İmmünolojik Başarısızlık: Nedenleri, Önemi

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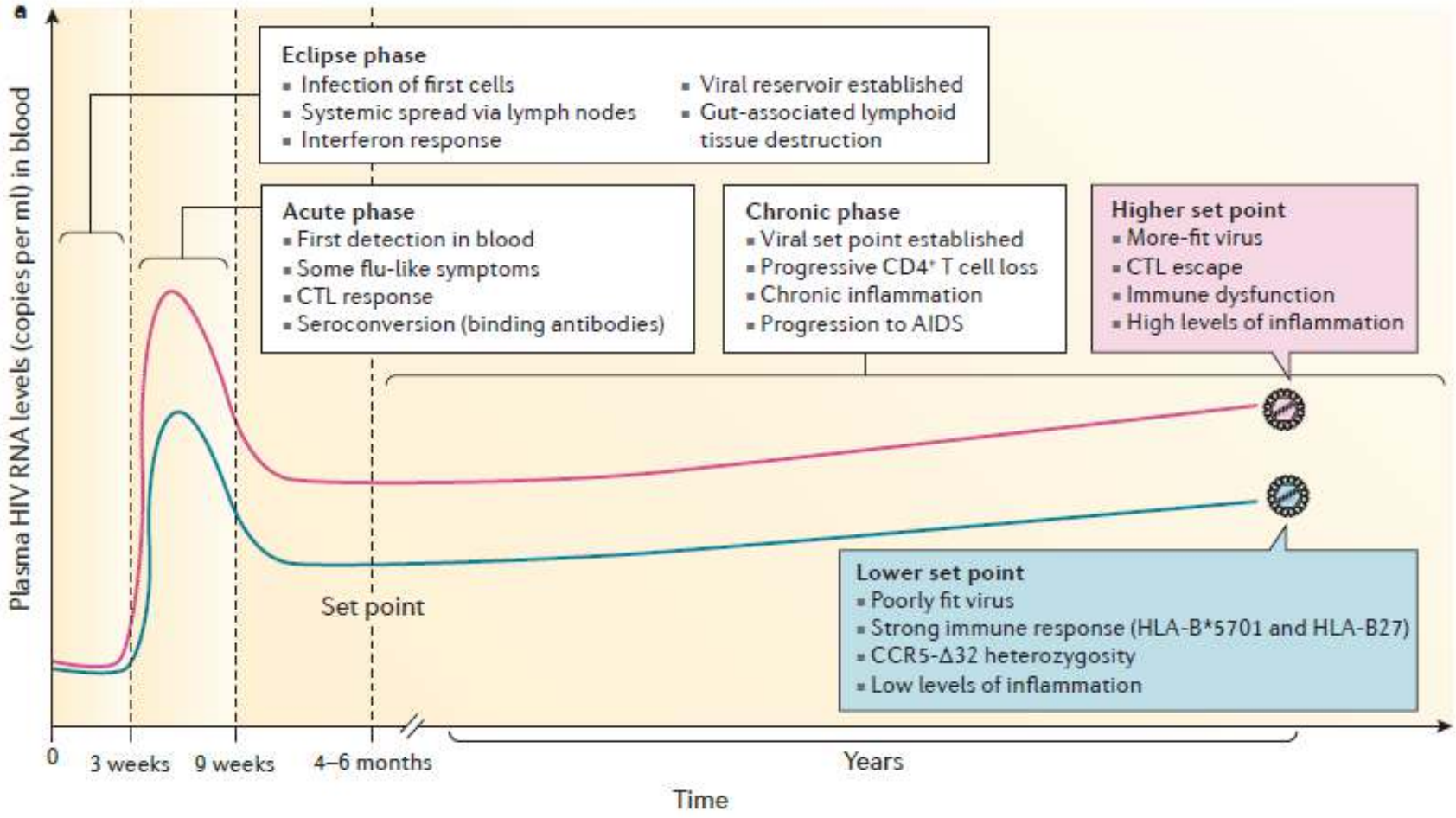
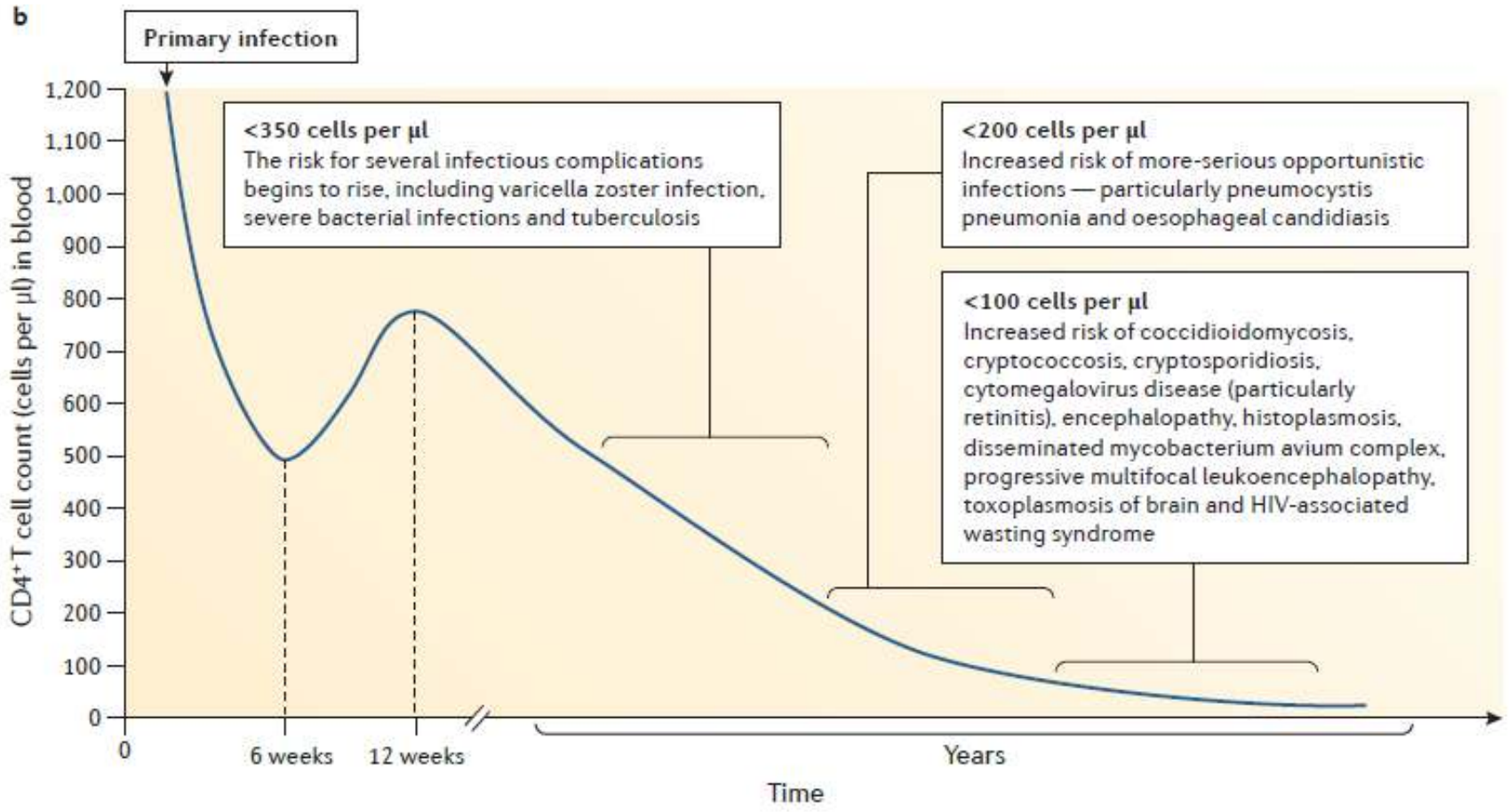
HIV/AIDS Korunma ve Eğitim Derneği

