Antiretroviral Direnç

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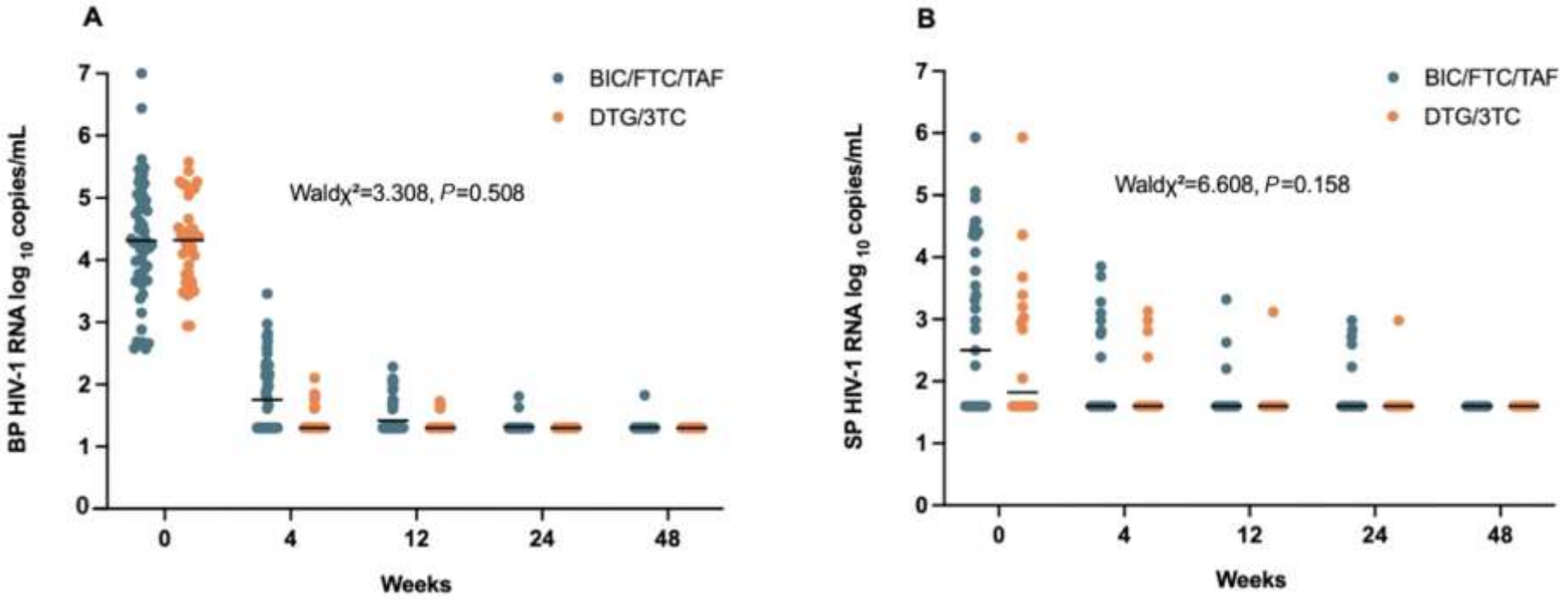
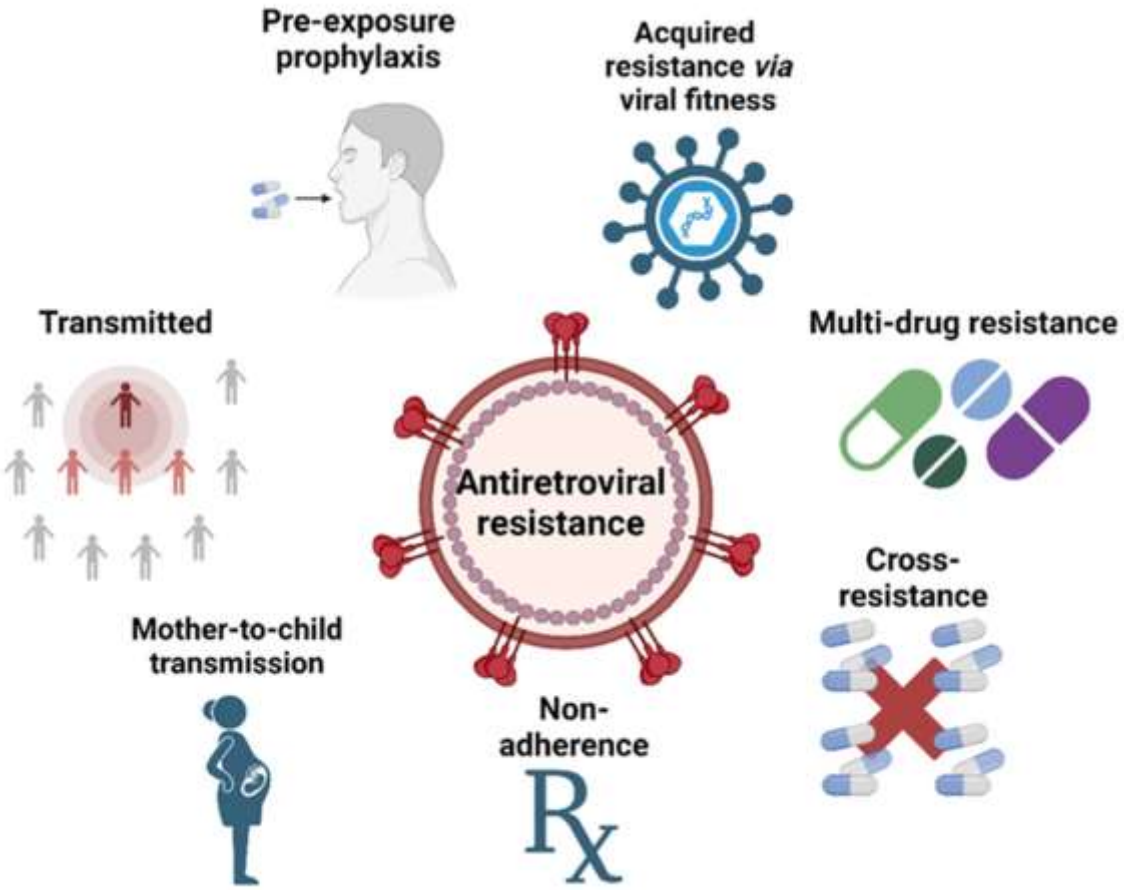
ART Altında Viral Yük Değişimi



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*

ARV Direnç: *Neden?*

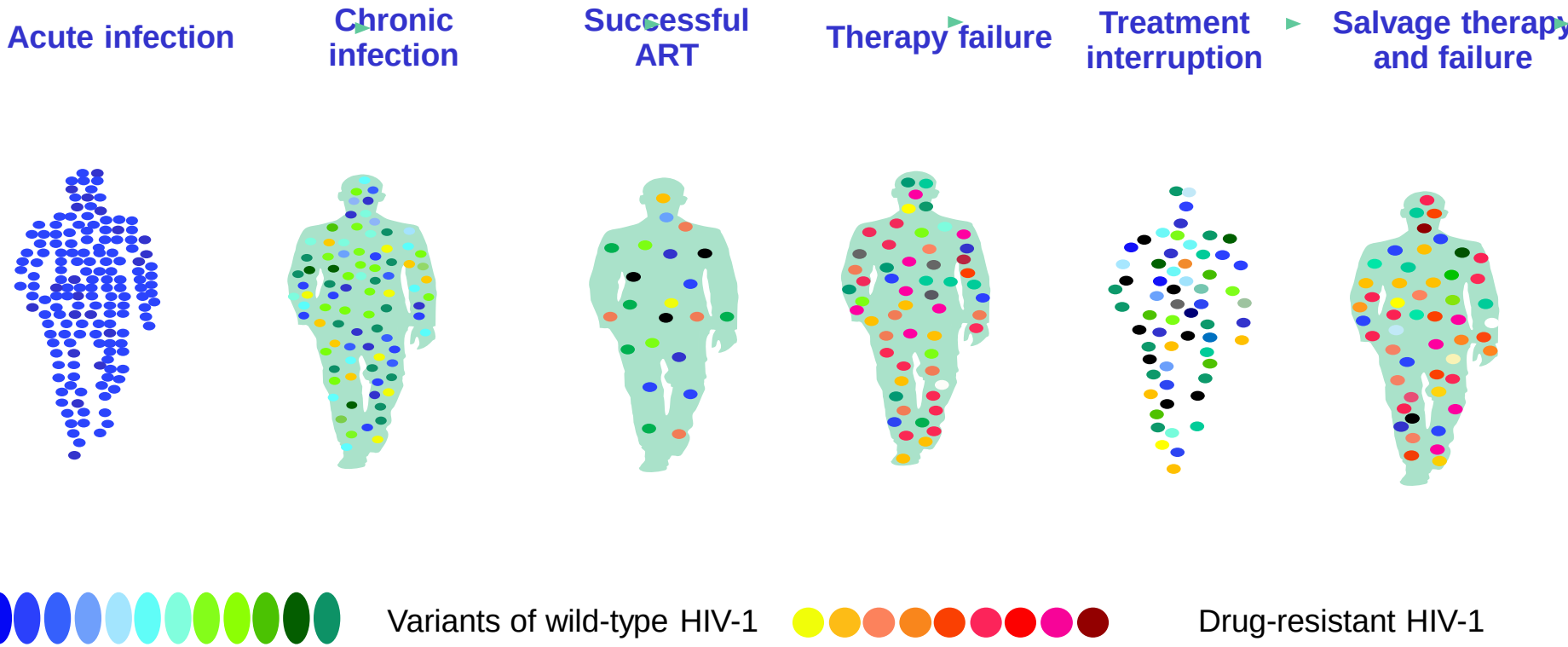


Apetroaei MM etal 2024 The Phenomenon of Antiretroviral Drug Resistance in the Context of Human Immunodeficiency Virus Treatment: Dynamic and Ever Evolving Subject Matter *Biomedicines*

Virüs Mutasyon Sebepleri I

- 10^9 - 10^{10} virion/gün → **quasispecies**
- HIV1 RT hata yapar ($1/10^4$)
- HIV-1 genom 10 000 (10^4)
- ART öncesi pek çok mutasyon gelişebilir.

HIV Enfeksiyon Seyrinde Virüsler



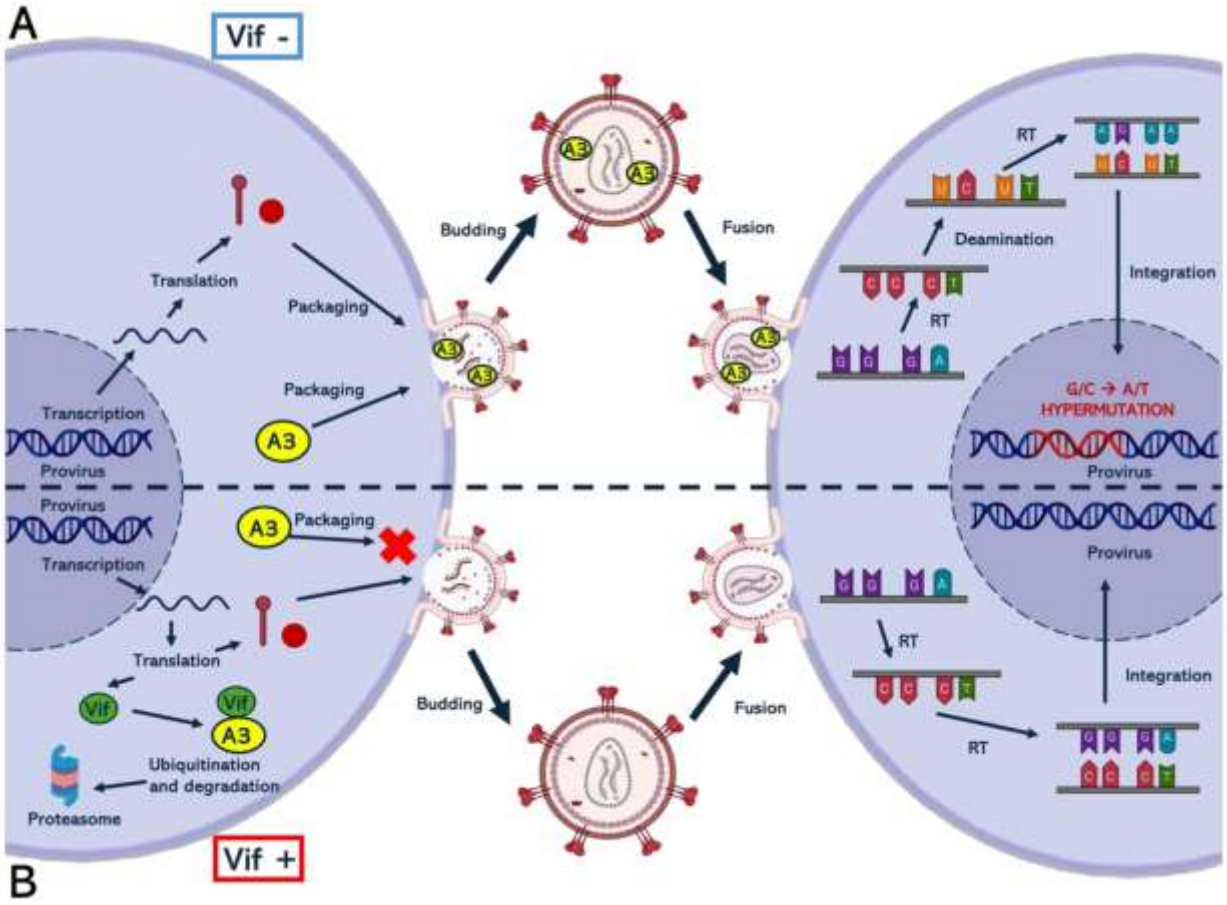
Adapted from Richman D. Presented at SAHCS Conference 2018.

