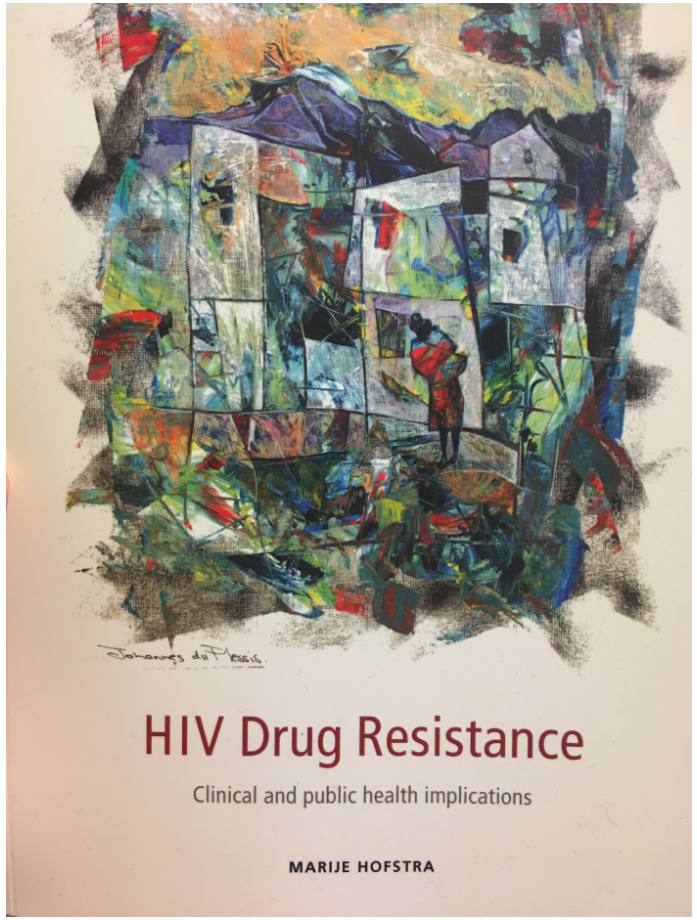
HIV/AIDS ve Direnç

Prof. Dr. Murat Sayan
Kocaeli Üniversitesi, Rutin PCR Lab. Sorumlu Öğr.Üyesi, İzmit, Kocaeli
Yakın Doğu Üniversitesi, DESAM Kurucu Öğr. Üyesi, Lefkoşa, KKTC
sayanmurat@hotmail.com
0533 6479020



KLİMİK Simpozyum
27 Haziran 2019, İstanbul

Finansal İlişki Beyanım

27 Haziran 2019

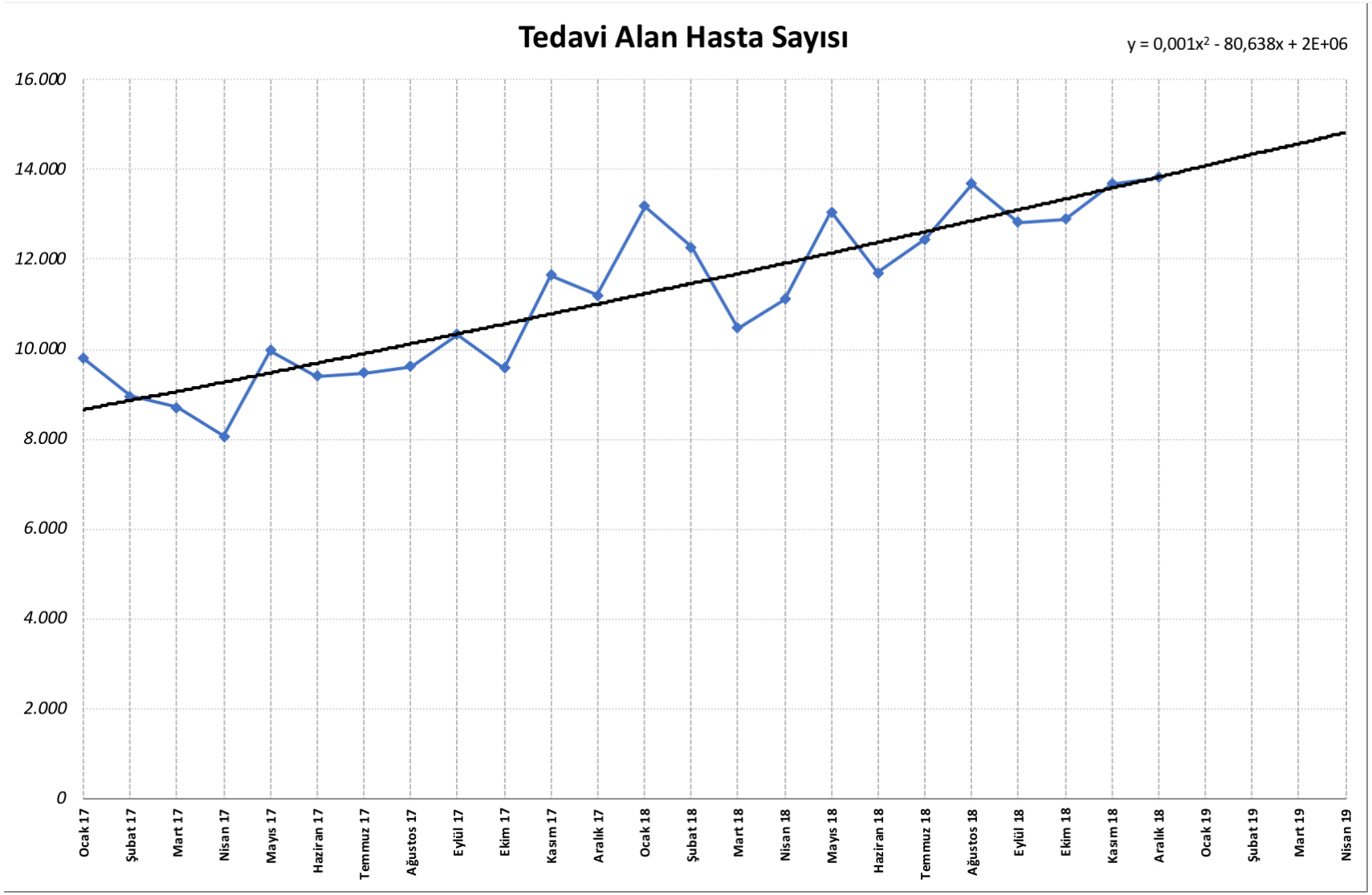
- Proje desteği (Gilead Fellowships 2016 ve 2017, Janssen, Santa Farma, Roche, BMS)
- Toplantı katılım/konaklama desteği (Gilead, GSK, Janssen, MSD, Abdi İbrahim ilaç)
- Konuşma ücreti (Gilead, GSK, BMS, Janssen)
- Analiz desteği (Gilead, GSK, Janssen, BMS, Abdi İbrahim İlaç)

Türkiye'de yetişkin ve çocuk hastalarda omurga antiretroviral ilaç dağılımı
Kutu satışı (2017- Mayıs 2019)

IMS Türkiye ilaç verisi							
Omurga ilaç (tb)	**Yetişkin**			**İlaç (şurup)**	**Çocuk**		
	2017	**2018**	**Mayıs 2019**		**2017**	**2018**	**Mayıs 2019**
Stribild/Genvoya	47 771	75 115	38 179	Epivir (lamivudin)	289	370	178
Truvada	38 929	27 788	9 624	Retrovir (zidovudin)	1 043	1 313	507
Hivent	16 959	20 753	9 347	Ziagen (abacavir)	200	204	78
Triumeq	4 629	12 655	9 003	Kaletra (lopinavir)	-	-	-
Tivicay	24 750	32 268	16 648	Videx (didanozin)	-	-	-
Combivir	2 508	1 836	713				

