Antiretroviral Direnç

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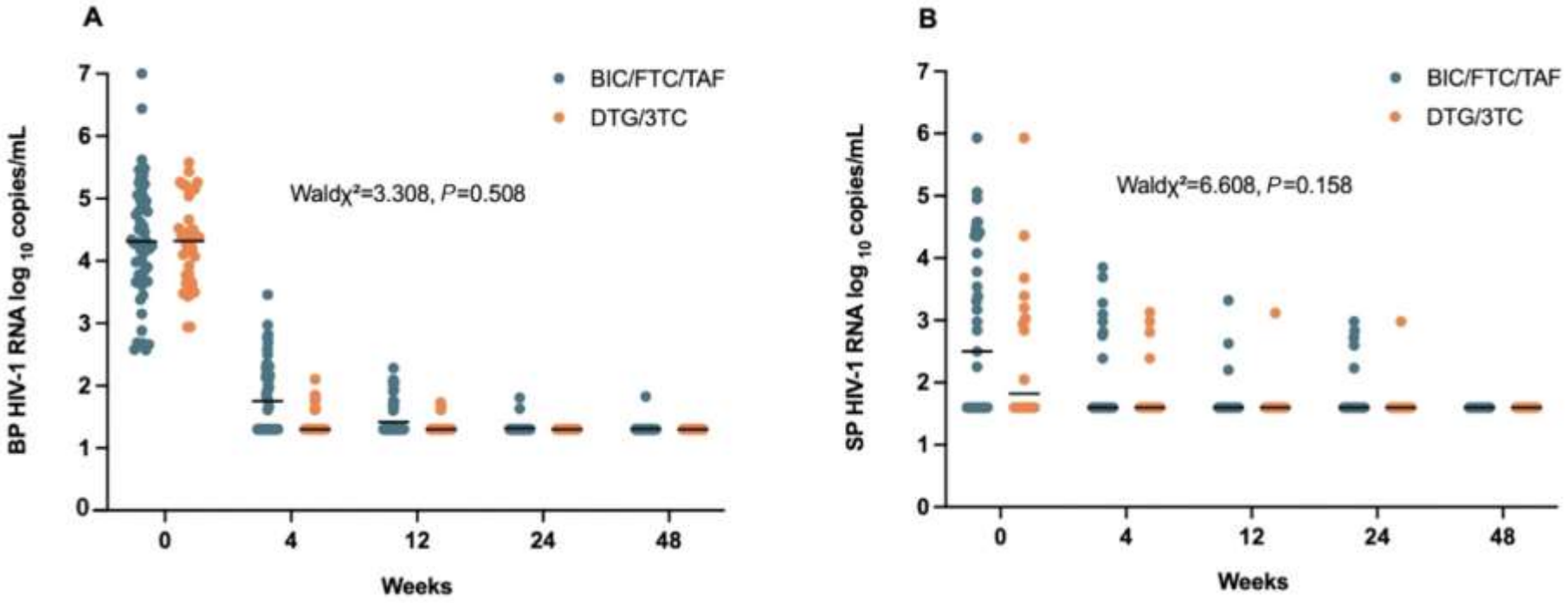
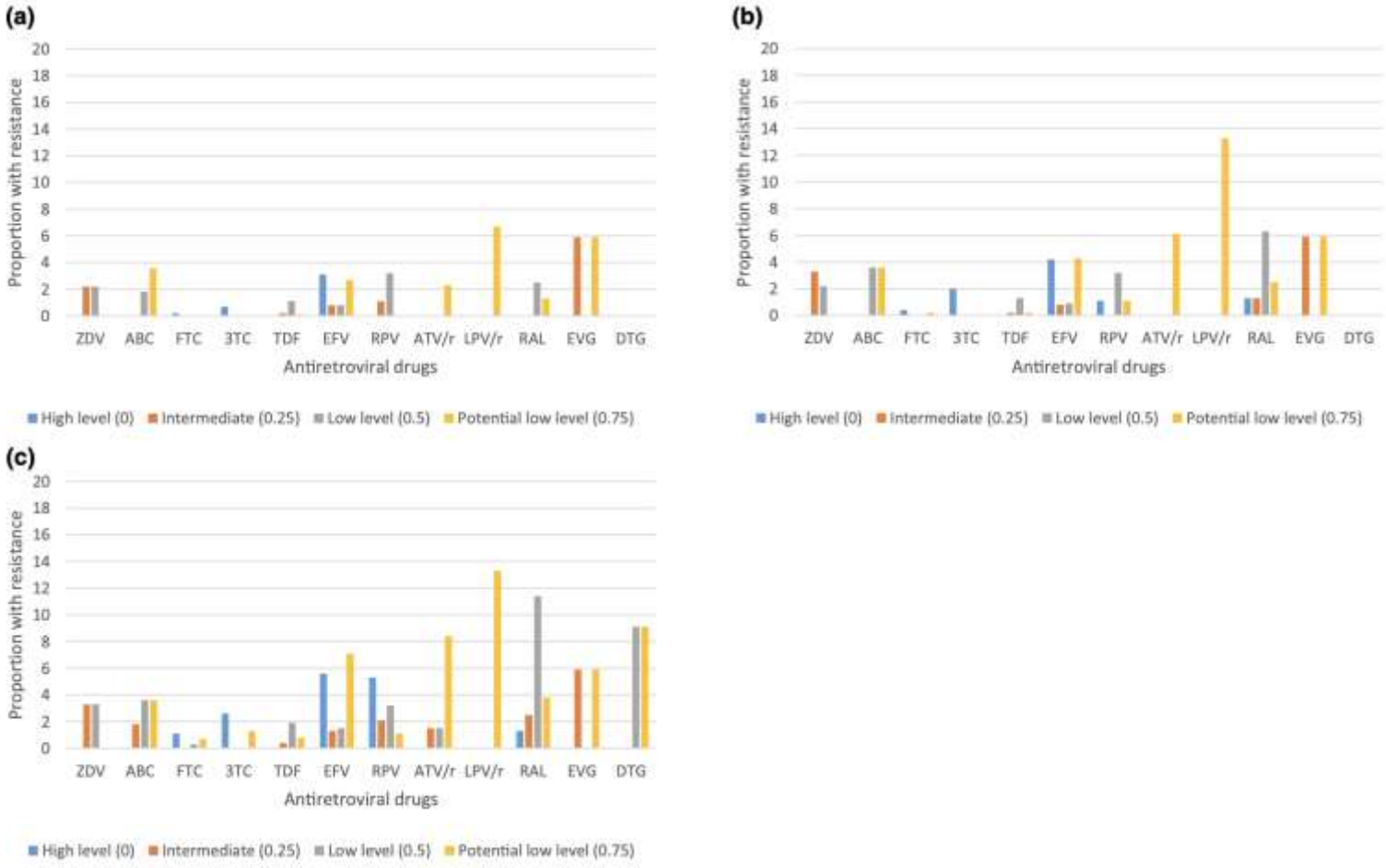
HIV/AIDS Korunma ve Eğitim Derneği

ART Altında Viral Yük Değişimi



Liu Y etal 2025 HIV-1 viral decay in blood and semen in antiretroviral-naïve adults initiating DTG/3TC vs BFTAF *Int J Antimicrob Agents*

