Türkiye'de Antiretroviral Direncin Moleküler Epidemiyolojisi

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KLİMİK 2016,
9 – 12 Mart, Antalya.

Tablo 1. Türkiye'de HIV-1 ile infekte olgu sayısı*.

Yıl	Yeni tanı, n	Kümülatif HIV/AIDS, n	Kümülatif artış, %
2010	516	4525	16
2011	632	5224	15
2012	973	5740	10
2013	1280	6802	19
2014	1767	9379	38
2015 Kasım	1730	11109	18.4
2015 (orantı ile)	1887	11266	20

Her gün yaklaşık 5 kişi HIV-1 ile infekte oluyor.

*T.C. Sağlık Bakanlığı

Tablo 2. Antiretroviral ilaç kullanımı

Özellik	Dünya	Türkiye
Antiretroviral ilaç (backbone)	15 milyon	650*

*IMS Türkiye verilerine göre Şubat 2016 itibariyle
http://imsturkey.com/

Tablo 3. HIV-1 ilaç direnci analizi: veritabanımdan*

Dönem	Tedavi naif hasta	ART deneyimli hasta	Toplam
2010 – Mart 2016	2404	565	2969**

*Türkiye' de 68 enfeksiyon hastalıkları kliniğine ait hasta analizini içermektedir
** Tekrarlanan ve/veya henüz sonuçlanmamış analizler dahildir.

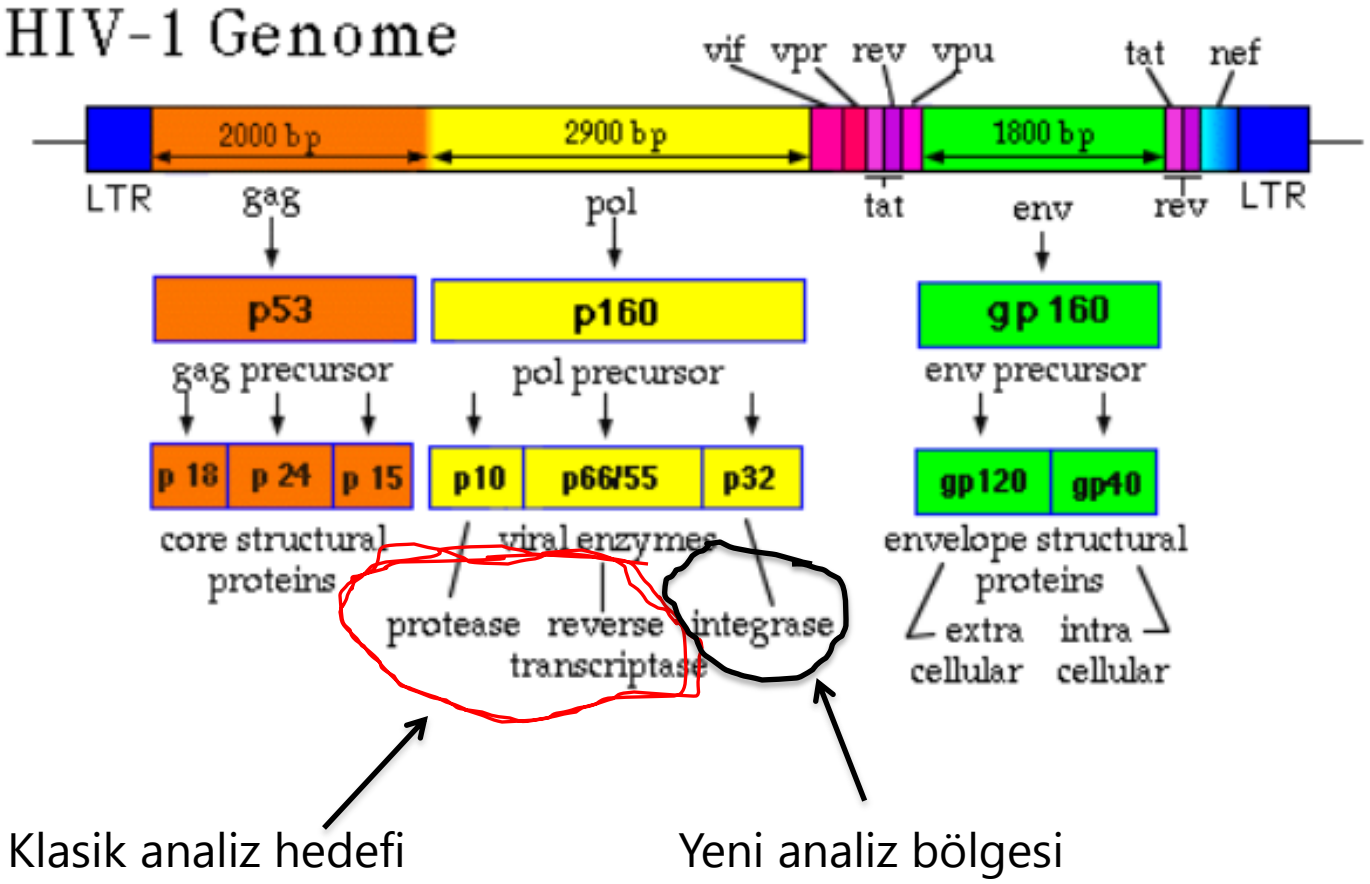
Neden antiretroviral ilaç direnci gelişir?