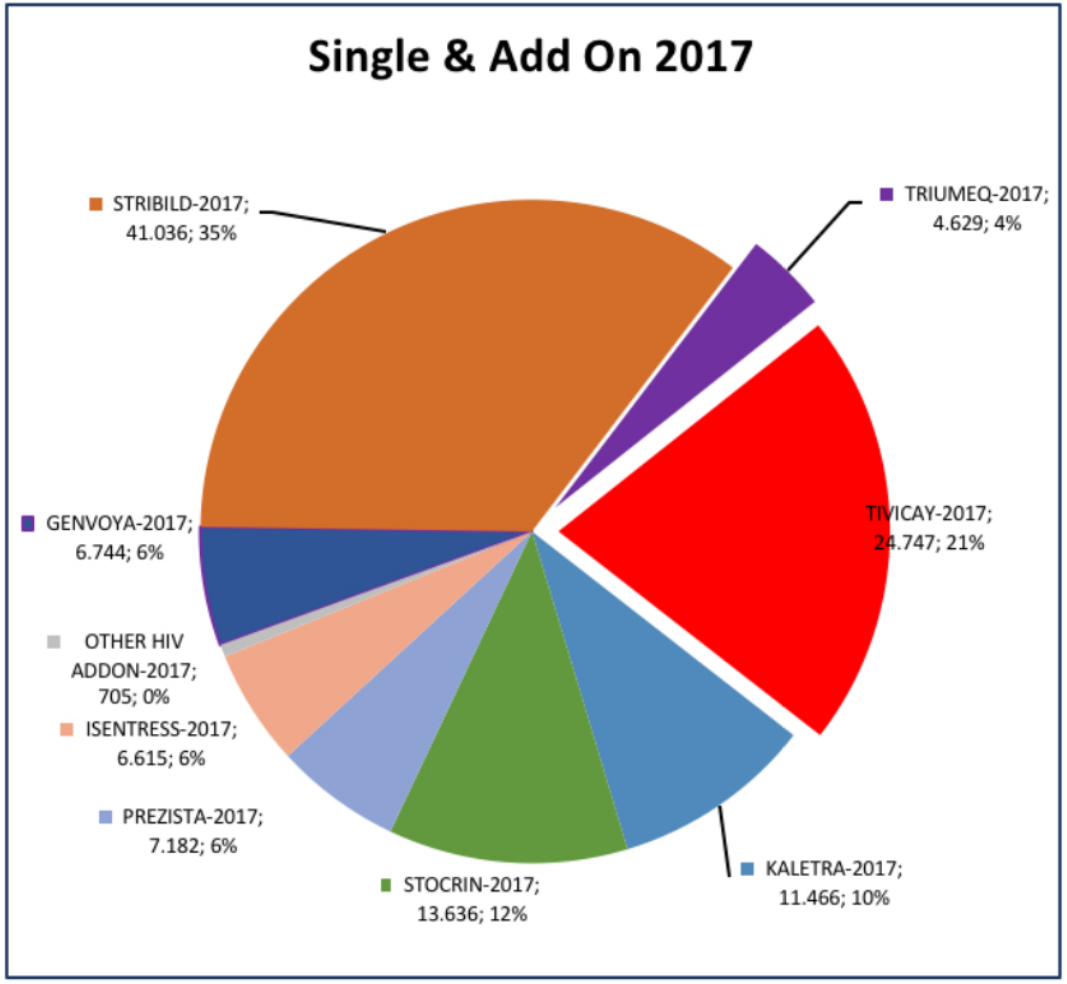
http://imsturkey.com/

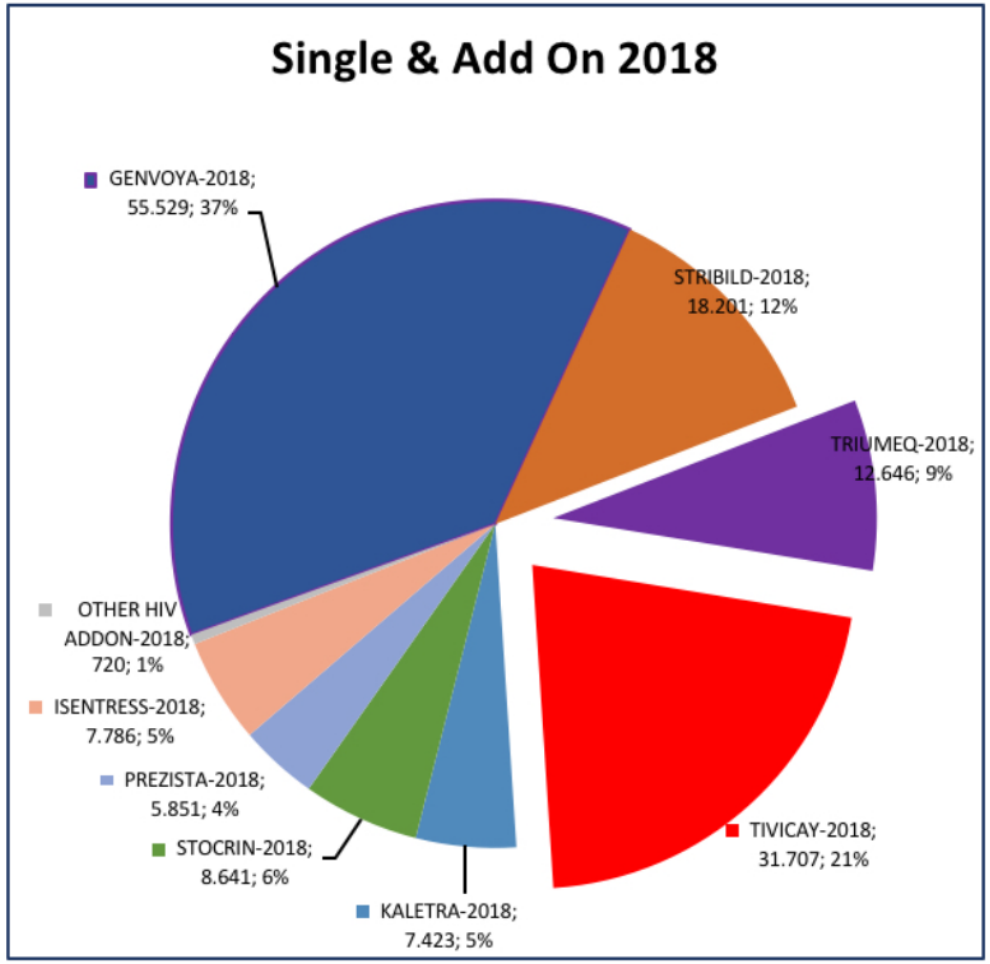
Türkiye'de yetişkin hastalarda omurga antiretroviral ilaç kullanımında 2017-2019 yılları dinamiği.



http://imsturkey.com/

Türkiye'de antiretroviral ilaç kullanımında genel görünüm



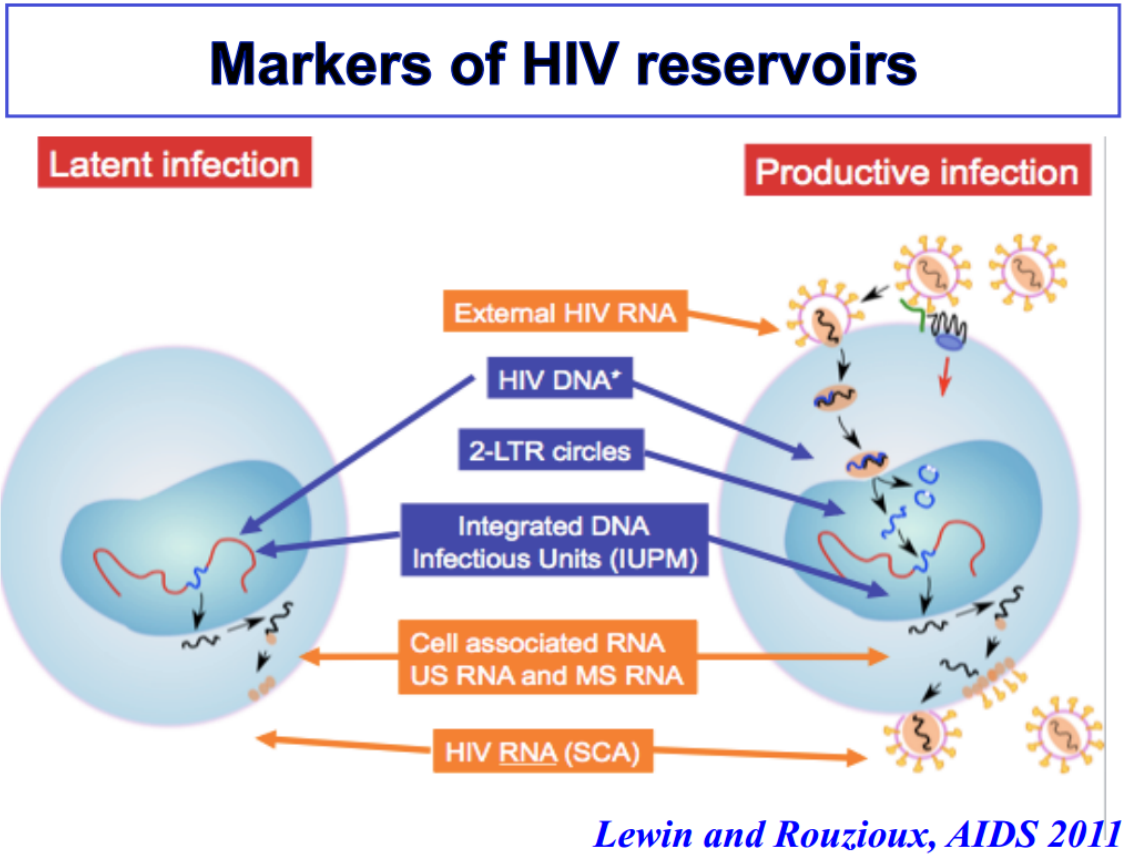


http://imsturkey.com/

HIV ilaç direncinin temelleri: **Samanlıktaki iğne**

http://theflyingtortoise.blogspot.com.tr/2014/12/for-my-next-trick-says-artist-sven.html

HIV'in rezervuarları



HIV'in bir çok farklı formu dolaşıma ve hücreye yerleşir:

- HIV RNA
- HIV DNA
- 2 sirküler LTR
- İntegre HIV DNA'sı (IUPM)
- İşlemlenmemiş RNA (US-RNA, MS-RNA)

Ek olarak;

- Sıçrayan HIV genleri (transpozonlar)
- Hücreler arası kargo vezikülleri (eksozomlar) bulunuyor.

HIV'in rezervuar potansiyeli

Latent HIV enfekte hücreler: CD4 + T hücreleri	Durum
Sıklığı	HIV taşıyan tüm hastalarda bulunur.
Sayısı	1/100 000 – 1/1 000 000
Ömür	T ½ = 44 ay
Dayanıklılık	T hücre onarım ve çoğalma mekanizmalarına rağmen hayatta kalırlar
Klirensi için ART tedavi sürekliliği	Tahminen 60 yıldan fazla

M. Schmidt, HIV Reservoir Symposium, 19th September 2016, Belgium.

HIV ilaç direncinin temelleri: **HIV'in kinetiği**

- HIV, kendini çok yüksek miktarda ve çok hızlı üretir (T1/2 - gün).
- Kendini çoğaltırken kullandığı rt enzimi, hatalarını düzeltemez (3×10^{-5} mutasyon/baz/replikasyon siklusu).
- Her gün yaklaşık 100 milyon yeni HIV ortaya çıkar.
- HIV, her 2 günde bir CD4 hücresi içinde kendini yeniden üretir.
- HIV'in kinetiği, mutasyonları doğal olarak üretir.
- Tedavi altında olmayan birinde HIV populasyonu homojen değildir ve çok sayıda varyantı içeren bir çorba gibidir.

