TÜRKİYE EKMUD HIV/AIDS Çalışma Grubu

4. TÜRKİYE EKMUD HIV AKADEMİSİ

16-18 Haziran 2023 Anemon Ege Otel

Laboratuvarda Direnç

Dr Mert Kuşkucu

Koç Üniversitesi, Tıp Fakültesi Tıbbi Mikrobiyoloji Anabilim Dalı

Koç Üniversitesi, İş Bankası İnfeksiyon Hastalıkları Merkezi (KUISCID)

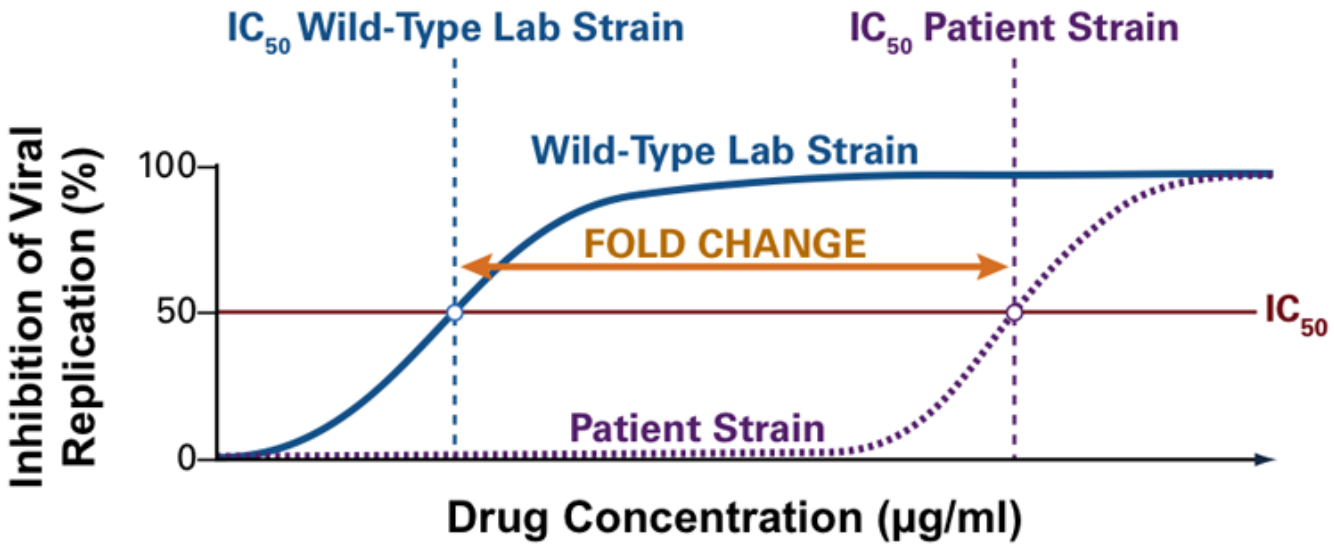
Sunum Akışı

- Biraz temel tanımlar (Sıkıcı ama gerekli)
- Antiretroviral direnç testleri (Biraz teknik, ama son söz Dizileme)
- Direnç testleri,
  - Nasıl rapolayayım?
  - Nasıl yoruma katkı sağlayayım?
- Tedavi kararları için ne yapabilirim (Bizde durum, Dumanlı Dağlar)

Direnç: Virusun mutasyon yeteneği ile birlikte antiretroviral ilaç varlığında virusun replike olabilmesi

Günlük 10^9-10^{12} yeni viryon oluşumu; RT hataları nedeni ile yüksek mutasyon hızı

10^{-3}-10^{-4} Mutasyon/Replikasyon
3-4 Rekombinasyon / replikasyon



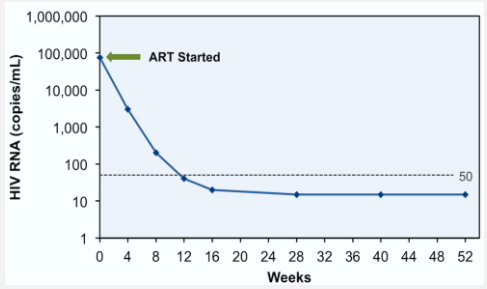
Direnç gelişimi viruslar arasında farklılık gösterir

- RNA'lı viruslarda daha hızlı
- Direnç mutasyonlarının evrim hızı değişken
- Bazen tek bir mutasyon yüksek düzeyde R kazandırabilir
- Bazı ilaç sınıflarına karşı R mutasyonların aşamalı bir biçimde birikimi sonucu gelişir
- R ile ilişkili bazı mutasyonlar virusun *fittness* ini düşürür → ilave mutasyonlar *fittness* i restore edebilir

David H. Spach, MD. Features of Genotypic and Phenotypic Resistance Assays. HIV Web Study (www.hivwebstudy.org)

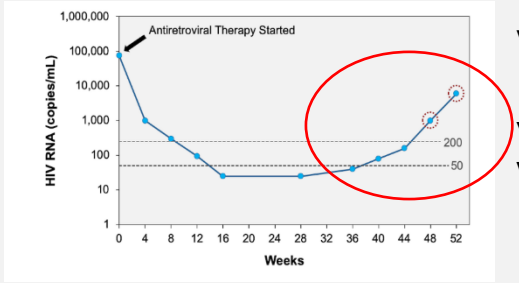
ART'ye Virolojik Yanıt

Tanımlar



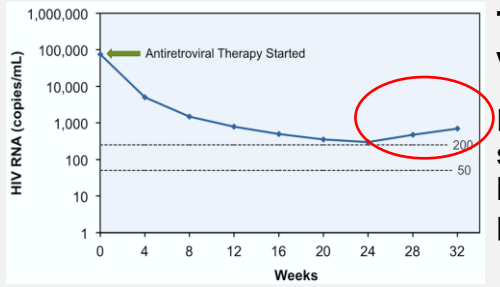
Virolojik Supresyon(VS)

Standart tahlillerin tespitinin alt sınırının altında onaylanmış bir HIV RNA seviyesi



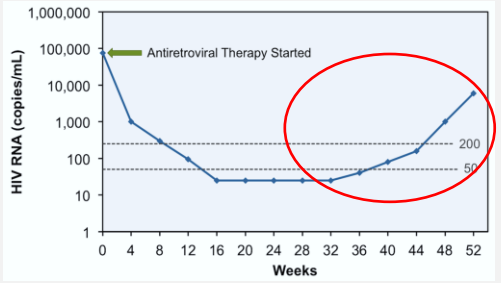
Virolojik Başarısızlık (VF)

Viral replikasyonun baskılanamaması veya baskılanmanın sürdürülememesi



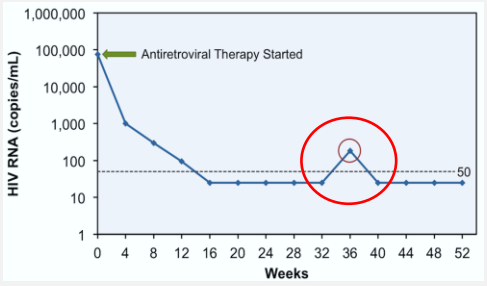
Tamamlanmamış (Incomplete) Virolojik Yanıt

Bu rejimde henüz virolojik baskılama sağlanmamış bir hastada ARV rejimi başlangıcından 24 hafta sonra iki ardışık plazma HIV RNA seviyesi ≥200 kopya/mL



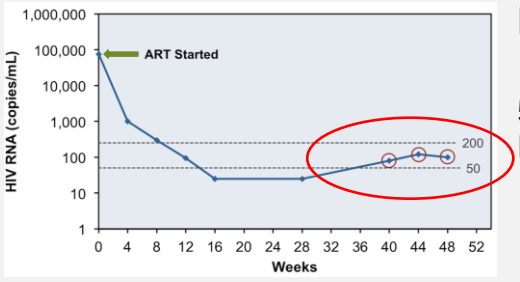
Virolojik Rebound

Virolojik baskılamadan sonra HIV RNA düzeyi ≥200 kopya/mL olarak görülmesi



Viral Blip

Virolojik baskılamadan sonra, izole bir tespit edilebilir HIV RNA düzeyi ve virolojik baskılanmanın ek girişm olmadan yeniden sağlanması



Düşük Seviyeli Viremi (LLV)

50 ila 200 kopya/ml arasında HIV RNA seviyesi

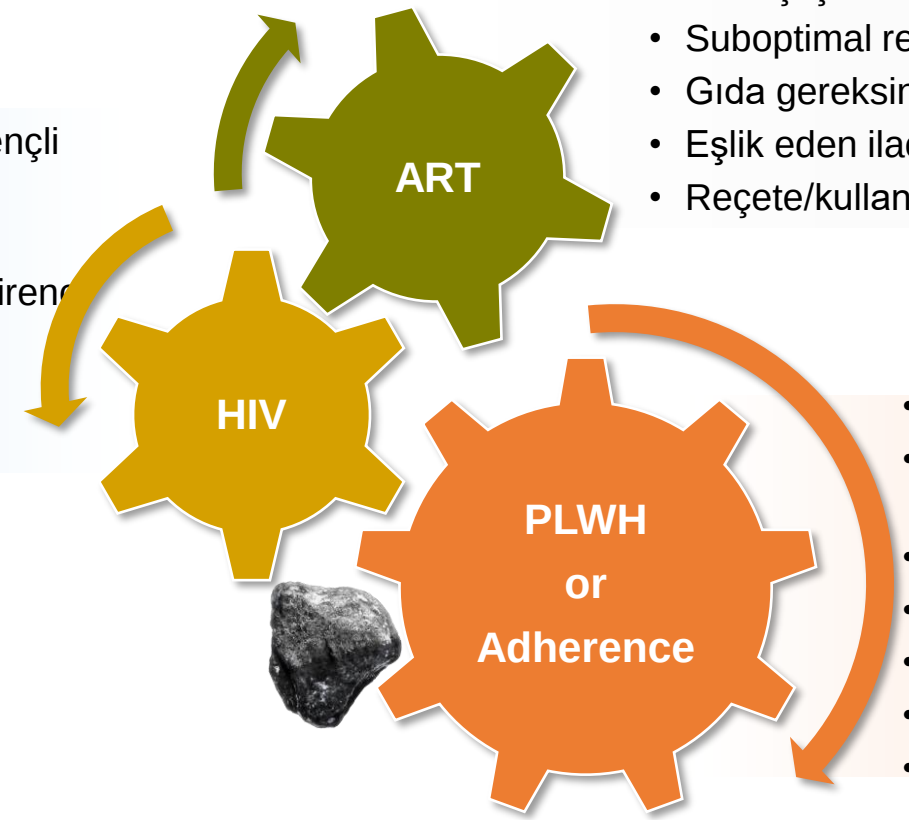
*A patient's baseline HIV RNA level may affect the time course of response, and some regimens may take longer than others to suppress HIV RNA levels

DHHS. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV, June 2021. Available at: http://aidsinfo.nih.gov/guidelines

Images courtesy of National HIV Curriculum. https://www.hiv.uw.edu/

Direnç Nasıl Gelişir?
Virolojik Başarısızlık

- Bulaşan veya edinilmiş ilaca dirençli virüsün varlığı
- Önceki tedavi başarısızlığı
- ARV'lere karşı doğuştan gelen direnç
- Yüksek ART öncesi HIV RNA seviyeleri
- ART öncesi düşük CD4 sayısı



