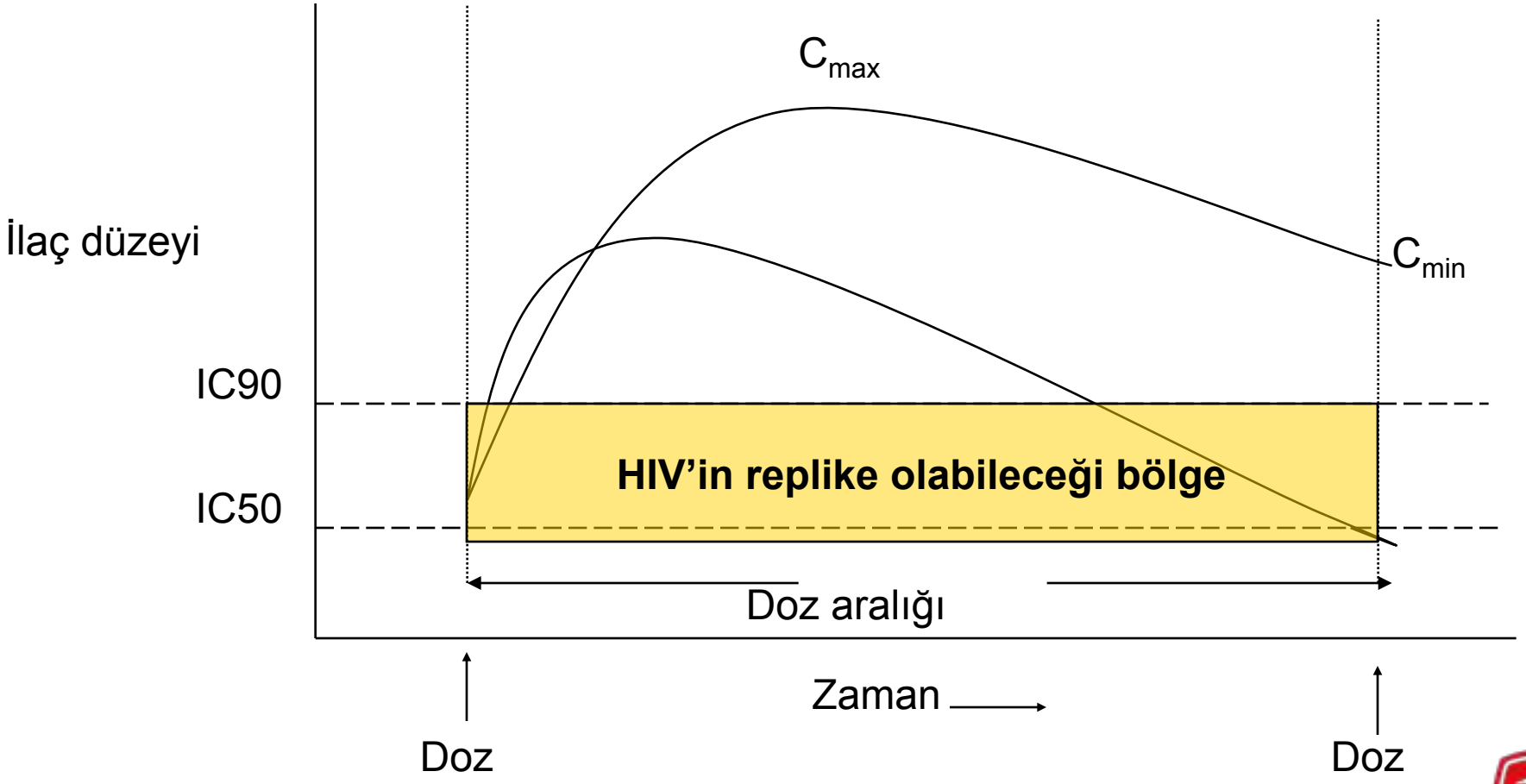
ANTİRETROVİRAL DİRENÇ

Dr. Ahmet Çağkan İnkaya

Direncin ortaya çıkması

- Dirençli virüsün ortaya çıkışı
  - Genetik bariyer (seçicici baskı).
  - Rezidüel replikasyon (potens).

Temel farmakolojik prensipler



1. İlaçlar genetik bariyerlerine göre farklılaşırlar
   - Tek bir nükleotid değişimiyle direnç gelişenler
   - 2’den fazla nükleotid değişimiyle direnç gelişenler

Direnç mutasyonlarının kaybolması

- Tedavi kesilirse
- Tedavi değiştirilirse
- Wild-type baskın hale geçerse
- Minority variant halde kalırlar

Bu tablo kime ait?

A. Michelangelo
B. Leonardo da Vinci
C. Marcel Duchamp
D. Frida Kahlo

A. Michelangelo
B. Leonardo da Vinci
C. Marcel Duchamp
D. Frida Kahlo

1919, L.H.O.O.Q

Ne zaman test yapalım?

- İlk saptandığında
- Tedavi başlanmadan önce
- Bazalde INSTI direncine bakmaya gerek yok
- Virolojik başarısızlık anında
- INSTI altında virolojik başarısızlık varsa INSTI sekans
- Suboptimal supresyon
- Viral yüksınırı 500kopya/ml

Tedavi almamış birine neden test yapalım?