Perelson AS, *et* al. Science 1996;271:1582-1586
Goldberg DE, *et* al. Cell 2012; 148, March 16.
.

HIV-1 İlaç direnci analizi: ne zaman? " Eğer bir toplumda HIV-1 ilaç direnci mutasyonları >%5 ise HAART tedavisi öncesi ilaç direnci analizi yapılması %96 oranında kuvvetle önerilir".

AIDS Rev. 2011;13:77-108

European Recommendations for the Clinical Use of HIV Drug Resistance Testing: 2011 Update

Anne-Mieke Vandamme[1,2], Ricardo J. Camacho[2,3], Francesca Ceccherini-Silberstein[4], Andrea de Luca[5], Lucia Palmisano[6], Dimitrios Paraskevis[7], Roger Paredes[8], Mario Poljak[9], Jean-Claude Schmit[10], Vincent Soriano[11], Hauke Walter[12], Anders Sönnerborg[13] and the European HIV Drug Resistance Guidelines Panel

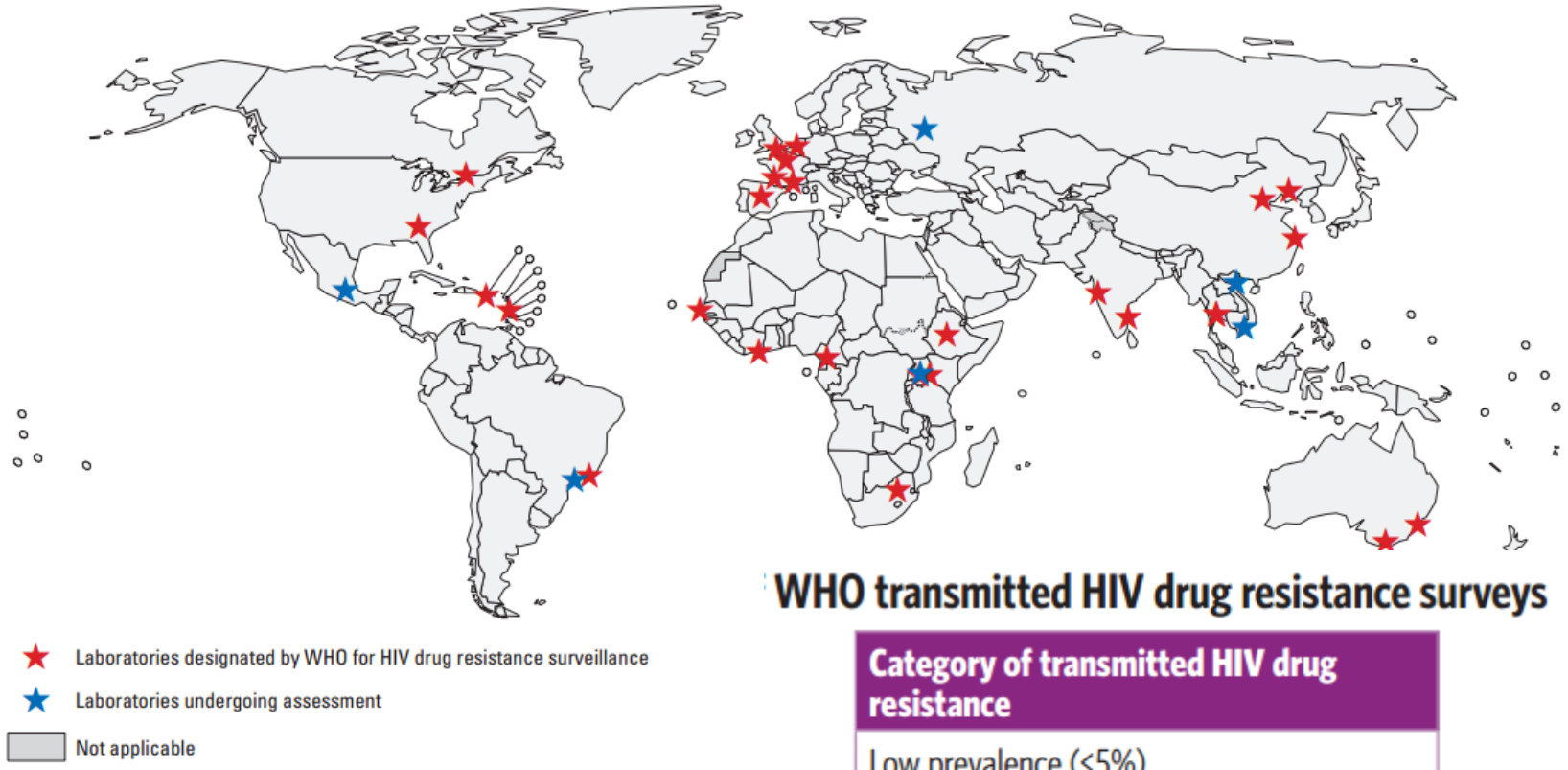
1. Yeni tanıda; ilaç direnci bulaşmış mı?
2. Tedaviye başlarken; ilaç seçiminin planlanmasında
3. Tedavi değişikliğinde; yan etki geliştiğinde
4. Düzensiz tedavilerde
5. Tedavi altında; viral rebound geliştiğinde
6. Tedavide blipler saptandığında
7. Gebelikte
8. CCR5 inhibitörü (örn; maraviroc) kullanımı öncesinde
9. PrEP (temas sonrası proflaxi) uygulamasında kaynağın değerlendirilmesinde

Başarılı antiretrovirallere rağmen başarısız tedaviler mümkündür.

Compliance; tedaviye bağlılık

WHO, HIV-1 ilaç direnci surveyans ağına sahiptir (HIV ResNet)

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



WHO transmitted HIV drug resistance surveys

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

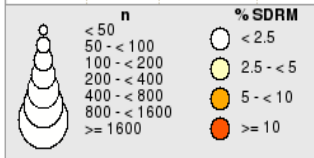
WHO surveyans verilerine göre;

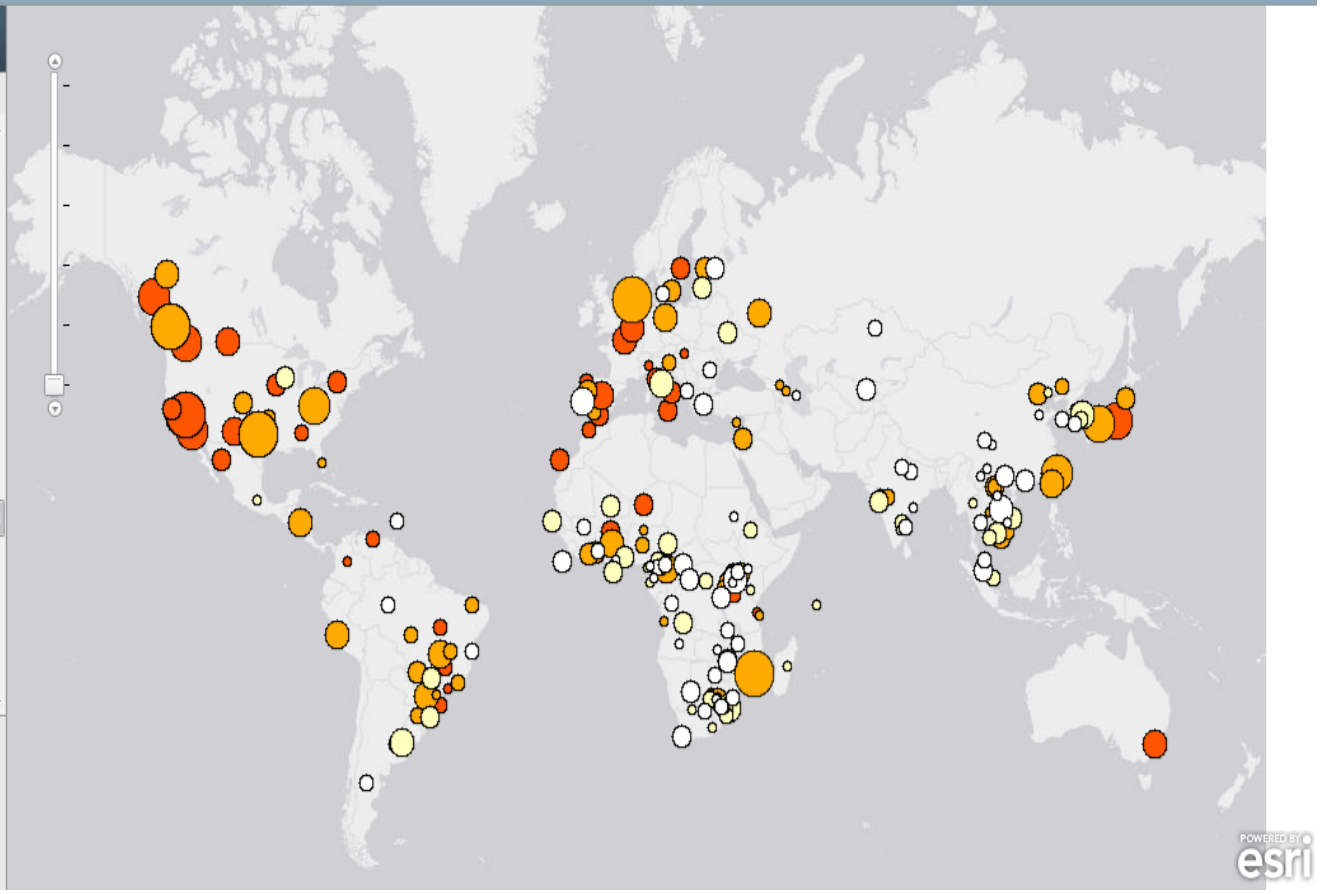
HIV-1 Drug Resistance in ARV-naive Populations

Compendium of published virus sequences from 32,290 persons, 213 studies according to region, year and subtype