- HIV-1 populasyon turnoveri çok hızlıdır (T1/2 - gün)
- Virusun hatalı replikasyon oranı çok yüksektir (3×10^{-5} mutasyon/baz/replikasyon siklusu)
- *In vivo*, geniş ölçekte ve genetik değişken viral populasyonlar meydana gelir.

Perelson AS, Science 1996;271:1582-1586.

HIV-1 ilaç direnci analizi: viral populasyonun sekanslanması

- Fransız ANRS algoritması
- Stanford Univ. veribankası
- WHO surveyans kriterleri



OPEN ACCESS Freely available online

PLoS one

Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance: 2009 Update

Diane E. Bennett[1], Ricardo J. Camacho[2], Dan Otelea[3], Daniel R. Kuritzkes[4], Hervé Fleury[5], Mark Kiuchi[6], Walid Heneine[7], Rami Kantor[8], Michael R. Jordan[9], Jonathan M. Schapiro[6], Anne-Mieke Vandamme[10], Paul Sandstrom[11], Charles A. B. Boucher[12,13], David van de Vijver[12], Soo-Yon Rhee[6], Tommy F. Liu[6], Deenan Pillay[14], Robert W. Shafer[6]*

- Integraz inhibitörleri WHO HIV TDRM surveyans listesinde yer almıyor.
- Kılavuzun güncellenmesini bekliyoruz.

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
85	V
N88	D, S
L90	M

WHO transmitted HIV drug resistance surveys

Figure 1.1 HIV drug resistance testing laboratories designated for public health surveillance by the WHO, 2011

★ Laboratories designated by WHO for HIV drug resistance surveillance

★ Laboratories undergoing assessment

Not applicable

Category of transmitted HIV drug resistance
Low prevalence (<5%)
Moderate prevalence (5%–15%)
High prevalence (>15%)

HIV-1 Transmitted Drug Resistance Mutations in Newly Diagnosed Antiretroviral-Naive Patients in Turkey.

Sayan M, Sargin F, Inan D, Sevgi DY, Celikbas AK, Yasar K, Kaptan F, Kutlu S, Fisgin NT, Inci A, Ceran N, Karaoglan I, Cagatay A, Celen MK, Koruk ST, Ceylan B, Yildirmak T, Akalın H, Korten V, Willke A.

AIDS Res Hum Retroviruses. 2016 Jan;32(1):26-31. doi: 10.1089/AID.2015.0110. Epub 2015 Oct 21.
PMID: 26414663

Table 2. Primary drug resistance mutations in newly diagnosed HIV-1 infected patients in Turkey (between 2010 – 2015, n=1306).

Drug class	Drug resistance mutation*	n	%
NRTI	K65R, M184V	8	0.6
TAM1	M41L, L210W, T215Y	97	7.4
TAM2	D67N, K70R, K219E/Q/N/R, T215F, T215C/D/S	52	3.9
TAM1 + TAM2	M41L + K219N, M41L + T215C/D/S	10	0.7
		107	8.1
NNRTI	L100I, K101E/P, K103N/S, V179F, Y188H/L/M, Y181I/C, G190A/E/S	44	3.3
PI	M46L, I50V, I54V, Q58E, L76V, V82A/C/L/T, N83D, I84V, L90M	30	2.3
Total		133	10.1

Abbreviations; NRTI; nucleoside RT inhibitors, NNRTI; non-nucleoside RT inhibitors, PI; protease inhibitors, TAM; thymidine analogue - associated mutation

*The number of "n" consisted with each mutation detected patient

*Subtype of HIV-1 is not a variable in identification of drug resistance mutation.

