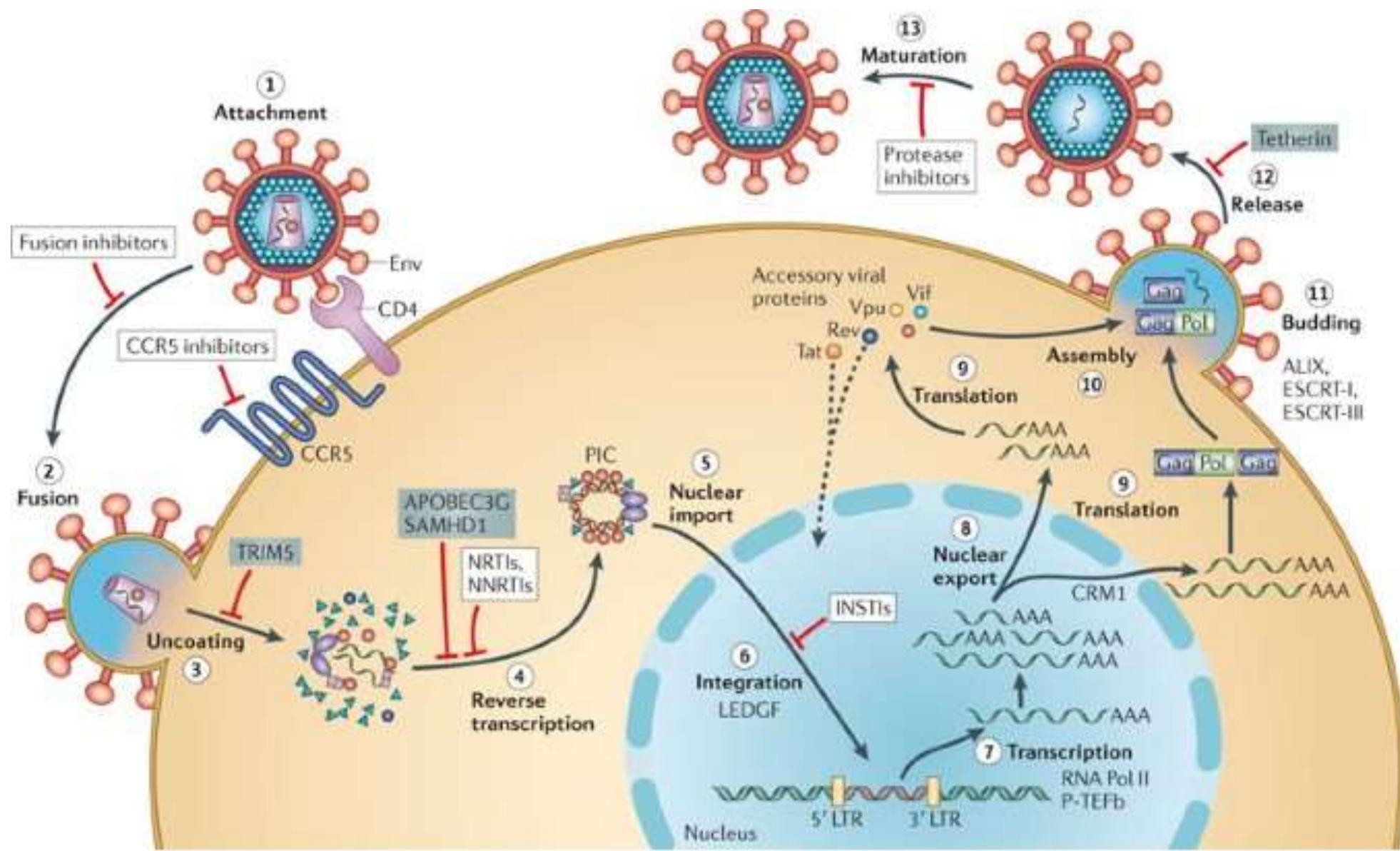
**Figure 1.** HIV-1 invasion is boosted by DC-mediated viral transmission in the mucosa and the migration to secondary lymphoid tissues. HIV-1 replication in the mucosa is facilitated by Siglec-1-expressing DCs that can mediate viral transmission to mucosal CD4<sup>+</sup> T cells or migrate to secondary lymphoid tissues where the interaction with other target CD4<sup>+</sup> T cells accelerates the settlement of systemic infection. HIV-1: human immunodeficiency virus type 1; VCC: viral containing compartment; DC: dendritic cell.

# Hücre İçi Kısıtlama Mekanizmaları

Hücre membranında, veziküllerde veya sitozolde yer alırlar

- APOBEC3G
- CARD8
- BST-2
- IFI16
- MX2
- RIG-I
- SAMHD-I
- SERINC3 ve SERINC5
- TRIM5 $\alpha$
- ZAP

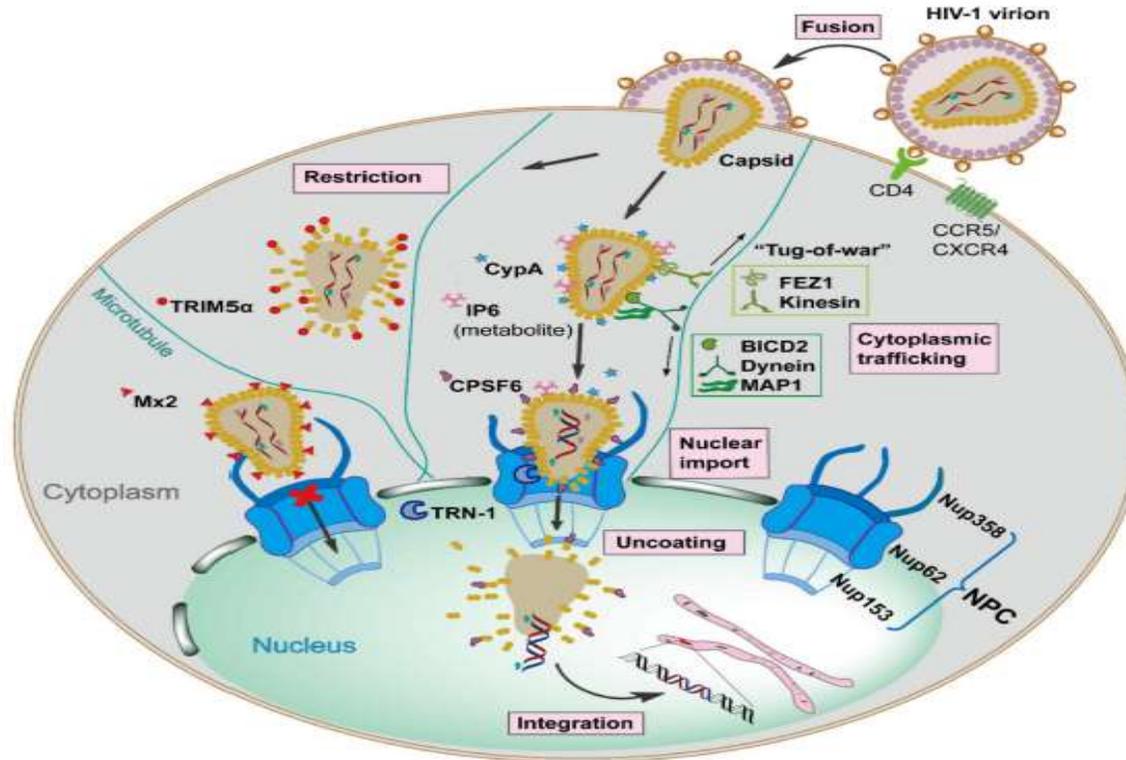
Virüsün aksesuar proteinleri bu kısıtlama mekanizmalarına rağmen efektif replikasyonu başlatabilme yeteneğine sahiptirler



Review

# Interactions of HIV-1 Capsid with Host Factors and Their Implications for Developing Novel Therapeutics

Shentian Zhuang <sup>1,2</sup> and Bruce E. Torbett <sup>1,2,3,\*</sup>

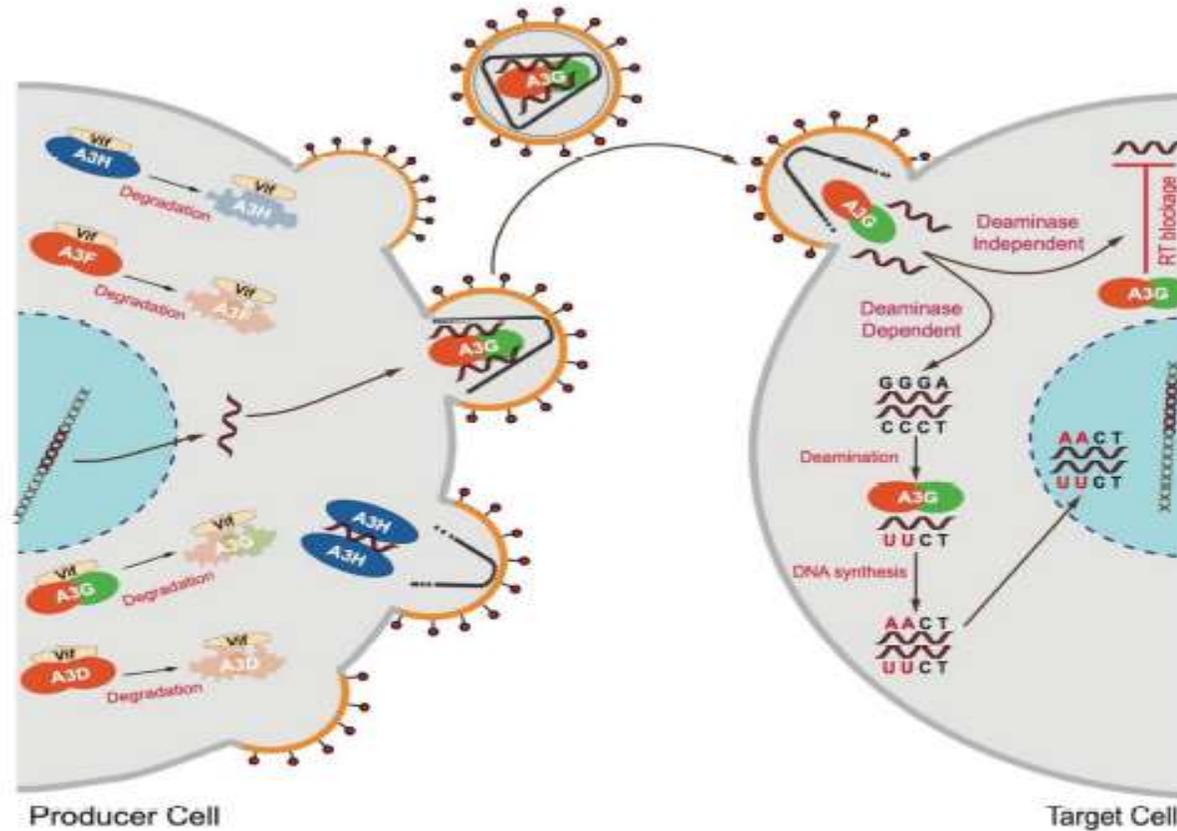


**Figure 1.** Schematic overview of the early stages of Human Immunodeficiency Virus type 1 (HIV-1) replication, which is spatiotemporally regulated by diverse capsid-interacting host factors. The HIV-1 virion binds to the CD4 receptor and the CXCR4 and/or CCR5 coreceptors via the viral envelope glycoproteins, resulting in fusion with the target cell, which releases capsid into the cellular cytoplasm. The capsid traffics towards the nucleus along the microtubule network by employing opposing adaptor and motor proteins such as FEZ1, kinesin, BICD2, dynein, and MAP1, a process that may result in a bi-directional “tug-of-war”. The host cellular protein CypA and metabolite IP6 bind to capsid and maintain core stability during cytoplasmic trafficking. The host innate immune system can respond to capsid, resulting in interferon (IFN) expression and inducing the IFN-induced viral restriction factors TRIM5 $\alpha$  and Mx2. TRIM5 $\alpha$  binds to the capsid causing premature uncoating, while Mx2 binds to the capsid impeding the nuclear import. When capsid arrives at the nuclear envelope, it presumably binds Nup358, and other factors, to promote import into the nucleus via the nuclear pore complex as an intact or nearly intact capsid. The host factors CPSF6, Nup153, and TRN-1 also appear to facilitate capsid nuclear import via direct capsid interactions. Reverse transcription is completed in the nucleus, followed by complete uncoating of the capsid and integration of the viral DNA into the host genome. All processes are detailed in the text.