Publications

Continent	Country	Publication	%SDRM	n
	AND THE GRENADIN			
Europe	ALBANIA	Ciccozzi05	1.5	66
Europe	AZERBAIJA	Saad06	0	41
Europe	BELGIUM	Vercauteren08	10.1	298
Europe	BYELORUS SSR,RUSSI FEDERATIC	Vazquez de Parga05	9.8	246
Europe	CYPRUS	Kousiappa09	5.4	37
Europe	DENMARK	Jorgensen03	2.1	97
Europe	ESTONIA	Avi09	0	134
Europe	ESTONIA	Avi10	5.5	145
Europe	FRANCE	Chaix03	13.3	233
Europe	GERMANY	Oette06	7.1	340
Europe	GREECE	Paraskevis05	1	100
Europe	HUNGARY	Mezei11	16.7	30
Europe	ITALY	Perno01	3.4	203
Europe	ITALY	Vicenti07	12.5	168
Europe	ITALY	Romano00	17.2	116
Europe	ITALY	Bonura10	18.3	109
Europe	ITALY	Balotta00	23.7	38
Europe	LATVIA	Balode10	3.4	117

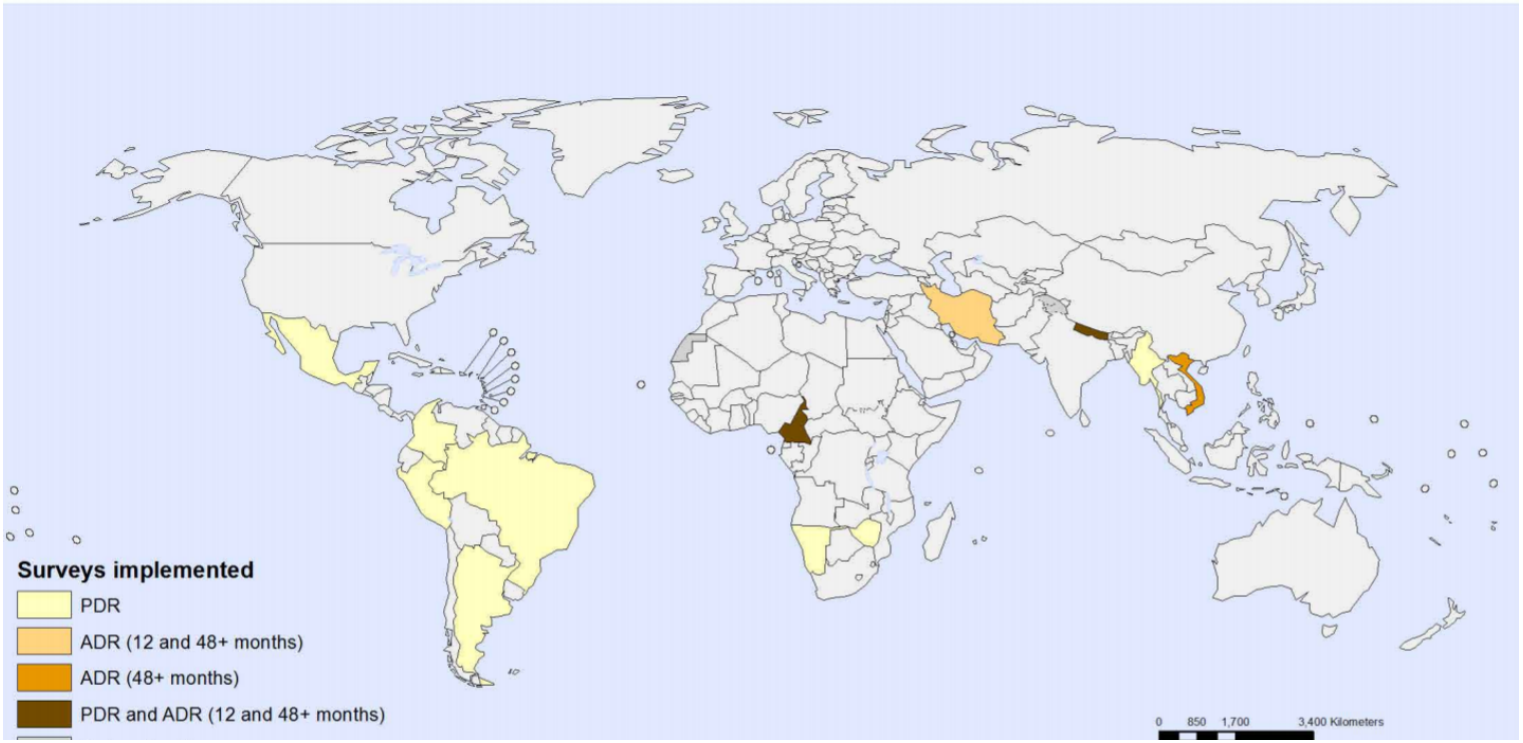




Kaç tür HIV ilaç direnci gelişir?

1. **Acquired HIV drug resistance (ADR)** develops when HIV mutations emerge due to viral replication in individuals receiving ARV drugs.
2. **Transmitted HIV drug resistance (TDR)** is detected in ARV drug-naive people with no history of ARV drug exposure. TDR occurs when previously uninfected individuals are infected with virus that has drug resistance mutations.
3. **Pretreatment HIV drug resistance (PDR)** is detected in ARV drug-naive people initiating ART or people with prior ARV drug exposure initiating or reinitiating first-line ART. PDR is either transmitted or acquired drug resistance, or both. PDR may have been transmitted at the time of infection (i.e. TDR), or it may be acquired by virtue of prior ARV drug exposure (e.g. in women exposed to ARV drugs for the prevention of mother-to-child transmission of HIV in people who have received pre-exposure prophylaxis, or in ilure).

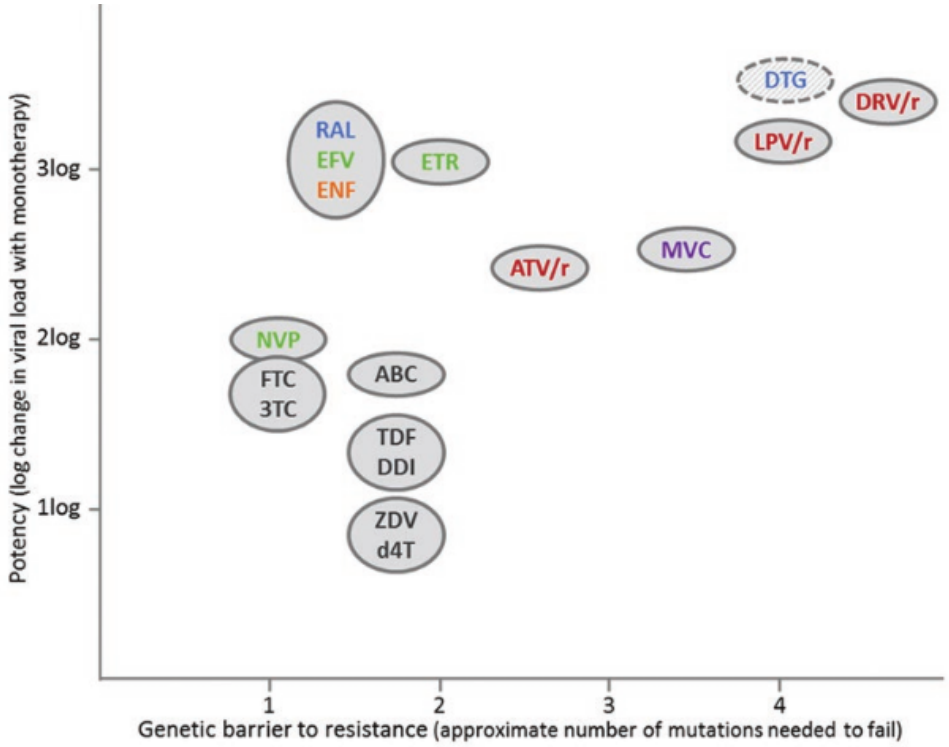
Countries implementing WHO surveys of pretreatment (PDR) and acquired HIV drug resistance (ADR) 2014–May 2016



World Health Organization CDC The Global Fund

HIV DRUG RESISTANCE REPORT 2017

Farklı antiretroviral ilaç sınıflarında direnç gelişir
Genetik bariyer.



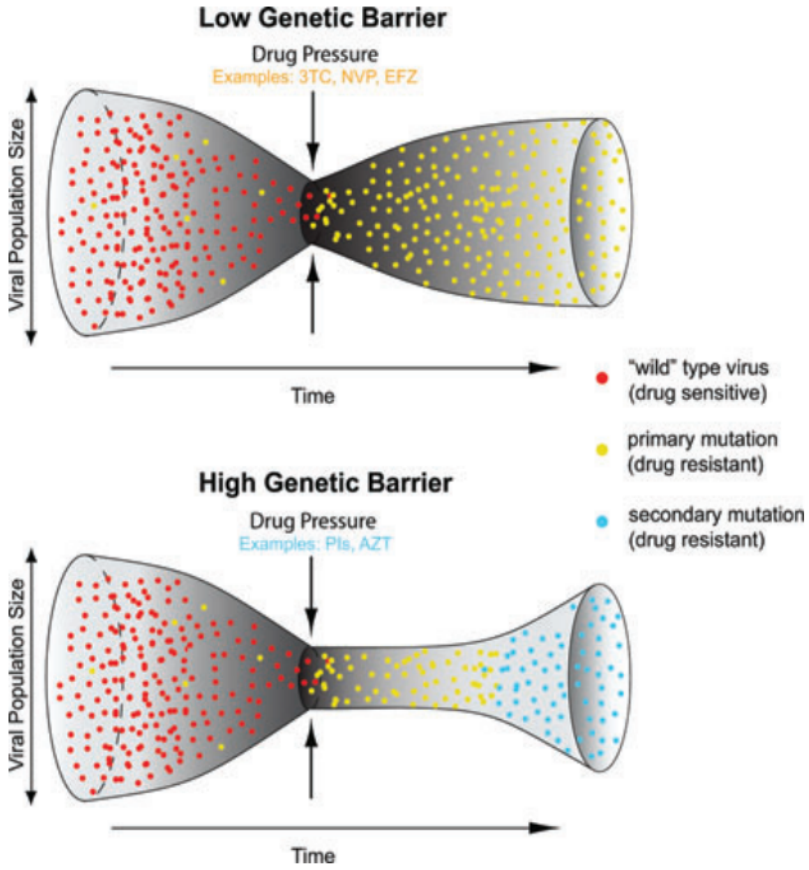


Figure 3. Figure showing the development of resistance focusing on low and high genetic barrier drugs. Low genetic barrier: selection of previously existing variants. High genetic barrier: selection as well as *de novo* mutations and evolution. Red: "wild" type virus. Yellow: primary mutations—strong effect on resistance combined with low or moderate fitness cost for low genetic barrier drugs and high genetic cost for high genetic barrier drugs. Blue: secondary, compensatory mutations—little or no effect on resistance, but restored fitness.

