Direnç Testlerinin Yorumlanması ve Ülkemiz Verileri

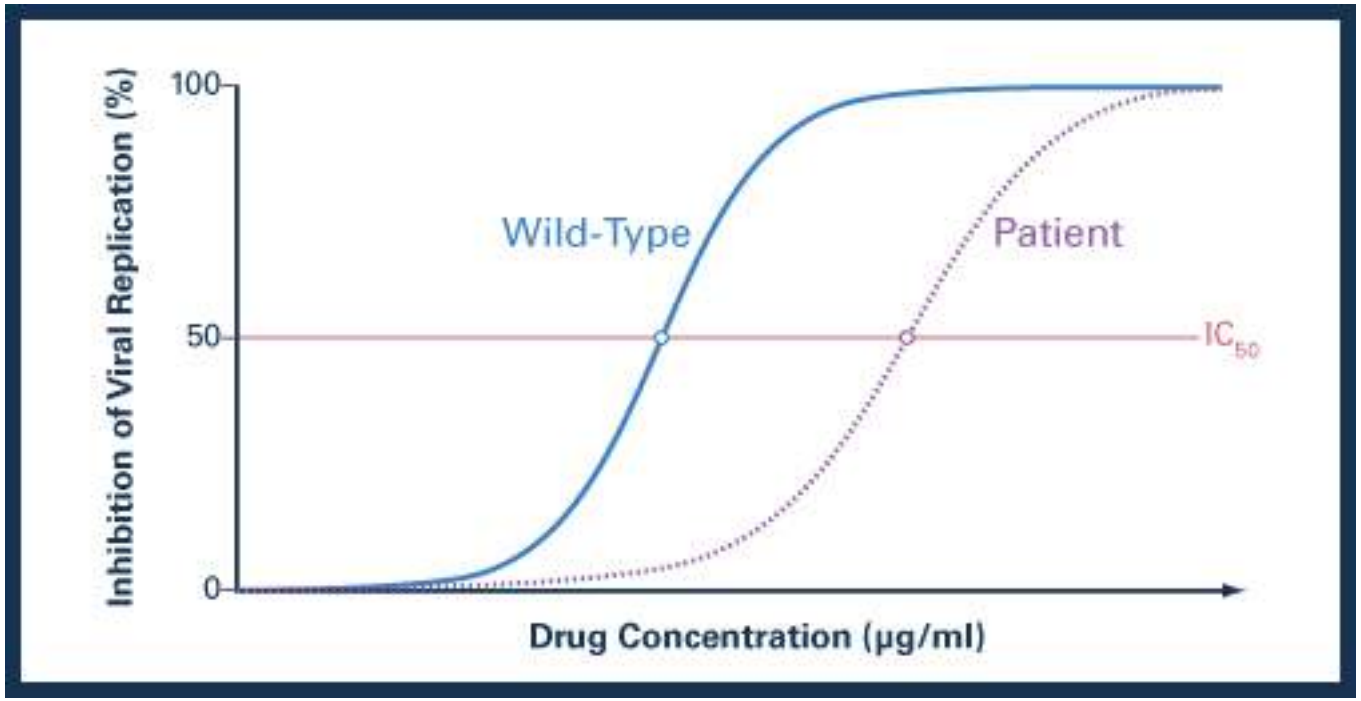
Prof. Dr. Kenan Midilli

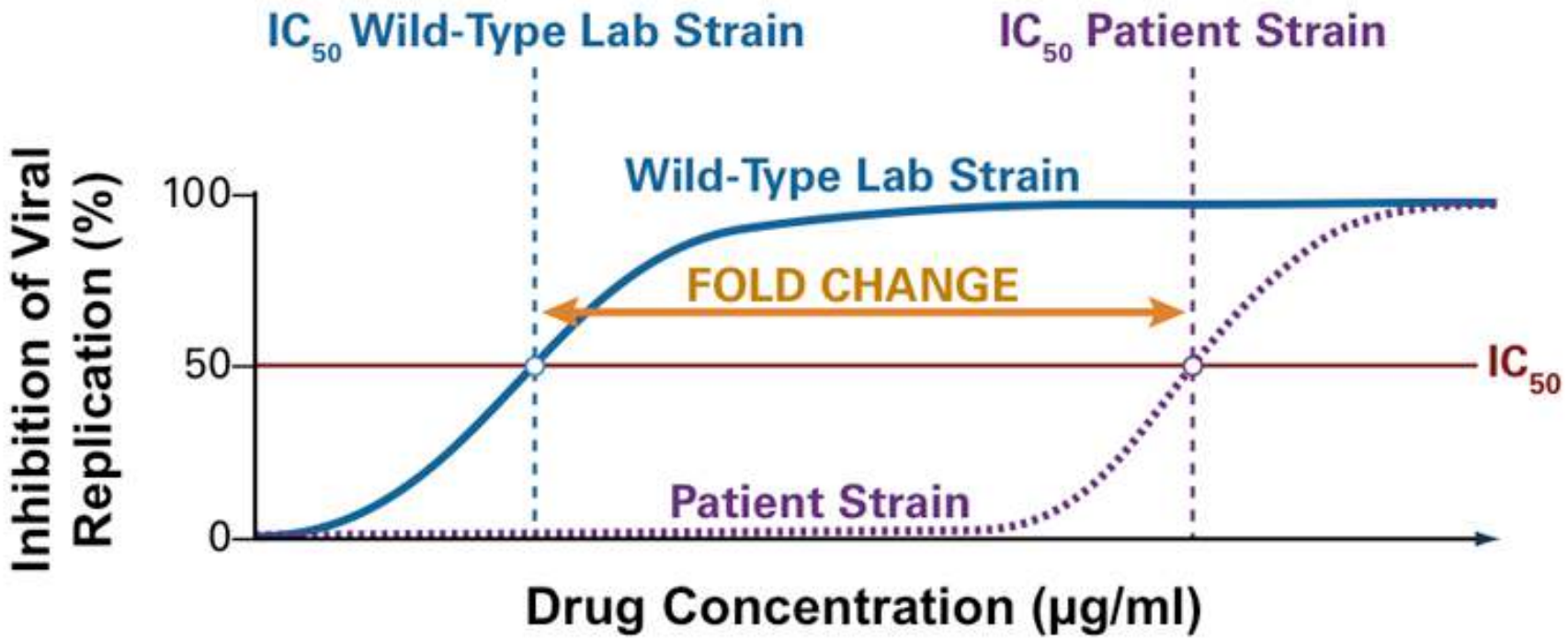
İ.Ü.

Cerrahpaşa Tıp Fakültesi

Tıbbi Mikrobiyoloji Anabilim Dalı

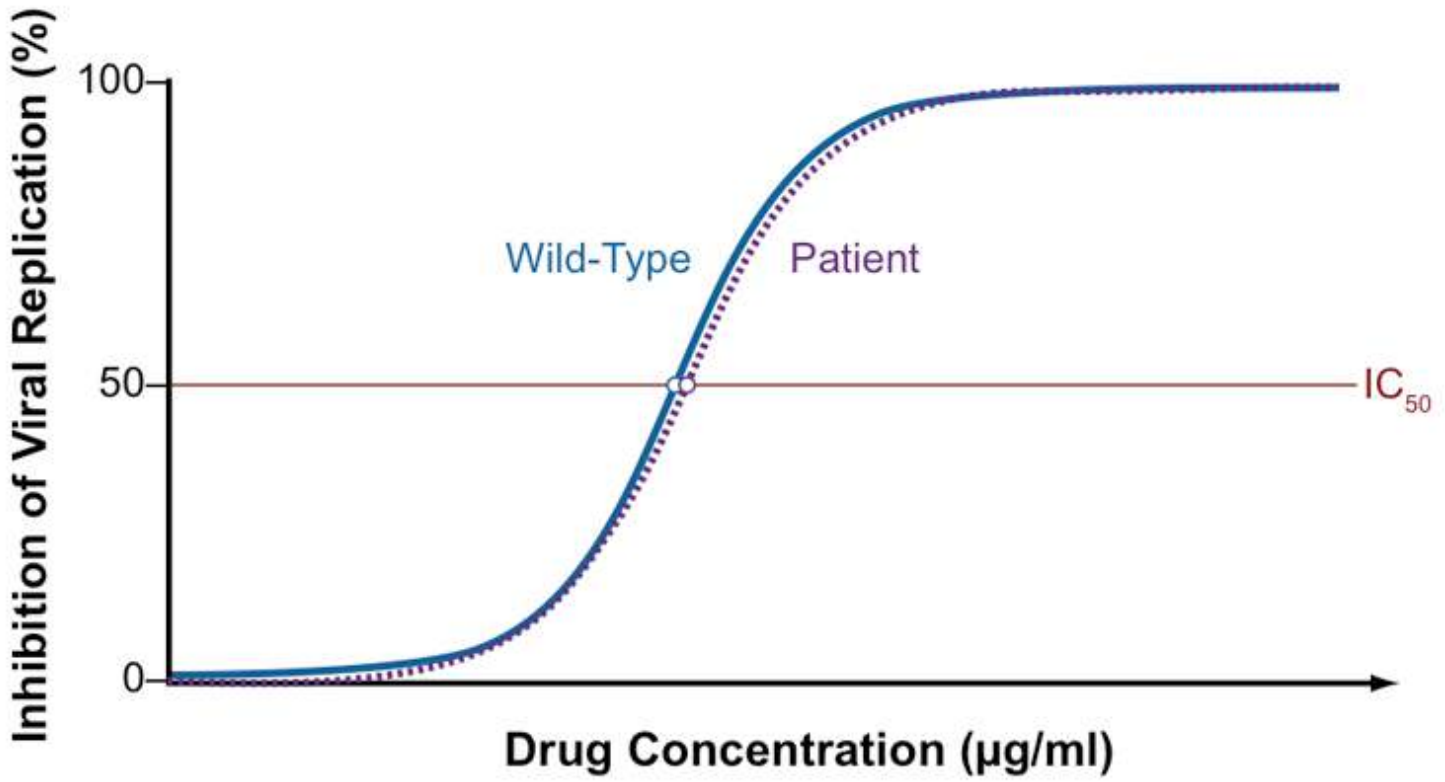
İnhibitör Konsantrasyon (IK_{50}; IK_{95})





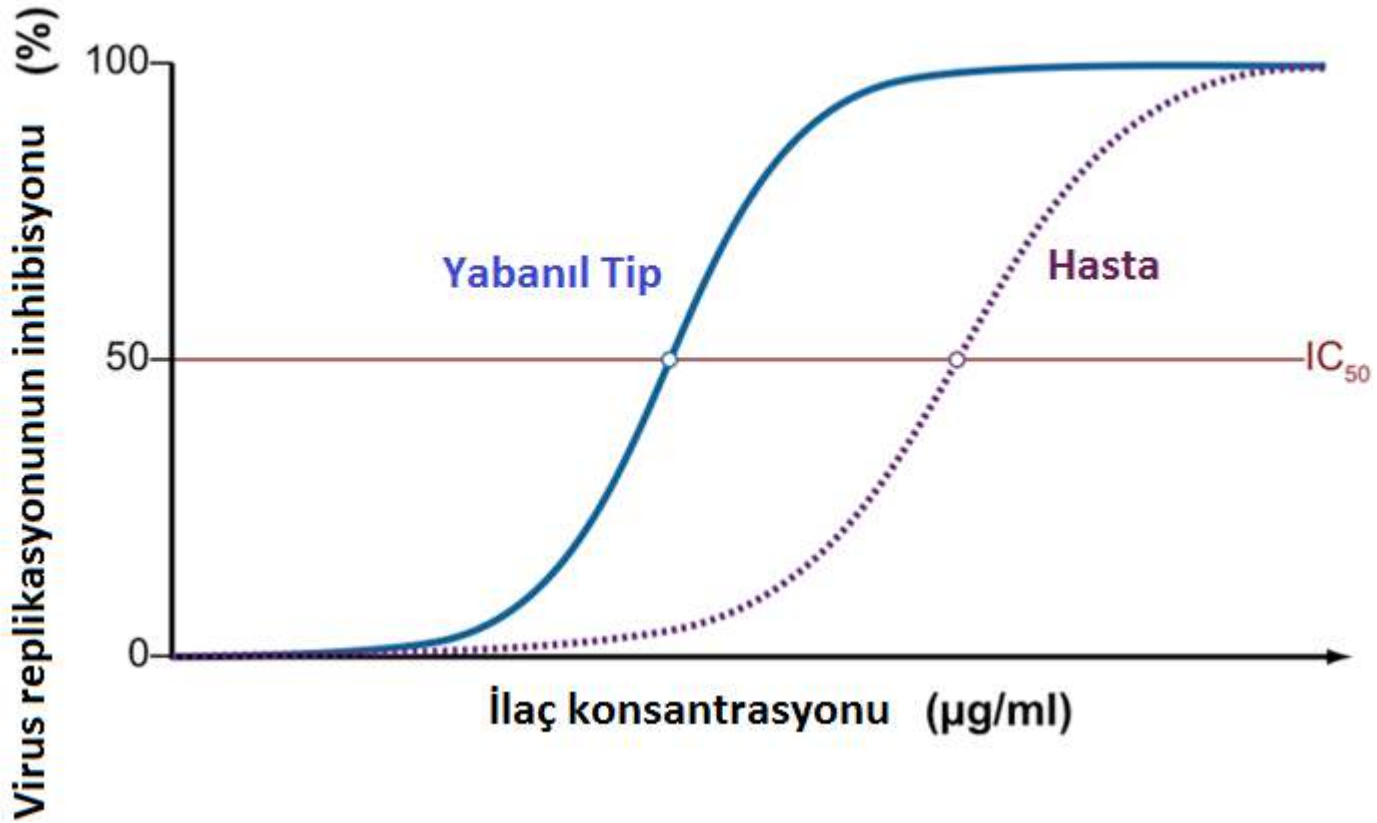
David H. Spach, MD. Features of Genotypic and Phenotypic Resistance Assays. HIV Web Study (www.hivwebstudy.org)