Tablo 4. Yeni tanı alan HIV (+) hastalarda TAMs.

Kategori	Mutasyon paterni	n=774 (2014 Mart)		n=1306 (2015 Mart)	
TAM1	M41L, L210W, T215Y	60	7.7%	97	7.4%
TAM2	D67N, K70R, K219E/Q/N/R, T215F, T215C/D/S	34	4.3%	52	3.9%
TAM1 + TAM2	M41L + K219N, M41L + T215C/D/S	18	2.3%	10	0.7%

Multi-nRTI Resistance: Thymidine Analogue-Associated Mutations[d,e] (TAMs; affect all nRTIs currently approved by the US FDA)

M	D	K	L	T	K
41	67	70	210	215	219
L	N	R	W	Y F	Q E

TAMs affect all NRTIs especially previously backbone therapy. However, there are revertant in the treatment naive patients.

Hoffmann - Rockstroh - Kamps

HIV Medicine 2007

www.HIVMedicine.com

HIVdb: Genotypic Resistance Interpretation Date: 08-Mar-2016

Seq ID: A.Y

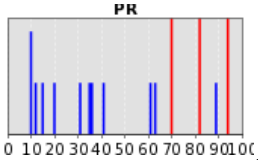
Summary Data

Sequence includes PR: codons: 1 - 99

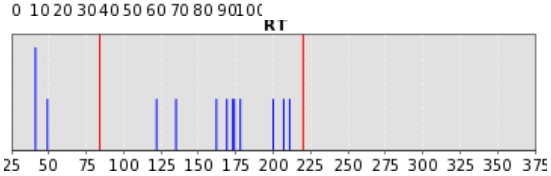
Sequence includes RT: codons: 41 - 222

Sequence Quality Assessment

Gene	QA Problem	Codons
PR	Stop Codons, Frame Shifts:	70, 82, 94
PR	Ambiguous Positions:	*None*
PR	Unusual Residues:	*None*



Gene	QA Problem	Codons
RT	Stop Codons, Frame Shifts:	84
RT	Ambiguous Positions:	220
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:	**L10V**
Other Mutations:	T12A, I15V, K20R, T31S, E35D, M36I, R41K, Q61N, L63T

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

Drug Resistance Interpretation: RT

NRTI Resistance Mutations:	**M41L**
NNRTI Resistance Mutations:	None
Other Mutations:	K49R, K122E, I135V, S162C, E169D, K173A, Q174K, I178L

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)	Potential low-level resistance		

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Cep: 0 533 647 9020

HIVdb: Genotypic Resistance Interpretation Date: 08-Mar-2016

Seq ID: T.A.A

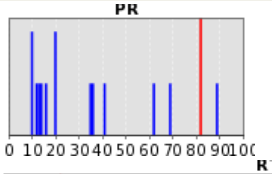
Summary Data

Sequence includes PR: codons: 1 - 98

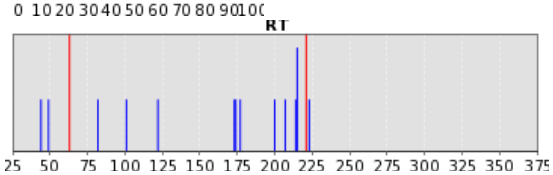
Sequence includes RT: codons: 43 - 223

Sequence Quality Assessment

Gene	QA Problem	Codons
PR	Stop Codons, Frame Shifts:	82
PR	Ambiguous Positions:	*None*
PR	Unusual Residues:	*None*



Gene	QA Problem	Codons
RT	Stop Codons, Frame Shifts:	63, 215, 221
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: **L10I, K20I**