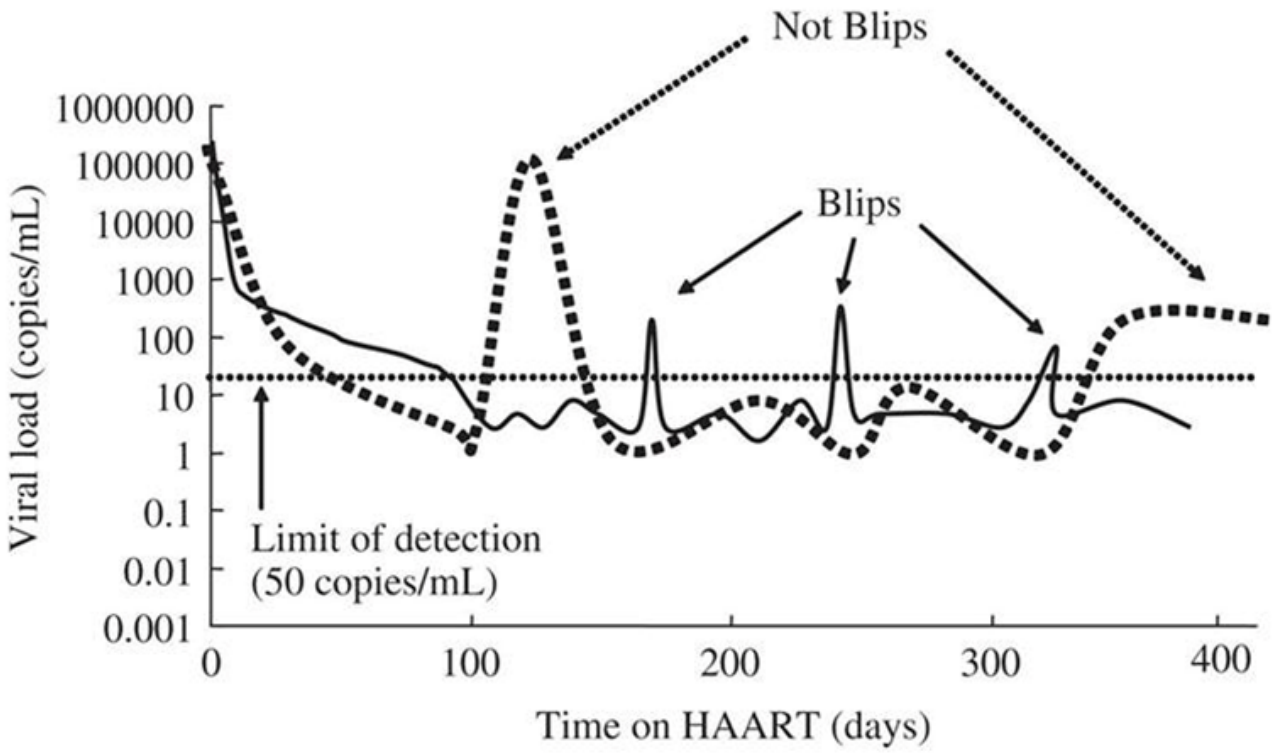
Düşük genetik bariyer (tek bir mutasyon yeterli)

- M184V: LAM, Emtrisitabin
- K103N: Efavirenz
- D30N: Nelfinavir

Viral fitness restorasyonu

Ann. N.Y. Acad. Sci. 2011;230:108–118

HAART tedavisinde blipler



Kaynak;http://jac.oxfordjournals.org/content/57/5/803/F1.expansion.html

Blip

- Viral yükte **bir defalık** 1000 kopya/ml'nin altında tespit edilen yükselme,
- **Blipler (blips);** düşük, tekrar eden, ölçülebilir plazma düzeylerinden ayırdedilmelidir.

DHHS,2012

HIV-2

HIV-2; patojenitesi daha düşük olmasına rağmen ilaç direnci HIV-1'e göre daha hızlı gelişir.
HIV-2'de NNRTI (Nevirapine, Efavirenz, Etravirin) ve Enfuvirtid doğal direnci yüksektir.
TDR HIV-2 mutasyonu çok nadir rapor edilmiş.
Ticari HIV-2 ilaç direnci analiz kiti bulunmuyor.

Table 1. Recommendations for drug resistance testing in the European setting

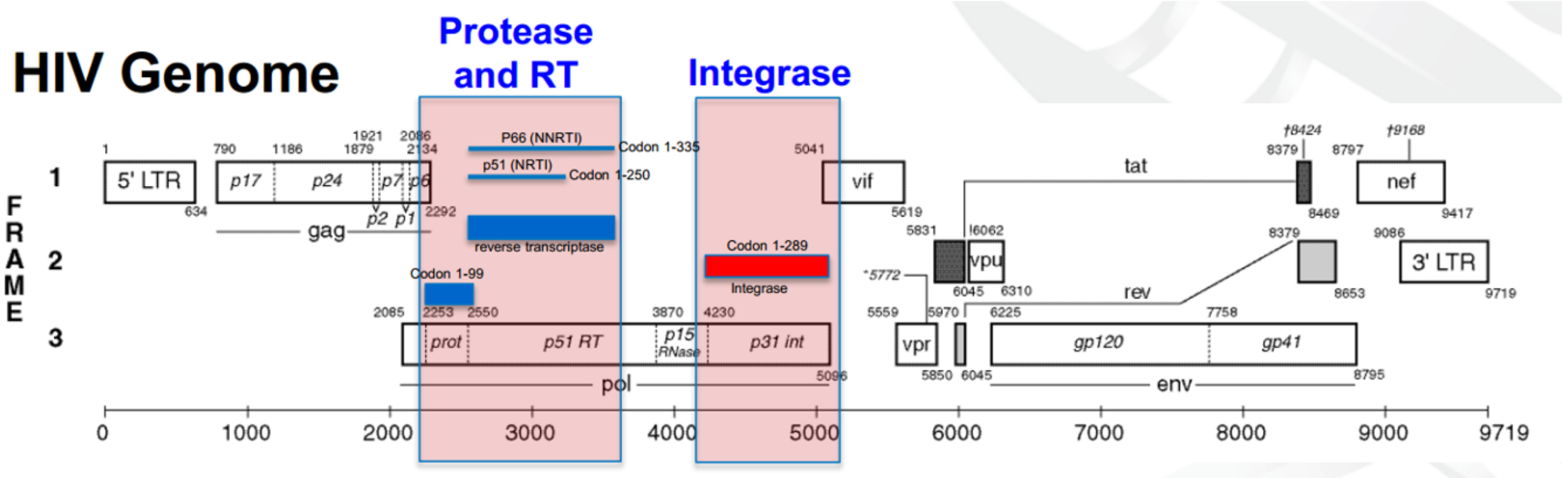
Clinical indication	Recommendation to clinicians	Recommendation and evidence level Academic consensus
HIV-2	Consider resistance testing when treatment change is needed after therapy failure.	CII Consensus: 96%

AIDS Rev. 2011;13:77-108

European Recommendations for the Clinical Use of HIV Drug Resistance Testing: 2011 Update

Anne-Mieke Vandamme[1,2], Ricardo J. Camacho[2,3], Francesca Ceccherini-Silberstein[4], Andrea de Luca[5], Lucia Palmisano[6], Dimitrios Paraskevis[7], Roger Paredes[8], Mario Poljak[9], Jean-Claude Schmit[10], Vincent Soriano[11], Hauke Walter[12], Anders Sönnerborg[13] and the European HIV Drug Resistance Guidelines Panel