Duyarlı



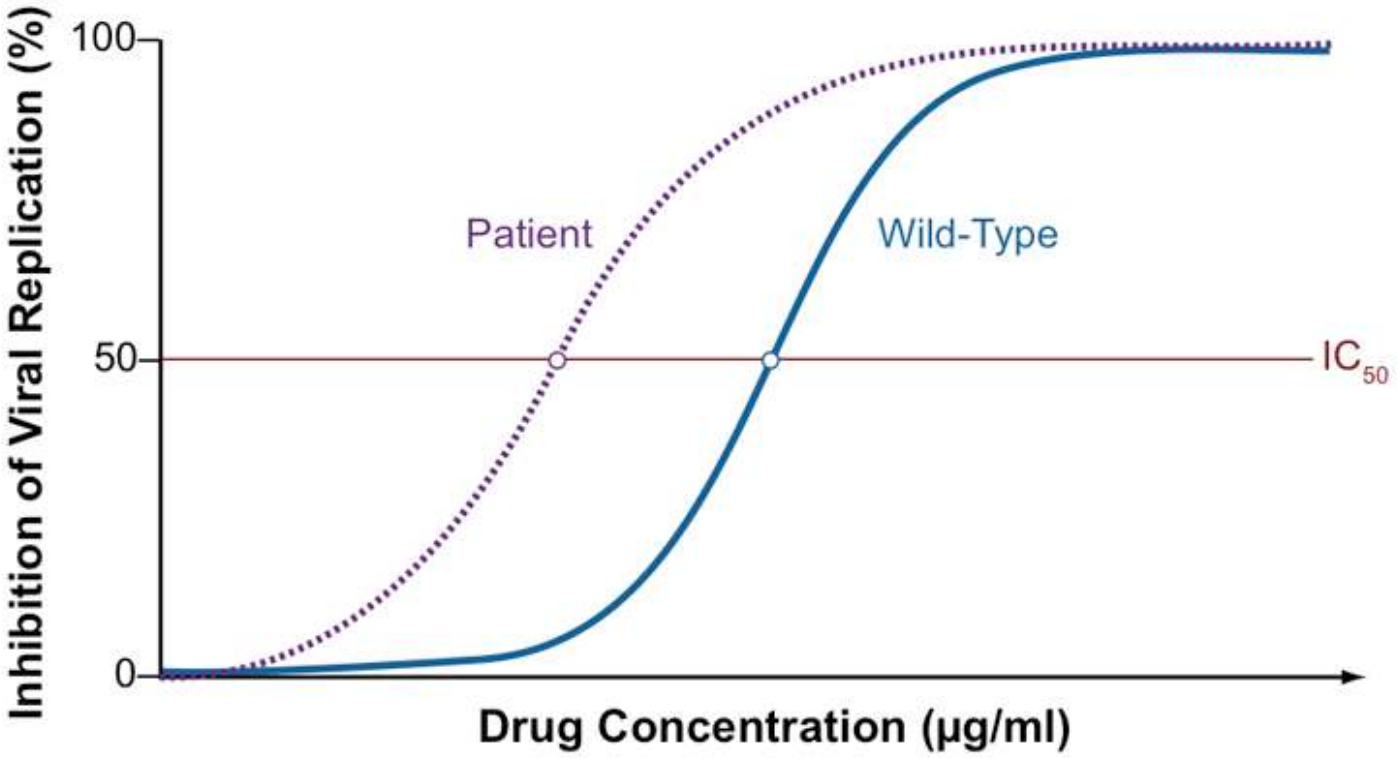
David H. Spach, MD. Features of Genotypic and Phenotypic Resistance Assays. HIV Web Study (www.hivwebstudy.org)

Azalmış Duyarlılık



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

Aşırı duyarlılık



Viruslarda Temel Direnç Mekanizmaları

- Random mutasyonların seçilmesi
- Rekombinasyon
- Reasortman

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

Direnç nasıl gelişir? Mutasyonlar

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

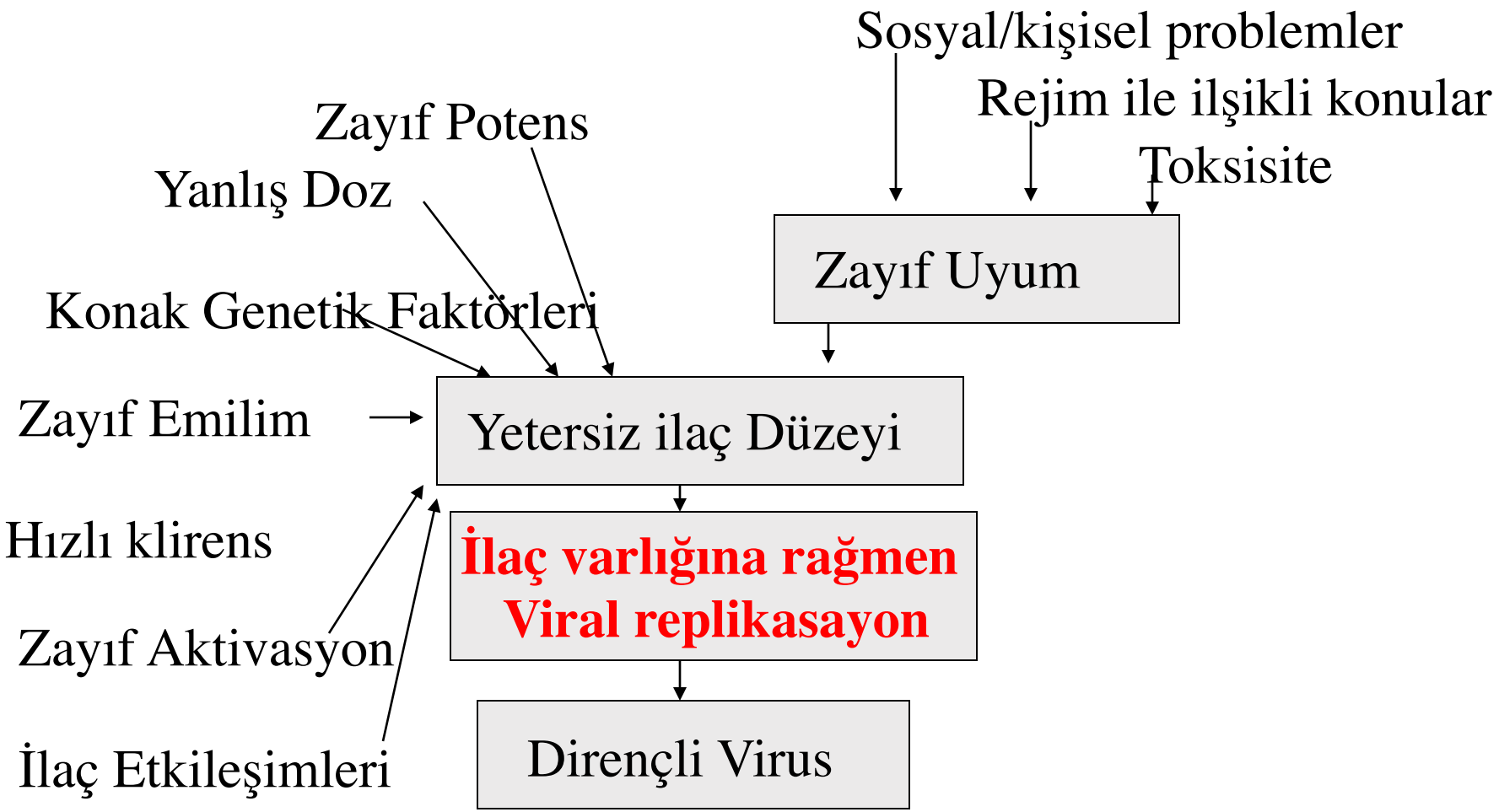
10^{-3}-10^{-4} Mutasyon/Replikasyon

3-4 Rekombinasyon / replikasyon

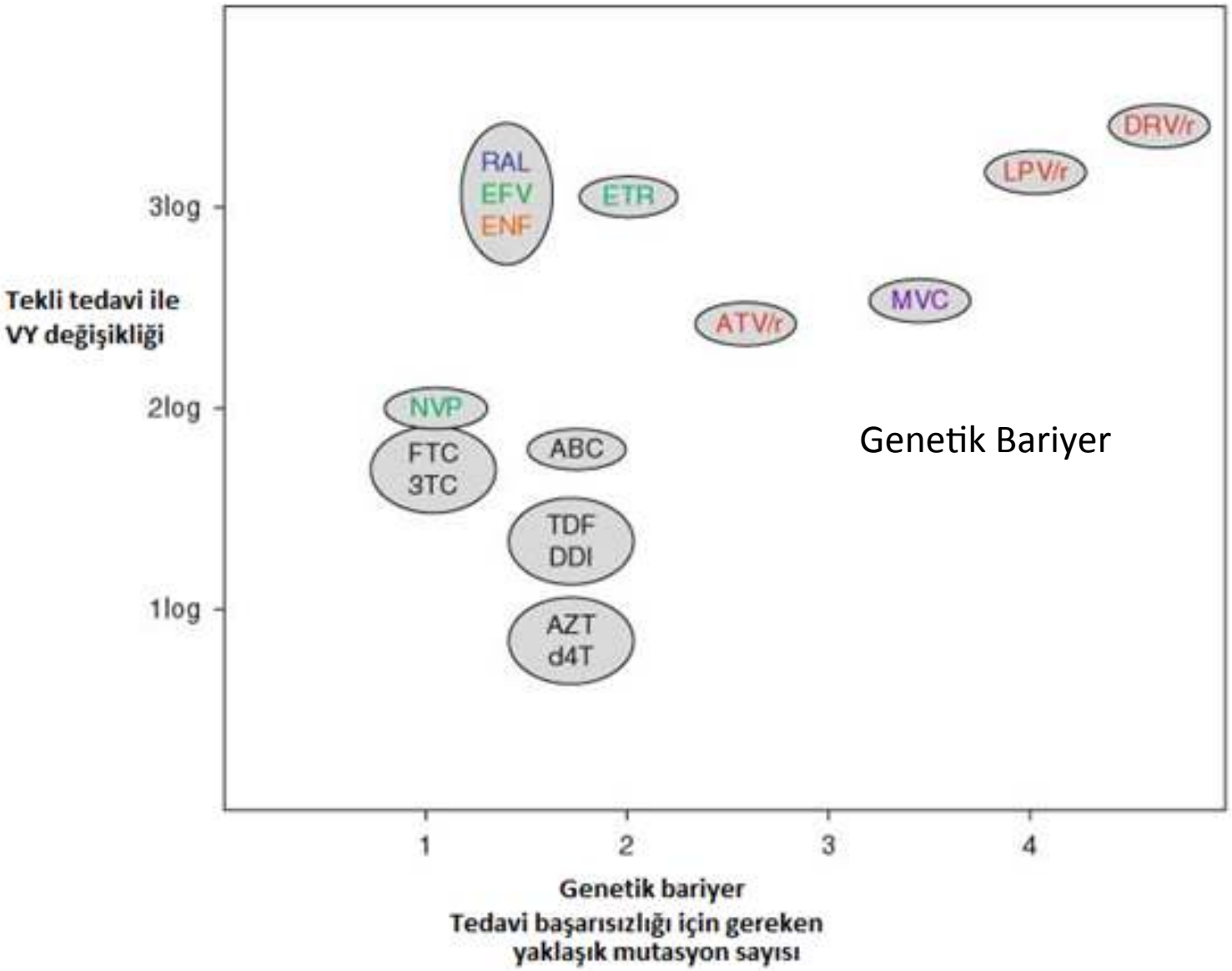
Virusa ait Özellikler:

1. Kodon kullanım farklılıkları
2. Alttipler arasında minör yapısal değişikliklere yol açan aminoasit farklılıkları ilacın hedefinde değişiklikle sonuçlanmaktadır. Örneğin aynı ilaç baskısı altında farklı mutasyonlar ortaya çıkabilmektedir.
3. Alttipler arasında belli aminoasit dizilimleri ilaç direnci ile ilişkili nükleotid değişimlerini kolaylaştırabilmektedir.

Direnç Nasıl Gelişir?



Antiretroviral ajanlar ve genetik bariyer.



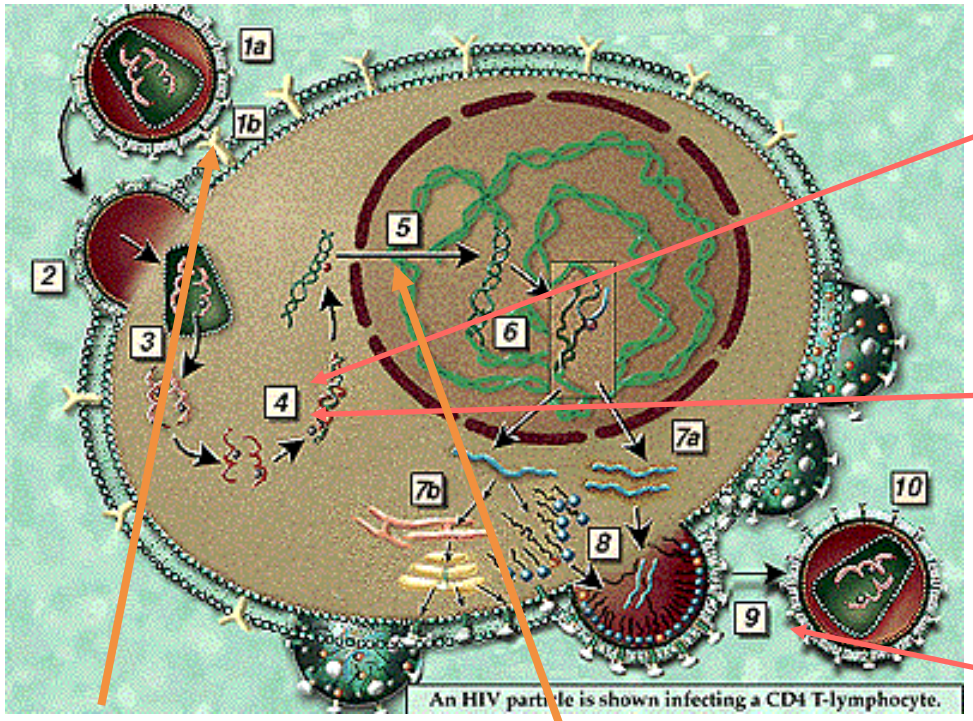
Genetik Bariyer

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.

