
22.11.2015
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KENAN
MİDİLLİ
3.Ulusal
Klinik Mikrobiyoloji

3. Ulusal Klinik Mikrobiyoloji Kongresi-2015
18-22 Kasım 2015
Titanic Kongre Merkezi
Belek, Antalya

İNTERAKTİF OTURUM

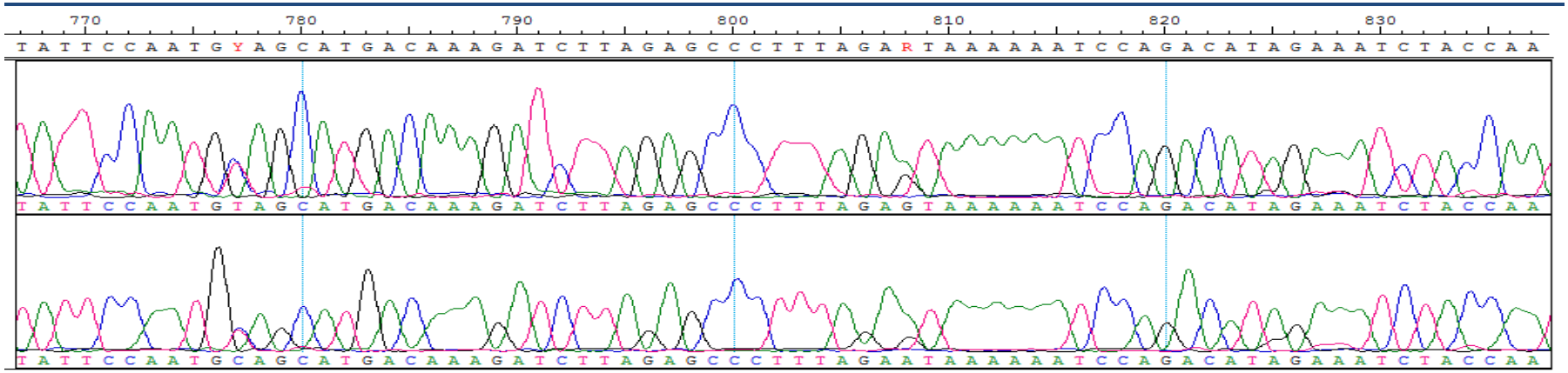
Antiviral Direnç - Olgular

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

Genotipik HIV Direnç Testi

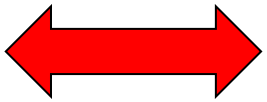


CCTCAGATCACTCTTTGGCAACGACCCATAGTCACAATAAAGATAGCGGGACAACTAAAGGAAGCTCTATTAGATACAGGAGCAGATGATACAGTATTAGAAGAA
ATGAATTTGCCAGGAAAATGGAAACCAAAAATAATAGTGGGAATTGGAGGGTTTACCAAAGTAAGACAGTATGATCATGTACAAATAGAAATCTGTGGACATAAA
GTTATAGGTGCAGTATTAATAGGACCTACACCTGCCAATATAATTGGAAGAAATCTGTTGACTCAGCTTGGCTGTACTTTAAATTTT