Review

# Human APOBEC3 Variations and Viral Infection

Shiva Sadeghpour <sup>1,†</sup>, Saeideh Khodaei <sup>2,†</sup>, Mostafa Rahnema <sup>3,†</sup> , Hamzeh Rahimi <sup>4</sup> and Diako Ebrahimi <sup>5,\*</sup> 



**Figure 1.** Inhibition of HIV-1 by APOBEC3 enzymes using deaminase-dependent and -independent mechanisms. APOBEC3 enzymes are often counteracted by the HIV-1 Vif protein. Those not counteracted by Vif can package into the budding virions and inhibit viral replication by inflicting C-to-U hypermutation in the HIV-1 cDNA or by deaminase-independent mechanisms such as the physical blockage of HIV-1 reverse transcription.

# Doğal İmmün Sistem - NK hücreleri

- Lenfoid orijinlidir fakat virüsü tanımak için antijene özgül reseptörleri kullanmazlar

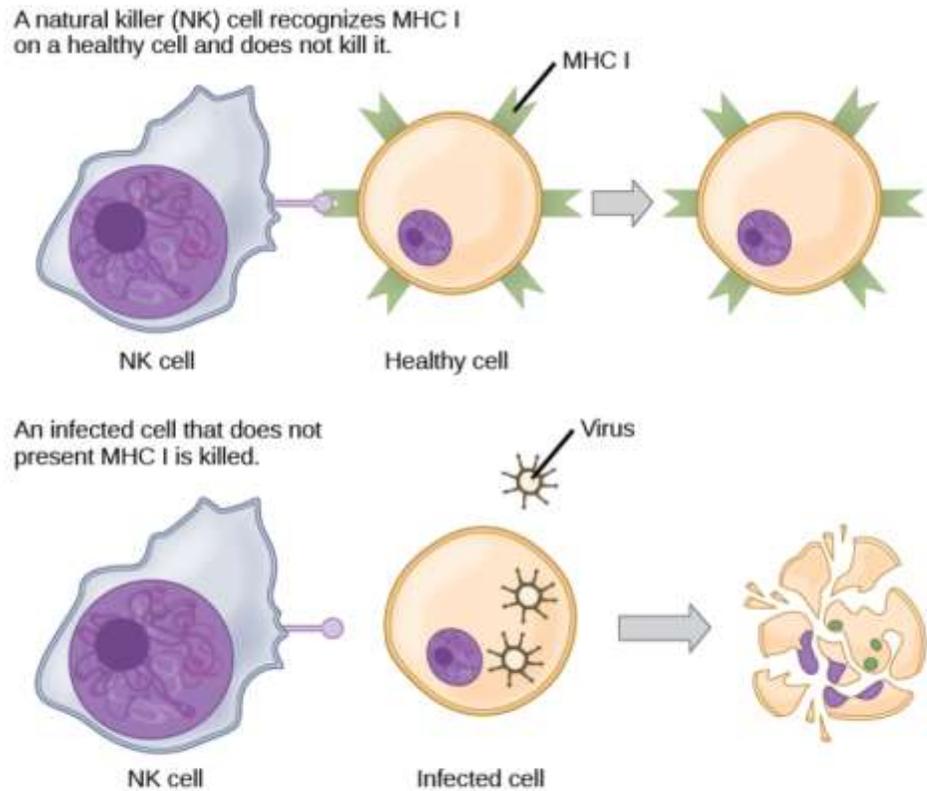


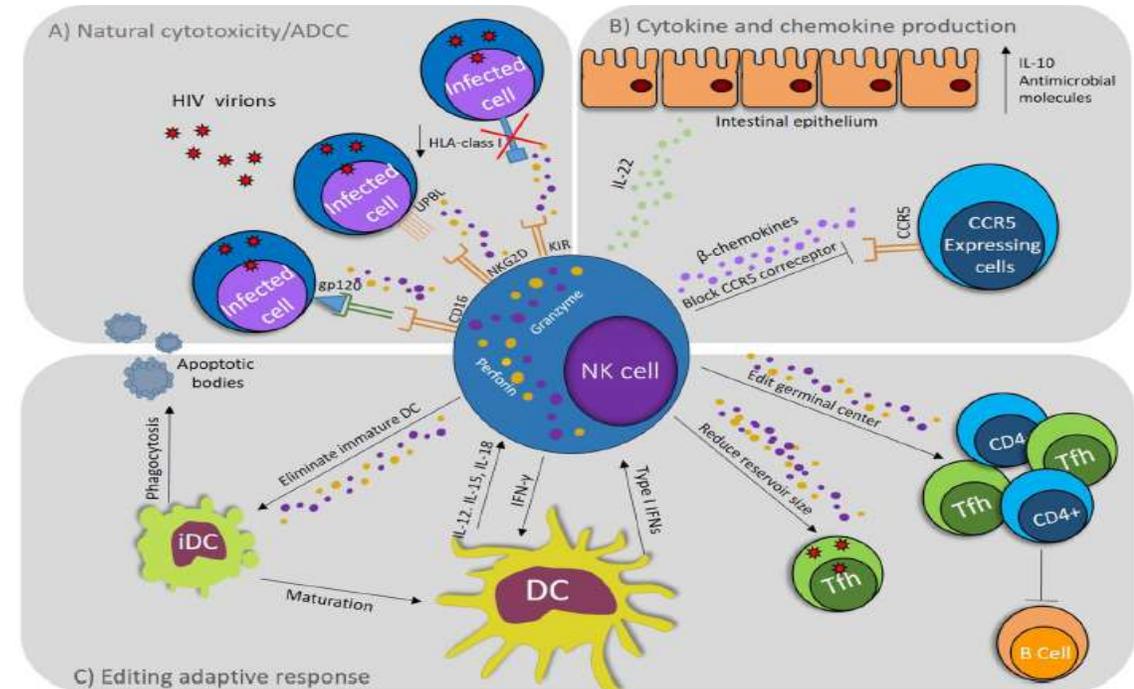
Figure 6. Natural killer (NK) cells recognize the MHC I receptor on healthy cells. If MHC I is absent, the cell is lysed.

Flórez-Álvarez et al.

NK Cells in HIV-1 Infection

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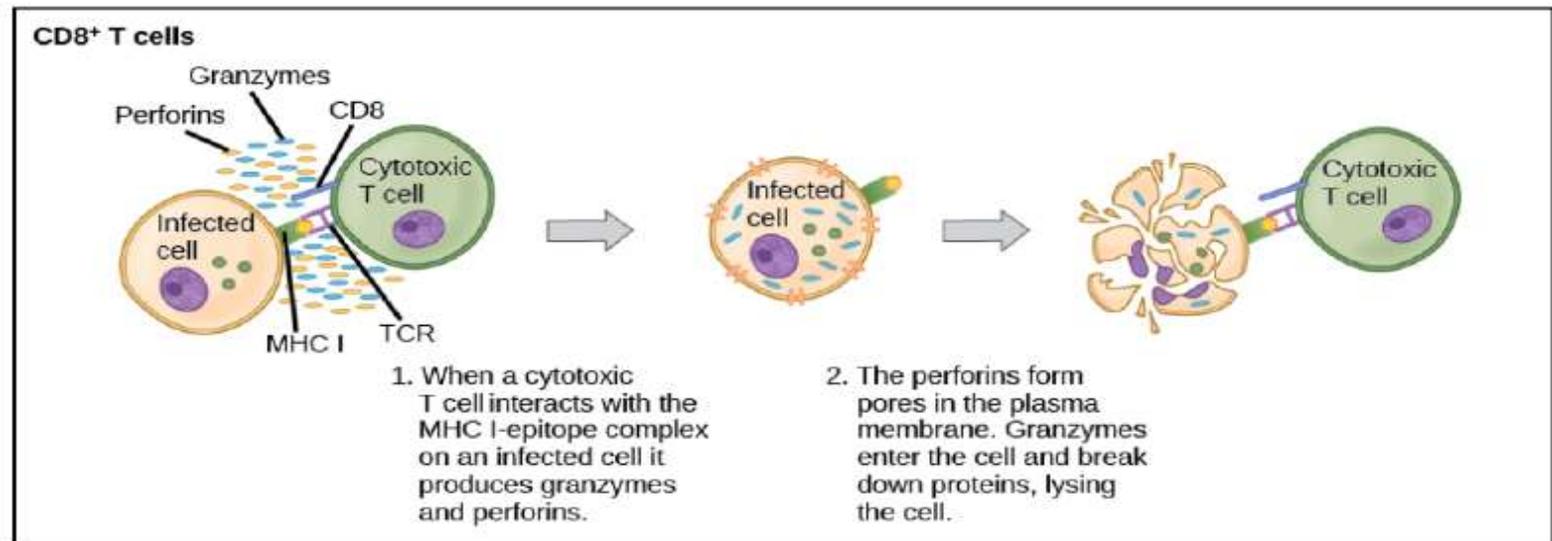
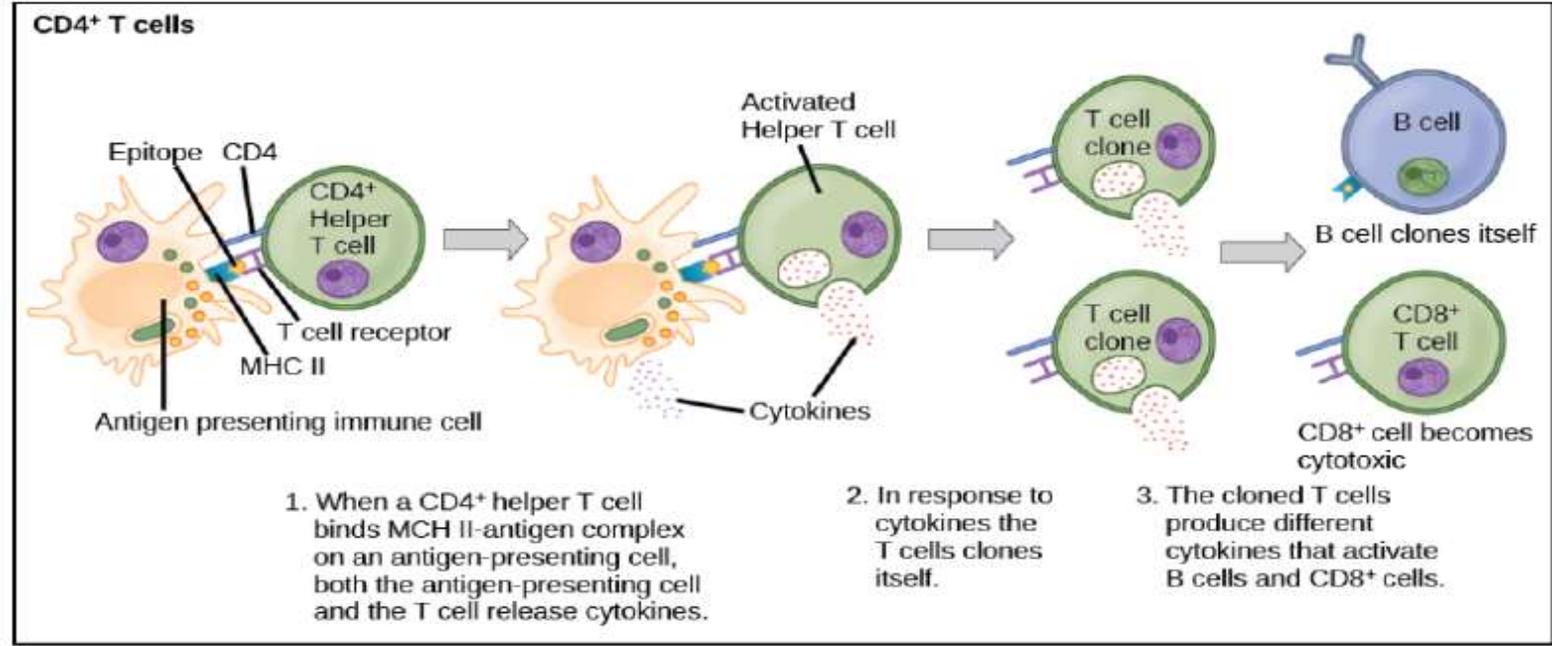
**FIGURE 1 |** NK cell role during HIV-1 infection. **(A)** NK cells degranulate in response to activating signals via CD16 (FcyRIII), which binds Abs recognizing HIV proteins; also, by activating signals via NKG2D that binds stress signals like UPBL1, 2 and 3, which are up regulated on infected cells. Down regulation of HLA class I molecules induces activation by absence of inhibitory signals through KIR. **(B)** NK cells produce IL-22, which induce the production of antimicrobial molecules and IL-10 by epithelial cells. NK cells produce β-chemokines, which exert anti-HIV-1 activity *in vitro* by displacing the viral envelope glycoprotein gp120 from binding to CCR5 and by promoting CCR5 endocytosis. **(C)** iDCs uptake apoptotic bodies produced by NK cells activity inducing their maturation. NK cells realize DC editing eliminating iDCs to select mature DCs. DCs induce the activation of NK cells by producing IL-12, IL-18, and type I IFNs and NK cells produce IFN-γ inducing maturation of DCs. NK cells can eliminate CD4+ T cells and follicular helper T cells (Tfh), editing germinal center and affecting Abs production, but at the same time, by eliminating the Tfh, they reduce the HIV reservoirs.