Other Mutations: T12P, I13V, K14E, G16E, E35D, M36I, R41K, I62K, H69K

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

Drug Resistance Interpretation: RT

NRTI Resistance Mutations: **T215N**

NNRTI Resistance Mutations: None

Other Mutations: E44G, K49R, K82R, K101R, K122E, K173T, Q174K, D177E

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		

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Cep: 0 533 647 9020

HIVdb: Genotypic Resistance Interpretation Date: 16-Nov-2015

Seq ID: M.T

Summary Data

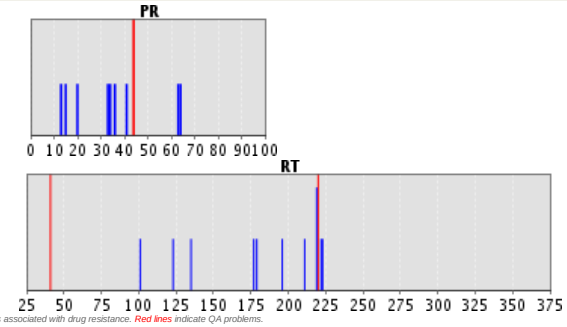
Sequence includes PR: codons: 1 - 99

Sequence includes RT: codons: 41 - 223

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:	41, 220



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:	I13V, I15L, K20M, L33V, E34G, M36V, R41K, L63H, I64V

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

Drug Resistance Interpretation: RT

NRTI Resistance Mutations:	**K219N**
NNRTI Resistance Mutations:	None
Other Mutations:	M41V, K101Q, D123E, I135K, D177G, V179I, G196E, R211K

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

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Table 1: Demographic characteristics of the patients infected with HIV-1.

Characteristic	**Study group**			
Patient, n	1306			
Gender, M/F (%)	1151/155 (88/12)			
Age, median years (range)	36 (3 - 74)			
$CD4^+$ T-cell count, median mm^3 (range)	361 (4 - 1351)			
HIV-RNA load, median IU/ml (range)	2.59+E6 (6.8+E2 - 3.29+E6)			
HIV-1 subtype, n (%)	Subtype B	885 (68)	-	-
	Non-subtype B	136 (10)	A1 C D F F1 F2 G K	48 (3.6) 21 (1.6) 3 (0.2) 2 (0.1) 24 (1.8) 1 (0.07) 36 (2.7) 1 (0.07)
	Circulating recombinant form (CRF)	285 (22)	CRF01_AE CRF 02_AG CRF 03_AB CRF 06_cpx CRF 07_BC CRF 08_BC CRF 11_cpx CRF 12_BF CRF 13_cpx CRF 14_BG	132 (10.1) 85 (6.5) 13 (1) 3 (0.2) 1 (0.07) 1 (0.07) 3 (0.2) 33 (2.5) 3 (0.2) 11 (0.8)

HIV-1 Transmitted Drug Resistance Mutations in Newly Diagnosed Antiretroviral-Naive Patients in Turkey.

Sayan M, Sargin F, Inan D, Sevgi DY, Celikbas AK, Yasar K, Kaptan F, Kutlu S, Fisgin NT, Inci A, Ceran N, Karaoglan I, Cagatay A, Celen MK, Koruk ST, Ceylan B, Yildirmak T, Akalın H, Korten V, Willke A.

AIDS Res Hum Retroviruses. 2016 Jan;32(1):26-31. doi: 10.1089/AID.2015.0110. Epub 2015 Oct 21.
PMID: 26414663

Table 1: Demographic characteristics of the patients infected with HIV-1.

Acquisition route, n (%)	Heterosexual contact	674 (52)
	MSM	563 (43)
	Bisexual contact	47 (3.6)
	Blood transfusion	8 (0.6)
	Injection drug use	4 (0.3)
	Tattoo	4 (0.3)
	Dental/medical surgery	2 (0.1)
	Breast-feeding	2 (0.1)
	Vertical route	2 (0.1)
	Total	**1306 (100)**

Yeni bir antiretroviral ilaç sınıfı: integraz inhibitörleri (INI).

HIV-1 integraz enzimi;

- Proviral DNAnın konak DNAsına entegrasyonundan sorumludur (ligasyon, strand transfer).
- Pre-entegrasyon komplexini stabilize eder.
- *pol* geninin 3' ucunda yer alan 288 aa. büyüklüğünde bir bölge tarafından kodlanır.

INI, strand transfer aksiyonunu bloklamak için dizayn edilen ilaçlar:

RAL: Raltegravir, (FDA onayı; 2007)
EVG: Elvitegravir (FDA onayı; 2012)
DTG: Dolutegravir (FDA onayı; 2013)

İntegraz inhibitörü direncine yol açan mutasyonlar tedavi öncesinde bulunabilir mi?

Evet, bulunabilir.

- integraz sekansları doğal aa varyasyonlarına açıktır.
- Tedavi naif bireylerde; bölgenin %16'sında primer dirençle ilişkili polimorfik mutasyonlar bulunur.
- Bu mutasyonların zamanla toplumda birikeceğini düşünüyorum.

