Human Retroviruses

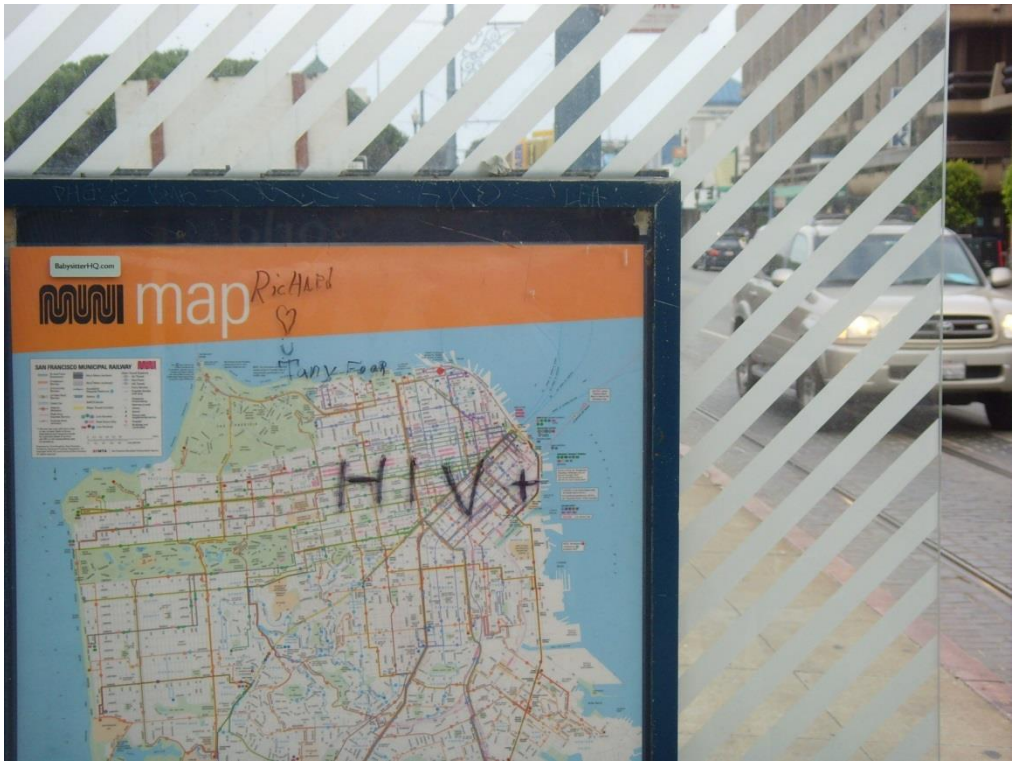
Assoc.Prof. Murat Sayan
Kocaeli Üniversitesi, Rutin PCR Lab. Sorumlu Öğt.Üyesi
Yakın Doğu Üniversitesi, DESAM Kurucu Öğrt. Üyesi
sayanmurat@hotmail.com
0533 6479020

Medical Virology,
14 Jan 2016.

Contents of Teaching in Medical Virology Lecture:

1. Introduction to virology
2. Laboratory diagnosis
3. Childhood illnesses
4. Human herpesviruses
5. Respiratory infections
6. Gastroenteritis
7. Acute neurological syndromes
8. Hepatitis
9. **Human retroviruses**
10. Human papillomaviruses

1981 *Mortality and Morbidity Weekly Report* (*MMWR*) reports of men treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at three different hospitals in Los Angeles, U.S.A.; All patients showed signs of severe immunodeficiency.