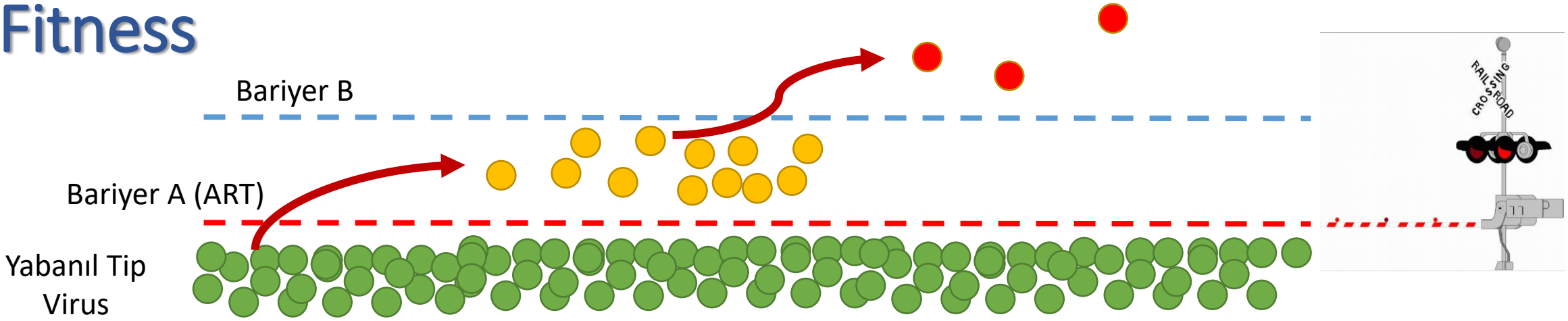
- Suboptimal farmakokinetik
- Suboptimal virolojik güç
- Direnç için düşük genetik bariyer
- Suboptimal rejimlere önceden maruz kalma
- Gıda gereksinimleri
- Eşlik eden ilaçlarla ilaç-ilaç etkileşimi (DDI)
- Reçete/kullanım hataları

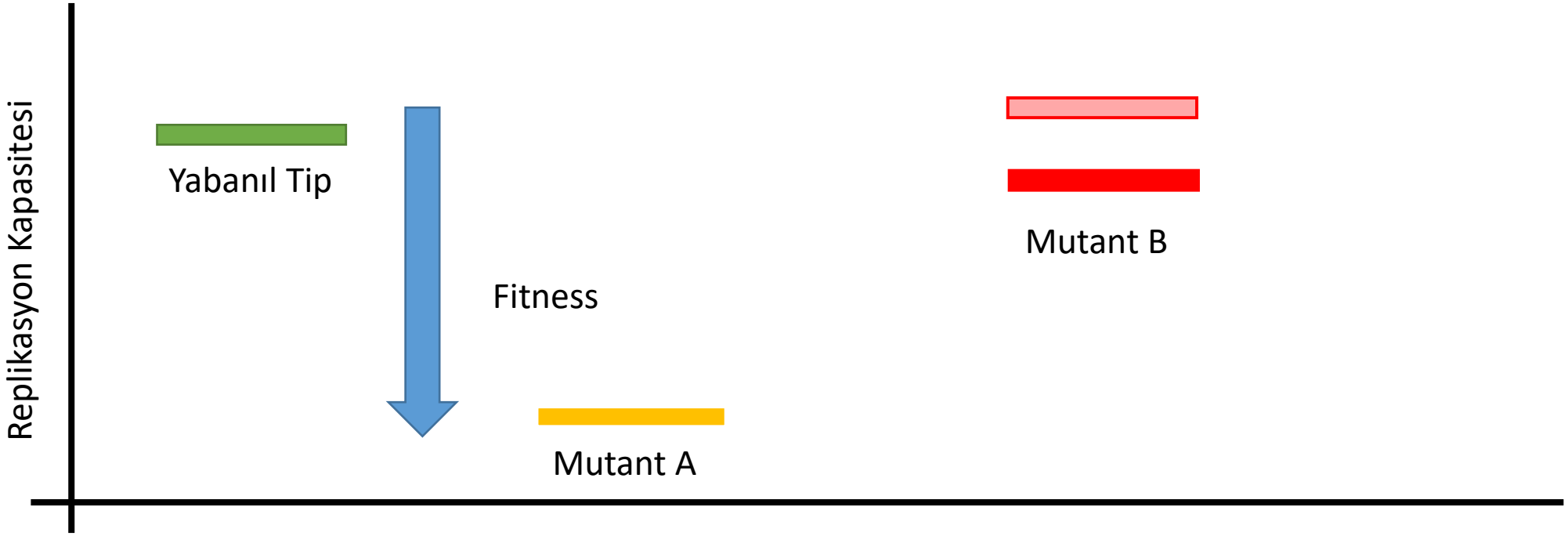
- Komorbiditeler
- Subtopimal barınma koşulları ve diğer psikososyal faktörler
- Kaçırılan klinik randevuları
- ART'a erişimin kesilmesi veya aralıklı olması
- ARV ilaçlarının maliyeti ve karşılanabilirliği
- Olumsuz ilaç etkileri
- Yüksek hap yükü ve/veya doz sıklığı

Birden fazla faktör yaşam boyu virolojik baskılama hedefini etkileyebilir

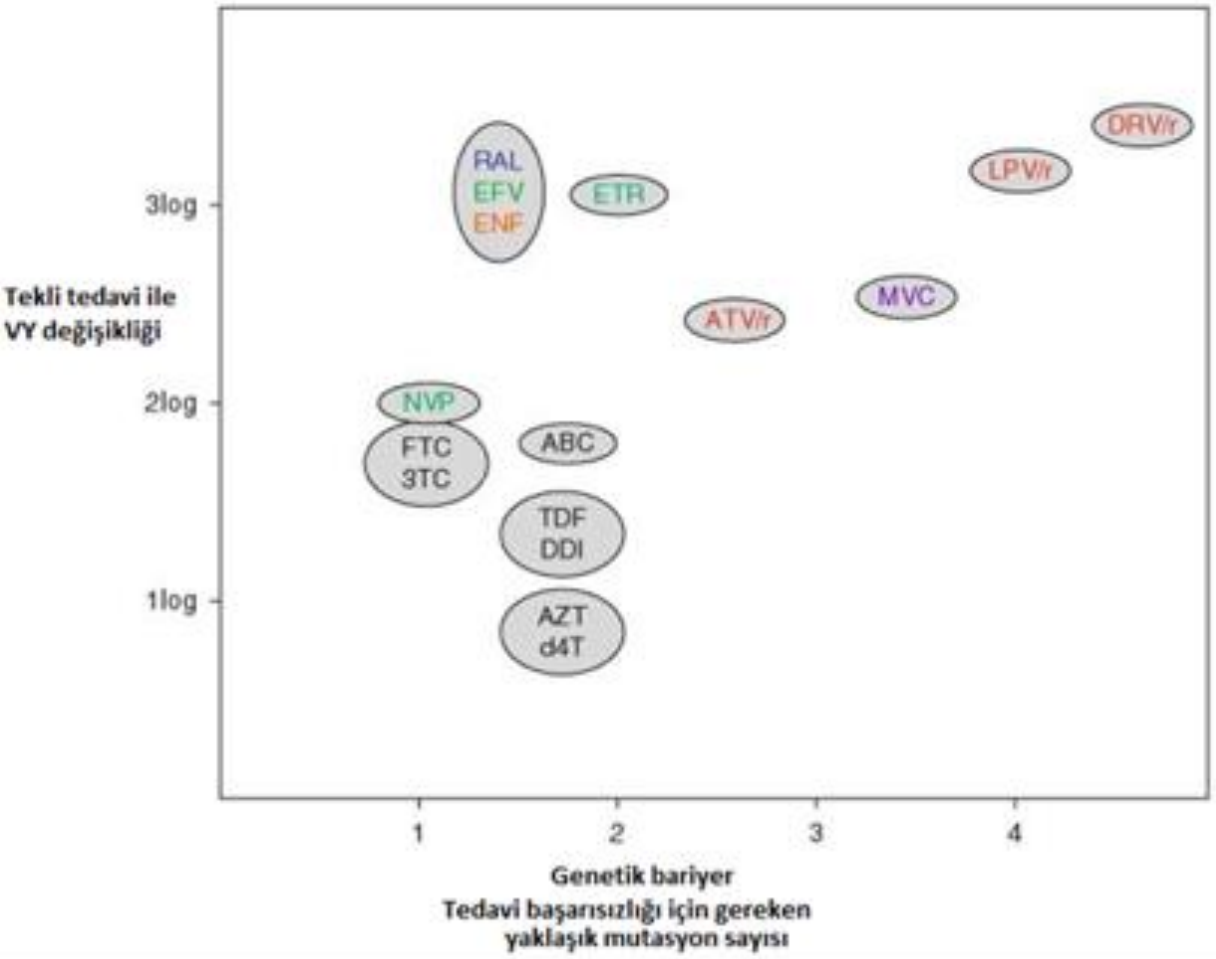
DHHS. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV, June 2021. Available at: http://aidsinfo.nih.gov/guidelines

