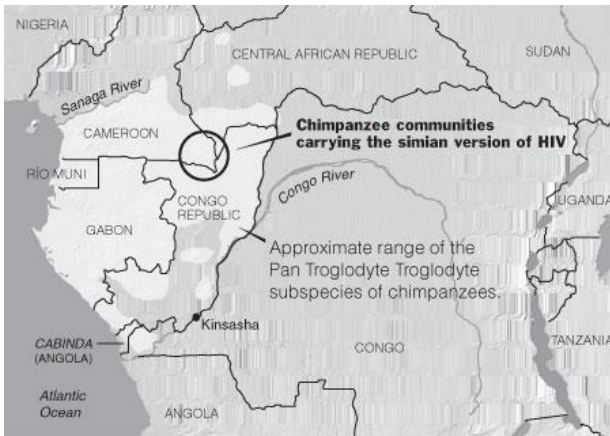
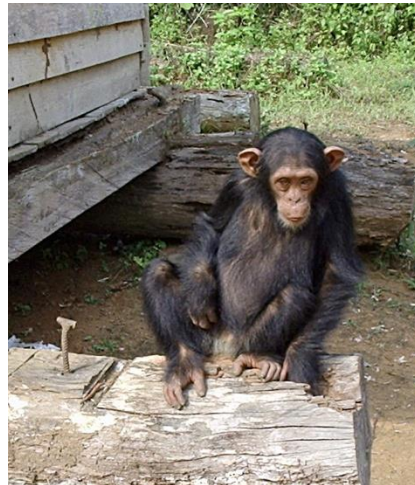


# Kür yolunda gelişmeler

Ahmet Çağkan İnkaya  
Hacettepe Üniversitesi Tıp Fakültesi  
Enfeksiyon Hastalıkları Anabilim Dalı  
[inkaya@hacettepe.edu.tr](mailto:inkaya@hacettepe.edu.tr)

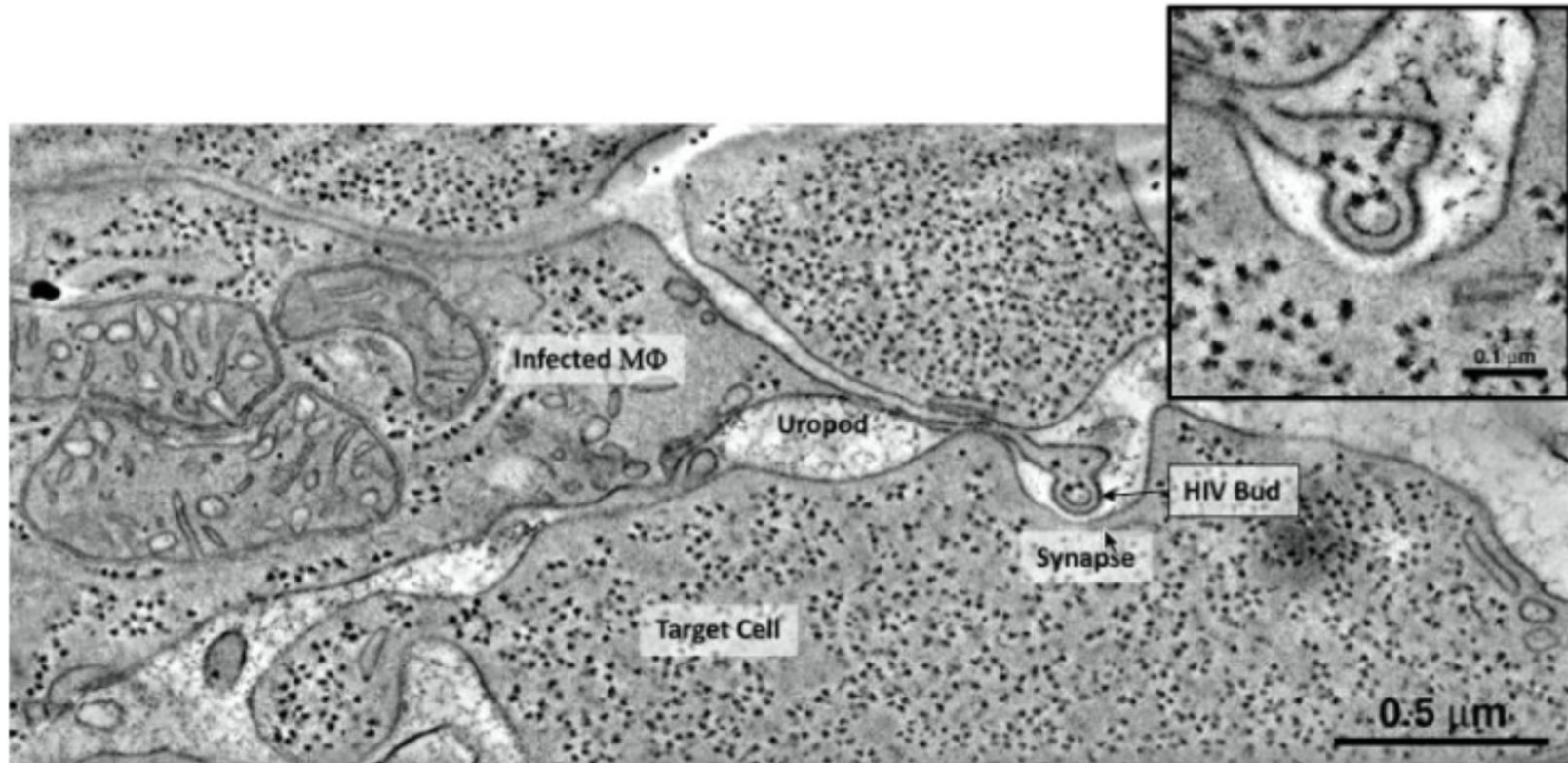


# Tarihçe

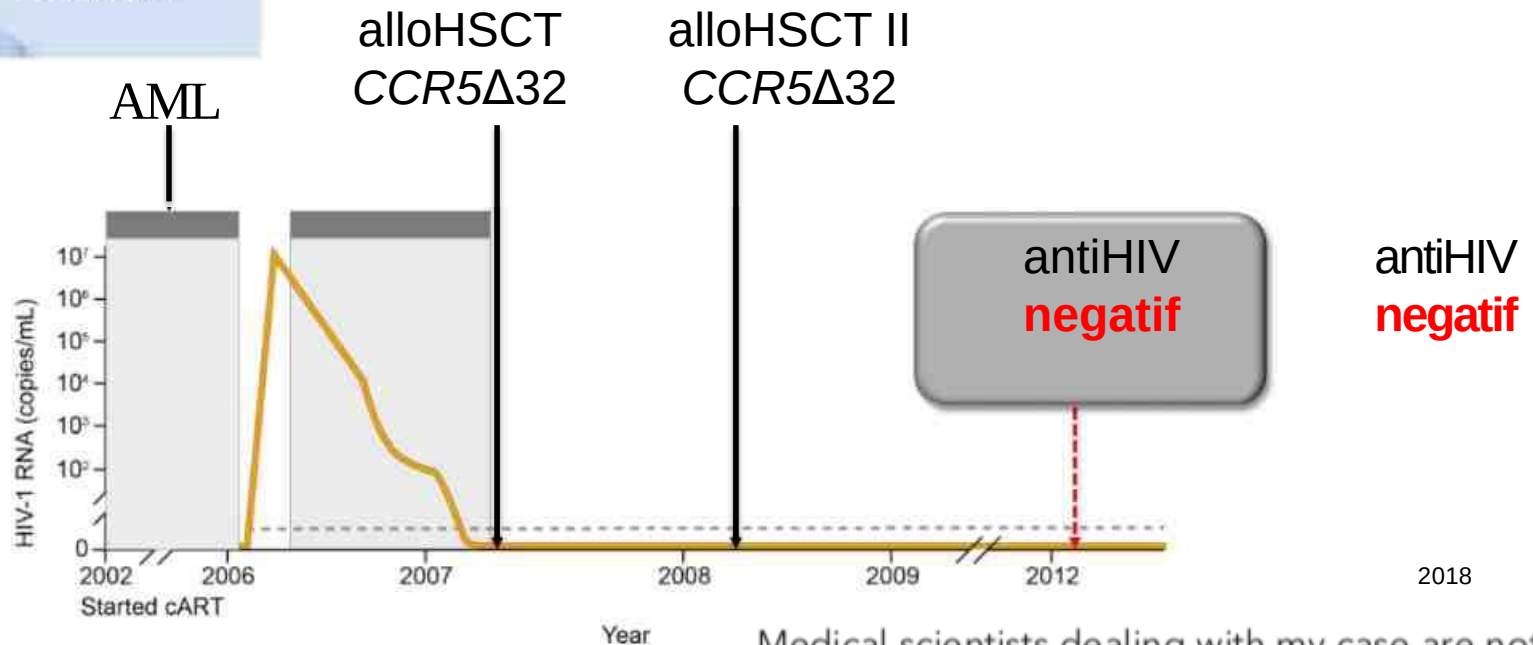


**AIDS PANDEMIC**

# Düşmanı tanımak lazım



# Biraz da şans lazım: HIV kürü mümkün olabilir



Medical scientists dealing with my case are not really certain what actually cured me of HIV. I think it was the lack of C-C chemokine receptor type 5 (CCR5) protein in the donor stem cells, but . . . I realize I could be wrong.

—Timothy Ray Brown (1)

# Kür neden gerekli?

- Maliyet
  - 326000 USD
  - 2020 yılı için global olarak 26 Milyar USD
- Stigma
- Biriken ilaç yan etkisi
- Bulaş tamamen engellenemiyor
- Uzun dönemli inflamasyon ve getirdikleri

Marsh Sung J, Margolis DM 2018 *HIV persistence on antiretroviral therapy and barriers to a cure in Advances in experimental Medicine and Biology* Springer Nature Singapore  
Aquila R 2018 *Learning about “known unknowns” and “unknown unknowns” to cure HIV* Annals of Internal Medicine



# Kür neden zor?

## ■ Rezervuar

- CD4 hücrelerde yarı ömür uzun: 43-44 ay
- ART ile tam eradikasyon 70 yıl

Marsh Sung J, Margolis DM 2018 *HIV persistence on antiretroviral therapy and barriers to a cure* in *Advances in experimental Medicine and Biology* Springer Nature Singapore  
Aquila R 2018 *Learning about “known unknowns” and “unknown unknowns” to cure HIV* Ann Int Med

# Ne yapılabilir?

## ■ Rezervuarı azaltmak için

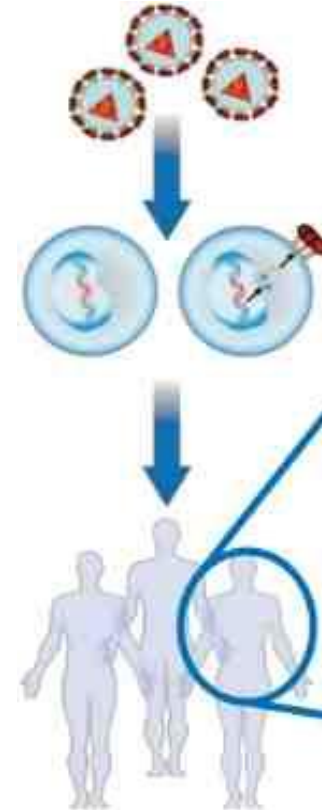
- Erken tedavi
- **KICK & KILL**
  - Latent rezervuarı uyarmak, bu sayede enfekte hücreleri açığa çıkarmak
- **Kes at**
  - CRISPR/CAS9
- **BLOCK & LOCK**
  - Süper latans