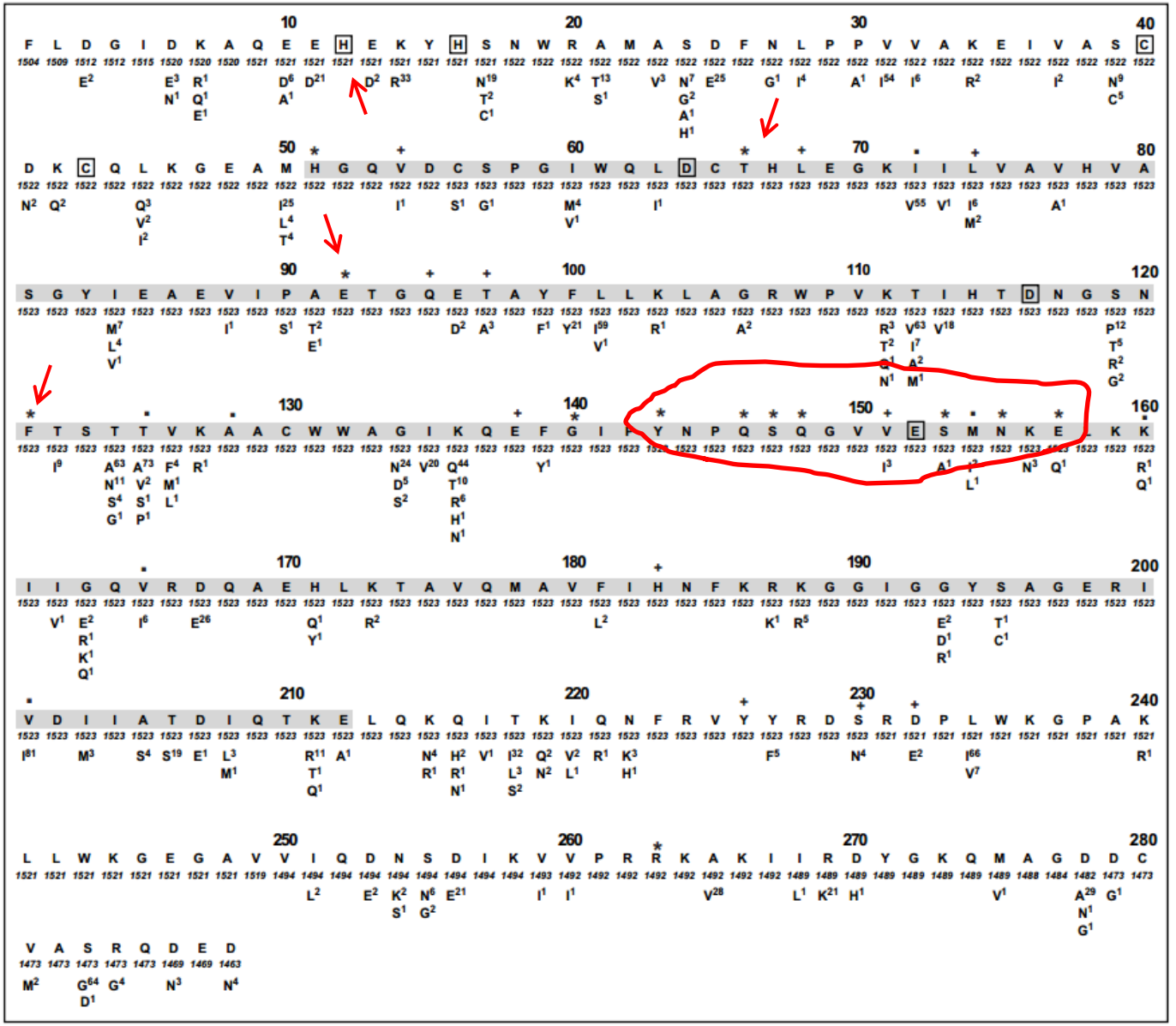

Figure 1
Distribution of variants among group M HIV-1 integrase sequences.