# Adaptif İmmün Sistem - HLA

- Bir grup yüzey reseptöründen oluşur
- Antijeni T hücre reseptörlerine sunar
- HLA-klas-I tüm çekirdekli hücrelerde bulunur
- B27, B57 gibi HLA-I alleleri artmış kontrol, B07 ve B35 hızlı progresyon
- HLA-Klas-II molekülleri özelleşmiş antijen sunan hücrelerde (B hücreleri, makrofajlar, dendritik hücreler) bulunurlar ve antijeni CD4+ Th hücrelere sunarlar

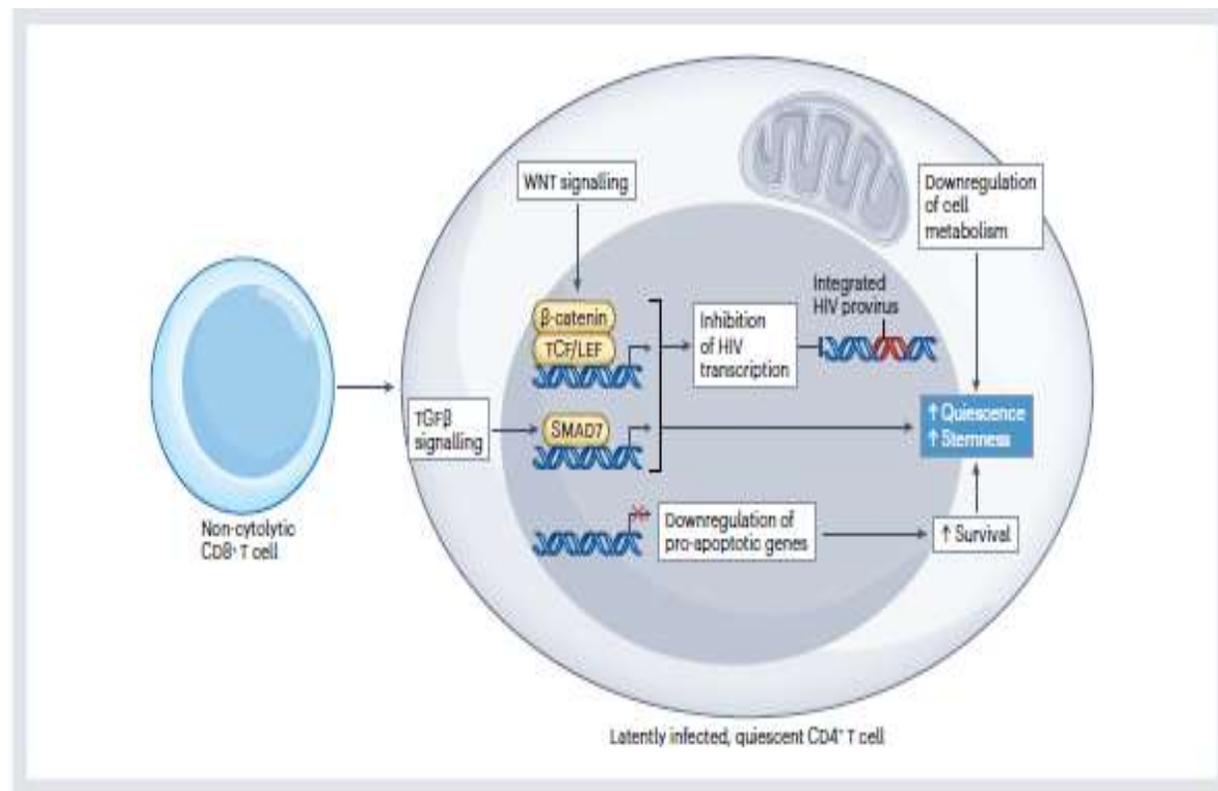
# Adaptif İmmün Sistem – CD8+ T hücreleri

- CD8+ T hücreleri HLA-klas-I ile birlikte sunulan spesifik antijenleri(HIV-1 peptidleri gibi) tanirlar
- HLA aracılı aktivasyonu takiben CD8+ T hücrelerinden perforin ve granzim sekresyonu
- Buna ek olarak bu hücreler MIP-1 $\beta$ , IFN- $\gamma$ , TNF- $\alpha$  ve IL-2 salgılar
- Viral varyantlar: CD8+ T hücrelerine karşı direnç mutasyonu olabilir
- Akut HIV enfeksiyonunda, HIV-1'in kontrolünde önemli rol oynarlar
- Viral set point: Akut enfeksiyondan sonra stabil viral yük



# Immune-mediated strategies to solving the HIV reservoir problem

Deanna A. Kulpa<sup>1,2</sup>, Mirko Palardini<sup>1,2</sup> & Guido Silvestri<sup>1,2</sup> 



**Table 1 | Cytolytic and non-cytolytic antiviral functions of CD8<sup>+</sup> T cells**

Feature	Cytolytic activity	HIV silencing
Suppression of virus replication in absence of ART	Yes	Yes
MHC class I restriction	Yes	No
Present in HIV-negative individuals	No	Yes
Requires cell-cell contact	Yes	Partly
Mediating factors	Perforin, granzyme B	Unclear, possibly WNT, IL-10, TGFβ
Subject to virus escape and immune exhaustion	Yes	Unknown
Effect on virus reservoir under ART	Clearance (limited)	Stabilization
Post-ART control of virus	Yes	Unknown (possible)
Effect on CD4 <sup>+</sup> T cell activation	None	Down-modulation
Effect on latency reversal	None	Inhibition

ART, antiretroviral therapy.

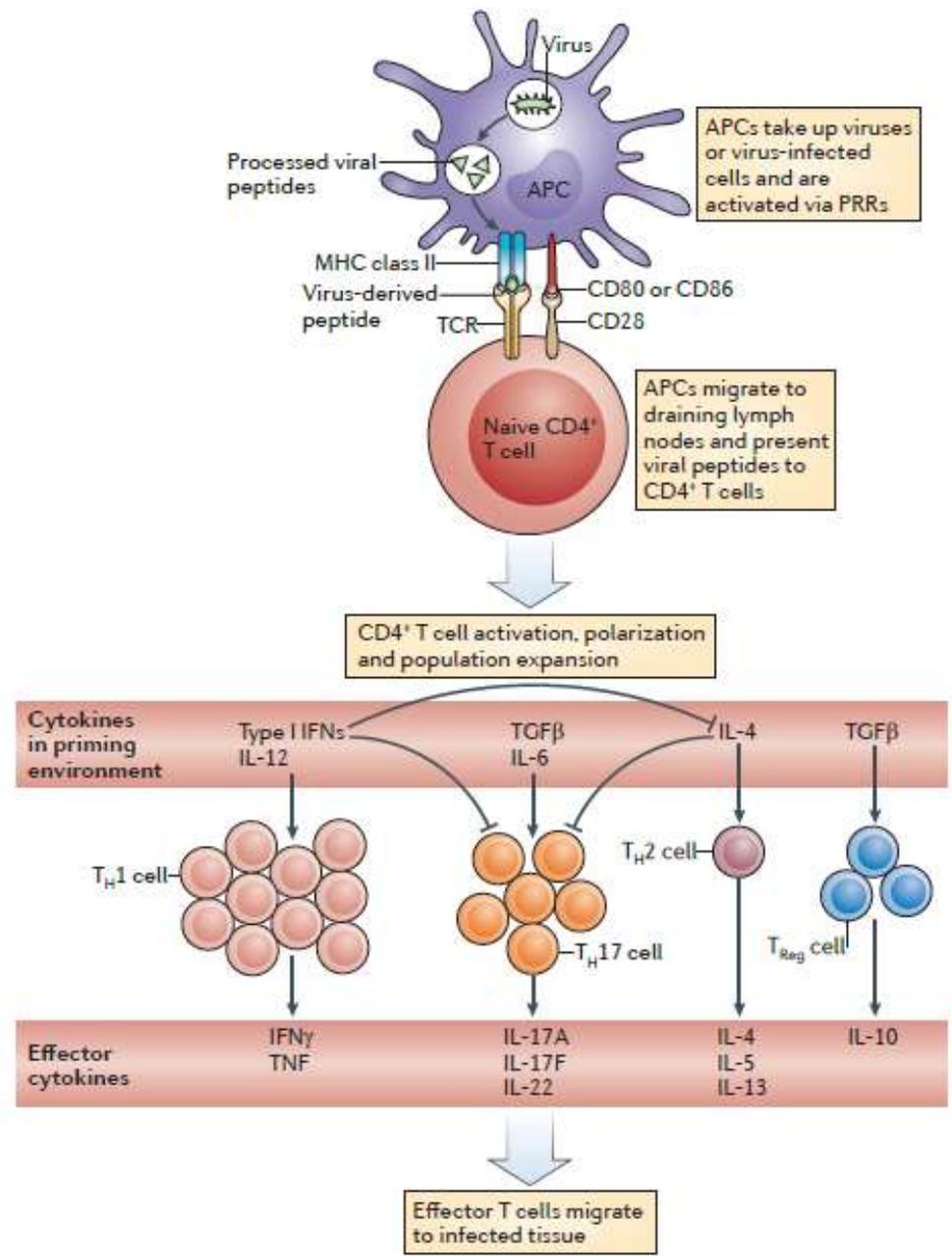
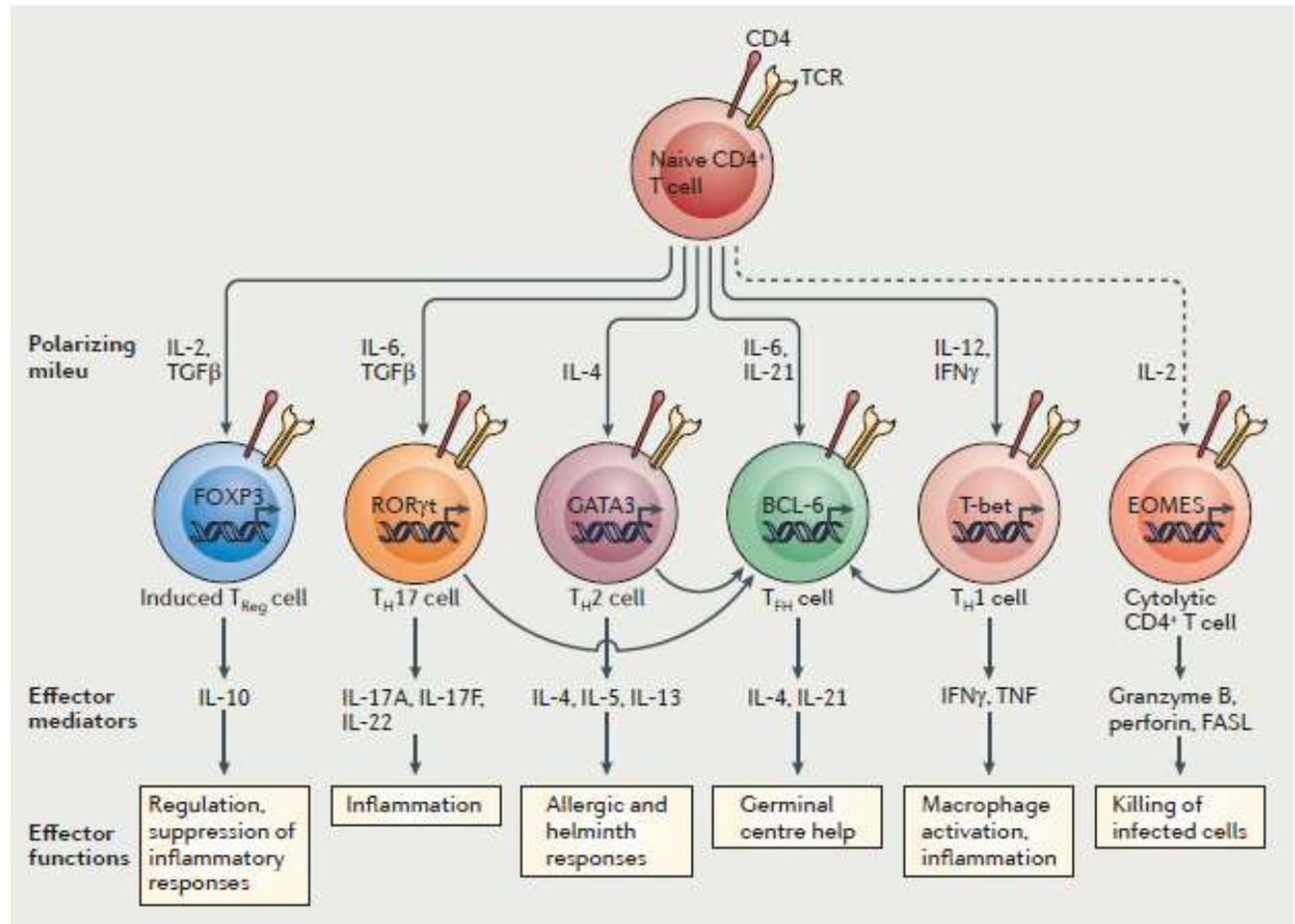
# Adaptif İmmün Sistem – CD4+ T hücreleri