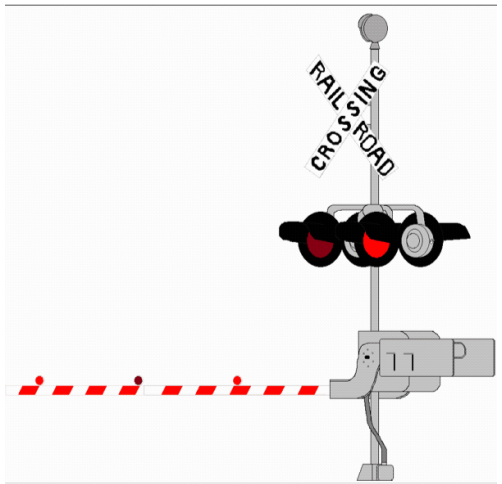
Genetik Bariyer & Fitness



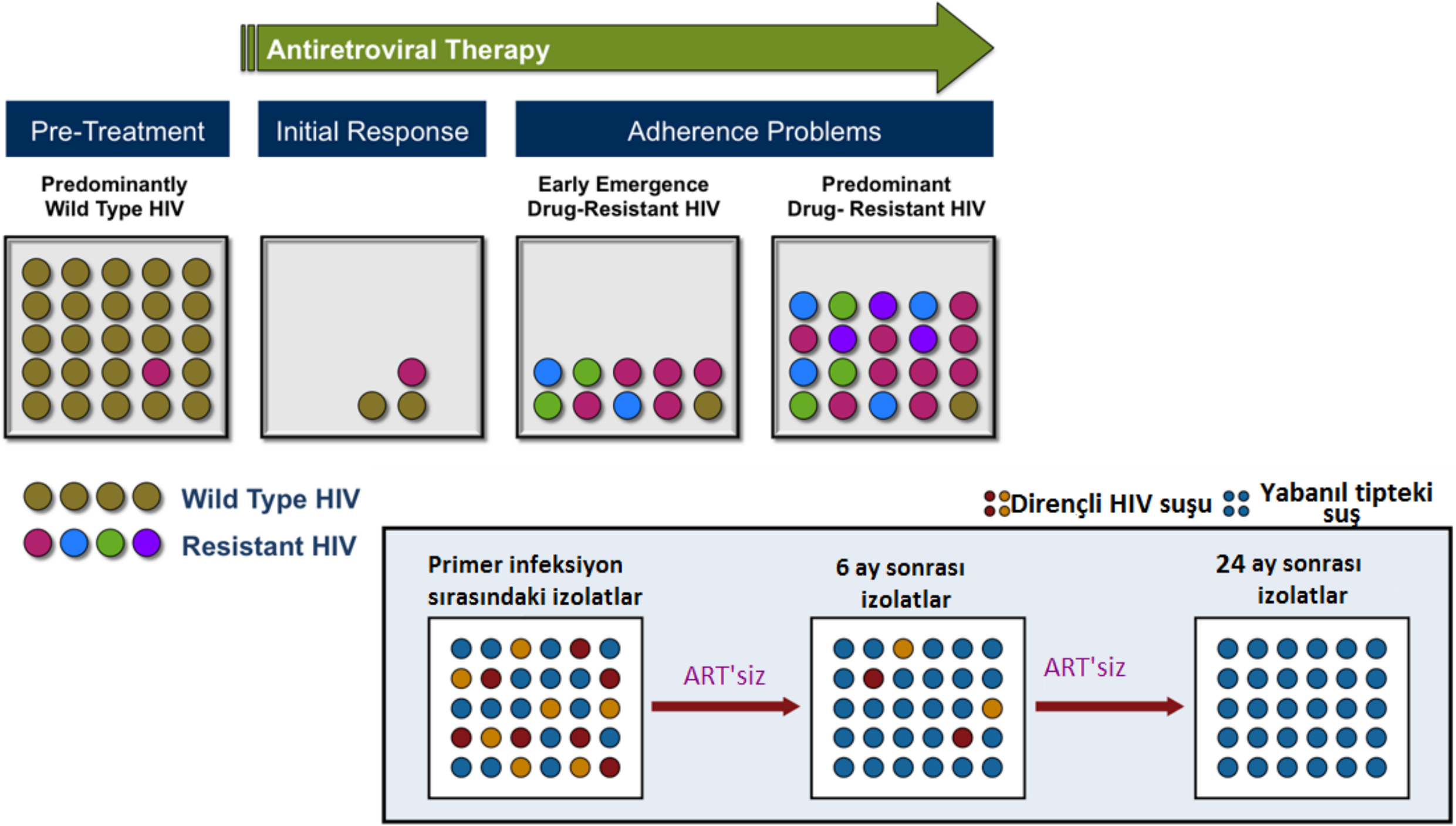


ART ve Genetik Bariyer





Bir virus bir AV tarafından inhibe edilirken bir yandan da direnç mutasyonları gelişen suşlar seçilir. Bu olayın ne kolaylıkla gerçekleşeceği, gelişecek olan olası mutasyonların virusun *fittness* ini azaltmaksızın direnç kazandırabilmesine bağlıdır. Bu olgu «**genetik bariyer**» olarak bilinmektedir.


Antiretroviral Therapy
Pre-Treatment
Initial Response
Adherence Problems
Predominantly Wild Type HIV
Early Emergence Drug-Resistant HIV
Predominant Drug- Resistant HIV
Wild Type HIV
Resistant HIV
Dirençli HIV suşu
Yabanıl tipteki suş
Primer infeksiyon sırasındaki izolatlar
ART'siz
6 ay sonrası izolatlar
ART'siz
24 ay sonrası izolatlar

Genetik Bariyer &

Oscar Pistorius wins the T44 100m event during the BT Paralympics World Cup Athletics on May 27 in Manchester, England.

10.91 (world record)

The Olympic records for the event are **9.63 seconds**, set by Usain Bolt

Genetik Bariyer &Fitness

400 m Avrupa Rekoru

Europe (*records*)	**44.33**	Thomas Schönlebe

Leeper

That summer, he had sprinted the 400-meter in **44.42 seconds**, breaking the record of Pistorius, the first below-the-knee amputee to compete against able-bodied runners at the Olympic games.

What will the 2056 Olympics look like?

By Loz Blain
July 28, 2021

ARV Direnç Testleri

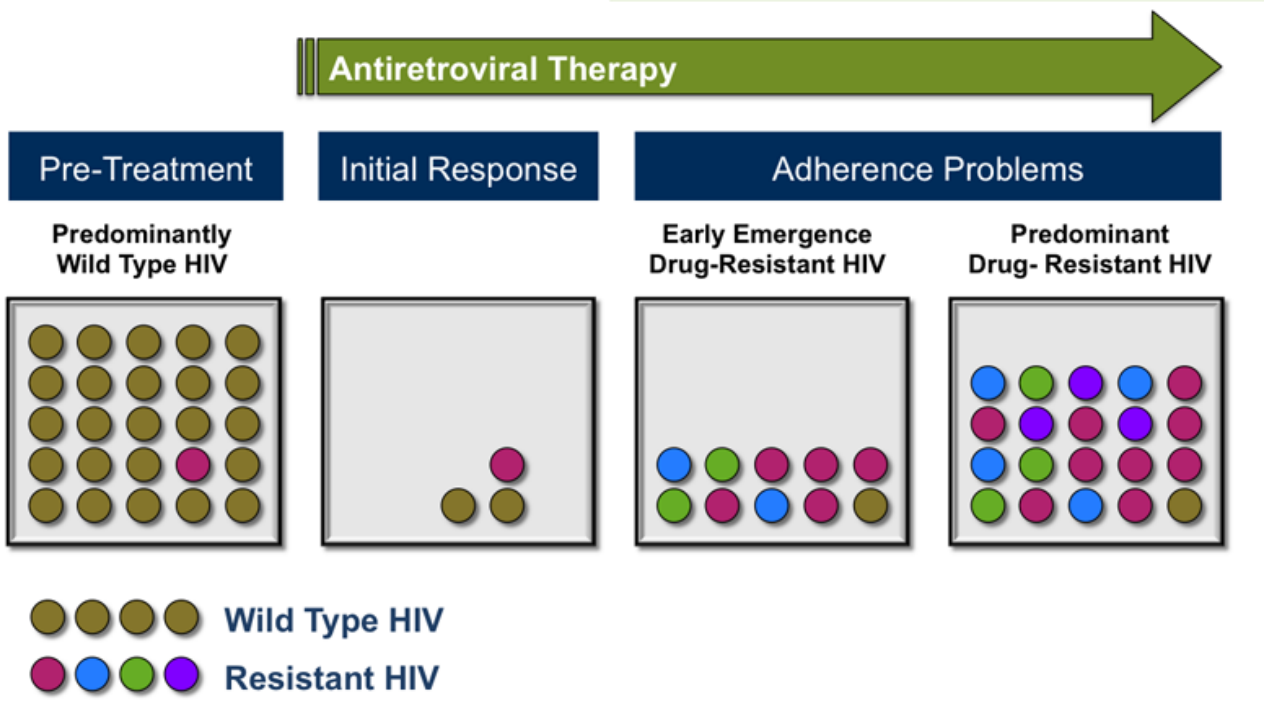
- **Genotipik testler:**

- RT-PCR sonrası:
  - Allel spesifik PCR
  - Revers hibridizasyon
  - OLA (Oligonükleotid ligation assay)
  - DNA Dizi Analizi
  - Klasik Yöntem, Sanger Dizileme (%20 varyant)
  - Yeni kuşak DNA dizileme (%1 varyant ???)

- **Fenotipik testler:** Ticari

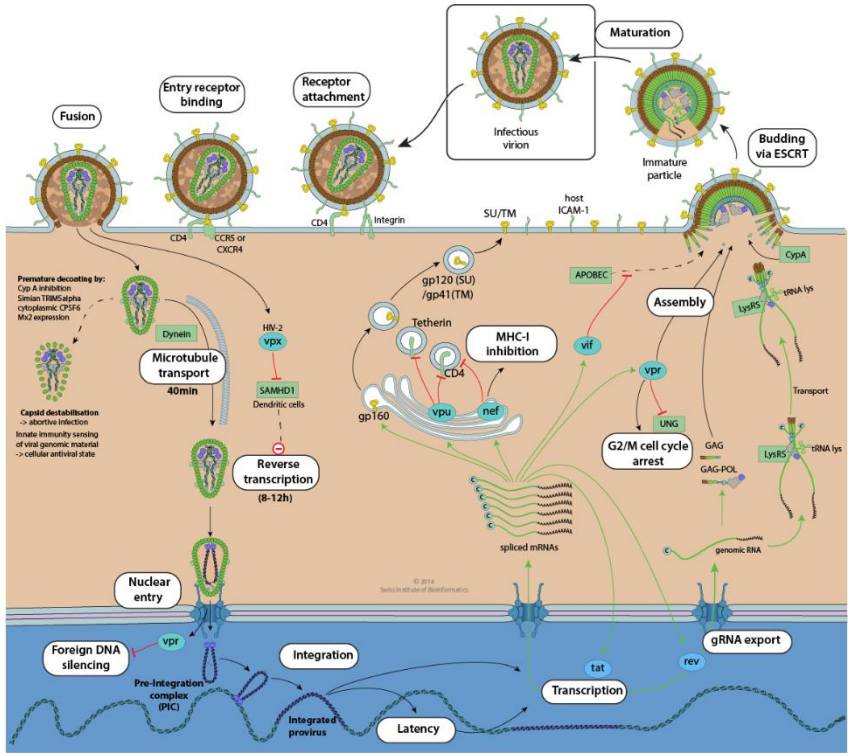
Direnç Saptamada Yeni Yaklaşımlar: Minör popülasyonlar

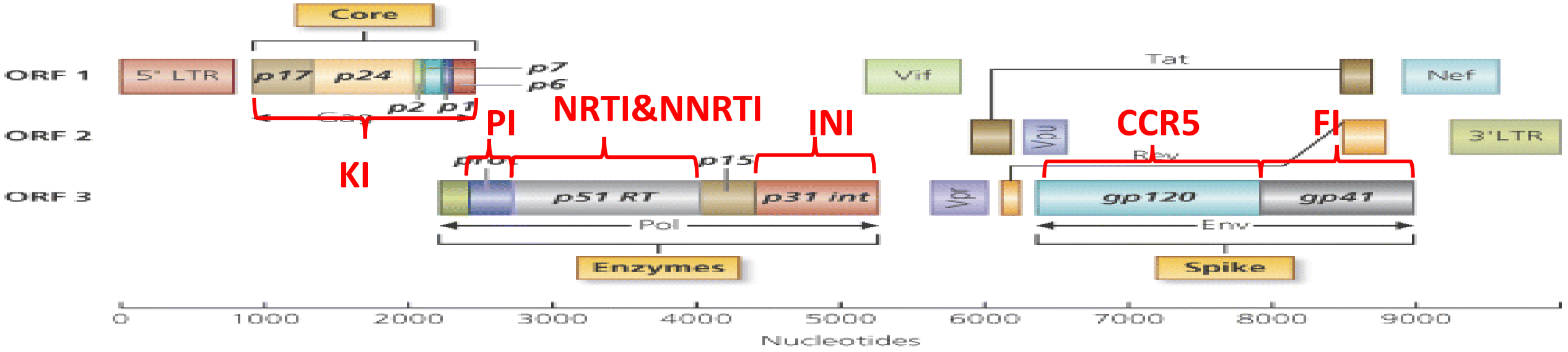
- Droplet (digital) PCR
  - Tek bir moleüklün çoğaltılması ve saptanması olanaklı,
  - Mutant kökenlerin daha hasas saptanmasını sağlayabilecek
- Ultra-Deep Sequencing
  - Klasik dizilemede popülasyonu oluşturan kökenlerin oran %20'nin üzerinde ise saptanabiliyor.
  - Ultra-deep dizileme ile %1 gibi minör varyantları bile saptamak mümkün