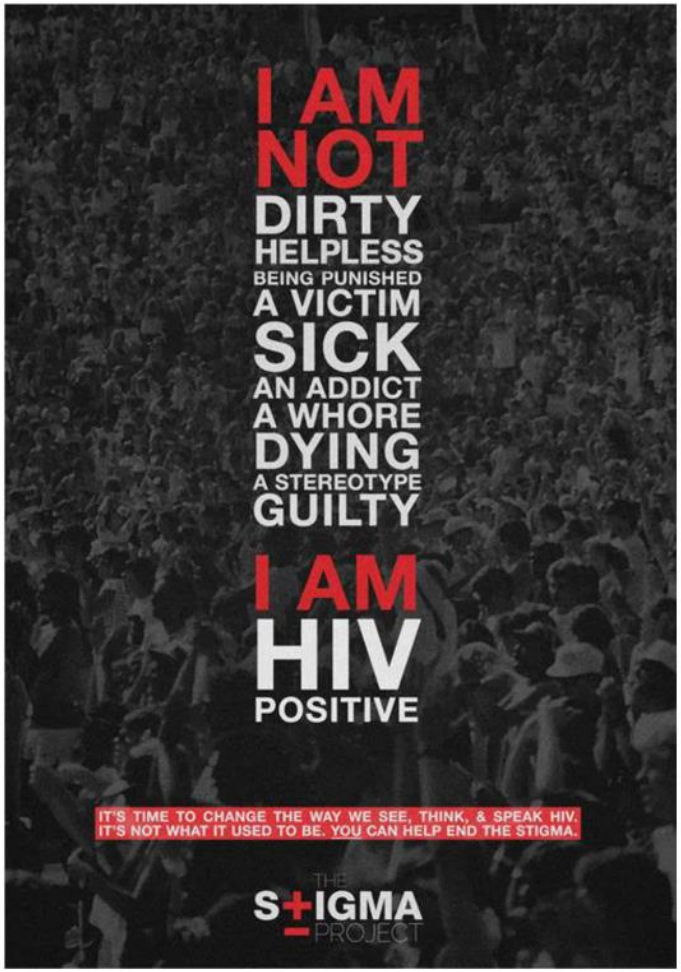
San Francisco'da bir otobüs durağı, 2011.

In 1983, a new retrovirus, termed lymphadenopathy associated virus (now called HIV 1) was isolated from the T-cells of a patient with persistent generalised lymphadenopathy.

25 yıl sonra (2008) Barre-Sinoussi'ye Nobel ödülü getirdi.

Kaynak: http://www.nobelprize.org/nobel_prizes/medicine/laureates/2008/barre-sinoussi-facts.html

Boston, USA - 2015



HIV (+) tanısı alan bir çok kişi benzer bir şekilde aşağıdaki deneyimleri yaşıyor:

-Test sonucundan sonra yaşanan şok

-İzolasyon

-İnkar

-Kendine zarar verme (bazen)

*HIV'in bulaşması kişinin kendi elinde değildir. Bu nedenle ilk aşamada bütün süreç kontrol dışıdır.

Kişi toparlanıp bilgi edinme ihtiyacı duymaya başlıyor. Bu aşamada sıklıkla şu soruların yanıtları aranıyor:

• Ne kadar yaşayacağım?

• Tedavi olabilecek miyim?

• Tedavi işe yarayacak mı?

• Tedavinin yan etkileri olacak mı?

*Her şey normale döner. Bu aşamada bütün süreç kişinin kontrolündedir

HIV ve AIDS terminolojisi oldukça sorunludur.

Yaşı küçük acısı büyük

AİDS'li 6 yaşındaki Y.Ç'nin zor yaşamı.

01 Aralık 2012

- Damgalama (stigma)
- Ayrımcılık (discrimination)