HIV Durduk Yere Neden Mutasyona Uğrar?
APOBEC3'ün Hikayesi

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

A3G: ss DNA
GG➔ GA

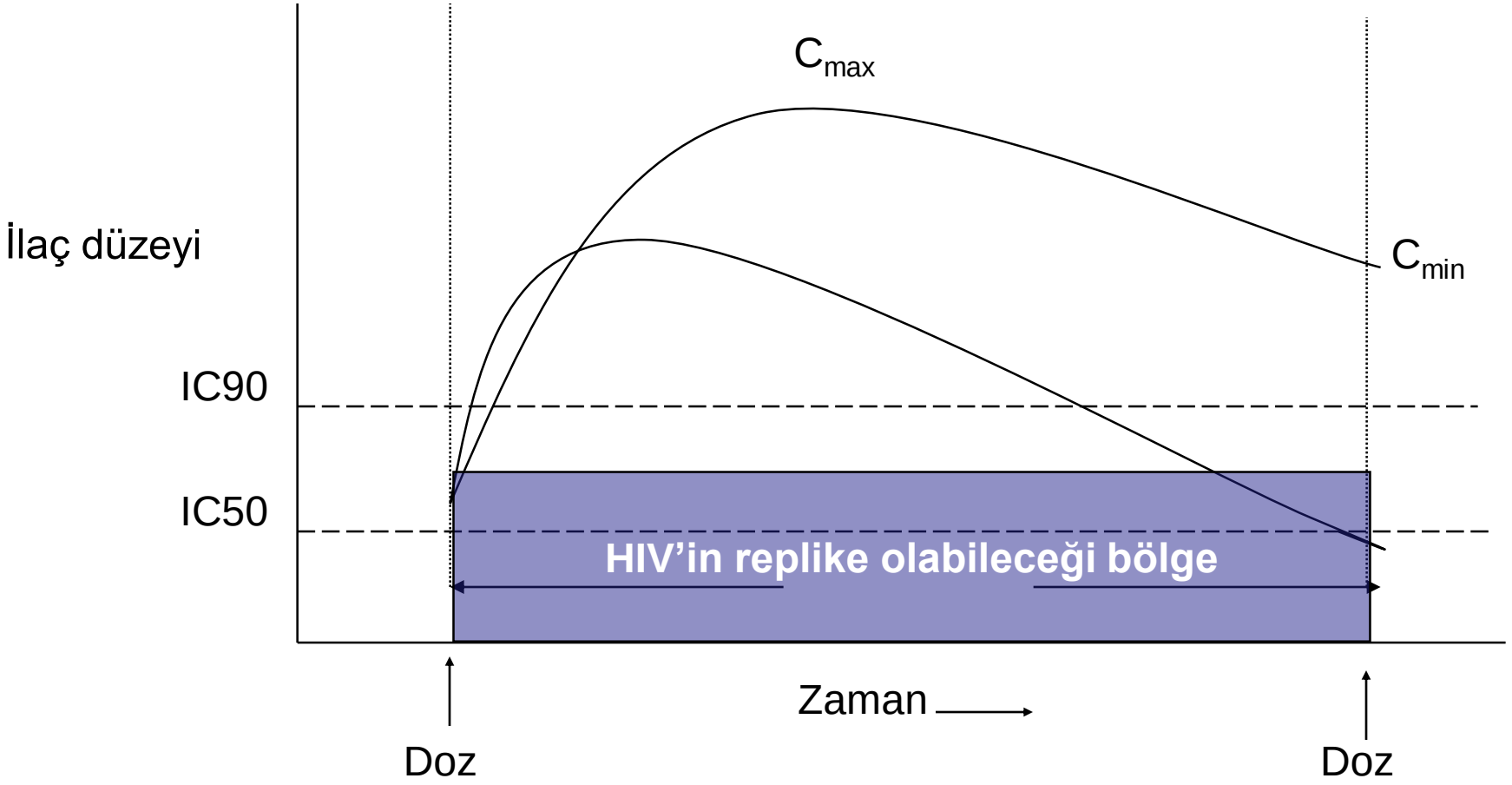
A3F: ss DNA
GA➔AA



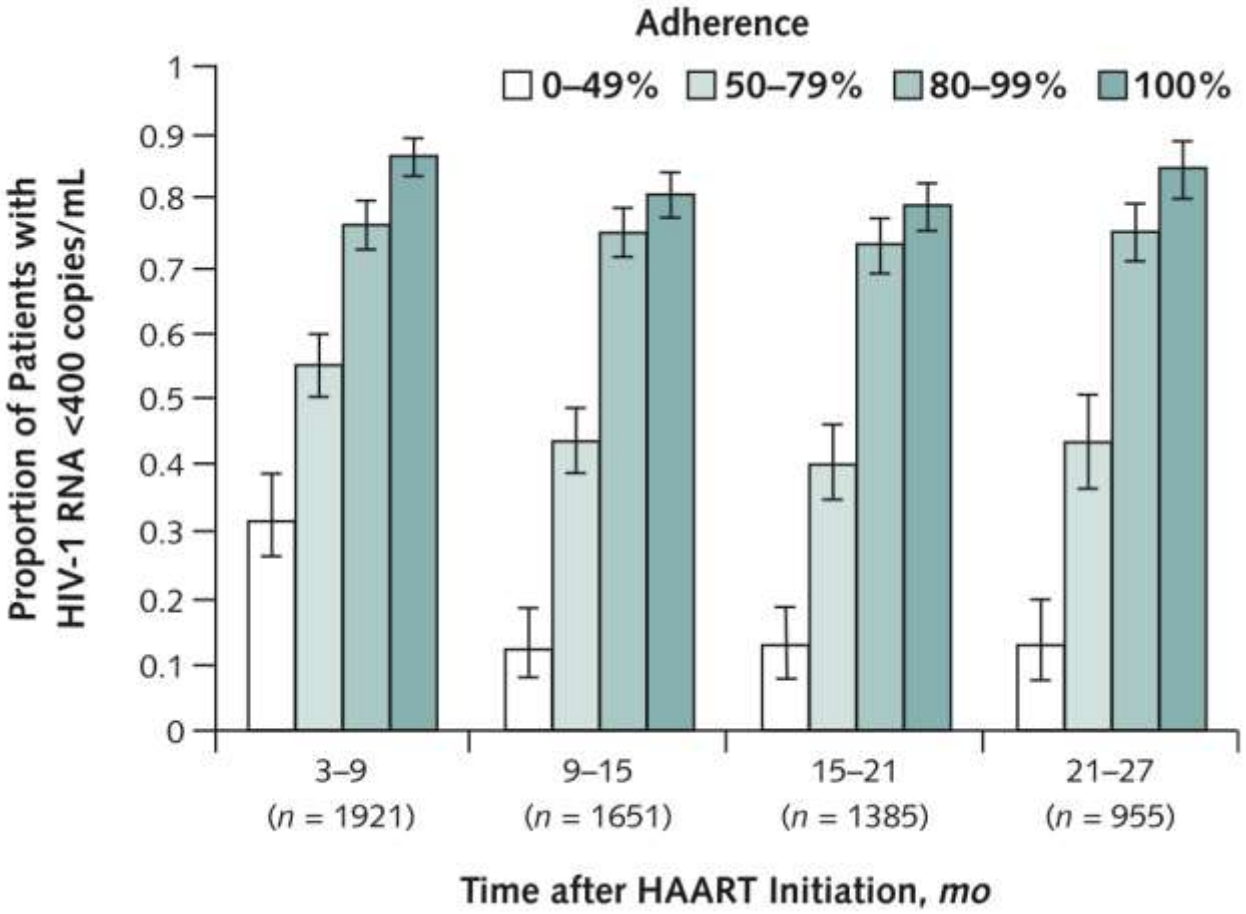
V90I
V106I
V108I
M184I
M230I
E138K

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*

Temel Farmakokinetik

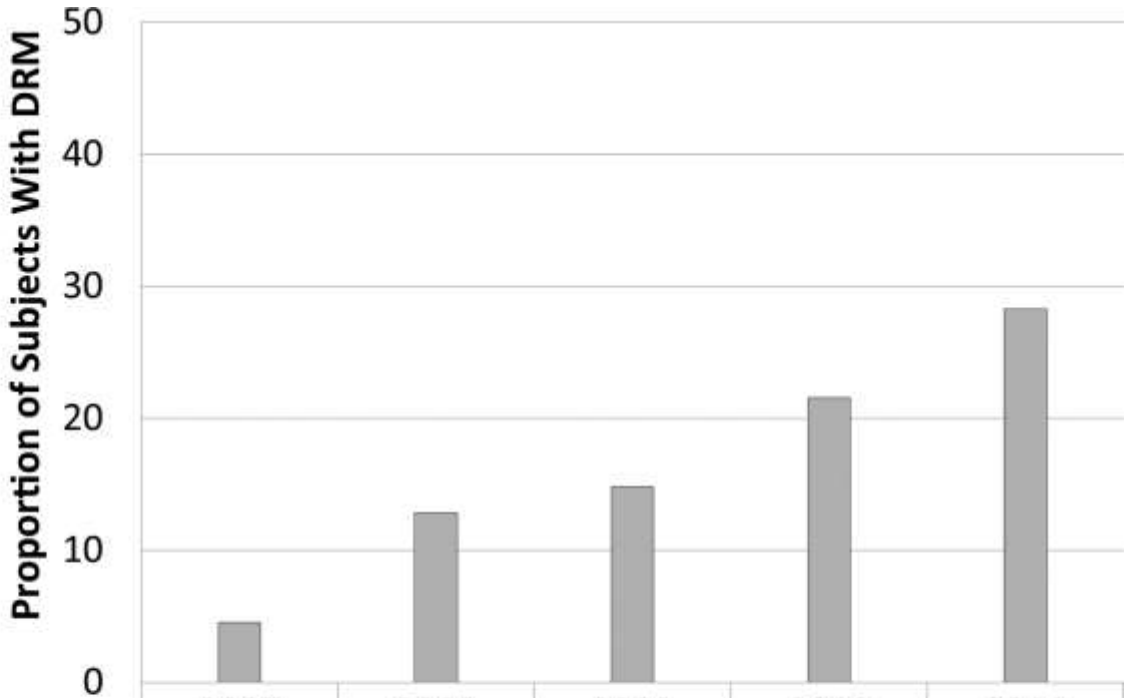


NNRTI Uyumu Virolojik Yanıtı Belirler II



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

ARV Direnci: *İlacı 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*

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

ARV Direnç Nasıl Gösterilir?