Dimonte S, Infection 2013; 41:1097–1102
Rhee SY, Retrovirology 2008;5:74

1. Nesil Integraz Inhibitörleri ; RAL ve EVG

- Tüm integraz inhibitörleri küçük moleküllerdir. HIV integrazın aktif bölgesine tutunurlar.
- Etkinlik miktarları nanomolar seviyesindedir.
- RAL ve EVG geniş ölçekte aynı direnç profiline sahiptir.
- RAL ve EVG direnci çok hızlı gelişir *(In vivo, In vitro*).
- İlaca duyarlılık 10 - 100 kat azalıyor.

- Major RAL direnç mutasyonları; Y**143**C/H/R, Q**148**H/K/R, N**155**H/S
- Major EVG direnç mutasyonları; T**66**I, E**92**G/Q, Q**148**H/K/R, N**155**H/S

RAL ve EVG arasında çapraz (overlaping) direnç mümkündür.

Y**143**H (RAL), Q**148**H (EVG + RAL) paternleri hastalar arasında aktarılabilirdir.

White KL, *Viruses* 2014;*6:* 2858-2879
Geretti AM, Antiviral Therapy 2010; 15 (Suppl 2): A62
Ceccherini SF, XVII Int HIV Drug Res Workshop 2008 Waters J, XVII Int HIV Drug Res Workshop 2008
Dimonte S, Infection 2013; 41:1097–1102
Rhee SY, Retrovirology 2008;5:74

2. Nesil Integraz Inhibitörleri ; DTG

- DTG genetik bariyeri RAL ve EVG' ye göre çok yüksektir.
- Henüz DTG ilişkili spesifik direnç mutasyonları tanımlanmış değil.
- DTG ile ilişkili olan ve ilaca duyarlılığı etkilemeyen non-polimorfik varyasyonlar var.

DTG direnci; Q**148**X +

*en az 2 ya da 3 polimorfik- sekonder-mutasyon; **L74I, E138A/K/T, G140S/A/C** eşlik ederse DTG duyarlılığı azalabilir

RAL ve EVG mutasyonları DTG' de çapraz dirence yol açmıyor.

White KL, *Viruses* 2014;*6:* 2858-2879,
Libre JM, Enferm Infec Microbiol Clin 2015;33 Suppl 1:20-5
Cavalcanti JS, J Antimicrob Chemother 2015; 70: 926–929

Integrase Strand Transfer Inhibitors (INSTIs) Resistance Mutations in HIV-1 Infected Turkish Patients

M. Sayan[1,2], A. Gündüz[3], G. Ersöz[4], A. İnan[5], A. Deveci[6], G. Özgür[7], F. Sargın[8], G. Karagöz[9], A. İnci[10], D. İnan[11], A Ülçay[12], İ. Karaoğlan[13], S. Kaya[14], S.S. Kutlu[15], K. Süer[16], A. Çağatay[17] and H. Akalın[18]

Table 2 Integrase strand transfer inhibitors (INSTIs) resistance analysis in Turkish patients infected with HIV-1

Drug class	Resistance mutation pattern					
	Antiretroviral naïve, (n = 78)	n	%	Antiretroviral experienced, (n = 91)	n	%
INI	–	–	–	INSTI – naive, (n = 89)		
				F121Y, Q148R, E157Q	4	4.4
				INSTI – experienced, (n = 2)		
				Y143R, E157Q	2	2.2
				Total	6	6.6

Lopinavir/r combination; 38 (42%)
Efavirenz combination; 31 (34%)
Lamivudin + zidovudin comb; 17 (19%)
Prezista/r combination; 2 (2%)
Raltegravir combination; 2 (2%)
Abacavir combination; 1 (1%)

Table 1 Clinical and laboratory characteristics of the patients studied

Characteristic	Antiretroviral naive	Antiretroviral experienced
Patient, no.	78	91
Gender, M/F (%)	71/7 (91%/9%)	80/11 (88%/12%)
Age, median years (range)	38 (23–61)	38.4 (2.5–66)
$CD4^+$ T-cell count, median mm^3 (range)	236 (6–626)	216 (3–884)
HIV-1 RNA load, median, copies/ml (range)	4.95E+5 (3.06E+2–3.33E+6)	1.08E+6 (1.48E+2–1.57E+7)
Acquisition route, n (%)		
Heterosexual contact	52 (67%)	62 (68%)
MSM	24 (31%)	20 (22%)
Bisexuel contact	2 (2%)	4 (5%)
Blood transfusion	–	2 (2%)
Dental surgery	–	1 (1%)
Vertical transmission	–	2 (2%)