GSS ve ART Altında Virolojik Başarı



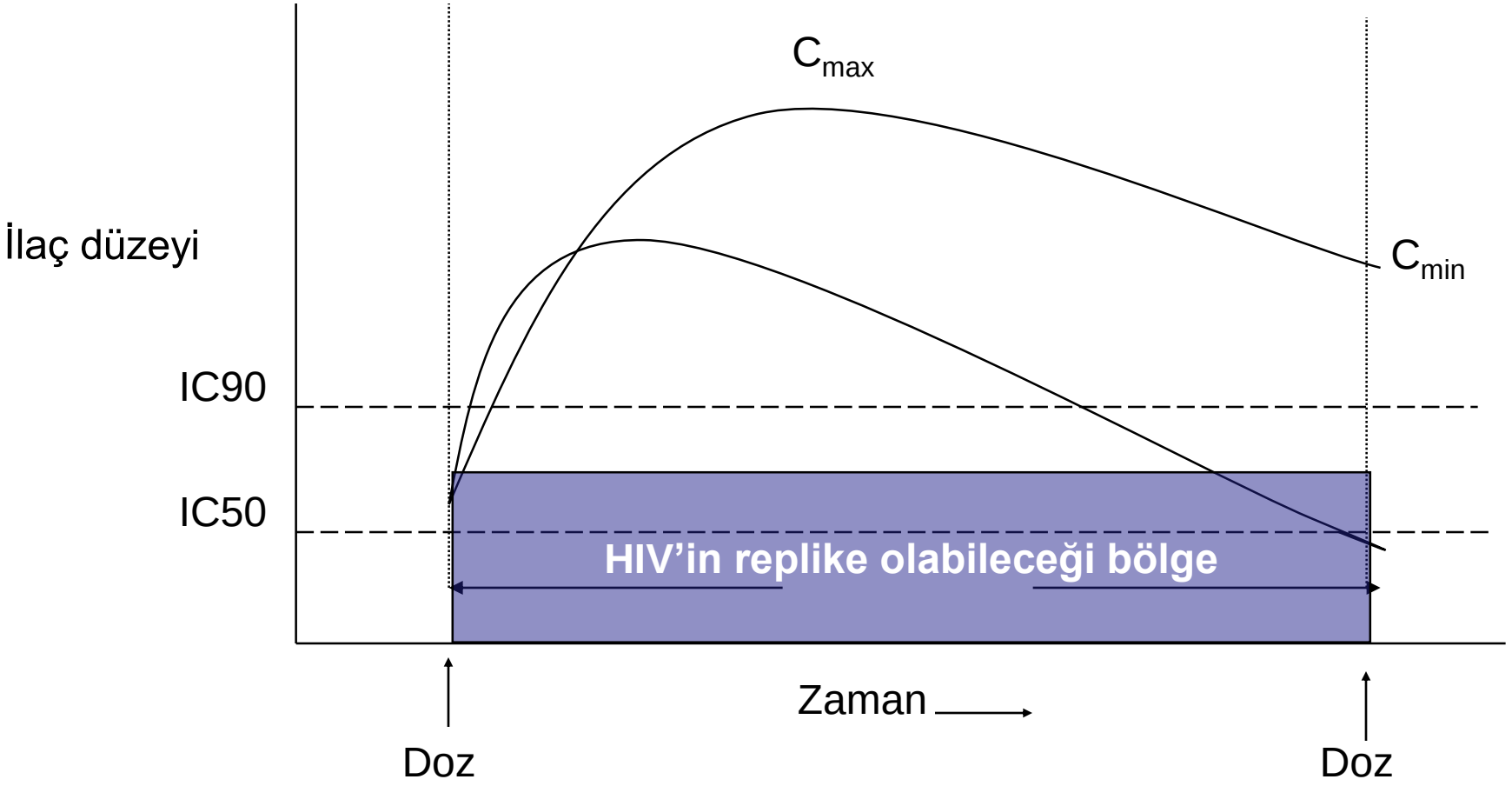
Cozzi-Leppri A etal 2023 *Rate of response to initial antiretroviral therapy according to level of pre-existing HIV-1 drug resistance detected by next-generation sequencing in the strategic timing of antiretroviral treatment (START) study* HIV Med

GSS ve ART Altında Virolojik Başarı

- GSS <3
  - %7 Sanger
  - %10, eşik >%5
  - %17, eşik >%2
- Eşik %2 alındığında: GSS 0-2.75 vs 3
  - başarısızlık 1.66 (%95 CI 1.01–2.74; p= 0.05)
  - NNRTI başlananlarda 2.32 (%95 CI 1.32–4.09; p= 0.003)
- %17 kişiye GSS <3 rejim başlanıyor
- **Bu da NNRTI bazlı rejim başlananlarda VF riskini arttırıyor**

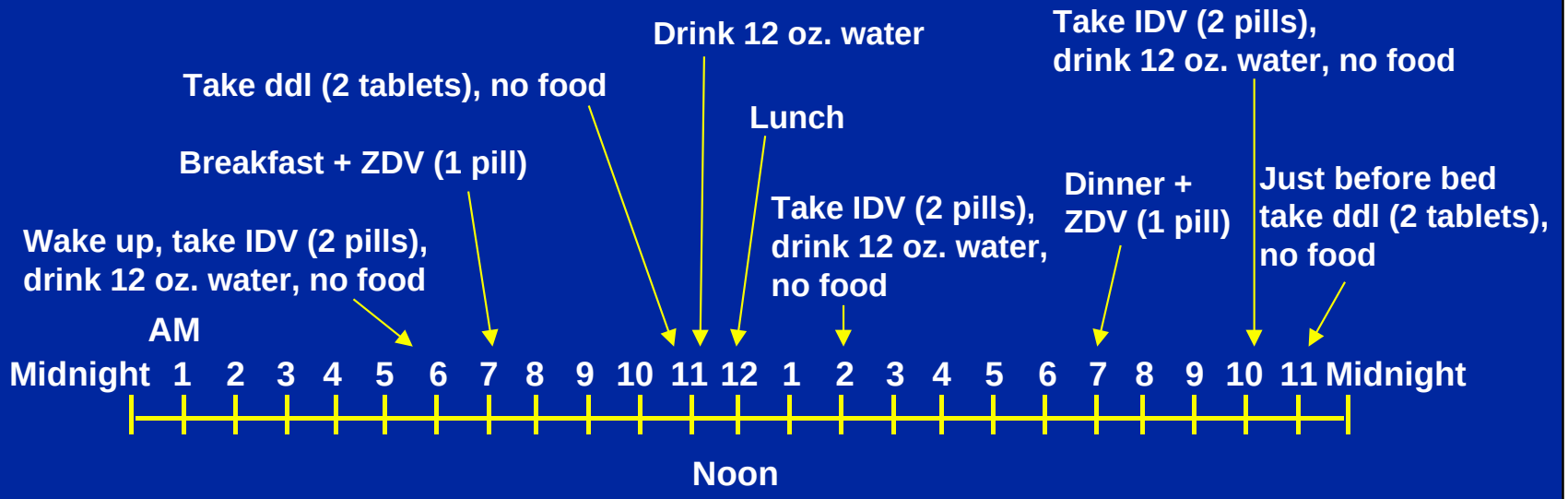
Cozzi-Leppri A etal 2023 *Rate of response to initial antiretroviral therapy according to level of pre-existing HIV-1 drug resistance detected by next-generation sequencing in the strategic timing of antiretroviral treatment (START) study* HIV Med