Hedefler;
HIV Yaşam Döngüsü
ART'ler

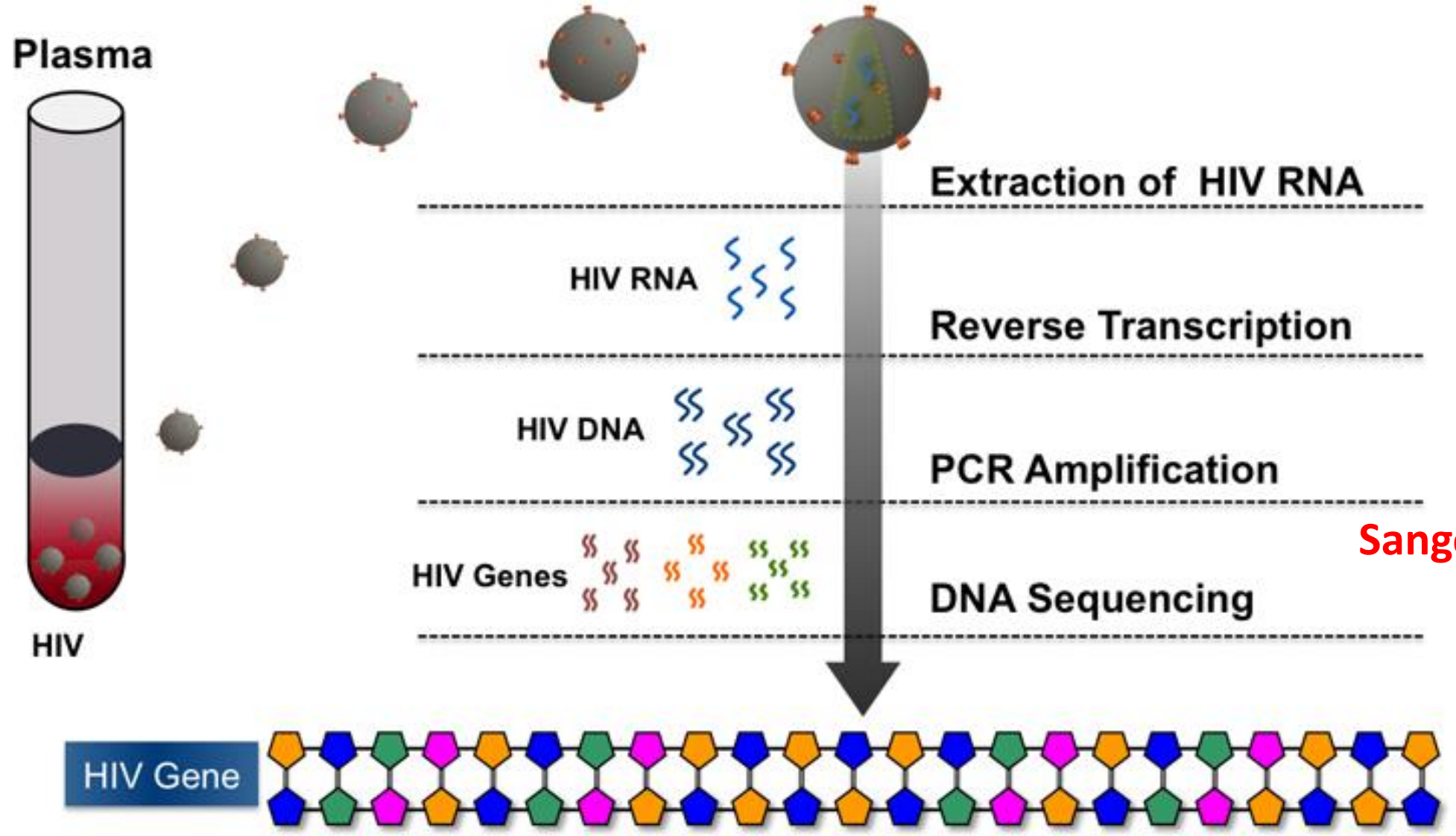
- PI
- NRTI; NNRTI
- INI
- CCR5, FI
- KI





Direnç Testleri Uygulama Zamanı

- İlk tanı konduğunda (tedavi kararından bağımsız olarak)
- Tedavi başarısızlıklarında: İlaç altında iken ya da tercihen ilaç kesildikten sonra ilk 4 hafta içersinde
- Tedaviye başlarken
- Viral yük > 500 kopya/ml olmalı



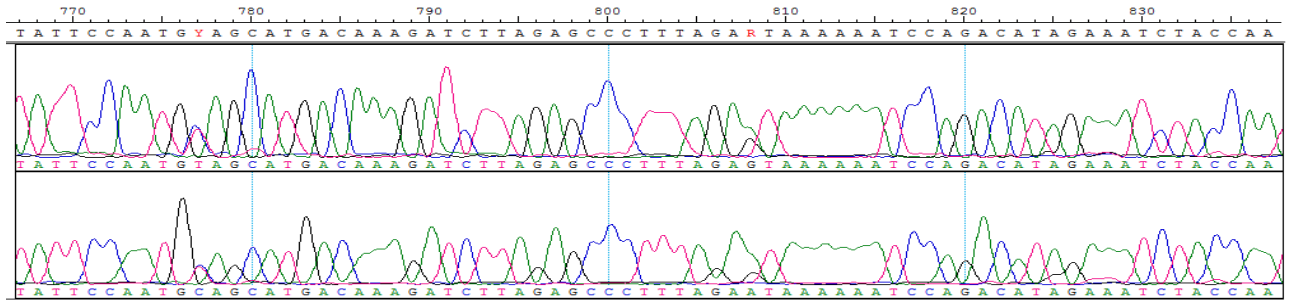
Sanger Sequencing
YND

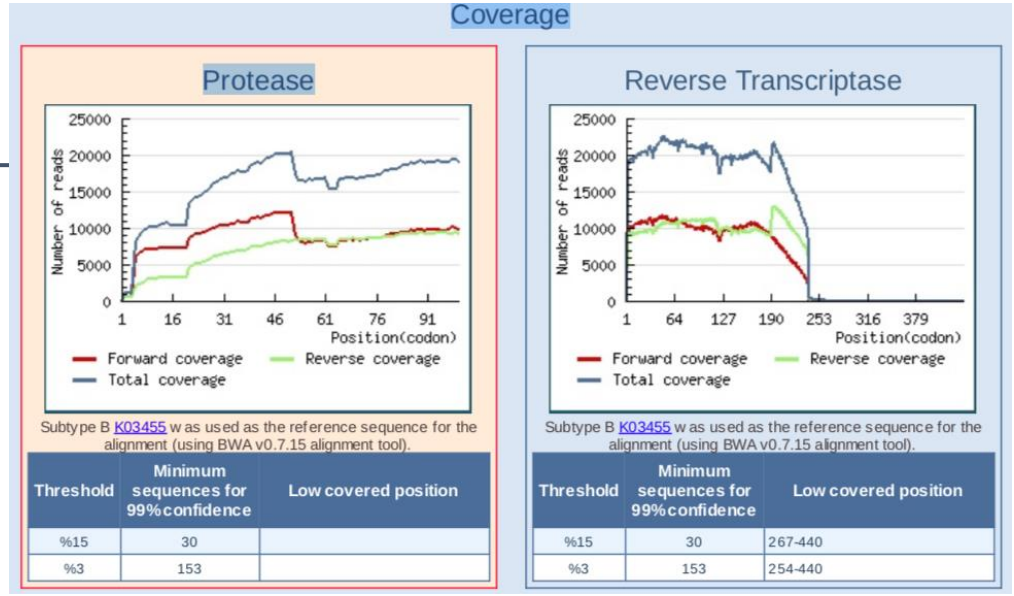
Örnek:
PLAZMA

- APOBEC3

David H. Spach, MD. Features of Genotypic and Phenotypic Resistance Assays. HIV Web Study (www.hivwebstudy.org)

Genotipik HIV Direnç Testi





Threshold	Minimum sequences for 99% confidence	Low covered position
%15	30	
%3	153	

Threshold	Minimum sequences for 99% confidence	Low covered position
%15	30	267-440
%3	153	254-440

CCTCAGATCACTCTTTGGCAACGACCCATAGTCACAATAAAGATAGCGGGACAACTAAAGGAAGCTCTATTAGATACAGGAGCAGATGATACAGTATTAGAAGAA
ATGAATTTGCCAGGAAAATGGAAACCAAAAATAATAGTGGGAATTGGAGGGTTTACCAAAGTAAGACAGTATGATCATGTACAAATAGAAATCTGTGGACATAAA
GTTATAGGTGCAGTATTAATAGGACCTACACCTGCCAATATAATTGGAAGAAATCTGTTGACTCAGCTTGGCTGTACTTTAAATTTT

PQITLWQRPIVTIKIAGQLKEALLDTGADDTVLEEMNLPGKWKPKIIVGIGGFTKVRQYDHVQIEICGHKVIGAVLIGPTPANIIGRNLLTQLGCTL
NF

Differences from Consensus B:

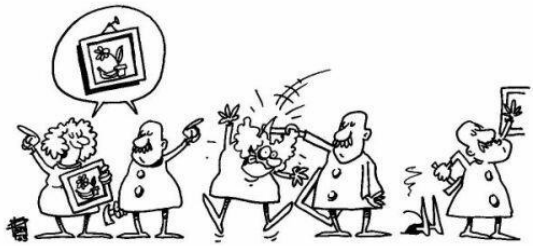
L10I, G17R, K20I, E35D, N37S, M46I, I62V, L63P, A71I, G73S, I84V, L90M, I93L

Direnç Analizinde İzlenecek Ana Yollar

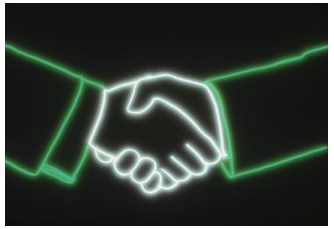
Kurala Dayalı Sistemler

	L	G	K	L		V	L	E		M
Atazanavir +/- ritonavir[s]	10	16	20	24		32	33	34		36
	I	E	R	I		I	I	Q		I
	F		M				F			L
	V		I				V			V
	C		T							
			V							