HIV infeksiyonu



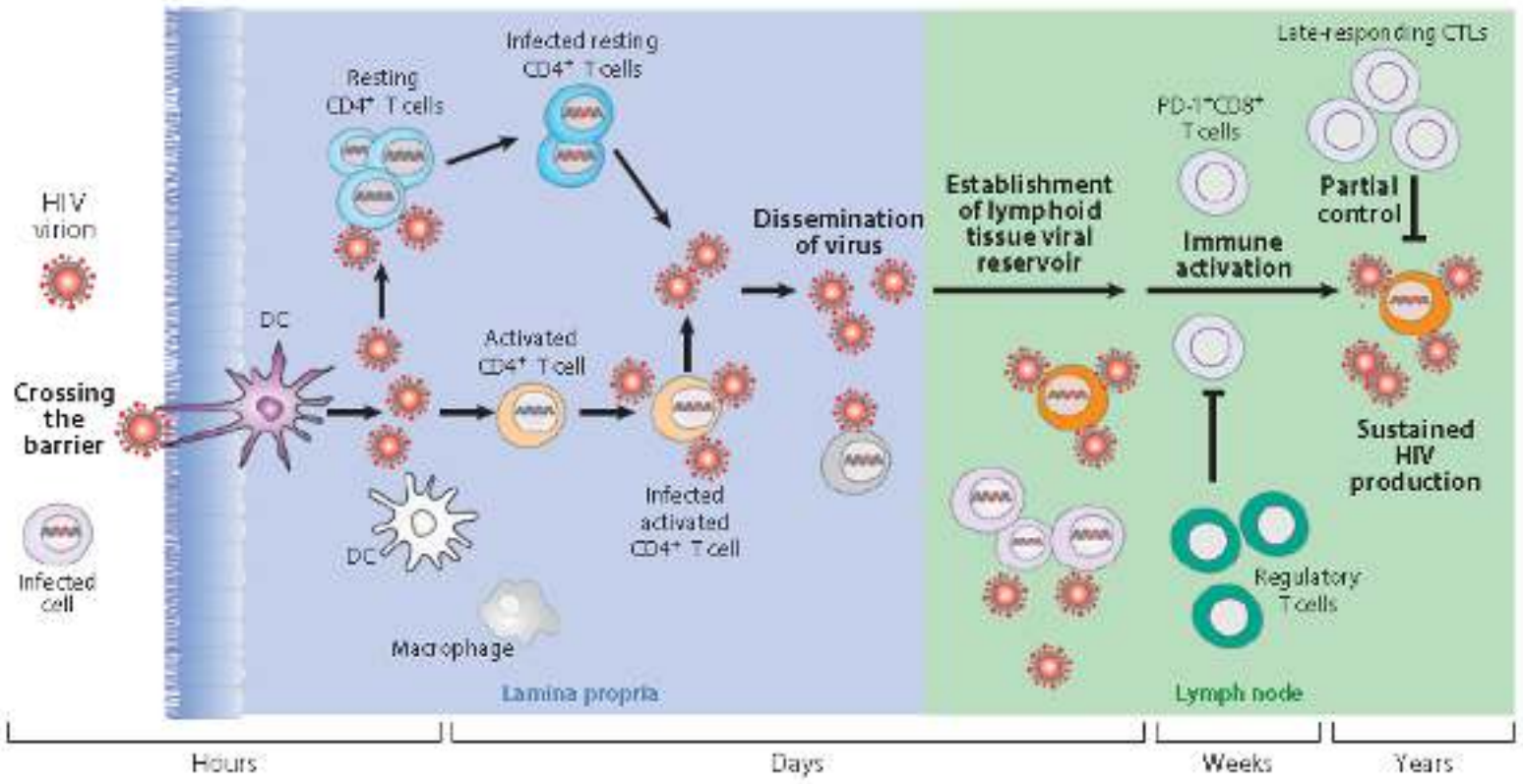
Deeks SG etal 2015 *HIV infection* Nat Rev Dis Primers

HIV infeksiyonu



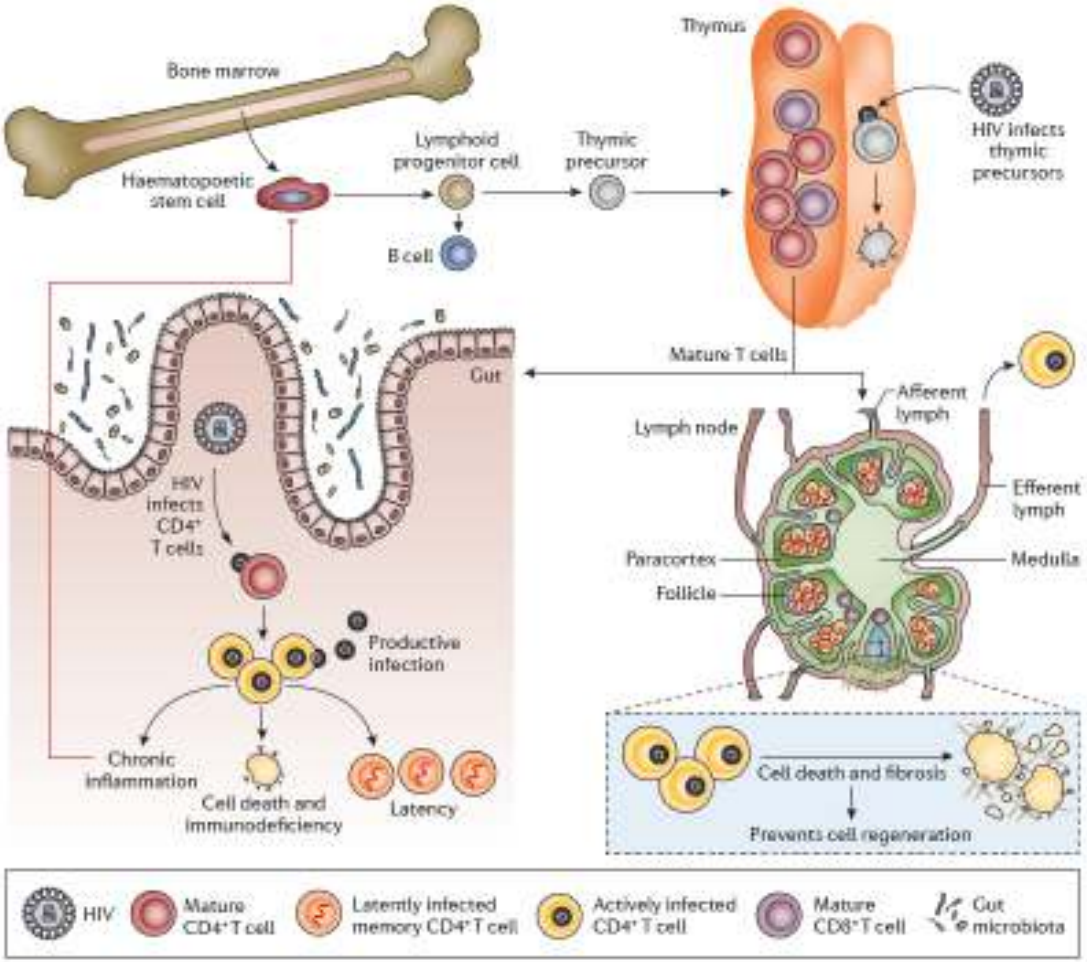
Deeks SG etal 2015 *HIV infection* Nat Rev Dis Primers

HIV patogenez



Moir S etal 2011 *Pathogenic mechanisms of HIV disease* Annu Rev Pathol

HIV infeksiyonu seyri



Deeks SG etal 2015 *HIV infection* Nat Rev Dis Primers

ART sayesinde

- Virolojik yanıt sağlanır
- CD4 düzeyi yükselir
- Fırsatçı hastalık riski azalır

Ama;