**Table 7.1** List of key definitions

| Term                        | Definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Anatomic sanctuary          | A site that may provide a sanctuary for the active reservoir, putatively due to either poor ART penetrance or poor access by cytotoxic immune effector cells                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Active reservoir            | Persistently infected cells that continue to transcribe HIV RNA, presenting HIV antigen                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Homeostatic proliferation   | Proliferation of cells under the regulation of cytokines such as IL-7 and IL-15 that allows for the self-renewal and expansion of a small population of cells                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Latent reservoir            | Intact HIV provirus that is transcriptionally silent, but capable of being induced to produce replication-competent viral particles                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Latency-reversing agent     | An intervention that reverses latency by inducing latently infected cells to produce detectable viral particles                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Productive infection        | HIV infection with active transcription and production of viral particles                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Replication-competent virus | The majority of HIV DNA that is measured represents defective virus of unclear relevance to cure efforts and thus overestimates the size of the latent reservoir. Replication-competent, inducible virus, in contrast, represents integrated HIV provirus that is capable of producing virions that will propagate further spread of infection in the absence of ART. The current gold standard to measure replication-competent virus is the quantitative viral outgrowth assay (see below and Chap. 11), but this assay underrepresents the true size of the latent reservoir |



- CD4 lenfositler HIV'in ana hedefi
  - Aktif çoğalan
  - Aktif çoğalmayan
- Viral sitopatik etki ile hızla CD4 kaybı
  - Bir grup CD4 hücre ölmeyebilir



# Replikasyon-yetkin virüs

- Her latent virüs replike olamaz
- HIV DNA
  - $T_{TM}$  (geçici hafıza)
  - $T_{CM}$  (merkezi hafıza)
  - $T_{SCM}$  (merkezi hafıza kök hücre)
- Replikasyon yetkinliği olan ana kompartman
  - $T_{CM}$

# Diğer rezervuar hücreleri

- Gama delta T hücreleri
  - Normalde CD4 negatiftir
  - Aktive olduklarında CD4 expresse eder
- Monosit/makrofajlar

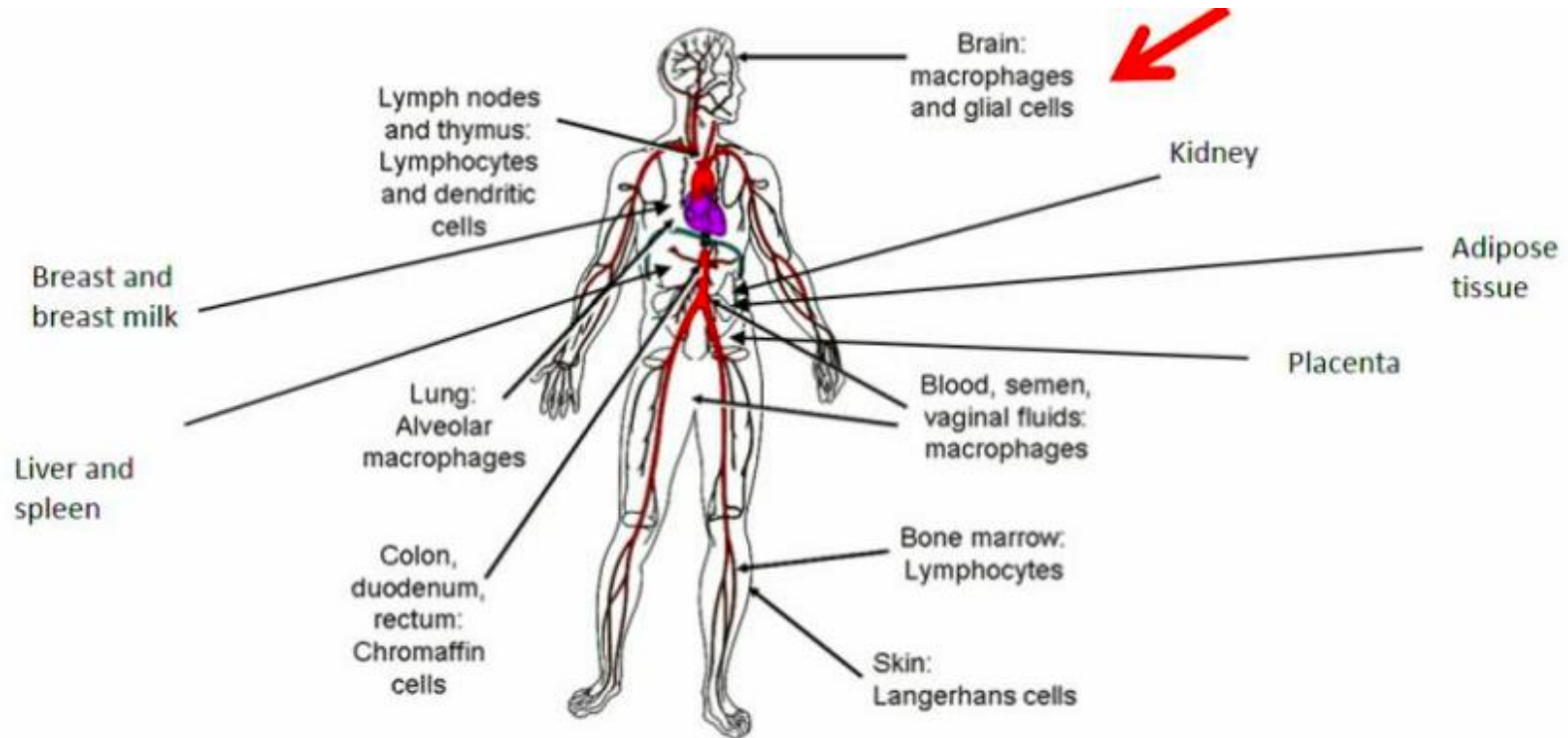
Soriano-Sarabia N etal *Peripheral Vgamma9Vdelta2 T cells are novel reservoir of latent HIV infection* PlosPathogens

Arainga M etal 2017 *A mature macrophage is principal HIV-1 cellular reservoir in humanized mice after treatment with long acting antiretroviral therapy* Retrovirology

# Rezervuar nasıl stabil kalıyor

- Aktif replikasyon
- Latent enfekte hücrelerin proliferasyonu
  - IL15, IL7

# Rezervuar nerede?



Adapted from Microbiology and Immunology online, R. Hunt, 2013 and Wong Curr\_Op\_HIV AIDS, 2016

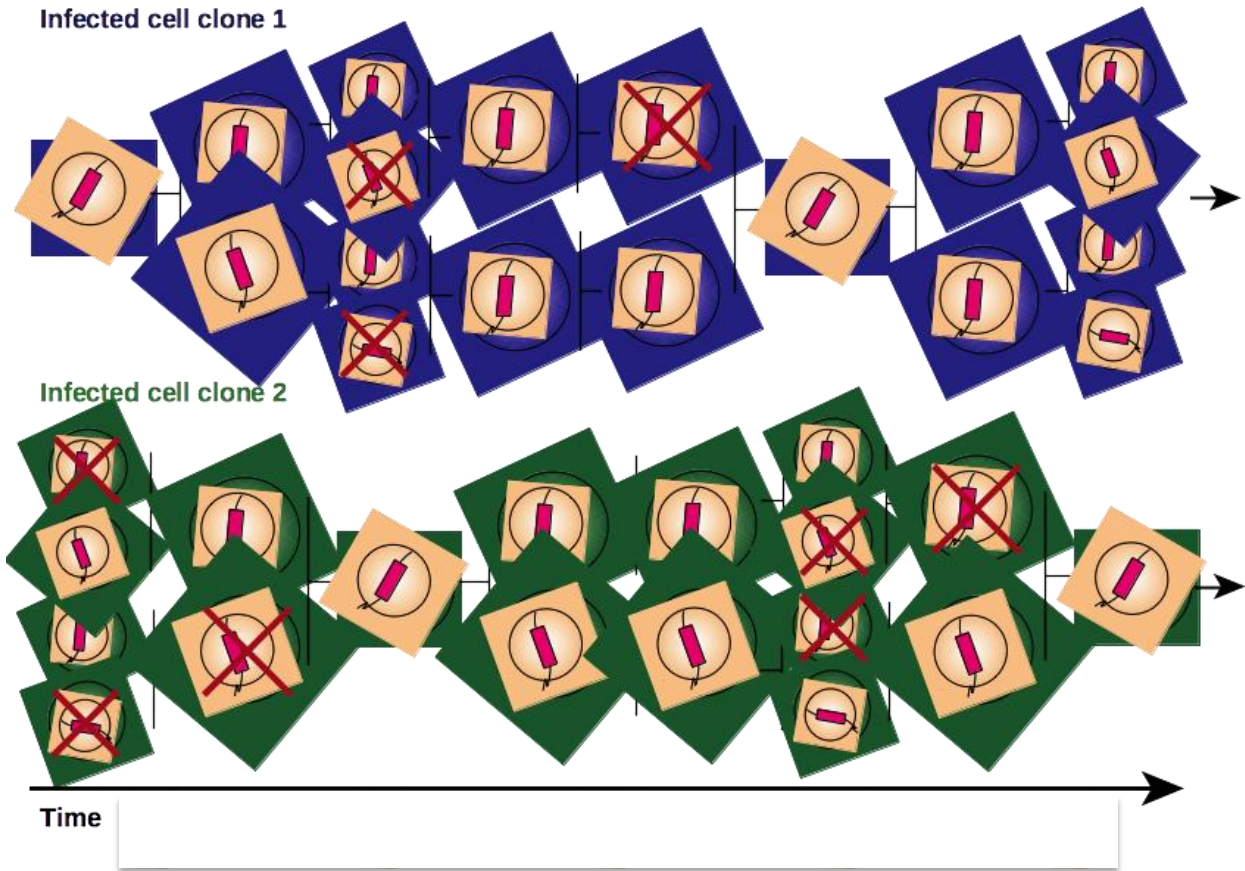
# Expanded cellular clones carrying replication-competent HIV-1 persist, wax, and wane

2018, PMC5856552

Zheng Wang<sup>a</sup>, Evelyn E. Gurule<sup>a</sup>, Timothy P. Brennan<sup>a</sup>, Jeffrey M. Gerold<sup>b</sup>, Kyungyoon J. Kwon<sup>a</sup>, Nina N. Hosmane<sup>a</sup>, Mithra R. Kumar<sup>a</sup>, Subul A. Beg<sup>a</sup>, Adam A. Capoferri<sup>a</sup>, Stuart C. Ray<sup>a</sup>, Ya-Chi Ho<sup>c</sup>, Alison L. Hill<sup>b</sup>, Janet D. Siliciano<sup>a,d,1</sup>, and Robert F. Siliciano<sup>a,d,1</sup>



Rezervuar dinamikdir



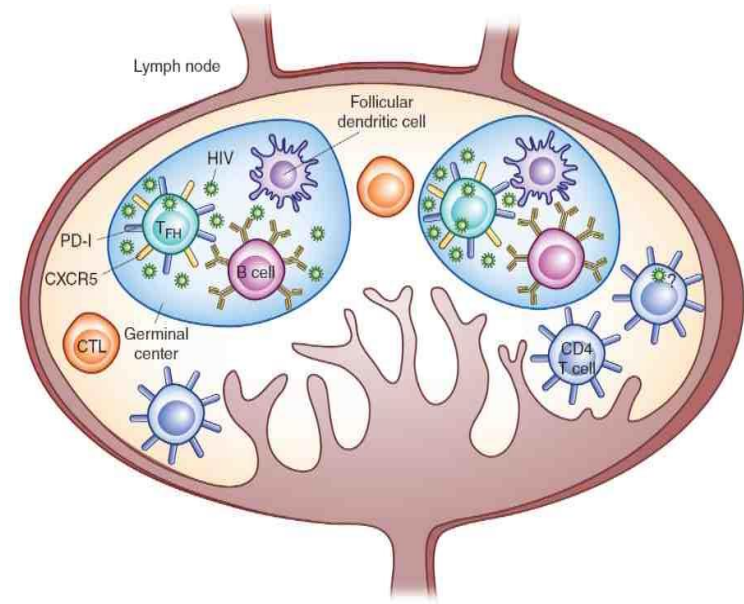


# HIV rezervuar düzeyi neden etkilenir?

- Erken tedavi
  - Fiebig I
- En yüksek HIV RNA
- En düşük CD4
- Immün aktivasyon düzeyi