ABD ve Fransa'da aktarılan direnç

CDC: Prevalence of TDR in MSM (*N*= 10,894) in US (2008-2011)

≥ 1 RAM	#	%
Any	1,894	17.4%
NNRTI	984	9.0%
NRTI	722	6.6%
PI	498	4.6%

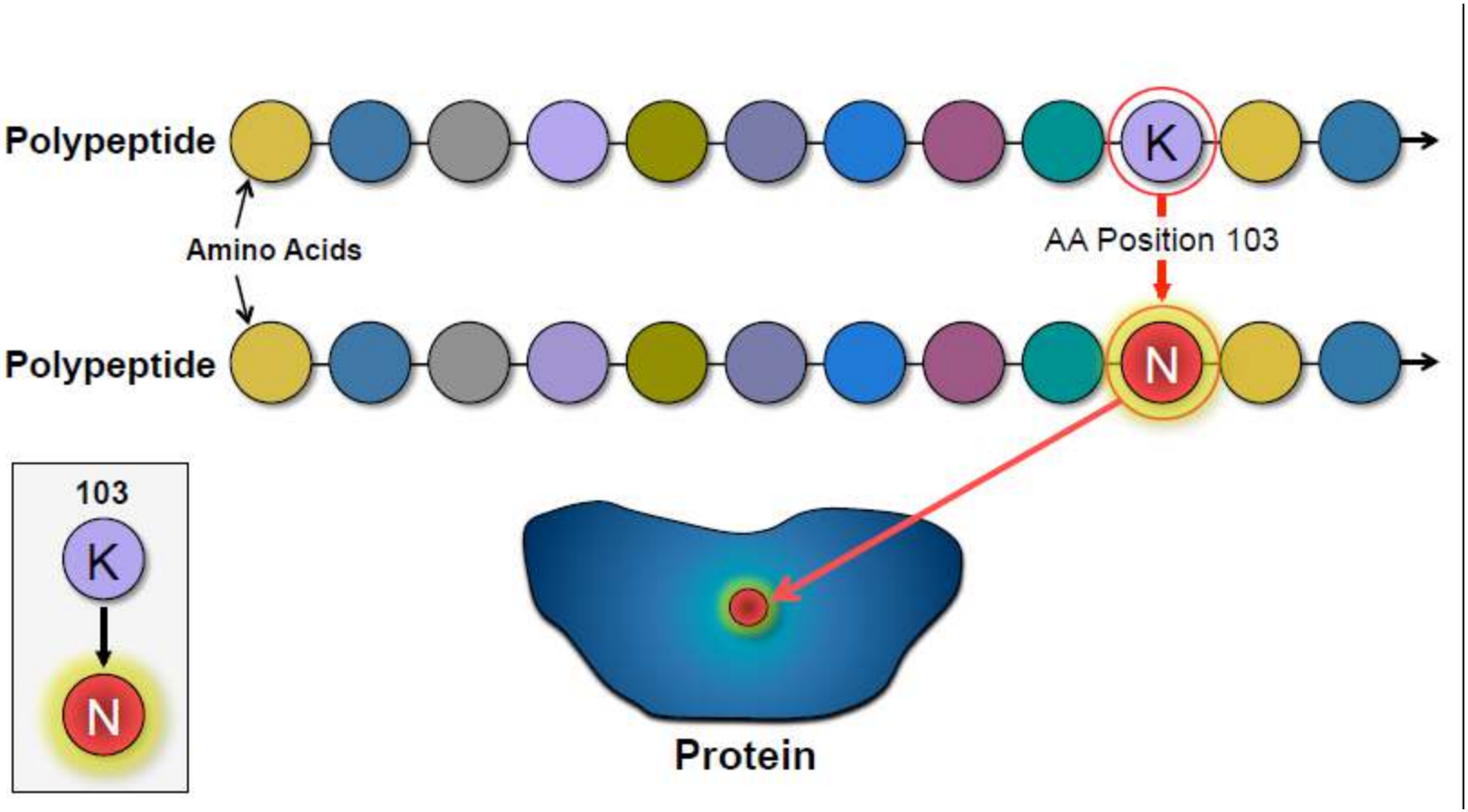
ANRS Survey: TDR from Patients (*N*=799) with Primary HIV Infection in France (2010-2013)

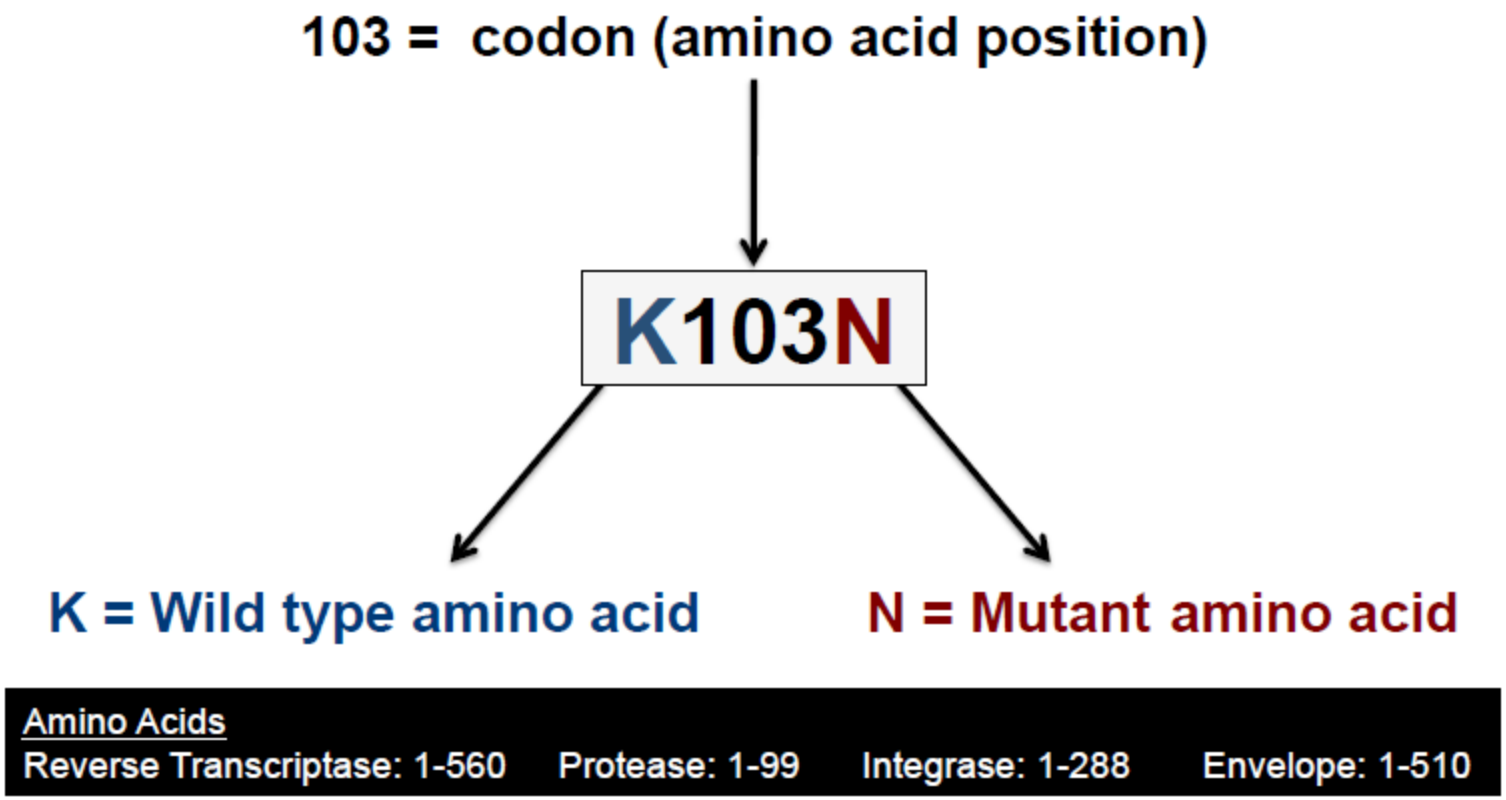
≥ 1 RAM, %	10.6
PI	2.0
NRTI	5.1
NNRTI	4.0
INSTI	1.5