Genotipik

Tüm nükleotid değişimleri

%20'lik popülasyonu gösterir

Erken uyarı

Raporları anlamak güç

Lablar arası uyum

Yüksek viral yük gerekir

Fenotipik

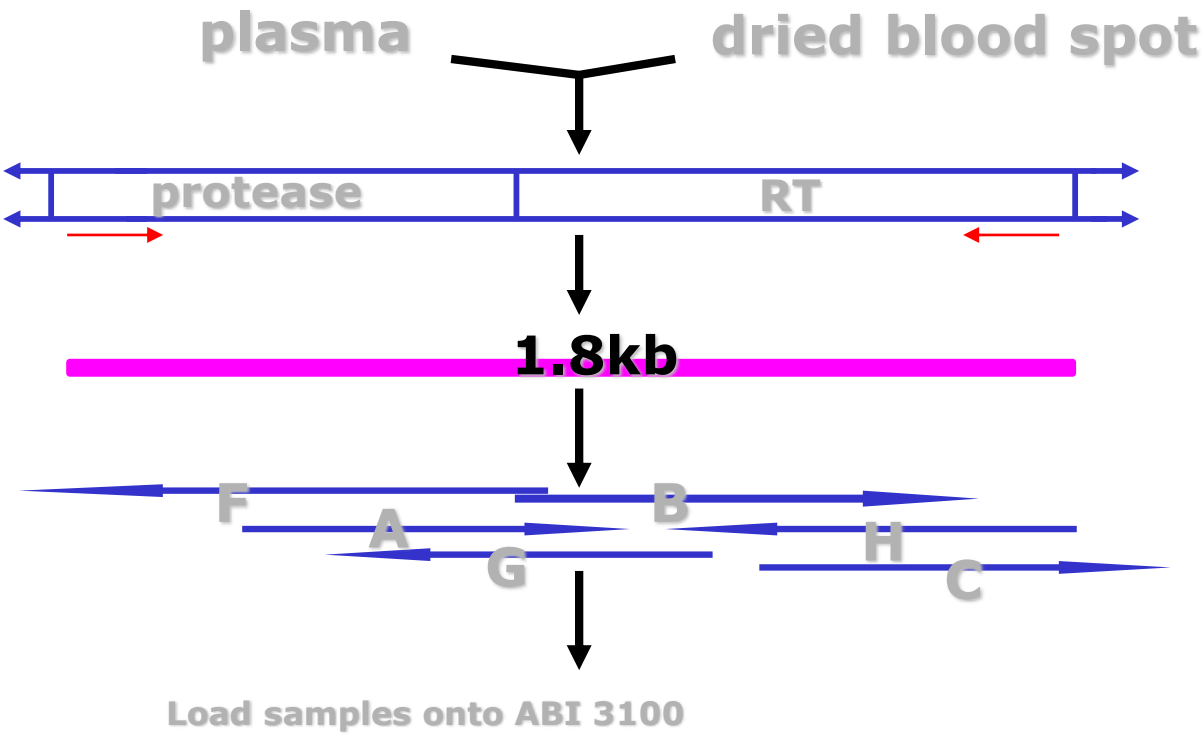
Tüm virüsler hakkında bilgi

Yapılması güç ve zahmetli

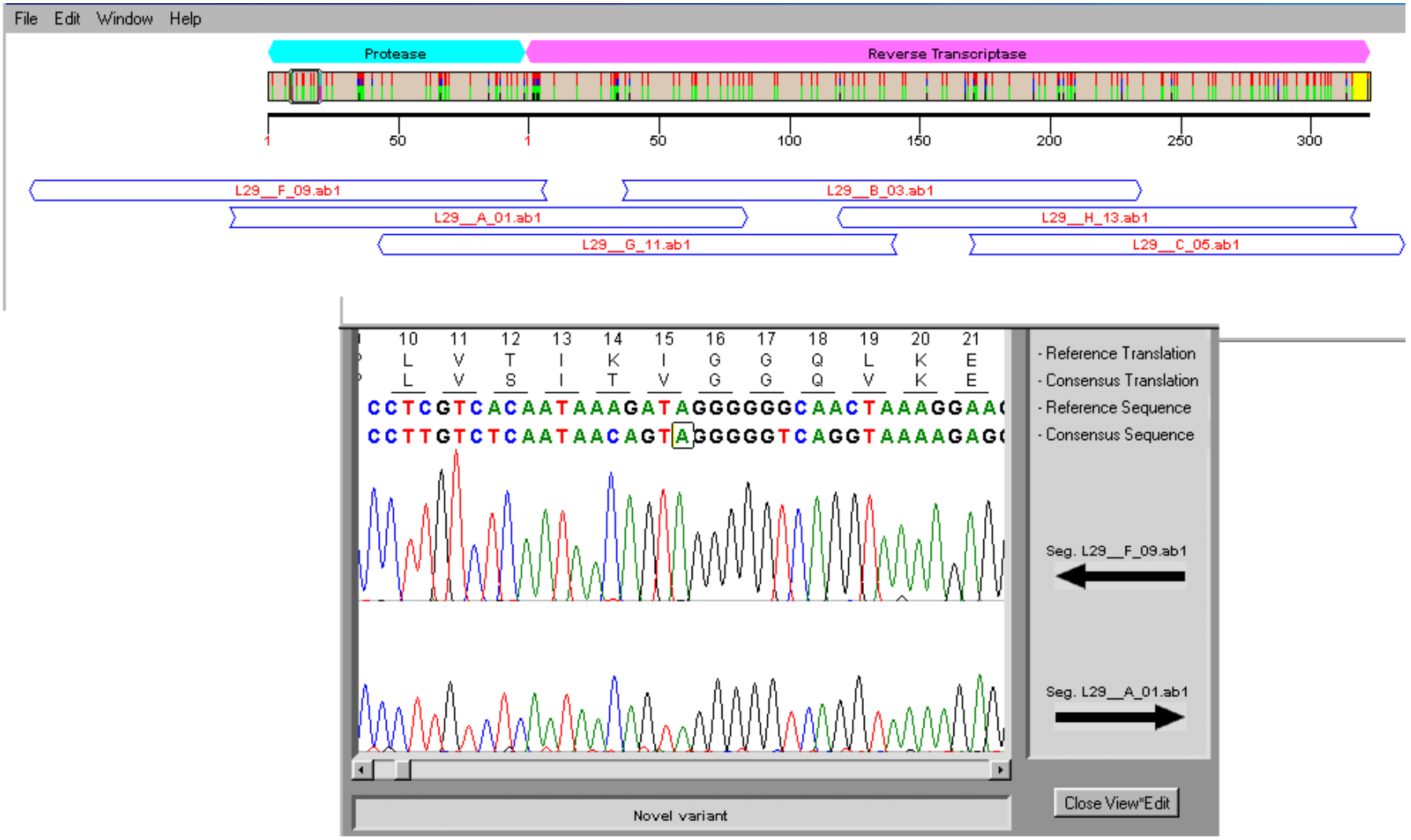
Çapraz direnç tanımlanması

Birden fazla direncin olduğu durumlarda kullanışlı

Genotipik Direnç: *Sanger Sekans*



Genotipik Direnç: *Sanger Sekans II*



Genotipik Direnç: *Kural bazlı okuma*

- TruGene (Bayer)
- Viroseq (Celera)
- HIVdb (Stanford)
- ANRS (French)
- Rega (Belgium)

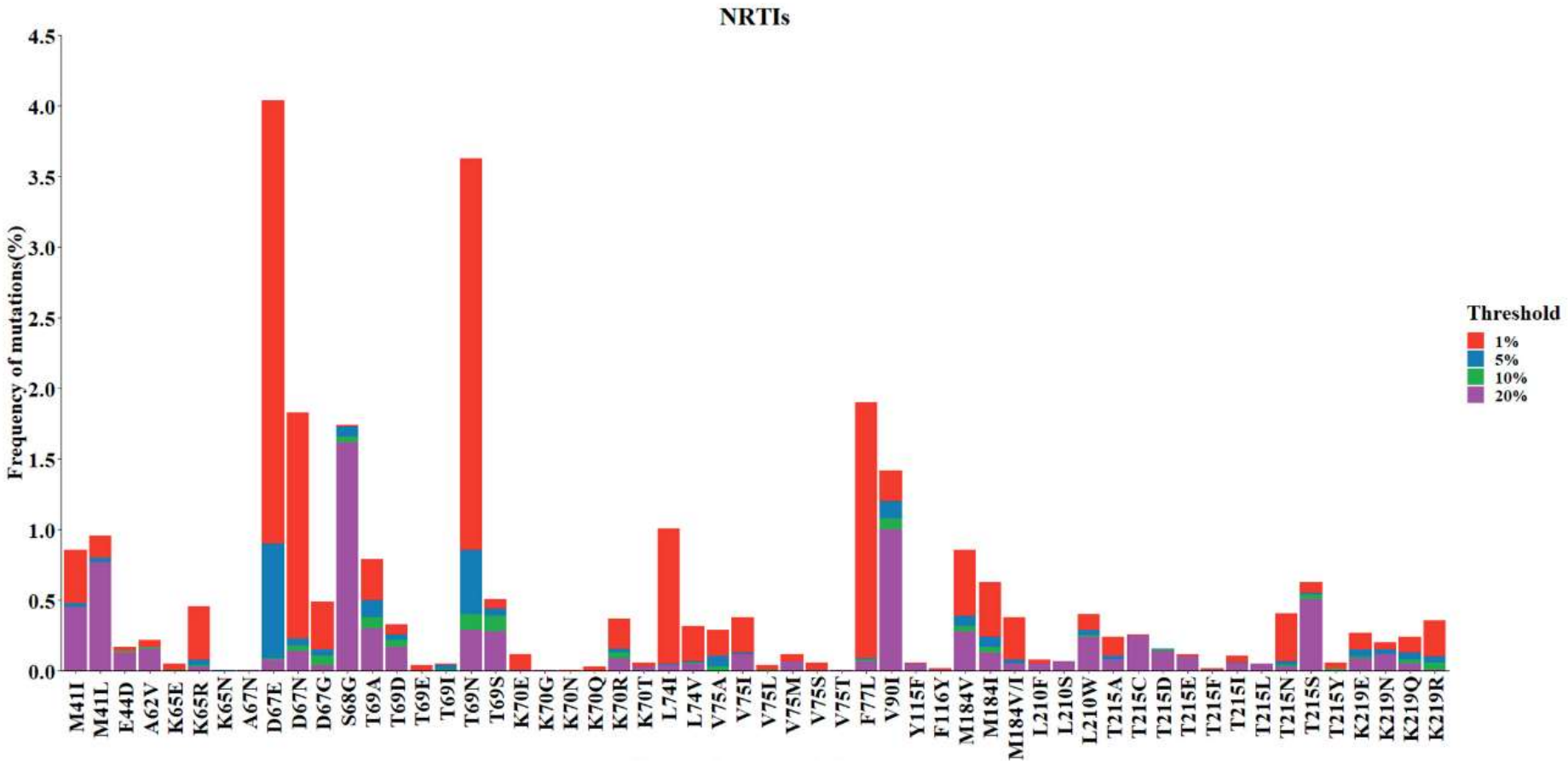
Sanger vs NGS

Sanger vs NGS

	Strengths	Weaknesses
Sanger sequencing	• Several validated methods for clinical use • Low sequencing errors • Relatively simple workflows and data analysis • Relatively shorter turnaround times • Common method in RLS • Easily accessible software for interpretation (such as Stanford HIVdb)	• High cost per test • Cannot reliably detect LA-DRVs • Not suitable for sequencing long genes/large genomes • Not suitable for parallel testing • High infrastructure costs • Require standard molecular biology workflows
Next generation sequencing	• Lower cost per test through pooling • High sensitivity for LA-DRVs • Suitable for sequencing long genes/large genomes • Massive parallel sequencing	• Only one validated method for clinical use (Sentosa HIV-1 genotyping kit) • High sequencing errors • Complex labor-intensive workflows and data analysis • Longer turnaround time • High infrastructure costs • Requires specialized facilities • No clear clinical significance of LA-DRVs • Can produce unequal sequencing coverage • Software for interpretation depend on data output files • Requires personnel with high-level expertise • Require standard molecular biology workflows

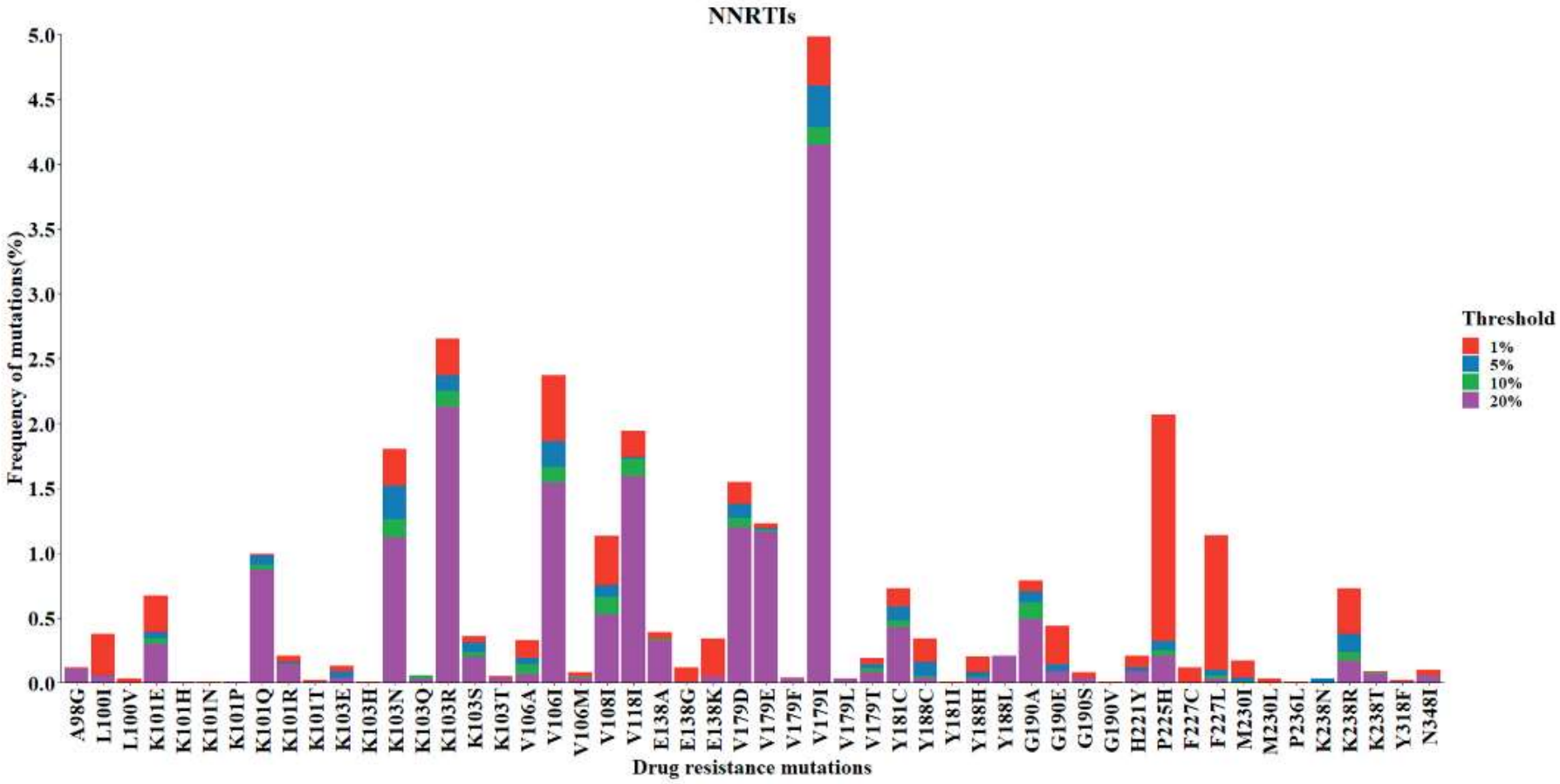
Manyana S etal 2021 HIV-1 Drug Resistance Genotyping in Resource Limited Settings: Current and Future Perspectives in Sequencing Technologies *Viruses*