Uzman Grup



Tartışma

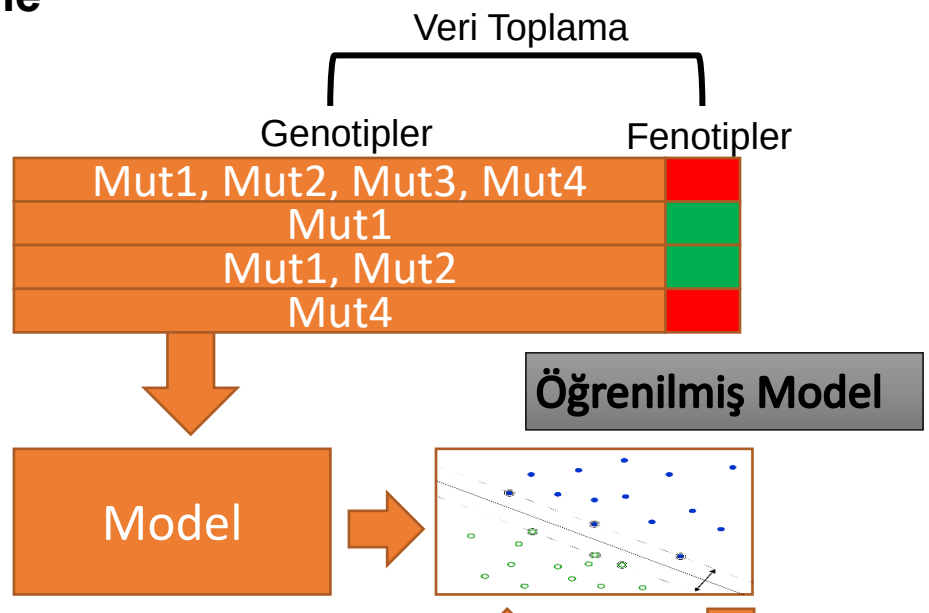


Uzlaşı

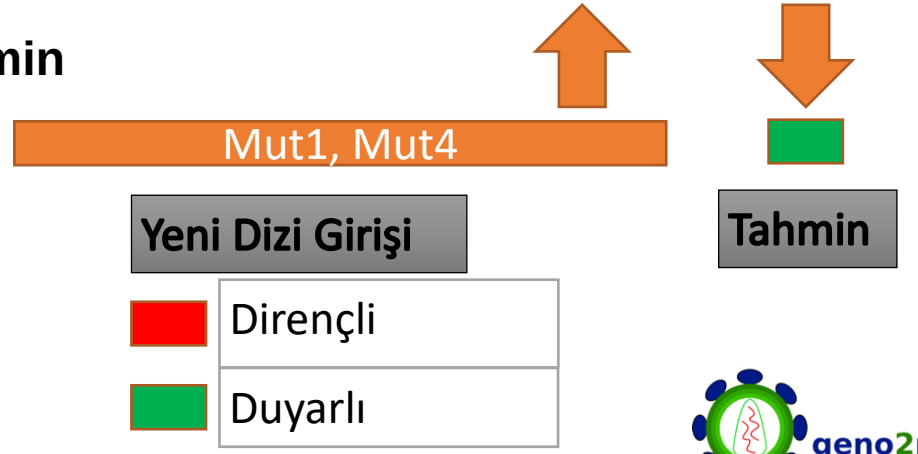
STANFORD UNIVERSITY
HIV DRUG RESISTANCE DATABASE
A curated public database designed to represent, store, and analyze the divergent forms of data underlying HIV drug resistance.

Yapay Zekaya Dayalı – Makine Öğrenmesine Dayalı(Zahiri)

1. Öğrenme



2. Tahmin



Matthias Döring
Max Planck Institute for Informatics,**ESCV Workshop "Techniques in Clinical Virology"**
December 4, 2015

geno2pheno [resistance]

HIV-Db mutasyon sınıflamaları

PR mutasyonları:

- Majör DRM
- Aksesuar DRM
- Diğer

RT Mutasyonları:

- NRTI DRM
- NNRTI DRM
- Diğer

IN mutasyonları:

- Majör DRM
- Aksesuar DRM
- Diğer

- None: Yukardaki sınıflamalara girmeyenler

Primer ya da Majör Mutasyonlar: Tek başlarına olsalar bile duyarlılığı doğrudan azaltırlar, M184 mutasyonları gibi

Aksesuar (Secondary, minör) Muutasyonlar: Virusun fitness'ını düzeltir. Duyarlılığı azaltır.

İmza (Signature) Mutasyonları: Özel ilaç için ilişkili mutasyonlar **(M184V ➘ Lamivudin, Emtircitabin, I50L➘atazanavir Direnci)**

Mutasyon Skorları

- (1) **0–9: Duyarlı**
- (2) **10–14: Olası düşük düzey direnç** → Büyük olasılıkla tam duyarlı, fakat değerlendirilen dizide daha önce ARV ile karşılaşmış olduğuna işaret eden mutasyonlar söz konusu
- (3) **15-30: Düşük düzeyde direnç**: Suboptimal virolojik yanıt
- (4) **30-59 (ortya düzeyde direnç):** İlaç illa kullanılmak isteniyorsa, ilacın genetik bariyerinin yüksek olması ya da fazla ilaç seçeneğinin bulunmaması gerekir.
- (5) **60 ve üzeri**: Yüksek düzeyde direnç.

Skorlama;

- Tek tek saptanan mutasyonların etkisi ve bunların kombine etkileri göz önünde bulundurulur.

L74I/V skoru 30,

M184I/V'nin skoru 15

L74I/V + M184I/V skoru 15

30 (L74I/V) + 15 (M184I/V) + 15 (L74I/V + M184/V) = 60

Değerlendirme

Mutation Scoring

PR	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	NFV	SQV/r	TPV/r
T74S	0	0	0	0	0	15	0	0
Total:	0	0	0	0	0	15	0	0

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF	EFV	ETR	NVP	RPV
M184V	60	15	-10	-10	10	60	-10	-	-	-	-
Total:	60	15	-10	-10	10	60	-10	0	0	0	0

0 -9 DUYARLI,
10 -14 OLASI DÜŞÜK DÜZEY DİRENÇ,
15-29 DÜŞÜK DÜZEY DİRENÇ,
30-59 ORTA DÜZEYDE DİRENÇ
>60 YÜKSEK DÜZEYDE DİRENÇ

MARVEL on RT mutations at position 184

HIVdb Algorithm: Comments & Scores

- M184V/I cause high-level 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. In combination with K101E or E138K, M184I synergistically reduces RPV susceptibility.

Mutation	3TC	FTC	ABC	AZT	D4T	DDI	TDF
M184I	60	60	15	-10	-10	10	-10
M184V	60	60	15	-10	-10	10	-10

Footnote: Mutation scores on the left are derived from published literature linking mutations and ARVs (the complete details can be found in the HIVdb Release Notes).

Mutation Scoring

PR	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	NFV	SQV/r	TPV/r
T74S	0	0	0	0	0	15	0	0
Total:	0	0	0	0	0	15	0	0

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF	EFV	ETR	NVP	RPV
M184V	60	15	-10	-10	10	60	-10	-	-	-	-
Total:	60	15	-10	-10	10	60	-10	0	0	0	0

Mutation Patterns	Number of Sequences	AZT fold$_n$	TDF fold$_n$	ABC fold$_n$	3TC fold$_n$
184V	7022	0.5_{124}	0.5_{63}	3.1_{125}	200_{175}
67N,70R,184V	1143	3.7_{32}	1.2_{26}	4.5_{31}	200_{50}
41L,184V,210W,215Y	821	18_{51}	1.6_{38}	6.5_{48}	200_{69}
41L,184V,215Y	798	6.0_{41}	1.1_{24}	5.1_{41}	200_{55}
41L,67N,184V,210W,215Y	795	30_{53}	1.6_{41}	6.5_{46}	200_{72}
70R,184V	697	0.8_{14}	0.7_{7}	3.4_{15}	200_{21}
67N,70R,184V,215F	380	7.7_{7}	1.0_{4}	5.5_{7}	200_{8}
65R,184V	376	0.4_{16}	1.2_{16}	8.4_{16}	200_{27}
74V,184V	371	0.3_{9}	0.4_{7}	5.2_{9}	200_{13}
41L,67N,69D,184V,210W,215Y	359	43_{28}	1.8_{19}	7.8_{26}	200_{38}

Footnote: Mutation patterns were defined by the presence or absence of major NRTI drug resistance mutations ; Sequences containing a mixture at a major drug resistance positions were excluded; For the cutoffs defined by PhenoSense, open the sample report form provided on this page; The full list of all mutation patterns are also available here.

Fold Resistance

AZT	3	10
D4T	1.5	2
TDF	1.5	4
ABC	3	6
DDI	1.5	2
3TC	3	20

Special Contribution

2022 Update of the Drug Resistance Mutations in HIV-1

Annemarie M. Wensing, MD, PhD; Vincent Calvez, MD, PhD; Francesca Ceccherini-Silberstein, PhD; Charlotte Charpentier, PharmD, PhD; Huldrych F. Günthard, MD; Roger Paredes, MD, PhD; Robert W. Shafer, MD; Douglas D. Richman, MD

MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH RESISTANCE TO REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)[1]

69 Insertion Complex[2] (affects all nRTIs currently approved by the US FDA)

	M	A	▼	K	L	T	K
Multi-nRTI Resistance	41	62	69	70	210	215	219
	L	V	Insert	R	W	Y	Q
						F	E

151 Complex[3] (affects all nRTIs currently approved by the US FDA except tenofovir)

	A	V	F	F	Q
Multi-nRTI Resistance	62	75	77	116	151
	V	I	L	Y	M

Thymidine Analogue-Associated Mutations[4,5] (TAMs; affect all nRTIs currently approved by the US FDA other than emtricitabine and lamivudine)

	M	K	L	T	K
Multi-nRTI Resistance	41	70	210	215	219
	L	R	W	Y	Q
				F	E

	K	L	Y	M
Abacavir[1,6]	65	74	115	184
	R	V	F	V
	E			
	N			

	K	M
Emtricitabine/ Lamivudine	65	184
	R	V
	E	I
	N	

	K	K
Tenofovir[1,7]	65	70
	R	E
	E	
	N	

	M	D	K	L	T	K
Zidovudine[4,5,8,9]	41	67	70	210	215	219
	L	N	R	W	Y	Q
					F	E

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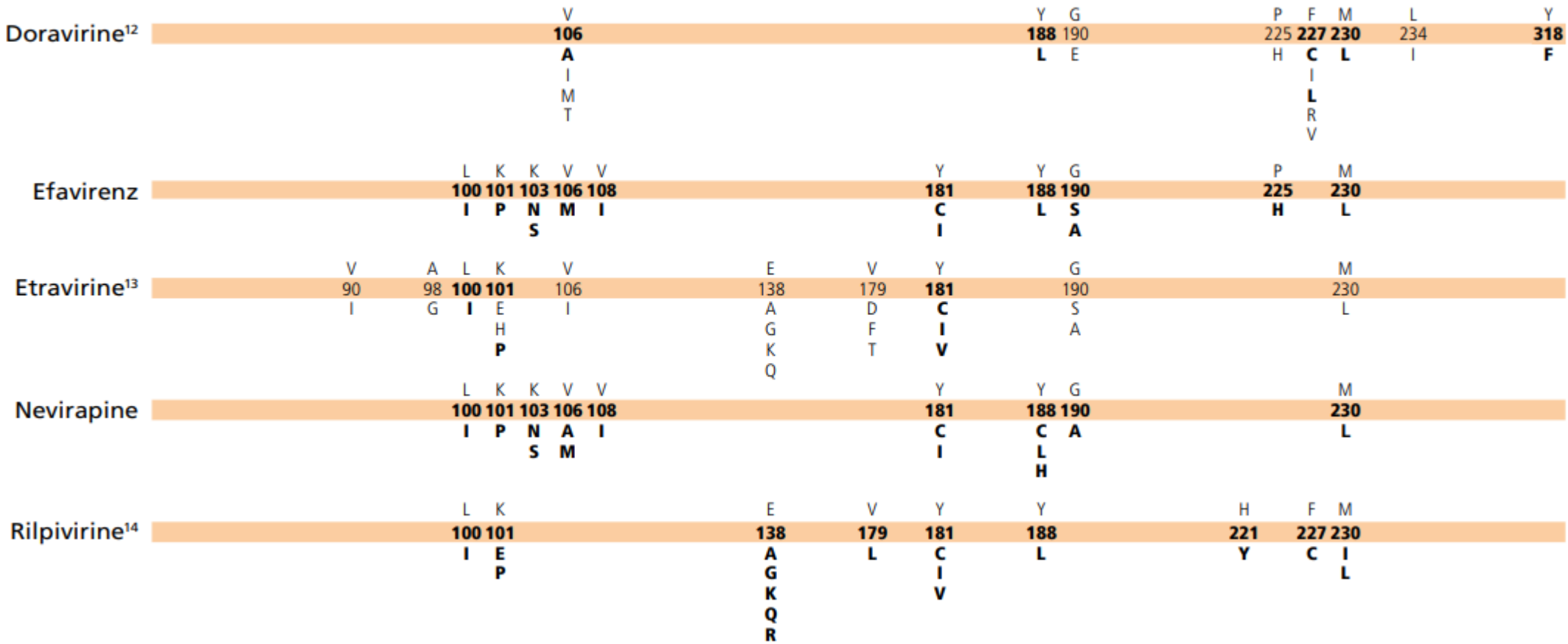
Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)[1,11]