- İmmün aktivasyon/inflamasyon
- Hiperkoagülasyon devam eder

Bu da non-infeksiyöz komorbidilerin gelişimine zemin hazırlar

İnkaya AÇ 2020 *HIV Enfeksiyonu ve Enflamasyon* Türkiye Klinikleri Enfeksiyon Hastalıkları
Tincati, C etal 2020 *Do Combination Antiretroviral Therapy Regimens for HIV Infection Feature Diverse T-Cell Phenotypes and Inflammatory Profiles? Open Forum Infectious Diseases*

Uzun dönem stabil hastalık

Key characteristics
Infected >10 years
Maintain low (LTNP) to undetectable plasma viremia (elite LTNP, <50 copies per milliliter)
Maintain normal and stable $CD4^+$ T cell counts
Maintain high levels of human immunodeficiency (HIV)-specific and functional $CD4^+$ T cells
Maintain strong innate immunity against HIV
Maintain strong anti-HIV immunity, particularly $CD8^+$ CTLs
Carry certain genetic traits
Genetic features
HLA B*5701
HLA B*5703
HLA B*2705
Heterozygosity for CCR5Δ32
Antiviral $CD8^+$ T cell immunity
High frequency of polyfunctional HIV-specific $CD8^+$ T cells
High capacity to produce perforin upon exposure to HIV antigens
High capacity to proliferate upon exposure to HIV antigens
Secretion of antiviral factors (C-chemokines)

Moir S etal 2011 *Pathogenic mechanisms of HIV disease* Annu Rev Pathol

İmmünolojik yanıt ve immünolojik yanıtsızlık

İmmünolojik yanıt	İmmünolojik yanıtsızlık
CD4 > 500/µl, 2–12 yıl ART	CD4+ < 500/µl 2-12 yıl ART
CD4 > 500, 7 yıl ART	CD4 < 500, 7 yıl ART
%20 < CD4 artışı, CD4 > 200/µl, 3 yıl ART	%20 > CD4 artışı, CD4 < 200/µl 3 yıl ART
CD4 > 500 µl ve CD4/CD8 > 1, 8 yıl ART	CD4 < 500 µl ve CD4/CD8 ratio < 1 8 yıl ART
CD4 > 400, 2 yıl ART	CD4 < 350, 2 yıl ART

Virolojik baskılanma (HIV RNA < 50/µl) sağlanmasına rağmen CD4 sayısının 500'ün altında kalması ve/veya CD4:CD8 oranının (0.5'den) düşük olması

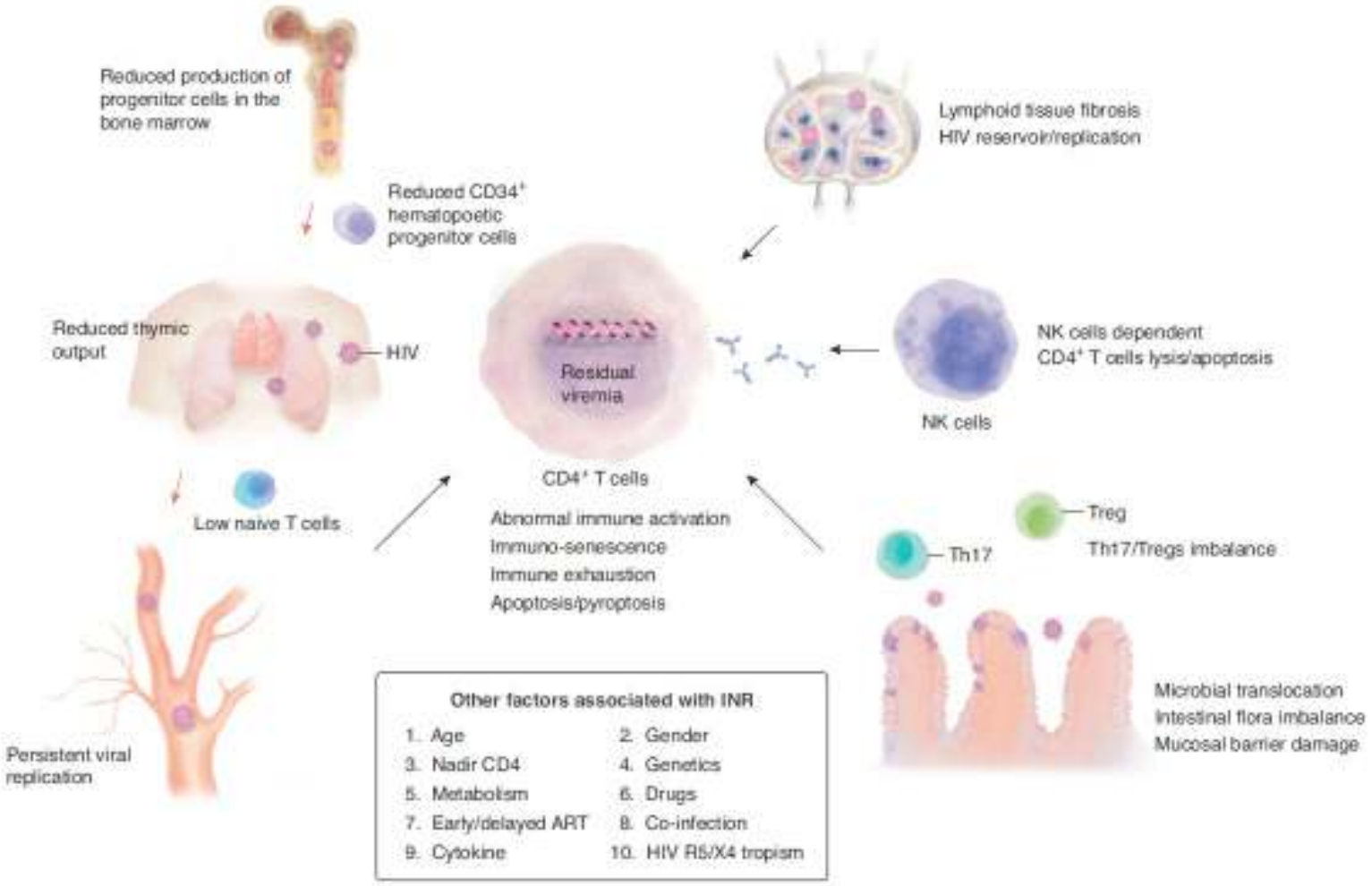
Yang X etal 2020 *Incomplete immune reconstitution in HIV/AIDS patients on antiretroviral therapy: Challenges of immunological non-responders* J Leukoc Biol

İmmünolojik yanıtsızlık

- %20-30
- Metabolik sendrom
- Karaciğer hastalığı
- Nefropati
- Kardiyovasküler hastalık
- AIDS-dışı kanserler
- Nörokognitif bozulma