- Fenotipik olarak farklı CD4+ T hücreleri mevcuttur
- Yardımcı T hücreleri sitokin salarak patojenlere karşı immün yanıtı regüle ederler
- HIV-1'in neden olduğu immün hasarı en iyi gösteren hücre

Gruell H, Schommers P, Klein F. Eds. Hoffmann and Roskstroh HIV 2023/2024

# Expanding roles for CD4<sup>+</sup> T cells in immunity to viruses

Susan L. Swain, K. Kai McKinstry and Tara M. Strutt

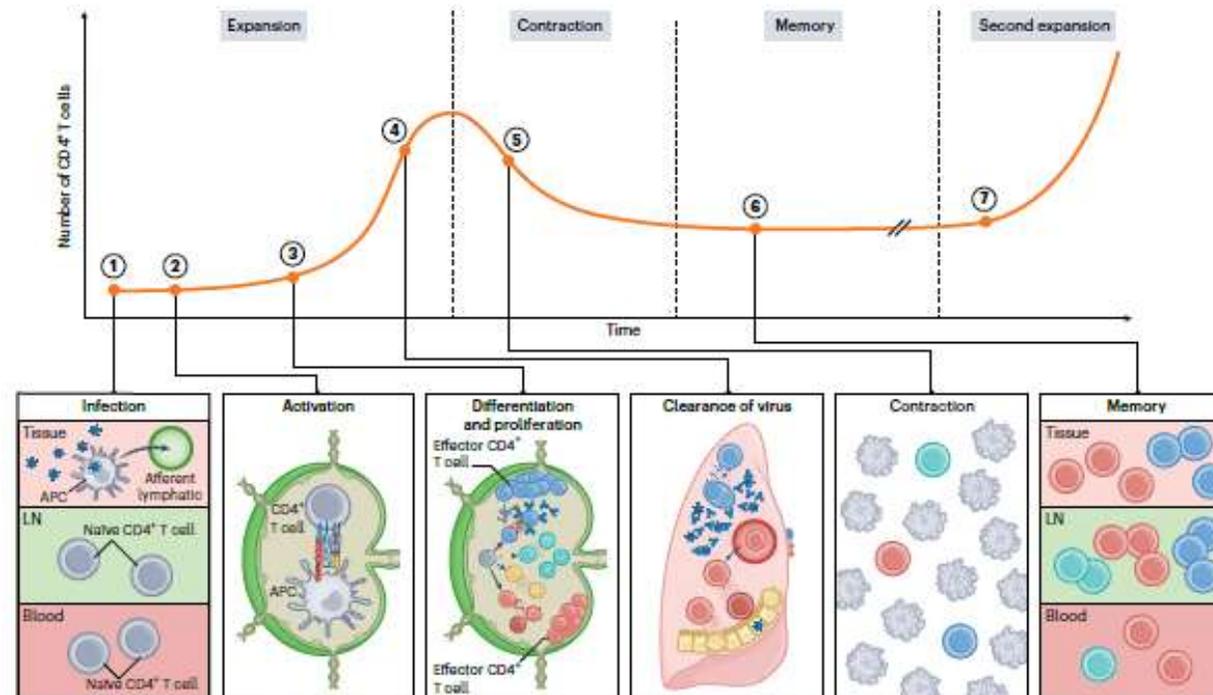


# CD4<sup>+</sup> T cell memory

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Marco Künzli  & David Masopust  

Review article

<https://doi.org/10.1038/s41590-023-01510-4>

**Fig. 1 | Dynamics of a CD4<sup>+</sup> T cell response.** 1. Naive CD4<sup>+</sup> T cells quiescently recirculate through blood (dark red) and lymphoid (light green) tissues. Upon infection, for example by a respiratory pathogen, APCs migrate from infected barrier sites (magenta) to the draining lymph nodes through afferent lymphatics and present peptides from the pathogen on MHC-II molecules. 2. Recognition of the peptide–MHC-II complex through TCR in combination with co-stimulation and cytokine signals lead to the activation, differentiation and expansion of naive CD4<sup>+</sup> lymph node T cells. 3. CD4<sup>+</sup> T cells proliferate and differentiate into various

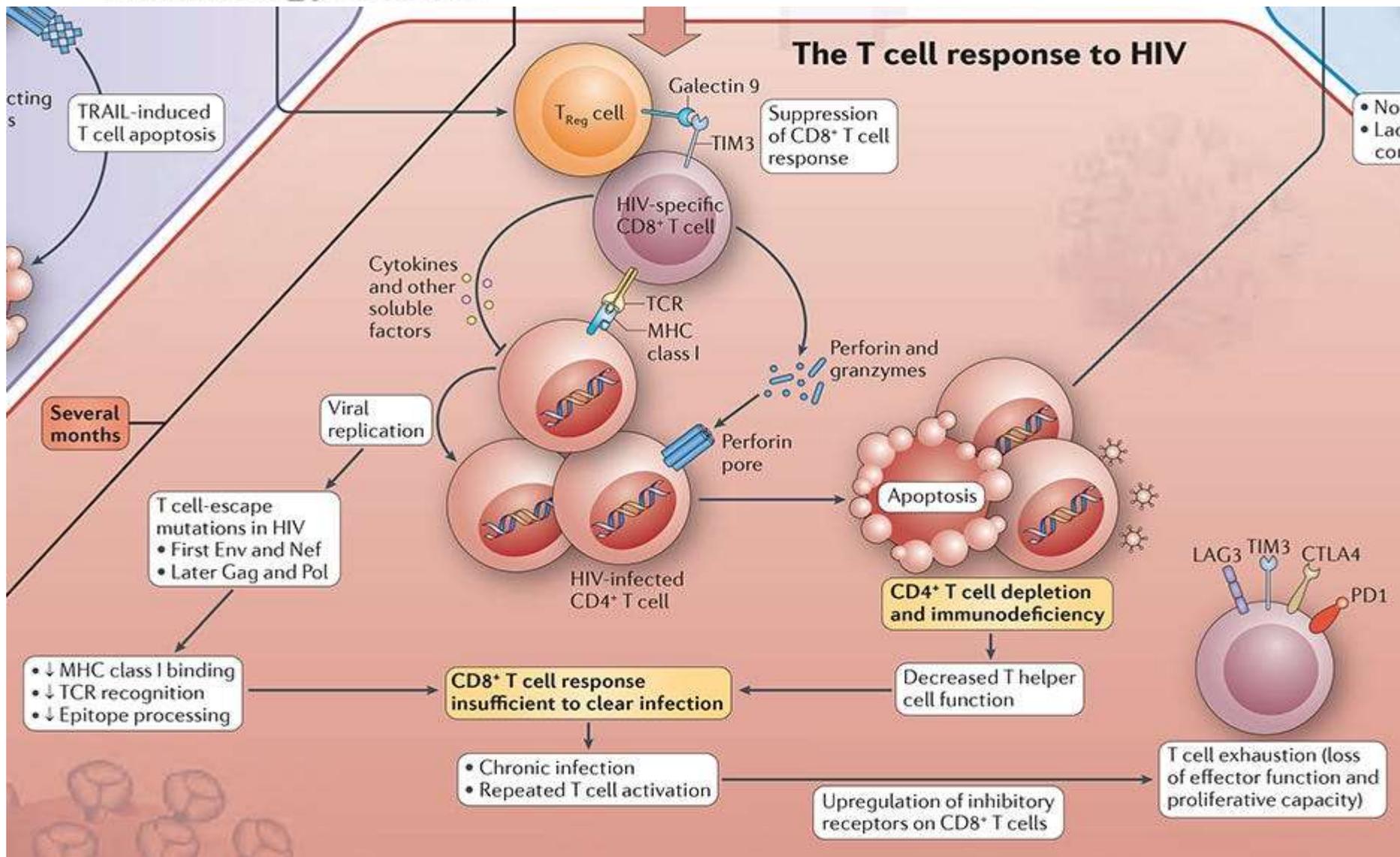
effector subsets that each become poised to make specialized contributions to immunity. 4. Many proliferated T cells leave the lymph nodes and migrate to the infected tissue through blood to assist in pathogen control at sites of infection. 5. Once the infection is cleared, most pathogen-specific CD4<sup>+</sup> T cells die resulting in contraction of the population. 6. However, a few survive to establish long-lived memory and stay widely distributed across the body. 7. Upon reinfection, memory CD4<sup>+</sup> T cells can mount anamnestic responses that are quicker and of higher magnitude than a primary response.