PQITLWQRPIVTIKIAGQLKEALLDTGADDTVLEEMNLPGKWKPKIIVGIGGFTKVRQYDHVQIEICGHKVIGAVLIGPTPANIIGRNLLTQLGCTL
NF

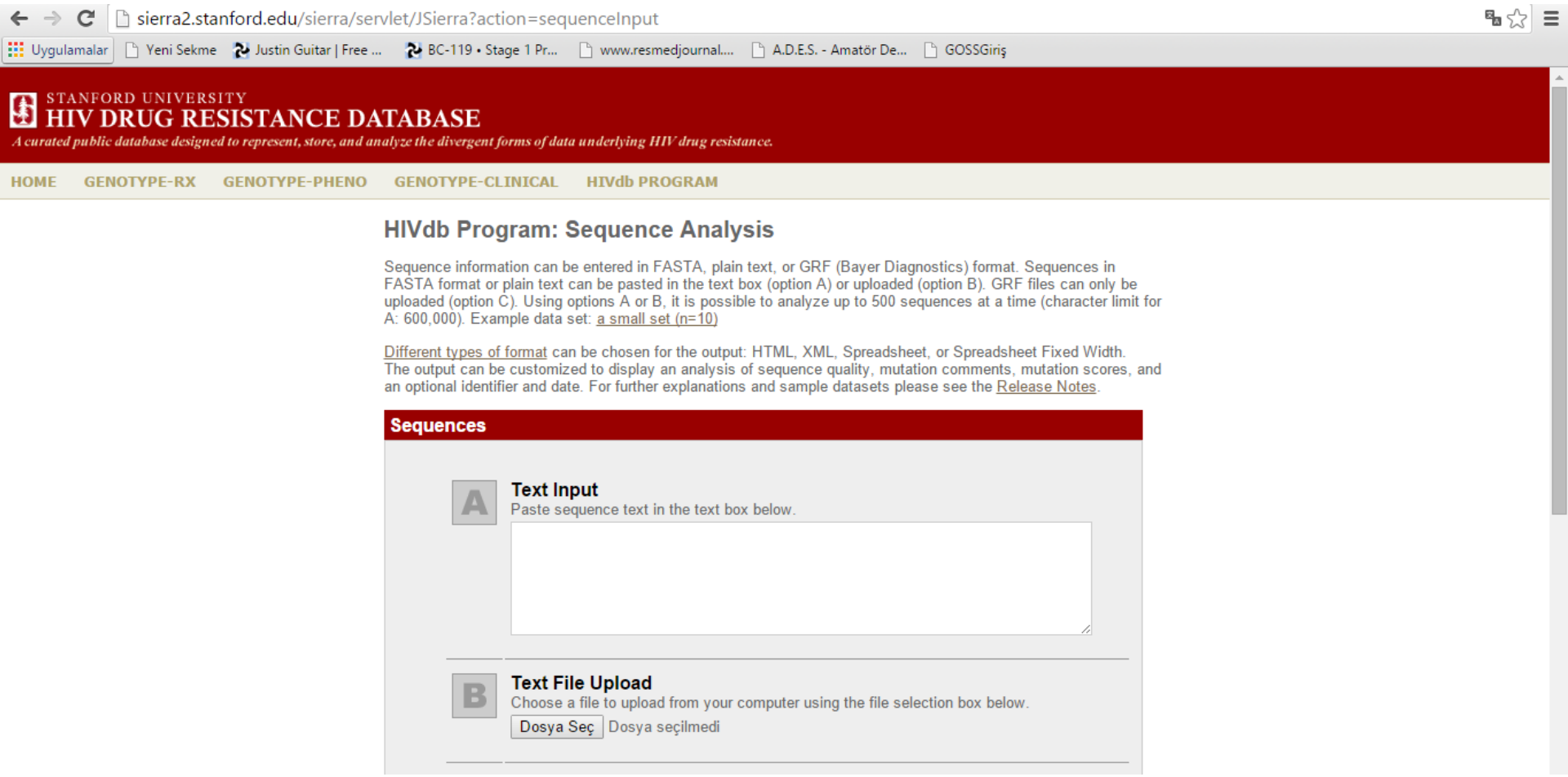
Differences from Consensus B:

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

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


sierra2.stanford.edu/sierra/servlet/JSierra?action=sequenceInput
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BC-119 • Stage 1 Pr...
www.resmedjournal....
A.D.E.S. - Amatör De...
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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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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:	**Expand** to set cutoff values explicitly (will slow down computation) show cutoffs
3. Pol-gene (PR and RT) nucleotide sequence:	upload from file (sequences in FASTA format, or single plain or FASTA sequence): Dosya Seç Dosya seçilmedi or paste in:
4. Therapy-na&#65533;ve tool:	enable therapy-na&#65533;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

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REGA HIV Subtyping Tool

HIV BIOINFORMATICS BIOAFRICA

You may bookmark this page to revisit these results later.

Analysis in progress... (Showing partial results).
This page will be automatically updated every 5 seconds... Cancel job

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

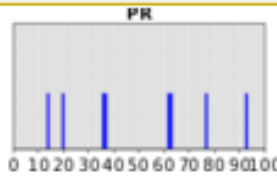
Summary Data

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:

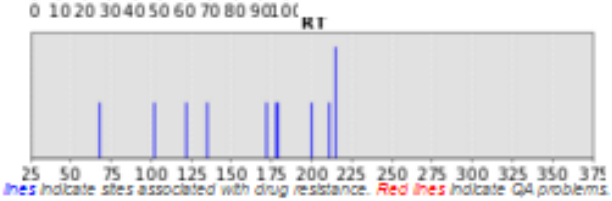
1. *PR: B (93.1%)*
2. *RT: B (96.0%)*

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	ATVr	DRVr	FPVr	IDVr	LPVr	NFV	SQVr	TPVr
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

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).

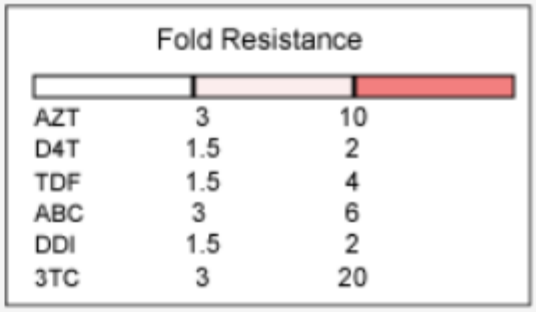
Mutation Scoring

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.



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 68G
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 57K
LPV	0.533	-2.232	74S 41K 89M 12I 70R 65D
TPV	1.312	0.498	89M 14R 15V 74S 36I 41K 63T
DRV	1.261	0.509	89M 74S 65D 14R 41K
ATV	0.575	-2.385	41K 36I 74S 62V

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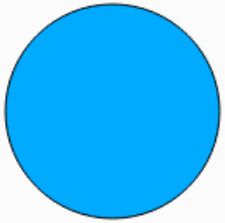
REGA HIV Subtyping Tool

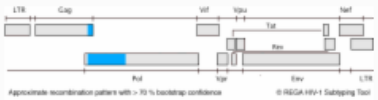
HIV BIOINFORMATICS BIOAFRICA

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.