Human retroviruses

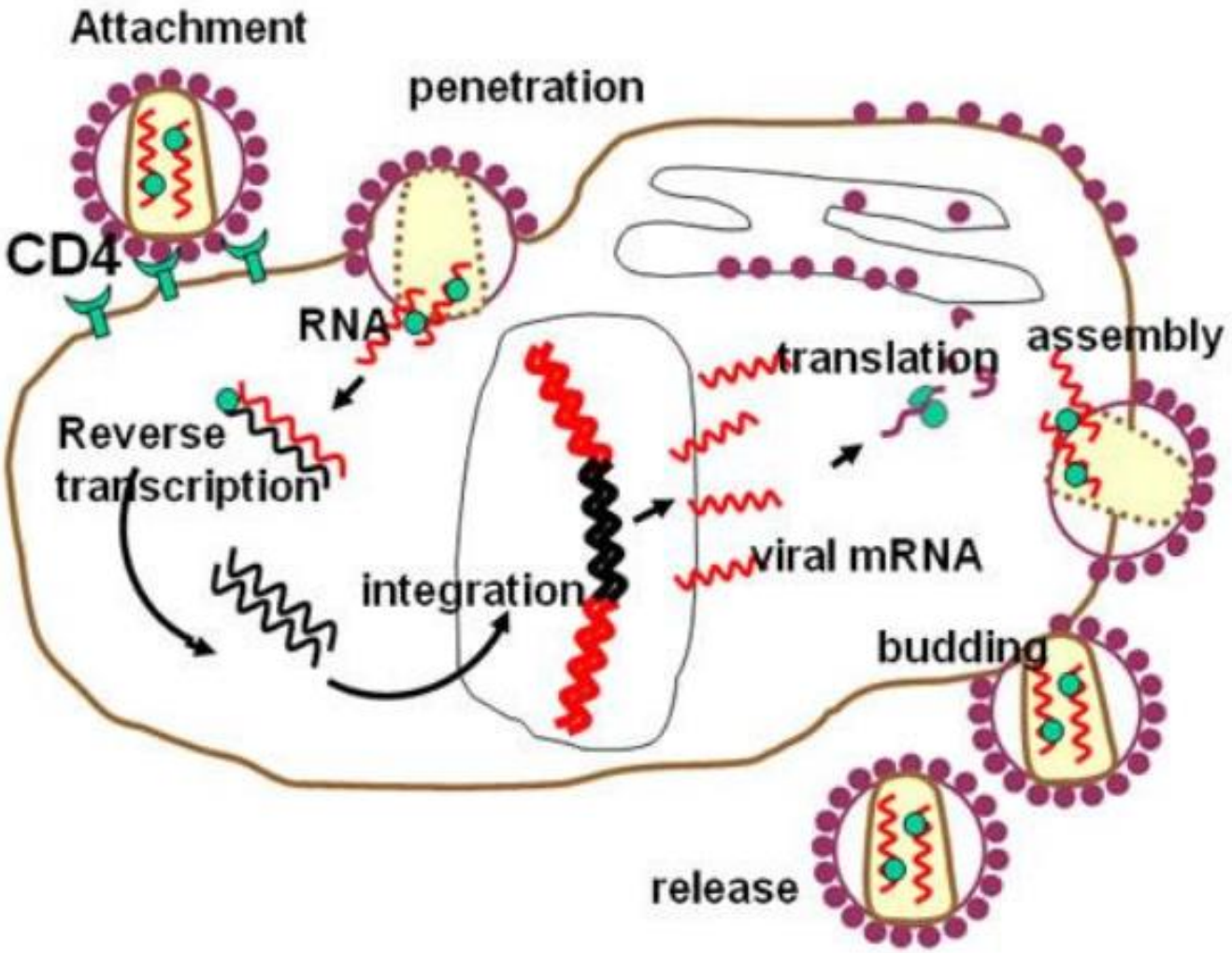
Six human retroviruses have so far been identified. All infect T cells.

HTLV 1 - T-cell leukaemias/lymphomas, Tropical spastic paraparesis

HTLV 2 - No known pathology

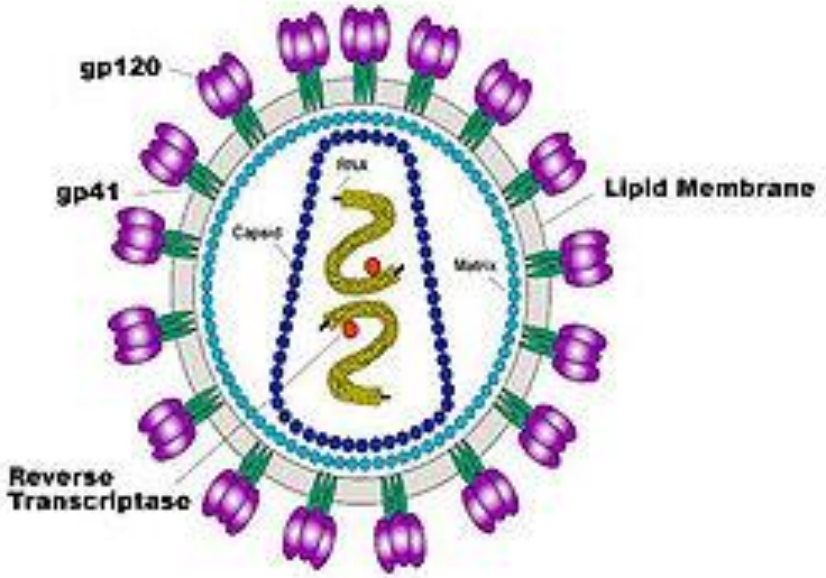
HIV 1 & 2 - AIDS

Two new human retroviruses were identified recently in a few individuals from Central Africa. They are related to HTLV1 and 2 and have been called HTLV 3 and 4. No pathology has yet been attributed to them.



Life cycle of a retrovirus

Organization of the HIV-1 Virion



Genome organization

Retroviruses have a diploid genome (2 copies of RNA genome per virus particle). The genome codes for at least three genes: *gag, pol* and *env*.