# Adaptif İmmün Sistem – CD4+ T hücreleri

- CD4+ T hücre sayısındaki düşme nedenleri
  - Apoptozis/Piroptozis
  - İmmün aktivasyon sonucu lenfosit kaybı
  - Timus ve kemik iliğinin HIV-1 tarafından hasarlanması sonucu azalmış üretim
  - CD4+ T hücrelerinin kandan lenfoid dokulara tekrar dağılması

# Immune Response to HIV: T Cell Dysfunction, Mechanisms, and Therapies

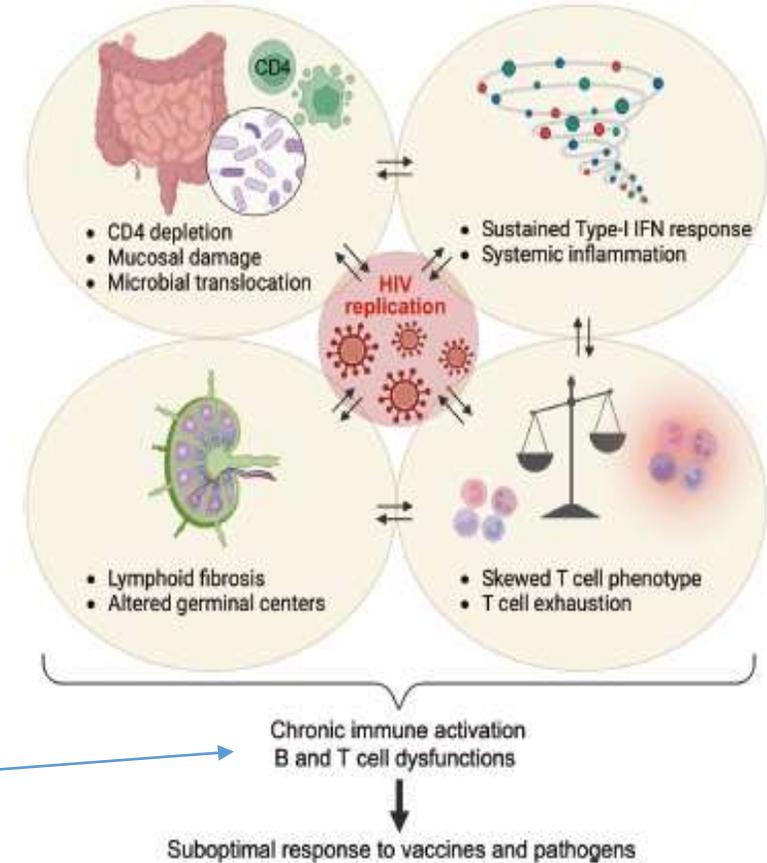
## Immunology Feature



# Adaptif İmmün Sistem - Hümmöral İmmün Yanıt

- Antikorlar lenfoid foliküllerde aktif B lenfositlerinden gelişen plazma hücreleri tarafından üretilir
  - Nötralizasyon
  - Antikora bağı hücresele sitotoksisite(NK hücreleri)
  - Antikora bağı hücresele fagositoz(Makrofajlar, dendritik hücreler)
- Nötralizan antikorlar kişiye özeldir(enfeksiyon nedeni olan virüse özel)
- Geniş nötralizan antikorlar: Envelope proteininin kısmen korunmuş bölgelerine karşı oluşan

- HIV enfeksiyonu sırasında immün sistemin tüm komponentlerinde fonksiyonel bozulmalar gösterilmiştir
- GALT CD4+ T hücrelerinin depleasyonu
- Mukozal bariyer integrasyonunda bozulma
- Proinflammatuar mikrobiyal ürünlerin translokasyonu(LPS gibi)
- İmmün aktivasyon(sistemik inflamasyon)
- Antiinflammatuar proteinlerin artışı(PD-1, IL-10 gibi)
- İmmün tükenme



**Fig. 1** HIV-associated immune dysregulation. In the early stages of HIV infection, a rapid burst of viral replication leads to rapid depletion of mucosal CD4+ T cells. Slower and progressive depletion of CD4+ T cells in peripheral tissues and blood ensues. HIV has a major impact on gut-associated lymphoid tissue and disrupts intestinal epithelial integrity, resulting in microbial translocation and onset of chronic immune activation and inflammation. This persistent immune activation further contributes to progressive depletion of CD4+ T cells, leading to alterations in T-cell phenotype and promotion of T-cell exhaustion. HIV infection also damages the fibroblastic reticular cell network within lymphoid tissues (LTs), affecting LT architecture and subsequently impacting germinal center reactions. The cumulative effect of HIV on the immune system compromises the capacity of the host to effectively coordinate immune responses against other pathogens or respond optimally to vaccines.

Review

# The Many Faces of Immune Activation in HIV-1 Infection: A Multifactorial Interconnection

Laura Mazzuti <sup>1</sup>, Ombretta Turriziani <sup>2</sup> and Ivano Mezzaroma <sup>3,\*</sup>

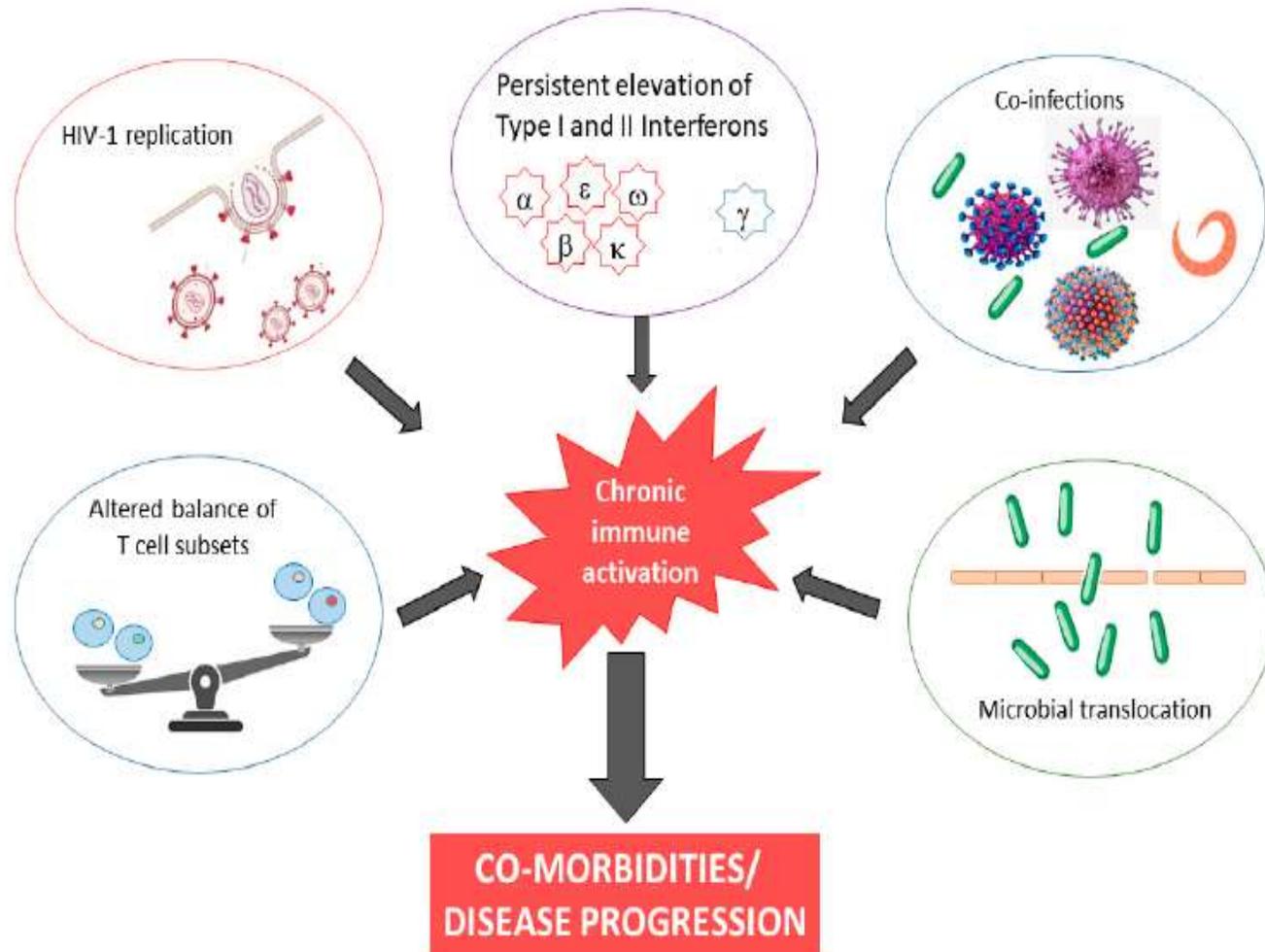


Figure 1. Causes and consequences of chronic immune activation in HIV-1 infection.

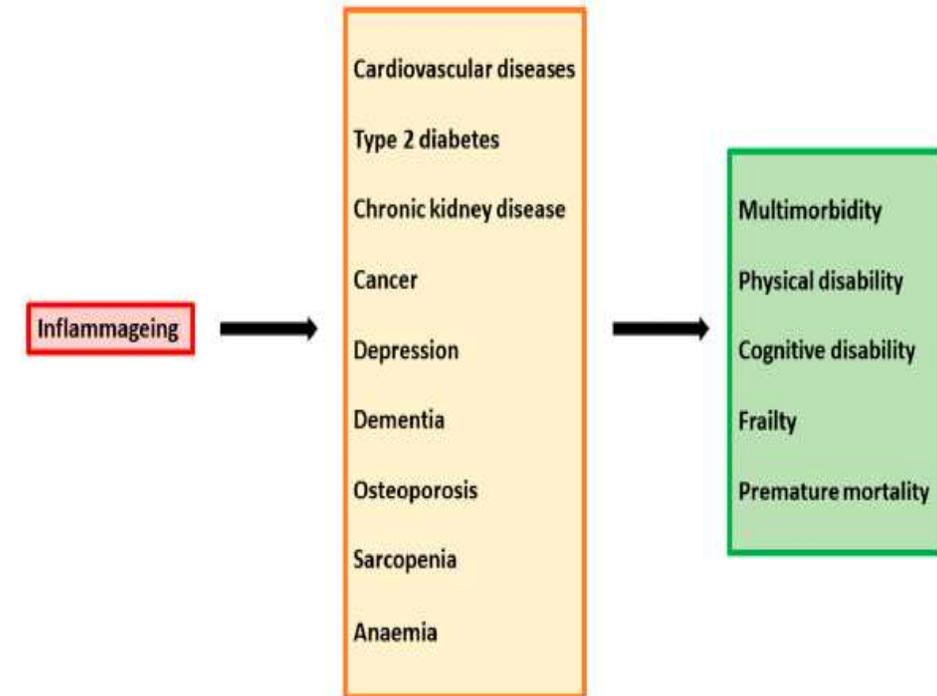
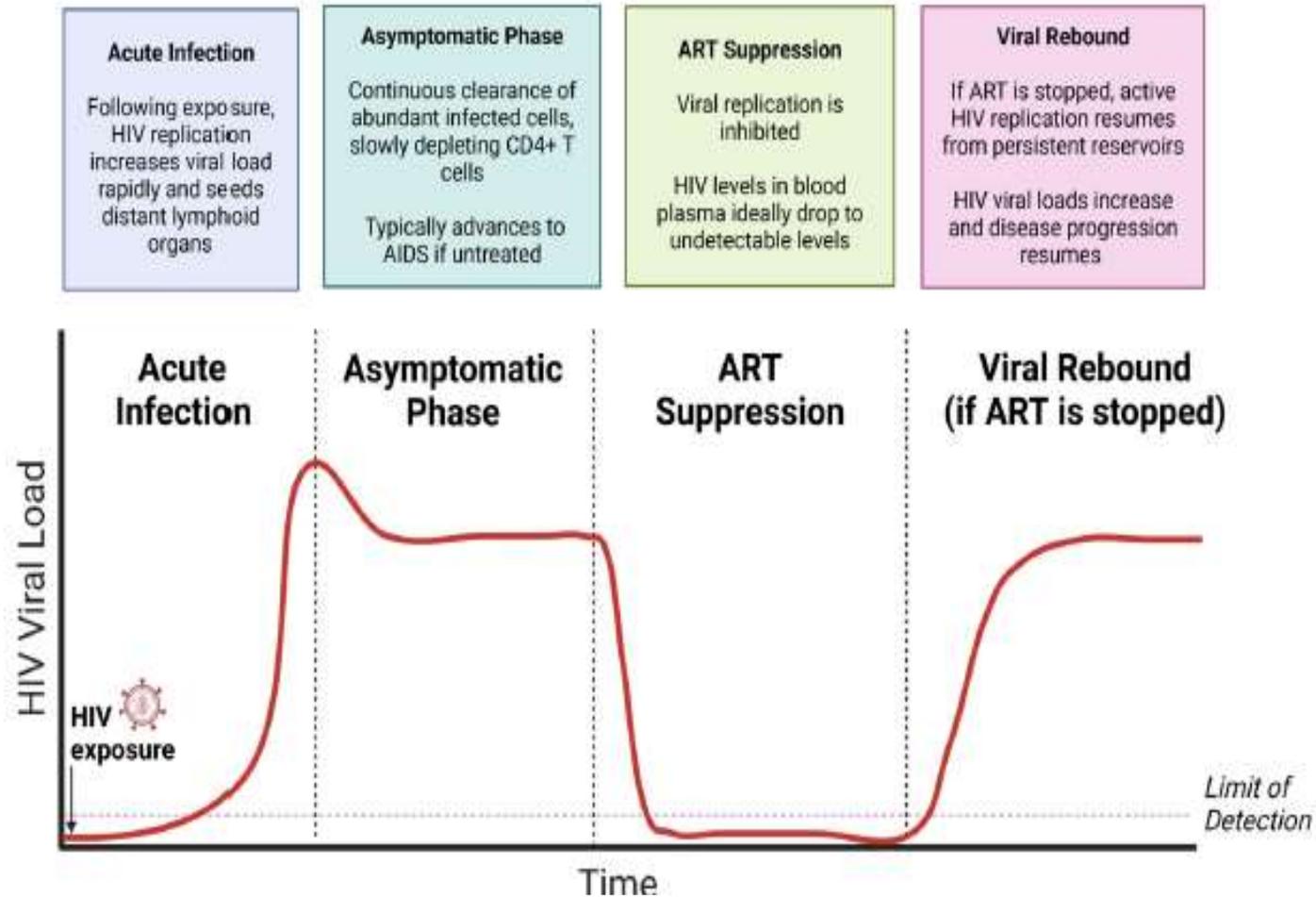


Figure 2. Inflammaging as a driver of multiple chronic diseases.