Temel Farmakokinetik



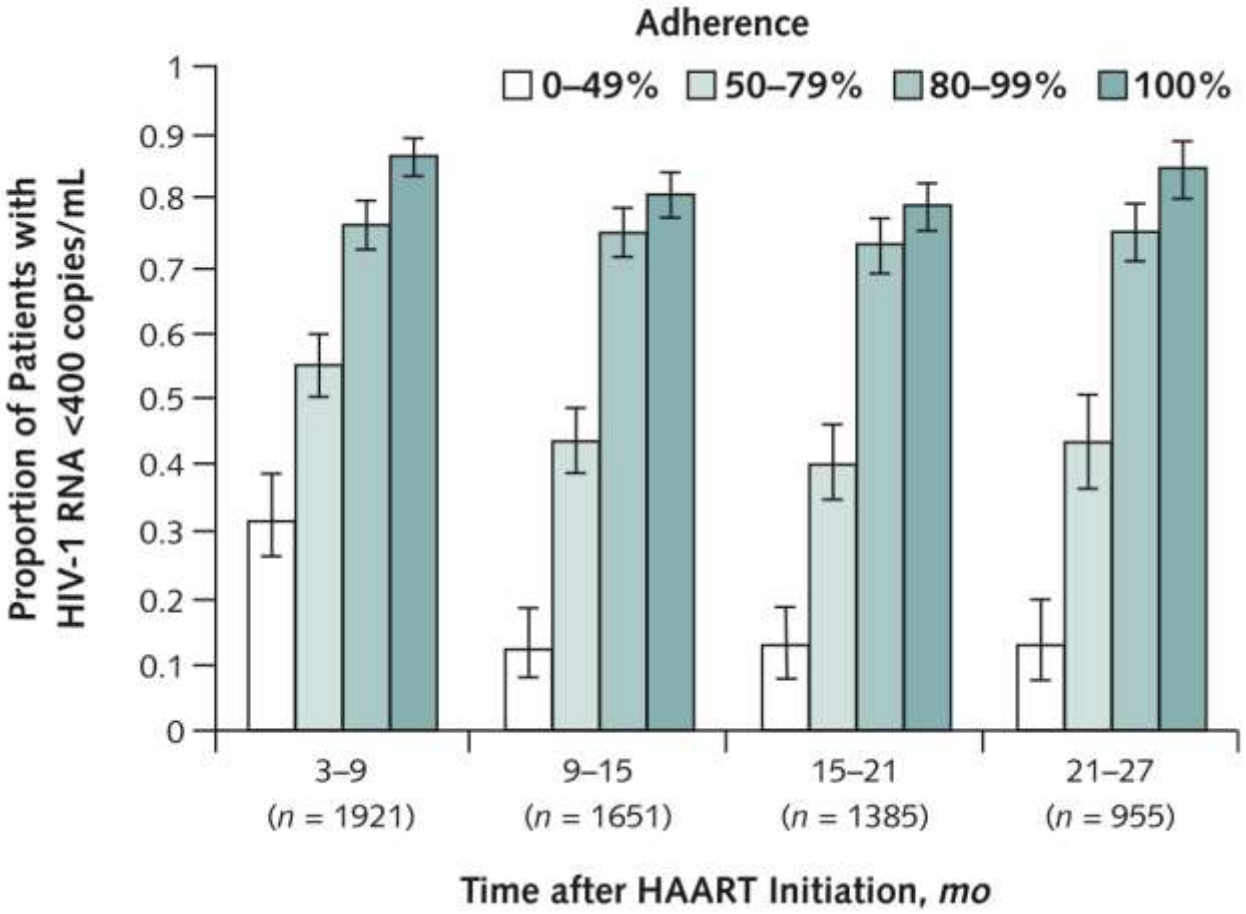
Uyumu Zor Rejim: *Sonuç kaçınılmaz*

Adherence Issues: ZDV + ddI + IDV



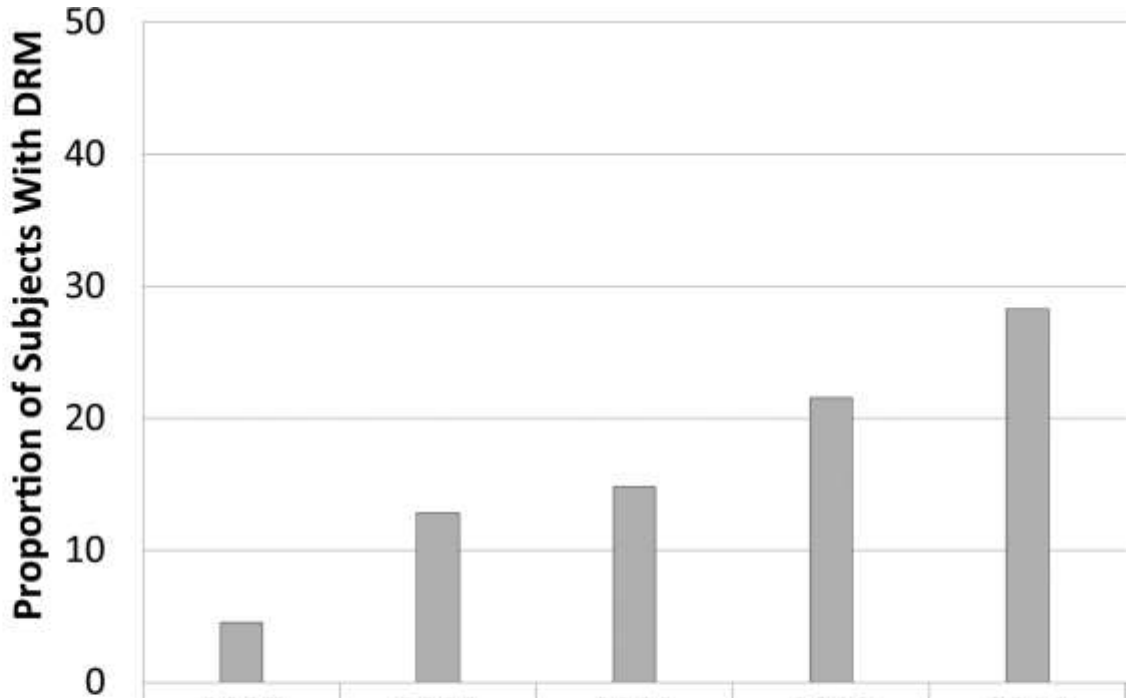
Source: *Physicians' Desk Reference*®. Medical Economics Co; 1997.

NNRTI Uyumu Virolojik Yanıtı Belirler



Nachega JB etal 2007 Adherence to nonnucleoside reverse transcriptase inhibitor-based HIV therapy and virologic outcomes *Ann Intern Med*

ARV Direnci: *Kullandıkça ve Araştırdıkça Artar*



	2007	2008	2009	2010	2011
DRM No.	1	5	8	11	13
Proportion of Subjects With DRM	5	13	15	22	28
Subjects Tested No.	22	39	54	51	46

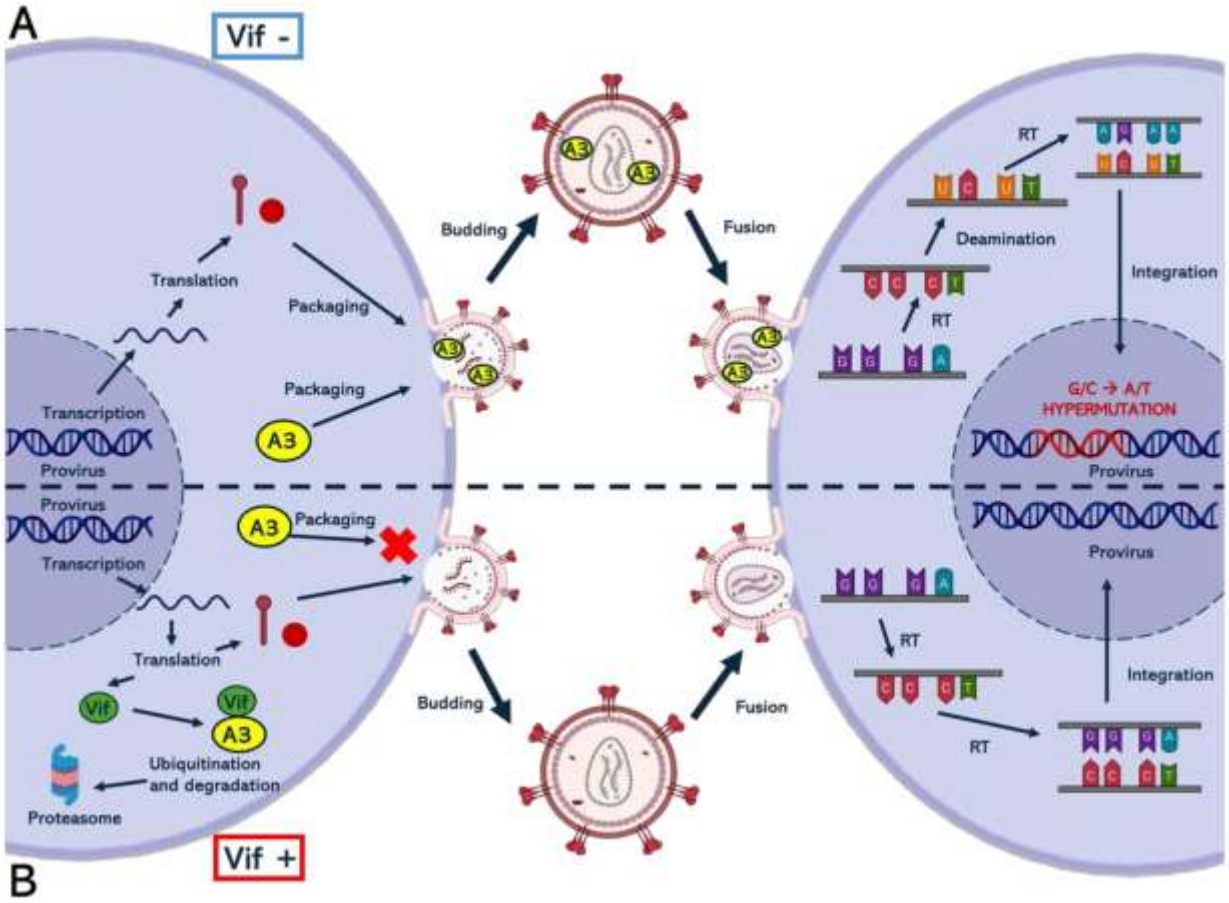
Gagliardo C etal 2014 A multicenter study of initiation of antiretroviral therapy and transmitted drug resistance in antiretroviral-naive adolescents and young adults with HIV in New York City *Clin Infect Dis*