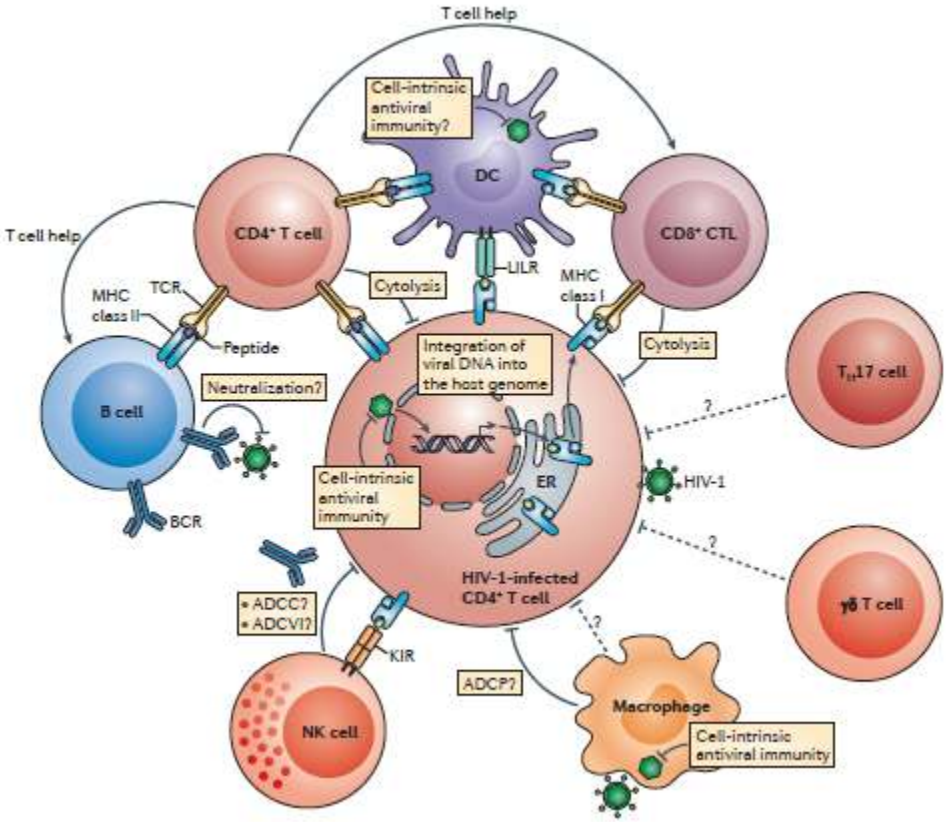
Engsig FN etal 2014 *Long-termmortality in HIV- positive individuals virally suppressed for >3 years with incomplete CD4 recovery* Clin Infect Dis
van Lelyveld SF et al. 2012 *Long-term complications in patients with poor immunological recovery despite virological suc- cessful HAART in Dutch ATHENA cohort* AIDS
Yang X etal 2020 *Incomplete immune reconstitution in HIV/AIDS patients on antiretroviral therapy: Challenges of immunological non-responders* J Leukoc Biol

İmmünolojik yanıtsızlık sebepleri



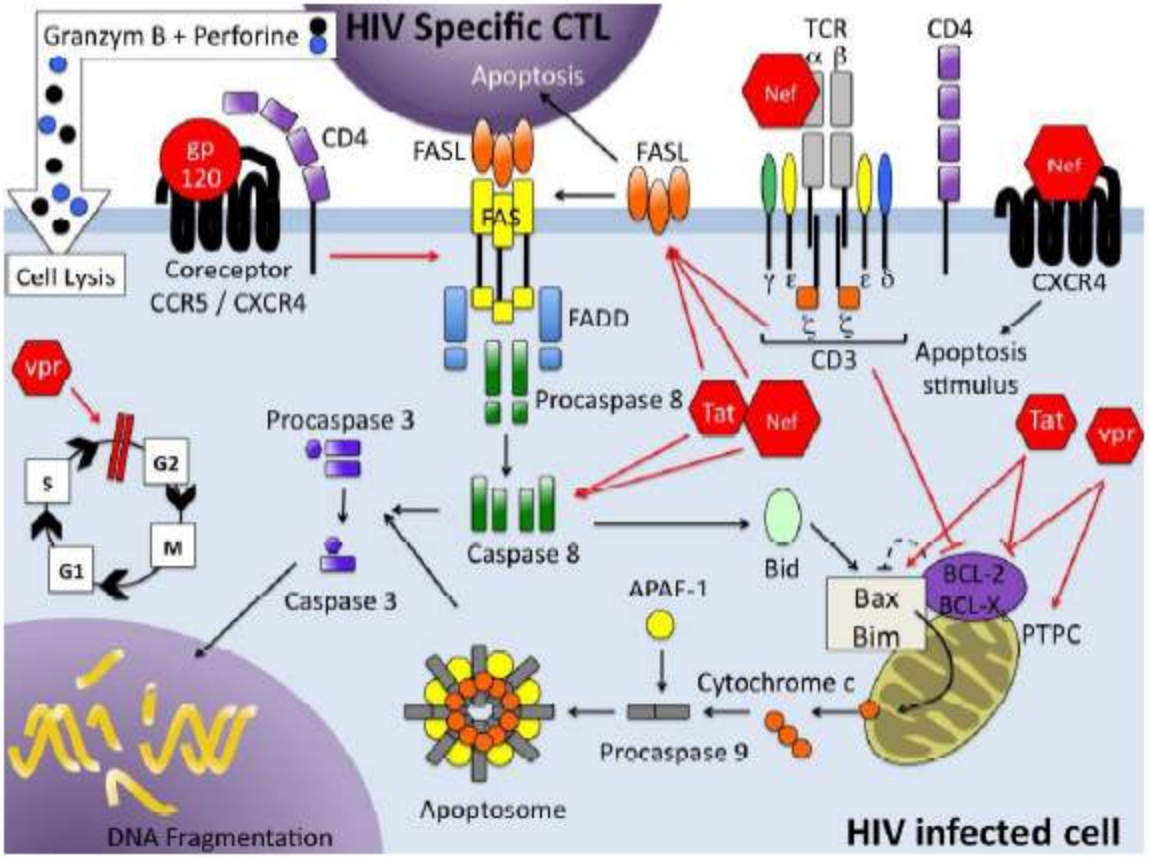
Yang X etal 2020 *Incomplete immune reconstitution in HIV/AIDS patients on antiretroviral therapy: Challenges of immunological non-responders* J Leukoc Biol

HIV patogenez II



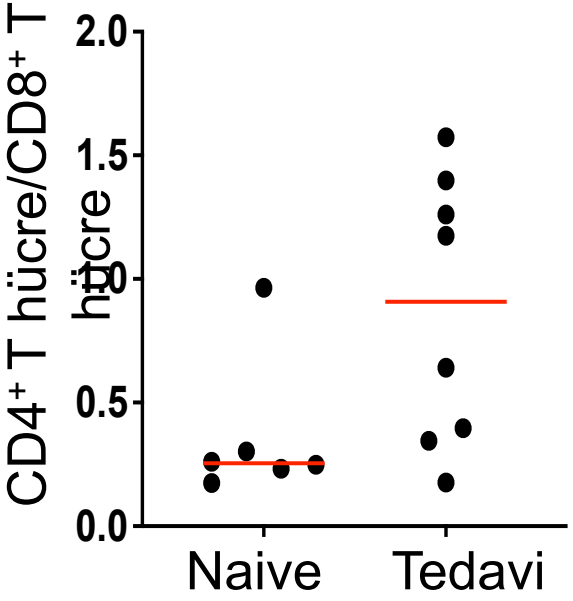
Février M etal 2011 *CD4+ T cell depletion in human immunodeficiency virus (HIV) infection: role of apoptosis* Viruses