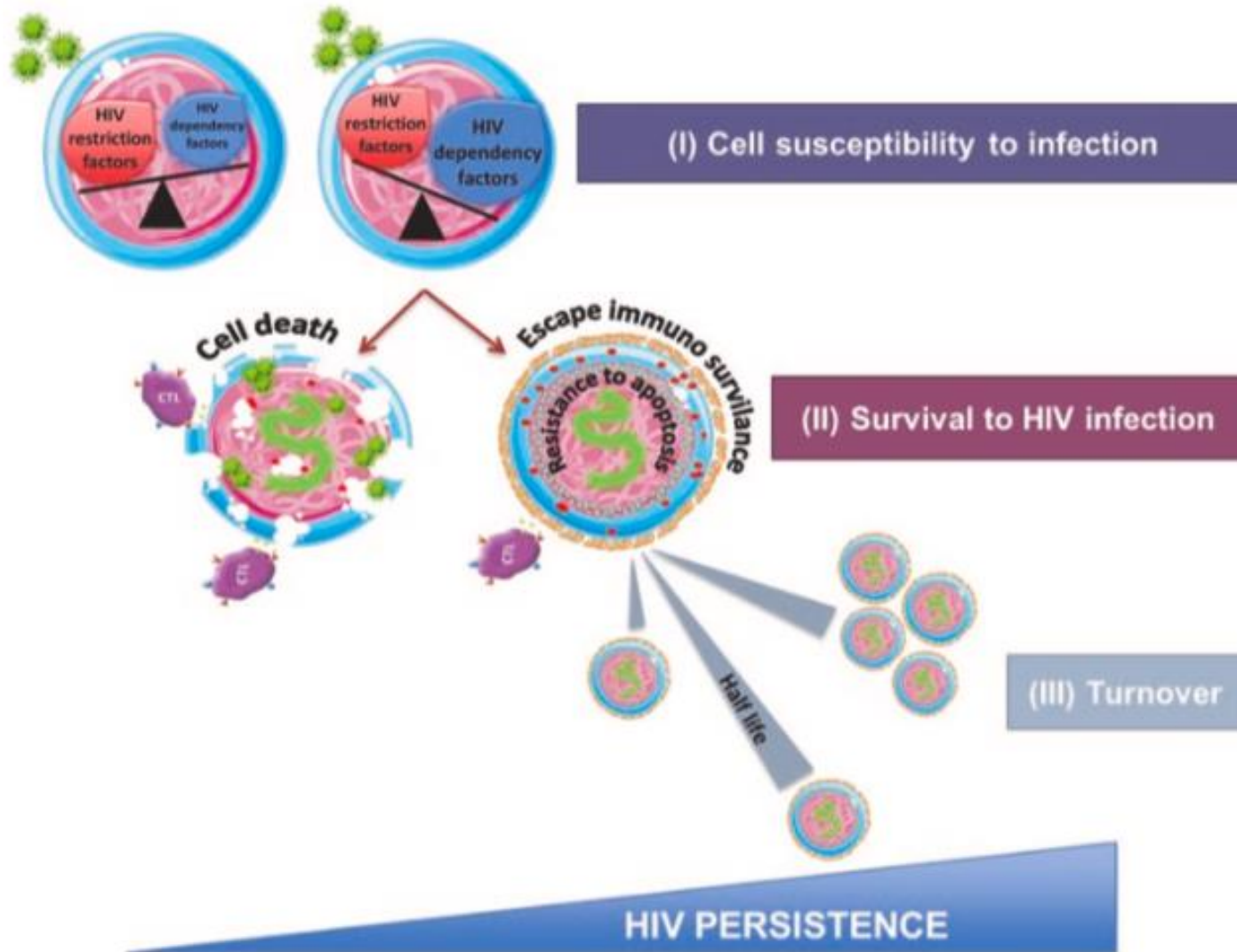
# Aktif rezervuar

- $T_{FH}$ 
  - CXCR5 ve PD1 pozitif
  - B lenfoid follikülde
  - Dentritik hücrelerle yakın ilişkide
- Anatomik kaçış bölgeleri

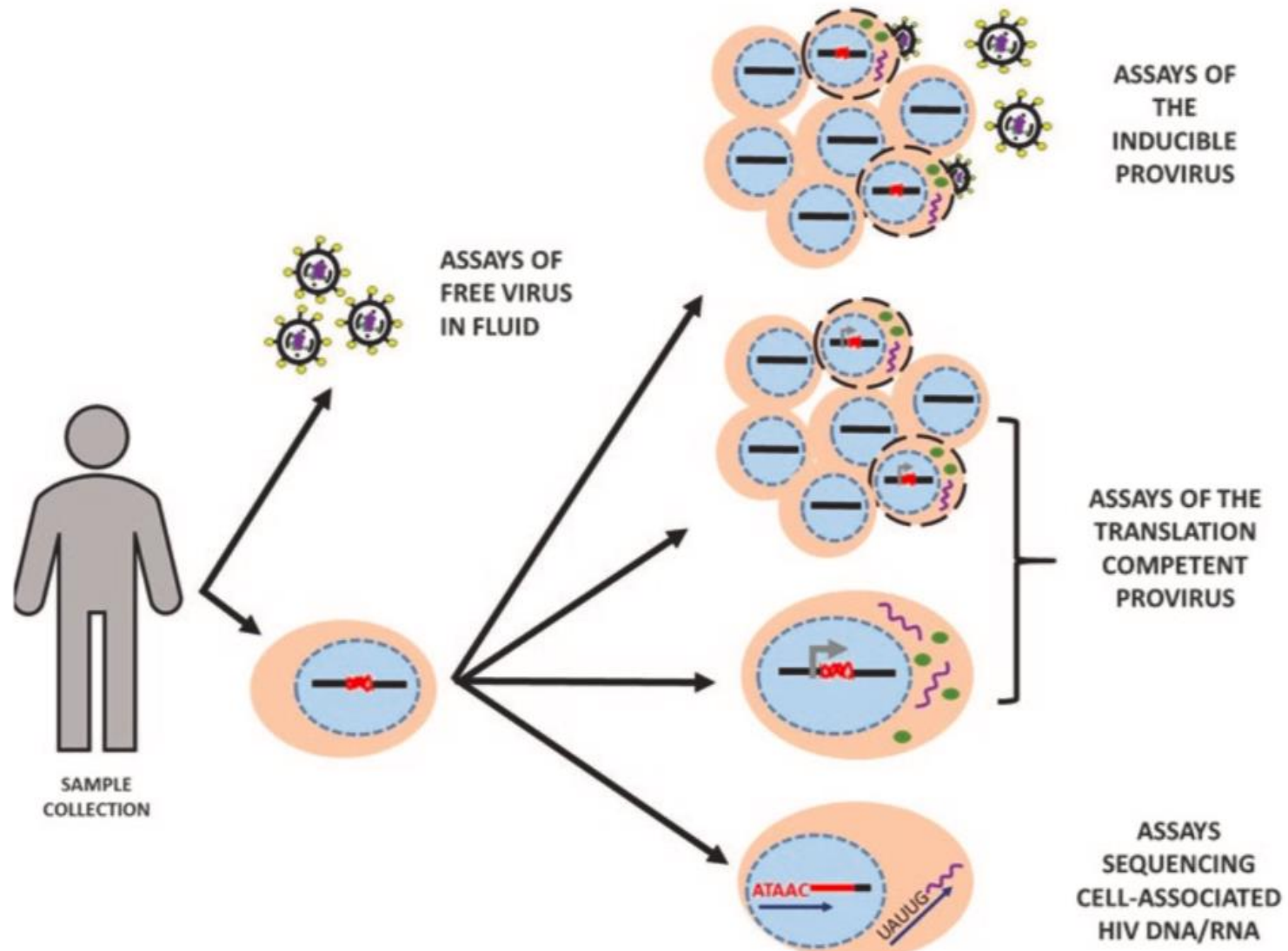


Banga R et al 2016 *PD1<sup>+</sup> and follicular helper T cells are responsible for HIV persistence on antiretroviral therapy in treated viremic individuals* Nat Med  
Marsh Sung J, Margolis DM 2018 *HIV persistence on antiretroviral therapy and barriers to a cure* in *Advances in Experimental Medicine and Biology* Springer Nature Singapore

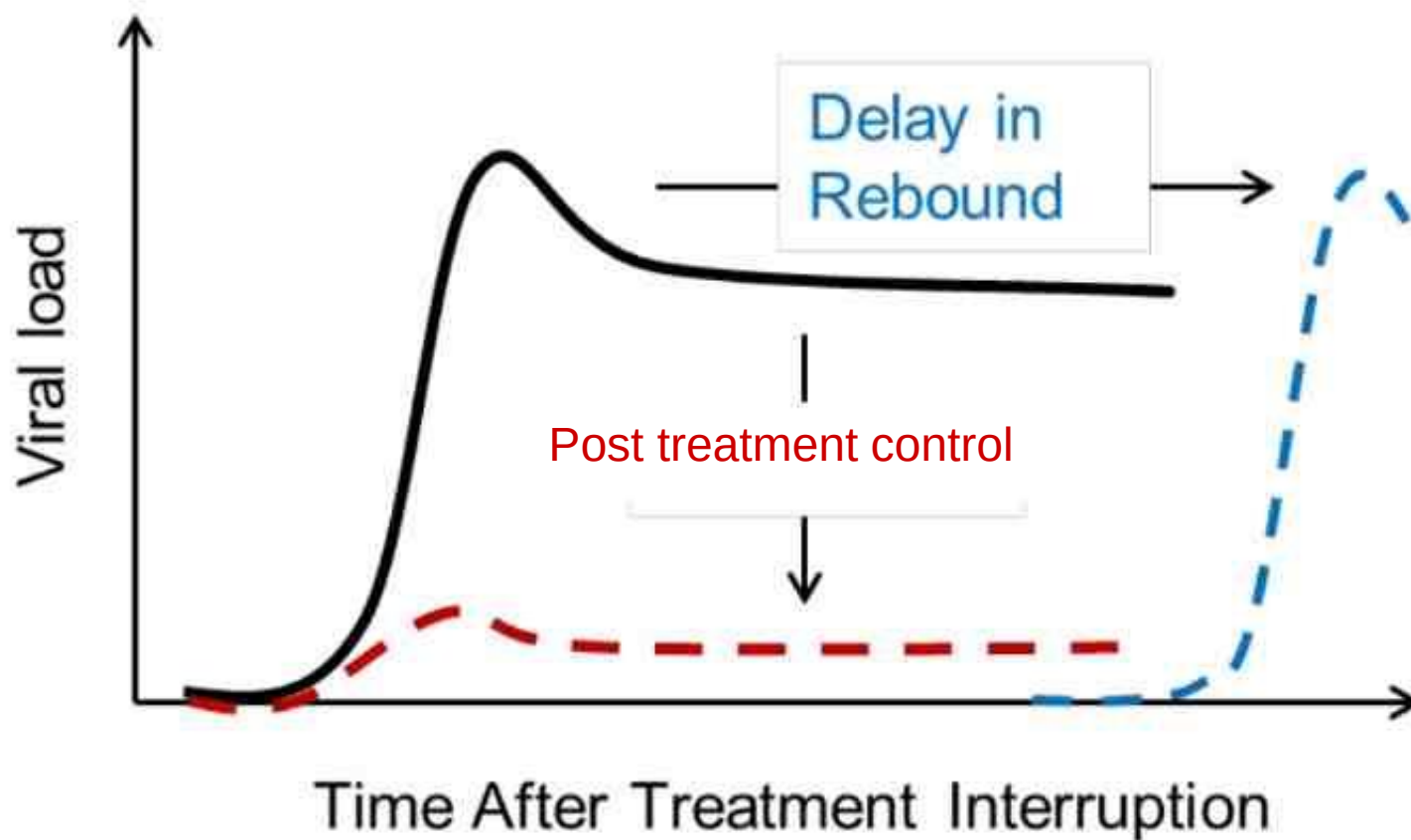
# HIV'in hücre içinde sağ kalması



# Tedavi altında HIV tespiti



# Treatment interruption is the only way to determine if an intervention is successful



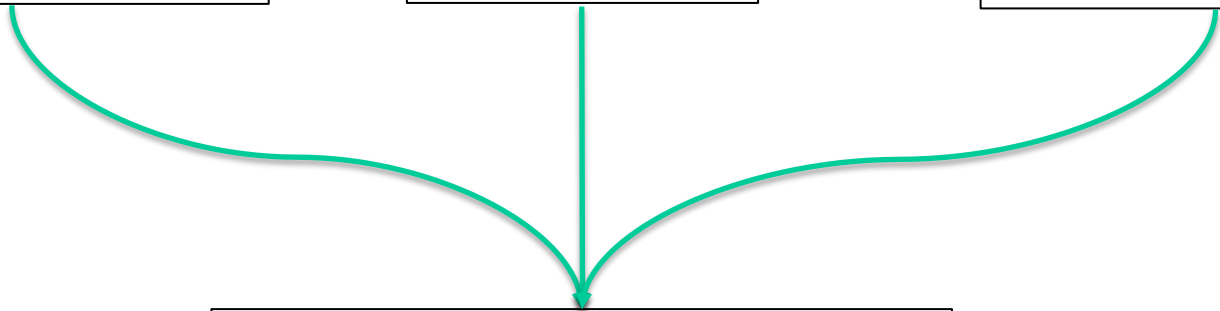
No biomarker available that can predict time to rebound or post treatment control