HIV Durduk Yere Neden Mutasyona Uğrar?
APOBEC3'ün Hikayesi

Apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like (APOBEC) 3

A3G: ss DNA
GG➔ GA

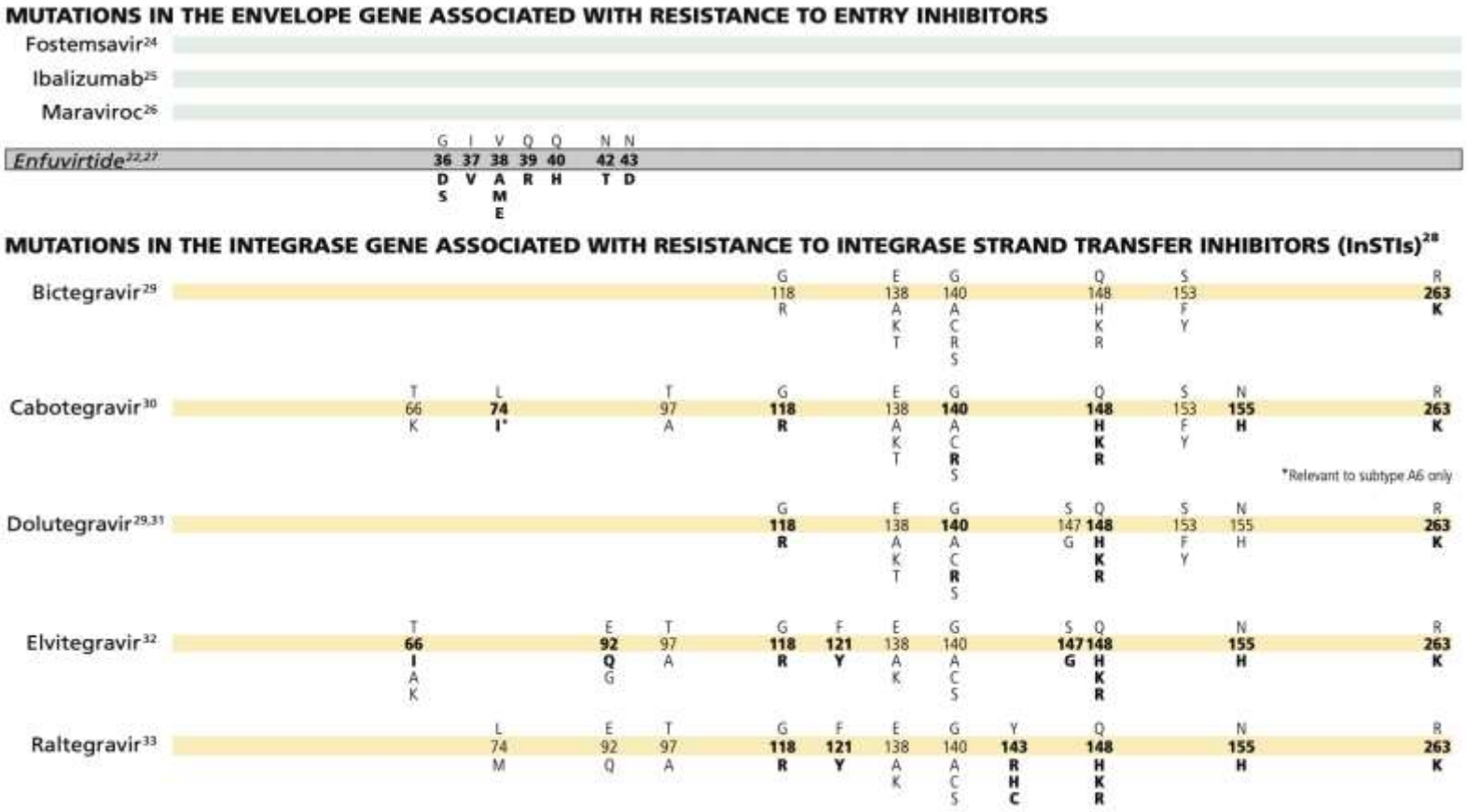
A3F: ss DNA
GA➔AA



V90I
V106I
V108I
M184I
M230I
E138K

Campagna R etal 2024 Archived HIV-1 Drug Resistance Mutations: Role of Proviral HIV-1 DNA Genotype for the Management of Virological Responder People Living with HIV *Viruses*

Mutasyonların Kutsal Makalesi



Wensing AMJ etal 2025 *2025 Update of the Drug Resistance Mutations in HIV-1 Topics in Antiviral Med*

Olgu1

- 35 yaş MSM
- PreP: TDF/FTC
- 3 ay önce rutin kontrol sorun yok
- Anti HIV: coi 4 pozitif
  - antijen pozitif, antikor yok
- HIV RNA: 2500 kopya/ml
- CD4: 870/mm^3
- PrEP kullanım süresi önemli mi?
- PrEP uyum önemli mi?

- ART başlar mısınız?
- Direnç var mıdır?
- Hangi rejim?

	Previous PrEP use (n=22)	No previous PrEP use (n=917)	p value
Age (years)	31 (23–52)	32 (18–74)	0·97
Gender and sexual behaviour			
Men who have sex with men	22 (100%)	878 (96%)	0·38
Men who don't have sex with men	0 (0%)	26 (3%)	..
Women	0 (0%)	13 (1%)	..
Baseline viral load (copies per mL)	7700 (<20–320 000)	58 000 (<20–1 000 000)	0·0004
Presence of Met184Val or Met184Ile	5 (23%)	5 (1%)	<0·0001
Unable to amplify genotypic resistance test	4 (18%)	20 (2%)	0·002

Data are median (range) and n (%). Data represent documented PrEP use in the 12 months before HIV diagnosis.

Table: Demographics and genotypic resistance test results of patients with HIV

İdrarda TFV Düzeyi ve Virolojik Başarı

- Nested cohort
- Viral yük >200 c/ml olanlar vs **<50**
- N=198, 281 örnek
- Saptanabilir TFV %37 vs **%100**
- Saptanmaz idrar TFV ➔ virolojik başarısızlık
  - %100 özgüllük, %69 duyarlılık

Hermans LE etal 2022 *Point-of-Care Tenofovir Urine Testing for the Prediction of Treatment Failure and Drug Resistance During Initial Treatment for Human Immunodeficiency Virus Type 1 (HIV-1) Infection* Clin Inf Dis

İdrarda TFV Düzeyi ve Virolojik Başarı

- Saptanabilir TFV + HIV RNA > 200c/ml
  - NRTI direnci %50
- Saptanamaz TFV
  - NRTI direnç %8
- Saptanabilir TFV + HIV RNA > 200c/ml
  - NRTI direnç öngörme OR: 10.4 [1.8–114.4]
  - Duyarlılık%83, özgüllük %69

Hermans LE etal 2022 *Point-of-Care Tenofovir Urine Testing for the Prediction of Treatment Failure and Drug Resistance During Initial Treatment for Human Immunodeficiency Virus Type 1 (HIV-1) Infection* Clin Inf Dis