Olgu - 1

- 30 Yaşında erkek hasta
- 2013’de tanı
- CD4; 670
- Viral yük 138,000 kopya/ml

HIVdb: Genotypic Resistance Interpretation Algorithm

Date: 24/03/2013

Seq ID: HD_2013_037

Summary Data

Sequence includes PR: codons: 8 - 99

Sequence includes RT: codons: 1 - 235

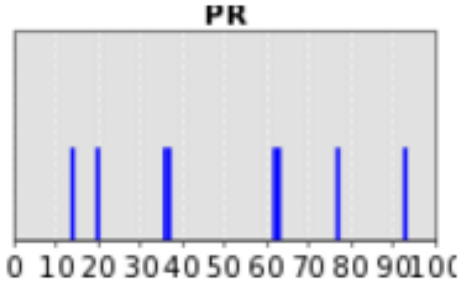
There are no insertions or deletions

Subtype and % similarity to closest reference isolate:

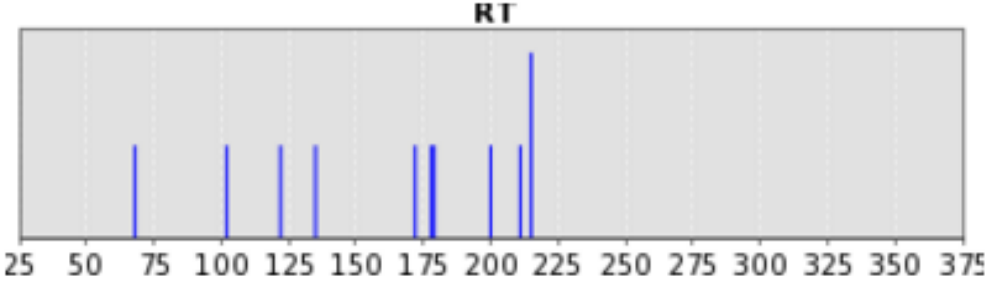
1. *PR: B (93.1%)*
2. *RT: B (96.0%)*

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

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.

- Özellikle orta ve alt gelir grubundan ülkelerde NRTI+NNRTI kombinasyonları yaygın olarak kullanılmakta.
- Düşük genetik bariyer → NRTI+NNRTI kombinasyonlarının uzun erimli tedavi başarı aralıkları dar
- Tedavi başarısızlıkları %10-30 / Hasta-yıl

- 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 zidovudine/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