NGS ve Sanger: *NRTI*



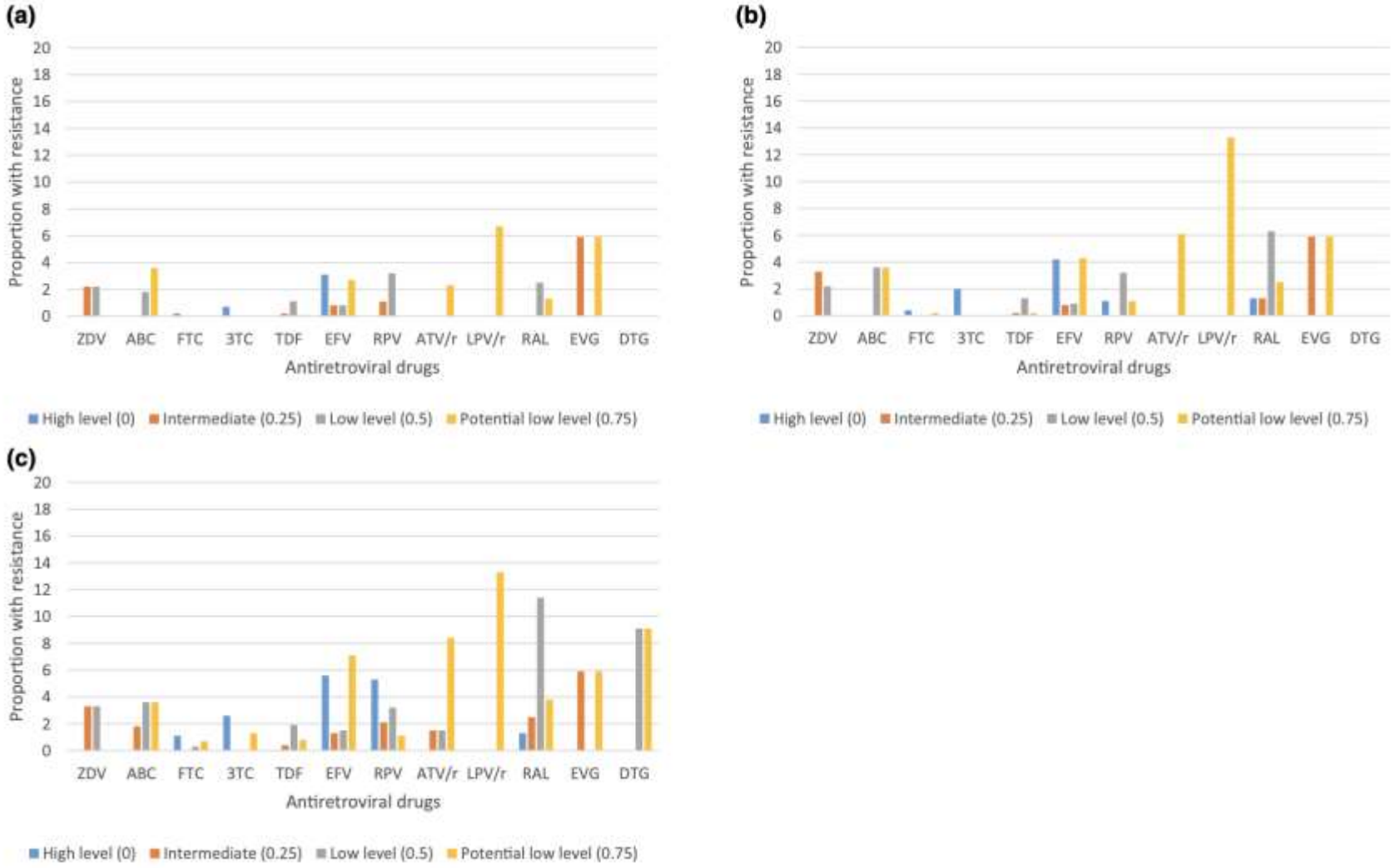
Ouyang F etal 2024 HIV-1 Drug Resistance Detected by Next-Generation Sequencing among ART Naïve Individuals: A Systematic Review and Meta-Analysis. *Viruses*

NGS ve Sanger: *NNRTI*



Ouyang F etal 2024 HIV-1 Drug Resistance Detected by Next-Generation Sequencing among ART Naïve Individuals: A Systematic Review and Meta-Analysis. *Viruses*

GSS ve ART Altında Virolojik Başarı



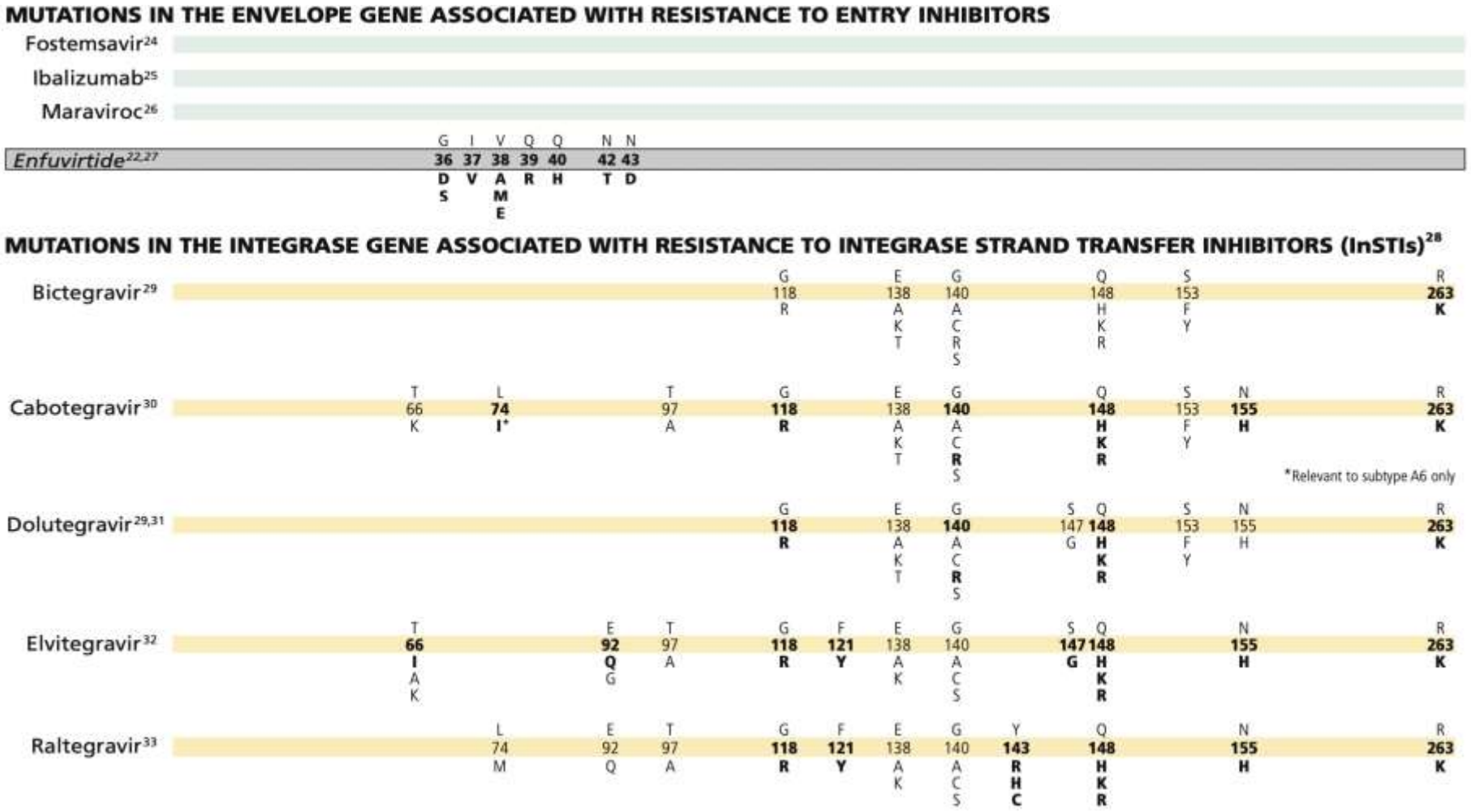
Cozzi-Leppri A etal 2023 *Rate of response to initial antiretroviral therapy according to level of pre-existing HIV-1 drug resistance detected by next-generation sequencing in the strategic timing of antiretroviral treatment (START) study* HIV Med

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

Mutasyonların Kutsal Makalesi



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

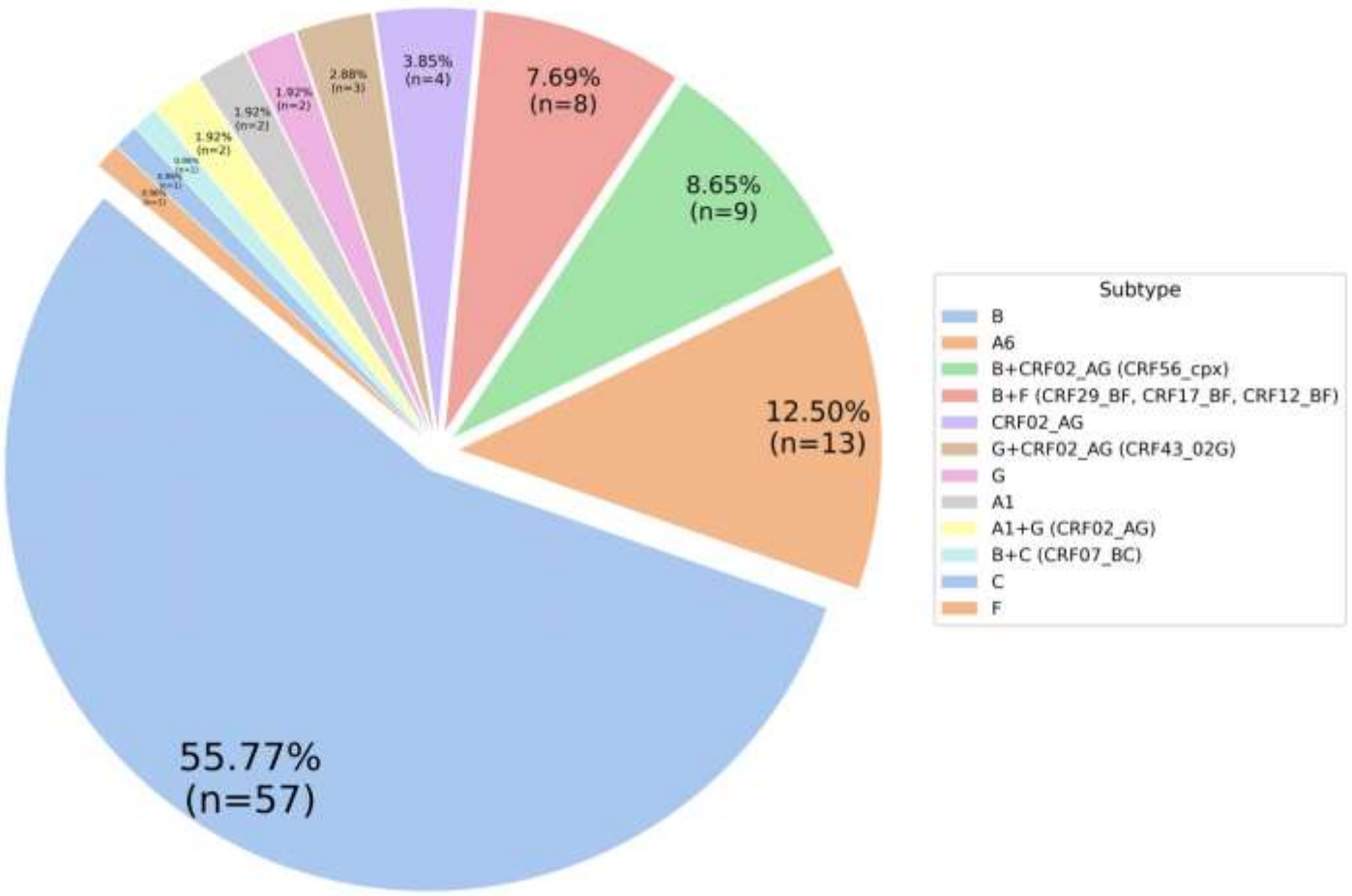
Aktarılan (Transmitted, primer, TDR)	Kazanılmış (indüklenmiş, acquired, ADR)	Tedavi öncesi (PDR)
ARV naïve Prevalans %6-11 **HIV-2: NNRTI doğal direnç**	En sık	Tedavi naive : TDR İkinci Tedavi öncesi: ADR TDR+ADR de olabilir. PrEP ve PEP

Türkiye’de Direnç

Study	Date of sampling	*n*	PI (%)	NRTI (%)	NNRTI (%)	Total (%)
Sayan et al. [10]	2009–2012	117	1.7	4.2	1.7	7.6
Sili et al. [11]	2013	36	0	8.3	0	8.3
Yalçınkaya et al. [12]	2010–2014	190	2.1	5.2	3.1	10.4
Sayan et al. [13]	2010–2015	1306	2.3	8.1	3.3	13.7
Tekin et al. [14]	2017	49	0	2	8.1	10.1
This study	2021–2022	104	1.92	4.80	7.69	14.41

Özdemir A etal 2025 *Molecular epidemiological analysis and investigation of antiretroviral drug resistance profile, including capsid inhibitors, among treatment-naïve individuals with HIV-1 in Türkiye* HIV MED

