

Dünyadan Yeni Haberler

Dr.Alper GÜNDÜZ

Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi



Birinci Basamak ART'nin Raltegravir ile Kuvetlendirilmesi ve IRIS Üzerindeki Etkisi

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Disclosure: Nothing to Disclose

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Çalışma Tasarımı

- 1805 ART-naïve HIV-infected adults, adolescents & children ≥ 5 years with $CD4 < 100$ cells/ μ l

1:1 randomisation

Initiate ART with
2NRTI+NNRTI+12 weeks
additional raltegravir

Initiate ART with
2NRTI+NNRTI alone
(standard of care)

Primer sonlanım: 24 haftalık mortalite



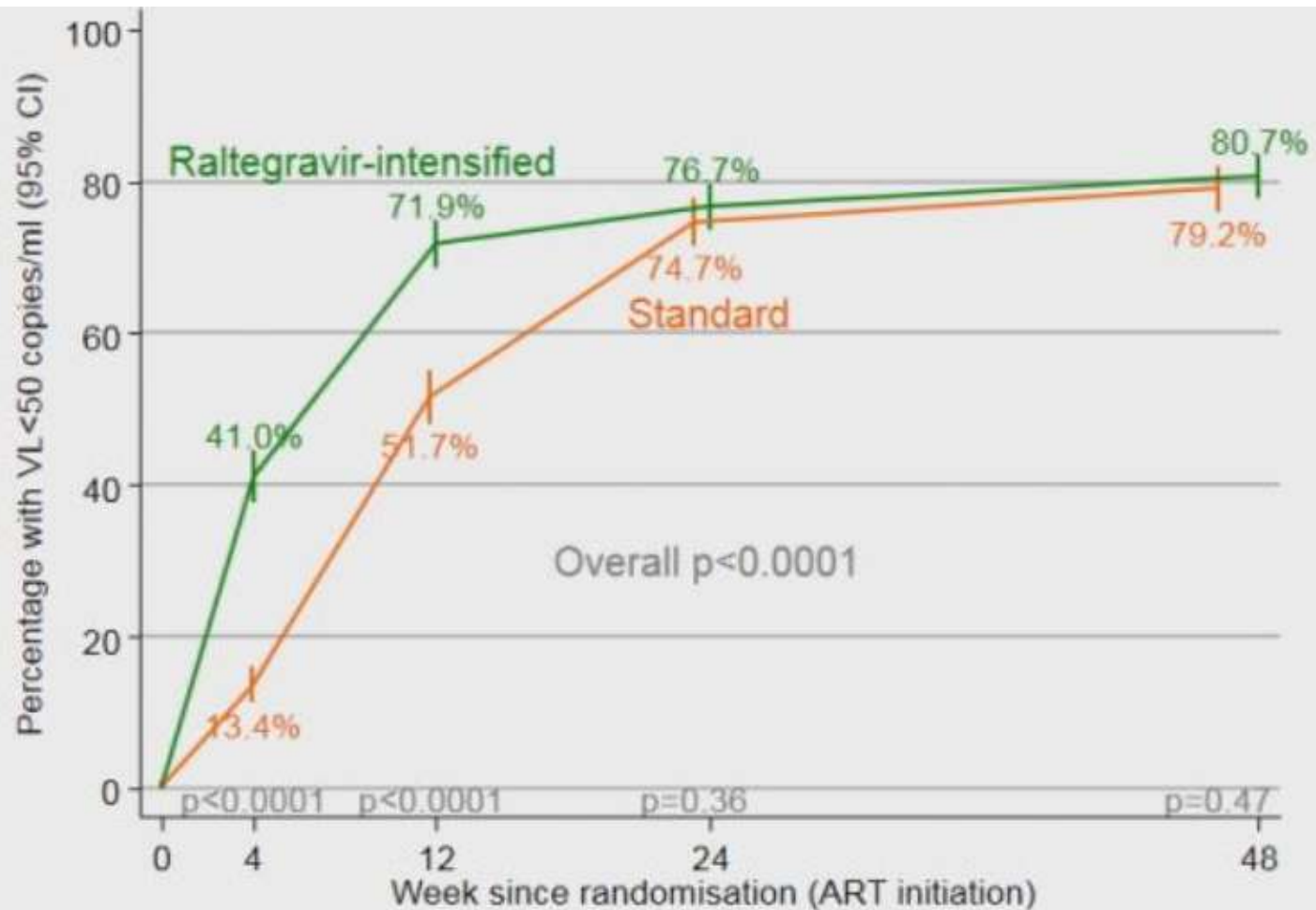
REALITY Trial Sites (ISRCTN43622374)



- **Uganda**
 - Fort Portal
 - Gulu
 - Mbale
 - Mbarara
- **Kenya**
 - Kilifi
 - Eldoret
- **Zimbabwe**
- **Malawi**