- Direnç testleri:

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

HIV'in Yaşam Döngüsü ve Anti-HIV İlaçların Hedefleri



İlaç sınıfları:

Nükleosid Revers Transkriptaz İnhibitörleri (NRTI)

AZT, ddI, d4T, 3TC, FTC, ABC,TDF, (TAF)

Non-Nükleosid Revers Transkriptaz İnhibitörleri (NNRTI)

EFV, NVP, ETR, RPV

Proteaz İnhibitörleri (PI)

SQV, IDV, RTV, NFV, fAPV, LPV, ATV, TPV, DRV

Giriş İnhibitörleri (EI)

T20,
Maraviroc/MVC,
Cinicriviroc/CNC)
(AMD3100 AMD 070)

İntegraz İnhibitörleri(INI)

RAL, EVG, DTG

Avrupa HIV direnç klavuzu - 2011

Test tercihi	Genotipik
Yorumlama	- Güncellenen bir veri tabanının kullanılması - Dizilerin saklanması - Yorumlarda klinik bağlamın, tedavi, direnç öyküsünün de göz önüne alınması
Kalite kontrol	- Her çalışmada PK ve NK kullanılması - Sekans edisyonları izlenebilir olmalı - Çift yönlü dizi analizi - Yılda en az 1 kez dış kalite kontrol - Her ay ya da 50 örnekte bir bilinen bir örneğin test edilmesi - Yorumların belgelenmesi
Örneklerin saklanması	Direnç testi o an yapılamıyorsa 2 ml örneğin -80'de saklanması

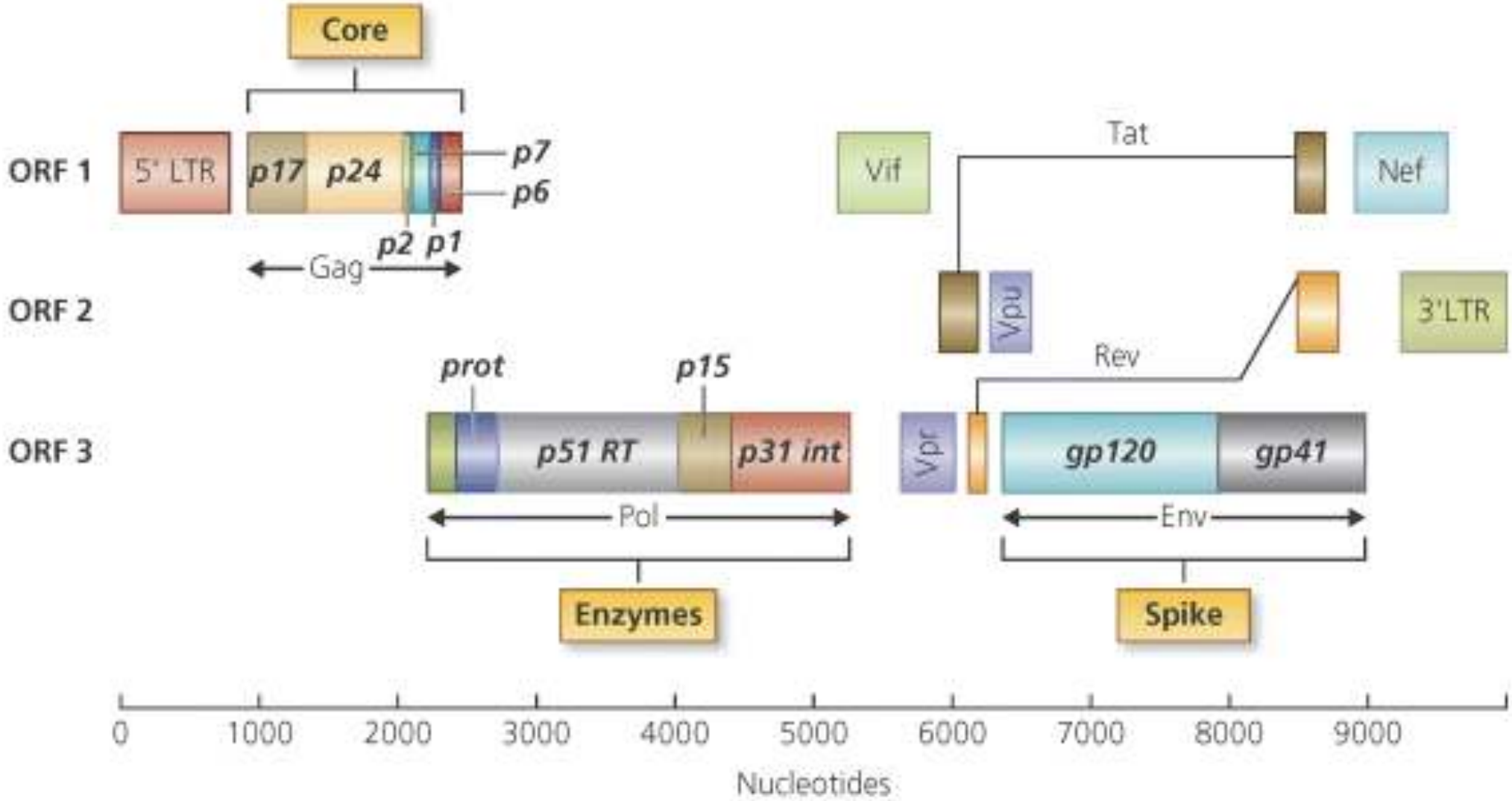
Tıbbi bakıma girişte; Viral yük $\geq$ 1000 ml olmalı; 500-1000 arası VY'lerde de denebilir; EACS 2015:
Tedavi başarısızlıklarında 350-500
Tedavi altında iken ya da kesildikten sonra tercihen ilk 4 hafta içerisinde

ARV direnç testleri

- **Genotipik testler:**

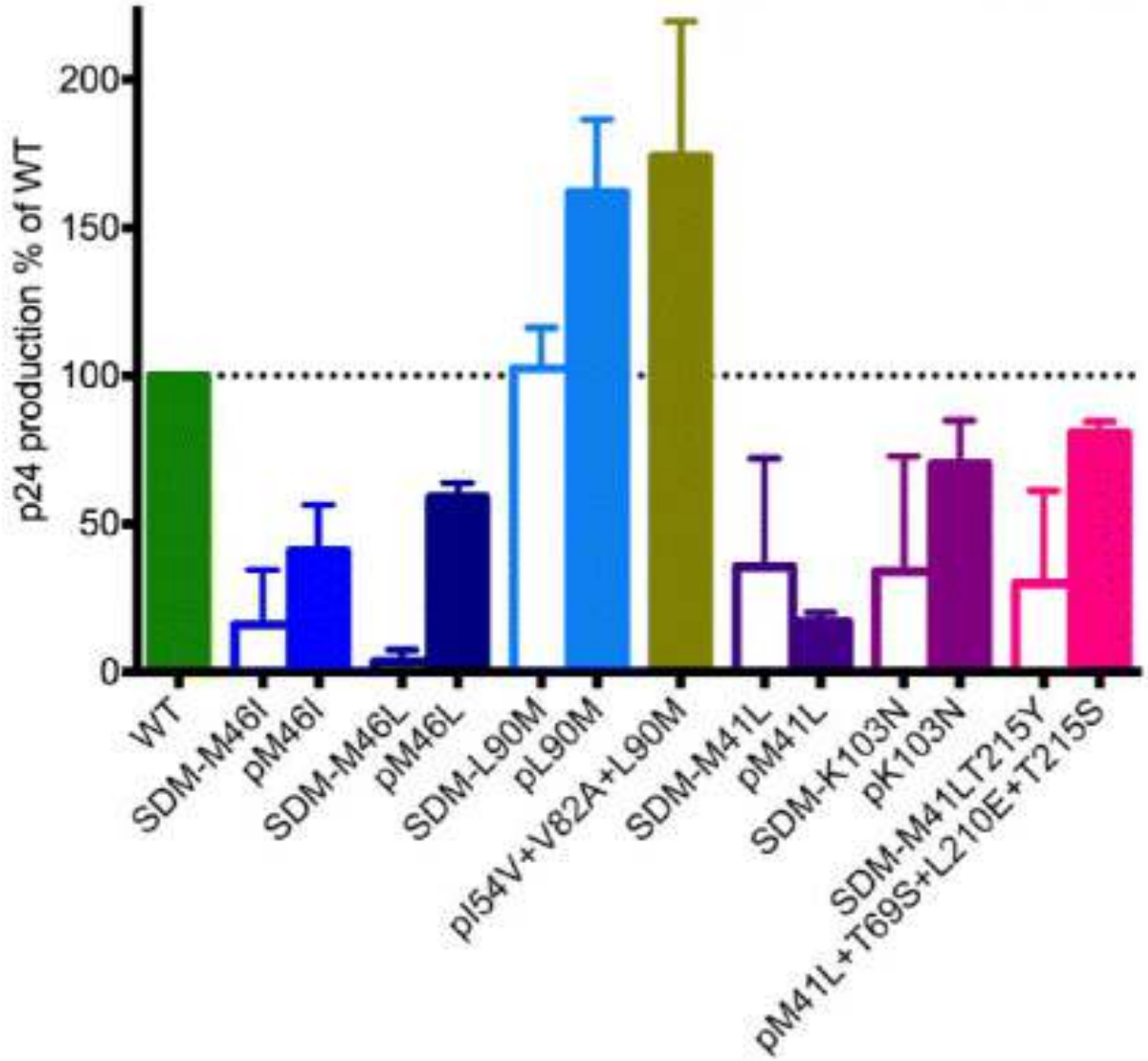
- RT-PCR sonrası:
  - Dizi analizi
  - Revers hibridizasyon
  - OLA (Oligonükleotid ligation assay)
  - Yeni kuşak DNA dizileme
  - Allel spesifik PCR

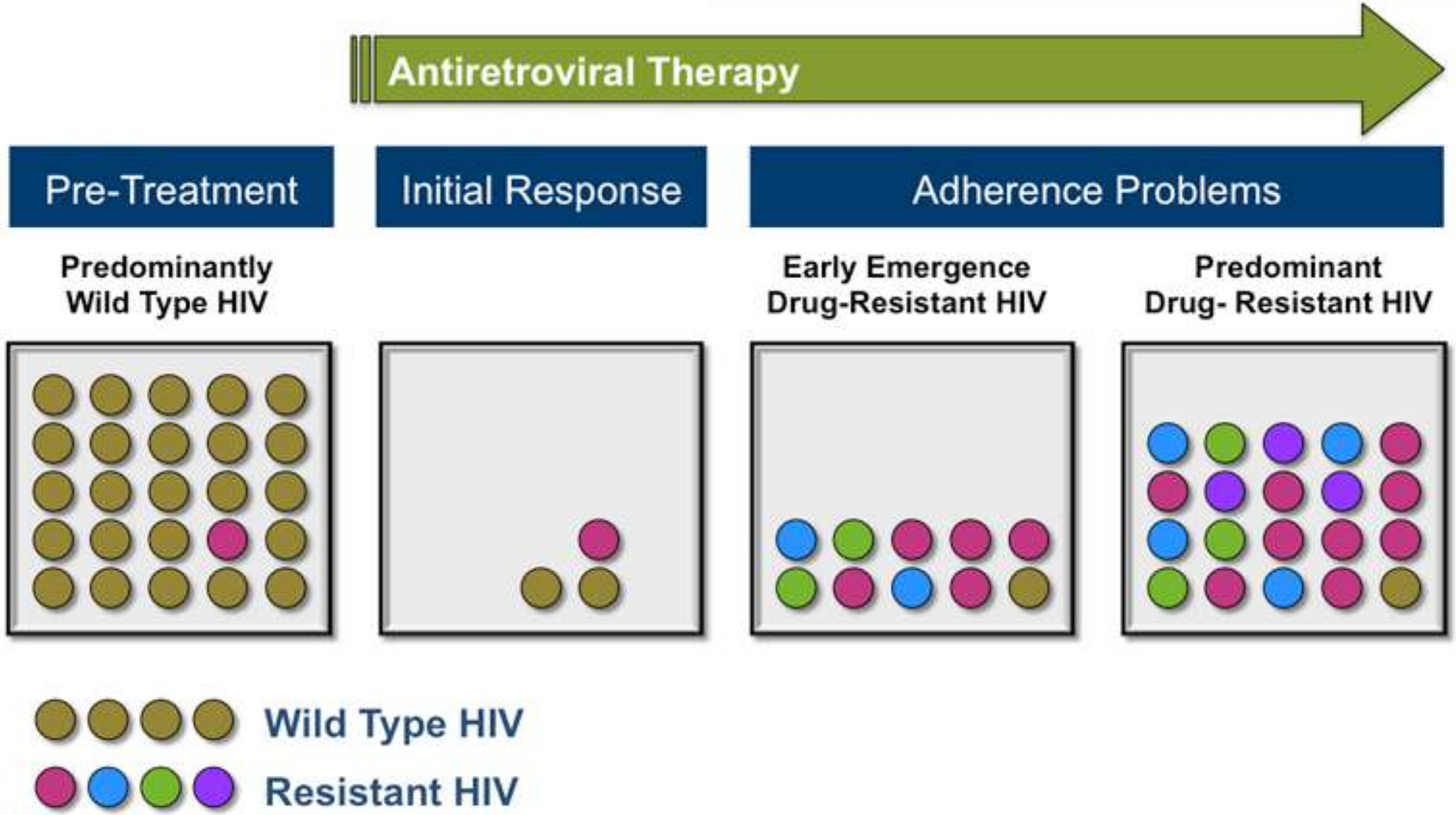
- **Fenotipik testler:** Ticari


Core
ORF 1
5' LTR
p17
p24
p7
p6
p2
p1
Gag
Vif
Tat
Nef
ORF 2
Vpu
3'LTR
Rev
prot
p15
ORF 3
p51 RT
p31 int
Vpr
gp120
gp41
Pol
Env
Enzymes
Spike
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
Nucleotides