LTR - gag - pol - env - (onc) - LTR

LTR - Long terminal repeat - non coding regulatory sequences at each end of the genome, which are necessary for integration into host chromosome and which also control gene expression

gag - codes for the **core** proteins, **structural** virion components

pol - reverse transcriptase (polymerase)

env - envelope glycoprotein

onc - oncogene

Diversity of HIV

Genotip	Grup	Grup M subtip	Grup M subsubtip	Grup M CRF
HIV-1	**M**,N,O,P	A-D, F-H, J-K	A1 - A4 F1, F2	50 CRF
HIV-2				

CRF: circulating recombinant form

Semwanga D et al. AIDS Research and Human Retroviruses. 2011, 27: DOI: 10.1089/aid.2011.0024

In 1986, a second closely related virus, termed HIV 2 was isolated from a patient from West Africa with AIDS.

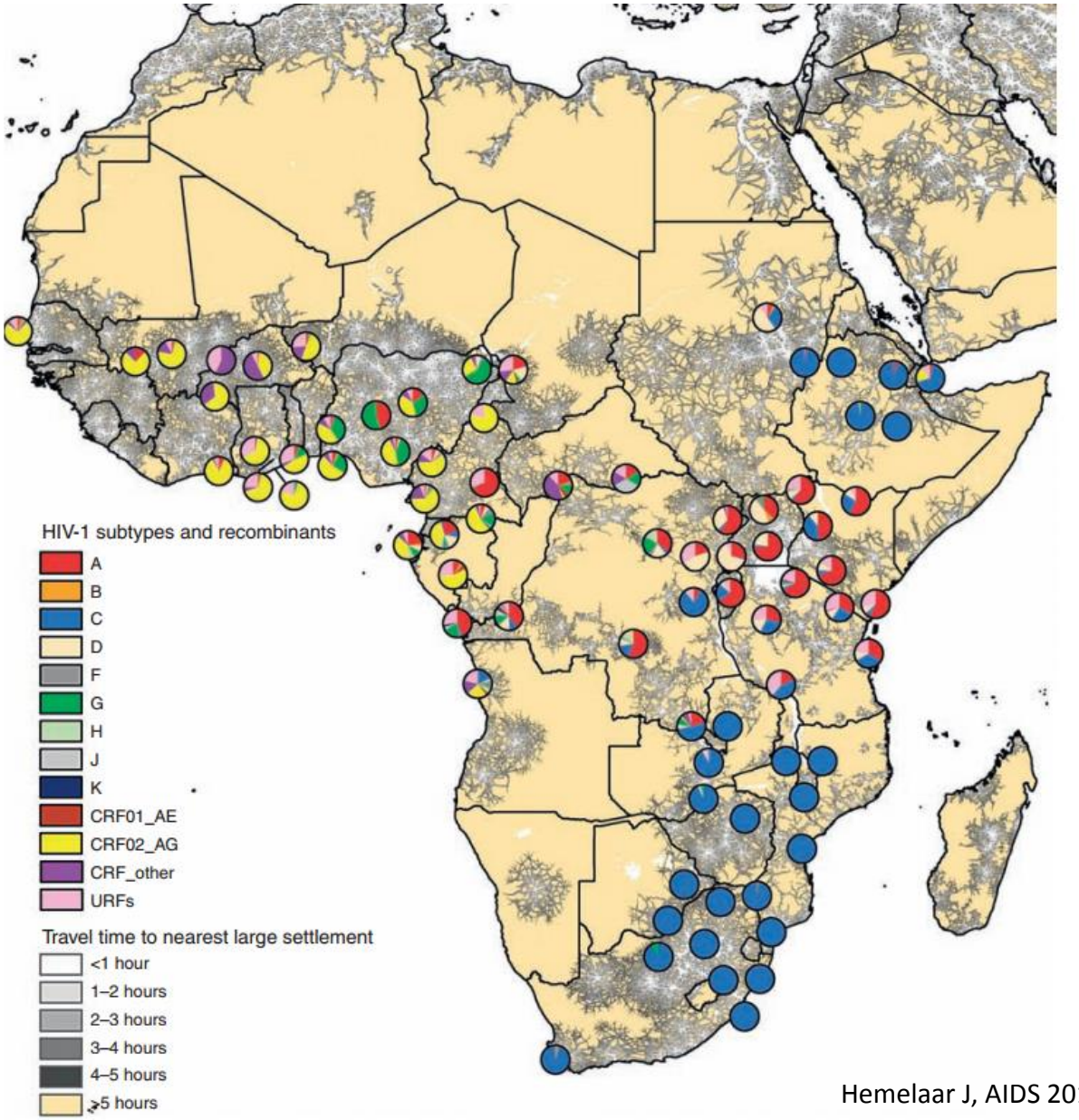
Complexity of HIV-1 CRF subtypes

Table 2. Circulating recombinant forms (CRFs) of HIV-1[a]