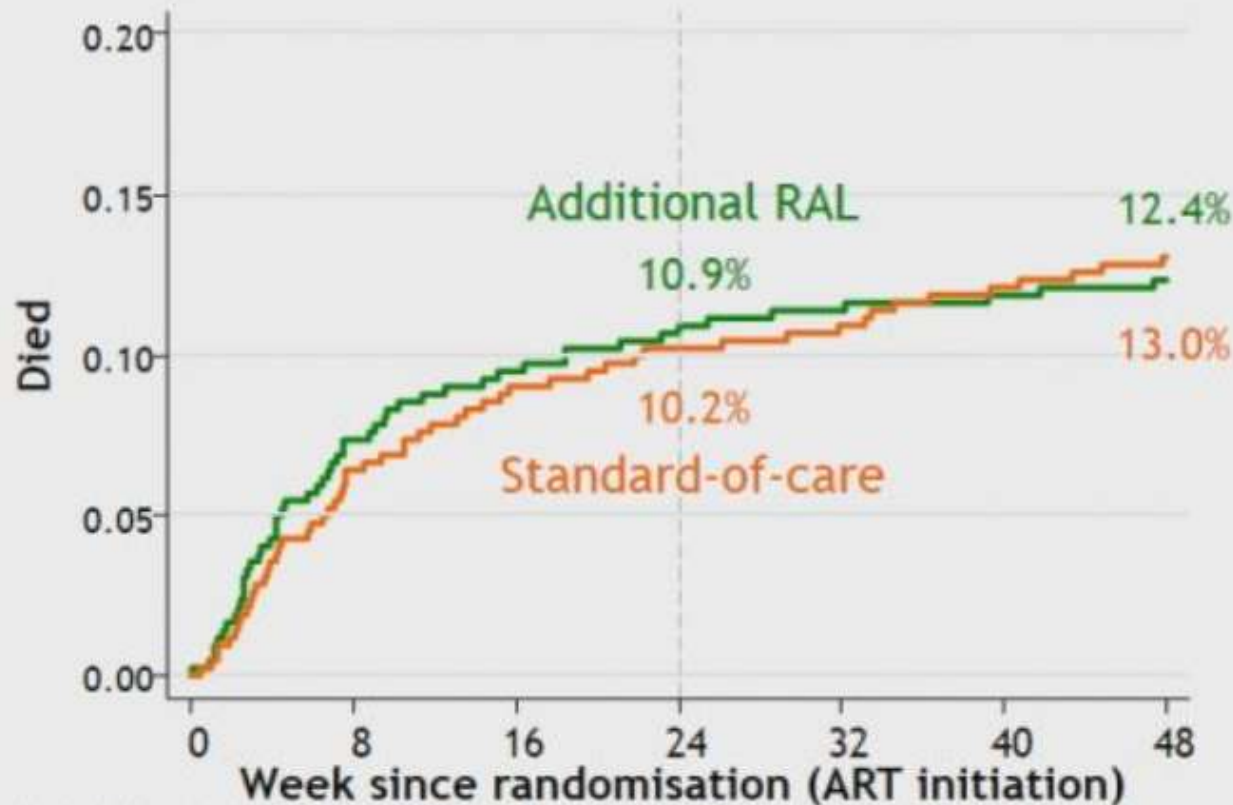


Viral Yük < 50 kopya/ml



Mortalite

- Mortality at 24 weeks: **10.9% RAL** vs **10.2% standard-of-care**



w24: HR=1.10
(95% CI 0.82-1.46)
p=0.53

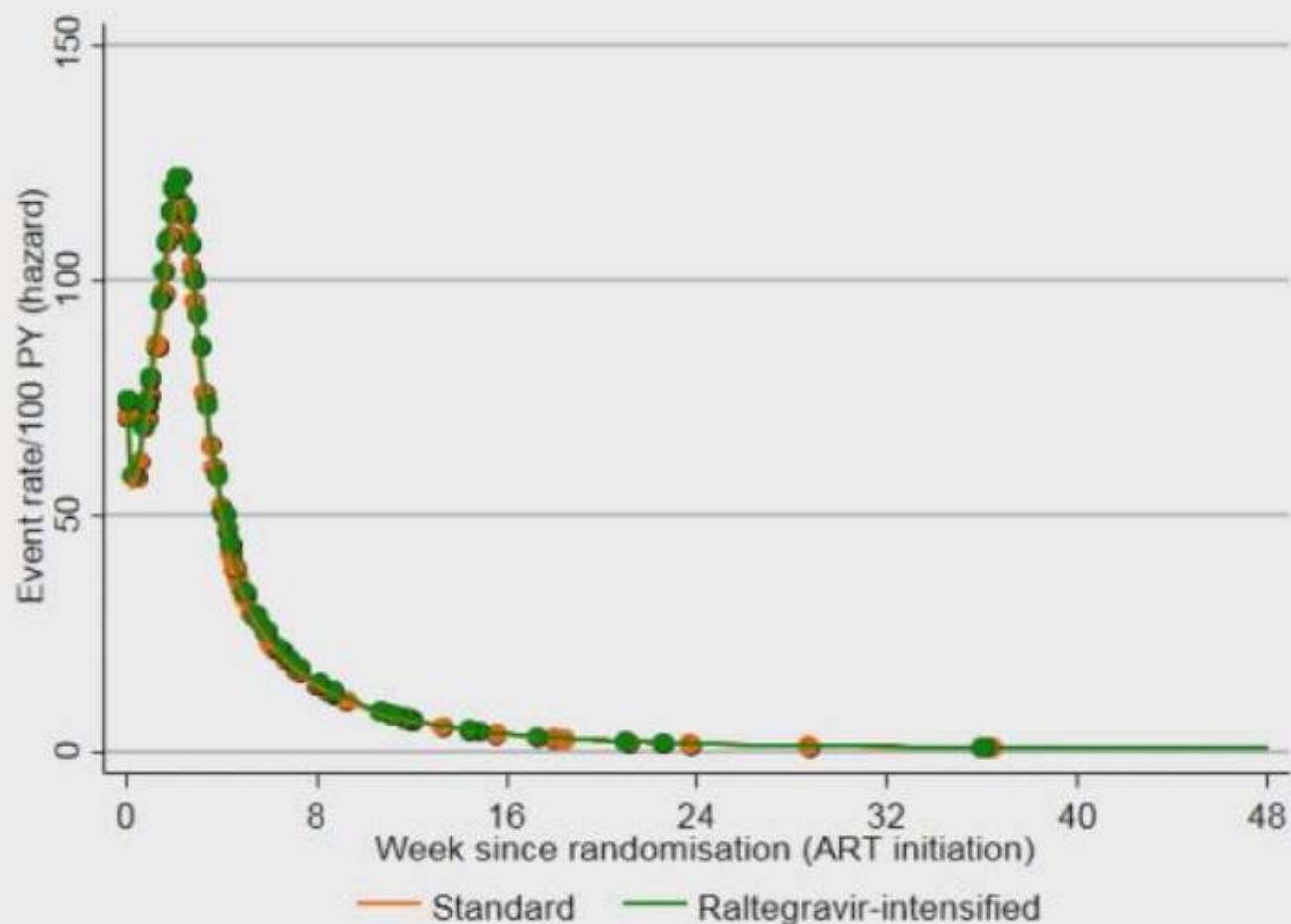
w48: HR=0.98
(95% CI 0.76-1.28)
p=0.91

Number at risk (deaths)

Standard-of-care	903	(57)	830	(23)	801	(10)	789	(7)	776	(10)	760	(8)	669
Additional RAL	902	(65)	825	(20)	801	(11)	786	(6)	775	(3)	766	(5)	657

- 56 (3.1%) lost to follow-up at 48 weeks
- No interactions with other randomisations ($p > 0.7$)


IRIS ile uyumlu olaylar



Fatal/non-fatal IRIS-compatible events occurred in **89 (9.9%) raltegravir-intensified** vs **86 (9.5%) standard** ($p=0.79$)

Sonuç

- ▶ Ağır immün yetmezliği olan hastalarda, raltegravir grubunda daha fazla IRIS görülmedi
- ▶ Bu bulgular, diğer integraz inhibitörleri için de uyarlanabilir.



İntegraz İnhibitörlerinin Lenfoid Doku Farmakokinetiği

Courtney V. Fletcher

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Omaha, NE, USA*

Disclosure: To self, paid to my institution: Recipient of research grant(s) from National Institutes of Health

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Neden Lenfoid dokuya odaklanmalıyız?

- ▶ HIV replikasyonun ve rezervuarın olduğu yer
- ▶ ART'nin sırasında HIV RNA < 50 kop/ml olmasına rağmen, dokularda replikasyon devam edebilir
- ▶ Antiretrovirallerin doku dağılımı homojen değil
- ▶ Lenfoid doku penetrasyonlarını belirleyen faktörler çok iyi bilinmiyor

Yöntemler

- ▶ HIV pozitif hastalar
- ▶ 2NRTI + DTG/EVG/RAL alan hastalar
- ▶ Periferik kandan mononükleer hücreler (PBMCs) ve lenfoid doku, ileum, rektumdan mononükleer hücreler elde edildi.
- ▶ İntegraz inhibitörlerinin hücre içi konsanrasyonları hesaplandı ^{1,2}

1. Fletcher CV et al. PNAS 2014;111:2307-12.

2. Podany AT et al, Antimicrob Agents Chemother 2014;58:2866-70.

Yöntemler

- ▶ İnhibitör katsayıları (IQ) saptandı:
= Hücre içi kons/proteine bağlı %90–95
inhibitör kons (${}_{pb}IC_{90-95}$)
- ▶ Yüksek IQ= Yüksek rölatif potans

■ ${}_{pb}IC_{90-95}$ values:

INSTI	${}_{pb}IC_{90-95}$ (ng/mL) ²
DTG	64.0 (${}_{pb}IC_{90}$)
EVG	44.9 (${}_{pb}IC_{95}$)
RAL	14.7 (${}_{pb}IC_{95}$)

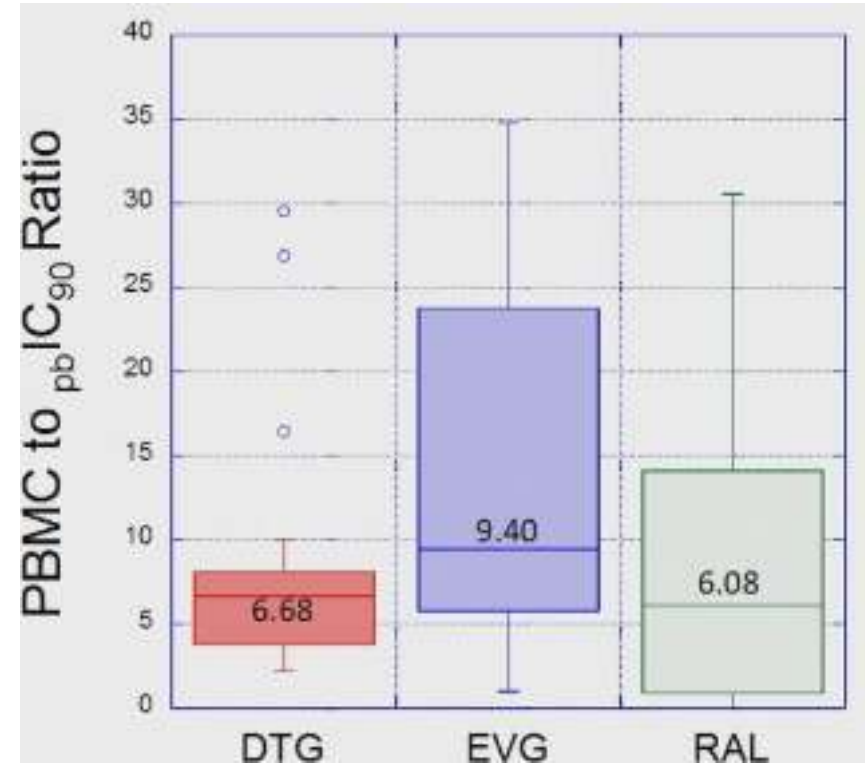
1. FDA. Guidance for Industry, Antiviral Product Development. June 2006.