**HIV Rezervuarı  
ölçmede güçlükler**

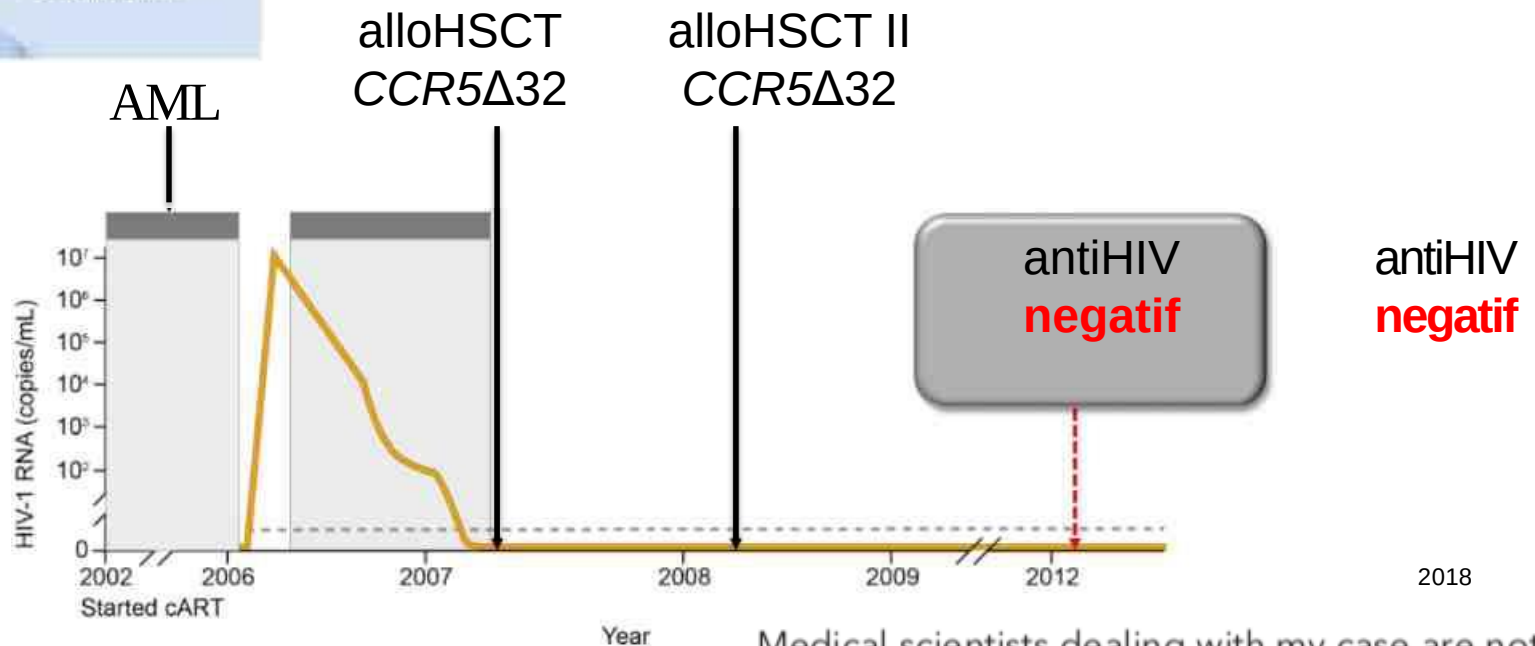
**Rezervuar  
dinamizmi**

**Rezervuar ölümsüz  
olabilir**

**Klinik çalışma sonuçları**



# HSCT



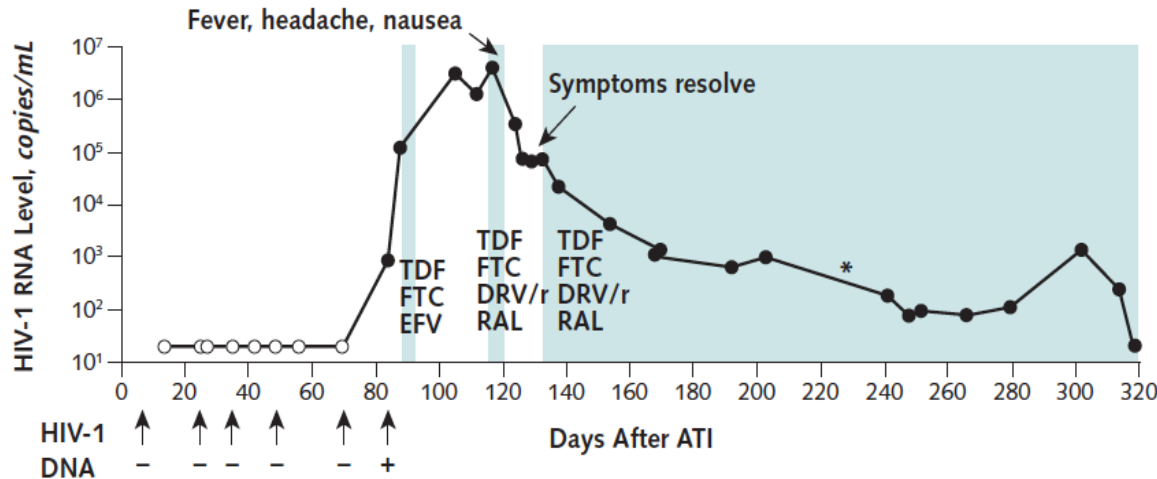
Medical scientists dealing with my case are not really certain what actually cured me of HIV. I think it was the lack of C-C chemokine receptor type 5 (CCR5) protein in the donor stem cells, but . . . I realize I could be wrong.

—Timothy Ray Brown (1)



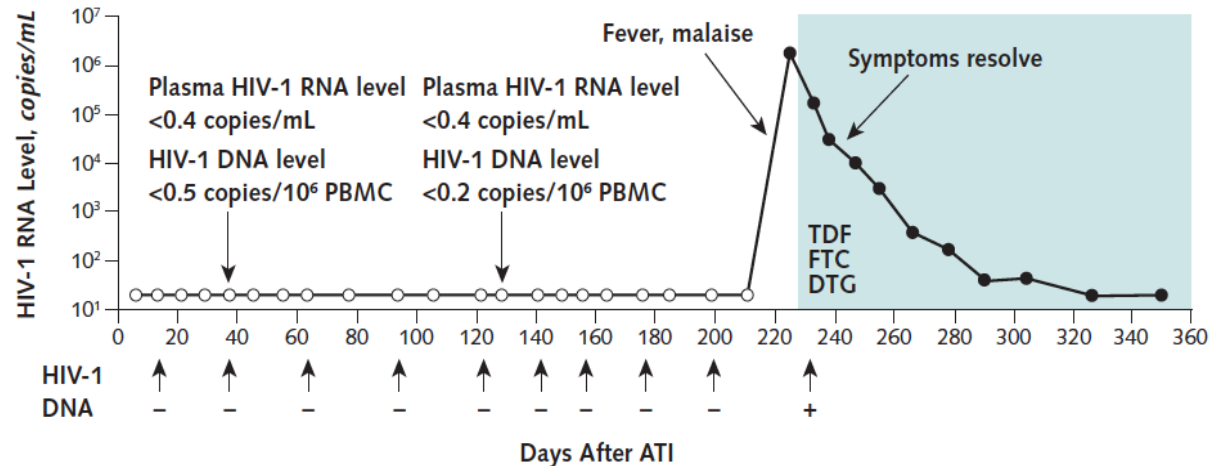
# Kür için HSCT

Patient A



(Boston hastaları)

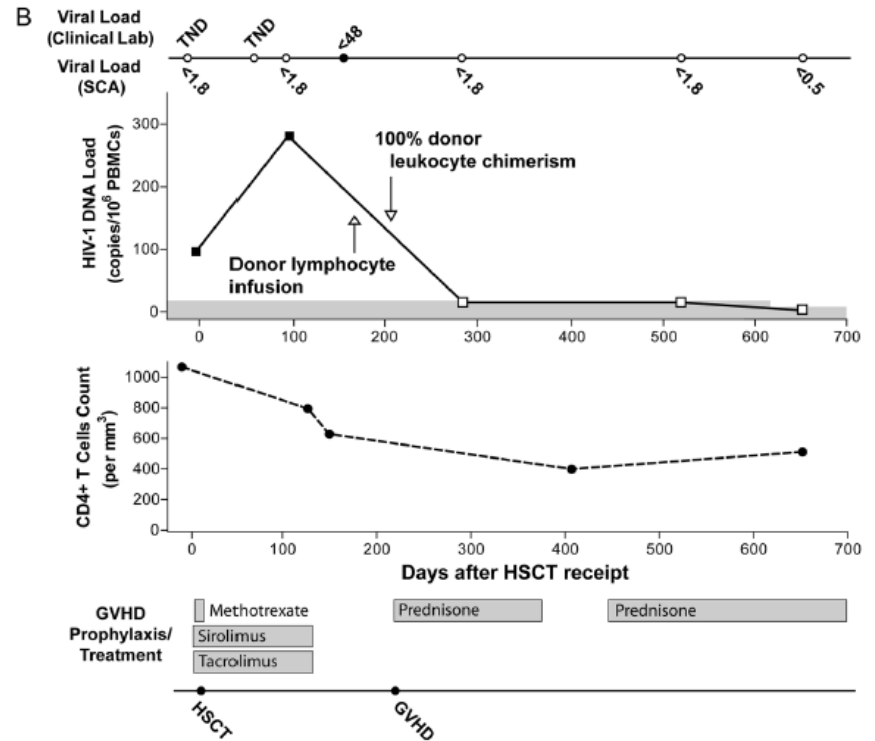
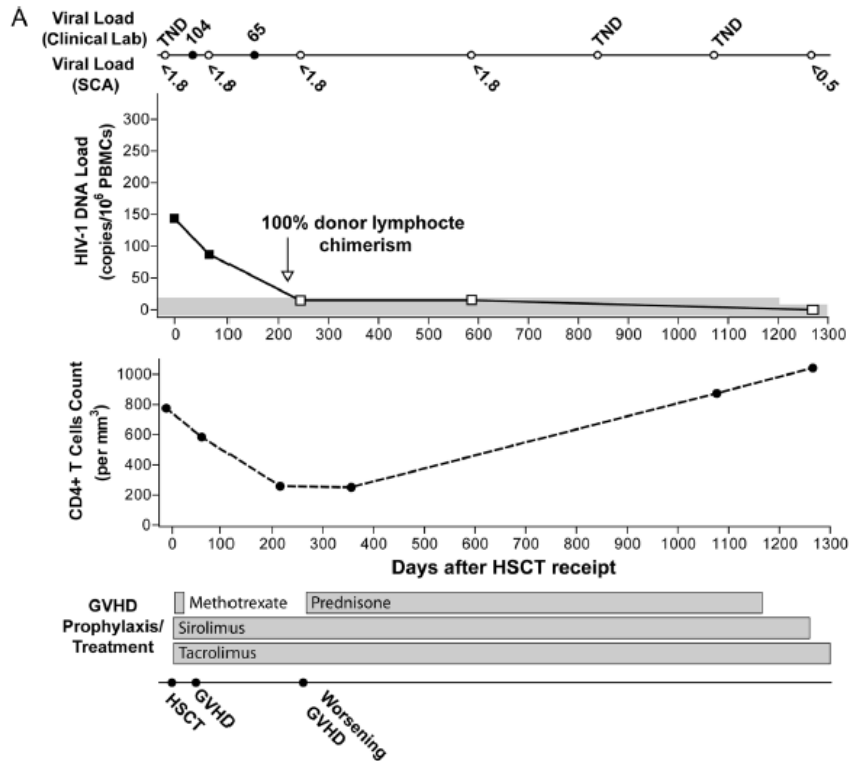
Patient B