Türkiye’de Genotip



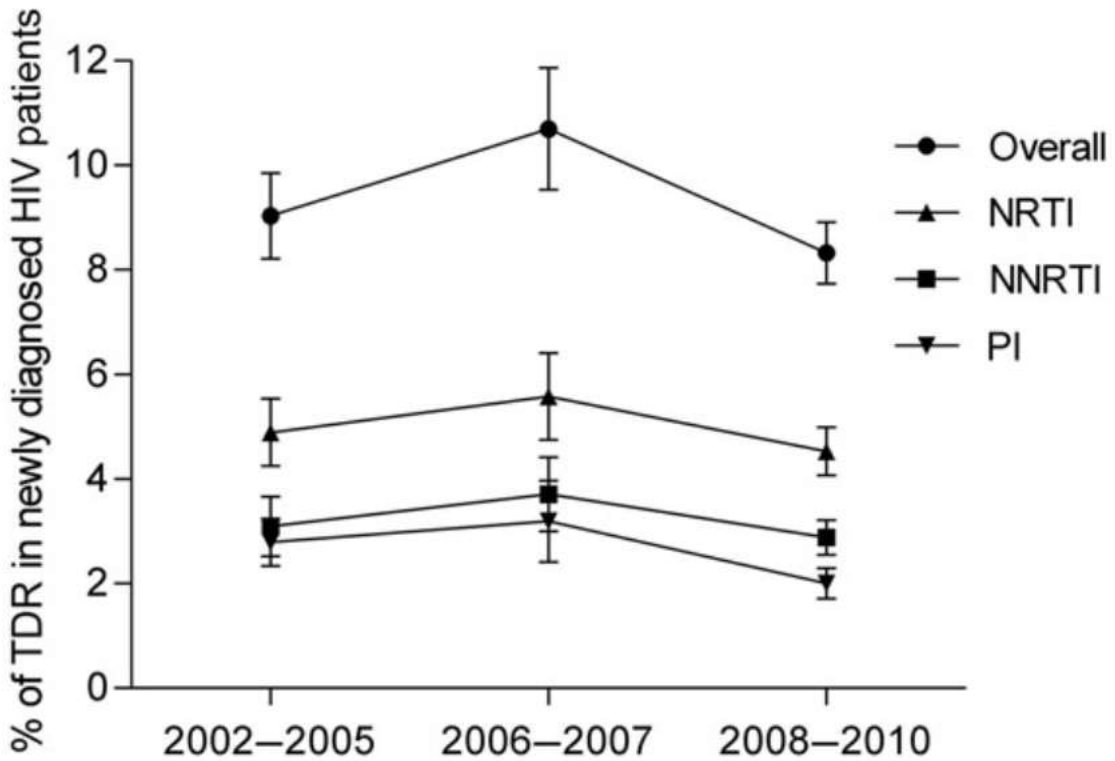
Özdemir A etal 2025 *Molecular epidemiological analysis and investigation of antiretroviral drug resistance profile, including capsid inhibitors, among treatment-naïve individuals with HIV-1 in Türkiye* HIV MED

Türkiye'de Genotip

PI (Major)	M46L	1	0.96
(Accessory)	L33F + K43T	1	0.96
	Not detected	102	98.08
NRTI	A62V	2	1.92
	M41L + T215E	1	0.96
	S68G + T215E	1	0.96
	S68G + L74I + M184V	1	0.96
	Not detected	99	95.19
	S68G[a]	54[a]	51.92[a]
NNRTI	E138A	3	2.88
	E138G	1	0.96
	K103N	1	0.96
	V108I	1	0.96
	V179D	1	0.96
	K103N + V106I	1	0.96
	Not detected	96	92.31
INSTI ($n = 76$)	Not detected	76	100
CAI ($n = 72$)	Not detected	72	100

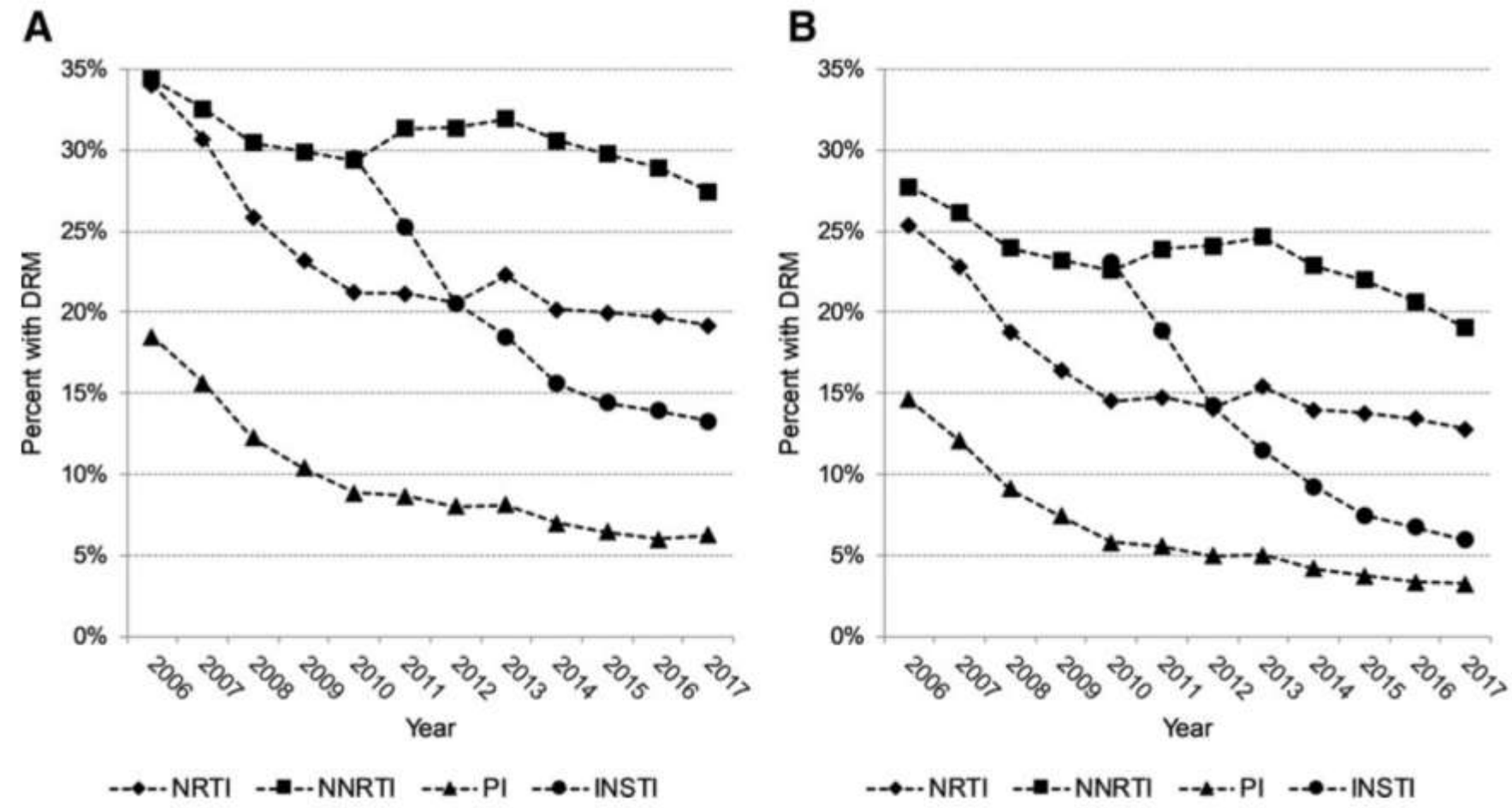
Özdemir A etal 2025 *Molecular epidemiological analysis and investigation of antiretroviral drug resistance profile, including capsid inhibitors, among treatment-naïve individuals with HIV-1 in Türkiye* HIV MED

Direnç Trendi: *Avrupa*



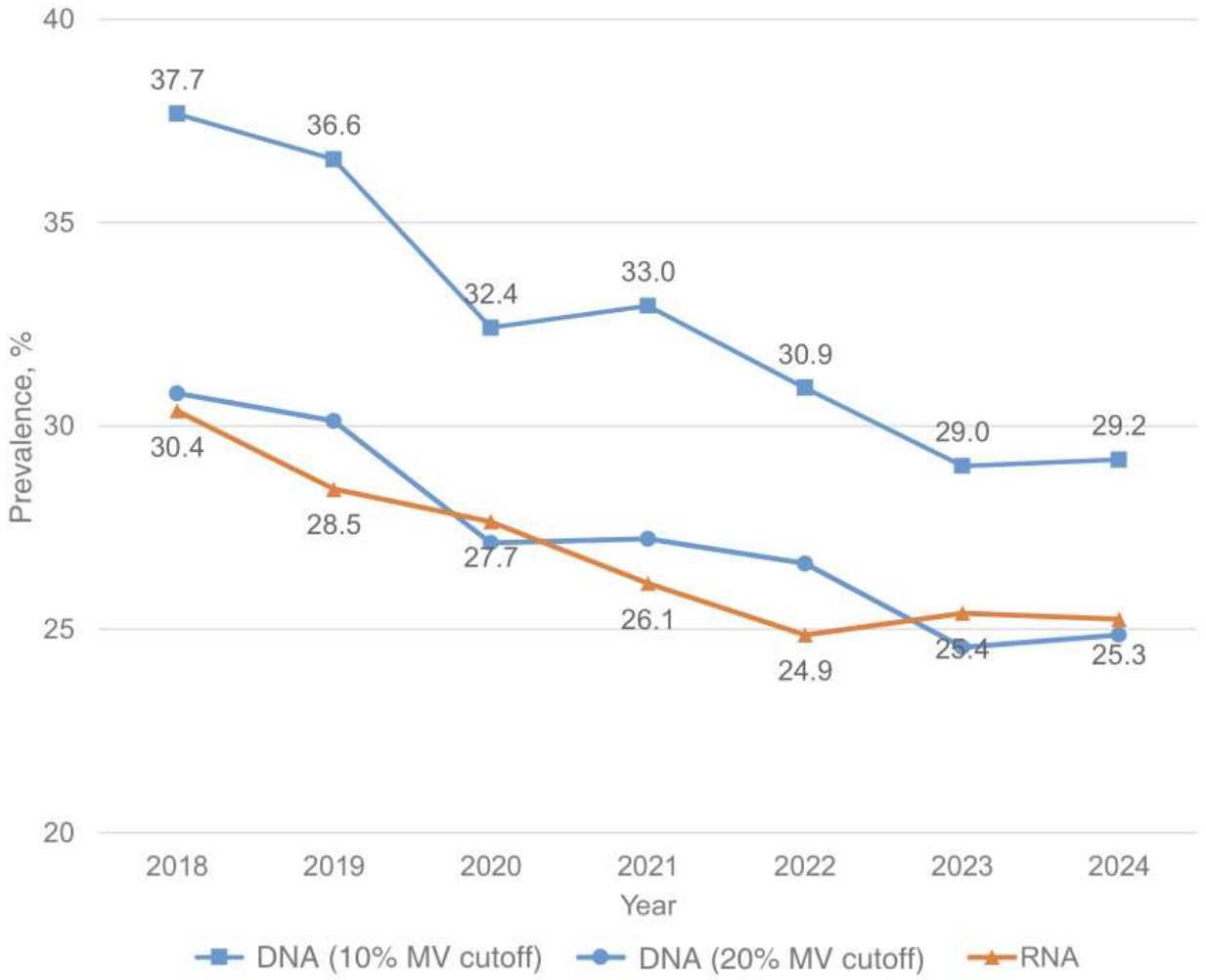
Hofstra LM etal 2016 *Transmission of HIV Drug Resistance and the Predicted Effect on Current First-line Regimens in Europe* Clin Infect Dis

Direnç Trendi: *ABD 2006-2017*



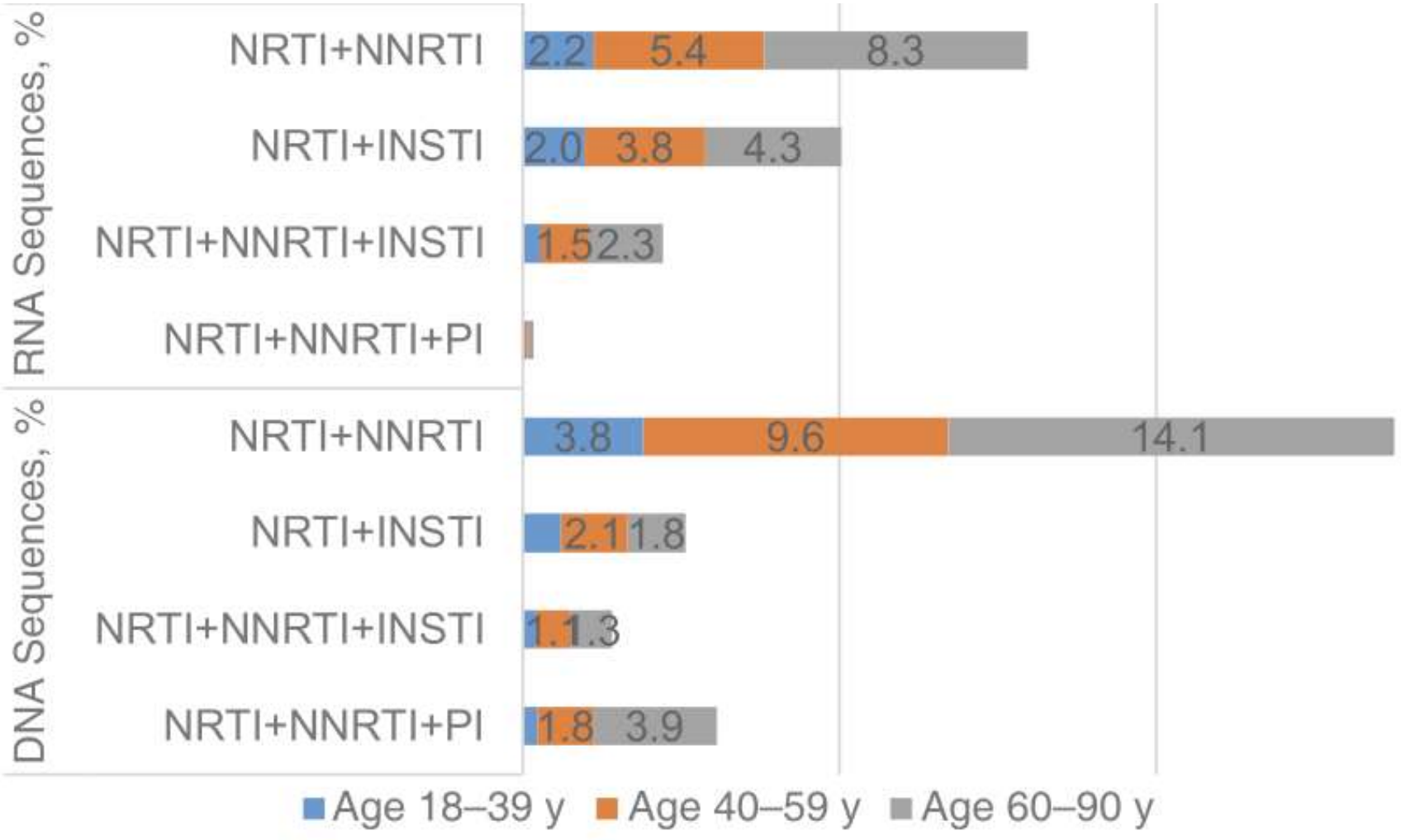
Kagan RM etal 2019 *Trends in HIV-1 Drug Resistance Mutations from a U.S. Reference Laboratory from 2006 to 2017* AIDS Res Hum Retroviruses