2. Podany AT, Scarsi KK, Fletcher CV. *Clin Pharmacokinet* 2017;56:25-40.

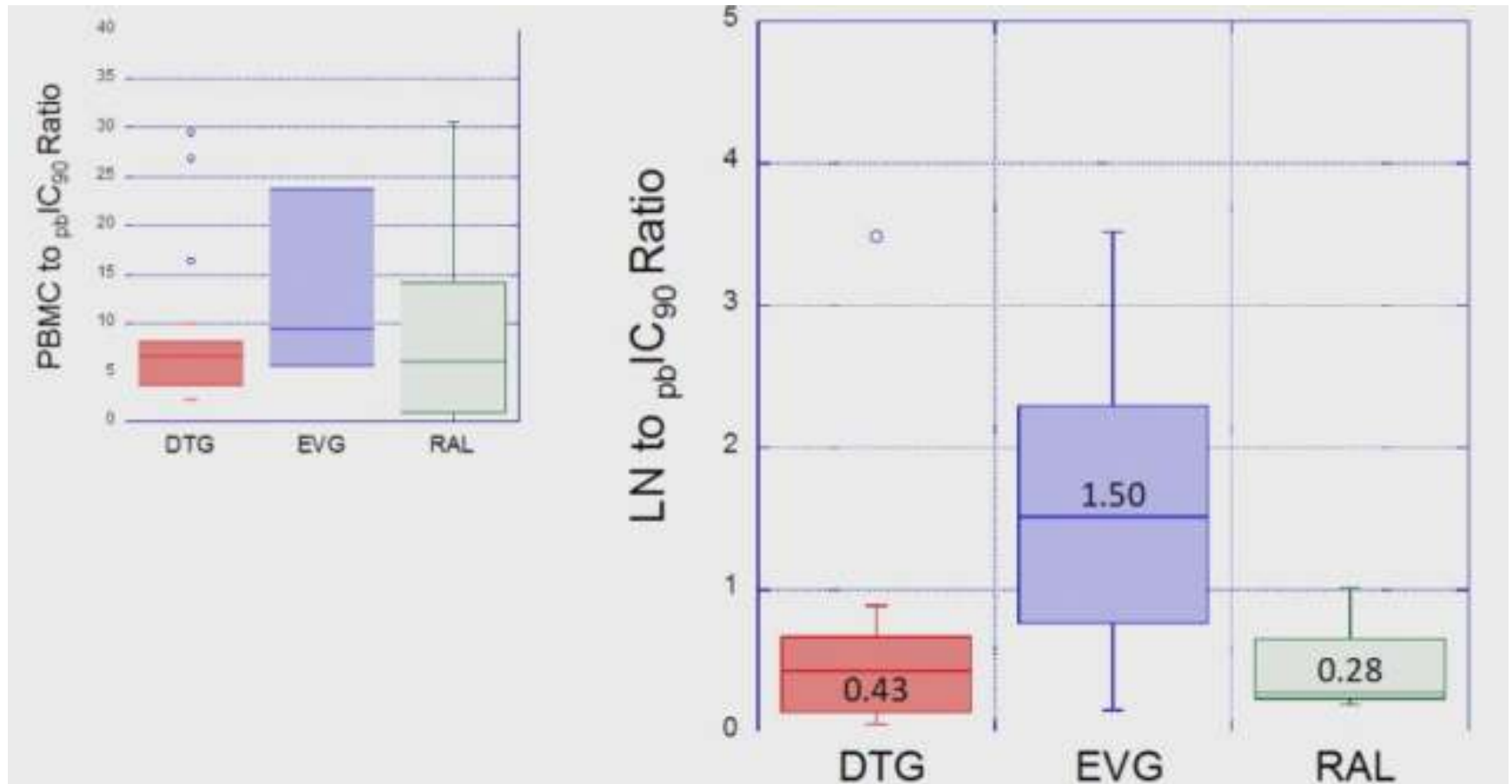
Bulgular–PBMCs inhibitör katsayıları

- ▶ Toplam 34 hasta

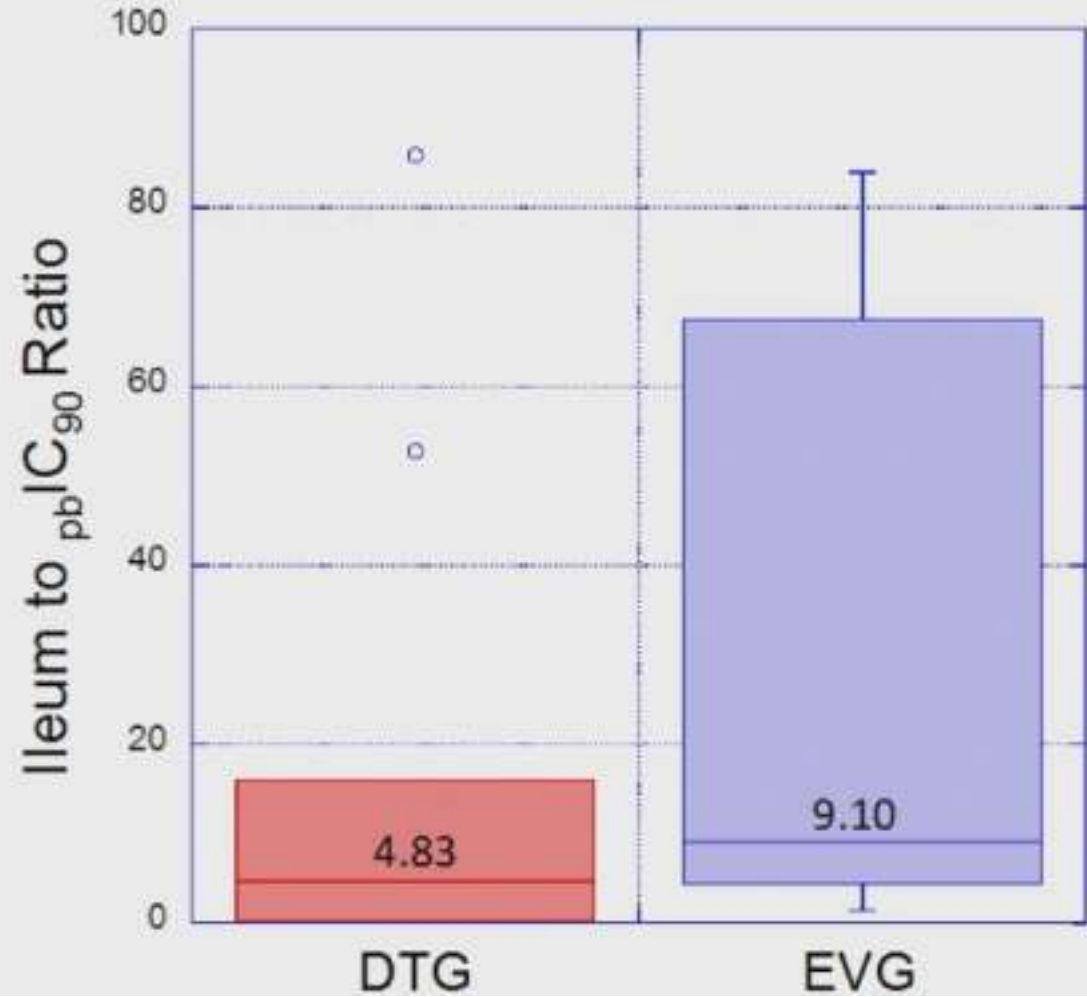
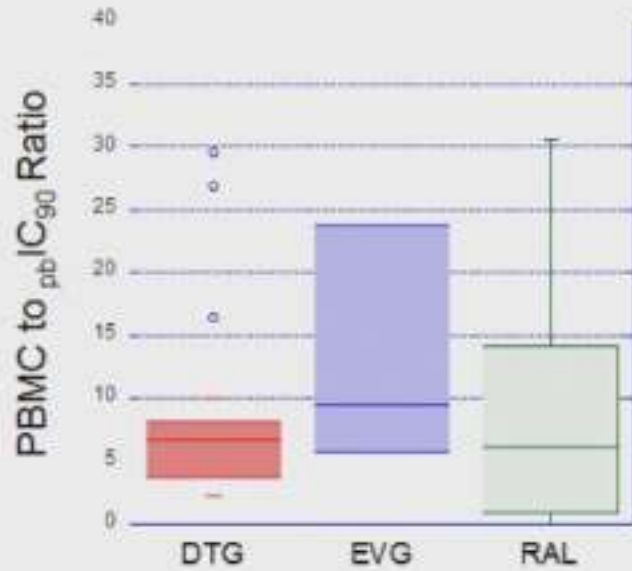
	IC & IQ Values in Plasma		
	DTG	EVG	RAL
IC ₉₀ , ng/mL	64	NA	NA
IC ₉₅ , ng/mL	NA	44.9	14.7
C _{trough} , ng/mL	1100	450	124
IQ	17	10	8