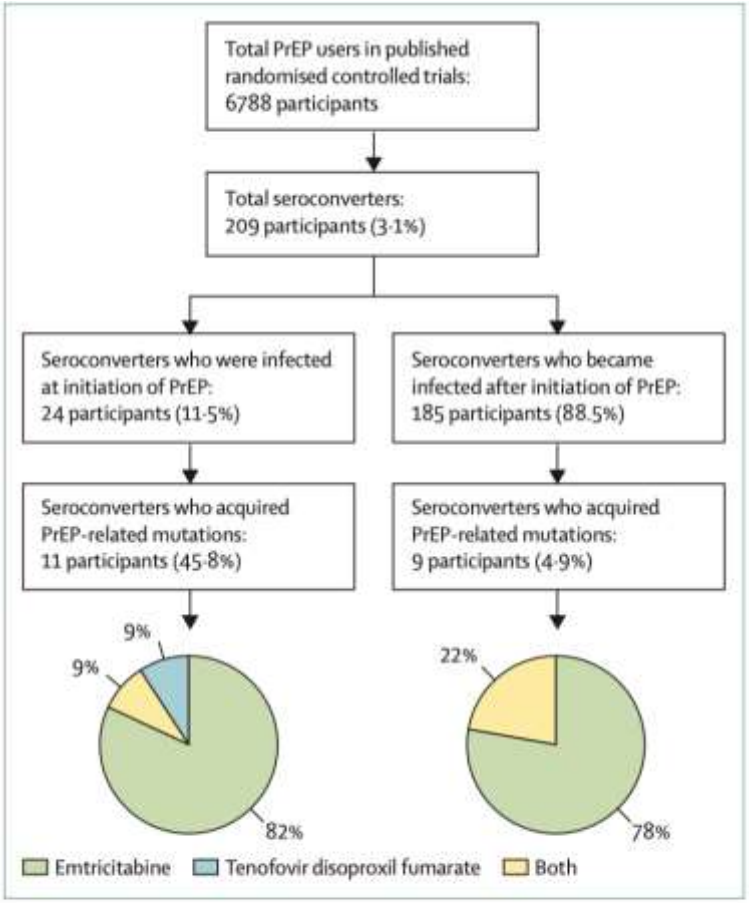


Figure 2: **Seroconverters and resistance development reported in major published randomised controlled trials on PrEP**

Overall data are from major published randomised controlled trials on PrEP: IPrEx, PARTNER, TDF2, PROUD, FEM-PrEP, VOICE, HPTN067, and IPERGAY (see table 3). PrEP=pre-exposure prophylaxis.

Olgu 2

- 38 yaşında erkek
- TDF/FTC/EFV 5 yıldır kullanıyor
- Son 6 aydır cezaevinde olduğu için ilaç kullanımı düzensiz
- HIV RNA: 225000 kopya/ml
- CD4: 276/mm^3

Ne yaparsınız?

A. Tedaviye yeniden başlarım

B. Direnç testi ister tedaviye başlarım

C. Direnç testi sonucu çıkana kadar beklerim

D. Tedavi değişikliği yaparım


Otokoç
pürsu
Otokoç
halley

NRTI Resistance Mutations:	**M184V**
NNRTI Resistance Mutations:	**Y188C**
Other Mutations:	None

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Low-Level Resistance
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Susceptible

Non-nucleoside Reverse Transcriptase Inhibitors	
doravirine (DOR)	Potential Low-Level Resistance
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	Susceptible
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	Susceptible

NRTI	ABC	AZT	FTC	3TC	TDF
M184V	15	-10	60	60	-10
Total	15	-10	60	60	-10

NNRTI	DOR	EFV	ETR	NVP	RPV
Y188C	10	60	0	60	0
Total	10	60	0	60	0

comments

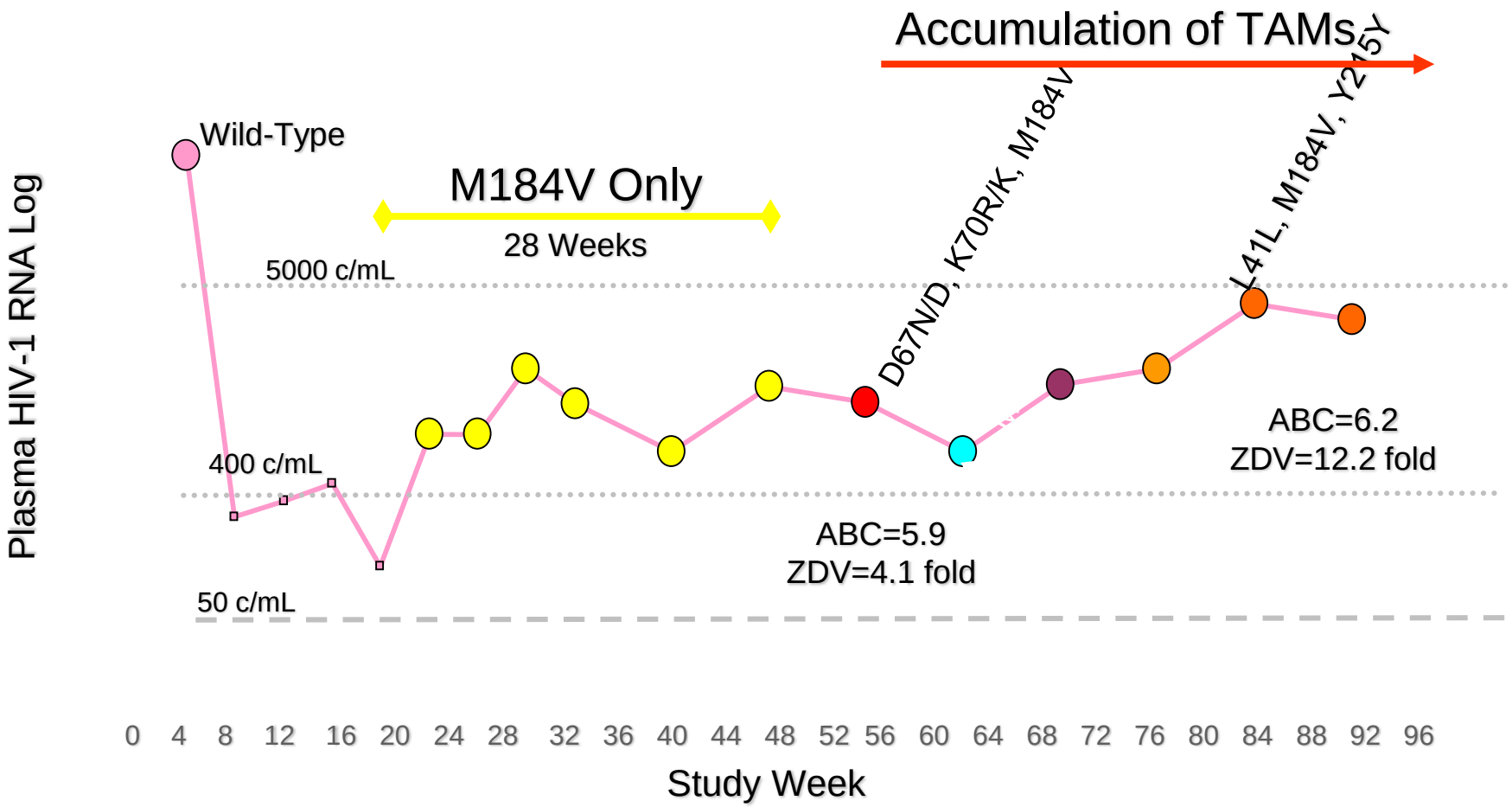
TI

- **M184V/I** cause high-level in vitro resistance to 3TC and FTC and low-level resistance to ddI and ABC. However, **M184V/I** are not contraindications to continued treatment with 3TC or FTC because they increase susceptibility to AZT, TDF and d4T and are associated with clinically significant reductions in HIV-1 replication.

RTI

- **Y188C** is a non-polymorphic mutation selected in patients receiving NVP and EFV. It confers high-level resistance to NVP and EFV. It appears to cause little if any reduction in susceptibility to RPV, ETR, or DOR.