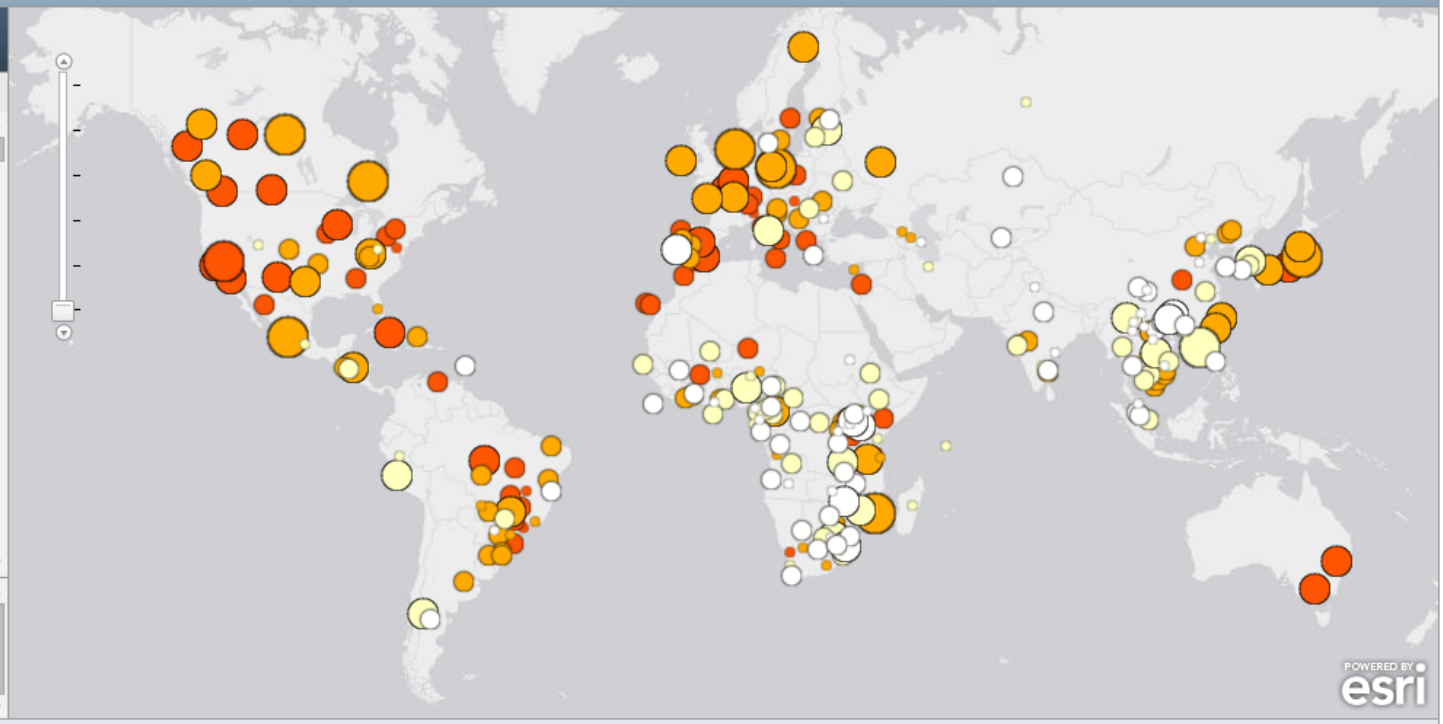

T215
T 215 S
T 215 C
T 215 D
T 215 E
T 215 I
T 215 V
T 215 N
T 215 A
T 215 L
T 215 Y
T 215 F
Revertan Mutasyonlar

HIV-1 Drug Resistance in ARV-naive Populations

Compendium of published virus sequences from 50,869 persons, 287 studies according to region, year and subtype

Publications

Continent	Country	Publication	Resistance (%)	n
Africa	ANGOLA	Yang10	0	39
Africa	ANGOLA	Bartolo14	2.1	140
Africa	ANGOLA	Bartolo09	4.1	121
Africa	ANGOLA	Castelbranco10	5.7	35
Africa	BENIN	Chamberland12	3.9	127
Africa	BOTSWANA	Bussmann05	0	71
Africa	BOTSWANA	Bussmann11	1.3	152
Africa	BURKINA FASO	Somda12	6.2	48
Africa	BURKINA FASO	Tebit09	12.5	104
Africa	BURKINA FASO,CAME	Vergne08	3.1	195
Africa	BURKINA FASO,COTE D'IVOIRE,SE	Ayouba09_Africa	0.7	147
Africa	BURUNDI	Vidal07	1	105
Africa	CAMEROON	Carr05_Africa	0	91
Africa	CAMEROON	Njai08	0	27



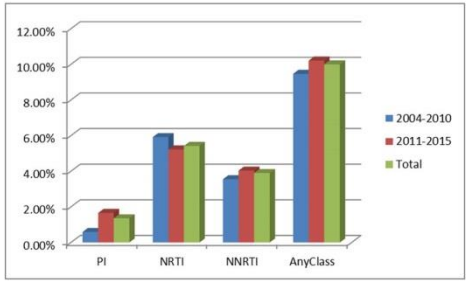
Abstract ID: 1698

Transmitted Drug Resistance (TDR) Prevalance Among Treatment Naive HIV-1 Infected Patients in Istanbul Remained Unchanged Between 2004-2015

Mert Ahmet Kuskucu[1], Kenan Midilli[1], Mucahit Yemisen[2], Ali Abdelkareem[1], Sevgi Ergin[1], Fehmi Tabak[2]
[1] I.U. Cerrahpasa School of Medicine, Department of Medical Microbiology
[2] I.U. Cerrahpasa School of Medicine, Department of Infectious Diseases

Prevalance of HIV in Turkey is low but during the last three years the number of the newly diagnosed HIV infections have been almost doubled each year. Due to rapid evaluation of HIV-1 the drug resistance mutations accumulate rapidly under the sellective pressure of antiretroviral (ARV) drugs. A genotypic antriretroviral drug resistance testing (ART) at the time of diagnosis or before the initiation of the ART recommended by all currently avialable guidelines. In this study, the transmitted drug resistance (TDR) prevalences between 2004-early 2015 were evaluated in 590 treatment naive patients.

As an academic center, we serve also to other centers caring HIV patients since 2004. A home-brewed genotyping resistance test relying on Sanger Sequencing following nested RT-PCR have been applied routinely and resistance muations were identified using Stanford HIV Drug Resistance Database (hivdb.stanford.edu). TDR was identified using the surveillance drug resistance mutations (SDRMs) listed by the World Health Organization. The antiretroviral resistance rates of two periods (2004-2010 and 2011- early 2015) were compared.



	PI (n/%)		NRTI		NNRTI		AnyClass	
	n	%	n	%	n	%	n	%
2004-2010	1	0.59%	10	5.92%	6	3.55%	16	9.47%
2011-2015	7	1.66%	22	5.23%	17	4.04%	43	10.21%
Total	8	1.36%	32	5.42%	23	3.90%	59	10.00%