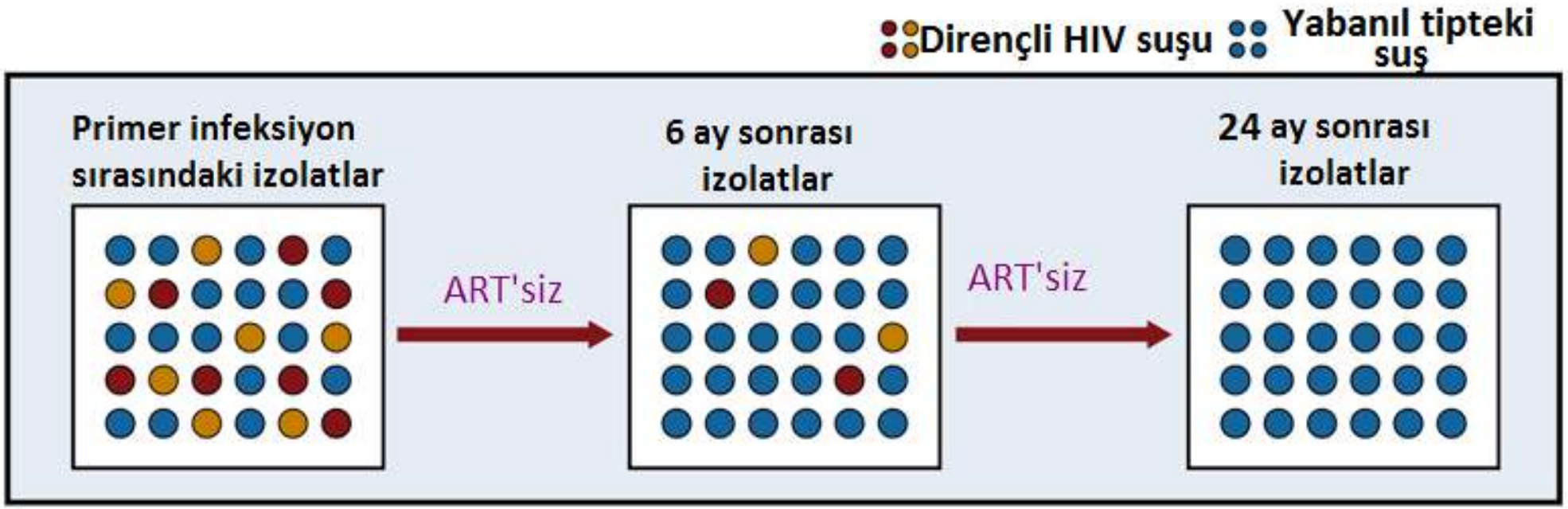
Primer ya da Majör Mutasyonlar: Tek başlarına olsalar bile duyarlılığı doğrudan azaltırlar, M184 mutasyonları gibi

Secondary (Accessory mutations): Enhance the viral fitness and decrease the susceptibility
Signature mutations: are are typically associated with resistance against a particular drug (I50L-atazanavir)


p24 production % of WT
200
150
100
50
0
WT
SDM-M46I
pM46I
SDM-M46L
pM46L
SDM-L90M
pL90M
pI54V+V82A+L90M
SDM-M41L
pM41L
SDM-K103N
pK103N
SDM-M41LT215Y
pM41L+T69S+L210E+T215S

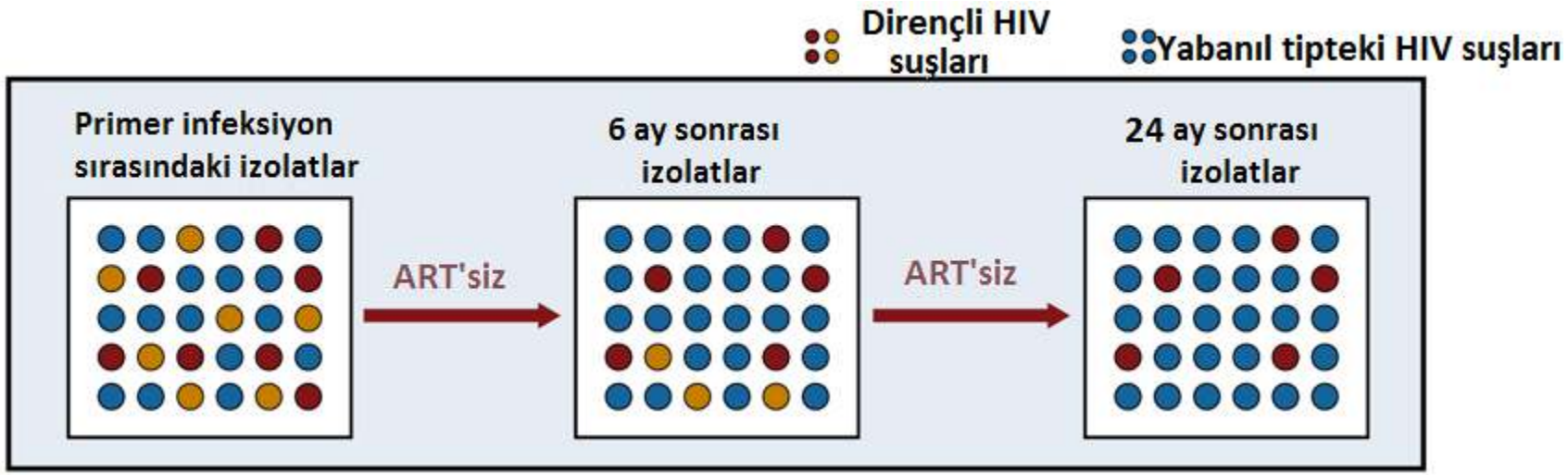


David H. Spach, MD. Features of Genotypic and Phenotypic Resistance Assays. HIV Web Study (www.hivwebstudy.org)



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

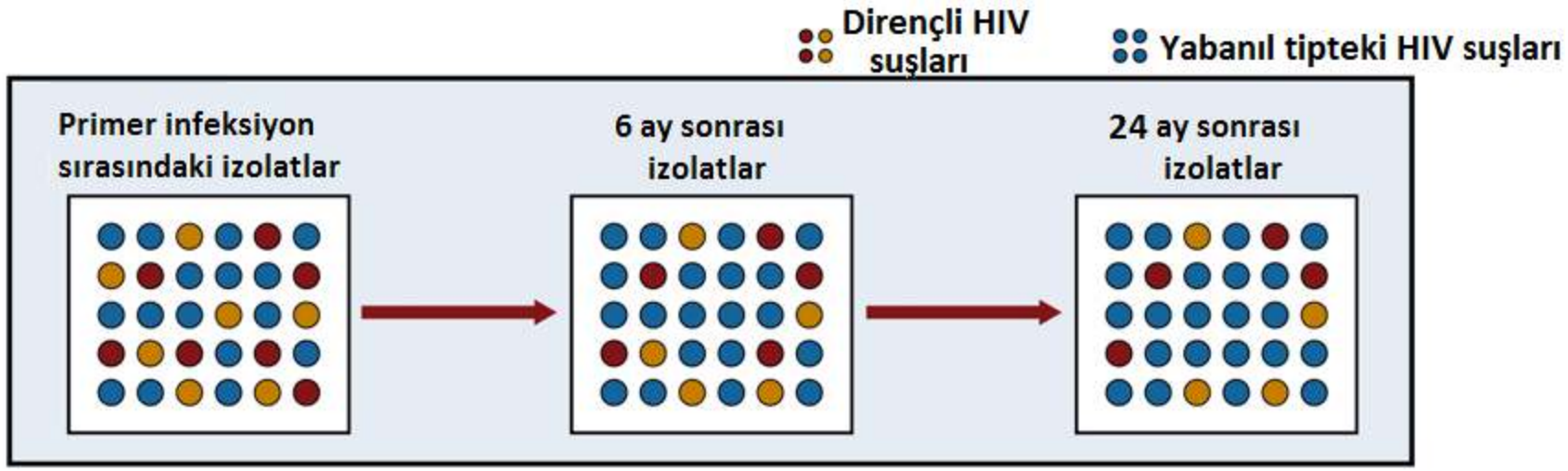
Bazen dirençli suşların bazıları zamanla saptanabilir düzeyin altına inebilir



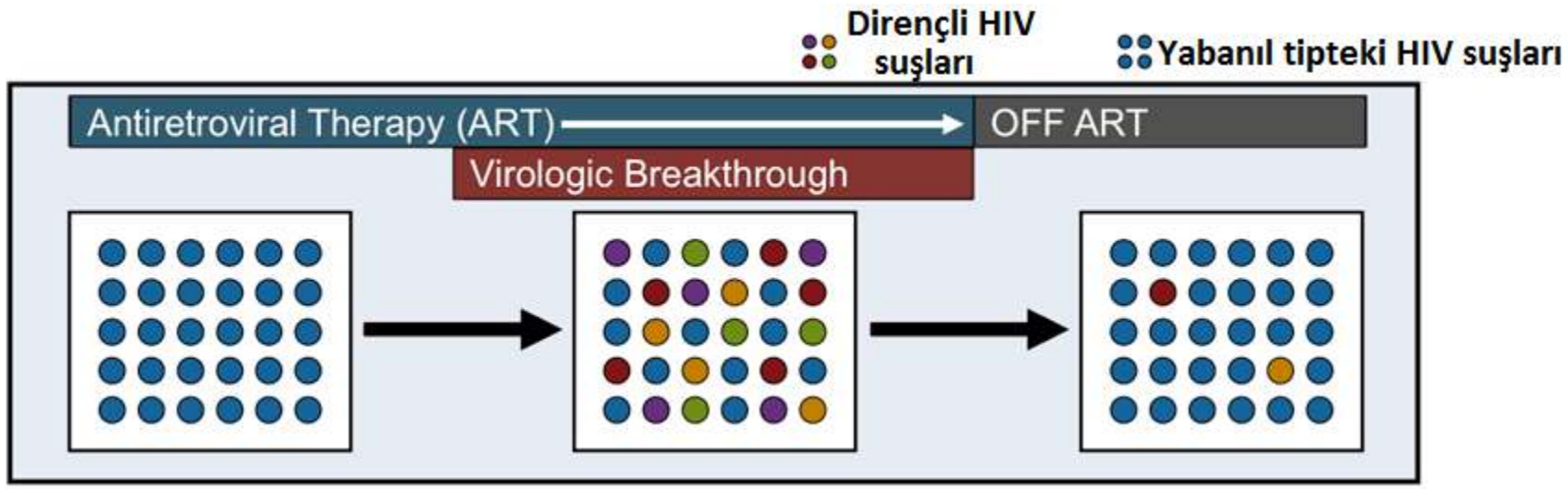
David H. Spach, MD. Features of Genotypic and Phenotypic Resistance Assays. HIV Web Study (www.hivwebstudy.org)

Bazen dirençli suşlar, mutasyonların sağladığı *fittness* üstünlükleri sayesinde persiste edebilir

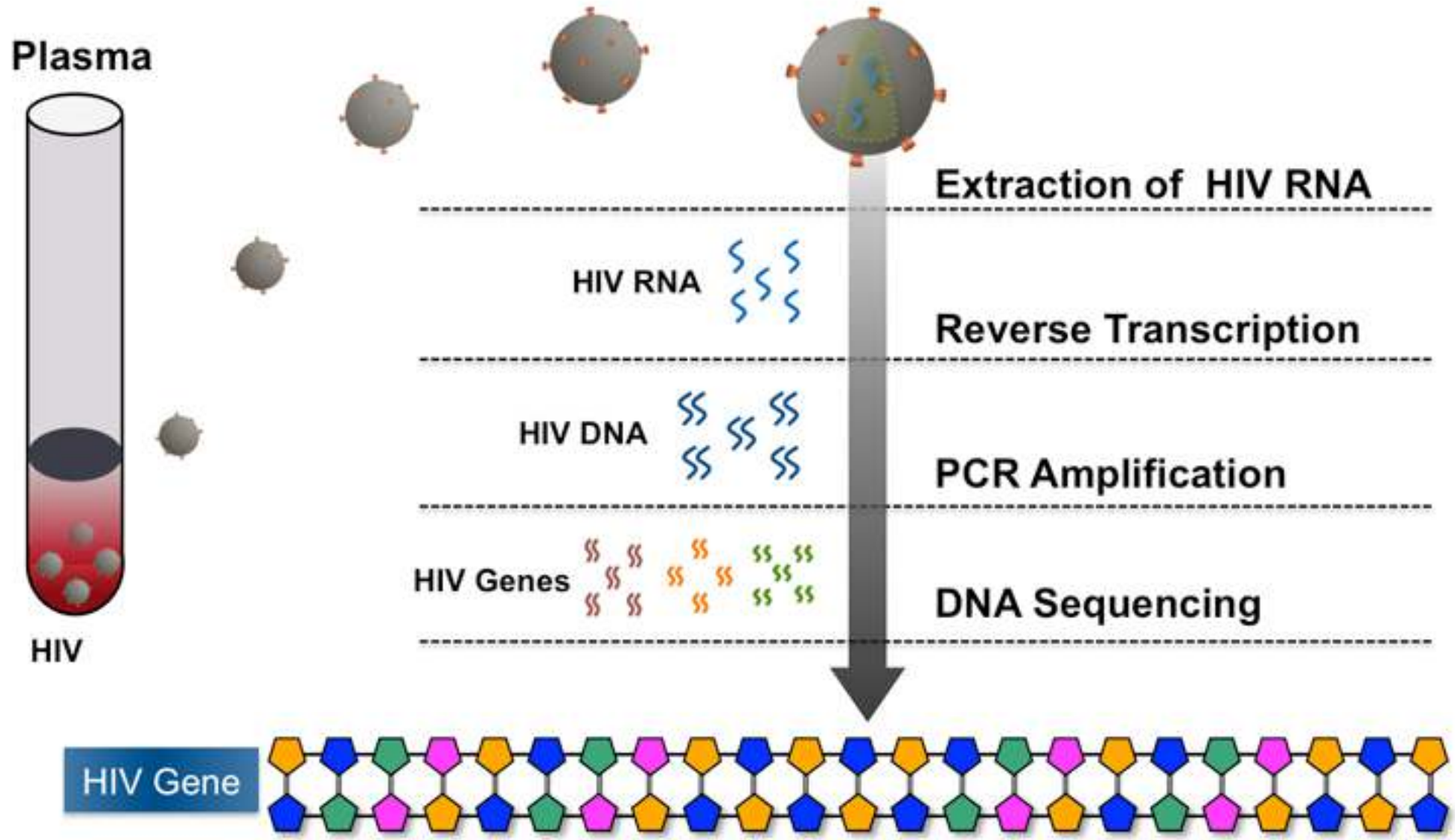
David H. Spach, MD. Features of Genotypic and Phenotypic Resistance Assays. HIV Web Study (www.hivwebstudy.org)



ART sırasında ortaya çıkan suşlar ART kesildikten sonra da persiste edebilir



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



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

RECall (beta v3.0) - Web based sequence analysis

At this time RECall only supports Firefox and Chrome.