HIV-1 subtip, n (%)		
Subtype B	48 (62%)	55 (60)
Non-subtype B	20 (26%)	17 (19)
A1	11 (14%)	5 (6%)
C	2 (3%)	3 (3%)
D	1 (1%)	1 (1%)
F1	5 (7%)	6 (7%)
G	1 (1%)	2 (2%)
Circulating recombinant form CRF01_AE	10 (13%)	19 (21%)
CRF02_AG	4 (5%)	12 (13%)
CRF03_AB	4 (5%)	4 (5%)
CRF07_BC	–	1 (1%)
CRF06_cpx	–	1 (1%)
CRF13_cpx	2 (3%)	–
	–	1 (1%)
Coinfection status, n (%)		
Hepatitis B	3 (4%)	1 (1%)
Hepatitis C	–	4 (4%)
Hepatitis D	1 (1%)	–
P.jirovecii pneumonia	1 (1%)	2 (2%)
Oral candidiasis	2 (3%)	3 (3%)
Pulmoner tuberculosis	1 (1%)	6 (7%)
CMV infection	–	1 (1%)
Cerebral toxoplasmosis	1 (1%)	2 (2%)

Tablo 6 : Dünyada tedavi öncesi integraz inhibitörü direnci ile ilişkili çok fazla veri bulunmuyor.

Ülke	Hasta grubu	Analiz yöntemi	Major INI direnci	Prevalans	Referans
Türkiye	Naif, n= 78	Populasyon sekanslama	-	%0	Sayan M, *et* al. HIV Clinical Trials 2016; in press
	ART deneyimli, n=91		F121Y, Y143R, Q148H, E157Q	%6.6	
Almanya	Naif, n=337	Populasyon sekanslama	RAL/EVG; E157Q	%2.4	Karolin M,J Int AIDS Soc 2014;17(Supl 3):19746
İtalya	Naif, n=335	Populasyon sekanslama	RAL/EVG; Q148H, Y143H	%3	Dimonte S, Infection 2013; 41:1097-1102
ABD	Naif, n=120	Populasyon sekanslama	RAL/EVG; E92Q, E157Q	%8.3	Eshleman S, AIDS Res Hum Retro 2009; 25 (3): 343-5
Güney Afrika	Naif; n=22 ART deneyimli; n=51	Populasyon sekanslama	-	-	Fish MQ, AIDS Res Hum Retro 2010; 26(4):489-493
Brezilya	Naif; n=105	Populasyon sekanslama	-	-	Passaes CB, J Acquir Immune Defic Syndr 2009;1;51(1):7-12

Sonuçlar

- Ülkemizde, yeni tanı almış ART naif hastalarda INI direnci mutasyonları bulunmuyor.
- INI, başlangıç tedavilerinde güçlü bir seçenek olabilir.
- Viral rebound gelişen hastalarda RAL ve EVG direnci bulunabilir.
- INI naif ve ART deneyimli hastalarda DTG direnci bulunmuyor.
- Tedavi geçişleri öncesinde INI direnci mutasyonları mutlaka analiz edilmelidir.

Sequence: S.E/2

Sequence Date	2-Aug-2014
Algorithms	ANRS_09/2013

Length of included Sequences:

- **Sequence includes INT: codons: 64 - 181**

Gene	Differences from Consensus B	Drug Resistance Mutations
INT	I72V, L74I, T112V, I113V, S119P, T124S, T125A, G134N, K136Q, D167E	L74I, S119P

II	ANRS_09/2013		
	Mutation List	Algorithm Result	SIR
Dolutegravir		Susceptible	S
Elvitegravir		Susceptible	S
Raltegravir		Susceptible	S

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HIVdb: Genotypic Resistance Interpretation Date: 10-Nov-2015

Seq ID: F.D 2

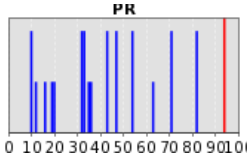
Summary Data

Sequence includes PR: codons: 6 - 99

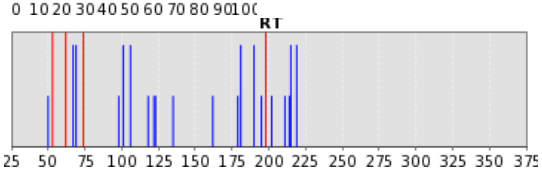
Sequence includes RT: codons: 50 - 221

Sequence Quality Assessment

Gene	QA Problem	Codons
PR	Stop Codons, Frame Shifts:	94
PR	Ambiguous Positions:	*None*
PR	Unusual Residues:	*None*