Henrich TJ et al 2014 *antiretroviral free HIV1 remission and viral rebound after allogeneic stem cell transplantation: report of 2 cases* Ann Intern Med

Rasmussen TA et al 2018 *Clinical interventions in HIV cure research* Advances in Experimental Medicine and Biology Springer Nature Singapore

# Kür için HSCT



Henrich TJ et al 2014 *antiretroviral free HIV1 remission and viral rebound after allogeneic stem cell transplantation: report of 2 cases* Ann Intern Med

Rasmussen TA et al 2018 *Clinical interventions in HIV cure research* Advances in Experimental Medicine and Biology Springer Nature Singapore

# Kür için HSCT

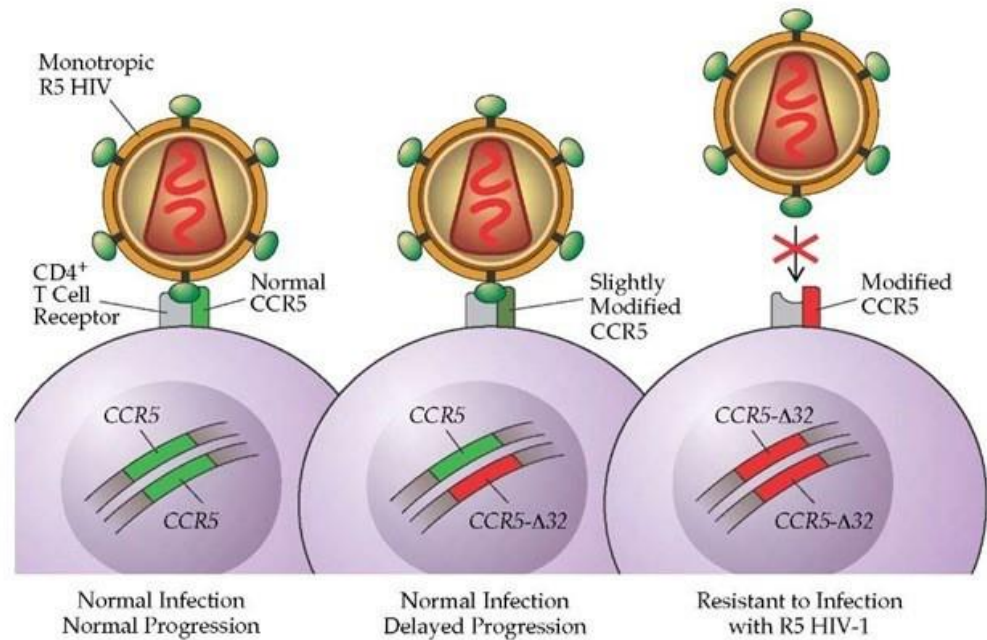
- Timothy Ray Brown'da neden başarılı?
  - Ciddi GVHD
  - Tedavi rejimi
    - Myeloablatif
    - Conditioning

Medical scientists dealing with my case are not really certain what actually cured me of HIV. I think it was the lack of C-C chemokine receptor type 5 (CCR5) protein in the donor stem cells, but . . . I realize I could be wrong.

–Timothy Ray Brown (1)

# Kür için genetik mühendislik

- Berlin hastasından alınan ilhamla
  - CRISPR/CAS
  - $CCR5\Delta32$



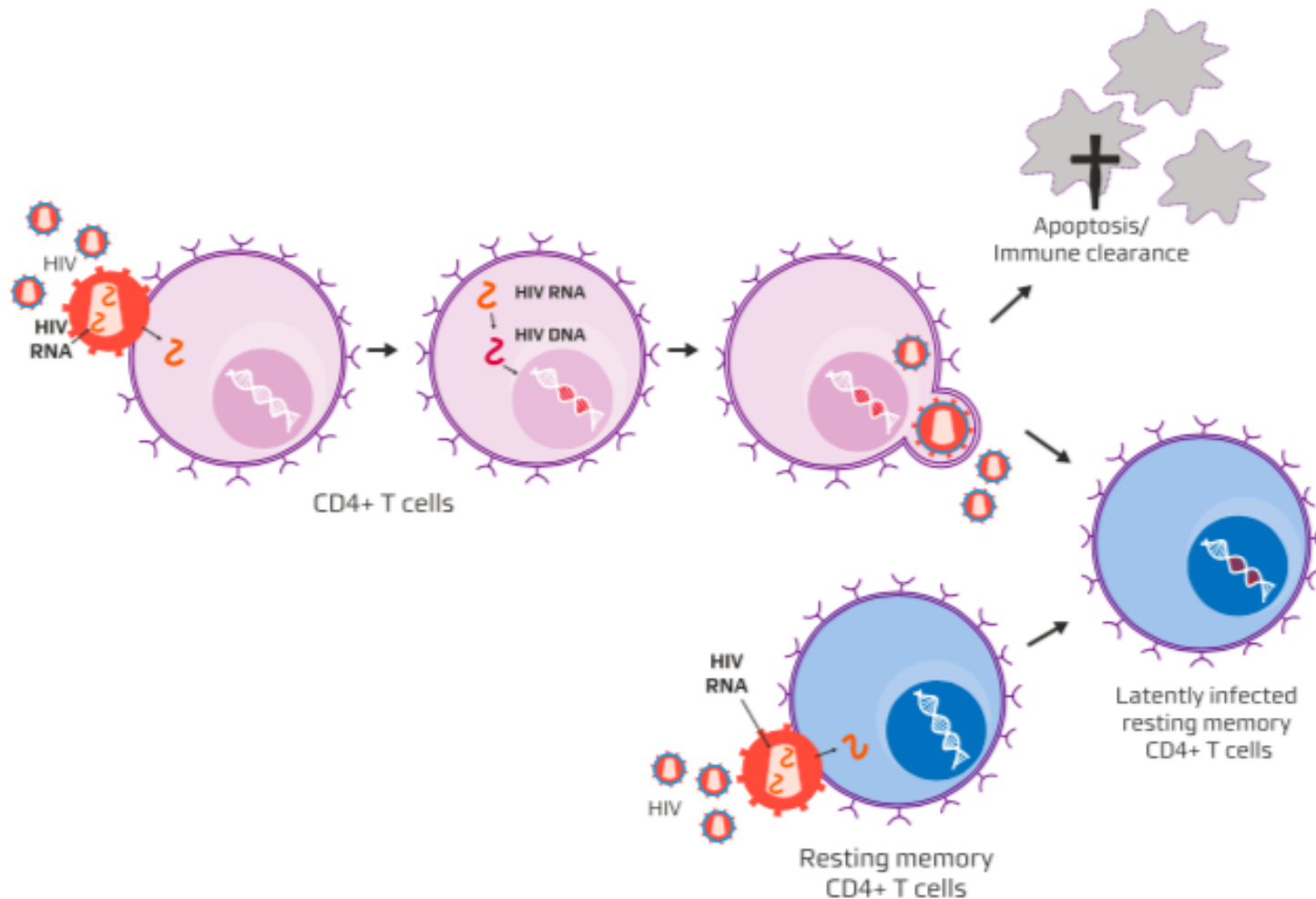
# Tedavi yoğunlaştırma

- Faydasız

# Erken tedavi

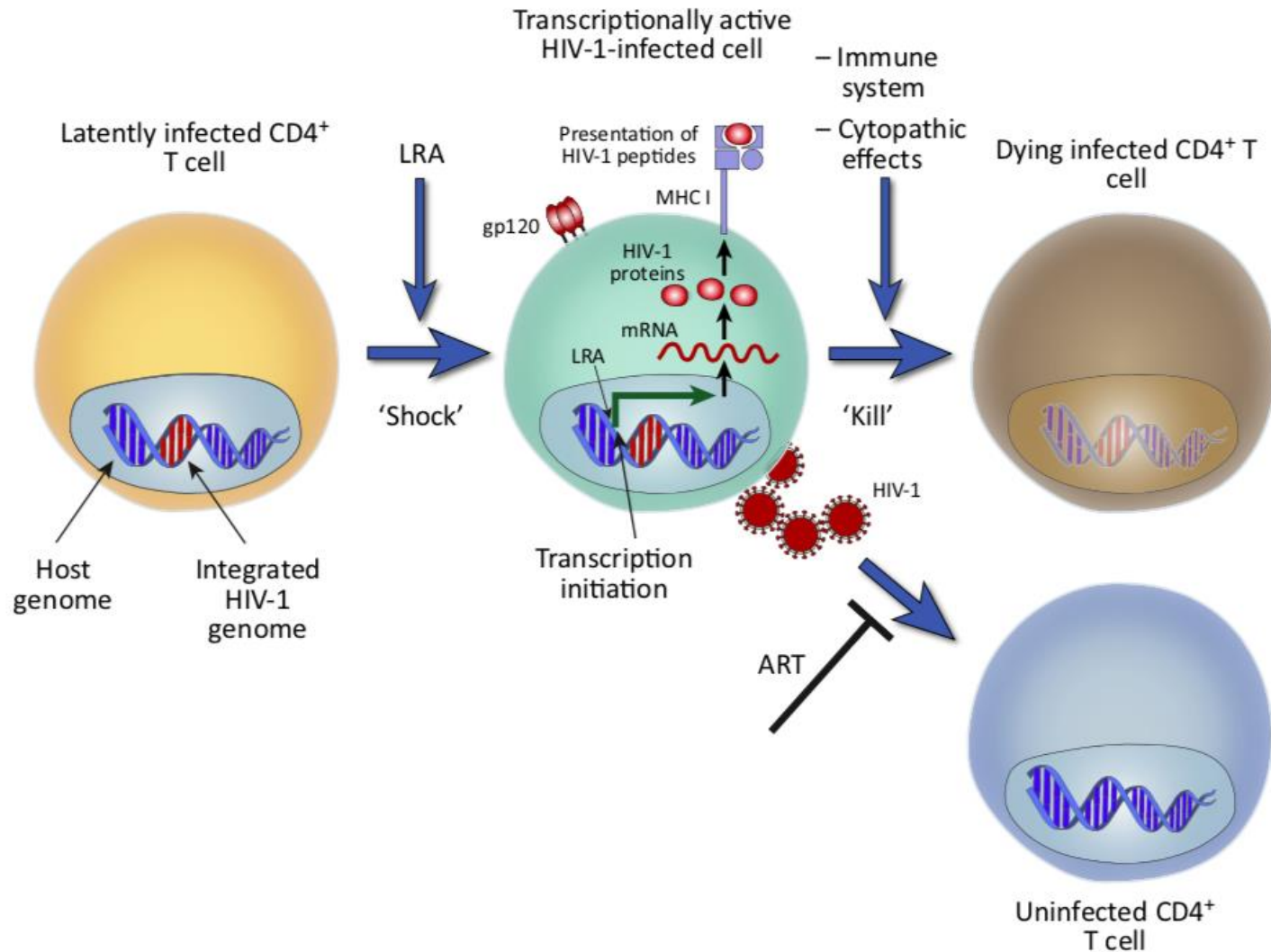
- Missisipi bebeği
  - Erken tedavi rezervuar miktarını azaltıyor
- Rhesus maymunlarında SIV bulaşı sonrası
  - Erken ART ile viremi ve DNA yok
  - ART kesilirse viremi