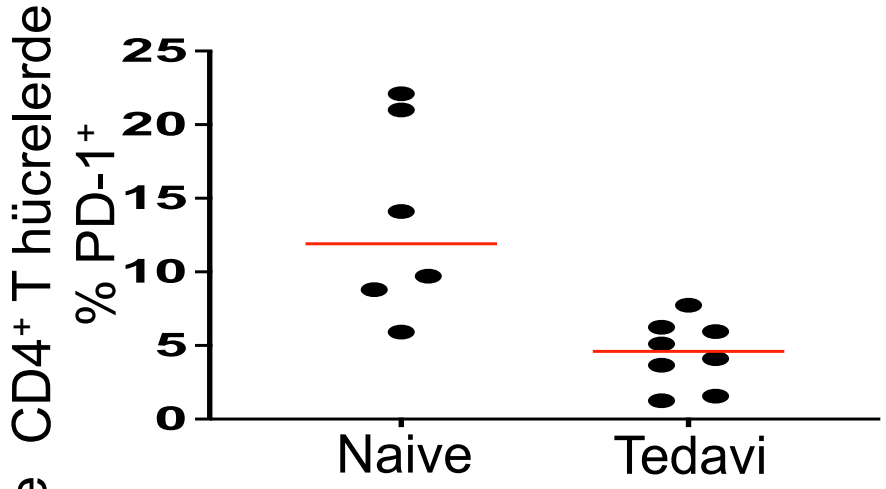
HIV patogenez III

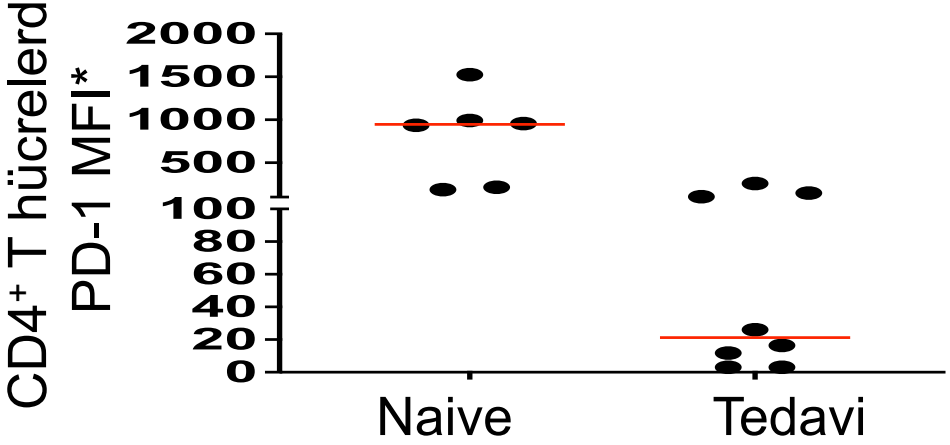


Février M etal 2011 *CD4+ T cell depletion in human immunodeficiency virus (HIV) infection: role of apoptosis* Viruses

ART ve immün yorulma

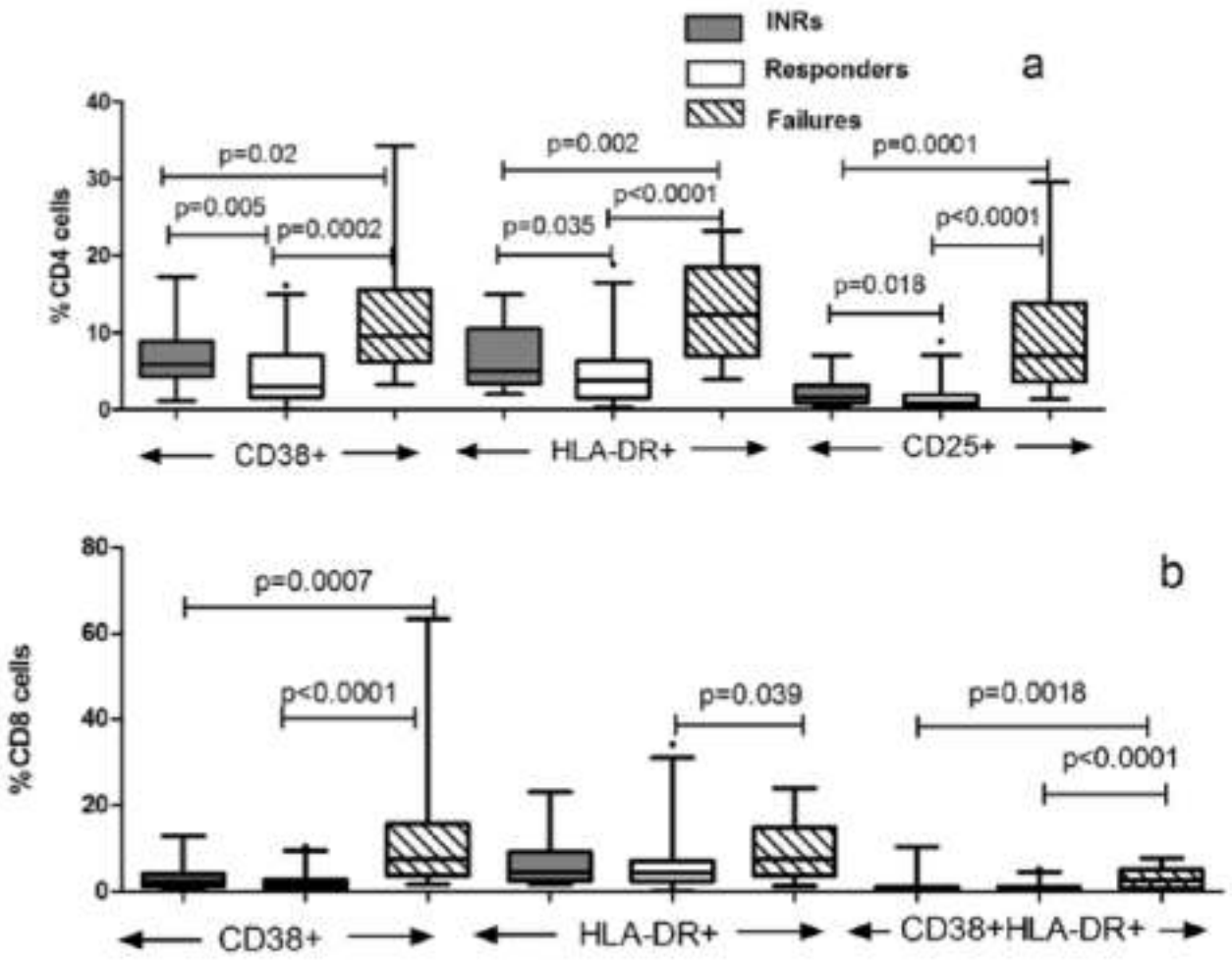






Özcan B etal yayınlanmamış veri

ART ve immün düzelme



Shete A etal 2019 *Incomplete functional T-cell reconstitution in immunological non-responders at one year after initiation of antiretroviral therapy possibly predisposes them to infectious diseases* Int J Infect Dis

İmmünolojik yanıtla ilişkili faktörler I

	Total participants (N = 4238)	Univariable			Multivariable*		
		Difference	95% CI	P	Difference	95% CI	P
Age at ART initiation (years)				< 0.001			**< 0.001**
≤ 30	1269	Ref			Ref		
31–40	1832	−1.6	(−13.5–10.4)	0.800	−7.6	(−19.2–3.9)	0.196
41–50	800	−12.67	(−26.8–1.5)	0.079	−23.1	(−37 to −9.3)	0.001
> 50	337	−46.3	(−66.4 to −26.1)	< 0.001	−53.3	(−72.5 to −34.1)	< 0.001
Sex							
Male	2759	Ref			Ref		
Female	1479	23	(12.2–33.7)	< 0.001	24.7	(13.9–35.6)	**< 0.001**
HIV exposure				0.241			
Heterosexual contact	3041	Ref					
Men who have sex with men	708	7	(−11.8–25.8)	0.464			
Injecting drug use	278	−14.7	(−36.4–7.1)	0.185			
Other/unknown	211	19.3	(−8.5–46.6)	0.175			
Pre-ART viral Load (copies/mL)							
<100 000	1123	Ref			Ref		
≥ 100 000	1092	44.4	(30.4–58.4)	< 0.001	32.7	(18.9–45.5)	**< 0.001**
Not done	2023	10.3	(−5.2–25.7)	0.193	1.14	(−14.9–17.2)	0.890
Pre-ART CD4 (cells/μL)				< 0.001			**< 0.001**
≤ 100	1885	Ref			Ref		
101–200	1050	−9.8	(−22.1–2.4)	0.116	−9.5	(−22.1–3.1)	0.139
201–350	990	−20.5	(−33.3 to −7.8)	0.002	−16.9	(−30.9 to −2.9)	**0.018**
> 350	313	−110.6	(−136.8 to −84.5)	< 0.001	−104.5	(−132.6 to −76.4)	**< 0.001**
Initial ART regimen				0.235			
NRTI + NNRTI	3861	Ref					
NRTI + PI	302	21	(−3.3–45.3)	0.090			
Other combination	75	10.7	(−31.9–53.2)	0.623			