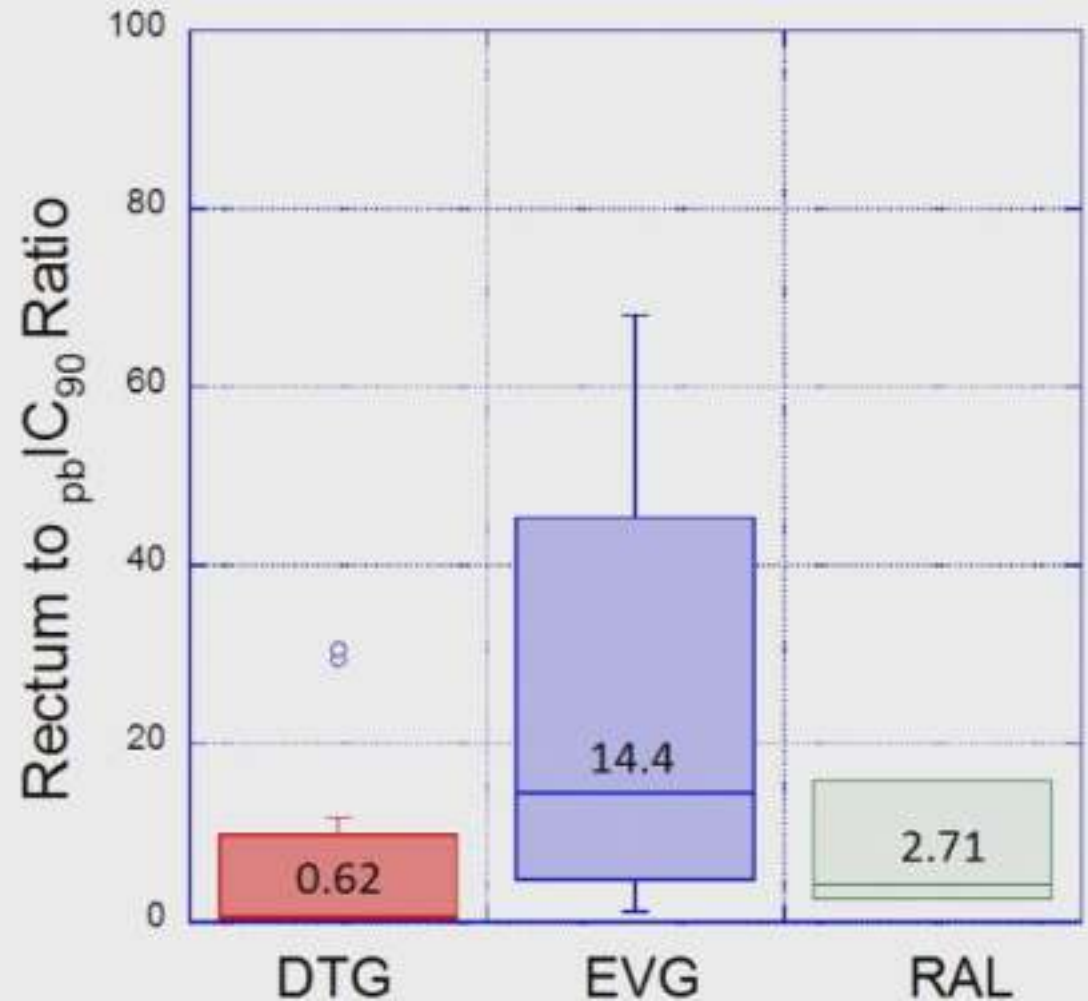
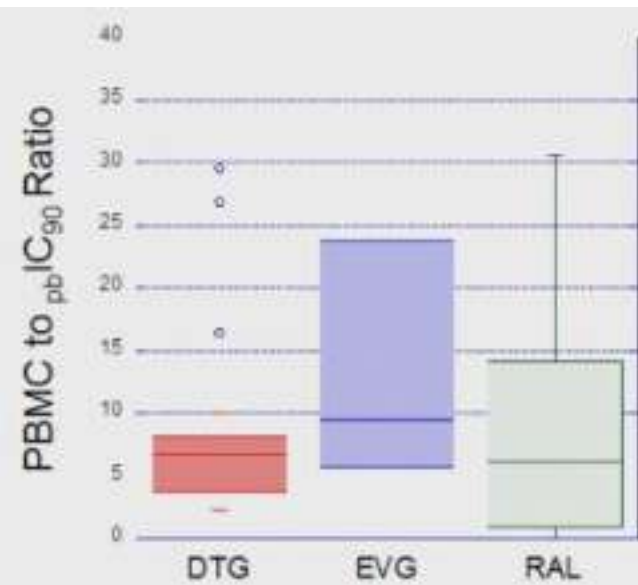
Bulgular-lenfoid dokuda inhibitör katsayıları



Bulgular-ileumda inhibitör katsayıları

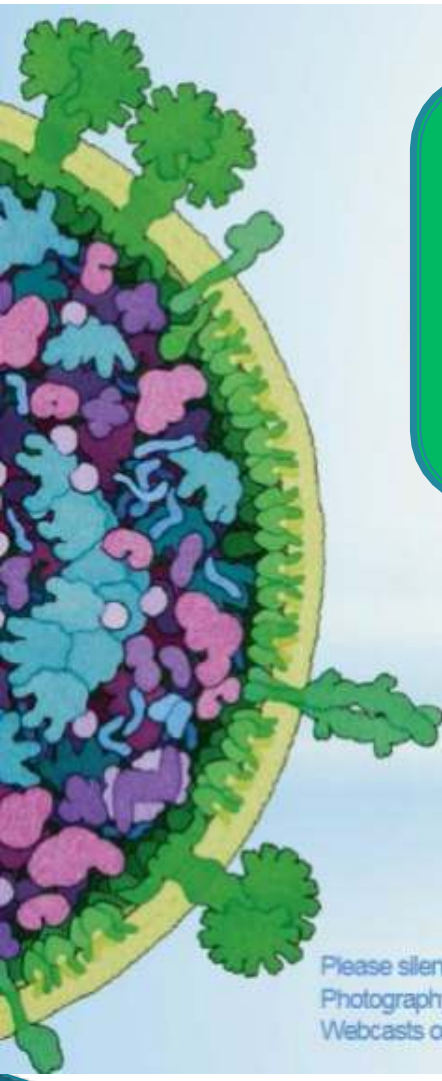


Bulgular-rektumda inhibitör katsayıları



Sonuç

- ▶ Periferik mononükleer hücrelerde tüm integraz inhibitörlerin IQ değerleri $_{pb}IC_{90-95}$ 'ye göre 6 kattan fazladır. Bundan dolayı hızlı viral baskılanma sağlanmaktadır.
- ▶ Lenfoid dokuda sadece EVG'nin IQ değeri 1'in üstünde
- ▶ Lenfoid dokudaki düşük konsantrasyonlar persistan viremiye yol açıyor mu???



HIV'in Önleme ve Tedavisinde Geniş Etkili Nötralizan Antikorlar (bNAb)

Daniel R. Kuritzkes

*Brigham and Women's Hospital, Harvard Medical School
Cambridge, MA, USA*

Disclosure: Self: Recipient of research grant(s) from and consultant for Gilead, Merck, ViiV; consultant for CytoDyn; relationship with Sanofi

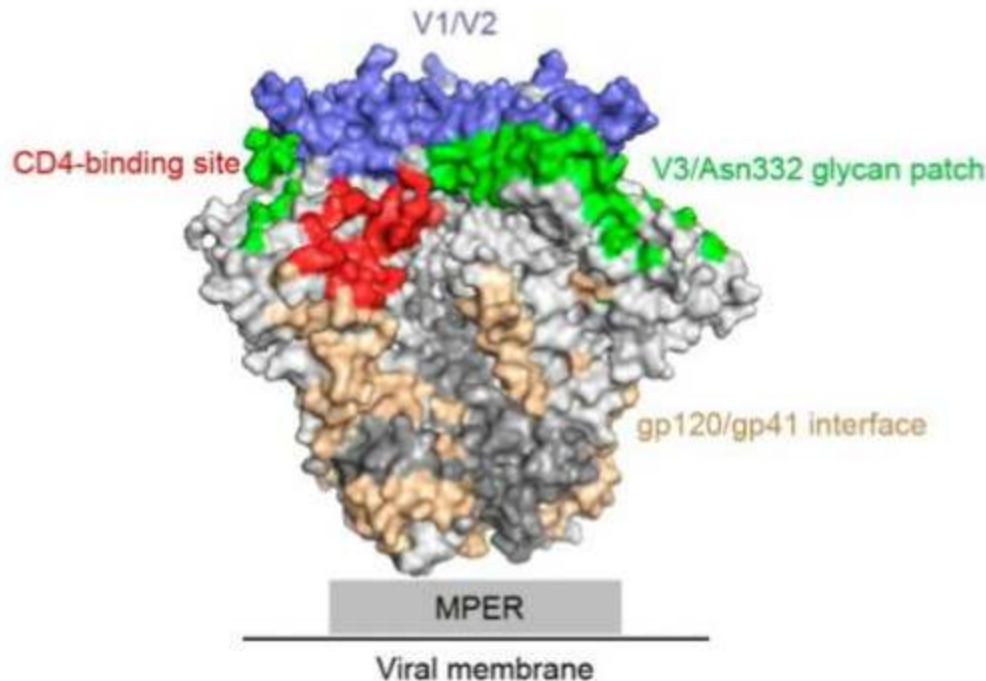
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Geniş Etkili Nötralizan Antikorlar (bNAb)- Bağlanma Yerleri