# Şokla ve öldür

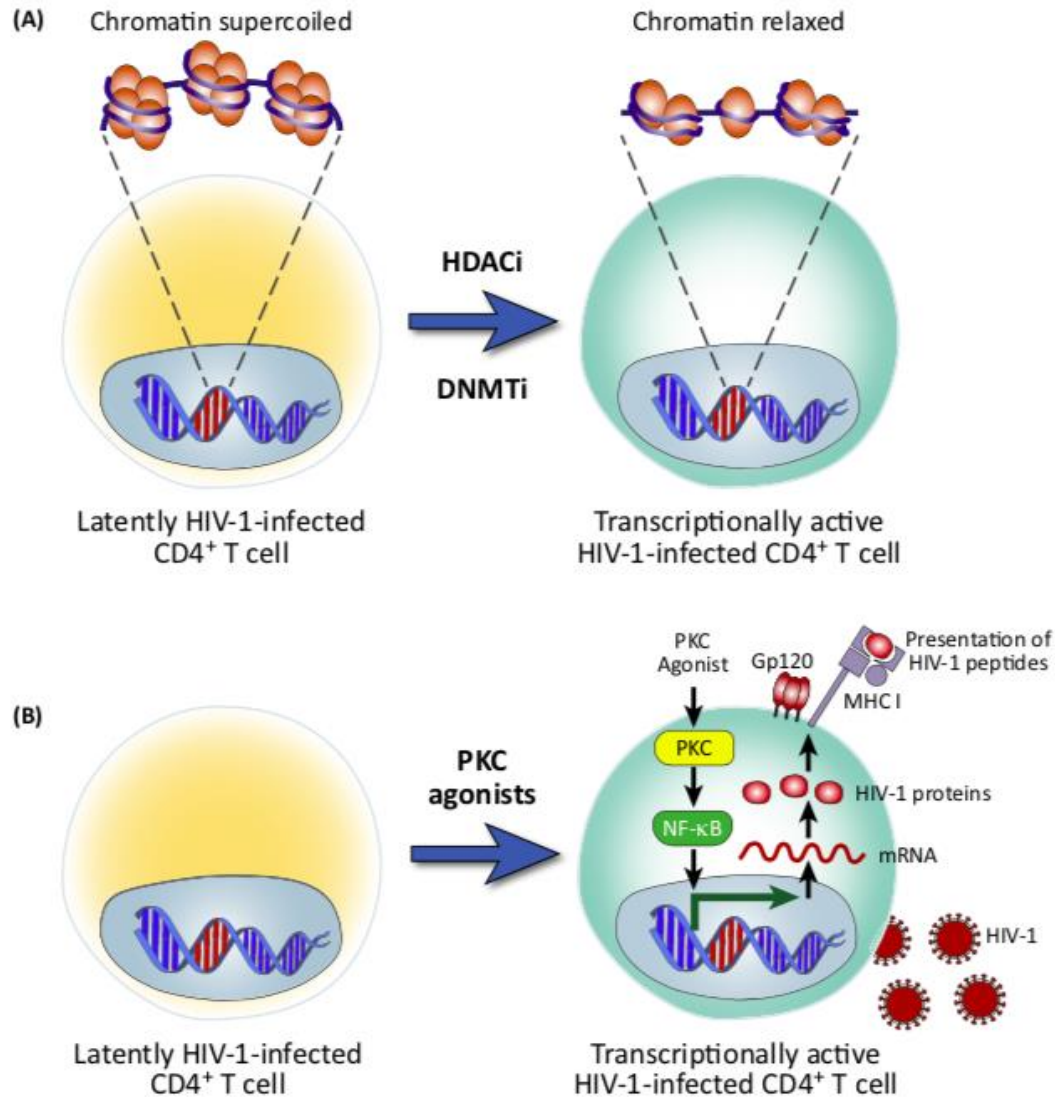




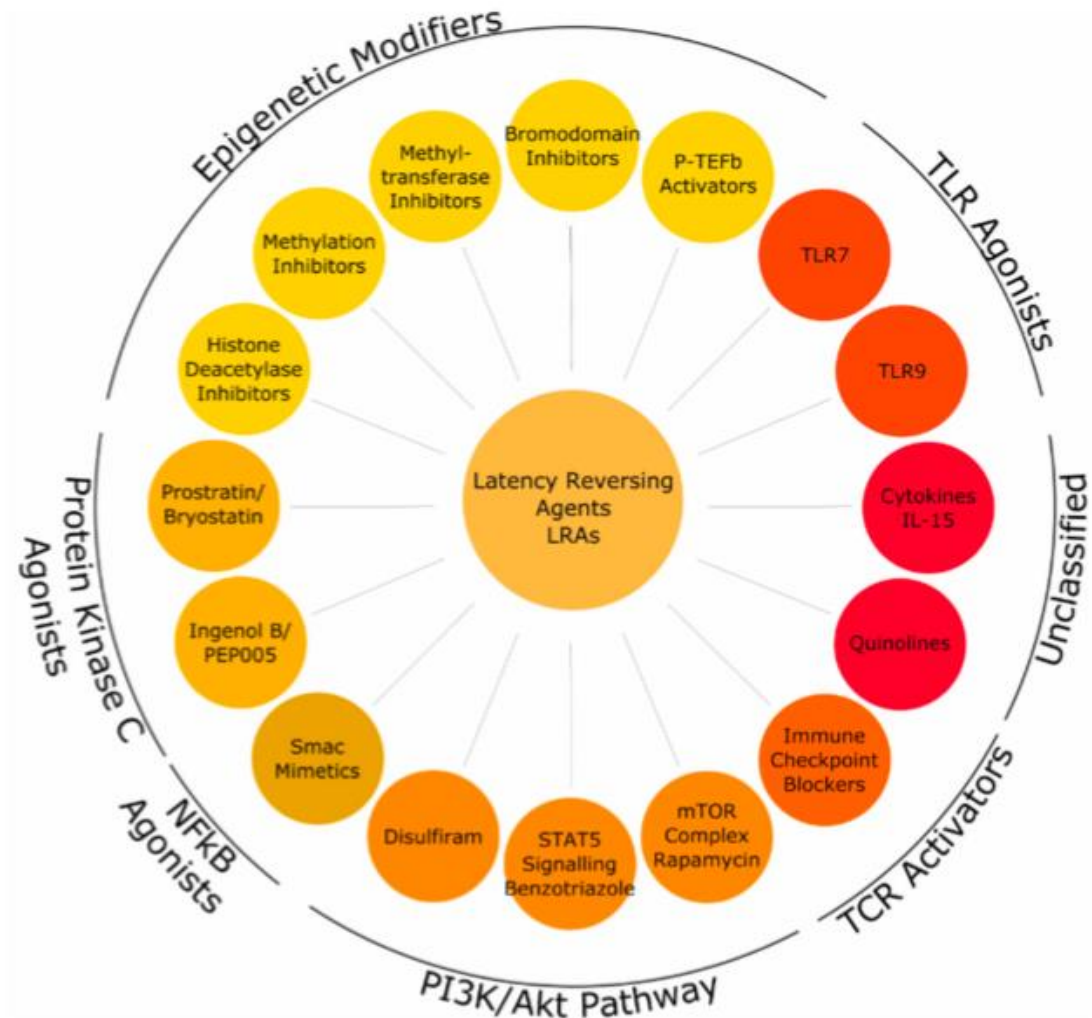
# Şokla ve Öldür



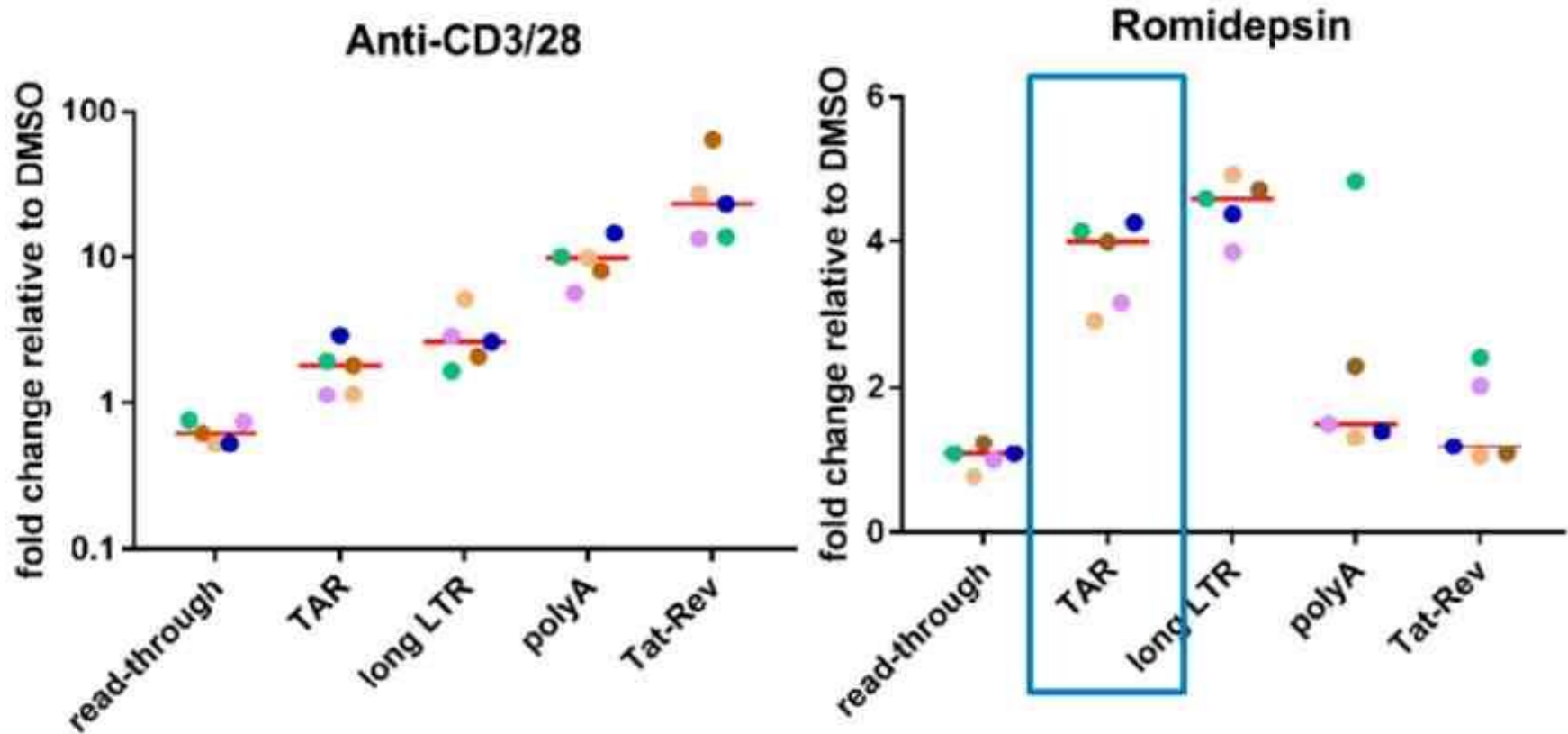
# Şokla ve Öldür



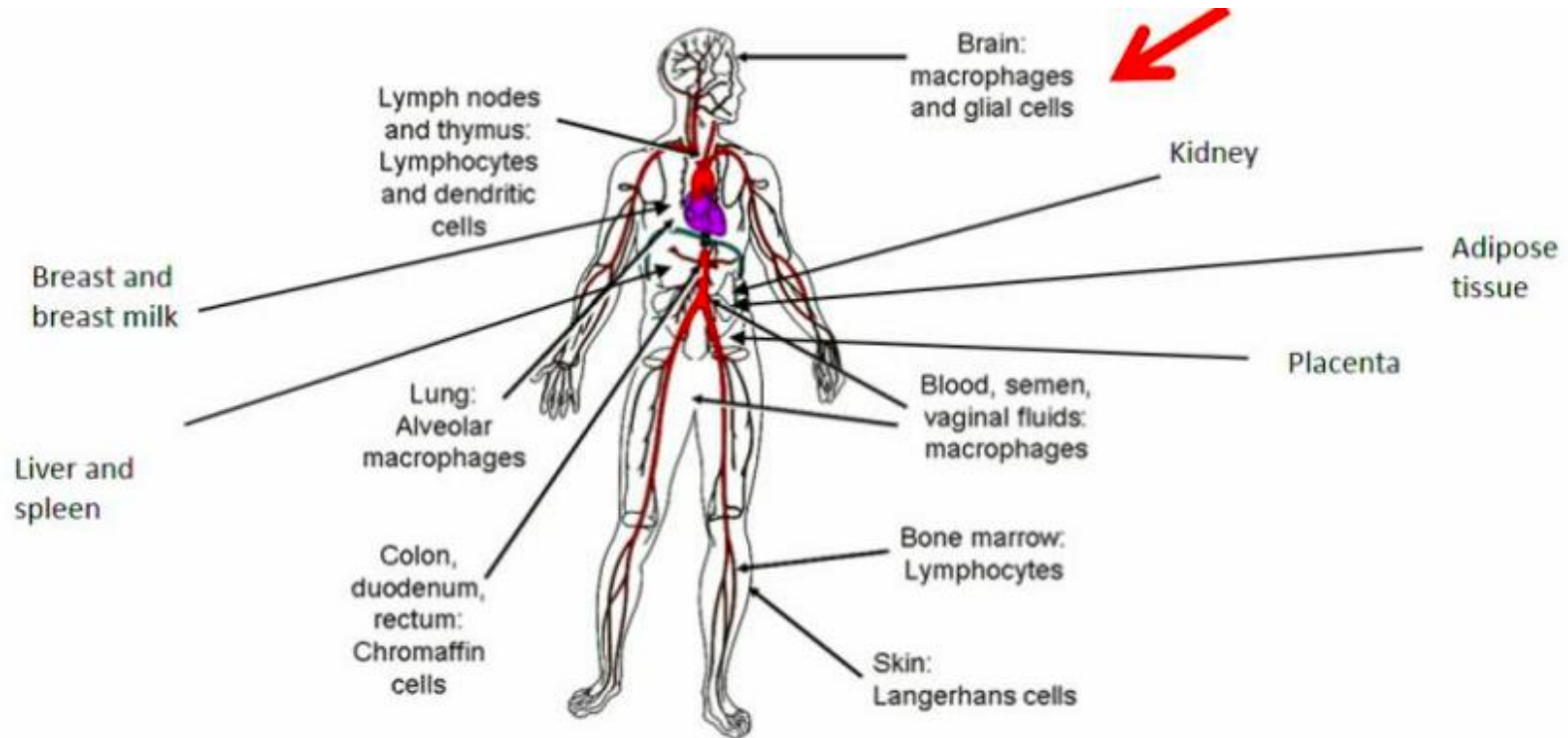
# Şokla ve Öldür



# Şokla ve Öldür: Sorun



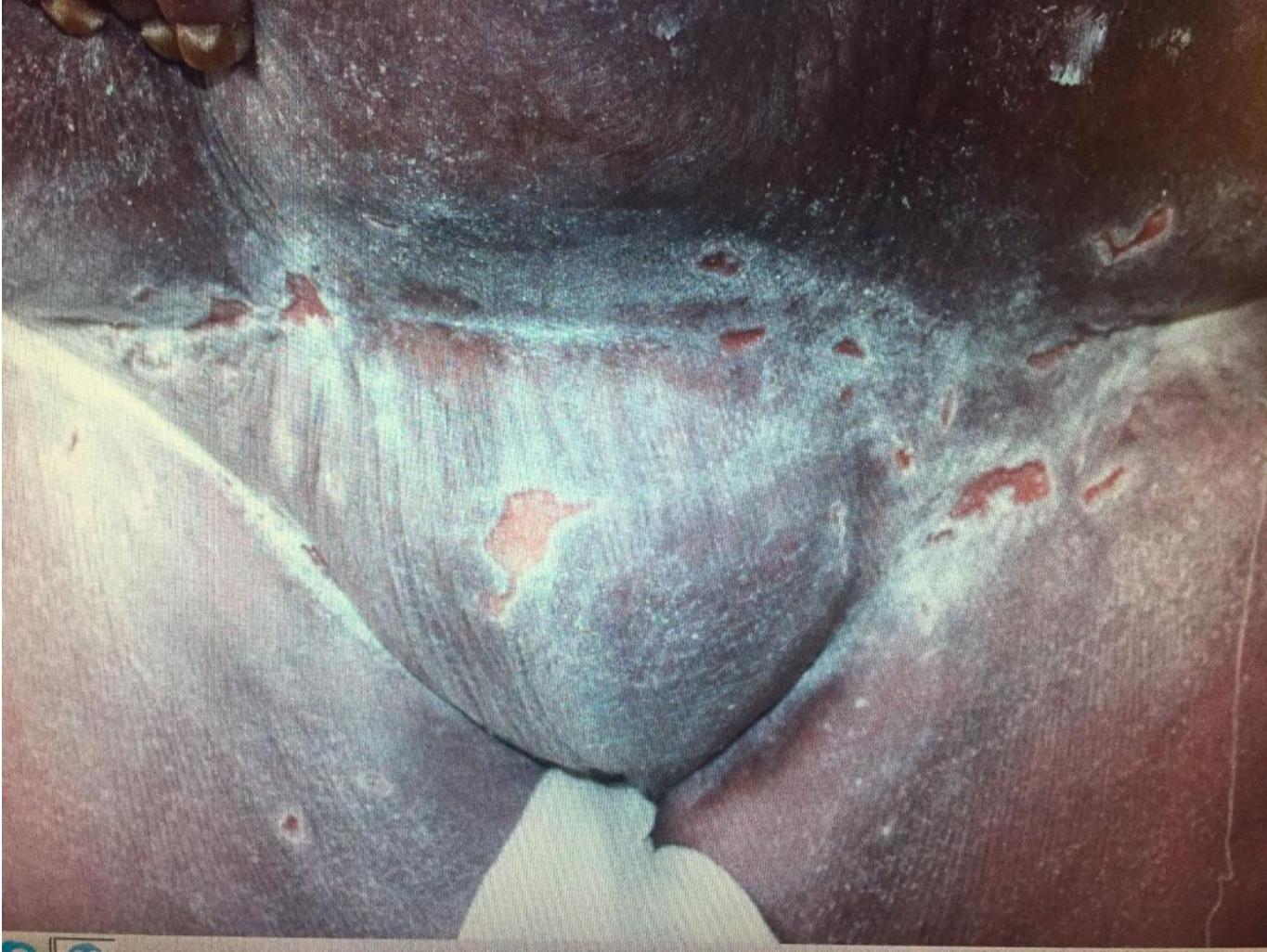