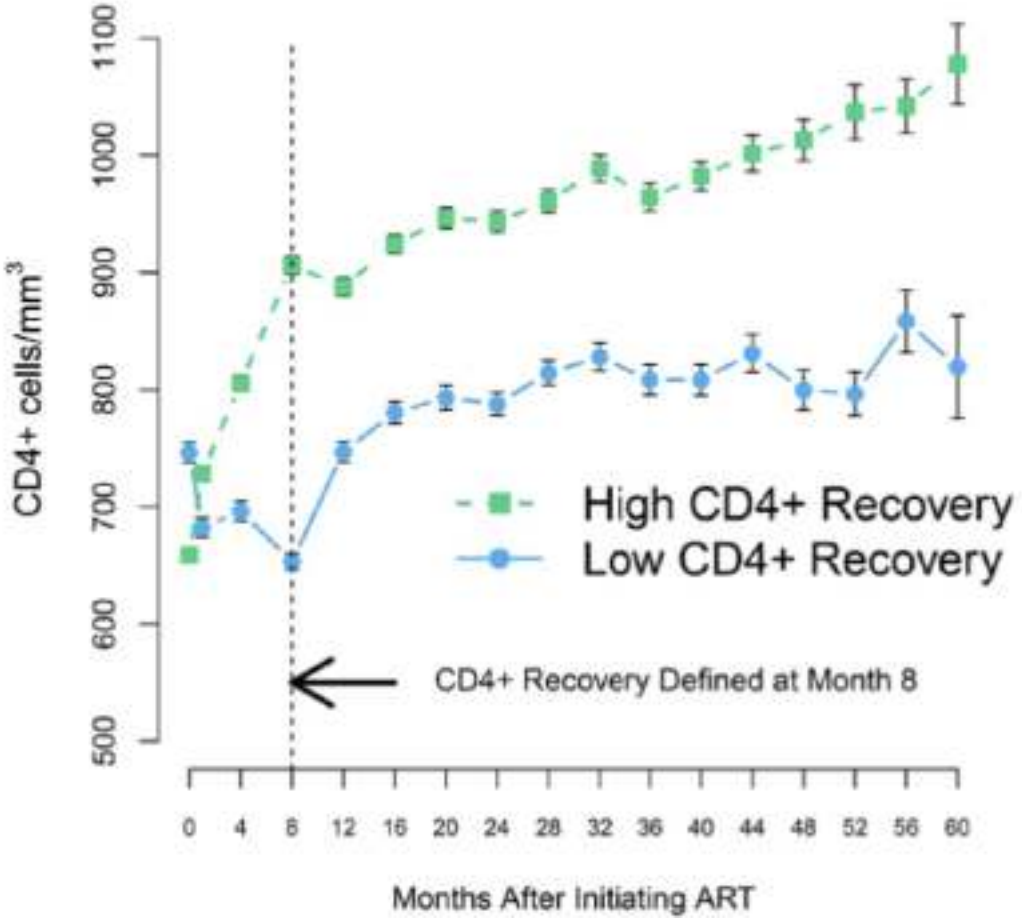
Han WM etal 2021 *Association of body mass index with immune recovery, virological failure and cardiovascular disease risk among people living with HIV* HIV Med

İmmünolojik yanıtla ilişkili faktörler II

Hepatitis B surface antigen				0.002			**0.002**
Negative	3293	Ref			Ref		
Positive	376	−28.7	(−45.1 to −12.3)	0.001	−26.7	(−42.1 to −11.3)	**0.001**
Not tested	569	−12.7	(−31.9–6.5)	0.195	−11.8	(−32.9–9.3)	0.272
Anti-HCV antibody				0.002			**0.014**
Negative	2937	Ref			Ref		
Positive	461	−31	(−48.2 to −13.8)	< 0.001	−25.1	(−41.9 to −8.2)	**0.001**
Not tested	840	−9.6	(−28.4–9.1)	0.315	−11.8	(−32.9–9.3)	0.272
Prior AIDS diagnosis							
No	2695	Ref			Ref		
Yes	1543	23.7	(12.6–34.8)	< 0.001	15.3	(3.4–27.3)	**0.012**
Pre-ART BMI (kg/m^2)				0.315			**0.04**
< 18.5	1046	8.2	(−4.1–20.6)	0.190	−1.1	(−12.6–11.5)	0.881
18.5–25.0	2663	Ref			Ref		
25.0–30.0	448	2.3	(−14.5–19)	0.793	11.3	(−4.5–29.2)	0.075
> 30.0	81	28.5	(−17.8–74.8)	0.227	43.5	(8.5–78.4)	**0.014**
Ever smoked				0.001			
Yes	1496	Ref					
No	2018	2.4	(−8.9–13.7)	0.680			
Not reported	724	−53.9	(−70.4 to −37.3)	0.001			

Han WM etal 2021 *Association of body mass index with immune recovery, virological failure and cardiovascular disease risk among people living with HIV* HIV Med

CD4 > 500 olarak başlandığında



Boatman JA etal 2018 *Risk Factors for Low CD4+ Count Recovery Despite Viral Suppression Among Participants Initiating Antiretroviral Treatment With CD4+ Counts > 500 Cells/mm3: Findings From the Strategic Timing of AntiRetroviral Therapy (START) Trial.* J Acquir Immune Defic Syndr

CD4 > 500 olarak başlandığında

Risk Factor	Univariable		Multivariable	
	OR (95% CI)	P	OR (95% CI)	P
Age, OR per 10 years higher	1.06 (0.97 to 1.16)	0.23	1.10 (0.98 to 1.24)	0.11
Female	1.00 (ref.)		1.00 (ref.)	
Male	0.93 (0.75 to 1.14)	0.47	1.53 (1.12 to 2.10)	0.007
Race				
White/other	1.00 (ref.)		1.00 (ref.)	
Asian	1.28 (0.89 to 1.83)	0.18	1.12 (0.33 to 3.78)	0.86
Black	1.51 (1.22 to 1.87)	<0.001	1.08 (0.73 to 1.59)	0.70
Hispanic	1.17 (0.88 to 1.55)	0.27	1.28 (0.90 to 1.81)	0.17
Geographic location				
United States	1.00 (ref.)		1.00 (ref.)	
Africa	1.70 (1.19 to 2.44)	0.004	1.62 (1.01 to 2.58)	0.043
Asia	1.26 (0.79 to 2.01)	0.33	1.27 (0.34 to 4.81)	0.72
Europe and Israel	1.02 (0.72 to 1.44)	0.92	1.03 (0.68 to 1.58)	0.88
Australia	1.09 (0.57 to 2.07)	0.80	1.09 (0.52 to 2.27)	0.82
Latin America	1.17 (0.82 to 1.67)	0.38	1.15 (0.75 to 1.76)	0.52
Treatment regimen				
NNRTI + 2 NRTIs	1.00 (ref.)		1.00 (ref.)	
Protease inhibitor + 2 NRTIs	0.67 (0.52 to 0.86)	0.002	0.78 (0.59 to 1.04)	0.09
Integrase inhibitor + 2 NRTIs	0.72 (0.44 to 1.17)	0.18	0.90 (0.52 to 1.56)	0.70
Other	2.80 (0.25 to 30.99)	0.40	1.52 (0.09 to 25.75)	0.77

Boatman JA etal 2018 *Risk Factors for Low CD4+ Count Recovery Despite Viral Suppression Among Participants Initiating Antiretroviral Treatment With CD4+ Counts > 500 Cells/mm3: Findings From the Strategic Timing of AntiRetroviral Therapy (START) Trial.* J Acquir Immune Defic Syndr