- Risk factors for transmitted resistance include: MSM and B subtype
- Prevalence of TDR mutations increased slightly in the US as observed by the CDC, whereas this has remained stable in France since 1996
- NNRTI transmitted resistance continues to be most prevalent in the US, so other treatment options may be considered for first-line therapy

Banez-Ocfemia C, et al. CROI; 2014 Boston. #579 & Chaix M, et al. CROI 2014; Boston. #582

Direnç nasıl okunur?




103 = codon (amino acid position)
K103N
K = Wild type amino acid
N = Mutant amino acid
Amino Acids
Reverse Transcriptase: 1-560
Protease: 1-99
Integrase: 1-288
Envelope: 1-510

Special Contribution

2017 Update of the Drug Resistance Mutations in HIV-1

Annemarie M. Wensing, MD, PhD; Vincent Calvez, MD, PhD; Huldrych F. Günthard, MD; Victoria A. Johnson, MD; Roger Paredes, MD, PhD; Deenan Pillay, MD, PhD; Robert W. Shafer, MD; Douglas D. Richman, MD

MUTATIONS IN THE ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS

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

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

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

Seq·ID:·234-14-VETA· VETA¶

¶

Summary·Data¶

Sequence includes PR: codons: 1 -- 99¤

Sequence includes RT: codons: 1 -- 335¤

¶

There are no insertions or deletions¤

¶

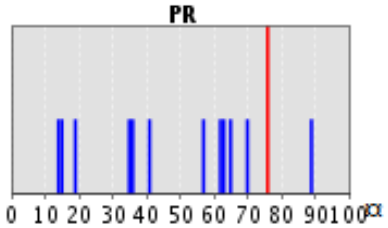
Subtype and % similarity to closest reference isolate¶