Direnç Trendi: 2018 – 2024



Kagan Rm etal 2025 *HIV-1 Drug Resistance Trends in the Era of Modern Antiretrovirals: 2018–2024* OFID

Çoklu Direnç Trendi: *Modern Zamanlar*



Kagan Rm etal 2025 *HIV-1 Drug Resistance Trends in the Era of Modern Antiretrovirals: 2018–2024* OFID

D2ARLING, Naive, Direnç Testi Yok
RCT 1:1, n=216, DTG/3TC vs TDF/XTC+DTG

HIV-1 RNA >100,000 DTG/3TC %94, TDF/XTC/DTG: %85
CD4<200, DTG/3TC: %81, TDF/XTC/DTG:%96
Kilo: DTG/3TC: +3.5 kg TDF/XTC/DTG +1.8 kg

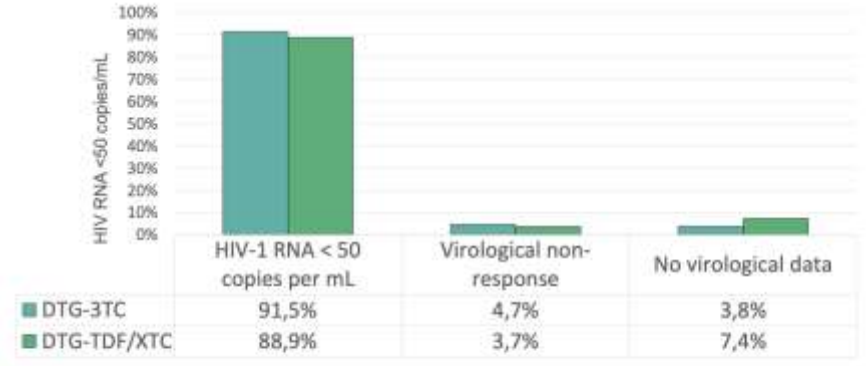
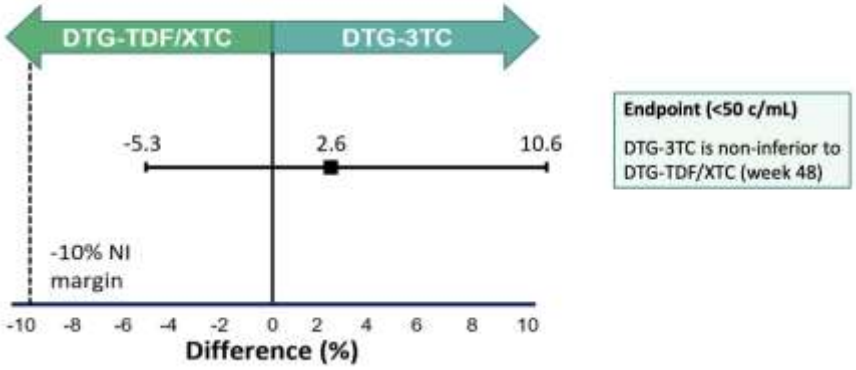


Figure 3. Adjusted treatment difference (95%CI)



Cordova E etal 2024 Efficacy of dolutegravir plus lamivudine in treatment-naive people living with HIV without baseline drug-resistance testing available (D2ARLING): 48-week results of a phase 4, randomised, open-label, non-inferiority trial. Lancet HIV

Tedavi Deneyimli Kişilerde NRTI/NRTI + DTG Virolojik Sonuçlar

Trial	Regions	Population [1]	DTG-Containing Regimen [2]	# PLWH	Weeks	# (%) VF [3]	# (%) Undergoing GRT	# (%) with INSTI DRMs [4]
SAILING 2013, 2015 [51,52]	Europe, North America, South America, Asia, Oceania, Africa	Adults; VL ≥ 400; INSTI-naïve, ≥2-class resistance	DTG + OBR	354	48	21 (5.9%)	9 (2.5%)	2 (0.6%)
DAWNING 2019, 2022 [53,54]	Europe, South America, Asia, Africa	Adults; VL ≥ 400 on a first-line NNRTI-containing regimen	DTG + 2 NRTIs (≥1 fully active)	312	48	11 (3.5%)	11 (3.5%)	3 (1.0%)
NADIA 2021, 2022 [55,56] [5]	Uganda, Kenya, Zimbabwe	Adults/Adolescents; VL ≥ 1000 on a first-line NNRTI-containing regimen	DTG + TDF/3TC or AZT/3TC	235	96	24 (10.2%)	21 (8.9%)	9 (3.8%)
ARTIST 2021, 2023 [57–59]	South Africa	Adults; VL ≥ 400 while on a first-line NNRTI-containing regimen	DTG + TDF/3TC	135	24	21 (15.6%)	4 (3.0%)	0 (0%)
			DTG BID + TDF/3TC	64	24	9 (14.1%)	3 (4.7%)	0 (0%)

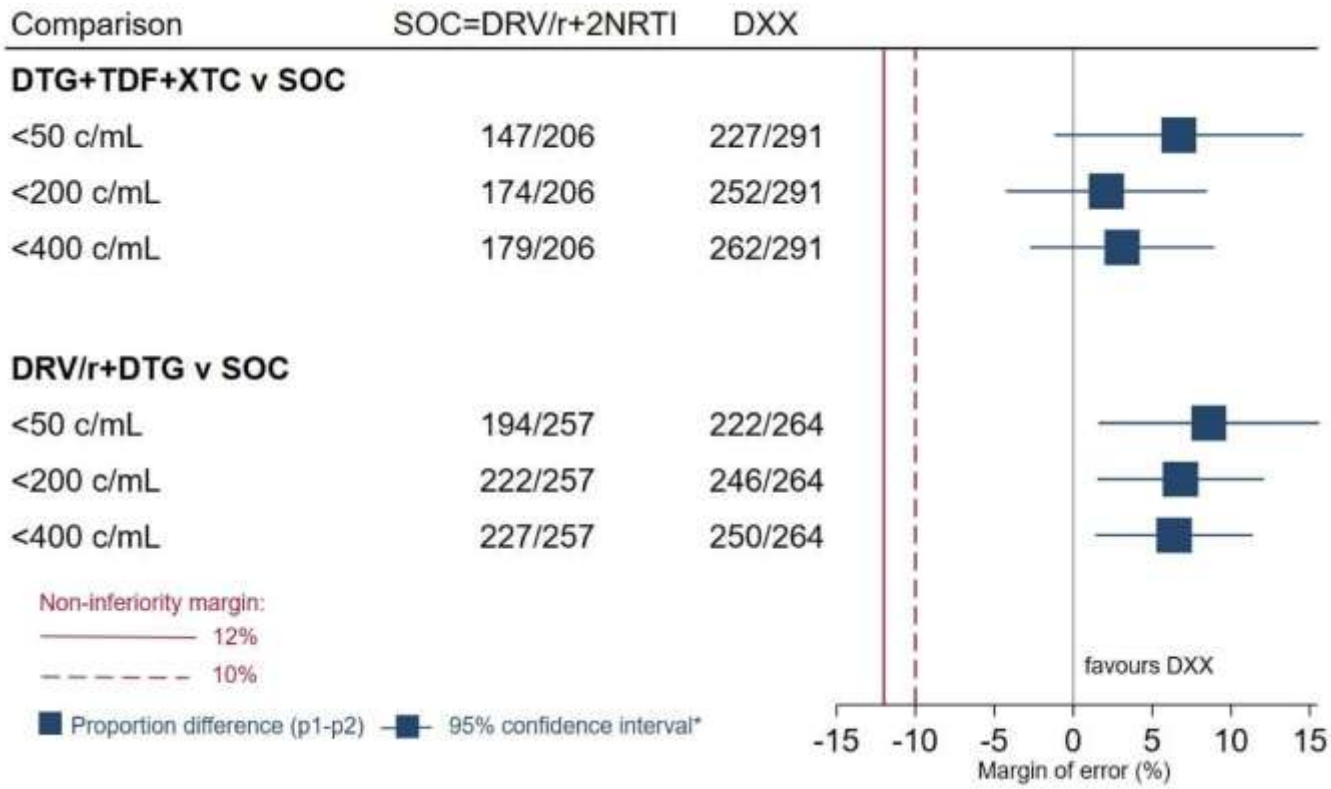
Başlangıç: %85 M184V, %50 K65R

Chu C etal 2024 *Prevalence of Emergent Dolutegravir Resistance Mutations in People Living with HIV: A Rapid Scoping Review* Viruses

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

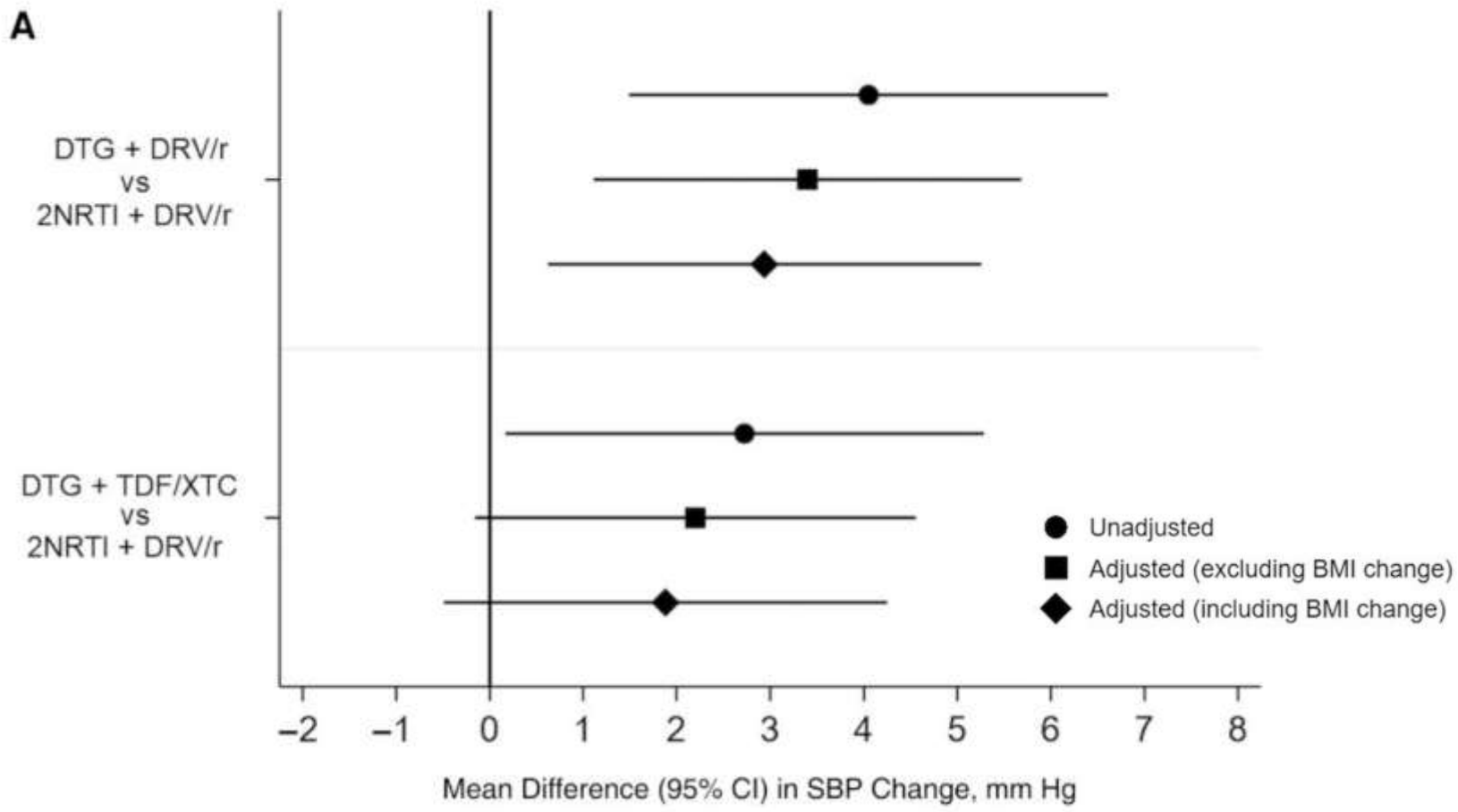
Arjantin, Şili, Kolombiya, hindistan, Malezya, Meksika, G. Afrika, Tayland, Zimbabwe, Brezilya, Gine, Endonezya, Mali, Nijerya