CD4-binding site

b12, VRC01, VRC07, NIH45-46,
3BNC117, VRC-PG04

V1/V2

PG9, PG16, CH01-04,
PGT141-145, PGDM1400

V3/Asn332 glycan patch

PGT121-123, PGT125-131,
PGT135, 10-1074, 2G12

gp120/gp41-interface

PGT151, 35O22, 8ANC195

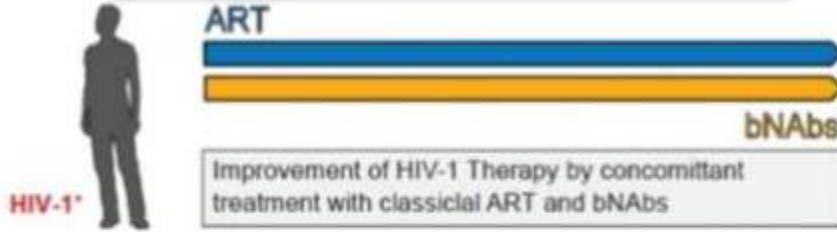
MPER

2F5, 4E10, 10E8

bNAB- potansiyel klinik kullanımları

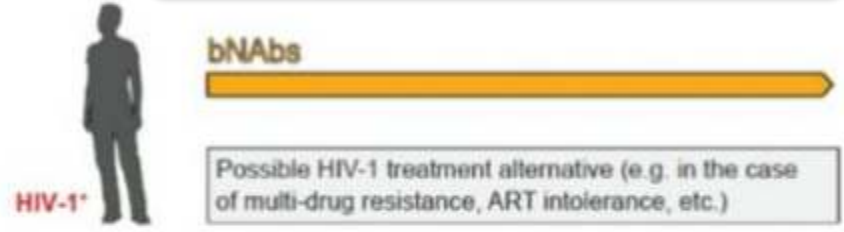
A

Tedavinin güçlendirilmesi



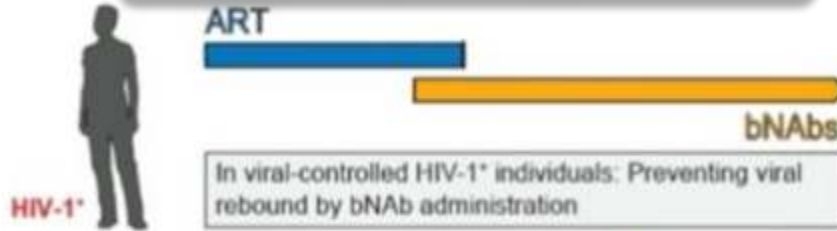
C

İmmünoterapi



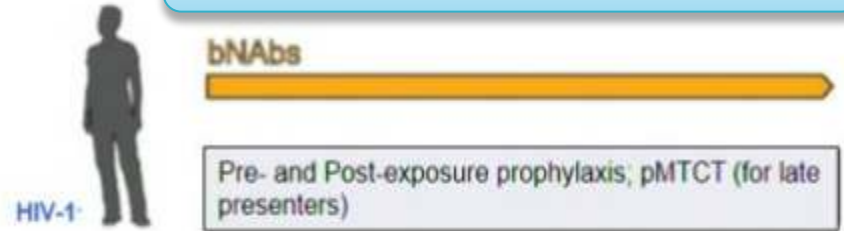
B

Süpresyonu kalıcı kılma

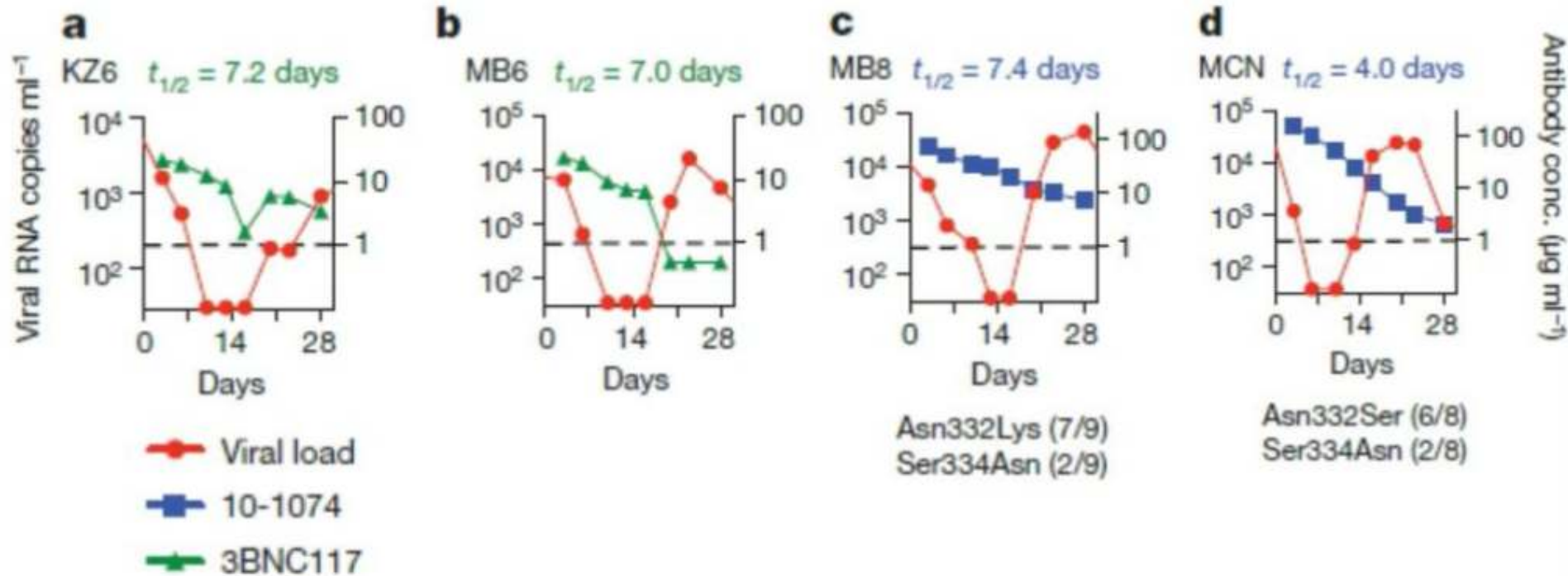


D

HIV-1 önlenmesi

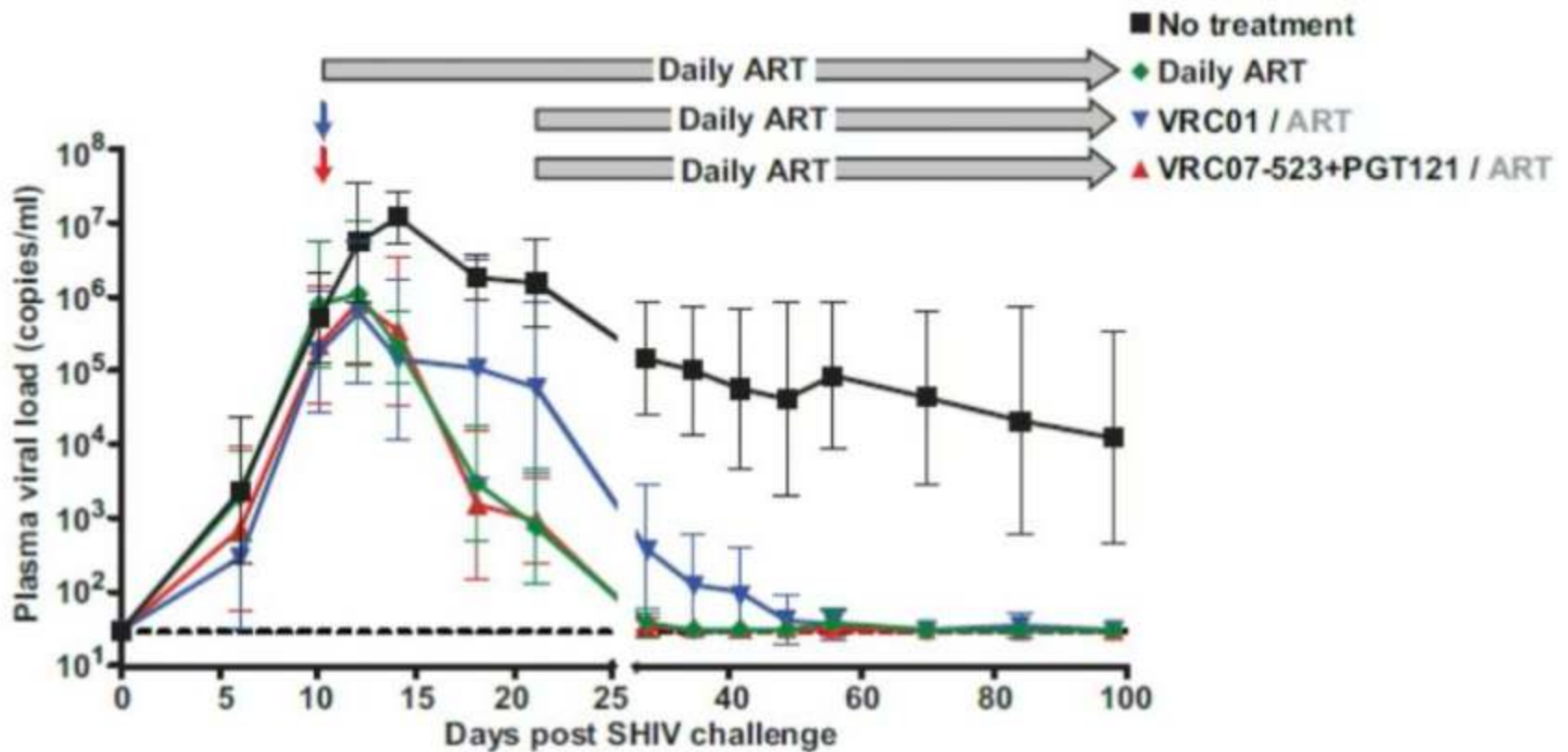


3BNC117 ve 10-1074 Antiviral Aktivitesi