Review

# HIV Persistence, Latency, and Cure Approaches: Where Are We Now?

Tessa C. Chou <sup>1</sup>, Nishad S. Maggirwar <sup>1</sup>  and Matthew D. Marsden <sup>1,2,\*</sup> 



# Immune-mediated strategies to solving the HIV reservoir problem

Deanna A. Kulpa<sup>1,2</sup>, Mirko Palardini<sup>1,2</sup> & Guido Silvestri<sup>1,2</sup> 

- ART kesilince virüs replikasyonu çoğunlukla tekrar başlar(rebound)
- Bu rebound virüs rezervuarına bağlıdır
- Rezervuar latent olarak enfekte hücrelerden oluşur
- Akut enfeksiyondan sonra haftalar içinde oluşur(<10 gün)
- Hafıza CD4+ Th(ana virüs rezervuarını oluşturur)
- Hafıza CD4+ Th(integre olmuş, replikasyon yeteneğine sahip virüsleri barındırır)
- ART altında rezervuarın uzun dönem persistansının nedenleri
  - Rezidüel virüs replike olabilir ve önceden enfekte olmayan hücreleri enfekte eder
  - Latent olarak enfekte olan hücreler uzun ömürlüdür
  - Latent olarak enfekte hücrelerin homeostatik veya antijene bağlı proliferasyonu
- ART altında rezervuarın boyutunu doğal immün hücreler, sitotoksik T-lenfositleri, NK hücreleri, nötralizan antikolar ve antikora bağlı hücrel sitotoksite etkileyebilir

# HIV Rezervuarı

- Latent HIV-1 enfeksiyonu 2 formdadır
  - İntegre olmamış viral DNA(2.9 gün)
  - İntegre olmuş viral DNA(Aktif CD4+ T lenfositleri istirahat haline geçtiğinde oluşur)(44 gün)
- Rezervuar:Uzun dönem ART altında stabil olarak bulunan, HIV DNA'sının tamamen integre olduğu ve viral genomun yeni hücreleri enfekte etme kapasitesine sahip hücreleri tanımlar
- Rezervuar temel olarak istirahat halindeki CD4+ T hücreleri, makrofajlar ve dendritik hücreleri içerir
- Rezervuar hücreler
  - Hafıza CD4+ Th(TCM)
  - Hafıza T kök hücre(TSCM)
  - Monositler, Makrofajlar, Dendritik hücreler, Hematopoietik progenitör hücreler, Mikroglial hücreler

# HIV Rezervuarı

- Rezervuar hücreler
  - Hafıza CD4+ T hücreler(TCM, TTM)
  - T foliküler h(pTfh)
  - Makrofajlar, monositler
- Rezervuar dokular
  - GALT(en yüksek virüs konsantrasyonu, periferik kandan 2-4 kat daha fazla)
  - Erkek genital traktüsündeki makrofajlar
  - Kadın üreme traktüsündeki dokuya yerleşmiş hafıza CD4+ T hücreleri
  - MSS(mikrogial hücreler, makrofajlar, astrositler)

# HIV-1 latency: From acquaintance to confidant

Chenbo Yang<sup>a,1</sup>, Ling Tong<sup>c,1</sup>, Jing Xue<sup>a,b,\*</sup>

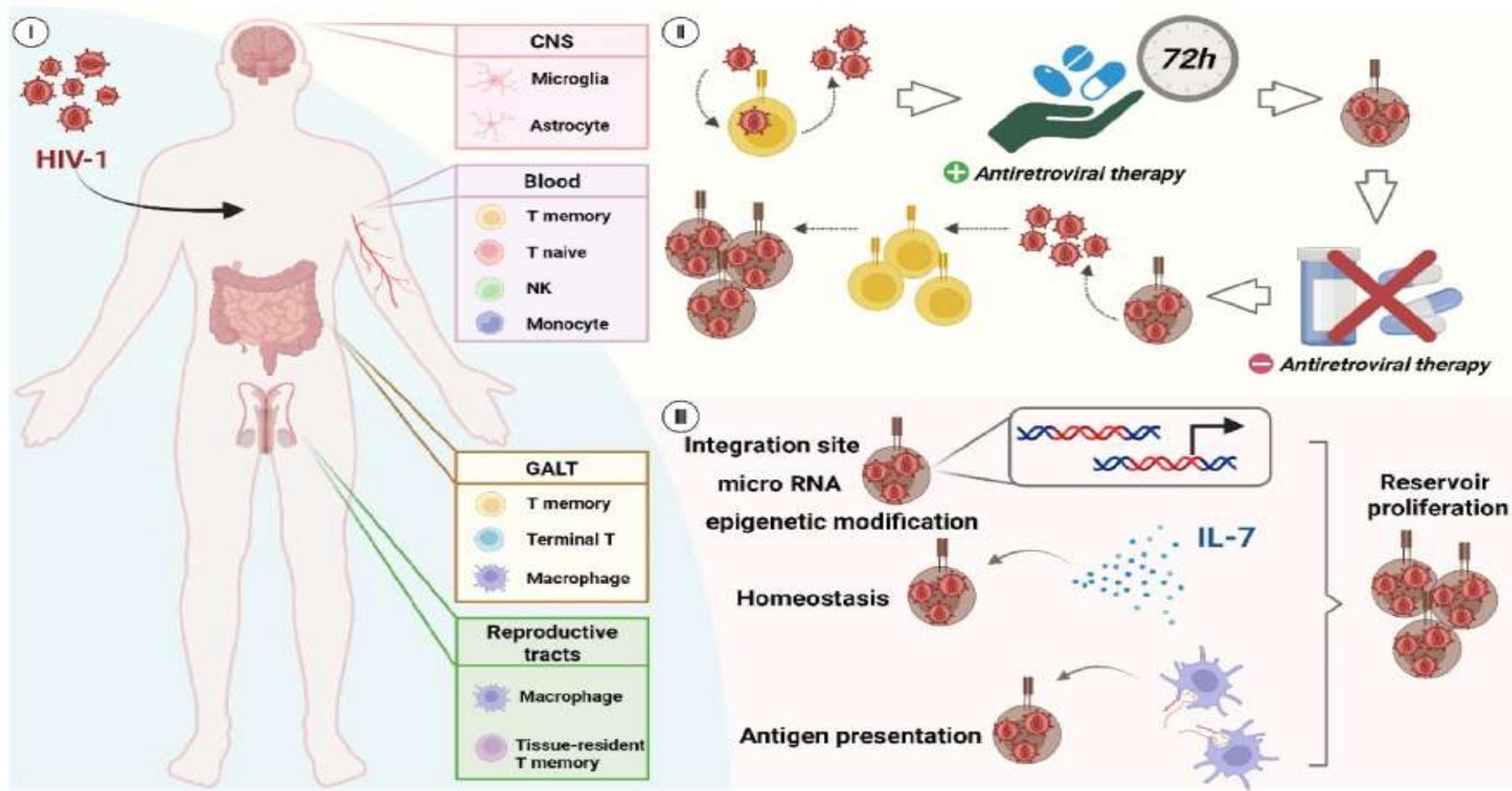


Fig. 1. Where, when and how is the latency established. The CNS, peripheral blood, GALT and reproductive tracts are the potential anatomical target for latency, consists of different subsets of immune cells. The HIV reservoir can be established shortly after infection. Administering antiretroviral therapy within 72 h can protect patients from productive infection; however, this intervention does not prevent viral rebound upon cessation of treatment, highlighting the swift establishment of the viral reservoir. Factors such as the integration site of the provirus, homeostatic mechanisms, and the regulation of certain cytokines and antigen presentation play significant roles in the maintenance and expansion of the viral reservoirs.

# ART Altında HIV Rezervuarı

- ART altında HIV rezervuarının persiste etme mekanizmaları
  - Rezidüel virüs replikasyonu, yeni hücreleri enfekte eder
  - Latent olarak enfekte hücrelerin uzun yaşam süresi
  - Homeostatik ve/veya antijen tarafından indüklenen latent hücre proliferasyonu(klonal ekspansiyon)

# HIV Rezervuarı

- Rezervuar hücreler ART altında viral partikül oluşturmazlar
- Latent durum, intakt veya defektif provirüsleri barındıran hücrelerin sürekli klonal ekspansiyonu ile persiste eder
- Klonal ekspansiyon hem homeostatik hem de antijenin indüklediği proliferasyon ile oluşur
- Homeostatik proliferasyon, viral reaktivasyon olmaksızın düşük düzeyde proliferasyon ile birlikte immün sistem tarafından saptanmaksızın latent durumun devam etmesine olanak sağlar
- Mikrobiyal peptidlere kronik maruz kalma da ekspansiyon ve latent durumun sürdürülmesini sağlar

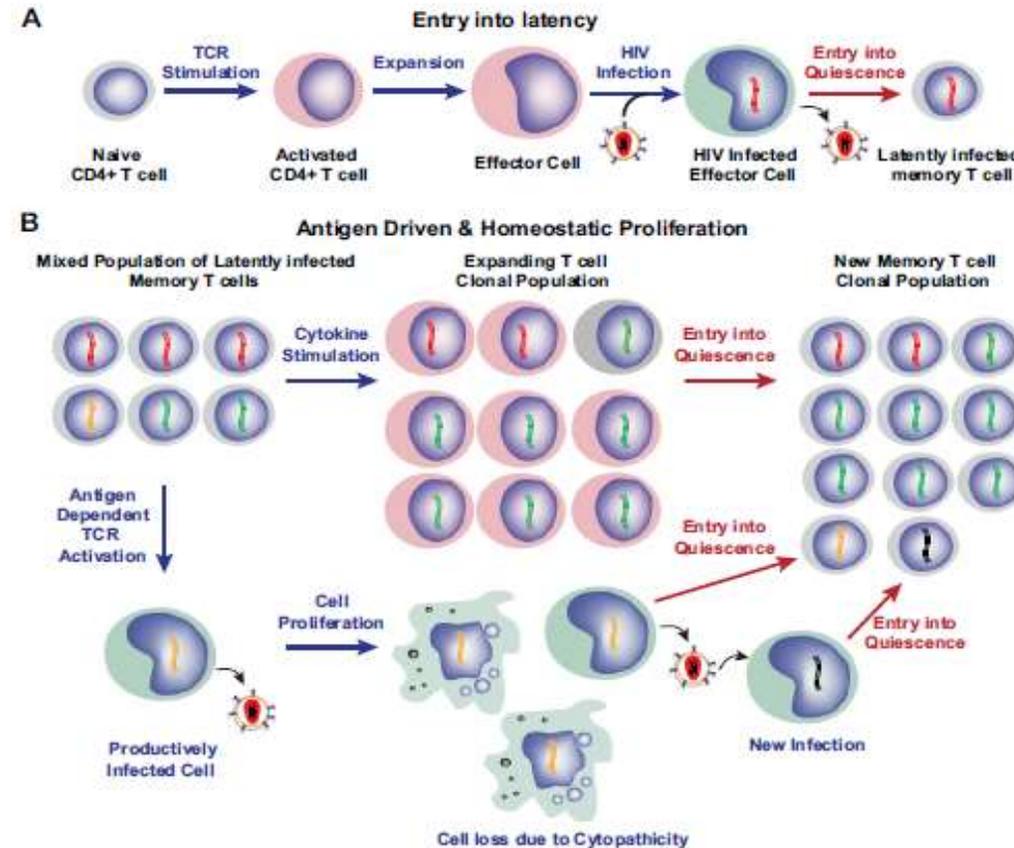
REVIEW

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# The cell biology of HIV-1 latency and rebound