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



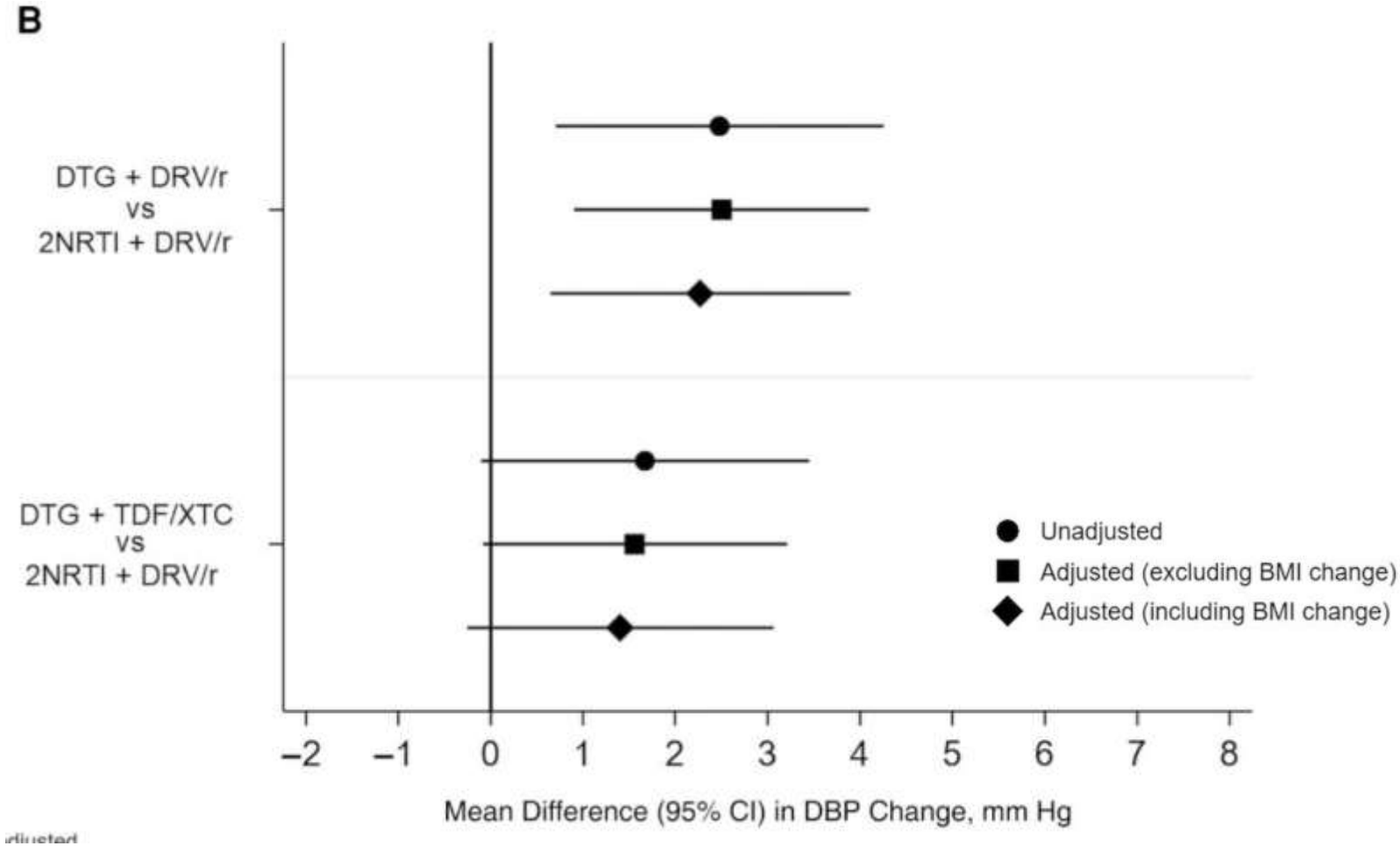
D2EFT Study Group. 2024 Dolutegravir plus boosted darunavir versus recommended standard-of-care antiretroviral regimens in people with HIV-1 for whom recommended first-line non-nucleoside reverse transcriptase inhibitor therapy has failed (D^2EFT): an open-label, randomised, phase 3b/4 trial. *Lancet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



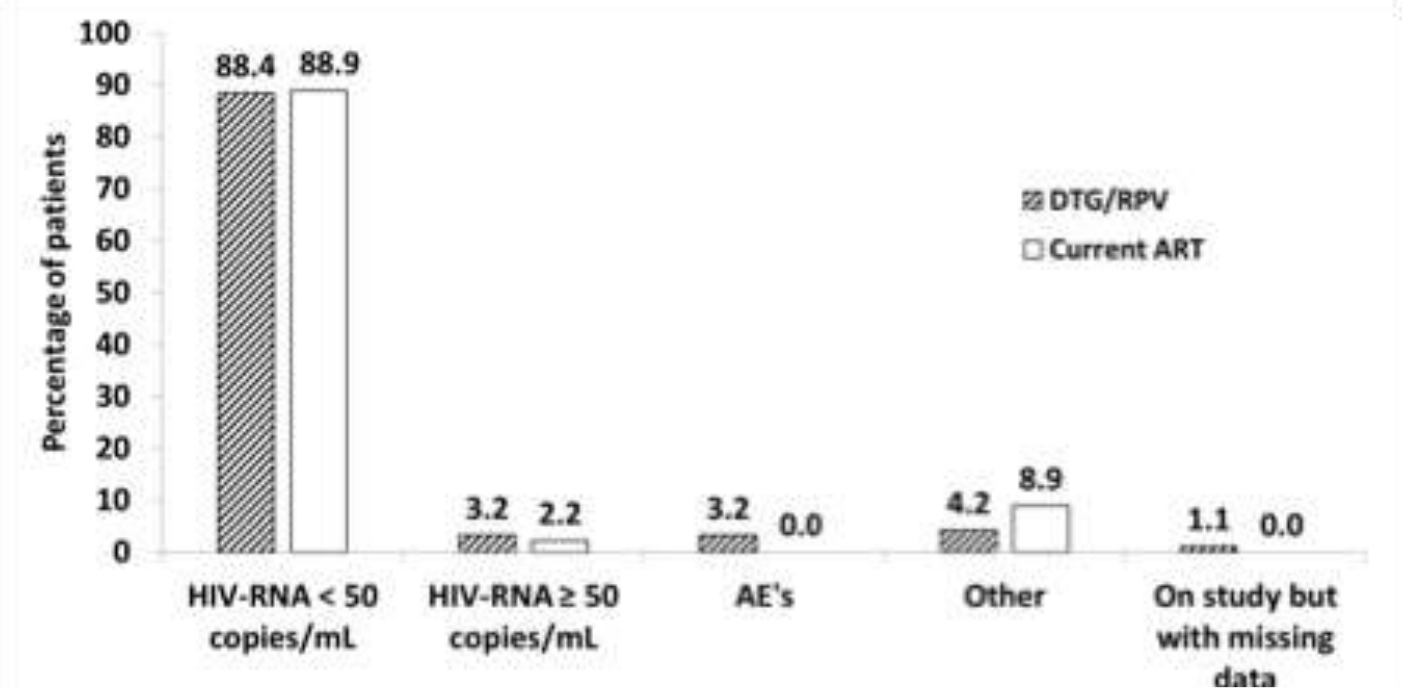
Nyein PP etal 2025 Associations Between Antiretroviral Regimen and Changes in Blood Pressure: Results From the D2EFT Study *Clin Infect Dis*

DTG/RPV Switch vs ART
RCT 2:1, K103N +, n=140

Belçika, Fransa, Almanya, İrlanda, İtalya, İspanya, UK

ART Süresi: 16 yıl (7-23), %32 antiHBctot: pozitif, ortalama 3 DRM

Kilo alım 1.2 vs 1.4kg, Tedavi bırakma 8 (agresif davranış, yağlı gaita, gaz, uyku bozukluğu) vs 4



Moyle G etal 2024 Switching to dolutegravir plus rilpivirine versus maintaining current antiretroviral therapy regimen in virologically suppressed people with HIV-1 and the Lys103Asn (K103N) mutation: 48-week results from a randomised, open-label pilot clinical trial *Lancet HIV*

TAF/FTC/BIC ➔ DOR/ISL Switch
RCT 1:1

11 Ülke, n=643

≥50 HIV-1 RNA copies per mL	2/322 (0·6%)	1/319 (0·3%)	0·3 (–1·2 to 2·0)
≥50 HIV-1 RNA copies per mL in week 48 window	1/322 (0·3%)	1/319 (0·3%)	..
Discontinued due to lack of efficacy	1/322 (0·3%)	0/319	..
<50 HIV-1 RNA copies per mL	302/322 (93·8%)	301/319 (94·4%)	–0·6 (–4·4 to 3·2)
No virological data in week 48 window	18/322 (5·6%)	17/319 (5·3%)	..
Discontinued due to adverse event or death and last measurement <50 HIV-1 RNA copies per mL	8/322 (2·5%)	7/319 (2·2%)	..
Discontinued for other reasons and last measurement <50 HIV-1 RNA copies per mL	8/322 (2·5%)	9/319 (2·8%)	..
On study treatment but missing data in window	2/322 (0·6%)	1/319 (0·3%)	..
<40 HIV-1 RNA copies per mL	300/322 (93·2%)	300/319 (94·0%)	–0·9 (–4·8 to 3·0)

Mills AM etal 2024 Switch to fixed-dose doravirine (100 mg) with islatravir (0·75 mg) once daily in virologically suppressed adults with HIV-1 on bictegravir, emtricitabine, and tenofovir alafenamide: 48-week results of a phase 3, randomised, controlled, double-blind, non-inferiority trial *Lancet HIV*

TAF/FTC/BIC ➔ DOR/ISL Switch
RCT 1:1

	Doravirine and islatravir group				Bictegravir, emtricitabine, and tenofovir alafenamide group			
	Number of participants with data for timepoint	Baseline mean*	Post-baseline mean*	Mean change (95% CI)†	Number of participants with data for timepoint	Baseline mean*	Post-baseline mean*	Mean change (95% CI)†
CD4 count, cells per µL								
Baseline	322	680	..	..	319	715	..	..
Week 24	304	677	688	10·9 (–10·0 to 31·8)	302	715	782	67·6 (45·5 to 89·8)
Week 48	301	680	661	–19·7 (–39·8 to 0·5)	298	721	761	40·5 (20·7 to 60·4)
Total lymphocyte count, × 10⁹/L								
Baseline	322	1·91	..	..	319	1·98	..	..
Week 24	309	1·91	1·82	–0·08 (–0·13 to –0·04)	300	1·98	2·06	0·08 (0·04 to 0·13)
Week 48	291	1·89	1·69	–0·20 (–0·25 to –0·15)	288	1·98	2·00	0·02 (–0·03 to 0·07)
Ratio of CD4 cell count to total lymphocyte count, %								
Baseline	322	36·66%	..	..	319	37·28%	..	..
Week 24	306	36·55%	37·67%	1·11 (0·68 to 1·55)	302	37·37%	37·35%	–0·02 (–0·54 to 0·51)
Week 48	290	36·91%	38·78%	1·87 (1·42 to 2·33)	291	37·34%	37·73%	0·38 (–0·18 to 0·95)

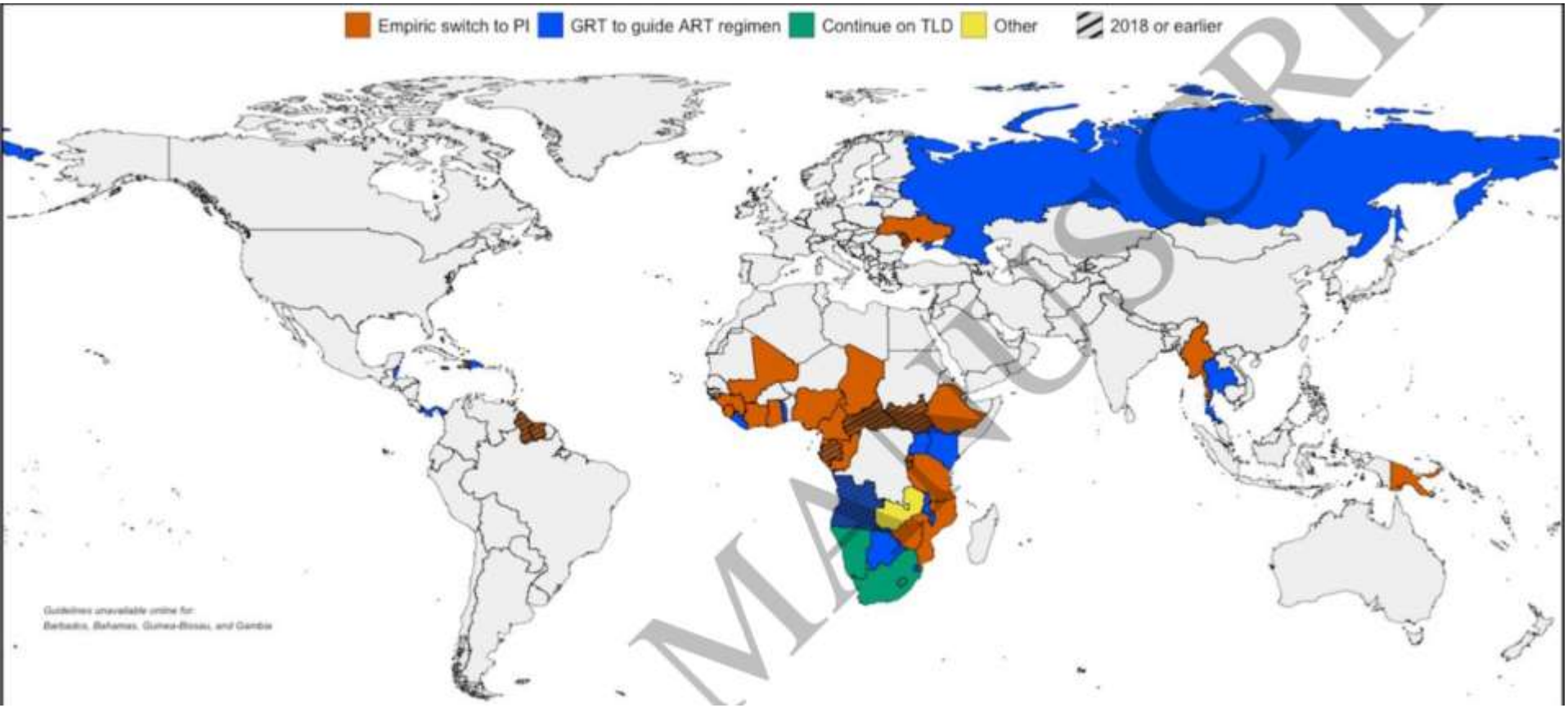
*Calculated on the basis of the number of participants with data available for the timepoint. †Mean change was calculated before rounding.