Login:

Password:

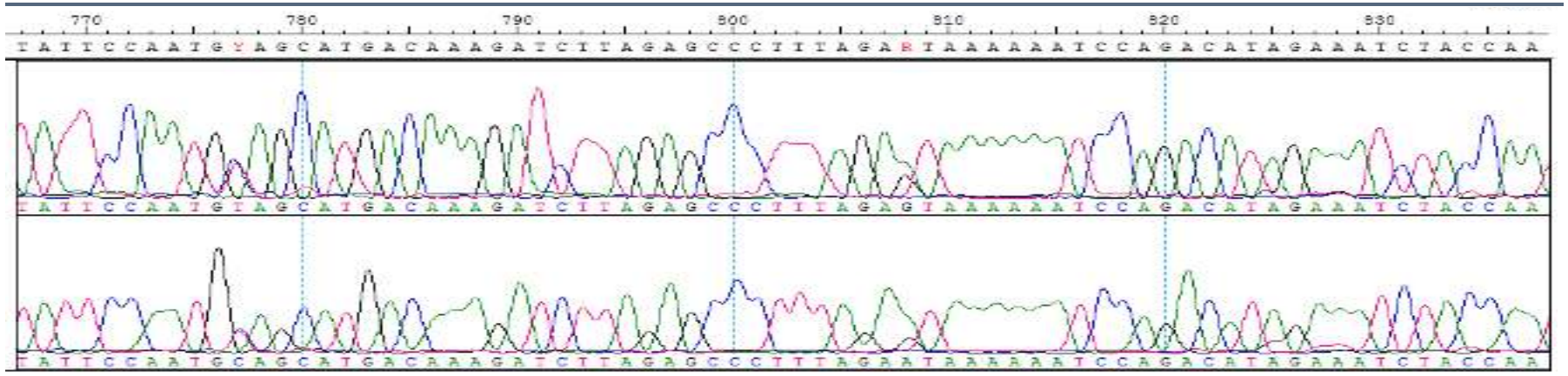
Log In | Register for a New Account

If you do not yet have an account and wish to give recall a try, you can log in under this test user:

Username: example
Password: test

And submit the example.zip file for processing under the POL1200 or WHO_PRRT projects.

Genotipik HIV Direnç Testi

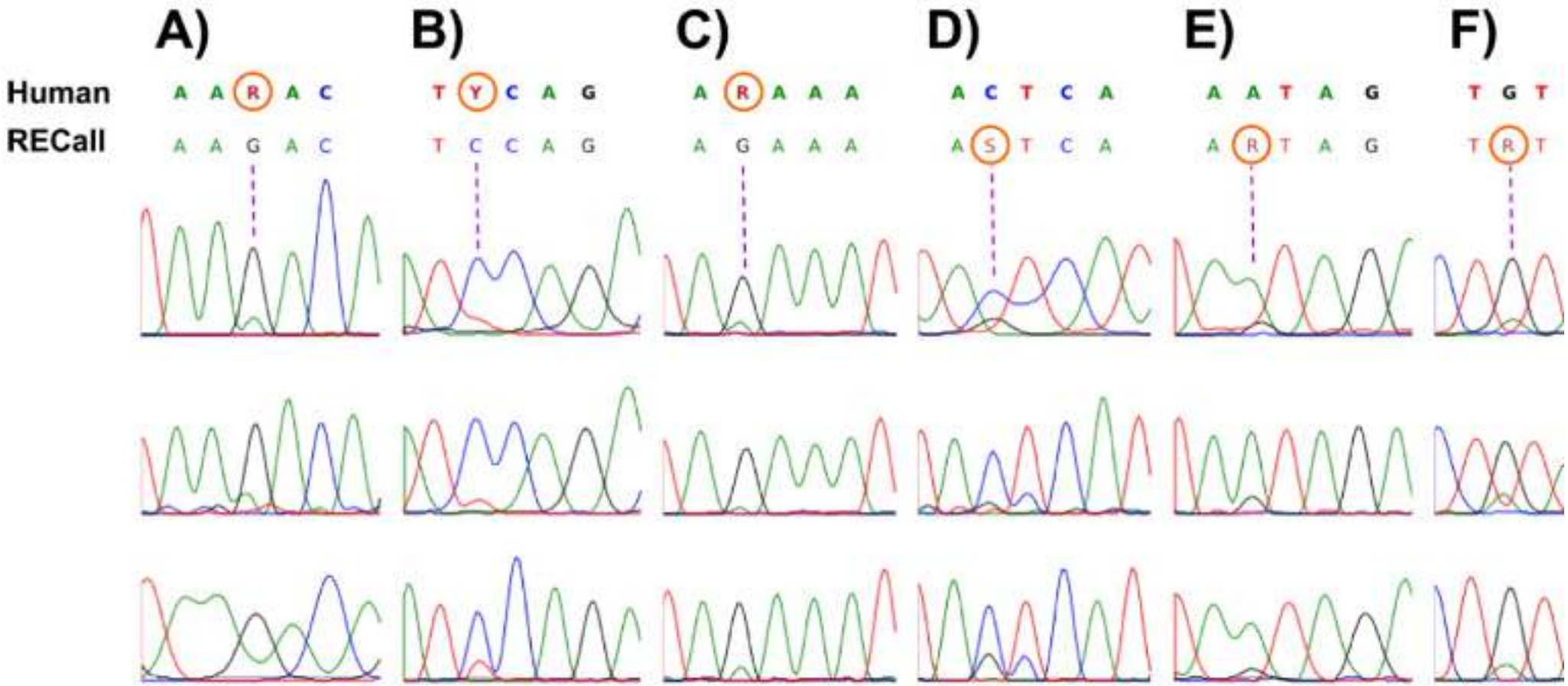


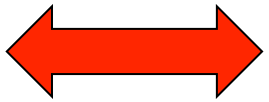
CCTCAGATCACTCTTTGGCAACGACCCATAGTCACAATAAAGATAGCGGGACAACTAAAGGAAGCTCTATTAGATACAGGAGCAGATGATACAGTATTAGAAGAA
ATGAATTTGCCAGGAAAATGGAAACCAAAAATAATAGTGGGAATTGGAGGGTTTACCAAAGTAAGACAGTATGATCATGTACAAATAGAAATCTGTGGACATAAA
GTTATAGGTGCAGTATTAATAGGACCTACACCTGCCAATATAATTGGAAGAAATCTGTTGACTCAGCTTGGCTGTACTTTAAATTTT

PQITLWQRPIVTIKIAGQLKEALLDTGADDTVLEEMNLPGKWKPKIIVGIGGFTKVRQYDHVQIEICGHKVIGAVLIGPTPANIIGRNLLTQLGCT
LNF

Differences from Consensus B:

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


A)
B)
C)
D)
E)
F)
Human
RECall
A A R A C
A A G A C
T Y C A G
T C C A G
A R A A A
A G A A A
A C T C A
A S T C A
A A T A G
A R T A G
T G T
T R T

Genotipik Veri  Direnç Analizi

On-Line direnç Analiz Yazılımları

- HIV Drug Resistance Database ➔ http://hivdb.stanford.edu/
- Geno2Pheno ➔ http://www.geno2pheno.org/
- HIV-GRADE ➔ http://www.hiv-grade.de/cms/grade/homepage/
- European system for computer-based clinical management of antiretroviral drug resistance ➔ http://www.euresist.org
- https://www.iasusa.org/sites/default/files/tam/23-4-132.pdf

Direnç Analizinde İzlenecek Ana Yollar

Kurala Dayalı Sistemler

	L	G	K	L		V	L	E		M
Atazanavir +/- ritonavir	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							

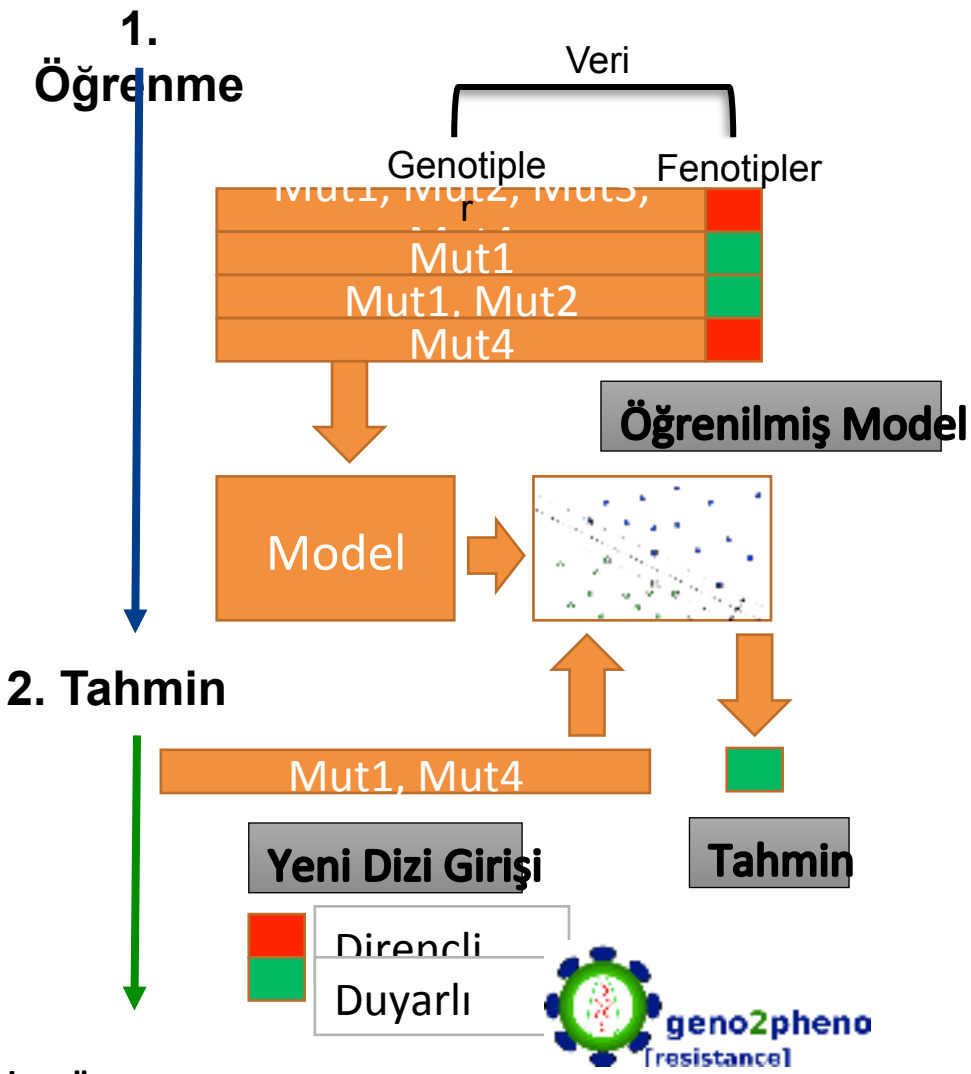
Uzman Grup

Tartışma

Uzlaşı

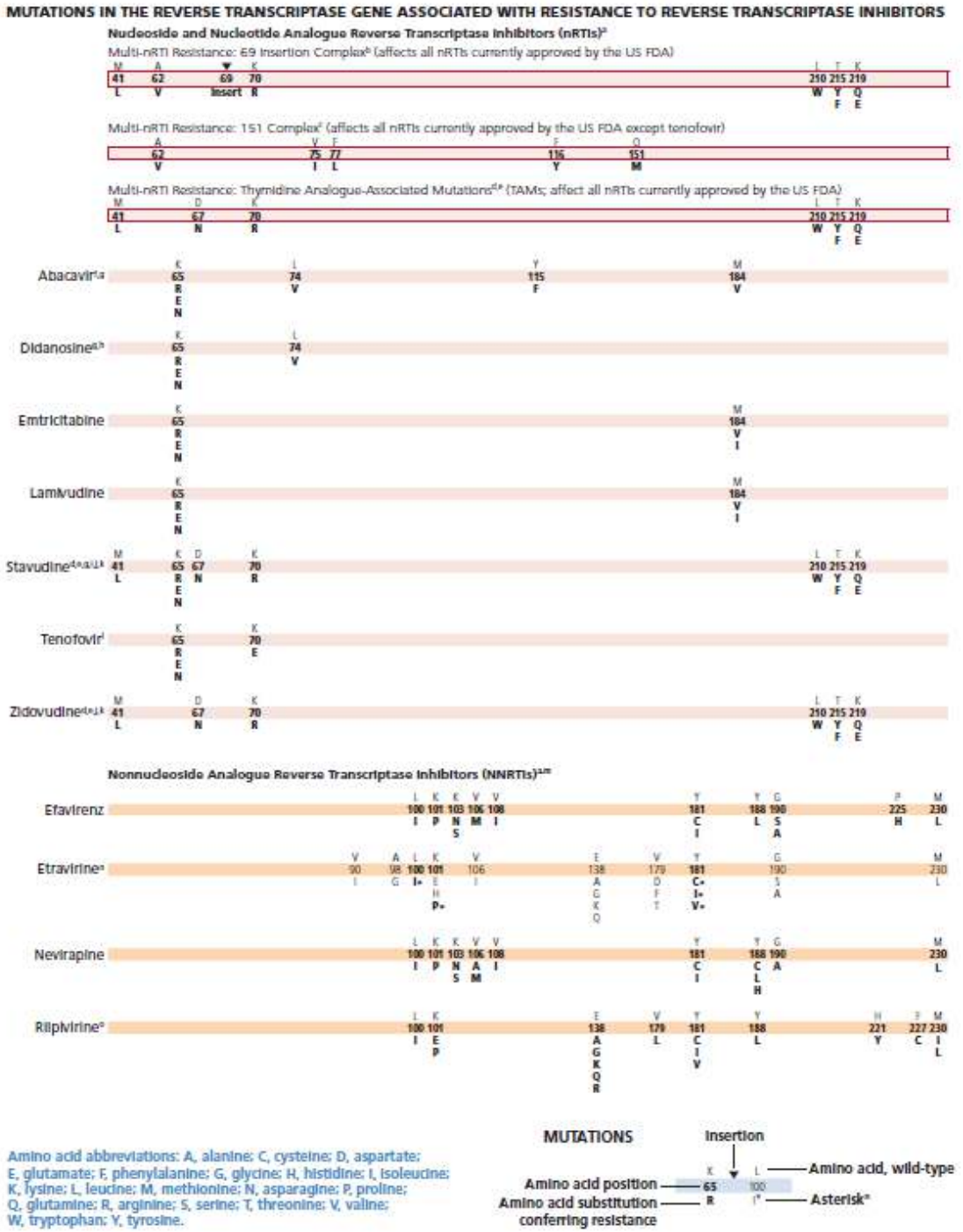
STANFORD UNIVERSITY
HIV DRUG RESISTANCE DATABASE
A curated public database designed to represent, store, and analyze the divergent forms of data underlying HIV drug resistance

Yapay Zekaya Dayalı – Makine Öğrenmesine Dayalı(Zahiri)



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

Wen'in AM1, Calvez V2, Günthard HF3, Johnson VA4, Paredes R5, Pillay D6, Shafer RW7, Richman DD8. 2015 Update of the Drug Resistance Mutations in HIV-1.



MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS[a,g,r]

	L 10	G 16	K 20	L 24	V 32	L 33	E 34	M 36	M 46	G 48	I 50	F 53	I 54	D 60	I 62	I 64	A 71	G 73	V 82	I 84	I 85	N 88	L 90	I 93
Atazanavir +/- ritonavir[b]	I F V C	E	R M I T V	I	I	I F V	Q	I L V	I L	V	L	L Y	L V M T A	E	V	L M V	V I T L	C S T A	A T F I	V	V	S	M	L M
Darunavir/ ritonavir[h]	V 11 I				V 32 I	L 33 F			I **47** V		I **50** V		I **54** M L					T 74 P	L **76** V		I **84** V		L 89 V	
Fosamprenavir/ ritonavir	L 10 F I R V				V 32 I				M 46 I L	I 47 V	I **50** V		I 54 L V M					G 73 S	L 76 V	V 82 A F S T	I **84** V			L 90 M	
Indinavir/ ritonavir[a]	L 10 I R V		K 20 M R	L 24 I	V 32 I			M 36 I	M **46** I L				I 54 V				A 71 V T	G 73 S A	L 76 V	V **82** A F T	I **84** V			L 90 M	
Lopinavir/ ritonavir[c]	L 10 F I R V		K 20 M R	L 24 I	V **32** I	L 33 F			M 46 I L	I **47** V A	I 50 V	F 53 L	I 54 V L A M T S		L 63 P		A 71 V T	G 73 S	L **76** V	V **82** A F T S	I 84 V			L 90 M	
Nelfinavir[a,w]	L 10 F I			D **30** N				M 36 I	M 46 I L								A 71 V T		V 77 I	V 82 A F T S	I 84 V	N 88 D S		L **90** M	
Saquinavir/ ritonavir[a]	L 10 I R V			L 24 I						G **48** V			I 54 V L		I 62 V		A 71 V T	G 73 S	V 77 I	V 82 A F T S	I 84 V			L **90** M	
Tipranavir/ ritonavir	L 10 V					L 33 F		M 36 I L V	K 43 T	M 46 L	I **47** V		I 54 A M V	Q **58** E		H 69 K R		T **74** P		V **82** L T	N **83** D	I **84** V		L 89 I M V	

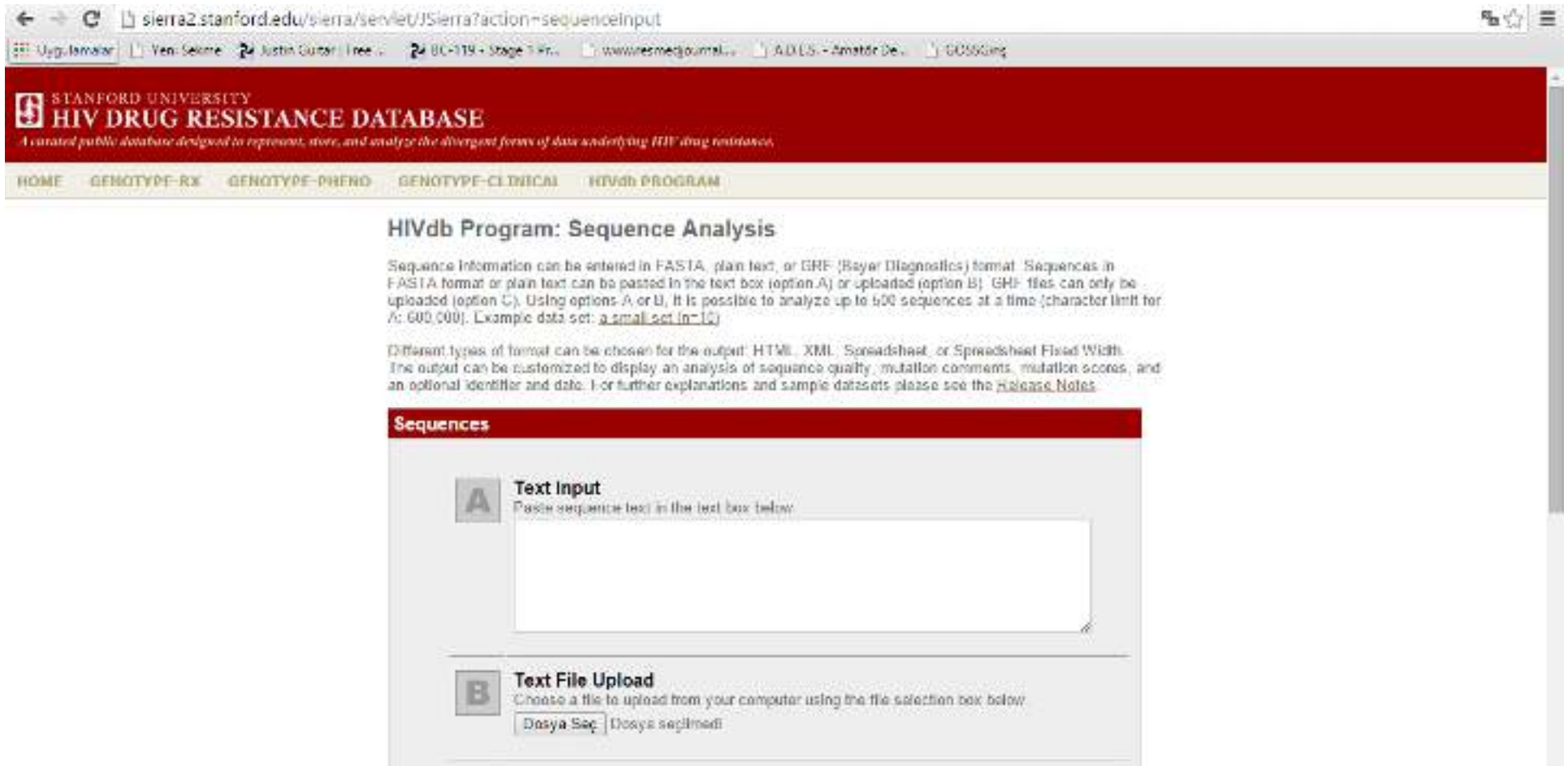
MUTATIONS IN THE ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS

	G **36** **D** **S**	I **37** **V**	V **38** **A** **M** **E**	Q **39** **R**	Q **40** **H**	N **42** **T**	N **43** **D**
Enfuvirtide[e]							

Maraviroc[f] See User Note

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

	T **66** **I** **A** **K**	E **92** **Q** G	T 97 A	F **121** **Y**	E 138 A K	G 140 A S	Y **143** **R** **H** **C**	S **147** **G**	Q **148** **H** **K** **R**	N **155** **H**	R 263 K
Dolutegravir[aa]				F 121 Y	E 138 A K	G 140 A S			Q **148** **H** **R**	N 155 H	R 263 K
Elvitegravir[aa]											
Raltegravir[x]		L 74 M	E 92 Q	T 97 A	F **121** **Y**	E 138 A K	G 140 A S		Q **148** **H** **K** **R**	N **155** **H**	R 263 K


sierra2.stanford.edu/sierra/servlet/JSierra?action=sequenceInput
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.
HOME
GENOTYPE-RX
GENOTYPE-PHENO
GENOTYPE-CLINICAL
HIVdb PROGRAM
HIVdb Program: Sequence Analysis
Sequence information can be entered in FASTA, plain text, or GRF (Bayer Diagnostics) format. Sequences in FASTA format or plain text can be pasted in the text box (option A) or uploaded (option B). GRF files can only be uploaded (option C). Using options A or B, it is possible to analyze up to 500 sequences at a time (character limit for A: 600,000). Example data set: a small set (n=10)
Different types of format can be chosen for the output: HTML, XML, Spreadsheet, or Spreadsheet Fixed Width. The output can be customized to display an analysis of sequence quality, mutation comments, mutation scores, and an optional identifier and date. For further explanations and sample datasets please see the release Notes
Sequences
A
Text Input
Paste sequence text in the text box below
B
Text File Upload
Choose a file to upload from your computer using the file selection box below
Dosya Seç
Dosya seçilmedi


www.geno2pheno.org
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Contact
Membership and Donations
Services
geno2pheno [resistance]
HIV Theo
geno2pheno [coreceptor]
geno2pheno [454]
geno2pheno [integrase]
geno2pheno [gag]
geno2pheno [hbv]
geno2pheno [hcv]
Service access statistics
Beta Services
Related Sites
Events
News
Links
Geno2pheno [resistance] 3.3
Page: Input Results Help References Contact Disclaimer
On submitting below an HIV-1 pol-gene DNA sequence you will obtain a sequence alignment to the reference strain HXB2, a list of mutations and different predictions of phenotypic resistance of the respective virus to 15 antiretroviral drugs
1. Identifier (optional):
Do not use patient names!
2. Cutoffs:
show cutoffs
3. Pol-gene (PR and RT) nucleotide sequence:
upload from file (sequences in FASTA format, or single plain or FASTA sequence)
Dosya Sec
Dosya secilmedi
or paste in:
4. Therapy-na◆ve tool:
enable therapy-na◆ve tool
5. Sequence ambiguities:
use resistance associated mutations at ambiguous sequence positions for phenotype prediction
6. Result layout options:
Alignment width: 60
7. Action:
Align and Predict
Go

KATHOLIEKE UNIVERSITEIT LEUVEN

REGA HIV Subtyping Tool

HIV BIOINFORMATICS BIOAFRICA

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This application is built and maintained by Tulio de Oliveira, Pieter Libin, Koen Deforche, Sharon Cassol and Anne-Mieke Vandamme.

HIVdb: Genotypic Resistance Interpretation Algorithm

Date: 21-Nov-2015 09:55:37 UTC

Seq ID: HD_2007_037

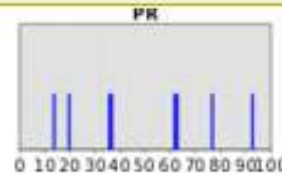
Summary Data

Sequence includes PR: codons: 8 - 99
Sequence includes RT: codons: 1 - 235
There are no insertions or deletions
Subtype and % similarity to closest reference isolate:

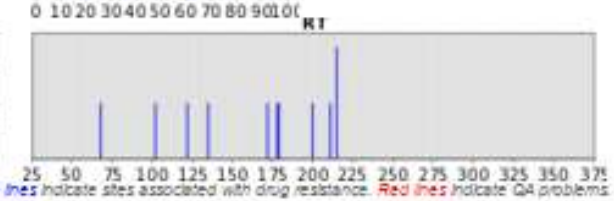
1. *PR: B (93.1%)*
2. *RT: B (96.0%)*

Sequence Quality Assessment

Gene	QA Problem	Codons
PR	Stop Codons, Frame Shifts:	None
PR	Ambiguous Positions:	None
PR	Unusual Residues:	None



Gene	QA Problem	Codons
RT	Stop Codons, Frame Shifts:	None
RT	Ambiguous Positions:	None
RT	Unusual Residues:	None



Blue lines indicate differences from consensus B; tall blue lines indicate sites associated with drug resistance. Red lines indicate QA problems.

Drug Resistance Interpretation: PR

PI Major Resistance Mutations: None
PI Minor Resistance Mutations: None
Other Mutations: K14R, K20R, M36I, N37D, I62V, L63Q, V77I, I93L

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

PR Comments

Other

- K20R is a highly polymorphic, PI-selected accessory mutation that improves HIV-1 replication fitness in viruses with other PI-resistance mutations.

Drug Resistance Interpretation: RT

NRTI Resistance Mutations:	T215V
NNRTI Resistance Mutations:	None
Other Mutations:	S68G, K102M, K122E, I135T, R172KR, I178L, V179I, T200A, R211K

Nucleoside RTI		Non-Nucleoside RTI	
lamivudine (3TC)	Susceptible	efavirenz (EFV)	Susceptible
abacavir (ABC)	Potential low-level resistance	etravirine (ETR)	Susceptible
zidovudine (AZT)	Low-level resistance	nevirapine (NVP)	Susceptible
stavudine (D4T)	Low-level resistance	rilpivirine (RPV)	Susceptible
didanosine (DDI)	Potential low-level resistance		
emtricitabine (FTC)	Susceptible		
tenofovir (TDF)	Susceptible		

RT Comments

NRTI

- T215Y/F cause intermediate/high-level resistance to AZT and d4T and low-level resistance to ABC, ddI and TDF. T215S/C/D/E/I/V/N/A/L do not reduce NRTI susceptibility but arise from viruses that once contained T215Y/F. The presence of one of these revertant mutations suggests the possibility that the patient may have once harbored a majority virus population with T215Y/F.

Other

- V179I is a polymorphic mutation that is frequently selected in patients receiving ETR and RPV. It has little, if any, effect on NNRTI susceptibility.