Uri Mbonye<sup>1\*</sup> and Jonathan Karn<sup>1\*</sup>



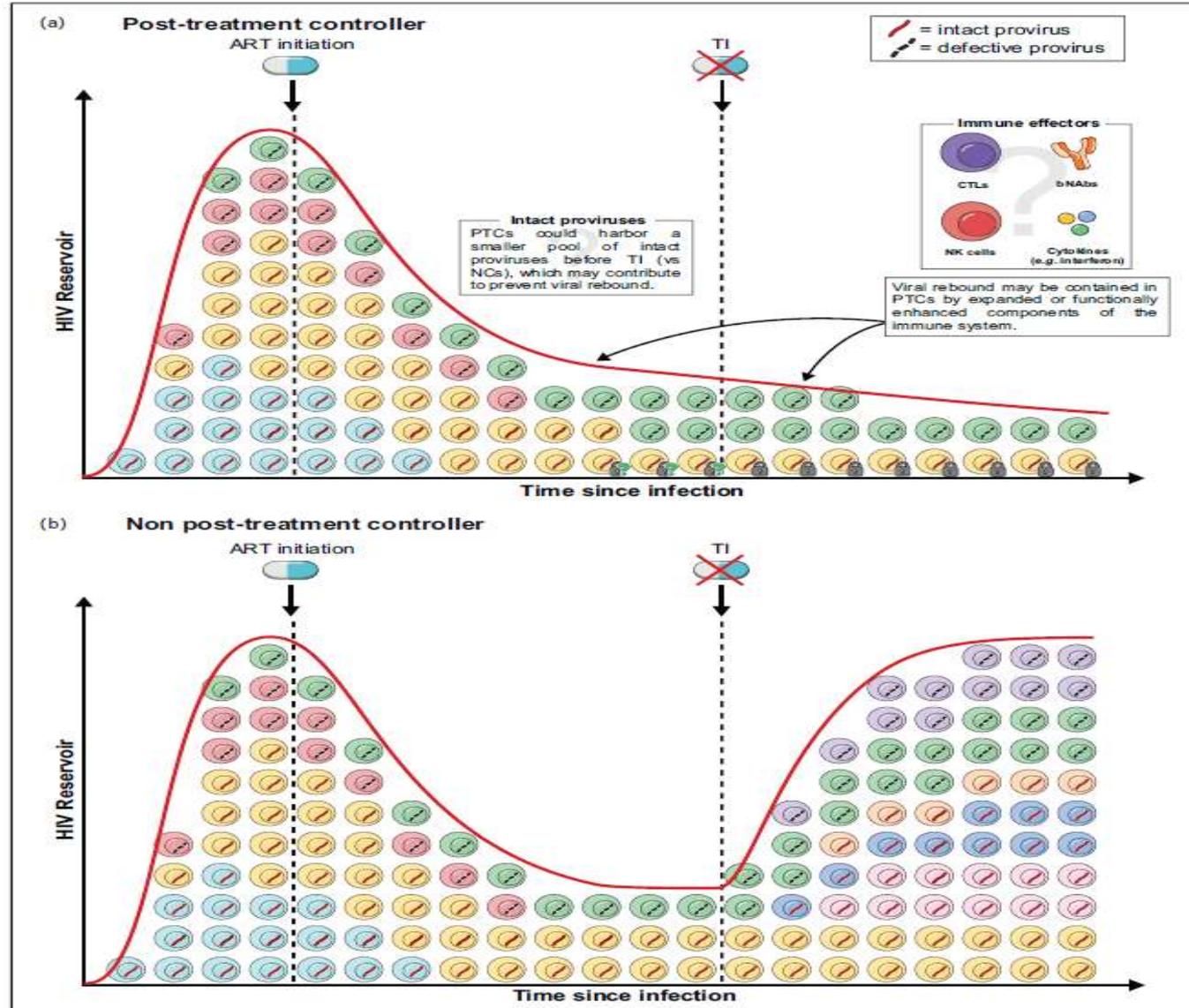
**Fig. 1** HIV reservoir formation and dynamics. **A** The reservoir is established primarily in memory CD4<sup>+</sup> T cells arising during the transition of infected effector cells to achieve immunological memory. Naive cells become activated during HIV-1 infection due to HIV-1 itself and other antigenic stimuli. The resulting activated effector cells are ideal targets for productive HIV-1 infection. A large fraction of the infected effector cells will not survive, but an important subset become quiescent and transition to a memory cell phenotype, thereby silencing HIV-1. **B** The primary mechanism for reservoir persistence is due to the clonal expansion of partially activated latently infected cells due to homeostatic proliferation driven by IL-7 or antigen stimulation. Different viral clones reactivate and expand under different conditions, with some clones being reduced or eliminated due to viral cytopathic effects. The result is a gradual simplification of the clonal population as demonstrated by recurring integration site sequences (denoted in the figure by different colors for the proviruses).

# HIV Rezervuarı

- Enfeksiyondan sonra 10 gün içinde başlanan tedaviye rağmen rebound olabiliyor
- Erken tedavi rezervuarın genişlemesini sınırılıyor
- Primer HIV enfeksiyonu(PHI) sırasında integre olmamış DNA ART ile kolayca temizlenir, uzun ömürlü hücrelere integrasyonu hafifletilebilir
- PHI döneminde kısa ömürlü geçici hafıza T hücreleri(TTM) predominant olarak enfekte durumdadır
- Kronik enfeksiyon döneminde ise(2-3 yıl sonra) integre olmuş DNA uzun ömürlü ve yüksek proliferasyon kapasiteli santral hafıza T hücrelerinde(TCM) predominant durumdadır
- Erken ART rezervuarın küçülmesini sağlasa da tedavi sonrası kontrol için(fonksiyonel kür) için ek immünolojik desteğe ihtiyaç var

Yang C et al. J Virus Eradication 2025

Charre C et al. Curr Opin HIV AIDS 2025



# Fonksiyonel Kür ve Sterilizan Kür

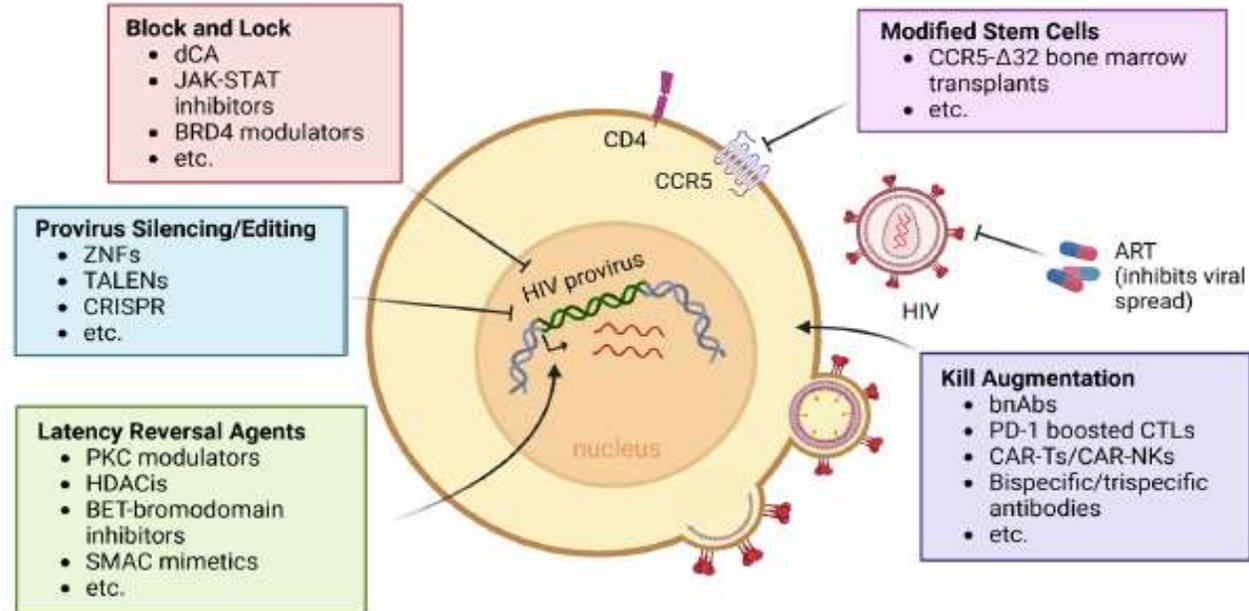
- Fonksiyonel Kür: Tedavi sonrası kontrol edenler(PTC)
  - ART kesildikten sonra düşük veya saptanamayacak düzeyde pVL
  - Erken ART PTC'yi sağlayabilir
  - ART kesilmesi sonrası hem PBMC hem de GALT'ta rezervuarın küçüklüğü
    - Kandaki PBMC rezervuarı EC'deki gibi
    - PHI sırasında ART başlanan hastalar gibi
    - PTC'lerde NC'lere göre NK hücre aktivasyonu artmış durumda
- Elit kontrol(EC)
  - HIV enfeksiyonu sonrası ART olmaksızın düşük düzey pVL
- Sterilizan Kür