Gene	QA Problem	Codons
RT	Stop Codons, Frame Shifts:	74, 198
RT	Ambiguous Positions:	53
RT	Unusual Residues:	62



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: **V32I, I47V, I54M, V82A**

PI Minor Resistance Mutations: **L10I, L33F, K43T, A71V**

Other Mutations: T12N, G16E, L19I, K20R, E35D, M36I, L63A

Protease Inhibitors

atazanavir/r (ATV/r)	High-level resistance
darunavir/r (DRV/r)	High-level resistance
fosamprenavir/r (FPV/r)	High-level resistance
indinavir/r (IDV/r)	High-level resistance
lopinavir/r (LPV/r)	High-level resistance
nelfinavir (NFV)	High-level resistance
saquinavir/r (SQV/r)	Intermediate resistance
tipranavir/r (TPV/r)	High-level resistance

Drug Resistance Interpretation: RT

NRTI Resistance Mutations: **D67N, T69D, T215L, K219E**

NNRTI Resistance Mutations: **K101E, V106I, Y181C, G190S**

Other Mutations: I50L, E53X, A62G, A98S, V118I, K122E, D123E, I135T, S162A

Nucleoside RTI

lamivudine (3TC)	Susceptible
abacavir (ABC)	Low-level resistance
zidovudine (AZT)	Intermediate resistance
stavudine (D4T)	Intermediate resistance
didanosine (DDI)	Intermediate resistance
emtricitabine (FTC)	Susceptible
tenofovir (TDF)	Low-level resistance

Non-Nucleoside RTI

efavirenz (EFV)	High-level resistance
etravirine (ETR)	High-level resistance
nevirapine (NVP)	High-level resistance
rilpivirine (RPV)	High-level resistance

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Sequence: F.D

Sequence Date	25-Nov-2015
Algorithms	GRADE_06/2014 ANRS_09/2013

Length of included Sequences:

- **Sequence includes INT: codons: 64 - 179**

Gene	Differences from Consensus B	Drug Resistance Mutations
INT	L101I, T112I, G163E	G163E

II	GRADE_06/2014			ANRS_09/2013			Final Rating
	Mutation List	Algorithm Result	SIR	Mutation List	Algorithm Result	SIR	
Dolutegravir		Susceptible	S		Susceptible	S	
Elvitegravir		Susceptible	S		Susceptible	S	
Raltegravir		Susceptible	S		Susceptible	S	

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Sequence: Y.B

Sequence Date	27-Jun-2014
Algorithms	ANRS_09/2013

Length of included Sequences:

- **Sequence includes INT: codons: 62 - 177**

Gene	Differences from Consensus B	Drug Resistance Mutations
INT	L74I, L101I, G106G_T, R107E, P109Q, V110Y, K111T, T112V, I113V, G118S, S119A, S119A_*, N120H, F121Y, T124S, T125A	L74I, G118S, S119A, S119A_*, F121Y, G163E

II	ANRS_09/2013		
	Mutation List	Algorithm Result	SIR
Dolutegravir		Susceptible	S
Elvitegravir	F121Y	Resistance	R
Raltegravir	F121Y	Resistance	R

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Sequence: R.A

Sequence Date	22-Mar-2015
Algorithms	ANRS_09/2013

Length of included Sequences:

- **Sequence includes INT: codons: 63 - 181**

Gene	Differences from Consensus B	Drug Resistance Mutations
INT	I72V, T112V, T124A, K156N, E157Q	E157Q

II	ANRS_09/2013		
	Mutation List	Algorithm Result	SIR
Dolutegravir		Susceptible	S
Elvitegravir	**E157Q**	Resistance	R
Raltegravir	**E157Q**	Resistance	R

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Sequence: H.Y

Sequence Date	16-Dec-2014
Algorithms	ANRS_09/2013

Length of included Sequences:

- **Sequence includes INT: codons: 67 - 179**

Gene	Differences from Consensus B	Drug Resistance Mutations
INT	K136X, F139X, Q148R	Q148R

II	ANRS_09/2013		
	Mutation List	Algorithm Result	SIR
Dolutegravir		Susceptible	S
Elvitegravir	Q148R	Resistance	R
Raltegravir	Q148R	Resistance	R

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Sorular & Yanıtlar