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MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS (PIs)[15,16,17]

Atazanavir +/- ritonavir[18]

Consensus	L	K	L	V	L	M	G	I	F	I	G	V	I	I	N	L
Position	10	20	24	**32**	33	46	48	**50**	53	**54**	73	**82**	**84**	85	**88**	90
Mutations	F	T	I	**I**	F	I, L	V	**L**	L, Y	L, **V**, M, T, A, S	C, S, T, A	**A**, T, F, L, M, S	**V**	V	**S**	M

Darunavir/ritonavir[19]

Consensus	V	V	L	I	I	I	T	L	I	L
Position	11	32	33	**47**	**50**	**54**	74	**76**	**84**	89
Mutations	I	I	F	**V**	**V**	**M**, **L**	P	**V**	**V**	V

Lopinavir/ritonavir[20]

Consensus	L	K	L	V	L	M	I	I	F	I	A	G	L	V	I	L
Position	10	20	24	**32**	33	46	**47**	**50**	53	**54**	71	73	**76**	**82**	**84**	90
Mutations	F, I, R, V	M, R	I	**I**	F	I, L	**V**, **A**	**V**	L	**V**, **L**, A, **M**, T, S	V, T	S	**V**	**A**, **F**, **T**, **S**	**V**	M

Tipranavir/ritonavir

Consensus	L	L	M	K	M	I	I	Q	H	T	V	N	I	L
Position	10	33	36	43	46	**47**	54	**58**	69	**74**	**82**	**83**	**84**	89
Mutations	V	F	I, L, V	T	L	**V**	A, M, V	**E**	K, R	**P**	**L**, **T**	**D**	**V**	I, M, V

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MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE STRAND TRANSFER INHIBITORS[25]

Drug	66	74	92	97	118	121	138	140	143	147	148	153	155	263
Bictegravir[26]					G 118 R		E 138 A K T	G 140 A C R S			Q 148 H K R	S 153 F Y		R **263** **K**
Cabotegravir[27]	T 66 K			T 97 A	G **118** **R**		E 138 A K T	G **140** A C **R** S			Q **148** **H** **K** **R**	S 153 F Y	N **155** **H**	R **263** **K**
Dolutegravir[28]					G **118** **R**		E 138 A K T	G **140** A C **R** S			Q **148** **H** **K** **R**	S 153 F Y	N 155 H	R **263** **K**
Elvitegravir[29]	T **66** **I** A K		E **92** **Q** G	T 97 A		F **121** **Y**				S **147** **G**	Q **148** **H** **K** **R**		N **155** **H**	R **263** **K**
Raltegravir[30]		L 74 M	E 92 Q	T 97 A		F **121** **Y**	E 138 A K	G 140 A S	Y **143** **R** **H** **C**		Q **148** **H** **K** **R**		N **155** **H**	R **263** **K**

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MUTATIONS IN THE CAPSID GENE ASSOCIATED WITH RESISTANCE TO CAPSID INHIBITORS

	L	M	Q	K	N	A	T
Lenacapavir[31]	56	**66**	**67**	70	74	105	107
	I	**I**	**H**	N S R	D S	T	N

MUTATIONS IN THE ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS

	G	I	V	Q	Q	N	N
Enfuvirtide[23]	**36**	**37**	**38**	**39**	**40**	**42**	**43**
	D **S**	**V**	**A** **M** **E**	**R**	**H**	**T**	**D**
Maraviroc[24]	See User Note						

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HIV DRUG RESISTANCE DATABASE
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HIV-1 Sequence Analysis Report

Generated at 10.02.2023 15:29:37

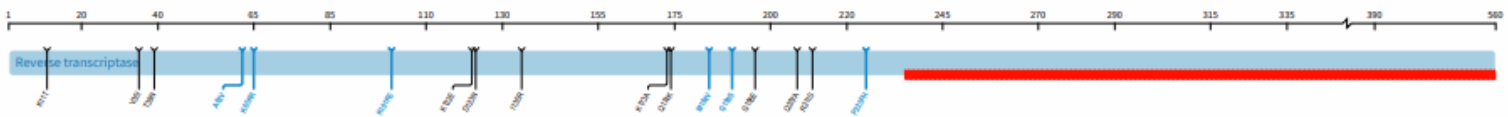
Sequence summary

Sequence includes PR:	codons 10 - 99 (missing: 1-9)
Sequence includes RT:	codons 1 - 234 (missing: 235-560)
Subtype:	⊞ A (3.29%)
PR SDRMs:	None
RT SDRMs:	K65R, K101E, M184V, G190S, P225H

Sequence quality assessment

Protease (PR)

Reverse transcriptase (RT)



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HIV-1 Sequence Analysis Report

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Drug resistance interpretation: PR — HIVDB 9.4 (2022-12-07)

PI Major Mutations:	None
PI Accessory Mutations:	None
PR Other Mutations:	L10V • I13V • G16E • E35D • M36I • R41K • L63S • H69K • L89M

Protease Inhibitors	
atazanavir/r (ATV/r)	Susceptible
darunavir/r (DRV/r)	Susceptible
fosamprenavir/r (FPV/r)	Susceptible
indinavir/r (IDV/r)	Susceptible
lopinavir/r (LPV/r)	Susceptible
nelfinavir (NFV)	Susceptible
saquinavir/r (SQV/r)	Susceptible
tipranavir/r (TPV/r)	Susceptible

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HIV-1 Sequence Analysis Report

Generated at 10.02.2023 15:29:37

Drug resistance interpretation: RT — HIVDB 9.4 (2022-12-07)

NRTI Mutations: **A62V** · **K65KR** · **M184V**
NNRTI Mutations: **K101KE** · **G190S** · **P225PH**
RT Other Mutations: K11T · V35I · T39N · K122E · D123N · I135R · K173A · Q174K · G196E · Q207A · R211S

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

HIV-1 Sequence Analysis Report

Generated at 10.02.2023 15:29:37

RT comments

NRTI

- **A62V** is an accessory mutation that often occurs in combination with the multi-NRTI resistance mutations K65R or Q151M. **A62V** is widespread in subtype A viruses in former Soviet Union countries but A62 is otherwise non-polymorphic.
- **K65R** confers intermediate reductions in susceptibility to TDF, ABC, and 3TC/FTC. It increases AZT susceptibility. In NRTI-experienced, INSTI-naive patients with **K65R**, TDF+3TC+DTG is usually highly effective and more effective than AZT/3TC/DTG. However, in patients receiving TDF+3TC+DTG, there is a risk of emergent DTG resistance that does not arise in NRTI-naive patients receiving TDF+3TC+DTG.
- **M184V/I** cause high-level in vitro resistance to 3TC and FTC and low/intermediate resistance to ABC (3-fold reduced susceptibility). **M184V/I** are not contraindications to continued treatment with 3TC or FTC because they increase susceptibility to AZT and TDF and are associated with clinically significant reductions in HIV-1 replication.

NNRTI

- **K101E** is a non-polymorphic accessory mutation that confers intermediate resistance to NVP and RPV and low-level reductions in susceptibility to EFV, ETR, and DOR when it occurs with other NNRTI-resistance mutations.
- **G190S** is a non-polymorphic mutation that confers high-level resistance to NVP and EFV. It may also be associated low-levels reductions in DOR susceptibility. It does not appear to be selected by ETR or RPV or to reduce their in vitro susceptibility.
- **P225H** is a non-polymorphic EFV-selected mutation that usually occurs in combination with K103N. The combination of **P225H** and K103N synergistically reduces NVP, EFV and DOR susceptibility.

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Rule	ABC	AZT	D4T	DDI	FTC	3TC	TDF
A62V	5	5	5	5	0	0	5
K65KR	45	-10	60	60	30	30	50
M184V	15	-10	-10	10	60	60	-10
A62V + K65KR	0	0	0	0	0	0	5
Total	65	-15	55	75	90	90	50

HIV-1 Sequence Analysis Report

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NRTI

- **A62V** is an accessory mutation that often occurs in combination with the multi-NRTI resistance mutations K65R or Q151M. **A62V** is widespread in subtype A viruses in former Soviet Union countries but A62 is otherwise non-polymorphic.
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- **M184V/I** cause high-level in vitro resistance to 3TC and FTC and low/intermediate resistance to ABC (3-fold reduced susceptibility). **M184V/I** are not contraindications to continued treatment with 3TC or FTC because they increase susceptibility to AZT and TDF and are associated with clinically significant reductions in HIV-1 replication.

NNRTI

- **K101E** is a non-polymorphic accessory mutation that confers intermediate resistance to NVP and RPV and low-level reductions in susceptibility to EFV, ETR, and DOR when it occurs with other NNRTI-resistance mutations.
- **G190S** is a non-polymorphic mutation that confers high-level resistance to NVP and EFV. It may also be associated low-levels reductions in DOR susceptibility. It does not appear to be selected by ETR or RPV or to reduce their in vitro susceptibility.
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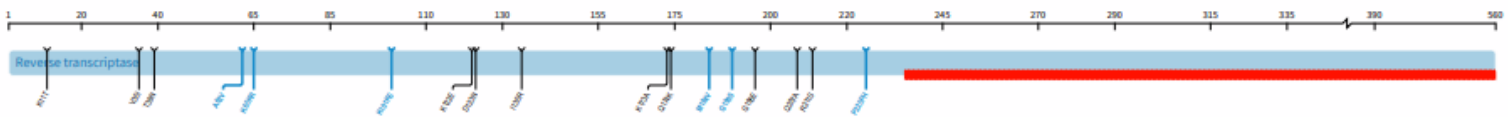

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K65KR	45	-10	60	60	30	30	50
M184V	15	-10	-10	10	60	60	-10
A62V + K65KR	0	0	0	0	0	0	5
Total	65	-15	55	75	90	90	50