# Sterilizan K r

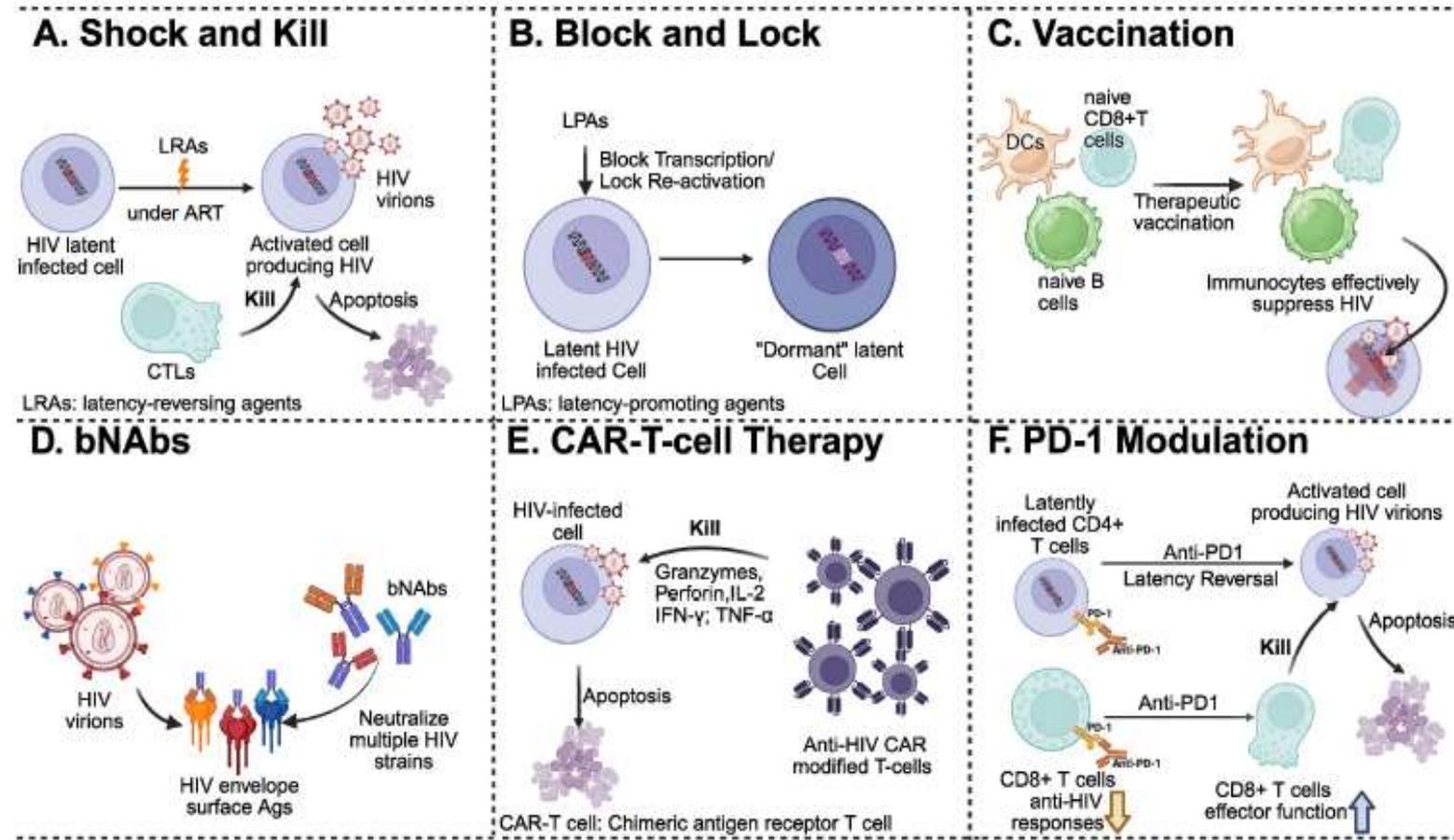
- Latent olarak HIV ile enfekte h crelerde( oğunlukla istirahat halindeki CD4+ T h creleri) proviral DNA transkripsiyonu zayıf ya da yoktur
- Viral protein ekspresyonunun olmaması, bu h crelerin dođal ve adaptif imm nite h creleri tarafından saptanması ve hasarlanmasını engeller
- Sterilizan k r, ancak latent olarak enfekte h crelerin elimine edilmesi ve enfekte olmayan h crelerin bunların yerini almasıyla(ideal olarak allo-HKHT gibi HIV enfeksiyonuna diren li h creler) oluřur

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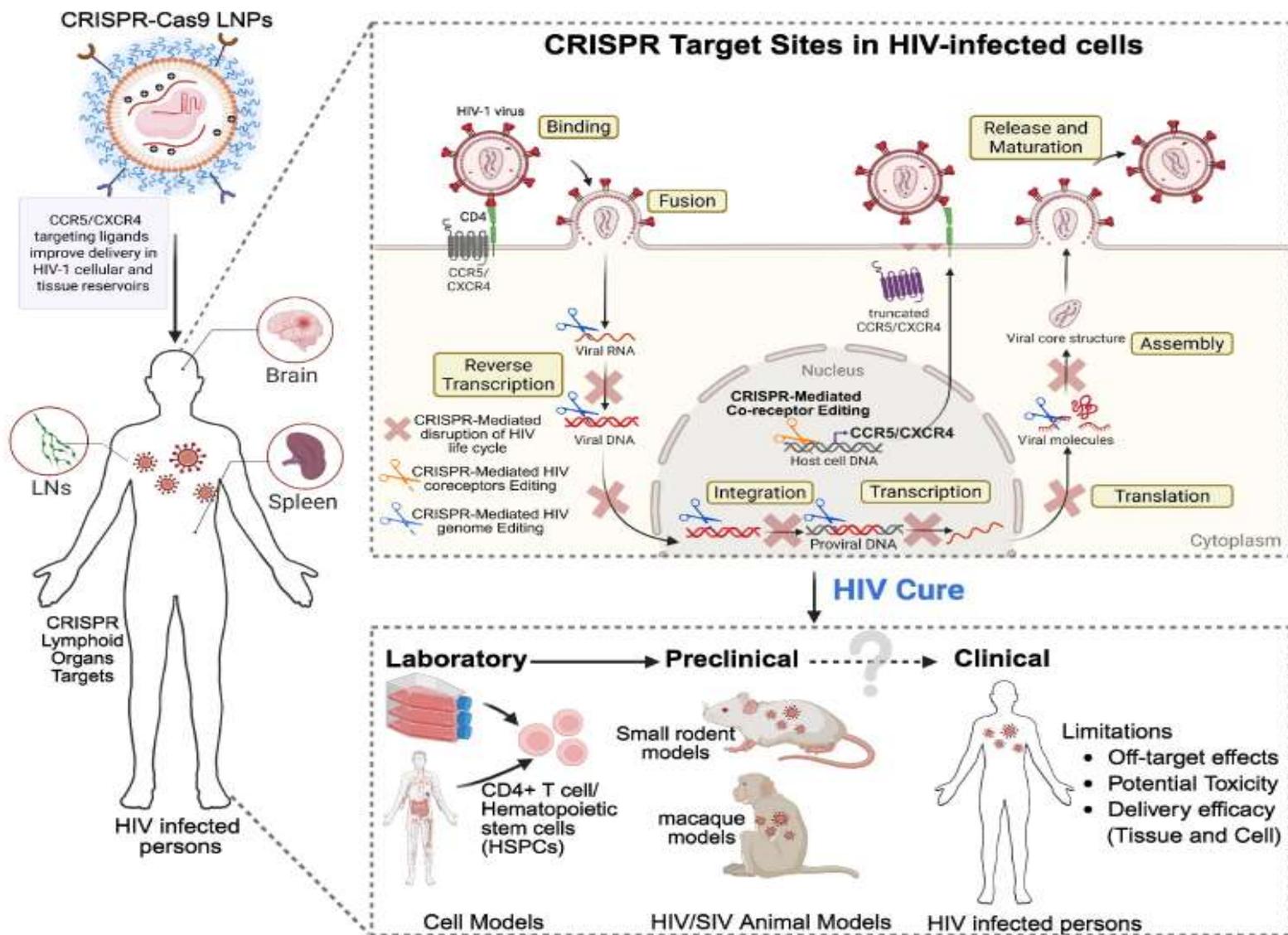
# HIV Persistence, Latency, and Cure Approaches: Where Are We Now?

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**Figure 4. Current HIV cure approaches.** General approaches to developing a cure for HIV that are currently being explored within the field include block and lock, provirus editing/silencing, latency reversal and kill augmentation (kick and kill), and stem cell transplantation/gene therapy. Block and lock agents include didehydro-cortistatin A (dCA), JAK-STAT inhibitors, and BRD4 modulators. Common provirus editing/silencing approaches have utilized zinc nuclease fingers (ZNFs), transcription activator-like effector nucleases (TALENs), and clustered regularly interspaced short palindromic repeats (CRISPR). Latency reversal cure approaches have included the use of protein kinase C (PKC) modulators, histone deacetylase inhibitors (HDACis), bromodomain extra-terminal motif (BET) bromodomain inhibitors, and second mitochondrial-derived activator of caspases (SMAC) mimetics. Kill augmentation has been explored with broadly neutralizing antibodies (bnAbs), programmed cell death protein (PD-1) boosted cytotoxic lymphocytes (CTLs), chimeric antigen receptor T and NK cells (CAR-T/CAR-NKs), and bispecific/trispecific antibodies, while modified stem cells with CCR5-Δ32 bone marrow transplants have been used to apparently cure HIV in a select few individuals.



**Figure 4. Current HIV elimination strategies.** **A)** The shock-and-kill strategy targets latent viral reservoirs using LRAs to “shock” the dormant virus into reactivation and render the virus detectable. The active virus then becomes vulnerable to attack by immune effector cells, like cytotoxic T cells (CTLs), or other treatments that “kill” infected cells or induce apoptosis. **B)** Block and lock approaches employ latency-promoting agents (LPAs) to permanently silence or control latency to prevent reactivation and rebound. This method triggers epigenetic changes that “block” viral transcription and “lock” the integrated virus into a dormant state, making reactivation impossible even if treatment is stopped. **C)** Vaccination strategies aim to stimulate or enhance humoral and/or cell-mediated immune responses to regulate viral replication and ultimately eradicate reservoirs. These strategies involve designing HIV immunogens, with or without adjuvants, that activate dendritic cells (DCs) to stimulate naïve CD8<sup>+</sup> T cells to become CTLs, or B cells to develop into plasma cells that produce HIV-specific antibodies (Abs) capable of killing HIV-infected cells. **D)** Broadly neutralizing antibodies (bNAbs) are a special type of Abs that can neutralize numerous HIV strains. They target conserved regions on the viral surface, such as Env proteins. Unlike naturally induced antibodies, bNAbs are typically engineered and administered passively rather than produced through vaccination. **E)** Chimeric antigen receptor (CAR) T-cell therapy involves genetic constructs that encode antigen-recognition chains, often derived from HIV-specific Abs, used to modify T cells of PLWH. These HIV-specific CAR T cells recognize and eliminate HIV-infected cells, including viral reservoirs, through cytotoxic mechanisms that induce apoptosis. **F)** Programmed death-1 (PD-1) modulation strategies use anti-PD-1 antibodies to target exhausted T cells expressing PD-1, aiming to either remove these T cells or restore their impaired effector functions to boost virus-specific immunity. Created with BioRender.com.



**Figure 5. Strategic HIV elimination targeting cellular and tissue reservoirs using CRISPR-Cas9.** CRISPR-Cas9-based systems provide high specificity for latent proviral DNA and represent a promising approach for eliminating viral reservoirs. In this system, viral guide RNAs (gRNAs) recognize complementary sequences in latent HIV DNA, which are then excised by Cas enzymes. Beyond targeting viral DNA, CRISPR-Cas9 can also be used to disrupt host genes (for example, CCR5 or CXCR4) to block co-receptor binding, inhibit viral entry, and suppress replication. CRISPR-Cas9 technology can intervene at multiple stages of the HIV life cycle, including reverse transcription, integration, viral protein transcription, and assembly, thereby disrupting viral core formation and replication. Despite its genetic specificity, delivery to infected cells remains a major challenge. Viral vectors (e.g., adeno-associated viruses (AAVs)) or LNPs are commonly used; however, optimizing efficient delivery to all reservoir cells is ongoing. To better target immune cells within viral reservoirs, strategies to incorporate ligands for immune cell receptors, such as for CCR5 and/or CXCR4, into the delivery platforms are anticipated to improve target specificity and delivery efficiency. Preclinical testing of targeted CRISPR-Cas9 delivery systems is currently undergoing in laboratory settings, including HIV-infected CD4<sup>+</sup> T cells and macrophages, small rodent models, and SHIV-infected macaques, with eventual translation to HIV-1-infected subjects. While the delivery and excision specificities of CRISPR-Cas9 systems are promising, potential limitations that may affect treatment outcomes include off-target editing of the host genome, inefficient delivery to latent reservoirs, endosomal degradation of LNP cargo, immunogenicity to bacterial CRISPR-Cas9 components, emergence of HIV escape variants, and possible toxicities. Created with BioRender.com.

# Viral Rezervuarın Elimine Edilmesinin Önündeki Engeller

- Bazı rezervuarlar ART'nin ulaşamadığı anatomik bölgelerde
- Rezervuar erken dönemde oluşuyor
- Rezervuar hücreleri uzun ömürlü
- Proviral DNA'nın yarılanma ömrü uzun
- Enfekte hücrelerde MHC-I ekspresyonunda baskılanma
- Rezervuarın özgül bir belirteci yok
- Bazı rezervuar hücreleri bağışıklık kontrol noktası moleküllerini yüksek derecede eksprese ederler
- Rezervuar, immün sistemi süreç olarak tükenmişliğe götürür