# Şokla ve Öldür: Ama kimi?



Adapted from Microbiology and Immunology online, R. Hunt, 2013 and Wong Curr\_Op\_HIV AIDS, 2016

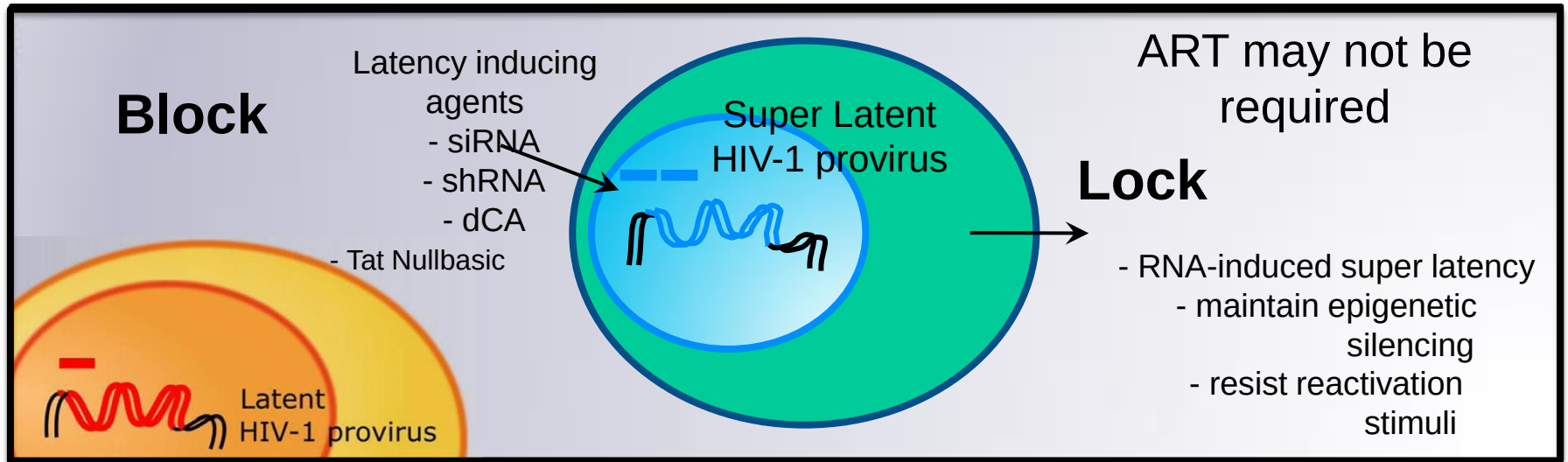


# Şokla ve öldür: Ama kimi?

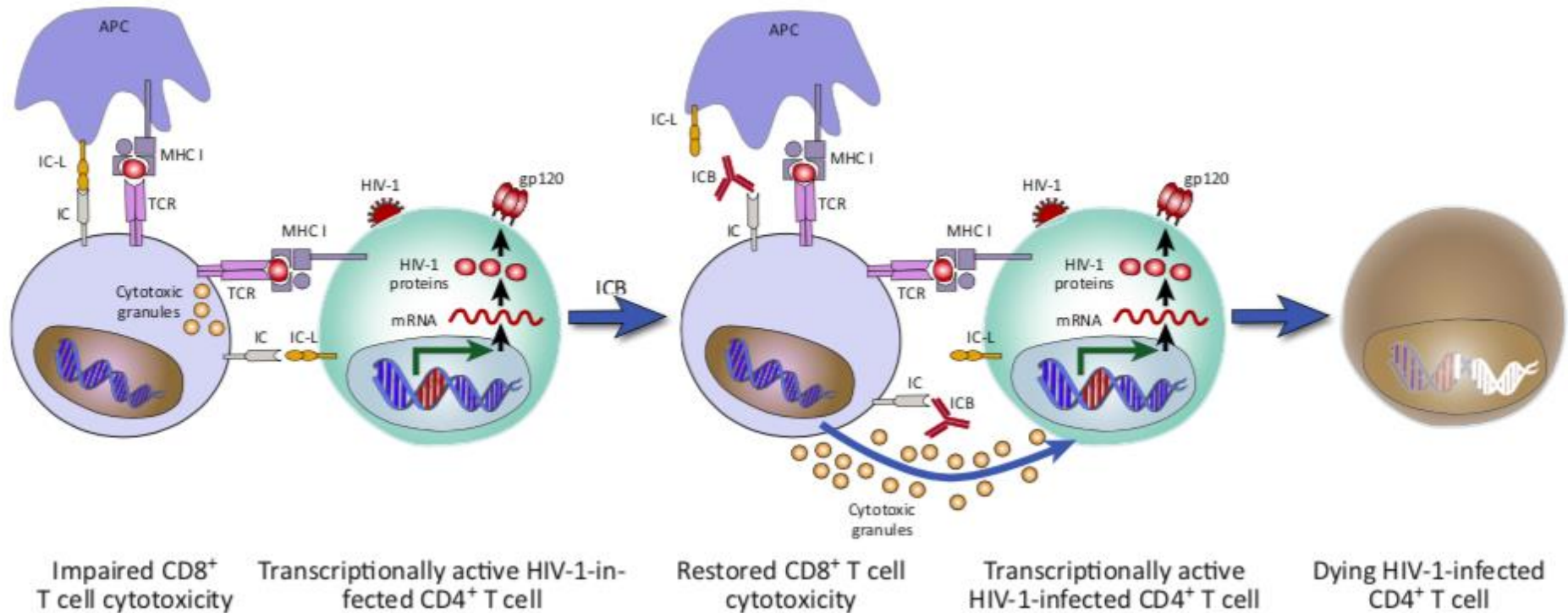


İnkaya AC etal 2018 *Concomitant HSV and CMV reactivations in mycosis fungoides patient under romidepsin treatment* ICHS Atina