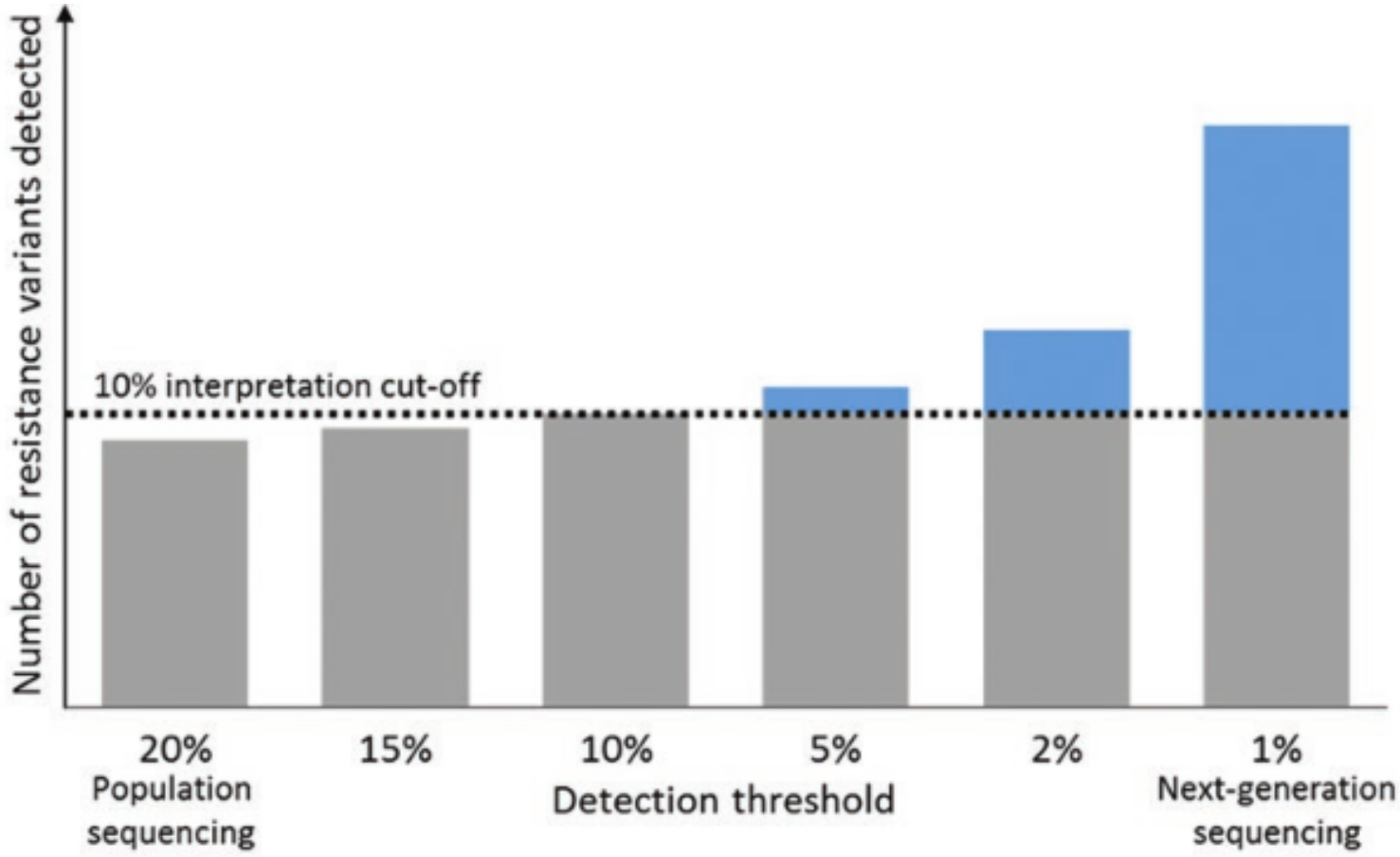
HIV-1 ilaç direnci mutasyonlarının ortaya çıkarılması için *pol* geninin analiz edilmesi gerekir.



- Standart HIV-1 ilaç direncinde analizinde; RT (NRTI ve NNRTI) ve Proteaz inhibitörleri (PI) analiz edilmektedir.
- Integraz inhibitörleri (INI) kullanıma girdiği için bu bölgeyi de analize eklemiş durumdayız.
- Plazma ve BOS için bu işlemler ayrı ayrı yapılmalıdır.

https://usfretroviridaejones.wikispaces.com/Important+Members

Teknolojik gelişmeler, analiz eşiği kararında
ve klinik yorumunda optimizasyon sorunlarına ve boşlukları yol açtı.



State of the Art in **HIV Drug Resistance**: Science and Technology Knowledge Gap.

Boucher CA, Bobkova MR, Geretti AM, Hung CC, Kaiser R, Marcelin AG, Streinu-Cercel A, van Wyk J, Dorr P, Vandamme AM.

AIDS Rev. 2018 Jan-Mar;20(1):27-42. **Review**.

The World Health Organization 2009 List of Mutations for Surveillance of Transmitted Drug Resistant HIV Strains

*Integraz inhibitörleri WHO HIV TDRM surveyansında yer almamaktadır.

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

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]*

1 World Health Organization, Geneva, Switzerland, **2** Molecular Biology Laboratory, Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal, **3** Molecular Diagnostics, "Prof. Dr. Matei Bals" Institute for Infectious Diseases, Bucharest, Romania, **4** Brigham and Women's Hospital Harvard Medical School, Boston, Massachusetts, United States of America, **5** Laboratoire de Virologie EA 2968, Université de Bordeaux, Bordeaux, France, **6** Division of Infectious Diseases, Stanford University, Stanford, California, United States of America, **7** Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America, **8** Division of Infectious Diseases, Brown University, Providence, Rhode Island, United States of America, **9** Tufts University School of Medicine, Boston, Massachusetts, United States of America, **10** Rega Institute for Medical Research, Katholieke Universiteit Leuven, Leuven, Belgium, **11** Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada, Ottowa, Ontario, Canada, **12** Department of Virology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands, **13** Department of Medical Microbiology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands, **14** Centre for Virology, Division of Infection and Immunity, University College London and Centre for Infections, Health Protection Agency, London, United Kingdom

HIV-1 ilaç direnci analizi: veri tabanımdan*

Dönem	Tedavi naif hasta	Antiretroviral deneyimli hasta	Toplam
2010 – Haziran 2019	5786	969	6755

*Türkiye'de 34 şehirden 106 enfeksiyon hastalıkları kliniğine ait hasta analizini içermektedir
** Tekrarlanan ve/veya henüz sonuçlanmamış analizler dahildir.

J Int AIDS Soc. 2014; 17(4Suppl 3): 19750.
Published online 2014 Nov 2. doi: 10.7448/IAS.17.4.19750
PMCID: PMC4225382

Transmitted antiretroviral drug resistance mutations in newly diagnosed HIV-1 positive patients in Turkey

Murat Sayan,[1] Fatma Sargýn,[2] Dilara Inan,[3] Dilek Yýldýz Sevgi,[4] Aysel Kocagül Celikbas,[5] Kadriye Yasar,[6] Figen Kaptan,[7] Selda Sayýn Kutlu,[8] Nuriye Tasdelen Fýsgýn,[9] Ayse Inci,[10] Nurgül Ceran,[11] Ýlkay Karaoðlan,[12] Atahan Cagatay,[13] Mustafa Kemal Celen,[14] Suda Tekin Koruk,[15] Bahadýr Ceylan,[16] Taner Yýldýrmak,[17] Halis Akalýn,[18] Volkan Korten,[19] and Ayse Willke[20]

Drug class	Transmitted drug resistance mutation patern	n	%
NRTI	K65R, M184V	6	0.7
NNRTI	K101E, K103N/S, G190A/E/S, Y181I/C, Y188H/L	32	**4.1**
PI	M46L, I54V, L76V, V82L/T, N83D, I84V, L90M	17	2.1
Total*		**52**	**6.7**

n=774

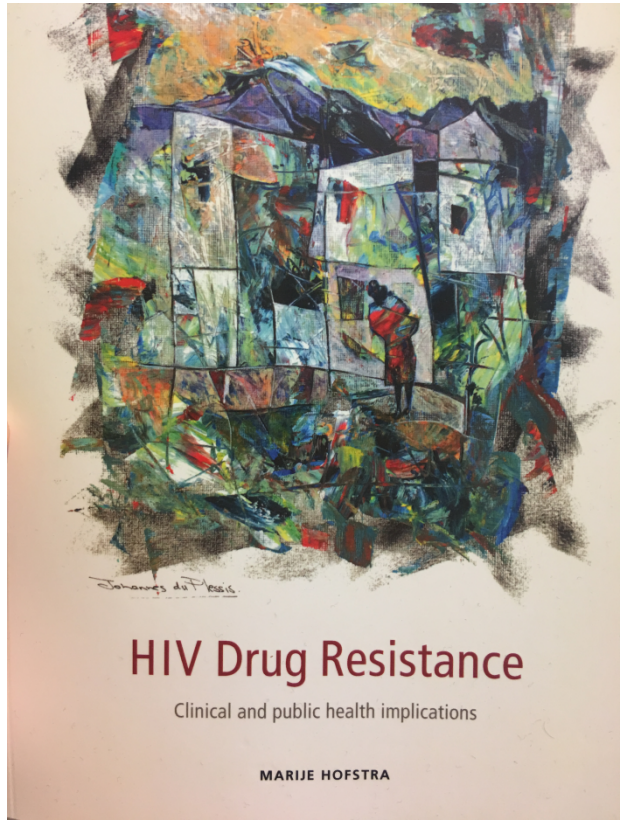
Tablo 6. Türkiye'de yeni tanı alan HIV (+) bireylerde ilaç direnci mutasyonları (2010 –2015).