3TC/ABC/AZT Altında Mutasyonların Evrimi



Tedaviye devam edilseydi

NRTI Resistance Mutations:	**D67N, K70E, M184V**
NNRTI Resistance Mutations:	**Y181C, Y188C**
Other Mutations:	None

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Intermediate Resistance
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Low-Level Resistance

Non-nucleoside Reverse Transcriptase Inhibitors	
doravirine (DOR)	Low-Level Resistance
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	Intermediate Resistance
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	Intermediate Resistance

NRTI	ABC	AZT	FTC	3TC	TDF
M184V	15	-10	60	60	-10
D67N	5	15	0	0	5
K70E	15	-10	10	10	15
K70E + M184V	0	0	0	0	10
Total	35	-5	70	70	20

NNRTI	DOR	EFV	ETR	NVP	RPV
Y181C	10	30	30	60	45
Y188C	10	60	0	60	0
Total	20	90	30	120	45

RT comments

NRTI

- **D67N** is a non-polymorphic TAM associated with low-level resistance to AZT and d4T. When present with other TAMs, it contributes reduced susceptibility to ABC, ddI, and TDF.
- **K70E/G** cause low-level resistance to TDF, ABC, DDI and possibly 3TC and FTC. **K70E/G** increase susceptibility to AZT.
- **M184V/I** cause high-level in vitro resistance to 3TC and FTC and low-level resistance to ddI and ABC. However, **M184V/I** are not contraindications to continued treatment with 3TC or FTC because they increase susceptibility to AZT, TDF and d4T and are associated with clinically significant reductions in HIV-1 replication.

NNRTI

- **Y181C** is a non-polymorphic mutation selected in patients receiving NVP, ETR and RPV. It reduces susceptibility to NVP, ETR, RPV, and EFV by >50-fold, 5-fold, 3-fold, and 2-fold, respectively. Although **Y181C** itself reduces EFV susceptibility by only 2-fold, it has been associated with a reduced response to an EFV-containing regimen in NNRTI-experienced patients. **Y181C** has a weight of 2.5 in the Tibotec ETR genotypic susceptibility score. Alone, it does not appear to reduce DOR susceptibility.
- **Y188C** is a non-polymorphic mutation selected in patients receiving NVP and EFV. It confers high-level resistance to NVP and EFV. It appears to cause little if any reduction in susceptibility to RPV, ETR, or DOR.

NRTI/NNRTI Altında Başarısız Hasta

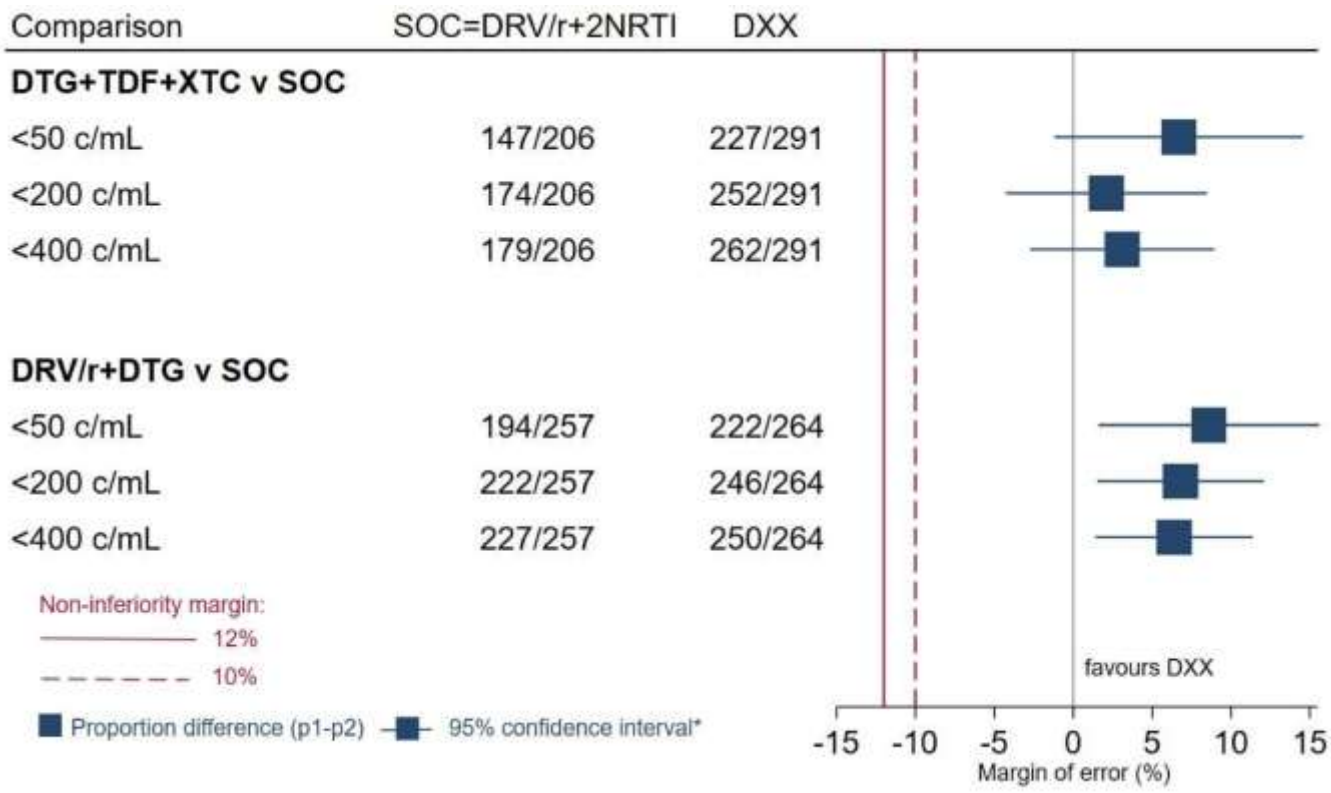
- Kadın %70
- ART: 5.8 yıl
- % 89 en azından TDF veya XTC düşük düzey direnç
- %37 K65R
- %83 M184V/I
- HIV RNA: 10850 kopya/ml (IQR: 2962-38291)
- Switch TDF/XTC/DTG
- 24. hafta: HIV RNA %85 baskılı
  - 6 kişi HIV RNA: 50 – 99 k/ml
  - 1 HIV RNA 100 – 999 k/ml,

Keene CM etal 2021 *Virologic efficacy of tenofovir, lamivudine and dolutegravir as second-line antiretroviral therapy in adults failing a tenofovir-based first-line regimen* AIDS

NRTI/NRTI + NNRTI Başarısızlığında DRV/r + DTG, TDF/XTC+DTV vs TDF/XTC+DRV/r vs SOC RCT, n=826