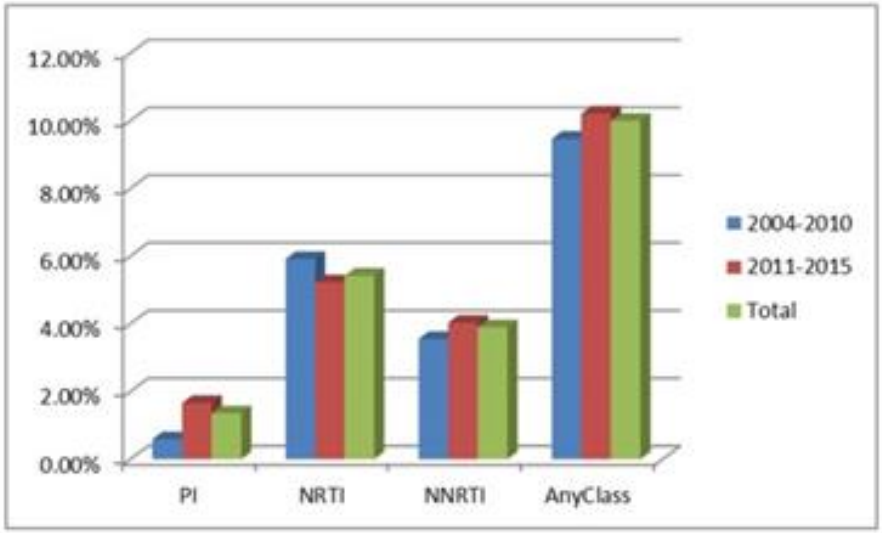
Among 590 patients 59 had at least one SDRM, giving a overall TDR prevalence of 10.0 %. Regarding the specific ARV classes, the prevalence of SDRMs was 5.42% for nucleoside reverse transcriptase inhibitors (NRTIs), 3.9 % for non-NRTIs (NNRTIs), and 1.36 % for protease inhibitors (PIs).

PI Mutations							
	D30N	M46I	I50L	F53Y	I54V	V82A	L90M
2004-2010	0	0	0	0	1	1	0
2010-2015	1	1	2	2	0	0	1
Total	1	1	2	2	1	1	1

NRTI Mutations					
	M41L*	L74V	M184V	T215*	K219R*
2004-2010	7	0	2	8	0
2010-2015	15	1	0	20	2
Total	22	1	2	28	2

NNRTI Mutations					
	K101E	K103R	V179D	Y181C	G190E
2004-2010	1	2	1	1	0
2010-2015	2	10	5	0	1
Total	3	12	6	1	1

The TDR rate for PIs was 0,6 % during the first period, but increased to 1,6 % after 2010. SDRMs conferring NRTI resistance were detected in 5.92 % and 5.23 % of the patients during the first and seceond periods, respectively. SDRMs related with NNRTI resistance incresed from 3.55 % to 4.04 %. The changes in the resistance prevalences did'nt reach statistical sinificance for any drug class. Mutations related to TDR to PIs were D30N (n=1), M46I (n=1), I50L (n=2), F53Y (n=2), I54V(n=1), V82A(n=1), L90M(n=1). The main NRTI related TDR mutations were TAMs (M41L (n=22), T215Y/F/I/S/C/D/V/E (n=28), K219Q/E/N/R (n=2). Other NRTIs related TDR mutations were L74V (n=1) and M184V/I (n=2). SDRMs related to NNRTI resistance were K103N/S (n=12) , K101E (n=3), V179D (n= 6), Y181C (n= 1), G190E (n= 1). Most of the changes at T215 were revertant mutations. Despite to the relative increases in the numbers of the newly diagnosed cases and the patients receiving ART, the prevalence of TDR remained unchanged in a period of about 10 year.



	PI (n/%)		NRTI		NNRTI		AnyClass	
	n	%	n	%	n	%	n	%
2004-2010	1	0.59%	10	5.92%	6	3.55%	16	9.47%
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Total	8	1.36%	32	5.42%	23	3.90%	59	10.00%

Olgu → T 215 V

Tedavi karalarını etkiler mi?

Virusun duyarlılık durumu ne?

Hastada T215 Y/F taşıyan alt popülasyonlar olablir mi?

Genotipik Testlerin Duyarlılıkları

- Topluluk sekanslamasına dayalı genotipik testlerde alt saptama sınırı %20 civarında
- Kesin olarak göstermek için NGS
- → Klinik açıdan anlamlı sınır % 1

Olgu-2

- 1986 Doğumlu Erkek,
- IVD ilaç bağımlılığı öyküsü var
- 2011 yılında tüberküloz nedeni ile hastaneye yatırılıyor ve bu sırada HIV-1 infeksiyonu tanısı konuyor.
- Viral yük 8 000 kopya/ml; CD4 sayısı 150/mm3
- ART ve anti-Tbc tedavi başlanıyor
- Hasta taburcu edildikten sonra ilaçlarını düzenli olarak almıyor

- 2015 yılı Mart ayında pnömoni ile tekrar yatırılıyor
- Bu sırada viral yük 1400 kopya/ml; CD4 sayısı 150/mm3
- Emtrisitabin/Efavirenz ve Lopinavir/ritonavir kombinasyonları ile tedaviye başlanıyor
- Tedavinin 3. ayında
  - Viral yük 750 kopya/ml;
  - CD4 120
- Tedavinin 6. ayında
  - viral yük 550 kopya/ml;
  - CD4 110
- Direnç Testi isteniyor

HIVdb: Genotypic Resistance Interpretation Algorithm

Report: HD_15_379 Date: 17/10/2015

Seq ID: HD_15_379

Summary Data

Sequence includes PR: codons: 8 - 99

Sequence includes RT: codons: 1 - 234

There is evidence of Apobec 3G/F Hypermutation

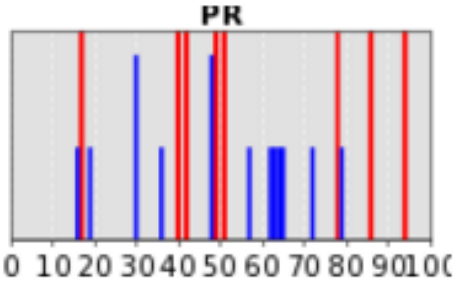
There are no insertions or deletions

Subtype and % similarity to closest reference isolate:

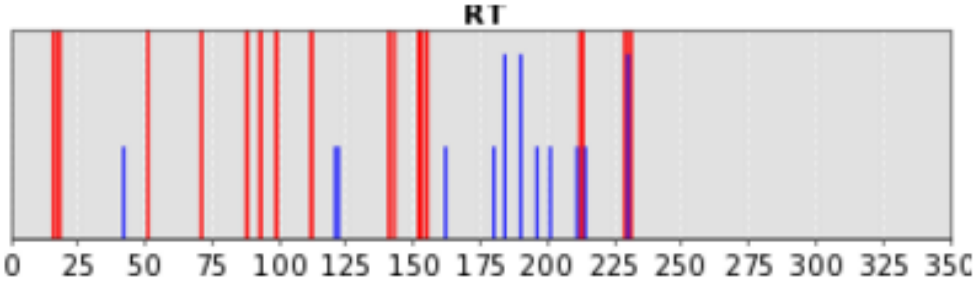
1. *PR: B (87.7%)*
2. *RT: B (92.0%)*

Sequence Quality Assessment

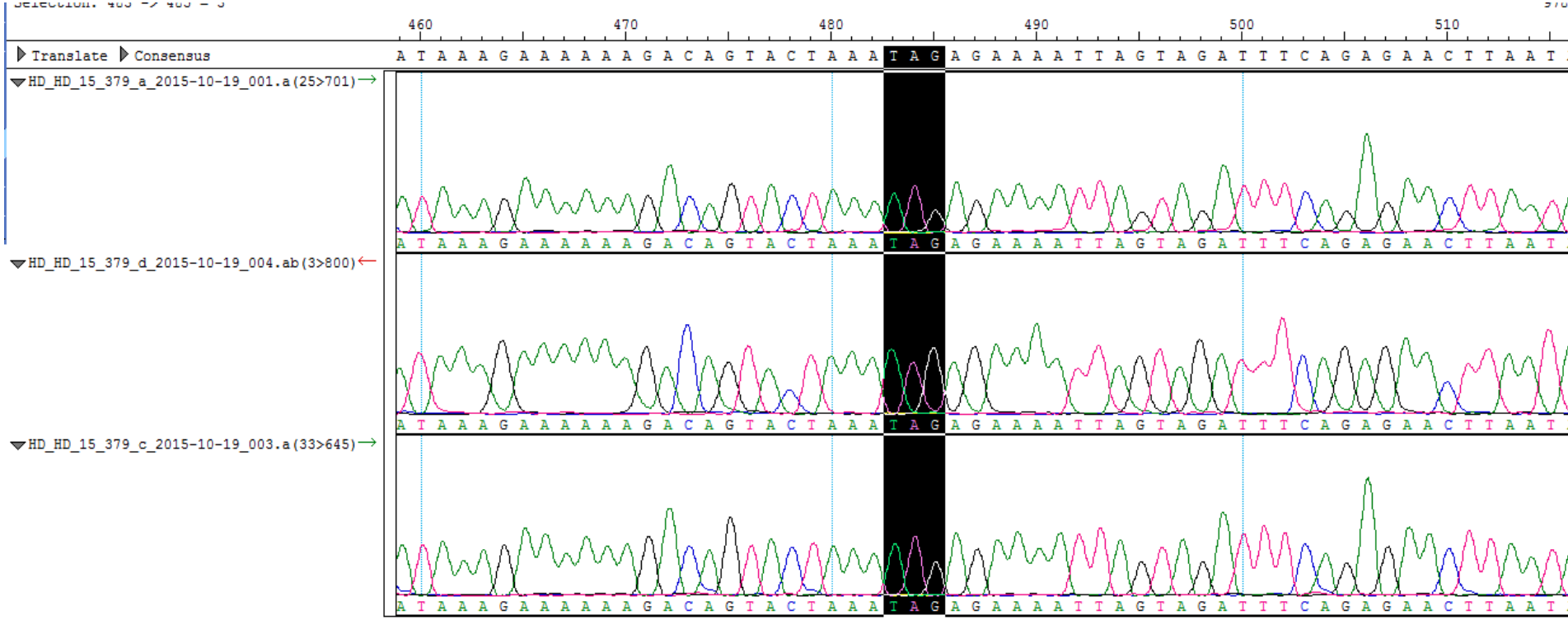
Gene	QA Problem	Codons
PR	Stop Codons, Frame Shifts:	42
PR	Ambiguous Positions:	*None*
PR	Unusual Residues:	17, 40, 48, 49, 51, 78, 86, 94
PR	Apobec 3G/F:	G17R, G40R, W42*, G48R, G49R, G51R, G86R, G94S