CD4 > 500 olarak başlandığında

Treatment regimen				
NNRTI + 2 NRTIs	1.00 (ref.)		1.00 (ref.)	
Protease inhibitor + 2 NRTIs	0.67 (0.52 to 0.86)	0.002	0.78 (0.59 to 1.04)	0.09
Integrase inhibitor + 2 NRTIs	0.72 (0.44 to 1.17)	0.18	0.90 (0.52 to 1.56)	0.70
Other	2.80 (0.25 to 30.99)	0.40	1.52 (0.09 to 25.75)	0.77
Body mass index, OR per kg/m^2 higher	0.99 (0.98 to 1.01)	0.55	0.98 (0.96 to 1.00)	0.08
Hepatitis C coinfection	1.06 (0.64 to 1.75)	0.84	0.99 (0.55 to 1.76)	0.96
Hepatitis B coinfection	1.60 (0.95 to 2.72)	0.08	1.45 (0.79 to 2.67)	0.24
Screening CD4$^+$, OR per 100 fewer cells/mm^3	1.00 (0.95 to 1.04)	0.85	1.09 (1.03 to 1.15)	0.004
Baseline CD8$^+$, OR per 100 more cells/mm^3	1.03 (1.02 to 1.05)	<0.001	1.05 (1.03 to 1.07)	<0.001
Baseline HIV RNA copies/mL, OR per $\log_{10}$ lower	1.68 (1.50 to 1.87)	<0.001	1.93 (1.68 to 2.22)	<0.001
Baseline IL-6 pg/mL, OR per $\log_2$ higher	1.01 (0.91 to 1.12)	0.89	1.07 (0.95 to 1.20)	0.28
*Baseline $\log_2$ D-dimer μg/mL	1.25 (1.03 to 1.52)	0.021	1.27 (1.03 to 1.57)	0.028
*Baseline ($\log_2$ D-dimer μg/mL)^2	1.09 (1.02 to 1.17)	0.013	1.11 (1.03 to 1.19)	0.006
Time since HIV diagnosis, OR per 1 year higher	1.04 (1.01 to 1.07)	0.011	1.03 (0.99 to 1.06)	0.15

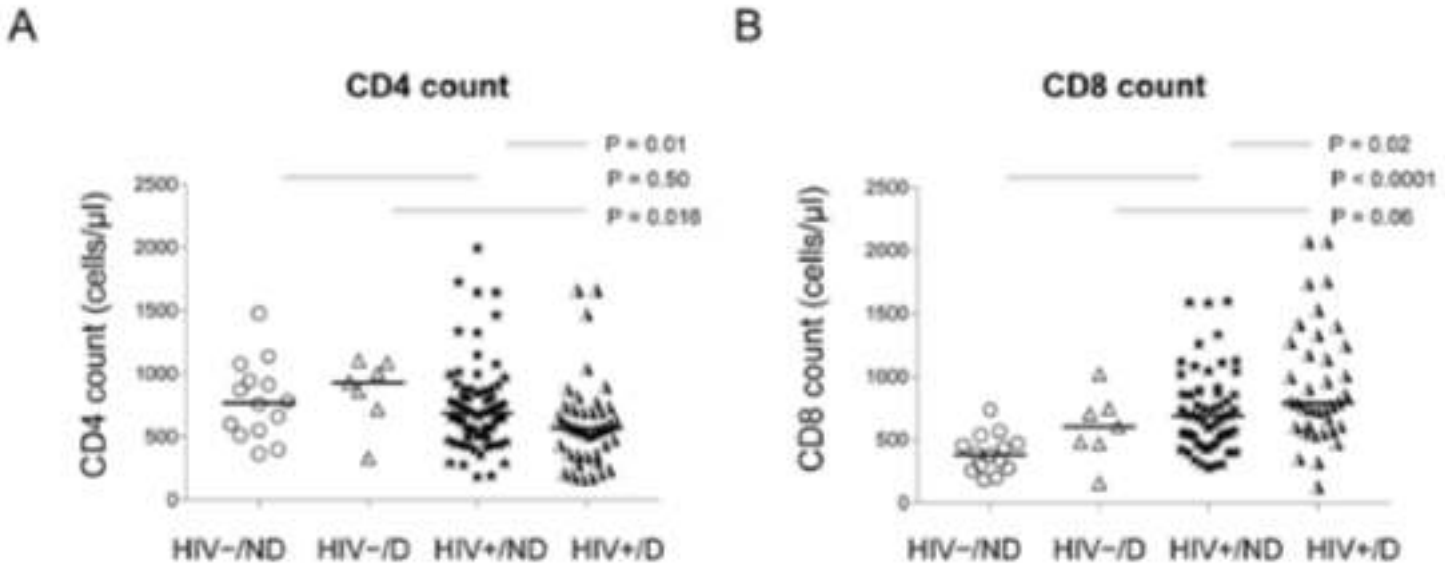
Boatman JA etal 2018 *Risk Factors for Low CD4+ Count Recovery Despite Viral Suppression Among Participants Initiating Antiretroviral Treatment With CD4+ Counts > 500 Cells/mm3: Findings From the Strategic Timing of AntiRetroviral Therapy (START) Trial.* J Acquir Immune Defic Syndr

İmmünolojik düzelme ile ilişkili faktörler

Model	Rate Ratio (95% CI)[a]	*P* Value
Univariate		
Sex, female vs male	1.18 (0.73-1.89)	.51
Ethnicity		
African American vs European American	0.92 (0.73-1.15)	.44
Other vs European American	0.80 (0.56-1.14)	.22
Age at ART initiation, each increase of 1 y	1.00 (0.99-1.02)	.86
Time from EDS to ART initiation, ≤12 vs >12 mo	1.53 (1.22-1.91)	<.001
Time from entry to ART initiation, ≤12 vs >12 mo	1.51 (1.21-1.89)	<.001
Study entry CD4$^+$, ≥500 vs <500 cells/μL	2.45 (1.98-3.05)	<.001
Pre-ART CD4$^+$, each increase of 10 cells	1.06 (1.05-1.06)	<.001
Pre-ART CD4$^+$, ≥500 vs <500 cells/μL	5.91 (4.77-7.32)	<.001
Pre-ART viral load, each increase of 1 $\log_{10}$ copies/mL	1.05 (0.90-1.21)	.57
Calendar year of ART initiation, each increase of 1 y	1.06 (1.04-1.09)	<.001
Antiretroviral regimen[b]		
PI-based vs NNRTI-based	1.39 (1.06-1.82)	.02
Other vs NNRTI-based	0.61 (0.47-0.80)	<.001
Other vs PI-based	0.44 (0.34-0.57)	<.001
Duration of VL-suppressive ART, each increase of 1 y[c]	0.88 (0.84-0.92)	<.001
Time from ART initiation to VL suppression, each increase of 1 mo	0.98 (0.97-0.98)	<.001
Multivariate[d]		
Model 1: time from EDS to ART initiation, ≤12 vs >12 mo	1.32 (1.04-1.67)	.02
Model 2: time from study entry to ART initiation, ≤12 vs >12 mo	1.77 (1.38-2.26)	<.001
Model 3: study entry CD4$^+$, ≥500 vs <500 cells/μL	2.00 (1.51-2.64)	<.001
Model 4: pre-ART CD4$^+$, ≥500 vs <500 cells/μL	4.08 (3.14-5.30)	<.001

Okulicz JF etal 2015 *Influence of the timing of antiretroviral therapy on the potential for normalization of immune status in human immunodeficiency virus 1-infected individuals* JAMA Intern Med

Madde kullanımı



Jiang W etal 2018 *Drug Use is Associated with Anti-CD4 IgG-mediated CD4+ T Cell Death and Poor CD4+ T Cell Recovery in Viral-suppressive HIV-infected Individuals Under Antiretroviral Therapy* Curr HIV Res

Hangi ART?