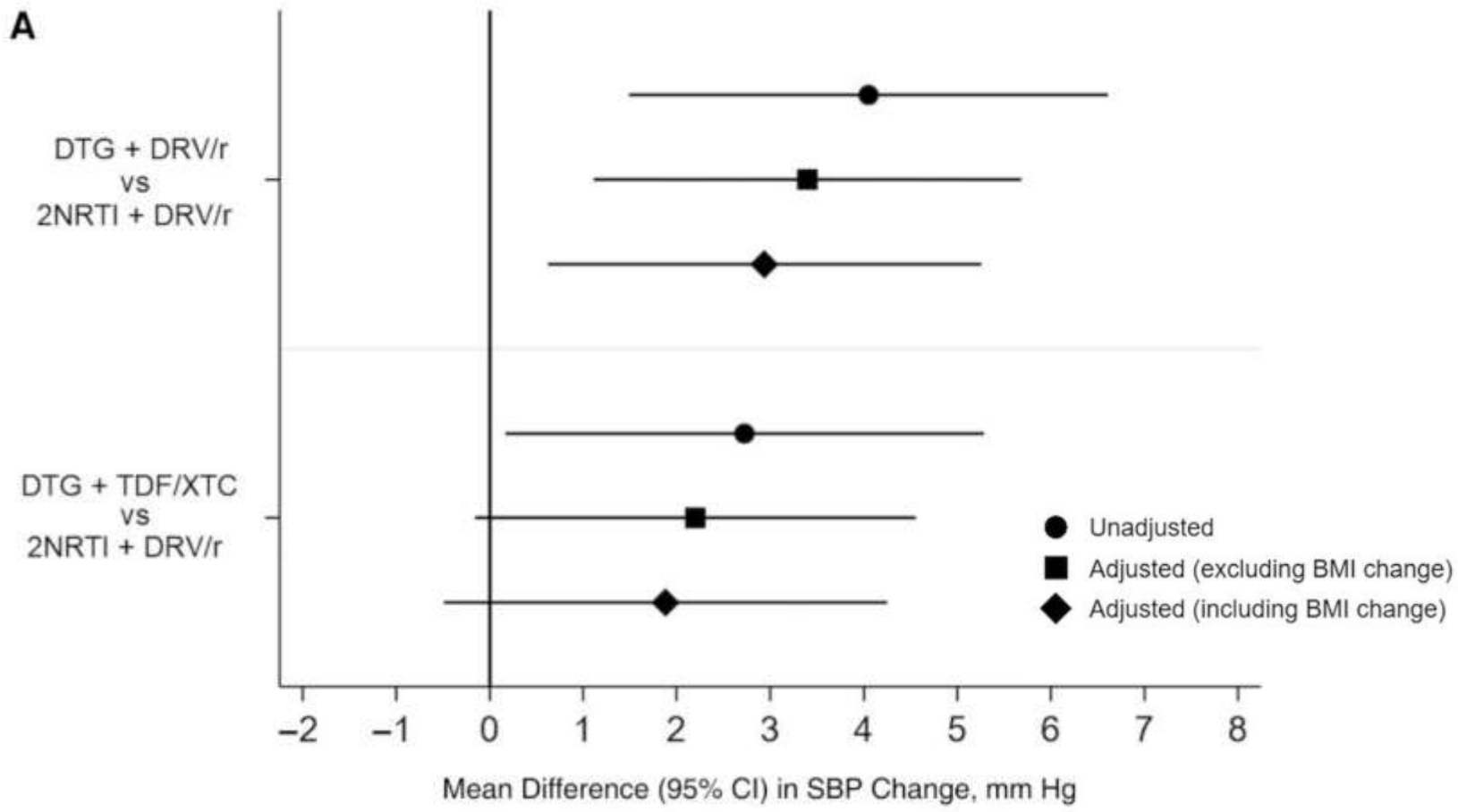
Arjantin, Şili, Kolombiya, hindistan, Malezya, Meksika, G. Afrika, Tayland, Zimbabwe, Brezilya, Gine, Endonezya, Mali, Nijerya

2NRTI + DRV/r: %75.5, DTG+DRV/r: %84.1, TDF/XTC +DTG: %78



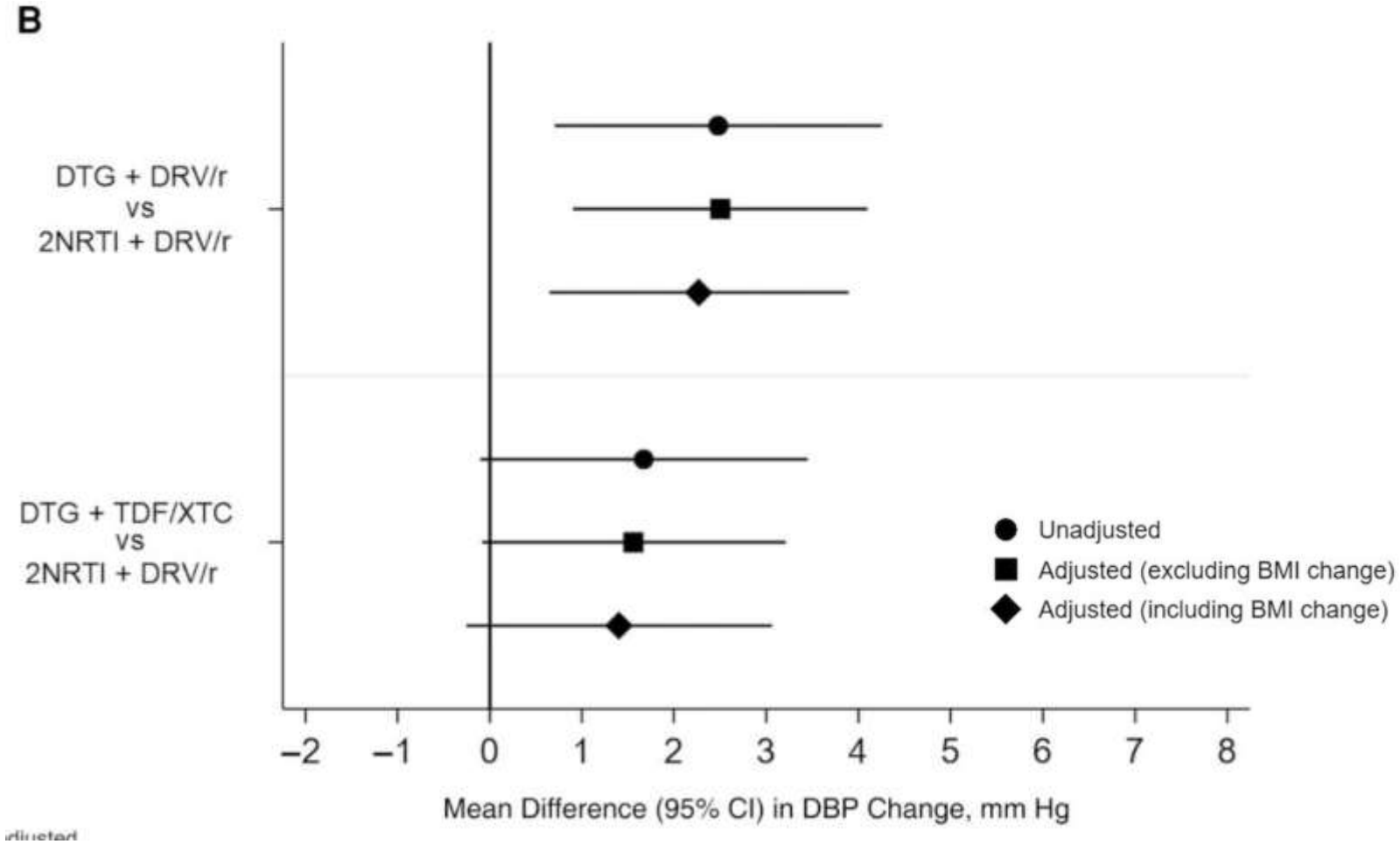
D2EFT Study Group. 2024 Dolutegravir plus boosted darunavir versus recommended standard-of-care antiretroviral regimens in people with HIV-1 for whom recommended first-line non-nucleoside reverse transcriptase inhibitor therapy has failed (D^2EFT): an open-label, randomised, phase 3b/4 trial. *Lancet HIV*

D2EFT: *Sistolik Kan Basıncı*



Nyein PP etal 2025 Associations Between Antiretroviral Regimen and Changes in Blood Pressure: Results From the D2EFT Study *Clin Infect Dis*

D2EFT: *Diastolik Kan Basıncı*



Nyein PP etal 2025 Associations Between Antiretroviral Regimen and Changes in Blood Pressure: Results From the D2EFT Study *Clin Infect Dis*


SIXT
23
21
4
90
26
7

Olgu 3

- MSM
- Tedavi uyumsuz
- Huysuz
- TAF/FTC/BIC alırken virolojik başarısızlık
- HIV RNA: 350000 k/ml
- CD4: 182/mL
- Direnç testi ister misiniz?
- Hangi bölgeler?