1.→*PR: F (91.2%)*¶
2.→*RT: B (95.0%)*¤

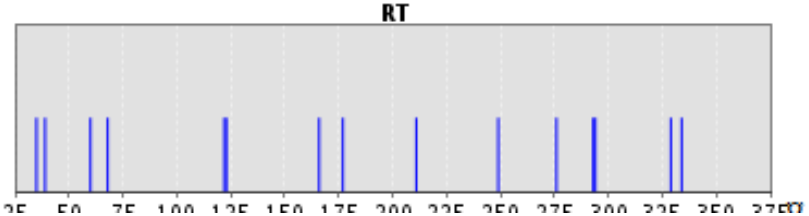
¶

Sequence·Quality·Assessment¶

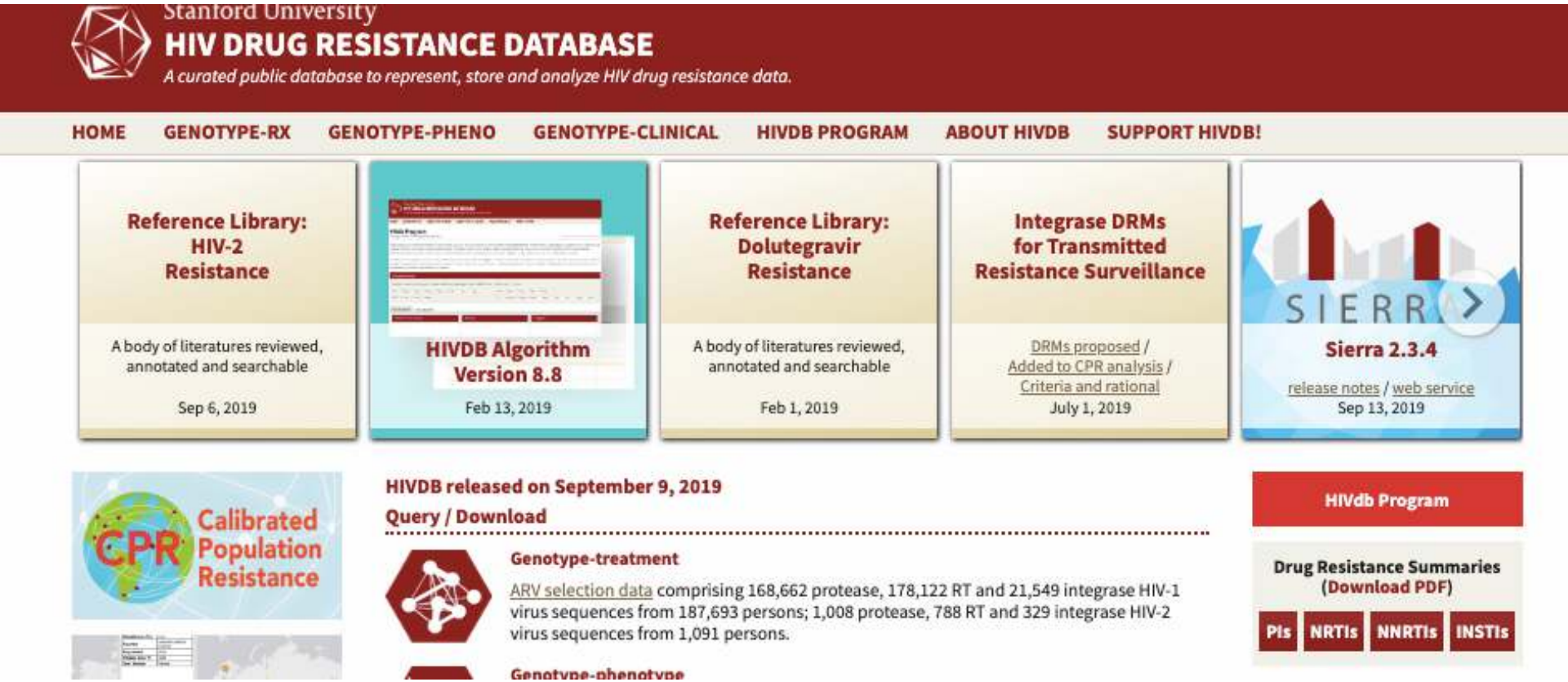
Gene	QA Problem	Codons
PR	Stop Codons, Frame Shifts:	76
PR	Ambiguous Positions:	*None*
PR	Unusual Residues:	*None*



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



http://hivdb.stanford.edu/



HIVdb Program

Genotypic Resistance Interpretation Algorithm

Sierra version 2.3.4 (last updated on 2019-09-13)

HIVdb version 8.8 (last updated on 2019-02-13)

HIVdb accepts user-submitted protease, RT, and integrase sequences or mutations and returns inferred levels of resistance to the most commonly used protease, nucleoside, non-nucleoside, and integrase inhibitors. Its purpose is educational and as such it provides extensive comments and a highly transparent scoring system that is hyperlinked to data in the HIV Drug Resistance Database. A detailed description of the program as well as all updates is in the Release Notes. A web service has been created to allow users to access HIVdb programmatically.

Protease, RT, and integrase mutations can be entered using either the text box or auto-suggestion boxes. To use the text box, type each mutation separated by one or more spaces. The consensus wildtype and separating commas are optional. If there is a mixture of more than one amino acid at a position, write both amino amino acids (an intervening slash is optional). Insertions should be indicated by "Insertion" and deletions by "Deletion".

Drug display options

By default, results will be shown for checked ARVs. Use checkboxes for additional ARVs. (select all ARVs, revert to default)

NRTI: ☑ ABC ☑ AZT ☑ FTC ☑ 3TC ☑ TDF ☐ D4T ☐ DDI

NNRTI: ☑ DOR ☑ EFV ☑ ETR ☑ NVP ☑ RPV

INSTI: ☑ BIC ☑ DTG ☑ EVG ☑ RAL

PI: ☑ ATV/r ☑ DRV/r ☑ LPV/r ☐ FPV/r ☐ IDV/r ☐ NFV ☐ SQV/r ☐ TPV/r

Input mutations | Input sequences

Reverse Transcriptase

Input mutation(s)

Select mutations:

40 ---	41 ---	44 ---	62 ---
65 ---	67 ---	68 ---	69 ---
70 ---	74 ---	75 ---	77 ---

Protease

Input mutation(s)

Select mutations:

10 ---	11 ---	13 ---	20 ---
23 ---	24 ---	30 ---	32 ---
33 ---	35 ---	36 ---	43 ---

Integrase

Input mutation(s)

Select mutations:

51 ---	66 ---	74 ---	92 ---
95 ---	97 ---	114 ---	118 ---
121 ---	128 ---	138 ---	140 ---

Input mutations | Input sequences

Reverse Transcriptase

K103N x M184V x T215D x

Input mutation(s)

Select mutations:

40	41	44	62
---	---	---	---
65	67	68	69
---	---	---	---
70	74	75	77
---	---	---	---
90	98	100	101
---	---	---	---
103	106	108	115
---	---	---	---

Protease

Input mutation(s)

Select mutations:

10	11	13	20
---	---	---	---
23	24	30	32
---	---	---	---
33	35	36	43
---	---	---	---
46	47	48	50
---	---	---	---
53	54	58	63
---	---	---	---

NRTI Resistance Mutations:	**M184V, T215D**
NNRTI Resistance Mutations:	**K103N**
Other Mutations:	None