Mutation Scoring

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

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF	EFV	ETR	NVP	RPV
T215V	0	10	20	20	10	0	5	-	-	-	-
Total:	0	10	20	20	10	0	5	0	0	0	0

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

- Yen infeksiyonlarda direnç nakli → Aktarılmış direnç

Mutasyon	Reversiyon süresi
T215Y	2 Ayda %23; 4 ayda %45
M184V	2 Ayda %40; 4 ayda %74
K103N	2 Ayda %36; 4 ayda %63

Timidin Analogları Mutasyonları (TAMs)

(Zidovudin ya da Stavudine)

Yolak -1

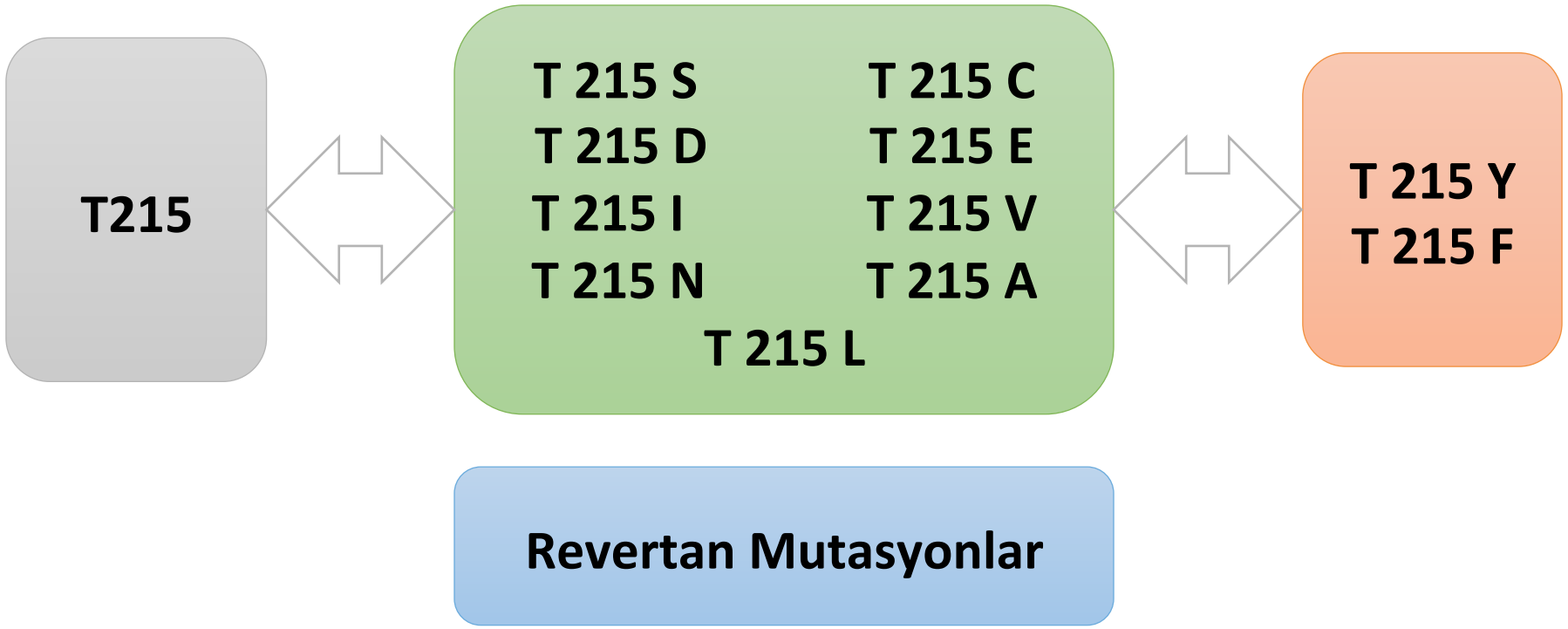
Yüksek düzeyde zidovu
stavudine
direnci ile birlikte
diğer NRTI'lara da
çapraz direnç.
Tenofovir dahil

M41L
L210W
T215Y/F

Yolak -2

Yüksek düzeyde zidovudine/
stavudine
direnci ile birlikte
diğer NRTI'lara da
Daha dşük düzeyede
çapraz direnç.
Düşük düzeyde
Tenofovir dahil
direnci

D67N
K70R
T215Y/F
K219Q/E


T215
T 215 S
T 215 C
T 215 D
T 215 E
T 215 I
T 215 V
T 215 N
T 215 A
T 215 L
T 215 Y
T 215 F
Revertan Mutasyonlar

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.

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_{89}
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

III. Phenotype prediction

Drug	Resistance Factor RF (*)	z-score	Scored Mutations (**)
ZDV	1.533	0.068	135T 35T 123E 122K 60I 166R
ddI	2.015	2.604	184V 122K 123E 60I 166R 214F 177E
d4T	0.842	-1.922	184V 122K 166R 123E 35T 69G
3TC	60.513	12.439	184V
ABC	2.398	4.474	184V 35T 123E 214F
TDF	0.825	-1.464	184V 60I 177E 135T 214F
NVP	0.584	-1.018	135T 35T 166R 211K 60I 122K
EFV	0.885	-0.537	135T 214F 60I 177E
ETR	1.427	0.316	35T 184V 123E 214F
SQV	0.794	-1.089	41K 14R 12I 37N 63T 65D 89M
IDV	0.537	-2.674	89M 65D 62V 74S 12I 63T 70R
NFV	0.728	-1.456	89M 74S 70R 62V 41K 63T 14R
APV	0.618	-1.588	89M 15V 41K 12I 74S 37N 53K
LPV	0.533	-2.232	74S 41K 89M 12I 70R 65D
TPV	1.312	0.498	89M 14R 15V 74S 36I 41K 65T
DRV	1.261	0.509	89M 74S 65D 14R 41K
ATV	0.575	-2.385	41K 36I 74S 62V

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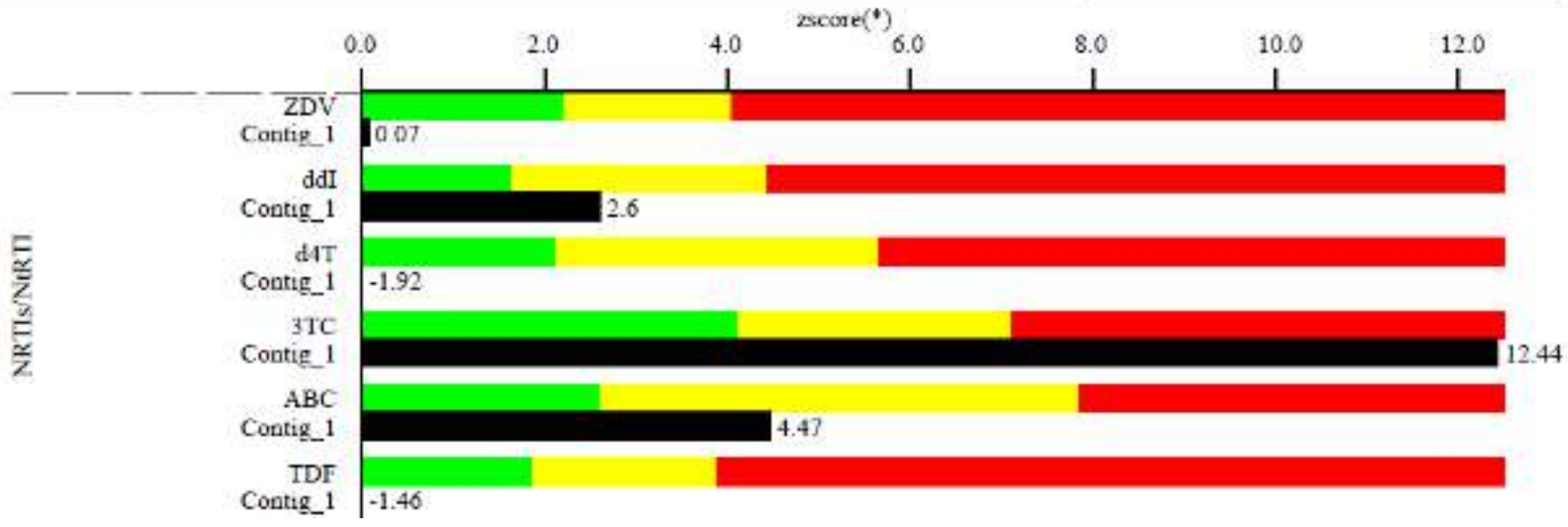

dbpartners.stanford.edu:8080/RegaSubtyping/stanford-hiv/typingtool/job/457074652/

Yeni Sekme | Justin Guitar | Free ... | BC-119 • Stage 1 Pr... | www.resmedjournal.... | A.D.E.S. - Amacor De... | GOSSGirls

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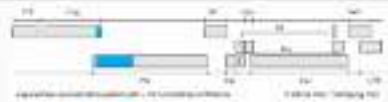
REGA HIV Subtyping Tool

HIV BIOINFORMATICS BIOAFRICA

Summary

Rega Assignment	Number of sequences	Percentage	Legend
HIV-1 Subtype B	1	100%	
Total	1	100%	

You may bookmark this page to revisit these results later.

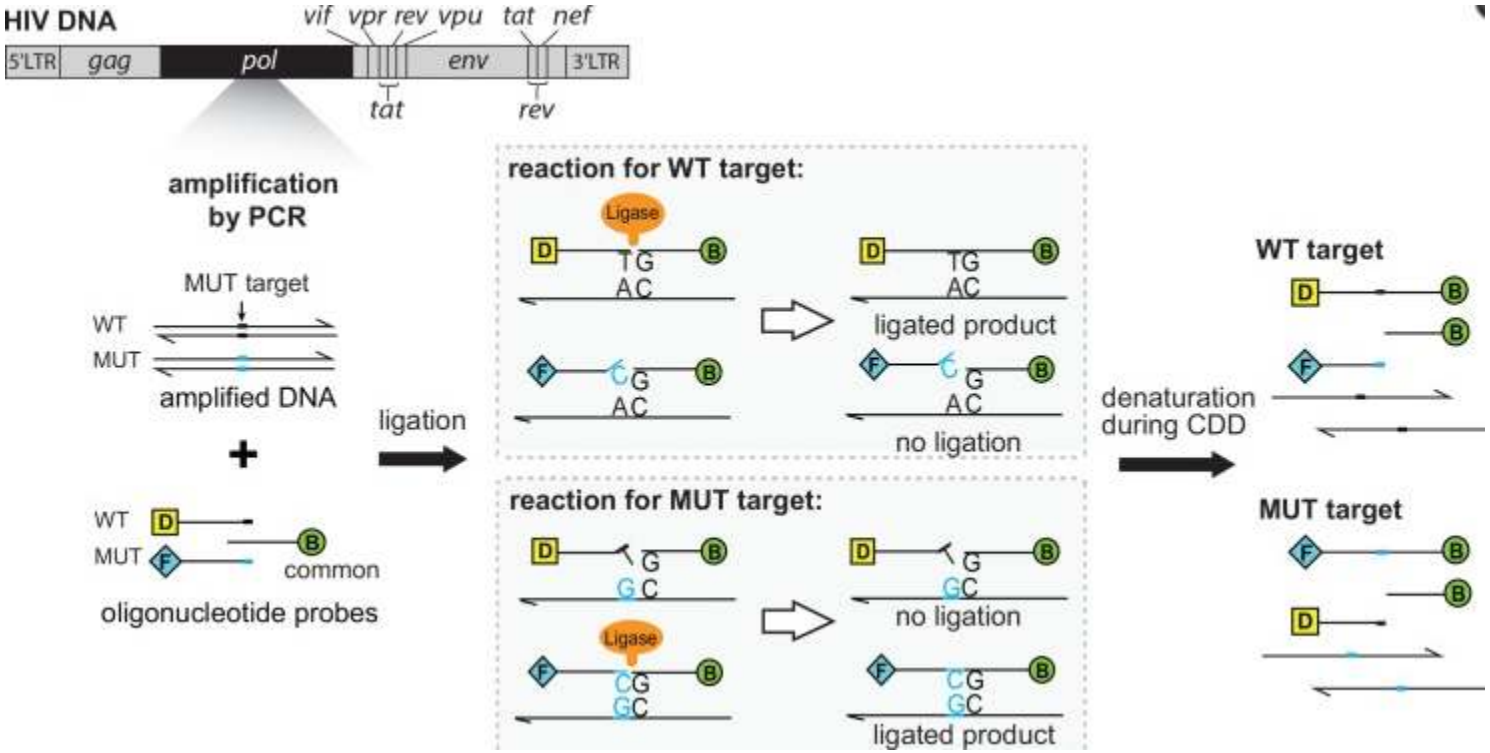
Name	Length	Report	Assignment	Support	Genome
HD_2007_037	983	Report	HIV-1 Subtype B	100.0	

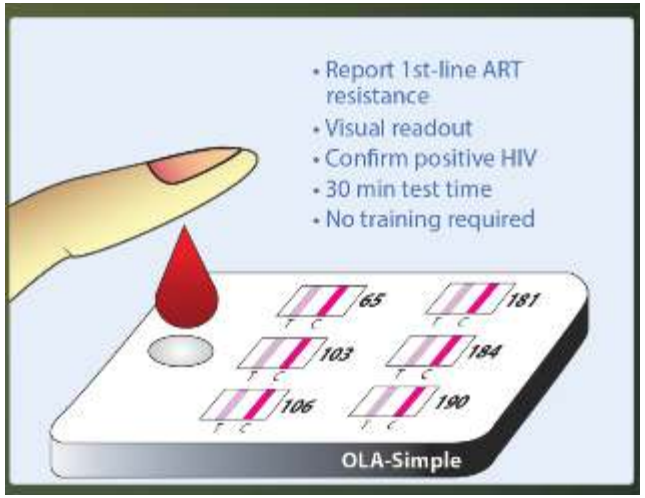
Download results: Table (Excel format) Table (CSV format) XML File Sequences (Fasta format)

Submit analysis | How to cite | Tutorial | Decision trees | Subtyping process | Example sequences | Contact us

This application is built and maintained by Tulio de Oliveira, Pieter Libin, Koen Deforche, Sharon Cassol and Anne-Mieke Vandamme

Oligonucleotide Ligation Assay



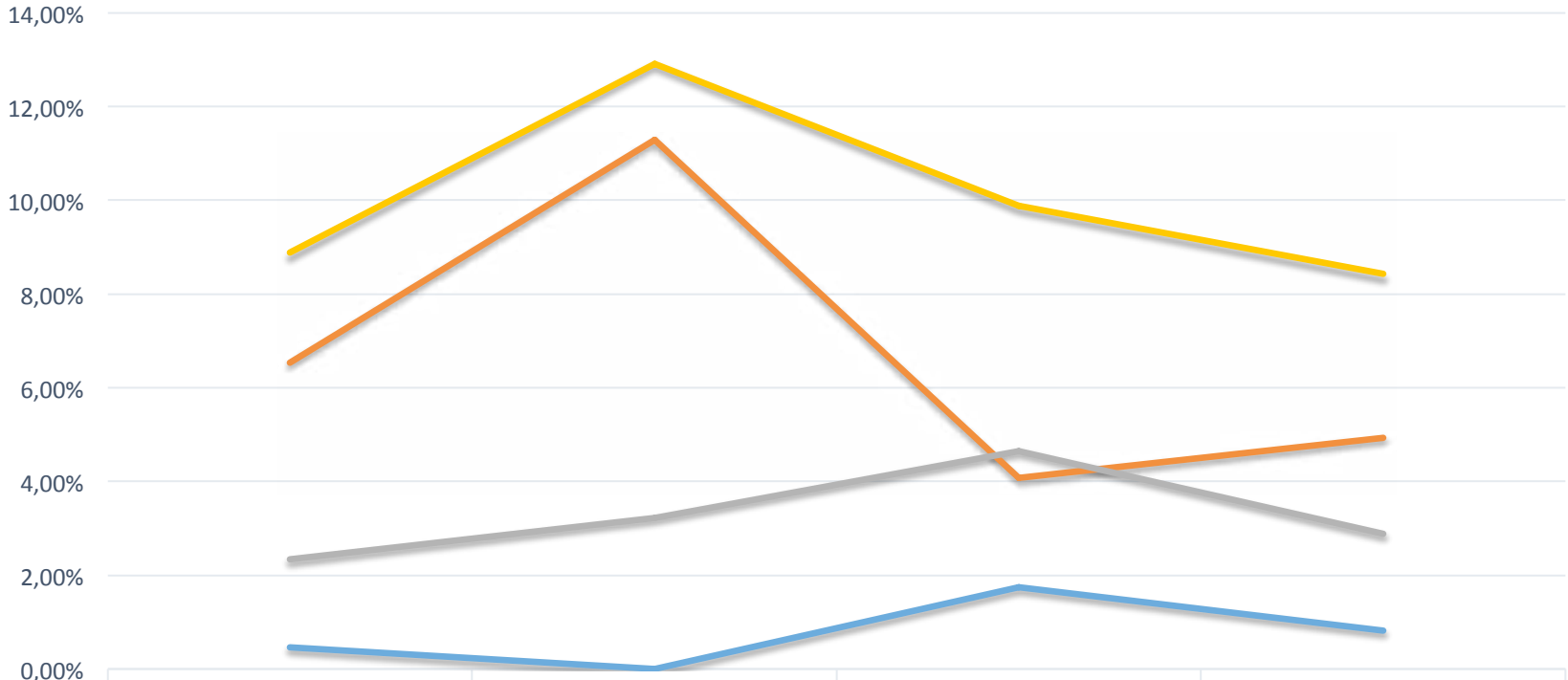


Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance: 2004-2015

Year	n (total 934)	PI	NRTI	NNRTI	Any
2004-2012	214	1	14	5	19
		0,47%	6,54%	2,34%	8,88%
2013	62	0	7	2	8
		0,00%	11,29%	3,23%	12,90%
2014	172	3	7	8	17
		1,74%	4,07%	4,65%	9,88%
2015	486	4	24	14	41
		0,82%	4,94%	2,88%	8,44%