Drug class	Transmitted drug resistance mutation patern	N	%
NRTI	K65R, M184V	7	0.5
NNRTI	L100I, K101E, K103N/S, V179F, Y188H/L/M, Y181I/C, G190A/E/S	42	**3.4**
PI	M46L, I50V, I54V, Q58E, L76V, V82A/C/L/T, N83D, I84V, L90M	30	2.4
Total		**79**	**6.3**

n=1243

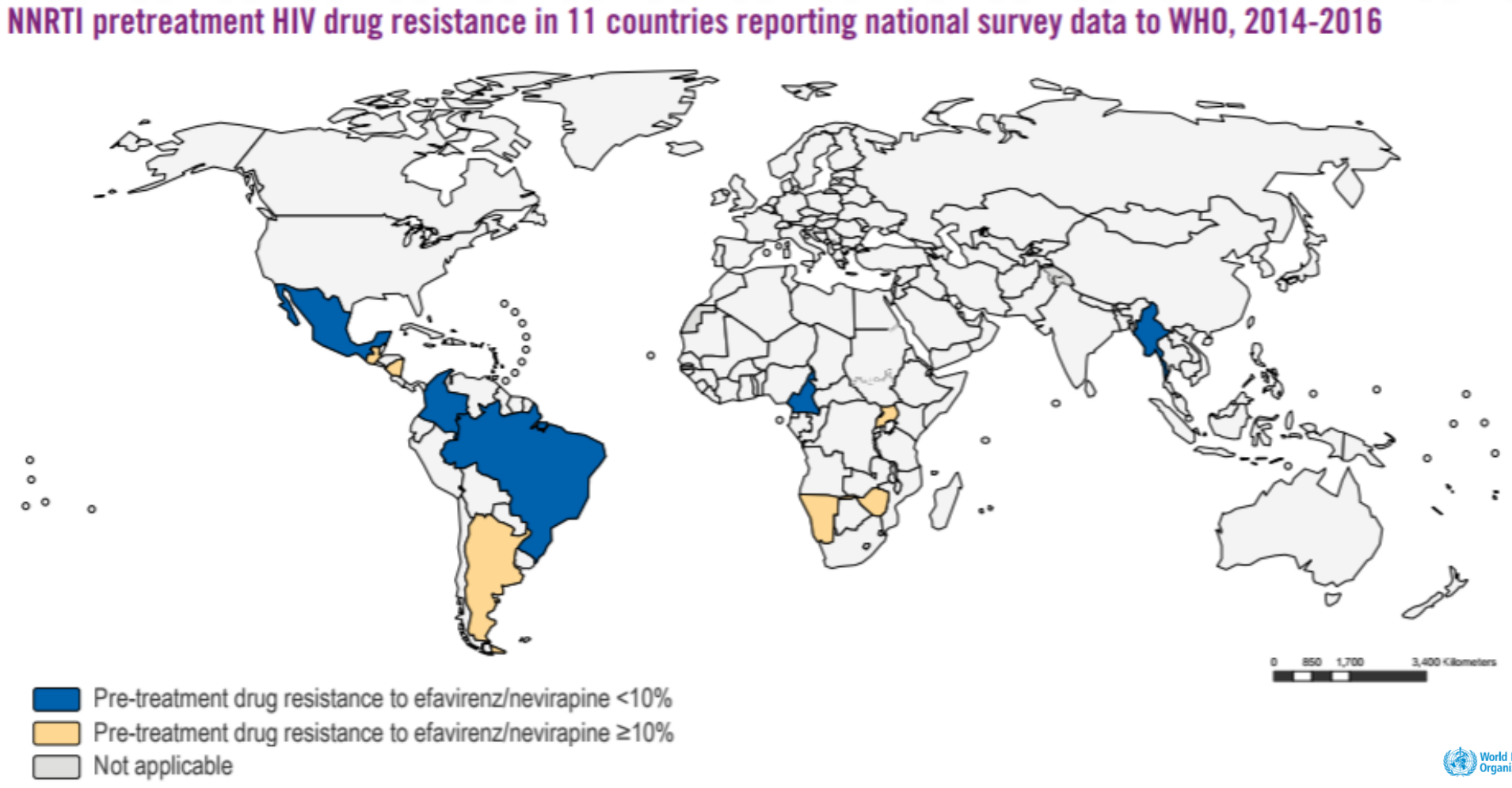
Avrupada HIV ilaç direncinin durumu: L.Marije Hofstra'nın PhD tezi, Utrect Universitesi, 2019.

- HIV ile yaşayan her 1/12 kişiye HIV ilaç direnci mutasyonu bulaşıyor.
- İlaç direncini anlamlı bir şekilde aktaranlar tedavi naif bireylerdir.
- Eğer tedavi öncesinde direnç mutasyonları bulunuyorsa ; TDF/FTC/Efavirenz tedavisinde viral ribound riski anlamlı derecede artıyor.
- INI tedavilerinden önce integraz direnci analizi gerekliliği için kanıt bulunmuyor. Fakat periyodik surveyansa devam edilmelidir.
- Tedavide, DTG'e duyarlılığın azalması için çok sayıda integraz bölge mutasyonunun birikmiş olması gerekiyor.



2016 WHO kılavuzu hala NNRTI bazlı rejim öneriyor.

http://www.who.int/hiv/pub/arv/arv-2016/en (accessed Nov 23, 2017)



Başarısız tedavilerde timidin analoğu mutasyonları (TAM) oluşur. Bu nedenle TA backbone tedavileri terkedildi.

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

TAM geriye dönebilir (revertant mutasyonlar).

Örneğin; T215D/N/S/Y mutasyonu ile AZT'ye direnç gelişir. Eğer bu mutasyon bir başkasına bulaşırsa ve bu kişi AZT kullanmıyorsa mutasyon bir süre sonra doğal tipe geri döner.

Poor and non-recommended backbones

Almost all guidelines now explicitly recommend avoiding the previously popular d4T+ddI combination. Mitochondrial toxicity is too high, and it is inferior to AZT+3TC (Robbins 2003). In cases of treatment failure, thymidine analog mutations (TAMs) are usually present, which can limit future options. In view of the wide selection of NRTIs available today, ddI+d4T is no longer justified at least for first-line therapy.

Hoffmann - Rockstroh - Kamps

HIV Medicine 2007

www.HIVMedicine.com

Yeni tanı alan HIV (+) hastalarda TAMs.

Kategori	Mutasyon paterni	n=774 (2014 Mart)		n=1243 (2015 Mart)	
TAM1	M41L, L210W, T215Y	60	7.7%	94	7.5%
TAM2	D67N, K70R, K219E/Q/N/R, T215F, T215C/D/S	34	4.3%	51	4.1%
TAM1 + TAM2	M41L + K219N, M41L + T215C/D/S	18	2.3%	22	1.7%

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	Q
				F	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

Tüm tedavi grubu hastalarının 113/208'inde (toplam **%54**) ilaç direnci mutasyonu var (Kocaeli Üniv, PCR Lab).

	Toplam direnç	Mutasyon paterni
NRTI	%46	K65R
		M184V/I ± TAM
		TAM
NNRTI	%38	K101E, K103N/S, V179D, Y181I, Y188L/H, G190S/E
PI	%11	M46I+ I47V +I54V+ V82A+ F53L+ N83D +L90M
INI	%6 (n=50)	T97A
		E157Q

Genotypic and Phylogenetic Insights on Prevention of the Spread of HIV-1 and Drug Resistance in "Real-World" Settings.

Brenner BG, Ibanescu RI, Hardy I, Roger M.

Viruses. 2017 Dec 28;10(1). pii: E10. doi: 10.3390/v10010010. **Review**.

Drug class	Drug (recommended regimen in green)	Resistance Mutations Primary resistance mutations	Frequency in first-line treatment failure	Fold Resistance	Fitness	Transmitted resistance
NRTIs	Lamivudine (3TC)	M184I/V	High	High	Low	Rare
	Emtracitabine (FTC)	M184I/V	High	High	Low	Rare
NRTIs	Zidovudine (AZT)	T215Y/F	High	High	High	Frequent
	Stavudine (d4T)	T215 Y/F	High	High	High	Frequent
	Didanosine (ddI)	L74V/I, K65R,	Moderate	High	Low	Rare
	Tenofovir (TDF)	K65R	Low	Low	Low	Rare
	Abacavir (ABC)	K65R, L74V/I, Y115F	Low	Low	Low	Rare
NNRTI	Nevirapine (NVP)	K103N/S, Y181C/I, G190A/S, V108I, V106M,Y188L/C	20-90%	High	High	Frequent
	Efavirenz (EFV)	K103N/S, Y181C/I, G190S/A, V108I, V106A/M, Y188L/C	20-90%	High	High	Frequent
INSTIs	Raltegravir (RAL)	Y143R Q148K/K/R,G140A/S N155H	Low-Moderate	Low-Moderate	Moderate	Rare
	Elvitegravir (EVG)	T66I/A/K, E92Q/G, S147G, N155H	Low	Low-High	Moderate	Rare
	Dolutegravir (DTG)	R263K or S153Y*	Rare	Low	Unfit	None

HIV ilaç direnci mutasyonlarının değerlendirilmesi dinamik bir süreçtir*.

TABLE 2. PRIMARY DRUG RESISTANCE MUTATIONS IN NEWLY DIAGNOSED HIV-1-INFECTED PATIENTS IN TURKEY (BETWEEN 2010 AND 2015, N = 1,306)

Drug class	*Drug resistance mutation*[a]	n[b]	%
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

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EPIDEMIOLOGY

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

Murat Sayan,[1,2] Fatma Sargin,[3] Dilara Inan,[4] Dilek Y. Sevgi,[5] Aysel K. Celikbas,[6] Kadriye Yasar,[7] Figen Kaptan,[8] Selda Kutlu,[9] Nuriye T. Fisgin,[10] Ayse Inci,[11] Nurgul Ceran,[12] Ilkay Karaoglan,[13] Atahan Cagatay,[14] Mustafa K. Celen,[15] Suda T. Koruk,[16] Bahadir Ceylan,[17] Taner Yildirmak,[18] Halis Akalın,[19] Volkan Korten,[20] and Ayse Willke[21]

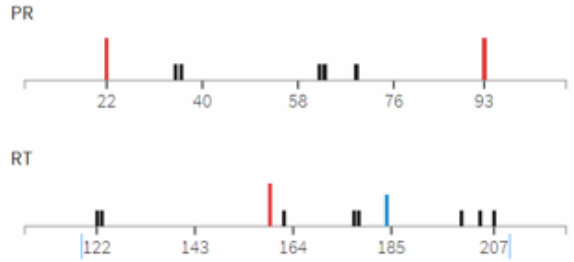
* Paredes R, *et* al. PLoSONE 2017; 12(7):e0181357.