THE WORLD HEALTH ORGANIZATION 2009 LIST OF MUTATIONS

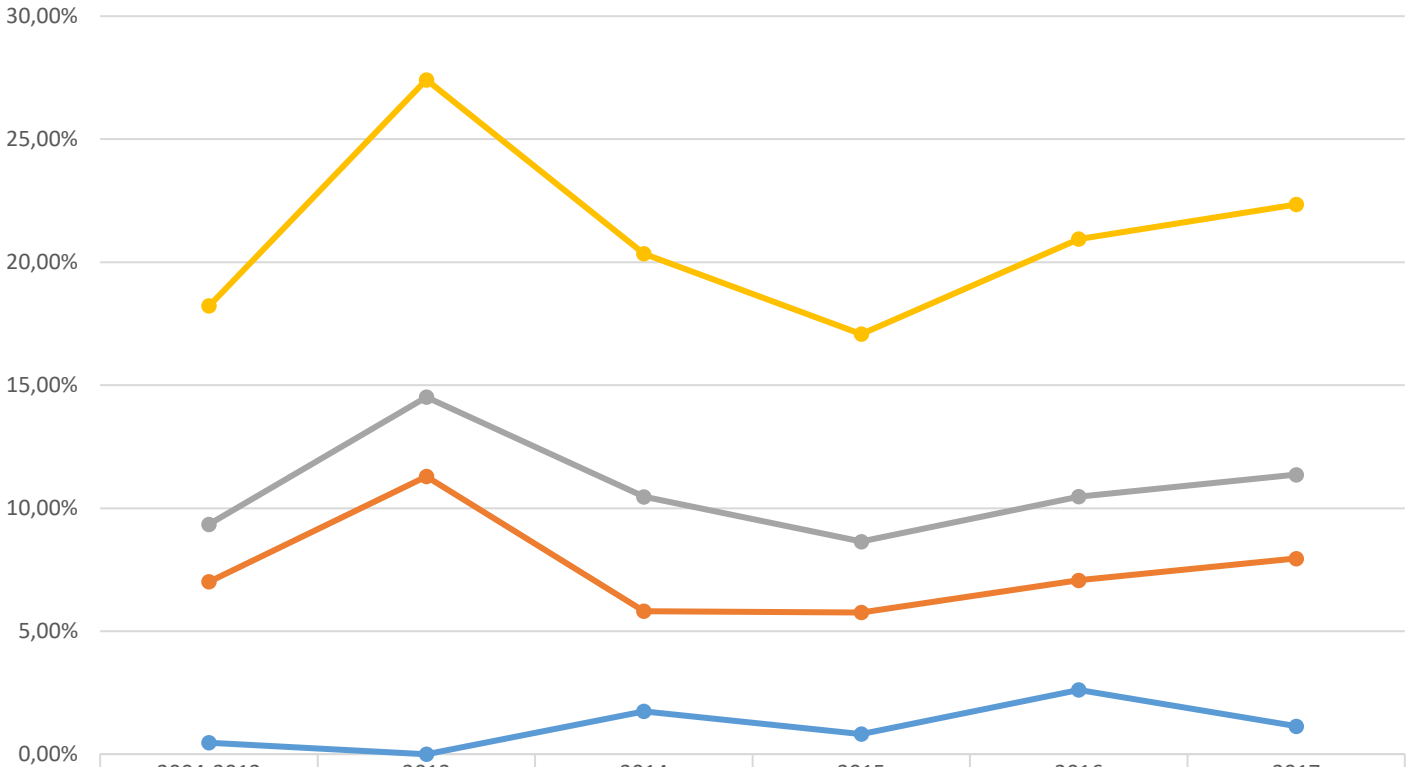
For Surveillance of Transmitted Drug Resistant HIV Strains

NRTI	
M41	L
K65	R
D67	N, G, E
T69	D, Ins
K70	R, E
L74	V, I
V75	M, T, A, S
F77	L
Y115	F
F116	Y
Q151	M
M184	V, I
L210	W
T215	Y, F, I, S, C, D, V, E
K219	Q, E, N, R

NNRTI	
L100	I
K101	E, P
K103	N, S
V106	M, A
V179	F
Y181	C, I, V
Y188	L, H, C
G190	A, S, E
P225	H
M230	L

PI	
L23	I
L24	I
D30	N
V32	I
M46	I, L
I47	V, A
G48	V, M
I50	V, L
F53	L, Y
I54	V, L, M, A, T, S
G73	S, T, C, A
L76	V
V82	A, T, F, S, C, M, L
N83	D
I84	V, A, C
I85	V
N88	D, S
L90	M

Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance: 2004-2017 (total 1580)



	2004-2012	2013	2014	2015	2016	2017
Herhangi Bir	8,88%	12,90%	9,88%	8,44%	10,47%	10,98%
NNRTI	2,34%	3,23%	4,65%	2,88%	3,40%	3,41%
NRTI	6,54%	11,29%	4,07%	4,94%	4,45%	6,82%
PI	0,47%	0,00%	1,74%	0,82%	2,62%	1,14%

Based on Bennett DE et all. Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance: 2009 Update.DOI: 10.1371/journal.pone.0004724

Ülkemizde Genel Durum

	Korten ve ark.	Sayan ve ark.	Kuskucu ve ark.		Sertöz ve ark.
n	273	1306	590		483
Dönem	2011	2010-2015	2004-2010	2011-2015	2008-2016
NRTI	6,90%	8,10%	5,92%	5,23%	3,0%
NNRTI	0,00%	3,30%	3,55%	4,04%	10,3% (5,0% E138A)
PI	1,70%	2,30%	0,60%	1,60%	1,8 %
Any	8,60%	10,10%	10,00%		15,0%

RESEARCH ARTICLE

Integrase Strand Transfer Inhibitor (INSTI) Genotypic Resistance Analysis in Treatment-nNaive, INSTI Free Antiretroviral-Experienced and INSTI-Experienced Turkish Patients Infected with HIV-1

Murat Sayan[1,2,*], Figen Sarigul Yildirim[3], Sila Akhan[4], Ilkay Karaoglan[5] and Halis Akalin[6]

Abstract: ***Background and Objective*:** Integrase strand transfer inhibitors (INSTIs) are currently the standard of practice for first-line HIV therapy for most patients. We evaluated the mutations associated with INSTI resistance in naive HIV-1 infected patients and treated them with antiretrovirals (ART).

***Methods*:** The study, conducted in the 2018 - 2020 period, included 50 ART-naïve patients, 69 INSTI free ART-experienced patients, and 82 INSTI-experienced patients. INSTI resistance mutations were interpreted using the Stanford University HIVdb Program algorithm.

***Results*:** INSTI resistance was not detected in ART naïve patients. At least one INSTI resistance mutation was detected in 10% of the INSTI-free patients and 29% of the INSTI-treated patients. Major INSTI-mutations E138K, Y143R, S147G, Q148R, N155H, and E157Q were found in raltegravir. Additional mutations, E92Q, E138K, G140A, S147G, and Q148R were found in elvitegravir; E192Q, E138K/T, G140A/S, S147G, Q148H/R, N155H, E157Q were found in dolutegravir (DTG) experienced patients. According to all drug classes, drug resistance mutation prevalences were determined at the rate of 60%, 46%, and 46% in the RAL, EVG, and DTG groups, respectively.

***Conclusion*:** Our findings provide data for treatment and resistance management of INSTIs and may provide feedback for INSTIs resistance surveillance consensus-building efforts. In viral rebound under INSTI treatment, INSTI-resistant mutations follow typical INSTI resistance pathways and high resistance rates. INSTI resistance genotypic analysis should be considered before any DTG-based regimes can be initiated in the future, and reduced DTG susceptibility should be carefully monitored and investigated.

ARTICLE HISTORY

Received: October 10, 2021
Revised: January 10, 2022
Accepted: January 28, 2022

DOI:
10.2174/1570162X20666220303104509

Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance: 2016-2017

2016

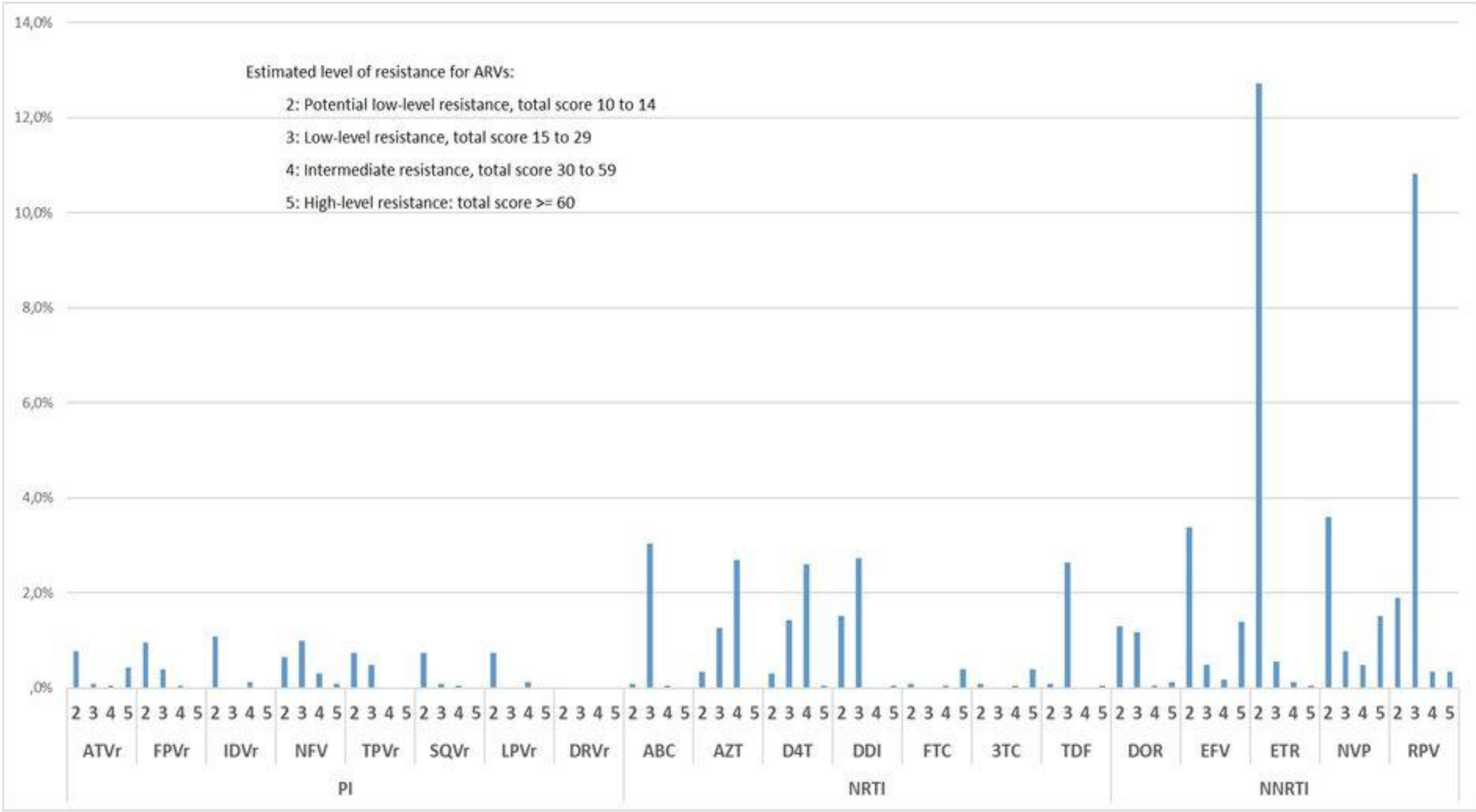
M46	I50	G73	V82	N83	M41	D67	M184	T215	K219	K101	K103	V106	G190
PI					NRTI					NNRTI			
I, L	V, L	S, T, C, A	A, T, F, S, C, M, L	D	L	N, G, E	V, I	Y, F, I, S, C, D, V, E	Q, E, N, R	E, P	N, S	M, A	A, S, E
2	4	1	2	1	10	1	1	13	1	5	5	1	3
0.524%	1.047%	0.262%	0.524%	0.262%	2.618%	0.262%	0.262%	3.403%	0.262%	1.309%	1.309%	0.262%	0.785%