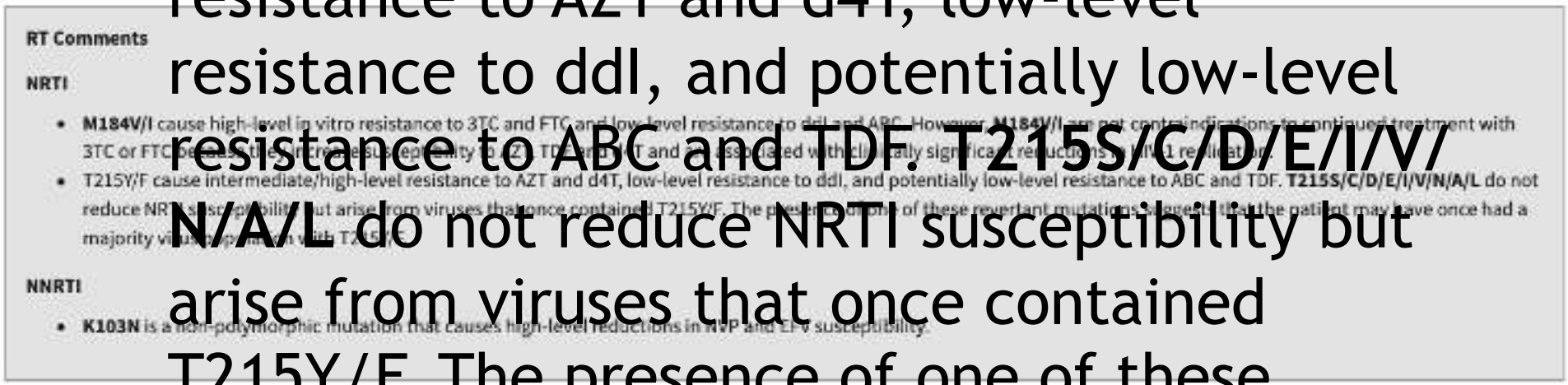
Nucleoside Reverse Transcriptase Inhibitors

abacavir (ABC)	Low-Level Resistance
zidovudine (AZT)	Potential Low-Level Resistance
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Susceptible

Non-nucleoside Reverse Transcriptase Inhibitors

doravirine (DOR)	Susceptible
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	Susceptible
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	Susceptible

- T215Y/F cause intermediate/high-level resistance to AZT and d4T, low-level resistance to ddI, and potentially low-level resistance to ABC 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 that the patient may have once had a majority virus population with T215Y/F.


RT Comments

NRTI

- **M184V/I** cause high-level in vitro 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 their presence may improve susceptibility to AZT, TDF and d4T and is associated with clinically significant reductions in HIV-1 replication.
- T215Y/F cause intermediate/high-level resistance to AZT and d4T, low-level resistance to ddI, and potentially low-level resistance to ABC 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 that the patient may have once had a majority virus population with T215Y/F.

NNRTI

- **K103N** is a non-polymorphic mutation that causes high-level reductions in NVP and EFV susceptibility.

Olgu I

- 37 yaş, erkek, MSM
- Partner tarama programlarında tanımlandı
- Sifiliz 7 yıl önce
- Penil travma
- Marihuana
- Sigara 2-3 paket
- Alkol
  - Türkiye' de günde 1 büyük

- Boy:190cm
- Kilo: 100kg
- Kan basıncı: 115/75 mmHg
- Fizik muayene: Normal

- Koenfeksiyon yok
- Komorbidite yok
- Aktarılan direnç
  - E138G

Drug resistance interpretation: RT

NRTI Resistance Mutations:	None
NNRTI Resistance Mutations:	**E138G**
Other Mutations:	None

Nucleoside Reverse Transcriptase Inhibitors

abacavir (ABC)	Susceptible
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	Susceptible
lamivudine (3TC)	Susceptible
tenofovir (TDF)	Susceptible

Non-nucleoside Reverse Transcriptase Inhibitors

doravirine (DOR)	Susceptible
efavirenz (EFV)	Potential Low-Level Resistance
etravirine (ETR)	Potential Low-Level Resistance
nevirapine (NVP)	Potential Low-Level Resistance
rilpivirine (RPV)	Low-Level Resistance

RT comments

NNRTI

- **E138Q/G** are non-polymorphic accessory mutations frequently selected in patients receiving ETR and RPV and occasionally in patients receiving NVP and EFV. In most studies, they cause low-level reductions in susceptibility to NVP, RPV, and ETR. Their effects on DOR are not known.

Mutation scoring: RT

NRTI	ABC	AZT	FTC	3TC	TDF
Total	0	0	0	0	0

NNRTI	DOR	EFV	ETR	NVP	RPV
E138G	0	10	10	10	15
Total	0	10	10	10	15

Olgu II

- 25 yaş kadın, Afrika göçmeni
- Hamilelik (G2P1) sırasında tespit ediliyor
- 14. gebelik haftası
- Aslında 2 yıldır biliyor
- İlk doğumu sırasında HIV enfekte olduğu biliniyor
- Ülkesinde ZDV/3TC + NVP almış
- HIV RNA: 225000 kopya/ml
- CD4: 320/ml

Drug resistance interpretation: RT

NRTI Resistance Mutations:	**T215E**
NNRTI Resistance Mutations:	**K103N**
Other Mutations:	None

Nucleoside Reverse Transcriptase Inhibitors

abacavir (ABC)	Susceptible
zidovudine (AZT)	Low-Level Resistance
emtricitabine (FTC)	Susceptible
lamivudine (3TC)	Susceptible
tenofovir (TDF)	Susceptible

Non-nucleoside Reverse Transcriptase Inhibitors

doravirine (DOR)	Susceptible
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	Susceptible
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	Susceptible

Mutation scoring: RT

NRTI	ABC	AZT	FTC	3TC	TDF
T215E	5	20	0	0	5
Total	5	20	0	0	5

NNRTI	DOR	EFV	ETR	NVP	RPV
K103N	0	60	0	60	0
Total	0	60	0	60	0

RT comments

NRTI

- T215Y/F cause intermediate/high-level resistance to AZT and d4T, low-level resistance to ddI, and potentially low-level resistance to ABC 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 that the patient may have once had a majority virus population with T215Y/F.

NNRTI

- **K103N** is a non-polymorphic mutation that causes high-level reductions in NVP and EFV susceptibility.