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

Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance: 2004-2015 (total 934)



	2004-2012	2013	2014	2015
PI	0,47%	0,00%	1,74%	0,82%
NRTI	6,54%	11,29%	4,07%	4,94%
NNRTI	2,34%	3,23%	4,65%	2,88%
Any	8,88%	12,90%	9,88%	8,43%

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

Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance: 2004-2015

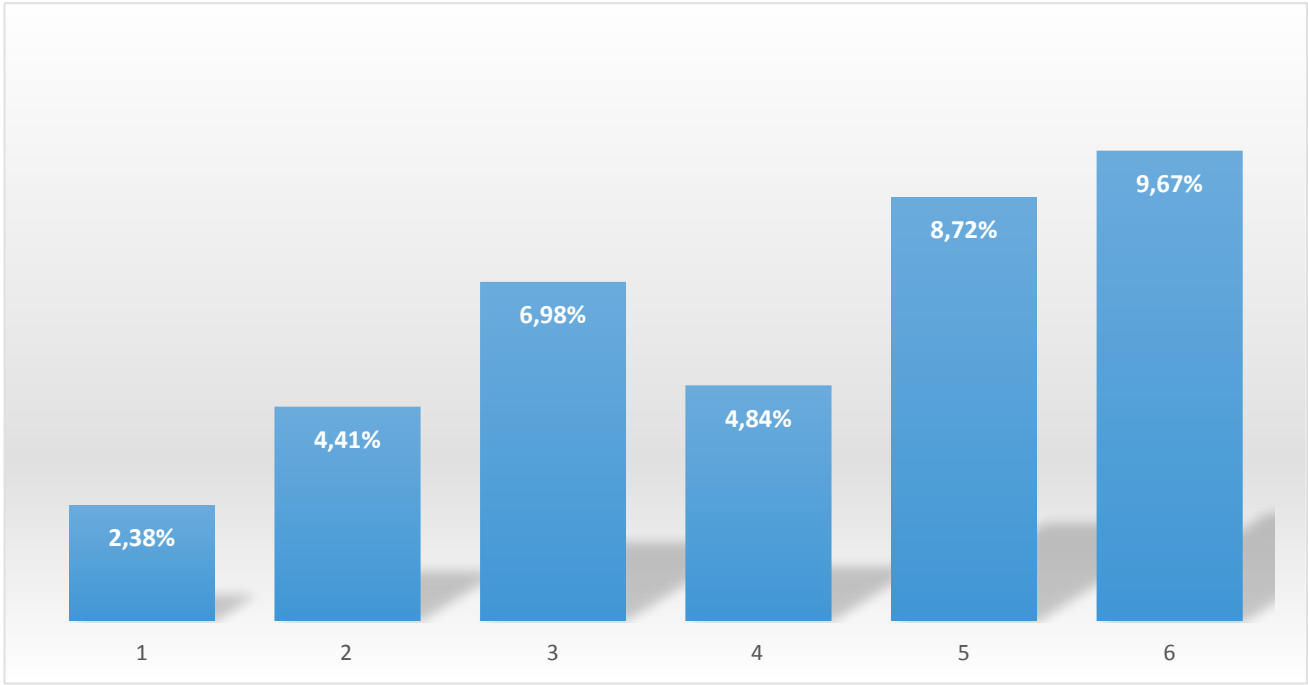
PI		
I50	I54	V82
VL	VLMTAS	ATSFLCM
1	3	2
0,21%	0,62%	0,41%

NRTI							
M41	K65	T69	L74	F77	Y115	M184	T215
L	R	D,Ins	VI	L	F	VI	YFSCDEIV
17	1	1	1	1	1	2	16
3,50%	0,21%	0,21%	0,21%	0,21%	0,21%	0,41%	3,29%

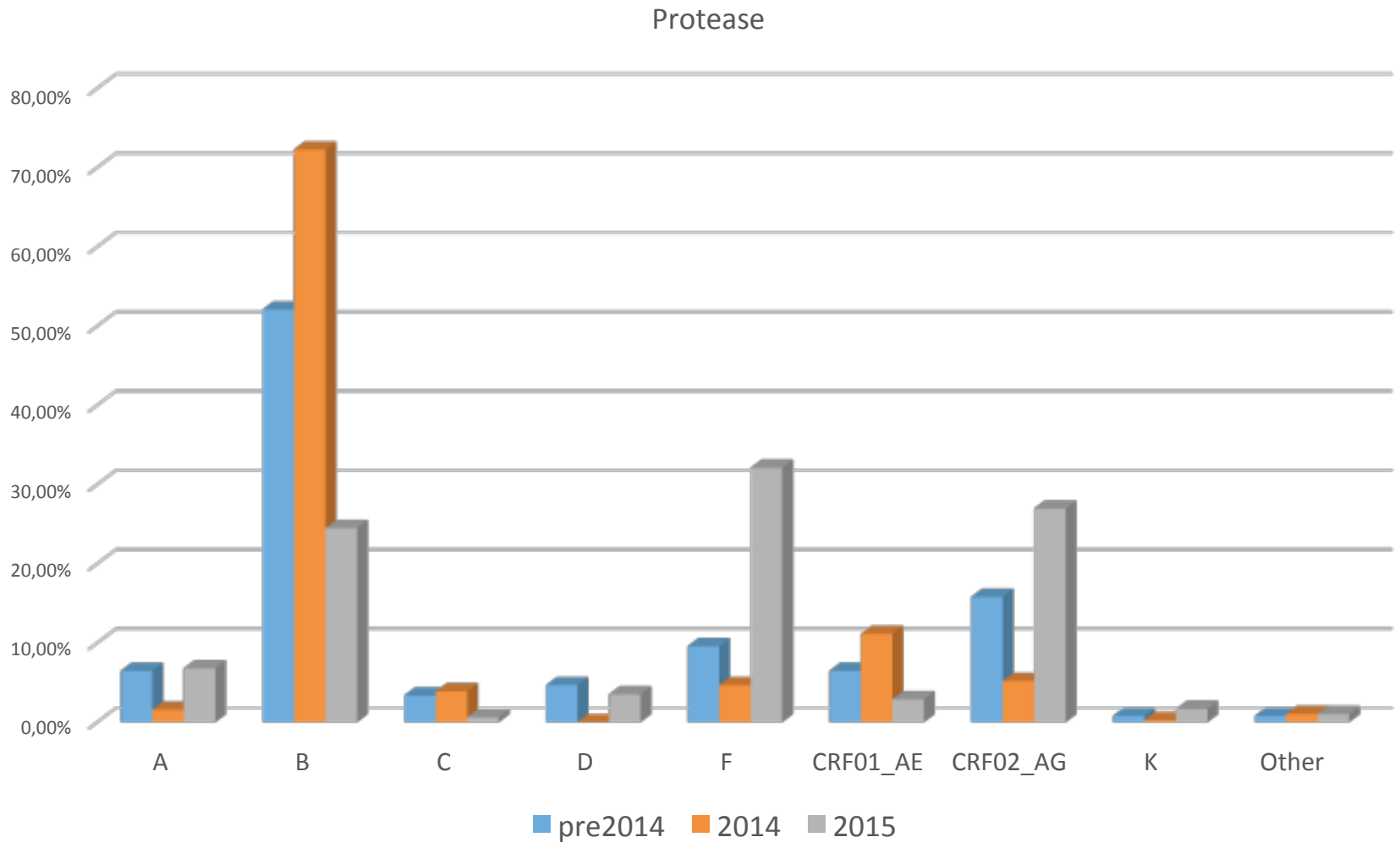
NNRTI						
K101	K103	V179	Y181	G190	V108	E138
EP	NS	F	CIV	ASE	I	KAGQ
1	4	7	2	1	1	47
0,21%	0,82%	1,44%	0,41%	0,21%	0,21%	9,67%

Emergence of E138 mutations among treatment naïve HIV-infected patients in Istanbul

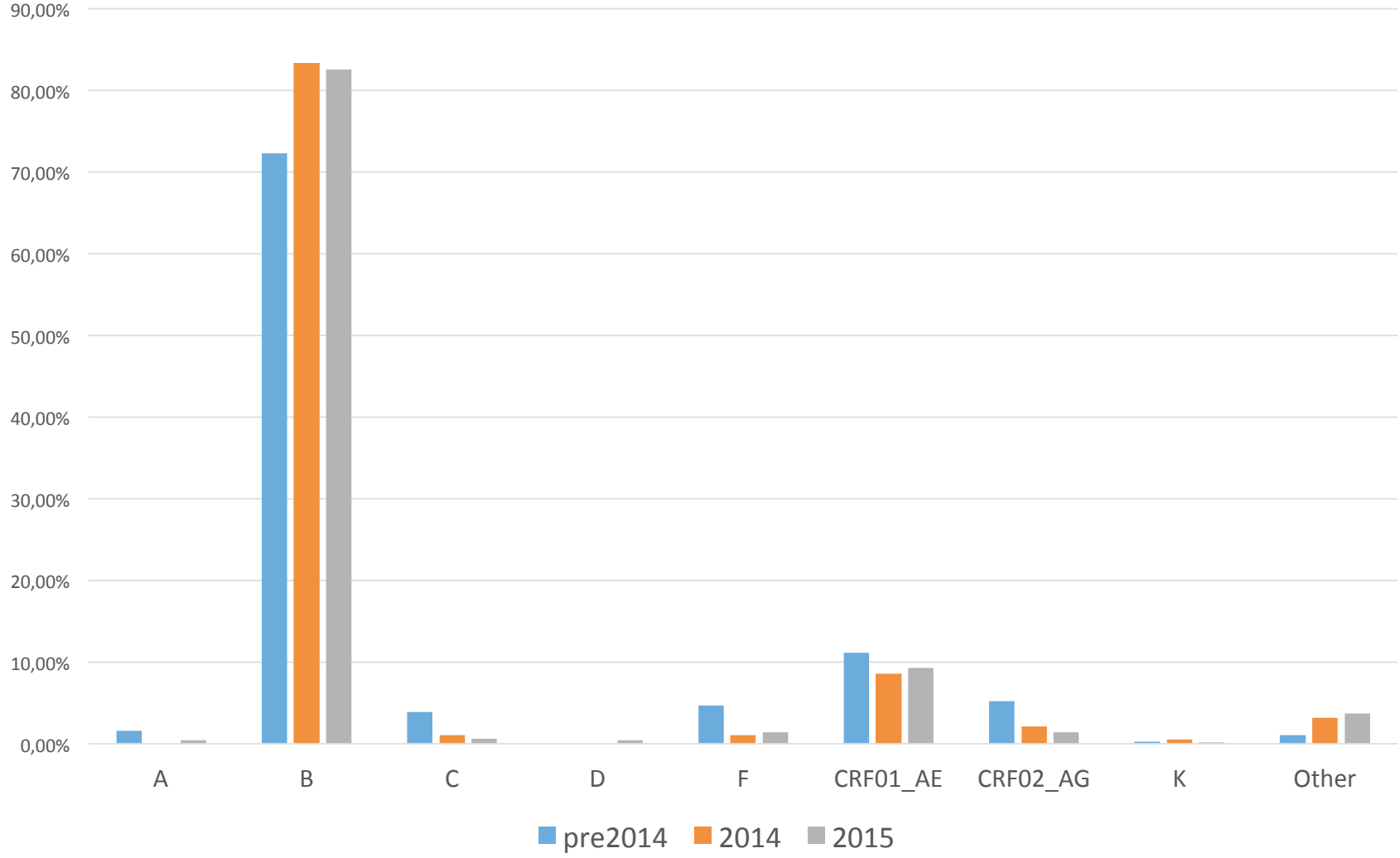
Year	n	E138AG	%
2009	42	1	2,38%
2010	68	3	4,41%
2011+2012	43	3	6,98%
2013	62	3	4,84%
2014	172	15	8,72%
2015	486	47	9,67%



Distrubition of HIV Genotypes Protease Based



Distrubition of HIV Genotypes RT Based



Transmitted Drug Resistance Mutation Rates

	Korten et all	Sayan et all	Kuskucu et all	
n	273	1306	590	
Years	2011	2010-2015	2004-2010	2011-2015
NRTI	6,90%	8,10%	5,92%	5,23%
NNRTI	0,00%	3,30%	3,55%	4,04%
PI	1,70%	2,30%	0,60%	1,60%
Any	8,60%	10,10%	10,00%	

Genetic subtypes of human immunodeficiency virus type 1 (HIV-1) in Istanbul, Turkey

Gülden Yılmaz*, Kenan Midilli, Salih Türkoğlu, Zübeyir Bayraktaroğlu, A. Mert Kuşkucu, Emine Özkan, Leman Atasever, Semra Çalangu, Kemal Altaş

Table 2 Distribution of the 19 HIV/AIDS patients with genotype B according to HIV acquisition route

HIV acquisition route	Number
Heterosexual contact	11
HIV-positive partner	1
Infant of an infected mother	1
Blood transfusion	2
Not defined	4

Table 3 The HIV genotypes of 27 patients

Genotype	Number
A	4
B	19
C	1
D	1
F1	2[a]

[a] One Russian sex worker and one high-risk sexual contact with a foreign partner.