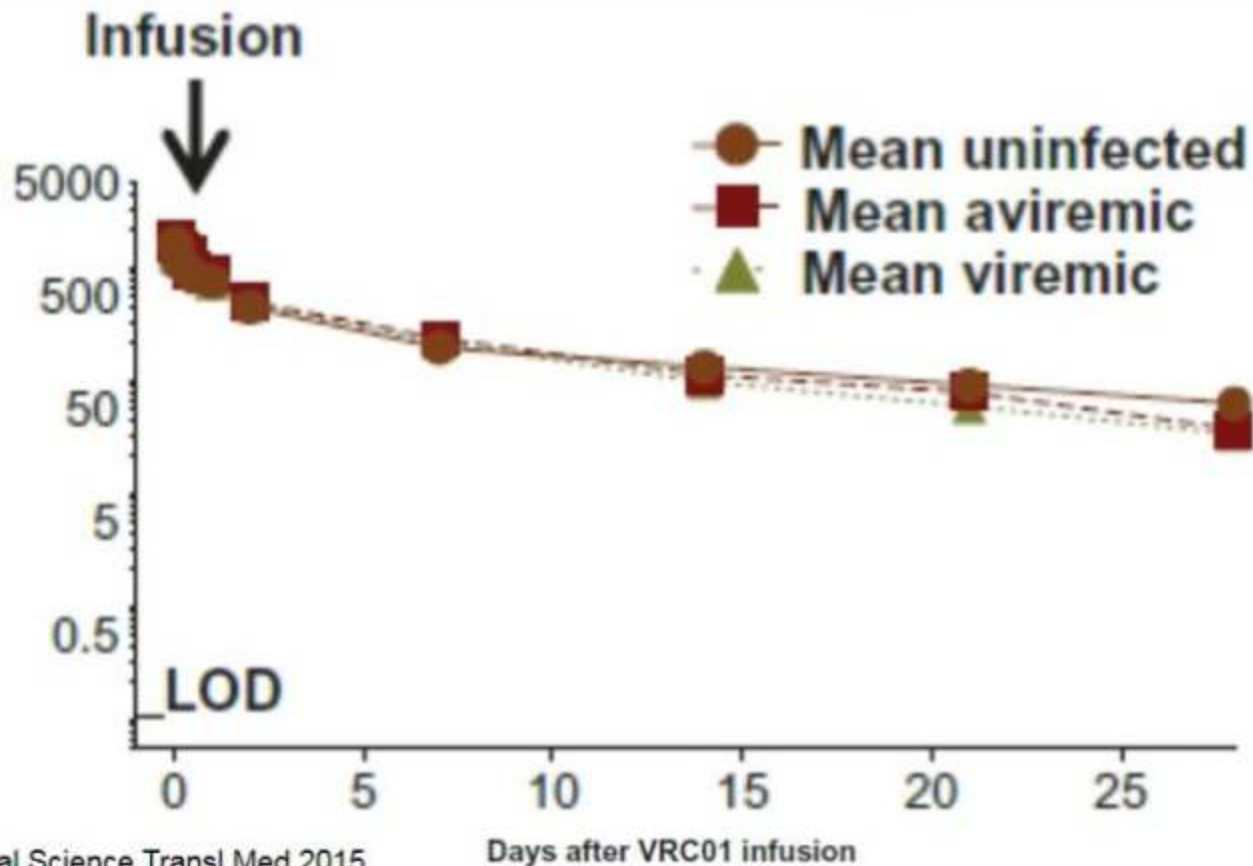


Shingai M et al Nature 2013
 Martin M CROI 2018 Abstr 49

Akut SHIV modelinde tek veya çift bNAb tedavisi



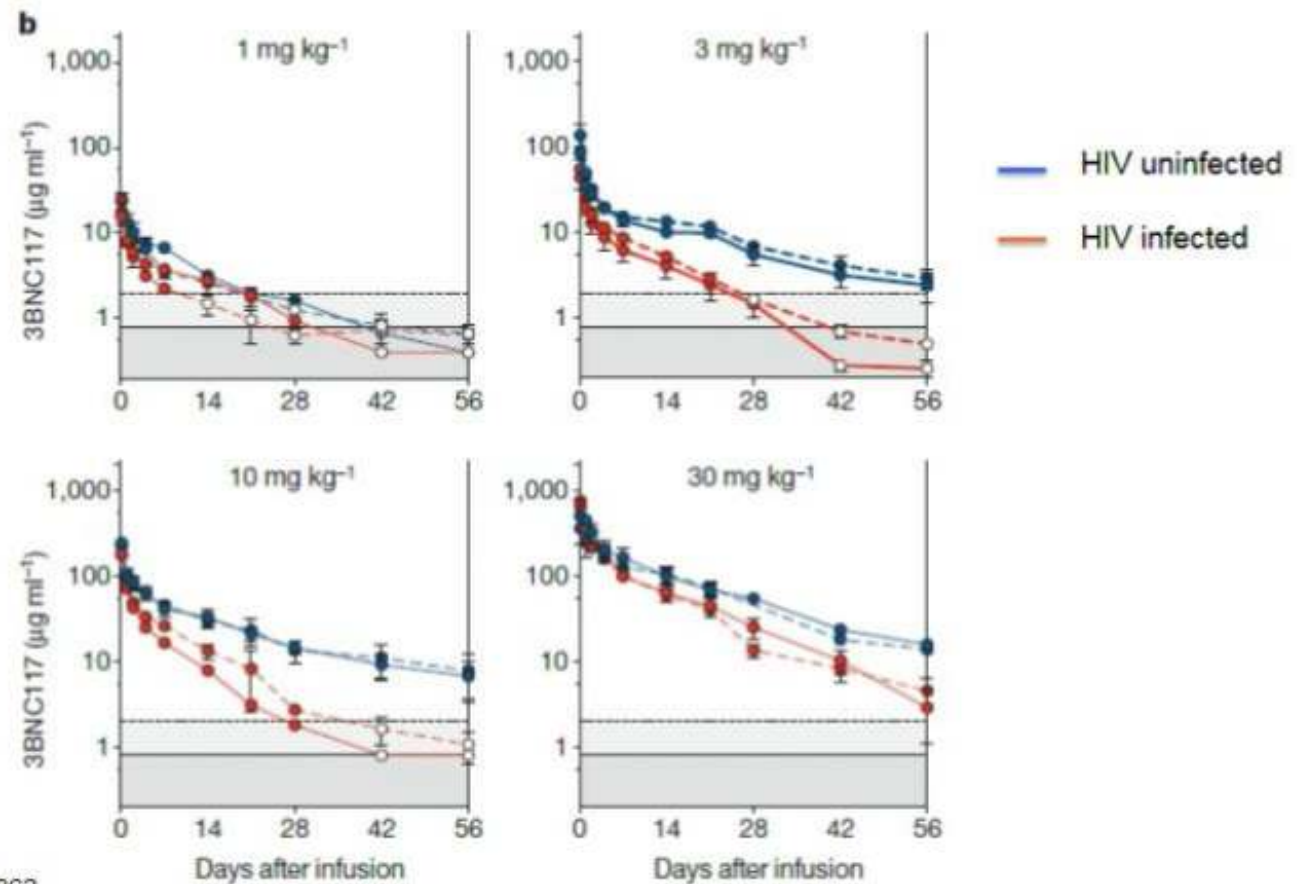
VRC01 – Tek doz farmakokinetiği



Temas öncesi profilakside VRC01 – klinik çalışmalar

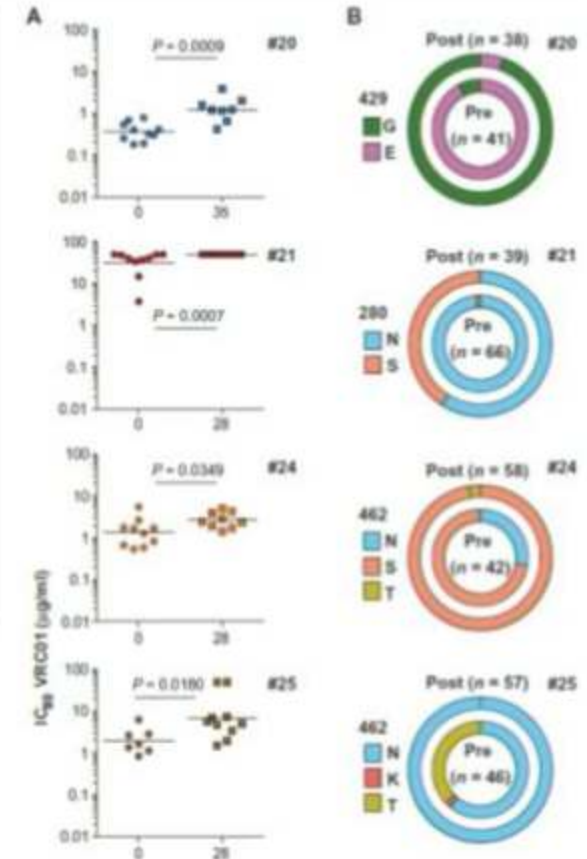
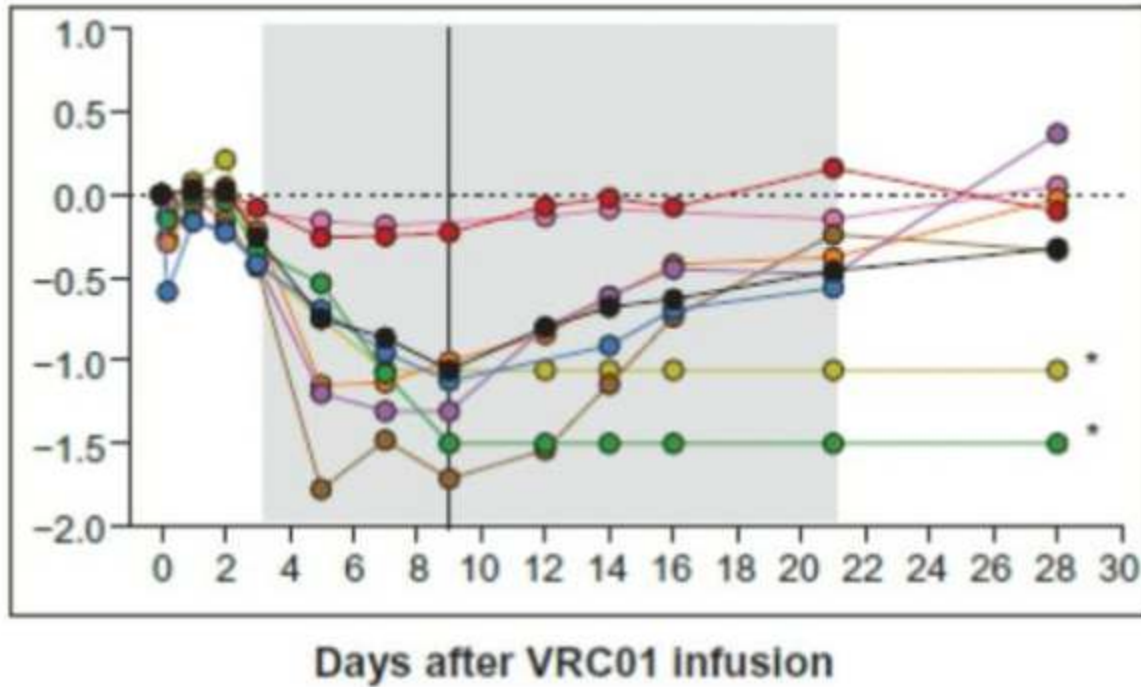
- **AMP (HVTN 703/HPTN 084)**
 - Phase 2b study of q8 wk VRC01 (2 dose groups) vs placebo
 - 1500 women in sub-Saharan Africa
 - PrEP permitted but not study provided
- **AMP (HVTN 704/HPTN 085)**
 - Phase 2b study of q8 wk VRC01 (2 dose groups) vs placebo
 - 2700 MSM and transgender women
 - North and South America
 - PrEP permitted but not study provided