İki tip TAM var

- M41L, L210W, and T215Y
  - ABC-, ddI-, TDF

- D67N, K70R, T215F, and K219Q/E

NRTI Resistance Mutations:	**M41L, L210W, T215Y**
NNRTI Resistance Mutations:	None
Other Mutations:	None

Nucleoside Reverse Transcriptase Inhibitors

abacavir (ABC)	High-Level Resistance
zidovudine (AZT)	High-Level Resistance
emtricitabine (FTC)	Low-Level Resistance
lamivudine (3TC)	Low-Level Resistance
tenofovir (TDF)	Intermediate Resistance

NRTI	ABC	AZT	FTC	3TC	TDF
L210W	5	15	0	0	5
L210W + T215Y	10	10	5	5	10
T215Y	10	40	0	0	10
M41L	5	15	0	0	5
M41L + L210W	10	10	0	0	10
M41L + L210W + T215Y	5	0	5	5	5
M41L + T215Y	15	10	5	5	10
Total	60	100	15	15	55

RT comments

NRTI

- **M41L** is a TAM that usually occurs with T215Y. In combination, **M41L** plus T215Y confer intermediate / high-level resistance to AZT and d4T and contribute to reduced ddI, ABC and TDF susceptibility.
- **L210W** is a TAM that usually occurs in combination with M41L and T215Y. The combination of M41, **L210W** and T215Y causes high-level resistance to AZT and d4T and intermediate to high-level resistance to ddI, ABC and TDF.
- **T215Y** is a TAM that causes intermediate/high-level resistance to AZT and d4T, low-level resistance to ddI, and potentially low-level resistance to ABC and TDF.

Olgu III

- 38 yaşında erkek
- TDF/FTC/EFV 5 yıldır kullanıyor
- Son 6 aydır cezaevinde olduğu için ilaç kullanımı düzensiz
- HIV RNA: 225000 kopya/ml
- CD4: 276/mm^3

Ne yaparsınız?

A. Tedaviye yeniden başlarım

B. Direnç testi ister tedaviye başlarım

C. Direnç testi sonucu çıkana kadar beklerim

D. Tedavi değişikliği yaparım

NRTI Resistance Mutations:	**M184V**
NNRTI Resistance Mutations:	**Y188C**
Other Mutations:	None

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Low-Level Resistance
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Susceptible

Non-nucleoside Reverse Transcriptase Inhibitors	
doravirine (DOR)	Potential Low-Level Resistance
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	Susceptible
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	Susceptible

NRTI	ABC	AZT	FTC	3TC	TDF
M184V	15	-10	60	60	-10
Total	15	-10	60	60	-10

NNRTI	DOR	EFV	ETR	NVP	RPV
Y188C	10	60	0	60	0
Total	10	60	0	60	0

Comments

TI

- **M184V/I** cause high-level in vitro 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.

RTI

- **Y188C** is a non-polymorphic mutation selected in patients receiving NVP and EFV. It confers high-level resistance to NVP and EFV. It appears to cause little if any reduction in susceptibility to RPV, ETR, or DOR.

Tedaviye devam edilseydi

NRTI Resistance Mutations:	**D67N, K70E, M184V**
NNRTI Resistance Mutations:	**Y181C, Y188C**
Other Mutations:	None

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Intermediate Resistance
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Low-Level Resistance

Non-nucleoside Reverse Transcriptase Inhibitors	
doravirine (DOR)	Low-Level Resistance
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	Intermediate Resistance
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	Intermediate Resistance

NRTI	ABC	AZT	FTC	3TC	TDF
M184V	15	-10	60	60	-10
D67N	5	15	0	0	5
K70E	15	-10	10	10	15
K70E + M184V	0	0	0	0	10
Total	35	-5	70	70	20

NNRTI	DOR	EFV	ETR	NVP	RPV
Y181C	10	30	30	60	45
Y188C	10	60	0	60	0
Total	20	90	30	120	45

RT comments

NRTI

- **D67N** is a non-polymorphic TAM associated with low-level resistance to AZT and d4T. When present with other TAMs, it contributes reduced susceptibility to ABC, ddI, and TDF.
- **K70E/G** cause low-level resistance to TDF, ABC, DDI and possibly 3TC and FTC. **K70E/G** increase susceptibility to AZT.
- **M184V/I** cause high-level in vitro 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.

NNRTI

- **Y181C** is a non-polymorphic mutation selected in patients receiving NVP, ETR and RPV. It reduces susceptibility to NVP, ETR, RPV, and EFV by >50-fold, 5-fold, 3-fold, and 2-fold, respectively. Although **Y181C** itself reduces EFV susceptibility by only 2-fold, it has been associated with a reduced response to an EFV-containing regimen in NNRTI-experienced patients. **Y181C** has a weight of 2.5 in the Tibotec ETR genotypic susceptibility score. Alone, it does not appear to reduce DOR susceptibility.
- **Y188C** is a non-polymorphic mutation selected in patients receiving NVP and EFV. It confers high-level resistance to NVP and EFV. It appears to cause little if any reduction in susceptibility to RPV, ETR, or DOR.