Gene	QA Problem	Codons
RT	Stop Codons, Frame Shifts:	71, 88, 153, 229
RT	Ambiguous Positions:	212
RT	Unusual Residues:	16, 18, 51, 93, 99, 112, 141, 143, 152, 155, 190, 213, 230, 231
RT	Apobec 3G/F:	M16I, G18R, G51R, W71*, W88*, G93K, G99R, G112S, G141R, G152R, W153*, G155R, G190R, G213K, W229*, G231S



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


460
470
480
490
500
510
Translate
Consensus
HD_HD_15_379_a_2015-10-19_001.a(25>701)
HD_HD_15_379_d_2015-10-19_004.ab(3>800)
HD_HD_15_379_c_2015-10-19_003.a(33>645)

Drug Resistance Interpretation: PR

PI Major Resistance Mutations:	**D30N**
PI Minor Resistance Mutations:	**G48R**
Other Mutations:	G16E, G17R, L19I, M36I, G40R, W42*, G49R, G51R, R57K, I62V, L63P, I64L, E65K, I72V, G78GV, P79HP, G86R, G94S

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)	High-level resistance
saquinavir/r (SQV/r)	Susceptible
tipranavir/r (TPV/r)	Susceptible

PR Comments

PIMajor

- D30N is a nonpolymorphic substrate-cleft mutation that causes high-level resistance to NFV.

PIMinor

- G48V causes high-level resistance to SQV, intermediate-level resistance to ATV and NFV, and low-level resistance to IDV and LPV. G48M is a less common mutation that appears to have similar effects on PI susceptibility. G48A/S/T/Q/L are rare PI-selected mutations. G48R is a highly unusual mutation at this position.

Drug Resistance Interpretation: RT

NRTI Resistance Mutations:	**M184I**
NNRTI Resistance Mutations:	**G190R, M230I**
Other Mutations:	M16I, G18R, E42K, G51R, W71*, W88*, G93K, G99R, G112S, D121Y, K122E, G141R, R143K, G152R, W153*, G155R, S162C, I180V, G196K, K201I, R211K, W212X, G213K, F214I, W229*, G231S

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

RT Comments

NRTI

- 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.

NNRTI

- G190A causes high-level resistance to NVP and intermediate resistance to EFV. G190S cause high-level resistance to NVP and EFV. G190E/Q cause high-level resistance to NVP, EFV, ETR and RPV. G190R is a highly unusual mutation at this position.
- M230I is an extremely rare mutation selected in vitro by RPV. Its effects on NNRTI susceptibility have not been well studied.

HIV'de Direnç Gelişimi

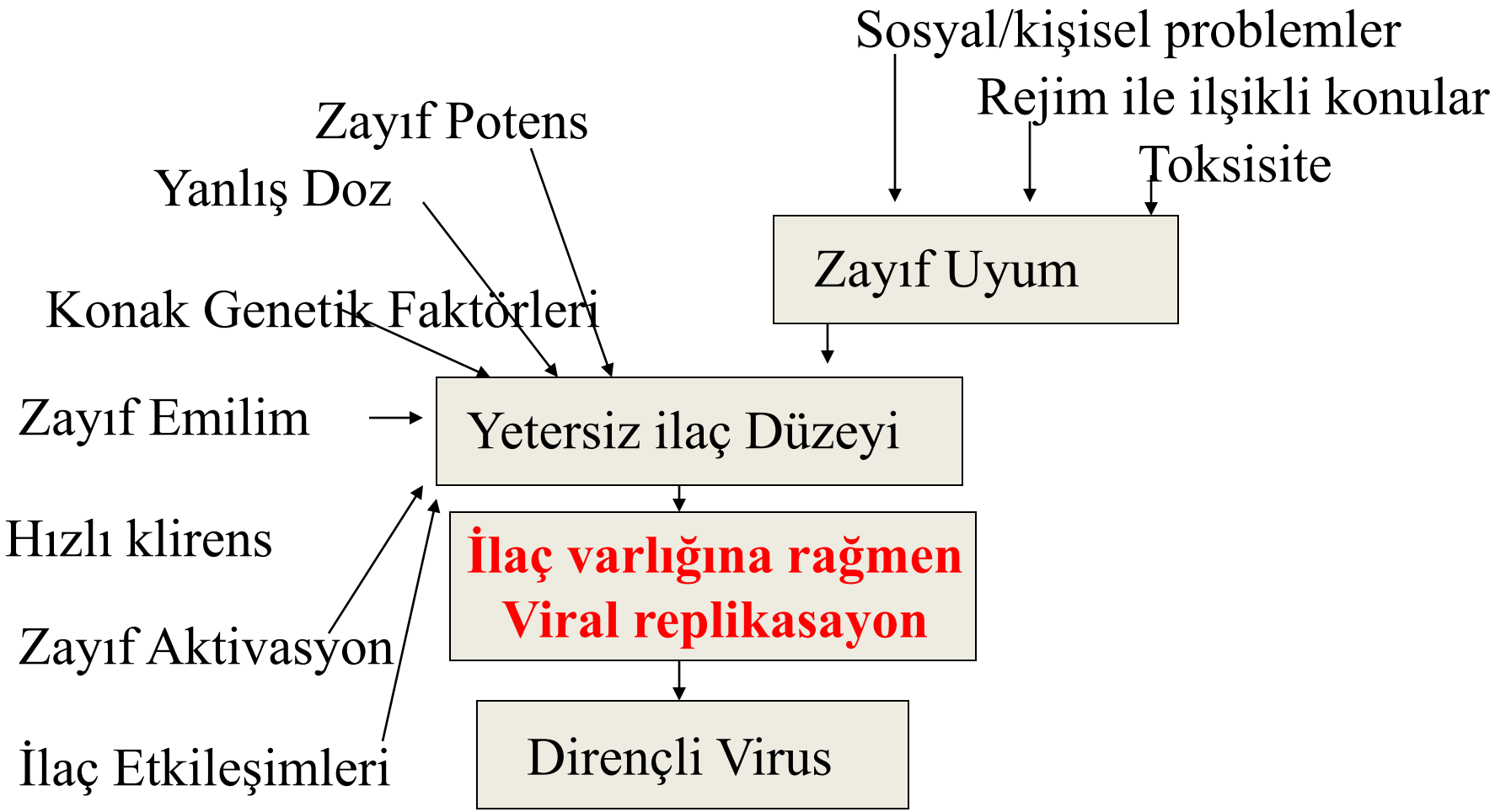
Günlük ➔ 10^9-10^{12} yeni viryon oluşumu; RT hataları nedeni ile yüksek mutasyon hızı