Olgu 4

NRTI Mutations:	**D67G** • **S68G** • **K70E** • **Y115F** • **M184V**
NNRTI Mutations:	**V106I** • **E138A**
RT Other Mutations:	V8I • V35I • K82R • K122E • D123N • I178L • V179I • R211K • V245Q

Nucleoside Reverse Transcriptase Inhibitors		Non-nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	High-Level Resistance	**doravirine (DOR)**	Potential Low-Level Resistance
zidovudine (AZT)	Susceptible	**efavirenz (EFV)**	Susceptible
stavudine (D4T)	Low-Level Resistance	**etravirine (ETR)**	Low-Level Resistance
didanosine (DDI)	Intermediate Resistance	**nevirapine (NVP)**	Potential Low-Level Resistance
emtricitabine (FTC)	High-Level Resistance	**rilpivirine (RPV)**	Low-Level Resistance
lamivudine (3TC)	High-Level Resistance		
tenofovir (TDF)	Intermediate Resistance		

PI Major Mutations:	None
PI Accessory Mutations:	None
PR Other Mutations:	L10I • I13V • M36I • N37K • R41K • L63P • E65D • I72T • L89M

INSTI Major Mutations:	E138K • S147G • Q148R • R263K
INSTI Accessory Mutations:	T97A • D232N
IN Other Mutations:	D6E • V31I • L63I • I72V • L74I • V75M • L101I • T112A • S119P • T122S • T124N • M154L • K156N • L172I • F181L • I208M • S230N • L234I • R269T

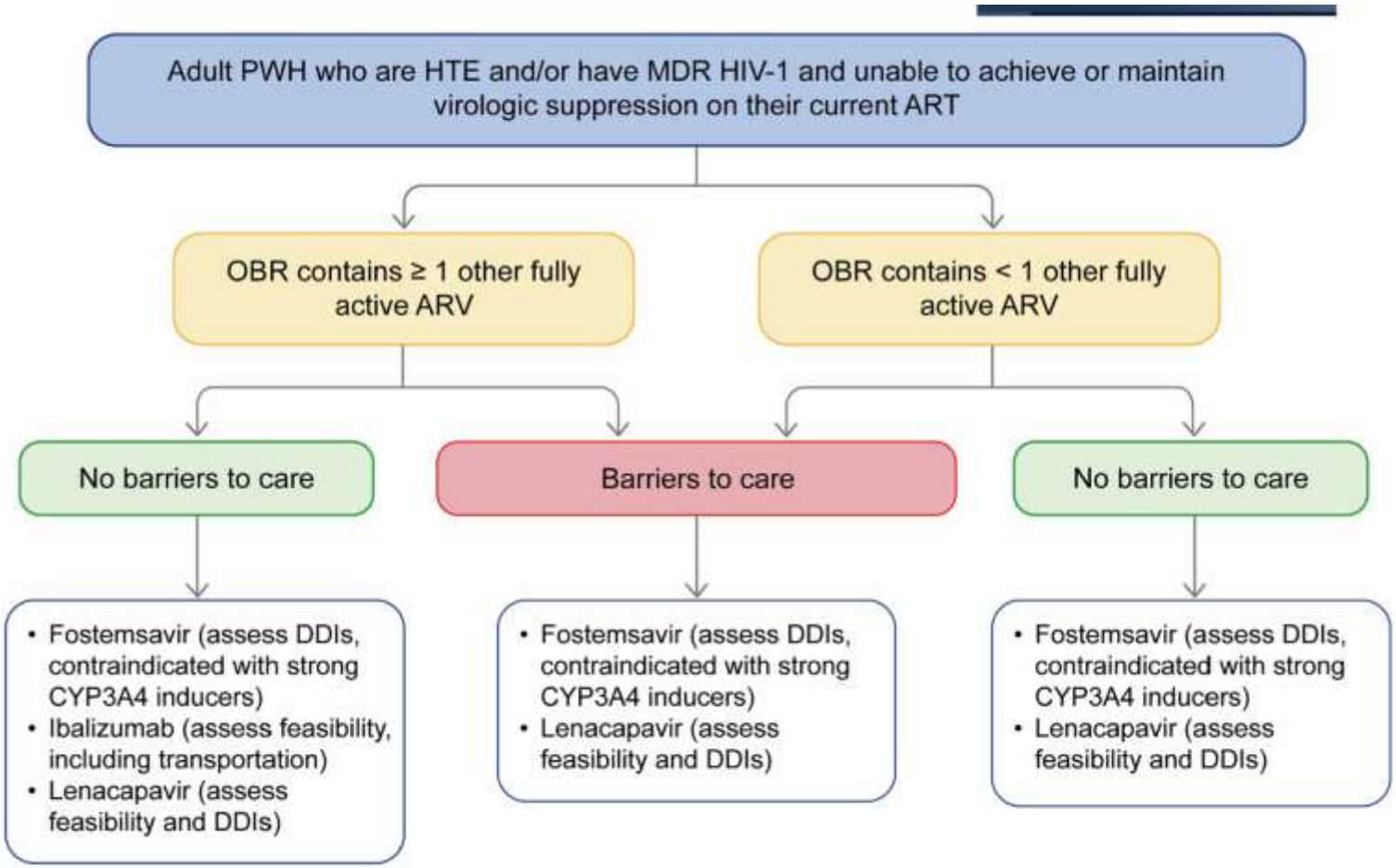
bictegravir (BIC)	High-Level Resistance
cabotegravir (CAB)	High-Level Resistance
dolutegravir (DTG)	High-Level Resistance
elvitegravir (EVG)	High-Level Resistance
raltegravir (RAL)	High-Level Resistance

Olgunun Hikayesinde Eksik Nedir?

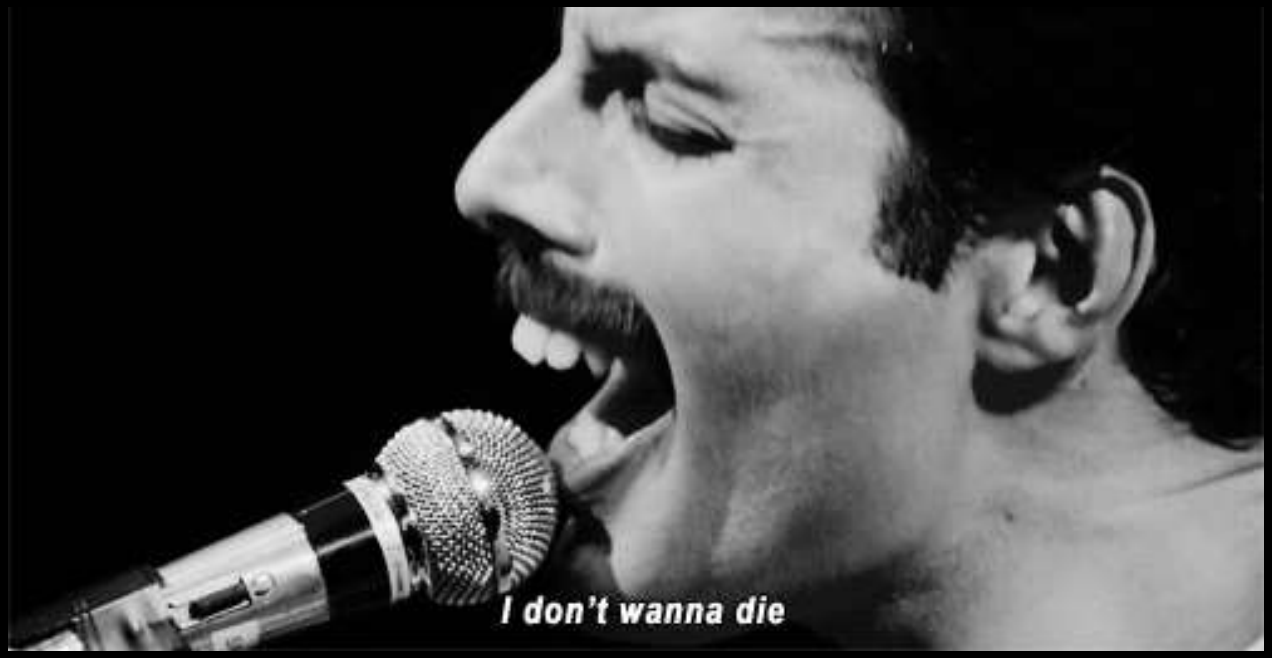
Dirençli Olgu Yönetimi

- NRTI mutasyonları nereden çıktı?
- NNRTI mutasyonları nereden çıktı?
- TAF/FTC/BIC altında INSTI mutasyonu hani olmazdı?

Çok İlaca Dirençli Olgular İçin



Cluck DB etal 2024 *Consensus recommendations for the use of novel antiretrovirals in persons with HIV who are heavily treatment-experienced and/or have multidrug-resistant HIV-1: Endorsed by the American Academy of HIV Medicine, American College of Clinical Pharmacy* Pharmacotherapy



1946 - 1991