HIVdb Program Report, HIVdb version 8.1.1 (2017-04-18)

[redacted]

SDRMs Pretty pairwise
Sequence includes PR:codons 14 - 99
Sequence includes RT:codons 1 - 230
Subtype:B (5.17%)
PR SDRMs:None
RT SDRMs:M184V

Sequence Quality Assessment



Drug Resistance Interpretation: PR

PI Major Resistance Mutations:None
PI Accessory Resistance Mutations:None
Other Mutations:A22AG, E35E_TN, M36L, I62IV, L63P, H69Q, I93IN

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:**M184V**
NNRTI Resistance Mutations:None
Other Mutations:K122P, D123E, I159M, S162C, D177E, I178V, T200E, E204Q, Q207E

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Low-Level Resistance
zidovudine (AZT)	Susceptible
stavudine (D4T)	Susceptible
didanosine (DDI)	Potential Low-Level Resistance
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Susceptible

Non-nucleoside Reverse Transcriptase Inhibitors	
efavirenz (EFV)	Susceptible
etravirine (ETR)	Susceptible
nevirapine (NVP)	Susceptible
rilpivirine (RPV)	Susceptible

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 they increase susceptibility to AZT, TDF and d4T and are associated with clinically significant reductions in HIV-1 replication.

Mutation Scoring: RT

NRTI	ABC	AZT	D4T	DDI	FTC	3TC	TDF
M184V	15	-10	-10	10	60	60	-10
Total	15	-10	-10	10	60	60	-10

Prof.Dr.Murat SAYAN
Kocaeli Üniversitesi, Tıp Fakültesi,
PCR Ünitesi, İzmit, Kocaeli.
sayanmurat@hotmail.com
http:/facebook.com/muratsayan.HIV
Cep: 0 533 647 9020

Ceza skoru kuralı
<10: susceptible
10 -14: potential low level resistance
15 -29: low level resistance
30 -59: intermediate resistance
≥ 60: high-level resistance

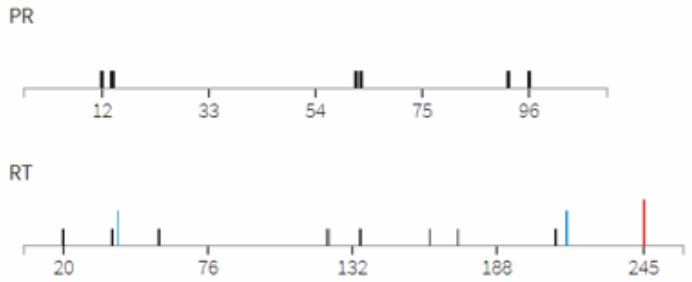
Paredes R, *et* al. PLoSONE 2017; 12(7):e0181357.

HIVdb Program Report, HIVdb version 8.1.1 (2017-02-09)

[redacted]

SDRMs Pretty pairwise
Sequence includes PR:codons 1 - 99
Sequence includes RT:codons 1 - 254
Subtype:B (5.1%)
PR SDRMs:None, RT SDRMs:M41L, T215S

Sequence Quality Assessment



Drug Resistance Interpretation: PR

PI Major Resistance Mutations:None
PI Accessory Resistance Mutations:None
Other Mutations:T12E, K14R, I62V, L63H, Q92QL, T96TP

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, T215S**
NNRTI Resistance Mutations:None
Other Mutations:K20R, T39D, N57NY, K122E, I135T, S162C, K173KR, R211G, V245*

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Low-Level Resistance
zidovudine (AZT)	Intermediate Resistance
stavudine (D4T)	Intermediate Resistance
didanosine (DDI)	Low-Level Resistance
emtricitabine (FTC)	Susceptible
lamivudine (3TC)	Susceptible
tenofovir (TDF)	Low-Level Resistance

Non-nucleoside Reverse Transcriptase Inhibitors	
efavirenz (EFV)	Susceptible
etravirine (ETR)	Susceptible
nevirapine (NVP)	Susceptible
rilpivirine (RPV)	Susceptible

RT Comments
NRTI

- **M41L** is a TAM that usually occurs with T215Y. In combinaton, **M41L** plus T215Y confer intermediate / high-level resistance to AZT and d4T and contribute to reduced ddI, ABC and TDF susceptibility.
- 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 may suggest that the patient may have once had a majority virus population with T215Y/F.

Mutation Scoring: RT

NRTI	ABC	AZT	D4T	DDI	FTC	3TC	TDF
M41L	5	15	15	10	0	0	5
T215S	5	20	20	10	0	0	5
M41L + T215S	5	5	5	5	0	0	5
Total	15	40	40	25	0	0	15

Prof.Dr.Murat SAYAN
Kocaeli Üniversitesi, Tıp Fakültesi,
PCR Ünitesi, İzmit, Kocaeli.
sayanmurat@hotmail.com
http:/facebook.com/muratsayan.HIV
Cep: 0 533 647 9020

Ceza skoru kuralı
<10: susceptible
10 -14: potential low level resistance
15 -29: low level resistance
30 -59: intermediate resistance
≥ 60: high-level resistance

Paredes R, *et* al. PLoSONE 2017; 12(7):e0181357.

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

Table 10. Patterns of relative INSTI susceptibility for 1,536 viruses in HIVDB with 209 distinct INSTI-Resistance patterns*.

RAL	EVG	DTG	% of Total Relative INSTI Susceptibility Profiles†	Example DRM Patterns§	DRM Pattern % with Profile	DRM Pattern % of Total
Susc	Susc	Susc	34.9	E157Q	65.7	22.9
				T97A	32.3	11.3
				Q95K	2.1	0.7
High	High	Int	18.4	G140S,Q148H	66.7	12.3
				G140S,Q148R	3.5	0.6
				E138K,Q148R	3.2	0.6
High	High	Susc	17.1	N155H	55.5	9.5
				N155H,G163R	12.5	2.1
				N155H,E157Q	12.2	2.1
Low	Low	Susc	6.5	G163R	30	2.0
				E138K	21	1.4
				G163K	17	1.1
High	High	High	5.3	E138A,G140S,Q148H	23.2	1.2
				E138K,G140S,Q148H	18.3	1.0
				E138T,G140S,Q148H	6.1	0.3
High	High	Low	4.5	E92Q,N155H	23.2	1.0
				Q148R	14.5	0.7
High	Ir					
High	Lo					
Int	High	Susc	1.8	E92Q	55.6	1.0
				E92Q,T97A	14.8	0.3
				T66A,G163R	7.4	0.1
High	Susc	Susc	1.4	Y143R	71.4	1.0
				Y143C	9.5	0.1
				Y143S	9.5	0.1
Low	Int	Low	1.2	R263K	94.4	1.1
				E157Q,R263K	5.6	0.1
High	Int	Low	1	L74M,T97A,Y143C,S230R	25	0.3
				L74I,T97A,Y143C,S230R	12.5	0.1

Table 11. In vitro susceptibilities associated with the 14 INSTI drug resistance mutation patterns.

Overall Pattern*	Specific Patterns*	%Exact†	%Include†	RAL§	EVG§	DTG§
E138KAT, G140SAC, Q148HRK	E138K, G140A, Q148R	0.00%	0.13%	>150$_2$	>150$_2$	-
	E138K, G140S, Q148H	0.98%	0.98%	>150$_3$	>150$_1$	8.4$_3$
	E138K, G140S, Q148R	0.07%	0.20%	>150$_1$	-	8.3$_1$

İntegraz inhibitörleri

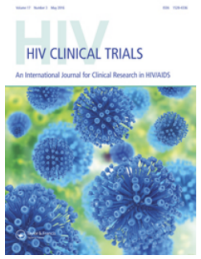
Genotipik analiz: Direnç mutasyonları

Fenotipik analiz: In vitro ilaç duyarlılığı

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

	Resistance mutation pattern					
Drug class	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

Türkiye'de ART naif hastalarda integraz inh. direnç mutasyonları bulunmuyor.
ART deneyimli hastalarda doğal ya da aktarılmış DTG direnci bulunmuyor.



HIV Clinical Trials

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

M. Sayan, A. Gündüz, G. Ersöz, A. İnan, A. Deveci, G. Özgür, F. Sargın, G. Karagöz, A. İnci, D. İnan, A Ülçay, İ. Karaoğlan, S. Kaya, S.S. Kutlu, K. Süer, A. Çağatay & H. Akalın

Table 2. Virological outcomes and drug resistance, by study.

Study	Follow-up (weeks)	N° patients	Resistance patterns (one line per patient)*
DTG-Mono			
Katlama *et al.*	24	28	**E138K,G140A, Q148R E92Q N155H**
Wijting *et al.*	48	96	**S230R R263K N155H**
Gubavu *et al.*	24	21	
Oldenbüttel *et al.*	24	31	**Q148H, G140S**
Rokx *et al.*	48	5	
Rojas *et al.*	24	31	118R**
Lecompte *et al.*	24	8	
Blanco *et al.*	24	31	**E138A, S147G, N155H, Q148R 138K, 155H, 140S**
DTG-3TC			
Borghetti *et al.*	24	36	
Maggiolo *et al.*	48	94	
Joly *et al.*	48	104	
Reynes *et al.*	48	27	
Blanco *et al.*	24	29	K70E***, K219E***, G190R§, M230I§
Maggiolo *et al.*	48	203	
Taiwo *et al.*	48	44	
DTG-RPV			
Llibre *et al.*	48	513	K101K/E
Gantner *et al.*	24	116	
Bonijoly *et al.*	24	268	
Revuelta *et al.*	48	32	
DTG-ATV			
Riva *et al.*	24	61	
Castagna *et al.*	48	116	
DTG-DRV			
Navarro *et al.*	48	27	

Viral supresyonun başarısız olduğu tedavilerde, basit DTG rejimlerinde direnç mutasyonları; metaanaliz sonuçları

F1000Research F1000Research 2019, 7:1359 Last updated: 17 MAY 2019

Check for updates

RESEARCH ARTICLE

REVISED Virologic failure and HIV drug resistance on simplified, dolutegravir-based maintenance therapy: Systematic review and meta-analysis [version 2; peer review: 3 approved]

Gilles Wandeler [1,2*], Marta Buzzi[3*], Nanina Anderegg[2], Delphine Sculier[3], Charles Béguelin[1], Matthias Egger[2], Alexandra Calmy [3]