CRF	Subtype composition	Geographical distribution
CRF01_AE	A, E	South-East Asia, East Asia, Central Africa
CRF02_AG	A, G	West Africa, Central Africa, MENA
CRF03_AB	A, B	Eastern Europe and Central Asia
CRF04_cpx	A, G, H, K, U	Greece, Cyprus
CRF05_DF	D, F	Central Africa, Europe
CRF06_cpx	A, G, J, K	Central Africa, West Africa, Estonia
CRF07_BC	B′, C	China
CRF08_BC	B′, C	China
CRF09_cpx	A, G, U	West Africa, Central Africa
CRF10_CD	C, D	Tanzania
CRF11_cpx	A, G, J, CRF01_AE	Central Africa
CRF12_BF	B, F	South America
CRF13_cpx	A, G, J, U, CRF01_AE, CRF11_cpx	Central Africa
CRF14_BG	B, G	Spain
CRF15_01B	CRF01_AE, B	Thailand
CRF16_A2D	A2, D	Kenya, Argentina, South Korea
CRF17_BF	BF	South America
CRF18_cpx	A1, F, G, H, K, U	Cuba, Central Africa
CRF19_cpx	A1, D, G	Cuba, Central Africa
CRF20_BG	B, G	Cuba
CRF21_A2D	A2,D	Kenya
CRF22_01A1	CRF01_AE, A1	Cameroon
CRF23_BG	B, G	Cuba
CRF24_BG	B, G	Cuba
CRF25_cpx	A, G, U	Central Africa, Saudi Arabia
CRF26_AU	A, U	Democratic Republic of the Congo
CRF27_cpx	A, E, G, H, J, K, U	Democratic Republic of the Congo
CRF28_BF	B, F	Brazil
CRF29_BF	B, F	Brazil
CRF30_0206	CRF02_AG, CRF06_cpx	Niger
CRF31_BC	B, C	Brazil
CRF32_06A1	CRF06_cpx, A1	Estonia
CRF33_01B	CRF01_AE, B	Malaysia, Singapore, Indonesia
CRF34_01B	CRF01_AE, B	Thailand