Olgu IV

- Kadın, göçmen
- 46 yaşında
- Yeni tanı
- HIV RNA: 47200kopya/ml

NRTI Resistance Mutations:	**A62V**
NNRTI Resistance Mutations:	**K101E**, **E138K**
Other Mutations:	K11T, I31L, V35I, T39E, K122E, D123N, I135T, K173L, Q174K, D177E, I178V, T200A, Q207K, R211S, V245M, A272P

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

NRTI	ABC	AZT	D4T	DDI	FTC	3TC	TDF
A62V	5	5	5	5	5	5	5
Total	5	5	5	5	5	5	5

NNRTI	DOR	EFV	ETR	NVP	RPV
K101E	15	15	15	30	45
E138K	10	10	10	10	45
Total	25	25	25	40	90

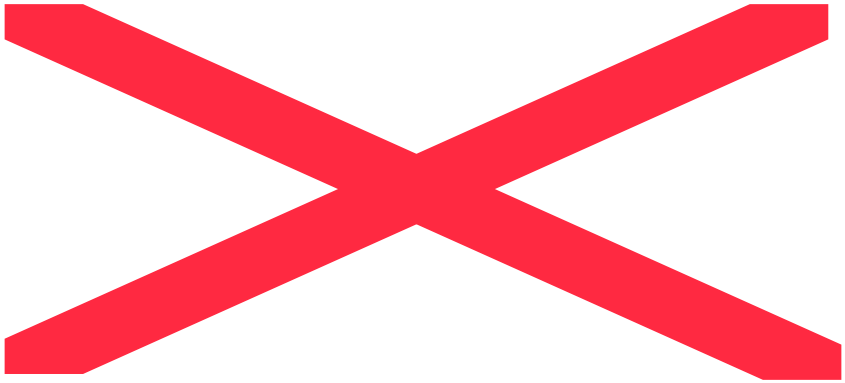
RT comments

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.

NNRTI

- **K101E** is a non-polymorphic primarily accessory mutation that causes intermediate resistance to NVP and RPV, low-level resistance to EFV, and potentially low-level resistance to ETR. It has a weight of 1.0 in the Tibotec ETR genotypic susceptibility score. It is associated with low-level reductions in DOR susceptibility.
- **E138K** is a non-polymorphic mutation selected in a high proportion of patients receiving RPV. It reduces RPV susceptibility by 2 to 3-fold and in combination with K101E or the NRTI-resistance mutation M184I, it is sufficient to cause virological failure on a first-line RPV-containing regimen. **E138K** causes low-level cross-resistance to ETR and possibly to DOR.



Özet

- Aktarılan direnç önemli
- Serorevertant mutasyon kavramı
- Mutlaka skorlamaya bakalım
- Düşük genetik bariyerli rejim kullananlarda virolojik başarısızlıkta direnç akla gelmeli
- İşe yaramayan rejimde ısrar etmeyin
- Direnç testi bize hastalığın kökeni hakkında da bilgi verebilir

- 45 yaş erkek
- Tanı: 1999
- ZDV/3TC, TDF/FTC, LPV/r, IND, EFV,
- CMV retinit, zona zoster
- Uyum sorunu
- Toksisite

Olgu

Direnç sonucu

Sınıf	Mutasyon
NRTI	D67N, T69N, K70R, V118I, M184V, T215F, K219Q
NNRTI	A98G, V108I, Y181C, G190S
PI	L10F, M46I, L76V, I84V

Yorum

Sınıf	Direnç
NRTI	TDF orta Diğer NRTI yüksek düzey
NNRTI	EFV, ETR, NVP, RPV yüksek düzey
PI	DRV, TPV orta Diğer PI yüksek düzey

Mutation Scoring: PR

PI	ATV/r	DRV/r	LPV/r	TPV/r
M46I	10	0	10	5
I84V	60	15	30	30
L10F	0	5	5	0
L76V	0	20	30	-5
M46I + L76V	0	0	10	0
Total	70	40	85	30

- CMV retinitis (sağ göz)
- HIV RNA: 300,000
- TDF/FTC + TPV/r + RAL
- Endikasyon dışı izin + TEB

Yeni direnç

	Mutasyon
NRTI	D67N, T69N, K70R, L74I, (V118I), M184V, T215F, K219Q
NNRTI	A98G, V108I, Y181C, G190S
PI	L10FCY, Q58EQ, A71AT, M46I, I47V, (L76V), V82L, I84V

Altı çizili olanlar yeni
Parantez içindekiler artık saptanmıyor

Mutation Scoring: PR

PI	ATV/r	DRV/r	LPV/r	TPV/r
M46I	10	0	10	5
M46I + V82L	10	0	10	0
I47V	10	10	15	30
V82L	10	0	10	45
I84V	60	15	30	30
L10F	0	5	5	0
I47V + I84V	0	5	5	0
Q58E	0	0	0	15
Total	100	35	85	125

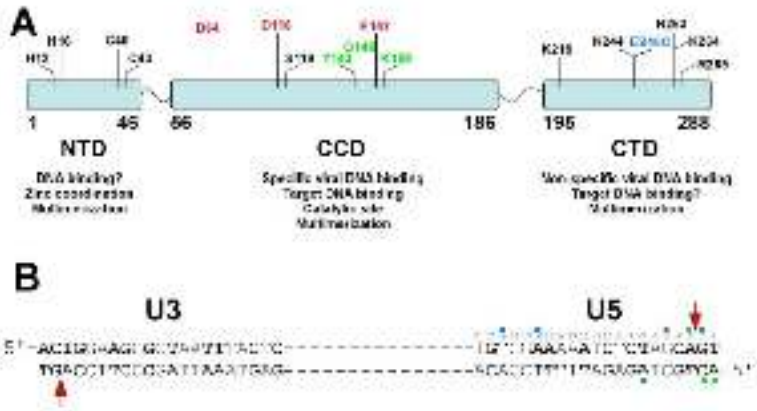
NRTI	TDF orta Diğer NRTI yüksek düzey
NNRTI	Yüksek düzey, EFV, ETR, NVP, RPV
PI	DRV orta düzey Diğer PI, ileri düzey

Dr. KT Yalçınkaya

Integraz ve V3 sekanslama

İntegraz sekanslama

	Mutasyon
INSTI	Y143R
Minör	L74M, T97A, E157Q, G163R



Integraz

Major	Y143R
Minor	L74M, T97A, E157Q, G163R
Direnç	RAL, EVG yüksek düzey DTG üzerinde muhtemel direnç?