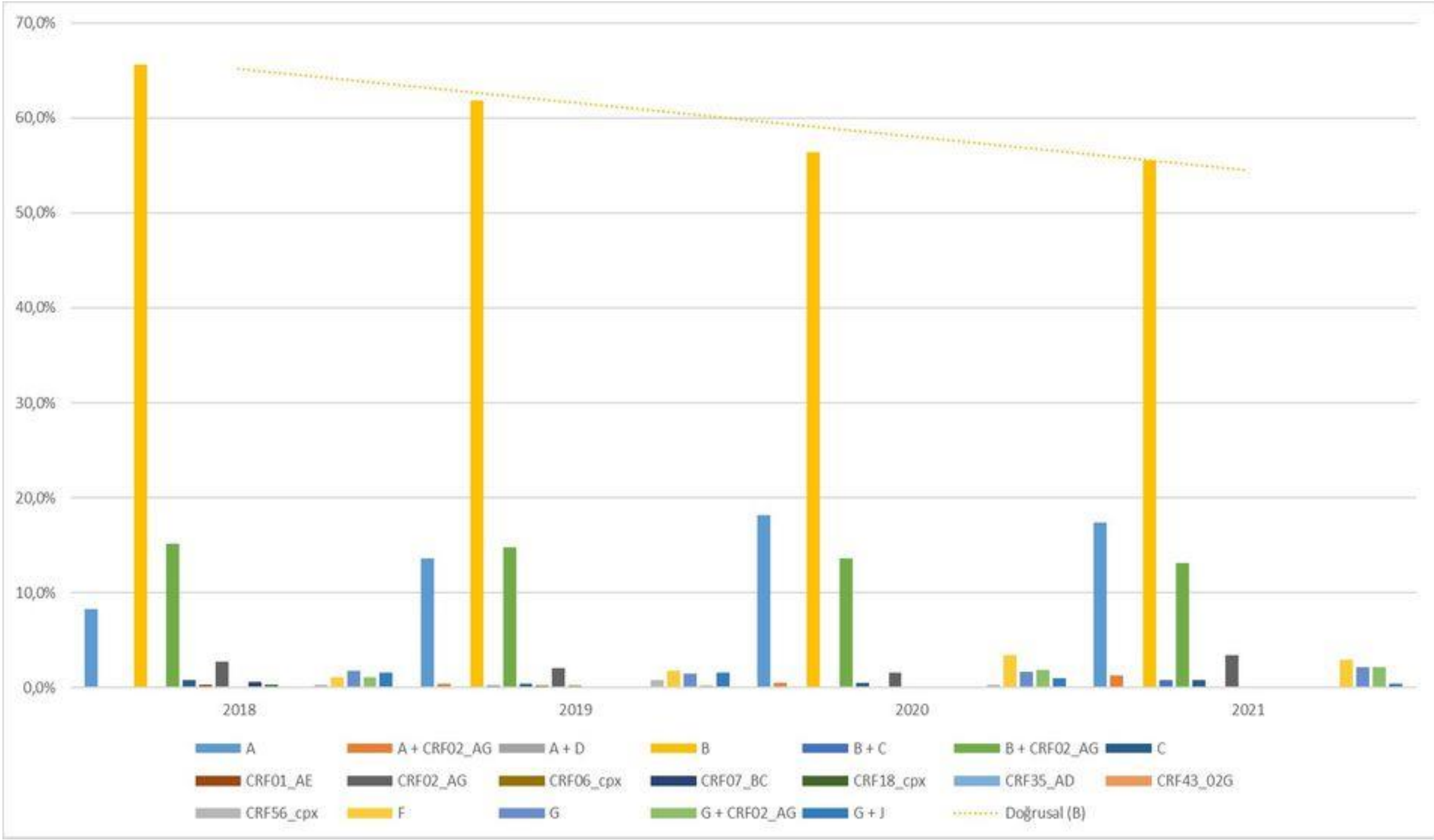
TAM1: M41L, L210W ve T215Y

TAM2: D67N, K70R, T215F ve K219Q/E

2017

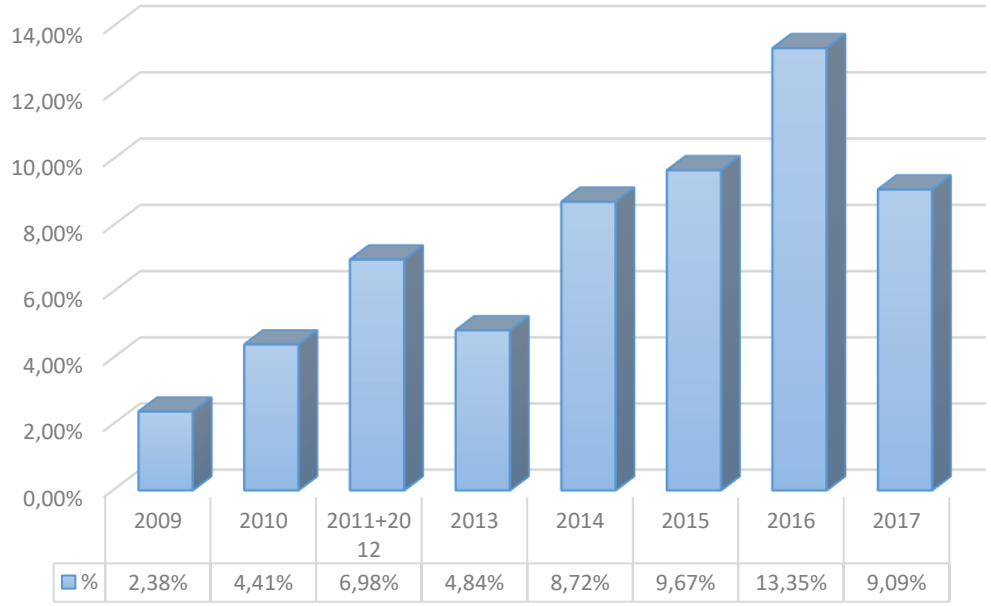
M46	I54	M41	D67	K70	M184	T215	K103	G190	P225
PI		NRTI					NNRTI		
I, L	V, L, M, A, T, S	L	N, G, E	R, E	V, I	Y, F, I, S, C, D, V, E	N, S	A, S, E	H
2	1	10	2	1	3	14	7	1	1
0.758%	0.379%	3.788%	0.758%	0.379%	1.136%	5.303%	2.652%	0.379%	0.379%

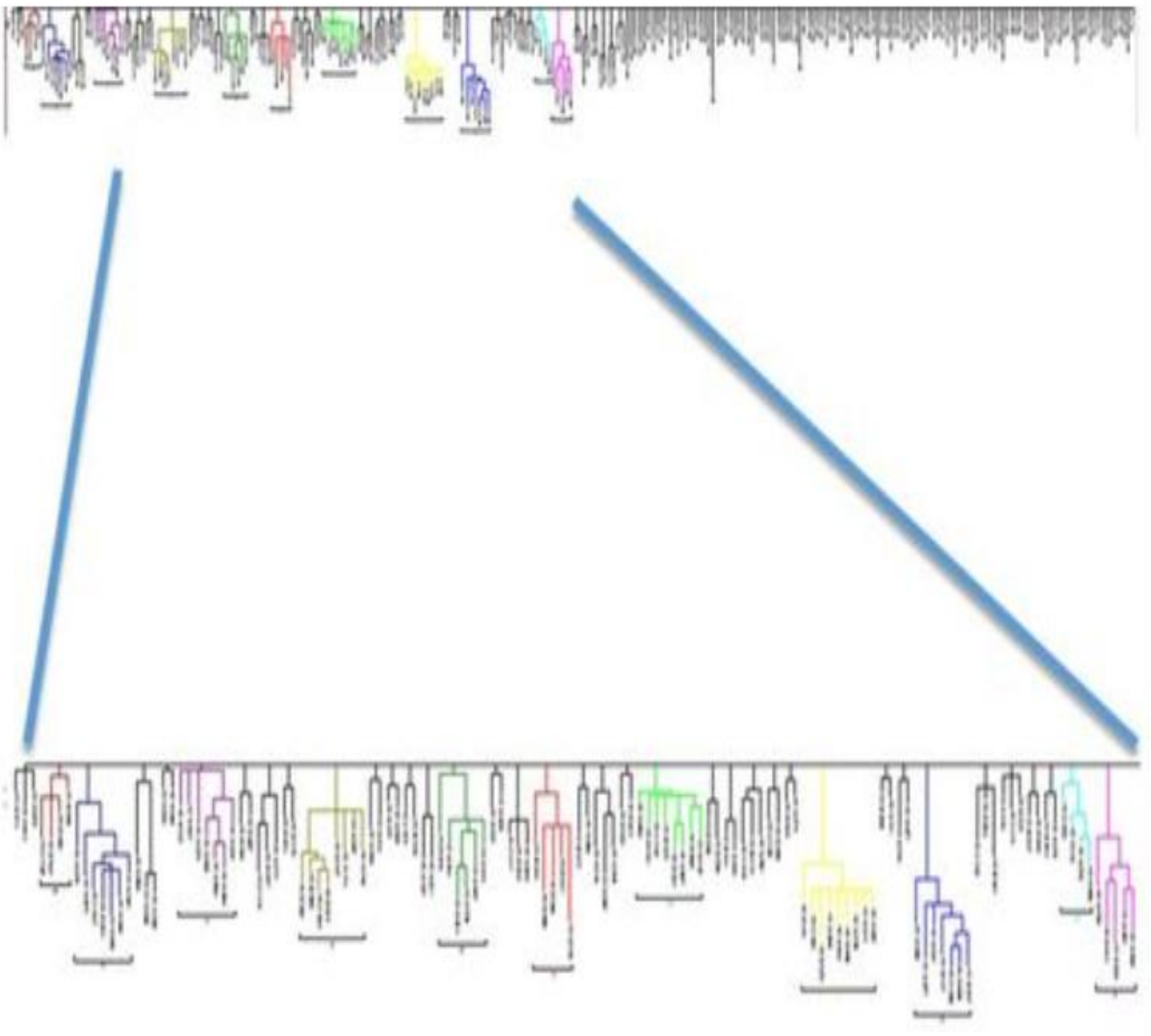

14,0%
12,0%
10,0%
8,0%
6,0%
4,0%
2,0%
,0%
Estimated level of resistance for ARVs:
2: Potential low-level resistance, total score 10 to 14
3: Low-level resistance, total score 15 to 29
4: Intermediate resistance, total score 30 to 59
5: High-level resistance: total score >= 60
2 3 4 5
ATVr
FPVr
IDVr
NFV
TPVr
SQVr
LPVr
DRVr
ABC
AZT
D4T
DDI
FTC
3TC
TDF
DOR
EFV
ETR
NVP
RPV
PI
NRTI
NNRTI


70,0%
60,0%
50,0%
40,0%
30,0%
20,0%
10,0%
0,0%
2018
2019
2020
2021
A
A + CRF02_AG
A + D
B
B + C
B + CRF02_AG
C
CRF01_AE
CRF02_AG
CRF06_cpx
CRF07_BC
CRF18_cpx
CRF35_AD
CRF43_02G
CRF56_cpx
F
G
G + CRF02_AG
G + J
Doğrusal (B)

E138 Mutasyonları

Yıl	n	E138AG	%
2009	42	1	2.38%
2010	68	3	4.41%
2011+2012	43	3	6.98%
2013	62	3	4.84%
2014	172	15	8.72%
2015	486	47	9.67%
2016	382	51	13.35%
2017	264	24	9.09%





Teşekkürler…