# Bloke et ve kitle



# Hiç bir şey yapamıyorsan bir katil bul





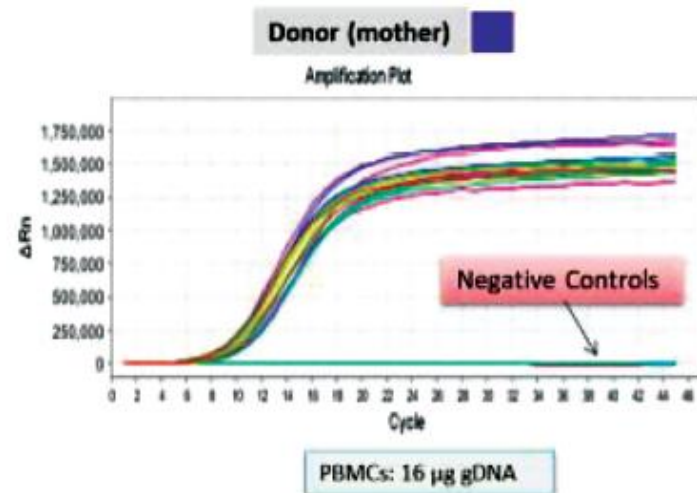
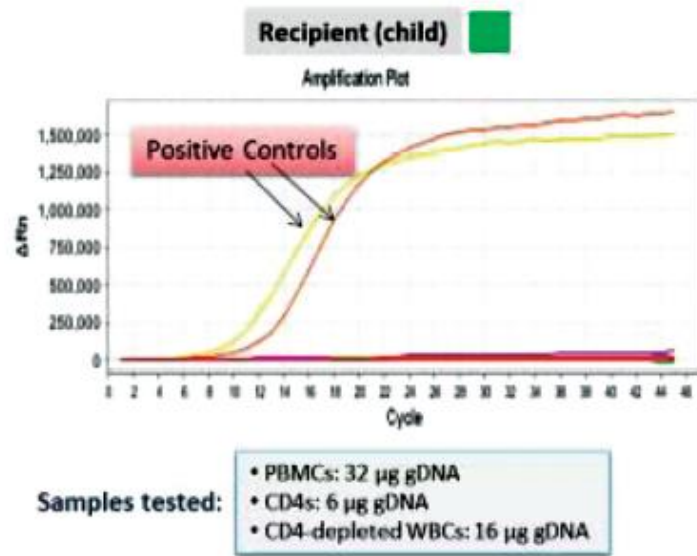
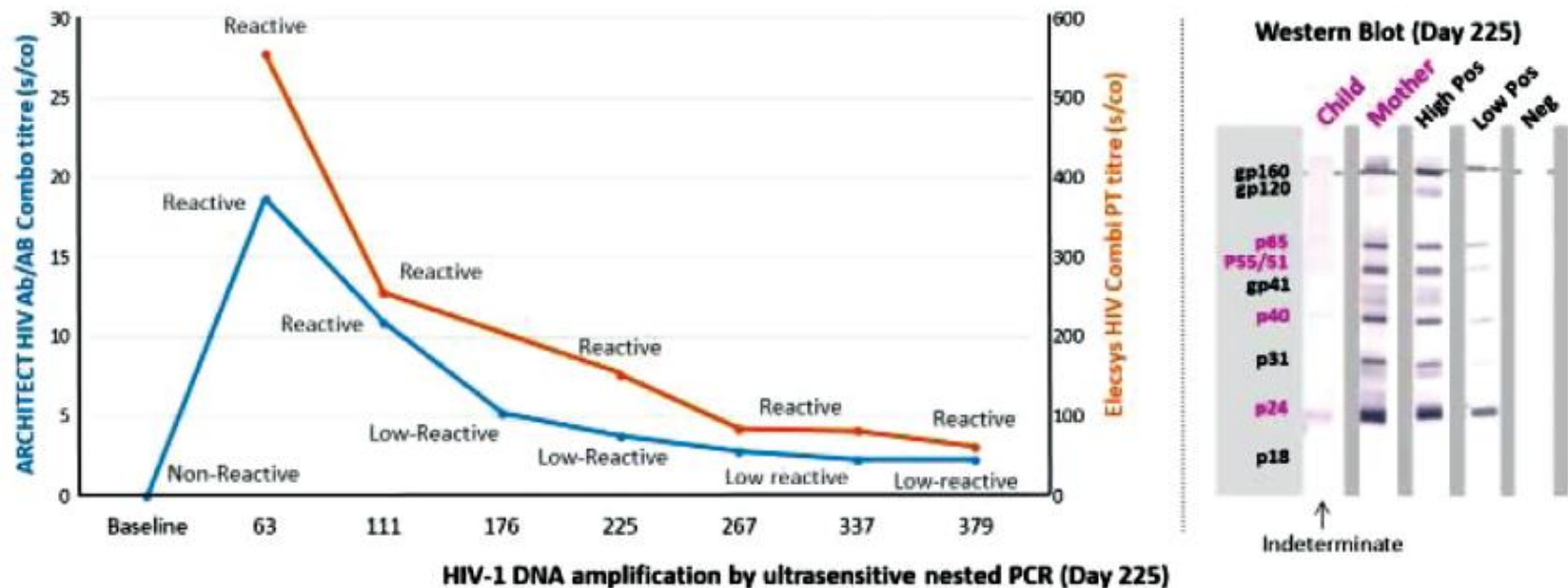
# CITN--12: Anti--PD--1 (pembrolizumab) in HIV and cancer

- Multicentre study of HIV and advanced cancers (n=36)
  - Pembrolizumab 200mg IV every 3 weeks for 2 years
    - Recruitment in 3 cohorts of different CD4 counts
      - Safety and AEx similar to HIV negative cohorts

| Immune Related  |         |         |         |             |
|-----------------|---------|---------|---------|-------------|
| Adverse Event   | Grade 1 | Grade 2 | Grade 3 | Total N (%) |
| Hypothyroidism  | 2       | 4       |         | 6 (35.3)    |
| ALT increased   | 1       |         | 1       | 2 (17.6)    |
| Joint stiffness | 1       |         |         | 1 (5.9)     |
| Pneumonitis     | 1       | 2       |         | 3 (11.8)    |

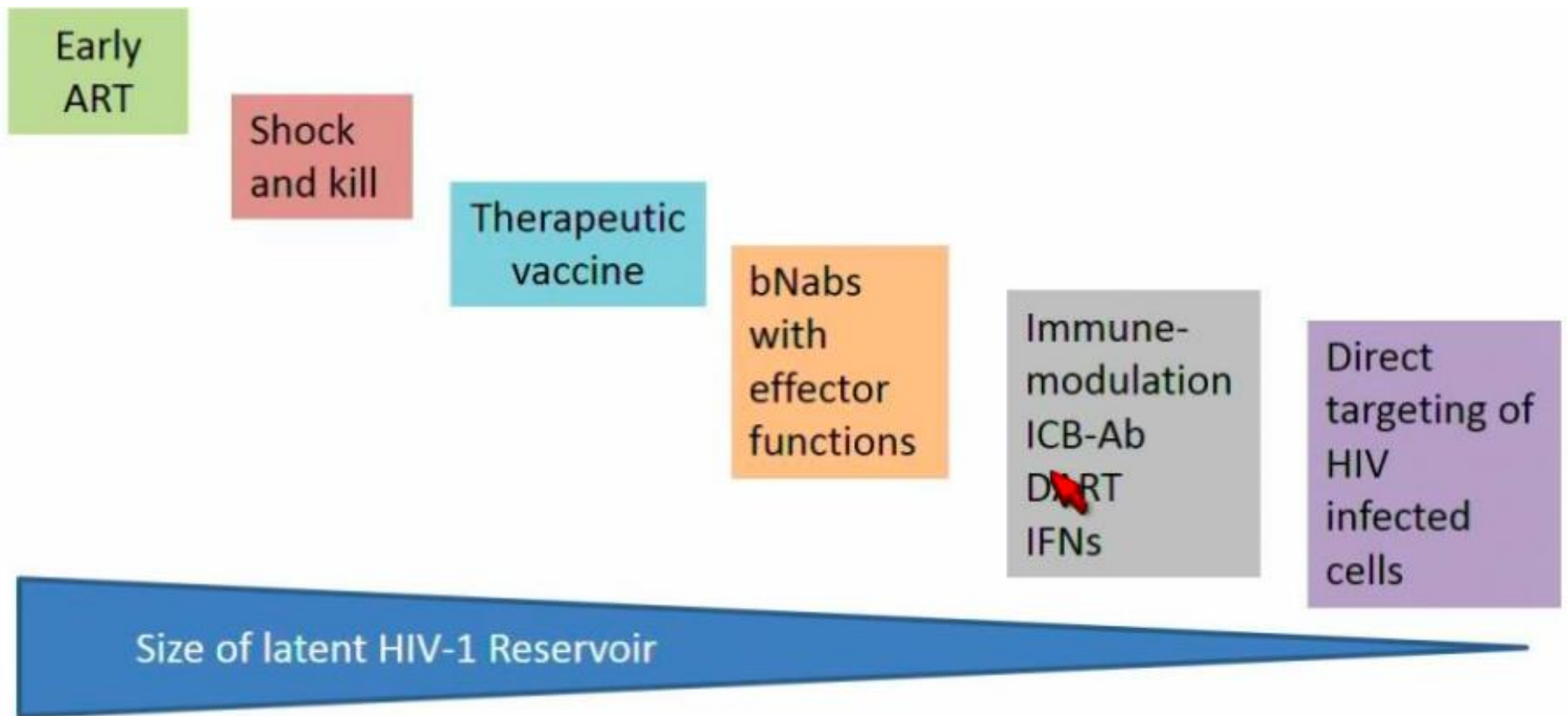
## A 5x6 grid of musical notes. Each row contains six identical musical notes, and there are five rows in total. Each musical note consists of a dark blue stem with two horizontal lines, and two dark blue circular notes positioned below the stem. The notes are arranged in a regular grid pattern on a light gray background.

(a) HIV-1 antibody/antigen detection by diagnostic immunoassays



Botha J et al 2018 *Living donor liver transplant from an HIV-positive mother to her HIV-negative child: opening up new therapeutic options AIDS*

# Özet



# Kür çalışmalarına inanç

## Önümüzdeki 10 yılda kür mümkün

| Tedavi olanlar | Tedavi edenler | p     |
|----------------|----------------|-------|
| %55<br>226/410 | %19<br>26/140  | 0.001 |

# Hayatını sürdürürken mutlu ve akıllı bir canlı var orada!