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

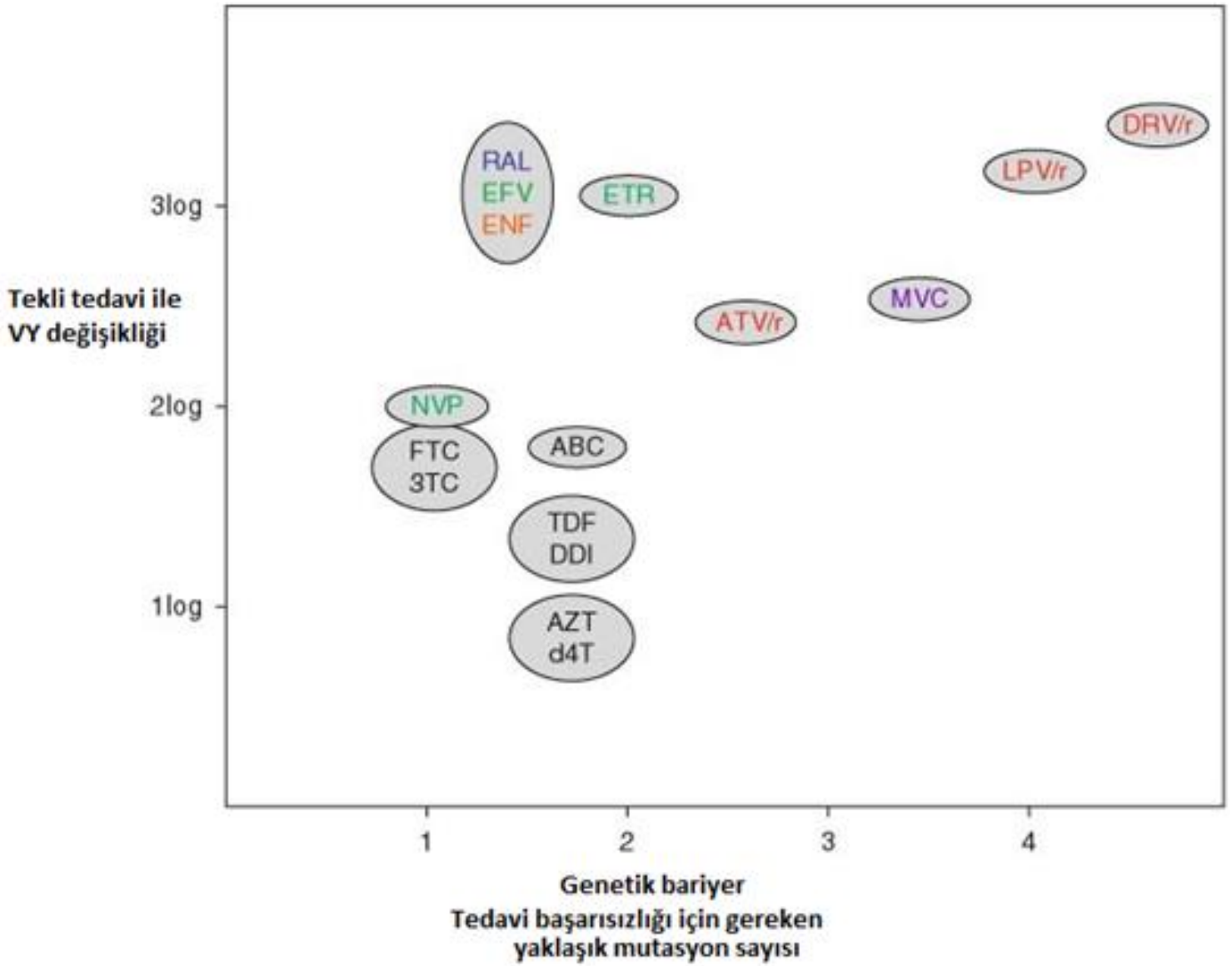
Virusa ait Özellikler:

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.



- 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