3BNC117 – Tek doz farmakokinetiği

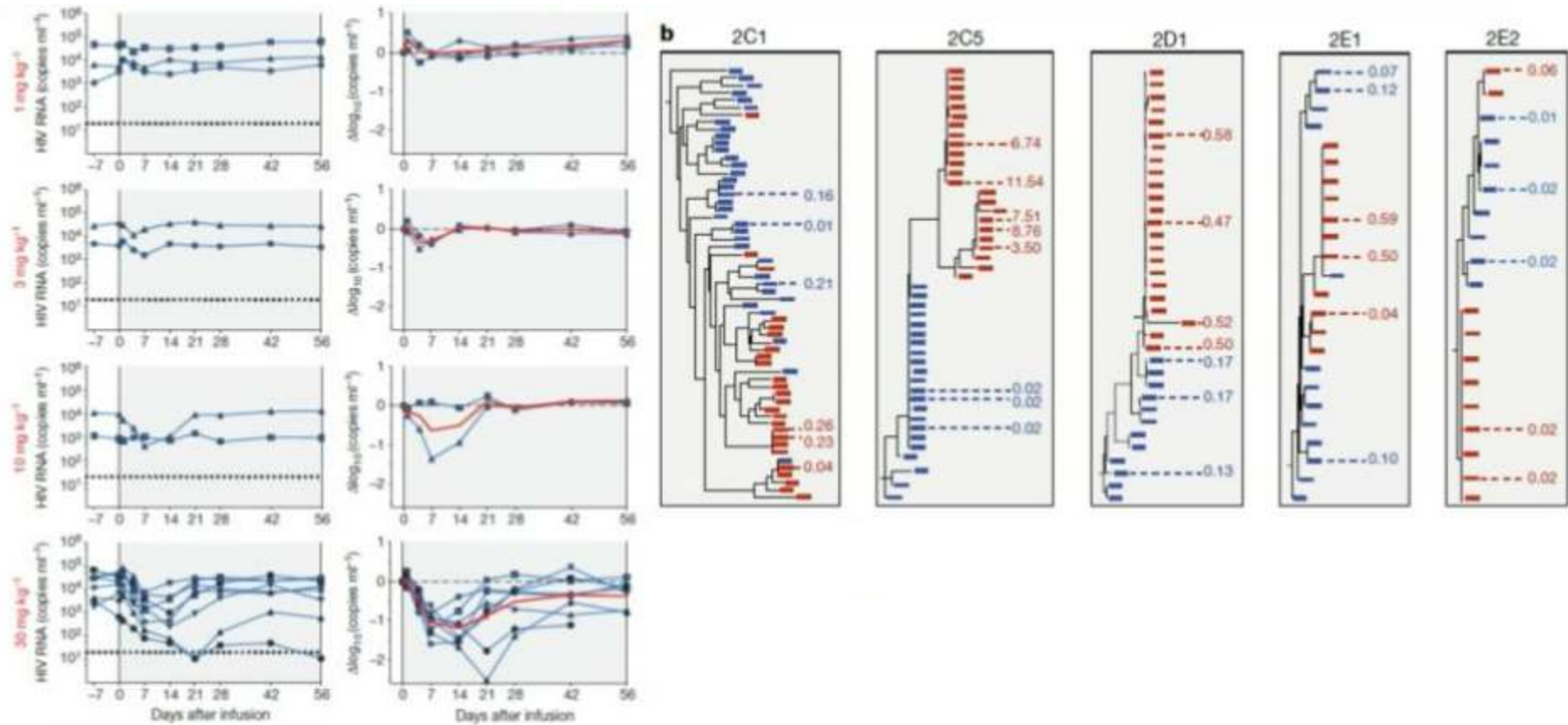


Caskey M et al Nature 2015
Cohen Y et al CROI 2018 Abstr 1062

VRC01 – Antiviral etkinlik

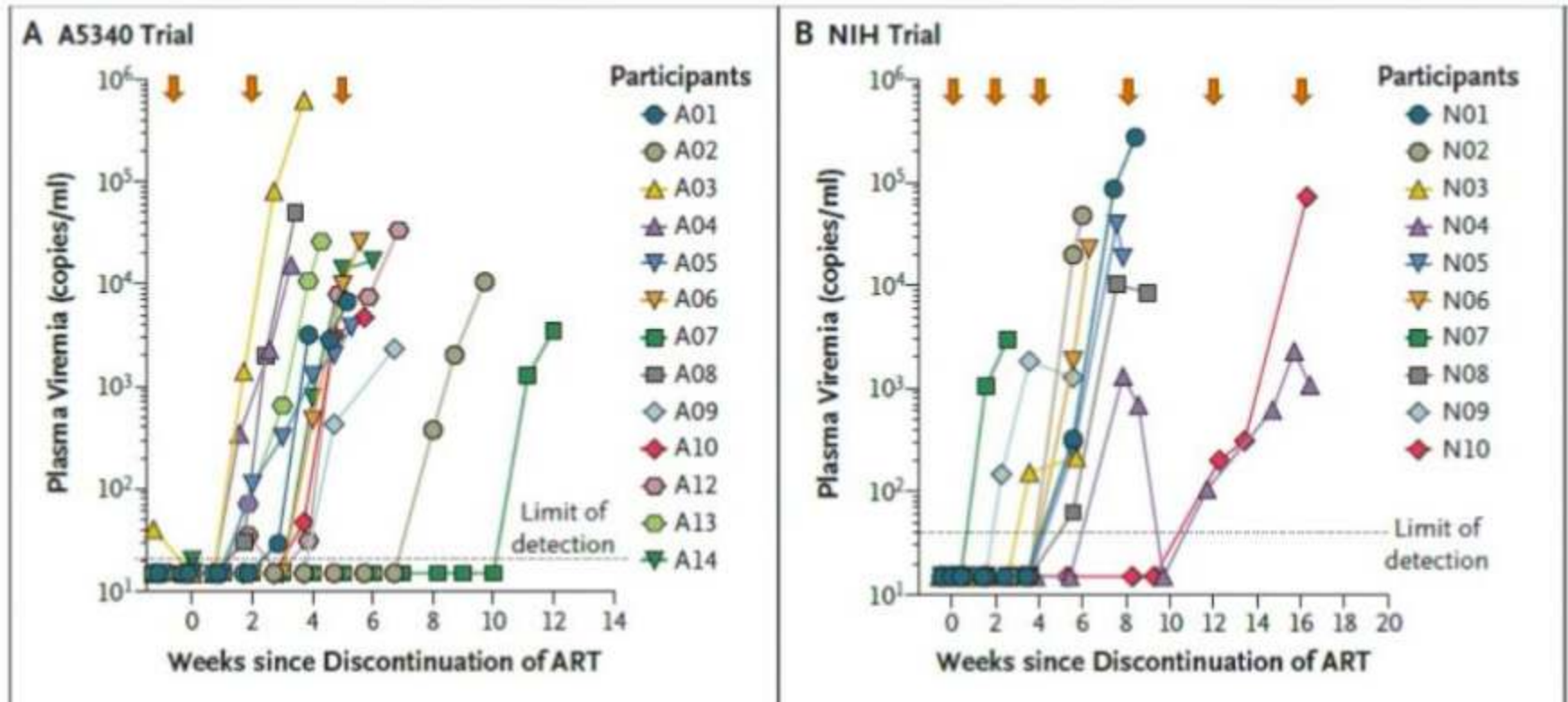


3BNC117-Antiviral etkinlik



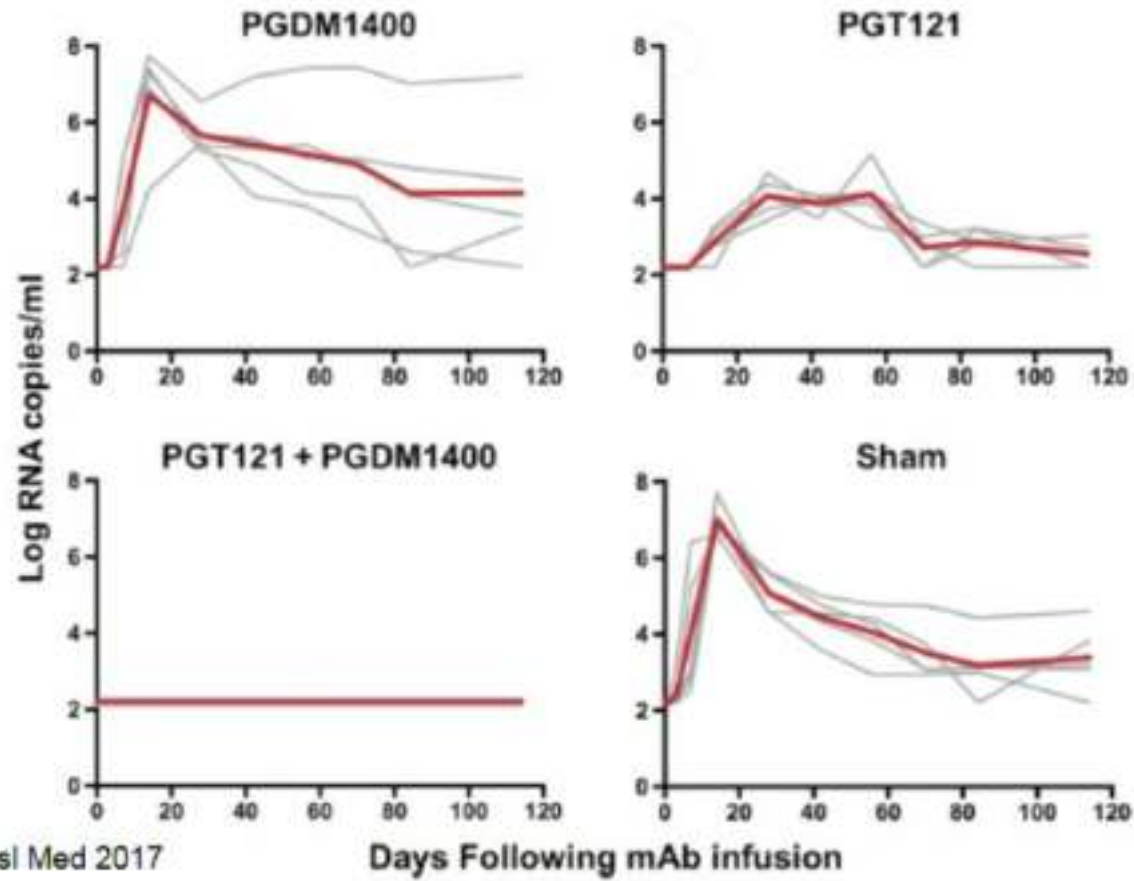
Caskey M et al Nature 2015

ART kesildikten sonra VRC01 monoterapisi- viral baskılanmayı sürdürmüyor

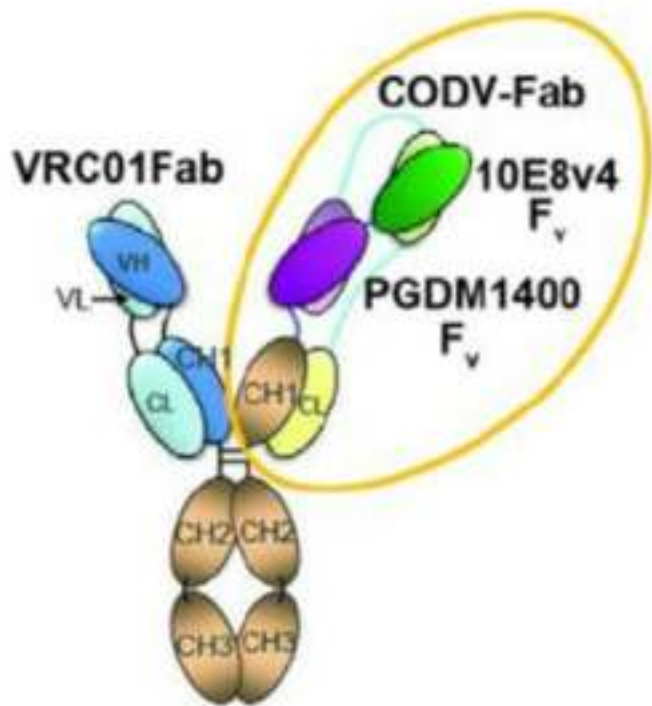


↓ VRC01 infusion

bNAb kombinasyonları- SHIV enfeksiyonunu önüyor



Üçlü-spesifik bNAb (SAR441236)

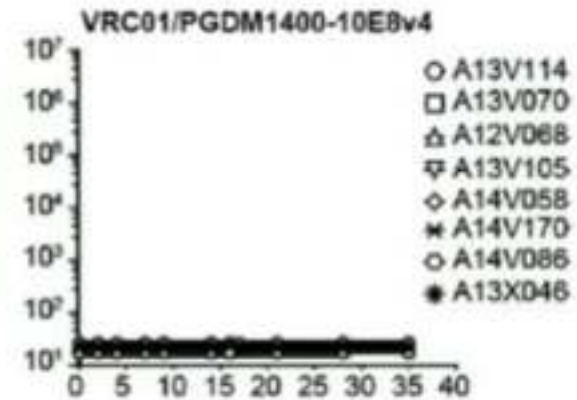
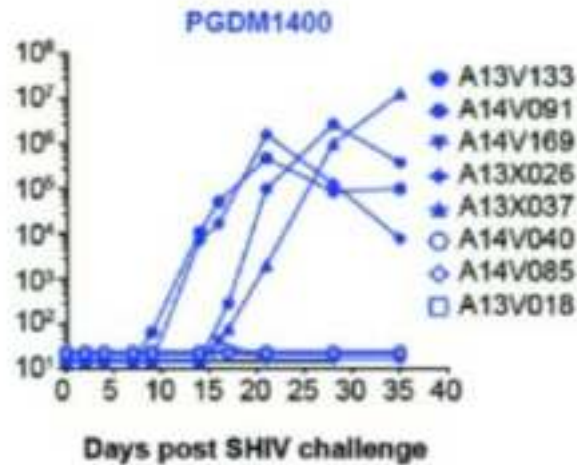