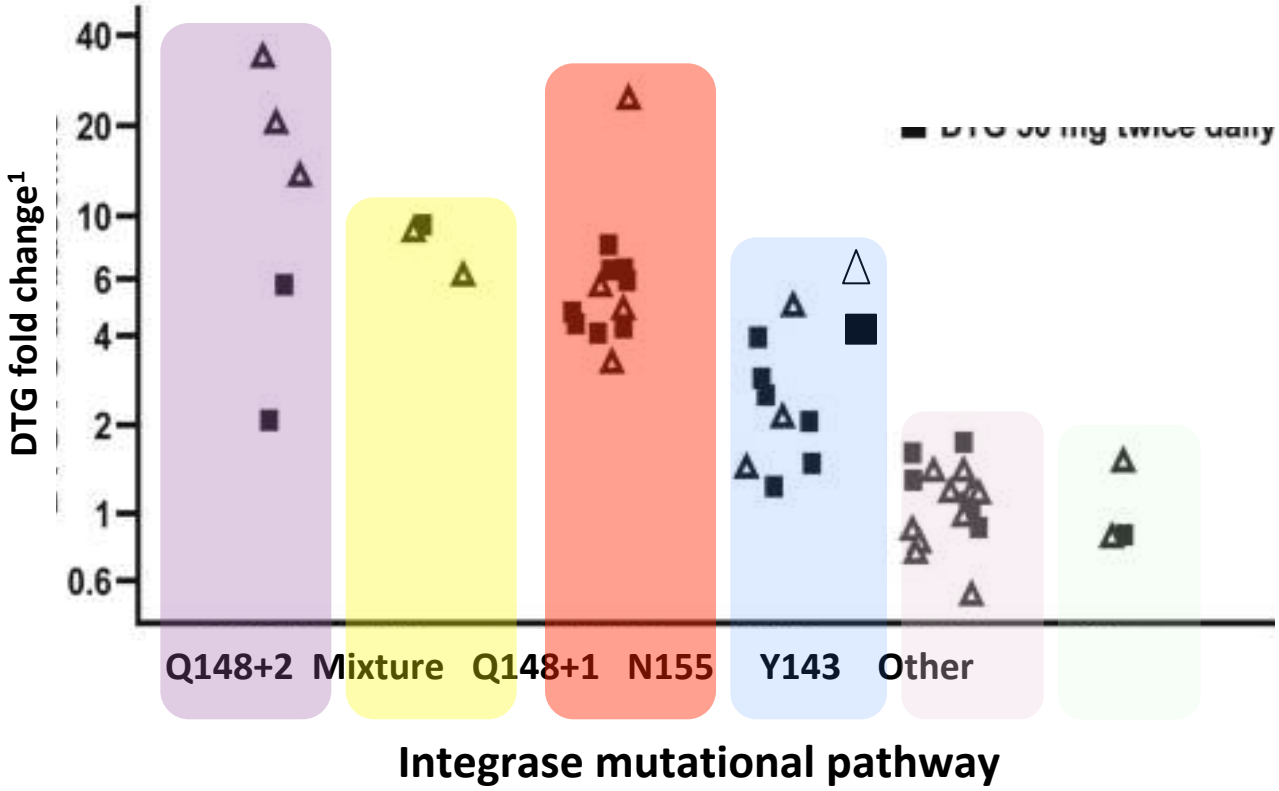
III. Aligned V3 region

IV. Coreceptor prediction

Model	Prediction	FPR	Remarks
Clonal	CCR5-antagonists like Maraviroc (Celsentri/Selzentry) are likely to be effective.	98.9%	

The significance level was set to:
"Recommendations from the European Consensus Group on clinical management of HIV-1 tropism testing"

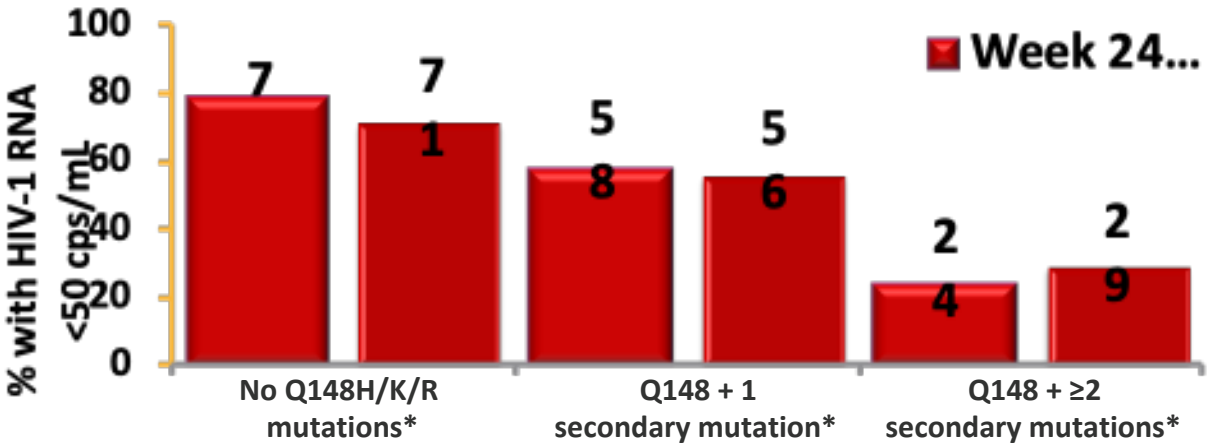
Cross-resistance of clinical isolates to DTG



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

VIKING: Response rates with increasing baseline integrase resistance

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



*Key secondary mutations were G140A/C/S, L741 and E138A/K/T

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

- MAYIS 2014
- DTG 2X1 + MVC 1-2 X 150
- VİRAL REPLİKASYON BASKILI
- AĞUSTOS 2019