Mills AM etal 2024 *Switch to fixed-dose doravirine (100 mg) with islatravir (0·75 mg) once daily in virologically suppressed adults with HIV-1 on bictegravir, emtricitabine, and tenofovir alafenamide: 48-week results of a phase 3, randomised, controlled, double-blind, non-inferiority trial Lancet HIV*

- >20000000 kişi DTG bazlı tedavi alıyor
  - Bir çoğu Afrika ve kurtarma rejimi olarak
- R263K 2x IC_{50}
- Q148H/R/K 1.4xIC_{50}
- N155H 0.8x IC_{50}
- G118R en az fit virüs
- Direnç özellikle
  - K65R/M184V + TAM + NNRTI + PI dirençli kişilerde

Fokam J etal 2024 *HIV drug resistance to integrase inhibitors in low- and middle-income countries* Nat Med

TLD Başarısızlığında Yaklaşım



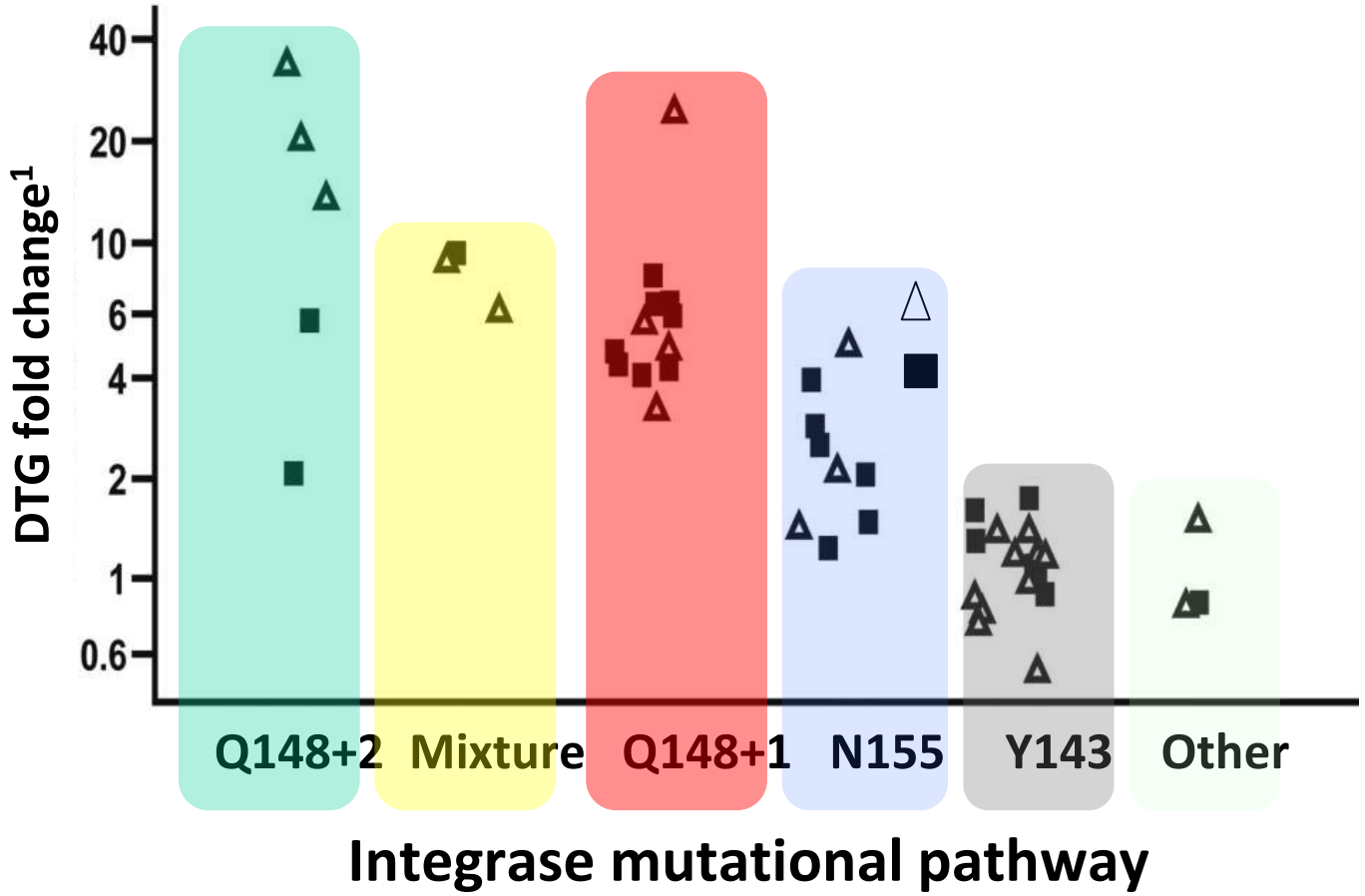
Nutt CT etal 2025 *Approaches to the Management of Virologic Failure on Dolutegravir-Based Antiretroviral Therapy in the 50 Countries with the Highest Adult HIV Prevalence* Clin Inf Dis

TLD Başarısızlığında Yaklaşım Farmakoekonomi

- GRT
- PLWH için yaşam beklenti artışı
- İdrar TFV testi ile birlikte
- Direkt TDF/XTC/DRVr geçişi gereksiz

Hyle EP etal 2025 *The clinical and economic impact of genotypic resistance testing for people diagnosed with persistent virological non-suppression on tenofovir–lamivudine–dolutegravir in South Africa: a modelling study* Lancet HIV

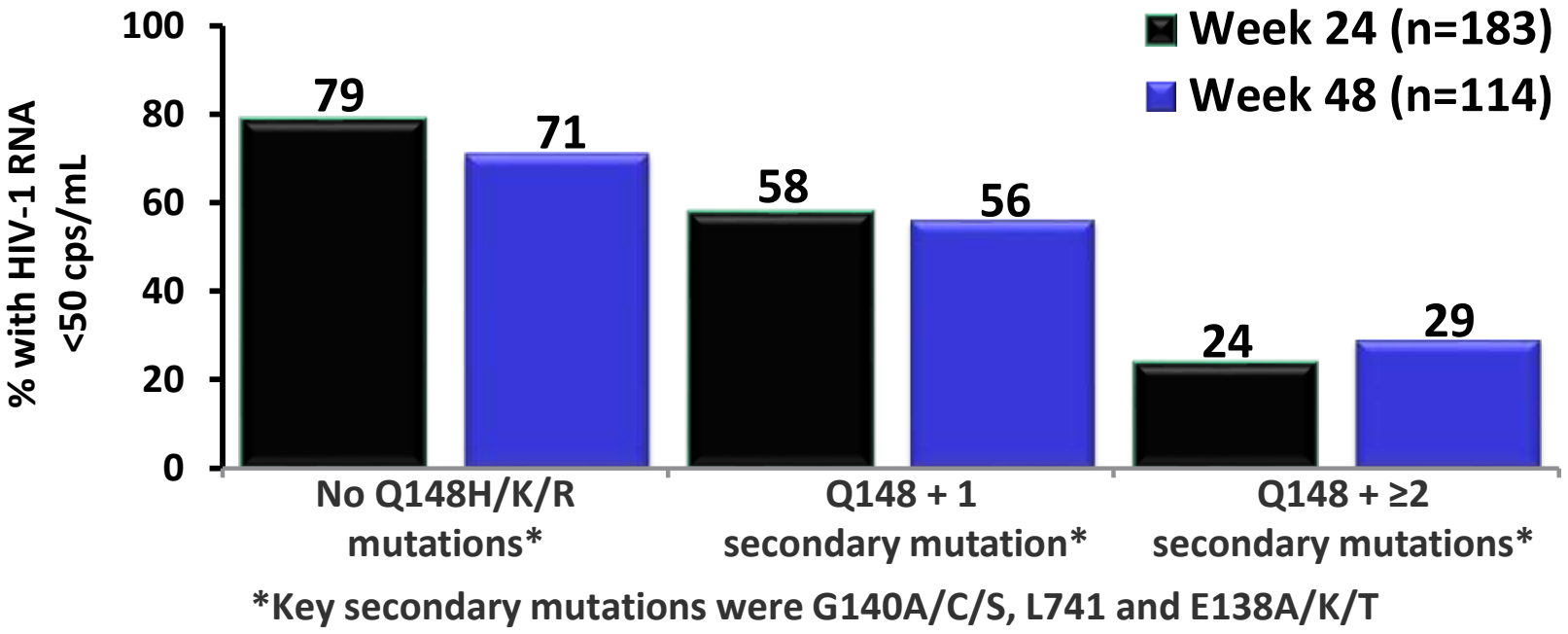
Mutasyon ve Çapraz Direnç



1. Eron et al. J Infect Dis 2013; 2. Underwood et al. JAIDS 2012

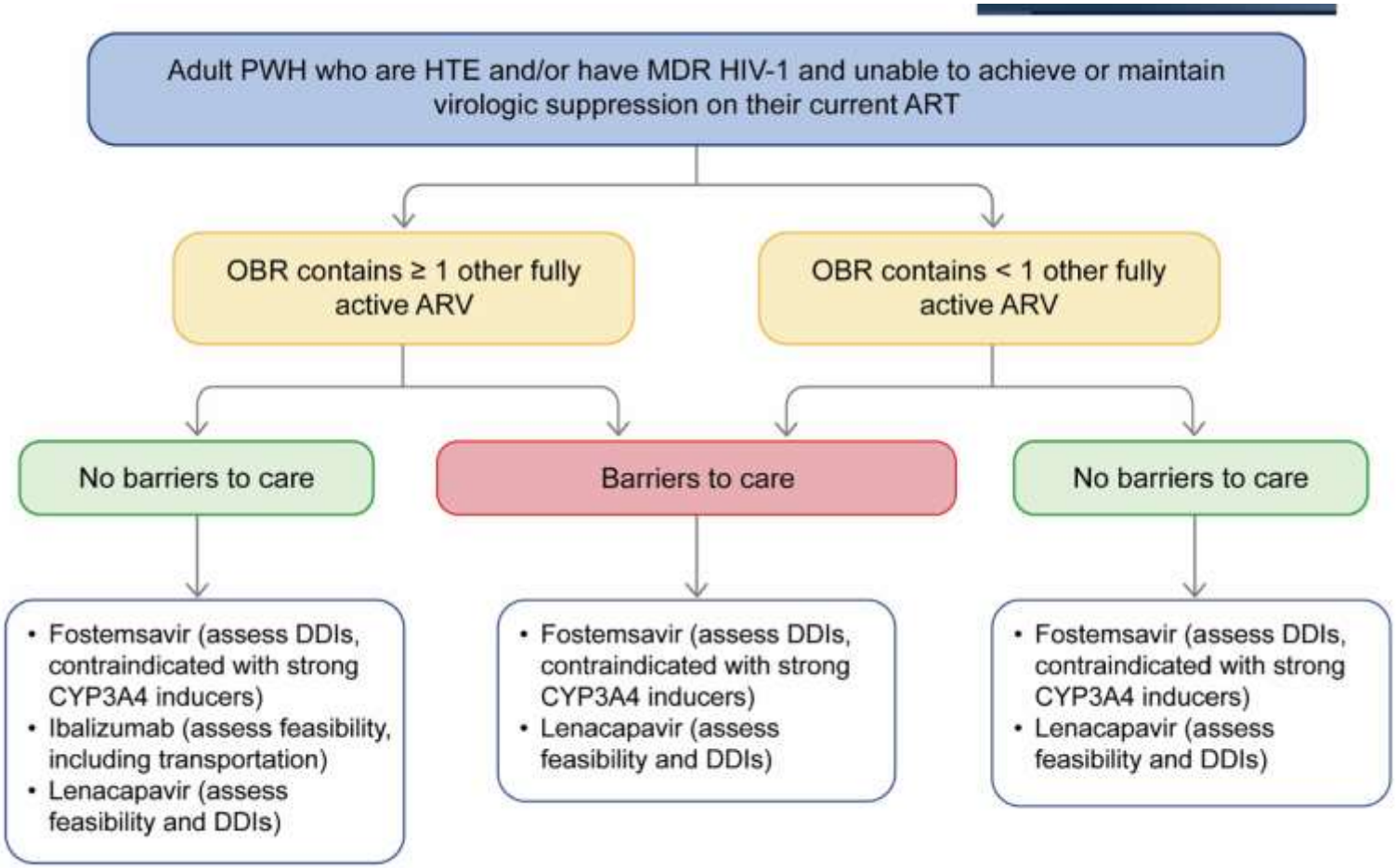
VIKING: Tedavi Yanıtı ve Mutasyon Sayısı

- Subjects with VL ≥500 cps and RAL/EVG resistance + ≥2 other ARV classes
- DTG 50mg BD for 8 days ➔optimisation of BR (≥1 active drug)
- Response rates (<50 cps) 69% at wk 24 and 56% at wk 48



Nichols et al. IAS 2013; Vavro et al. EUDRW 2014

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*