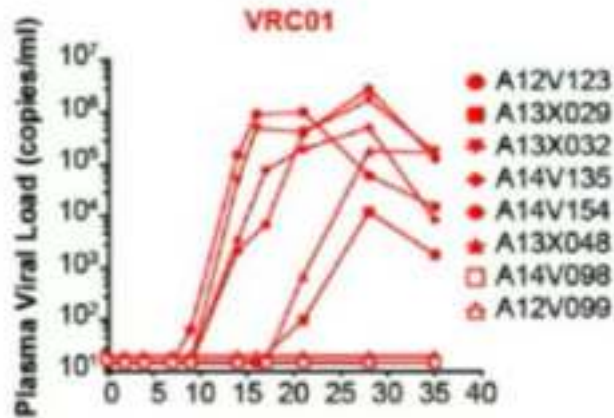


Antibody	SHIV BaLP4	SHIV 325c
VRC01	0.067	>50
PGDM1400	>50	0.015
VRC01/ PGDM1400-10E8v4	0.055	0.168


Xu L et al Science 2017.

Peau A et al CROI 2018 Abstract 113LB.

Üçlü-spesifik bNAb- SHIV enfeksiyonunu önüyor



Sonuç

- ▶ Geniş Etkili Nötralizan Antikorlar (bNAb) uzun etkili ajanlar olarak– tedavi ve profilaksideki kullanımları umut vericidir
 - ▶ Kombinasyonlar? İkili–Üçlü spesifik bNAb
- 
- ▶ Etkinlik ve uzun vadede güvenilirlik?
 - ▶ HIV–1'in rezervuarı üzerindeki etkinlikleri?
 - ▶ Maliyet?

**LETS
KICK
ASS.
HIV**

TEŞEKKÜRLER...