- TDF/FTC+RAL vs TDF/FTC+EFV ➔ RAL daha iyi
- RAL vs DRV/r ➔ immün aktivasyon ve senescence benzer
- INSTI temelli rejimler diğerlerine nazaran daha iyiler
- TDF/FTC/EFV vs ABC/3TC/DTG
  - EFV grubu: CD4/CD8 yüksek
- Maraviroc
  - İntestinal düzelme ile ilişkili,
  - EFV vs MVC ➔ EFV daha iyi

Serrano-Villar S etal 2017 *Different impact of raltegravir versus efavirenz on CD4/CD8 ratio recovery in HIV-infected patients* J Antimicrob Chemother
De Salvador-Guillouët F etal et al 2015 *Antiretroviral regimens and CD4/CD8 ratio normalization in HIV-infected patients during the initial year of treatment: a cohort stud*y PLoS One
Tincati, C etal 2020 *Do Combination Antiretroviral Therapy Regimens for HIV Infection Feature Diverse T-Cell Phenotypes and Inflammatory Profiles? Open Forum Infectious Diseases*

bPI/3TC vs bPI/NRTI/NRTI

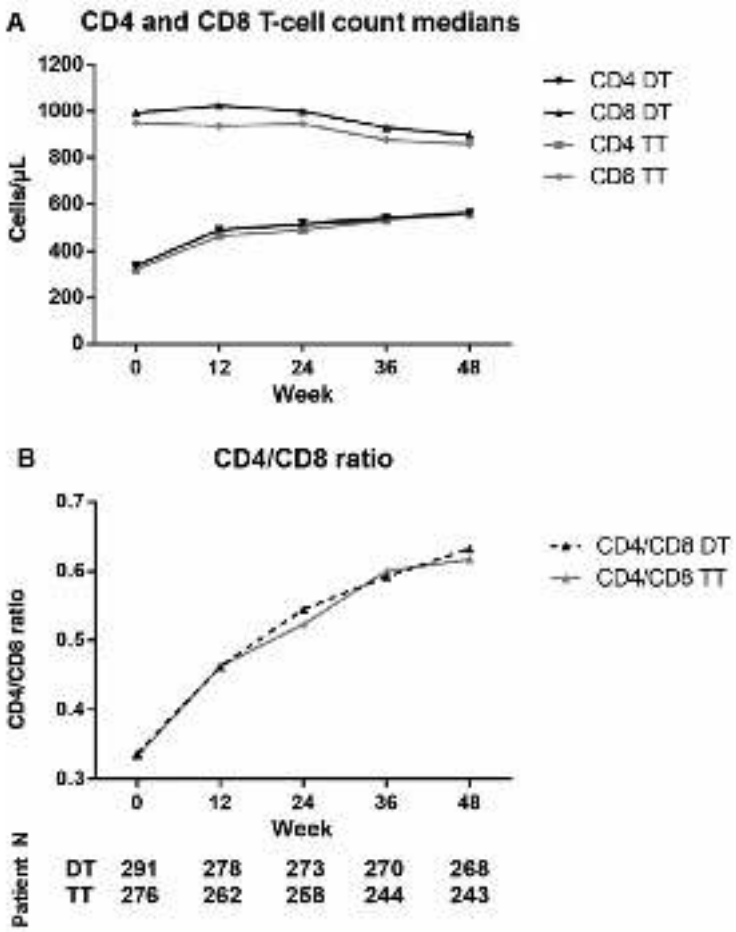


Table 4 Multivariate logistic regression for achieving a CD4/CD8 ratio > 1

Variable	Odds ratio	*P*-value	95% CI
TT *vs.* DT	0.819	0.427	0.500–1.340
Female *vs.* male	1.281	0.504	0.619–2.650
LPV/r *vs.* DRV/r based therapy	0.801	0.516	0.410–1.563
Ethnicity (compared with African-American)			
Caucasian	0.670	0.537	0.188–2.385
Hispanic or Latino	0.559	0.34	0.168–1.848
Other	1.008	0.995	0.073–13.931
Baseline BMI (increment per unit)	0.985	0.652	0.923–1.050
Baseline CD4 (compared with ≤ 200 cells/µL)*			
201–350 cells/µL	8.717	0.038	1.125–67.553
> 350 cells/µL	53.308	< 0.001	7.119–399.184
Baseline RNA > 100 000 copies*	2.069	0.027	1.088–3.932
Age (decades) at ART initiation	1.008	0.949	0.784–1.297

DRV/r, darunavir/ritonavir; TT, triple therapy; DT, dual therapy; LPV/r, lopinavir/ritonavir; BMI, body mass index.
*$P < 0.05$.

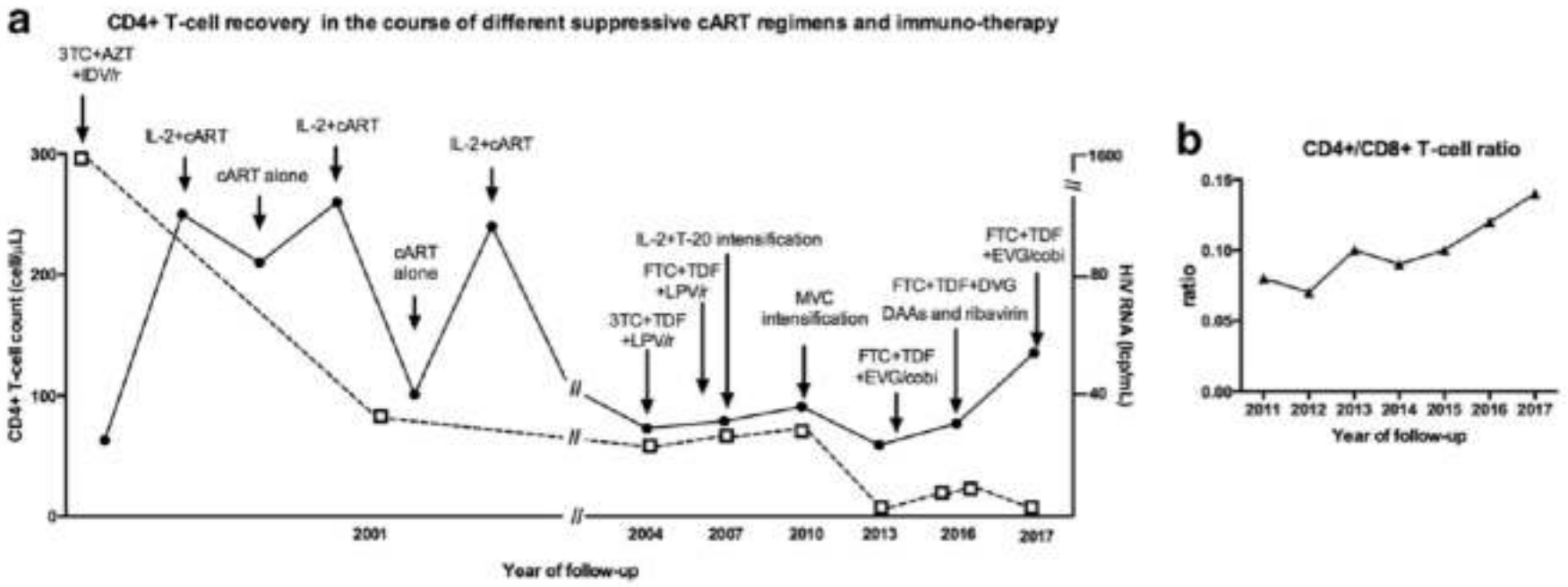
Figueroa MI etal 2021 *The effect of protease inhibitor-based dual antiretroviral regimens on CD4/CD8 ratio during the first year of therapy in ART-naïve patients with HIV-infection* HIV Med

Hangi ART?

Marker	Backbone regimen		p	3rd agent			p
	TDF+FTC	*ABC+3TC*		*Integrase inhibitors*	*Protease inhibitor*	*NNRTI*	
ΔCD4/CD8	+0.36 (-0.48, +2.64)	+0.34 (-0.32, +0.62)	0.828	+0.38 (-0.35, +2.64)	+0.28 (-0.36, 0.94)	+0.19 (-0.48, +0.93)	0.007

Şahin EA etal 2021 *Changes in inflammation scores among people living with HIV (PLWH) under different antiretroviral treatment (ART) regimes* IAS2021

Bir olgu, HCV ko-enfekte



Tincati C etal 2018 *Is weak CD4+ gain in the course of suppressive combination antiretroviral therapy for HIV infection a current clinical challenge? A case report and brief review of the literature.* BMC Infect Dis

Peki o zaman ne yapalım?

- Daha yakın takip
- Kardiyovasküler hastalık riski için dikkat!
- İlaç değiştirmek, ilaç eklemek gereksiz
- Koenfeksiyon varsa etkin tedavi
- Madde kullanımı açısından danışmanlık
- Ileride özel immün modülatör tedaviler gündeme gelebilir