HemelaarJ,Trends Mol Med 2012;18(3):182-192

Afrika is a major source for HIV-1 CRF subtypes



Hemelaar J, AIDS 2012,26:2351–2360

Afrika is important basin for HIV co-infections

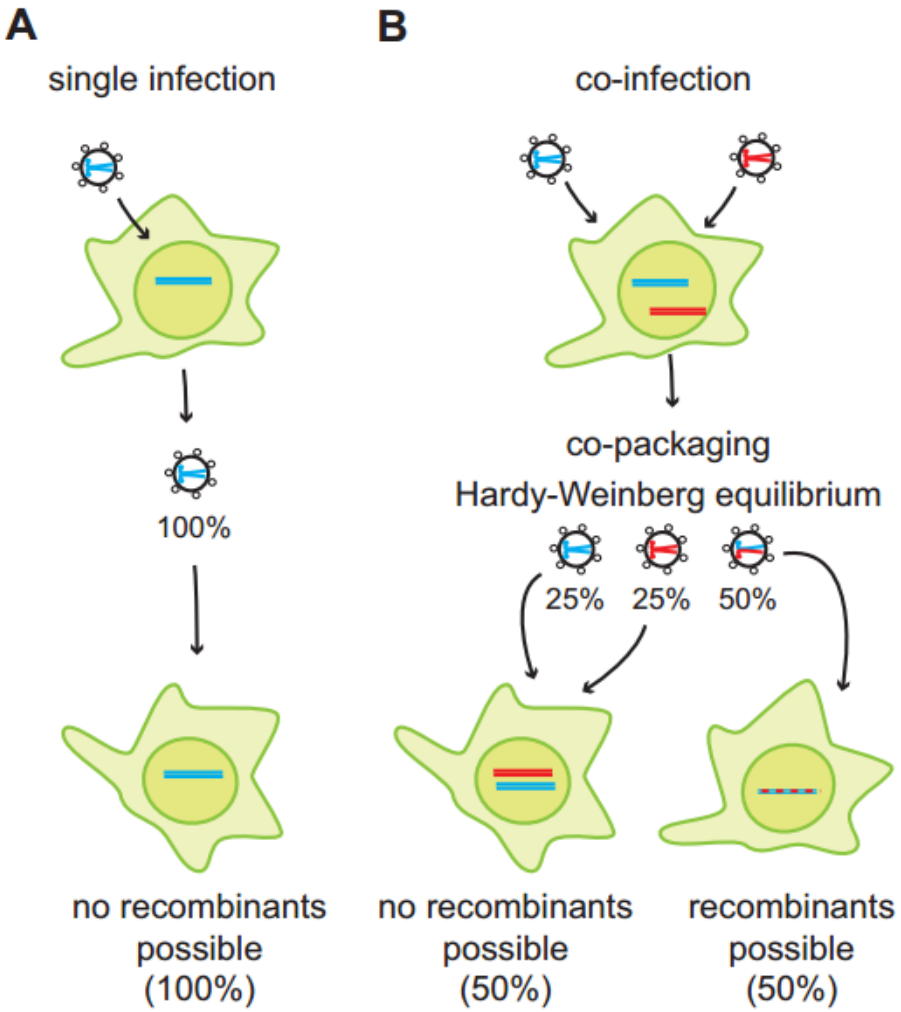


Fig. 5. Co-infection is necessary for genetic recombination.

doi.org/10.1016/j.virusres.2012.06.015

Why we survey that the diversity of HIV-1 subtype

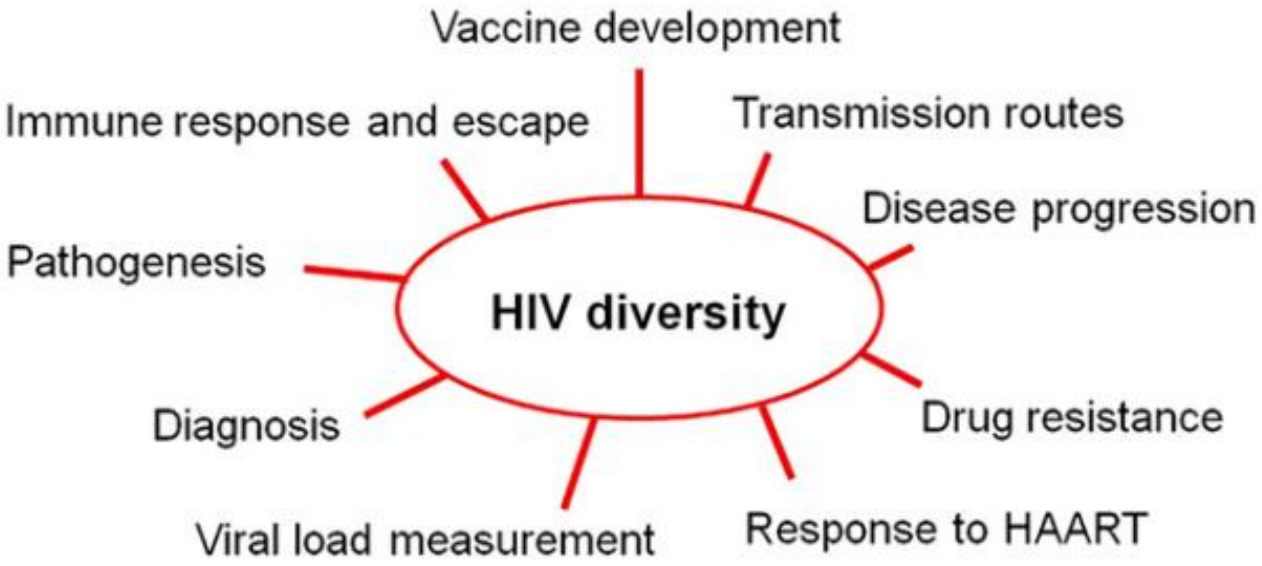


Figure 3 The central importance of HIV diversity. Aspects of HIV infection which are affected by HIV genetic variability are shown.

Hemelaar J,Journal of Infection 2013; 66, 391-400

Currently (2012), about 35.3 million people are believed to be infected with HIV, world-wide; 22 million of these are in sub-Saharan Africa. HIV-1 is the major cause of the pandemia; HIV-2 is of lower virulence and infection has largely remained confined to West Africa.

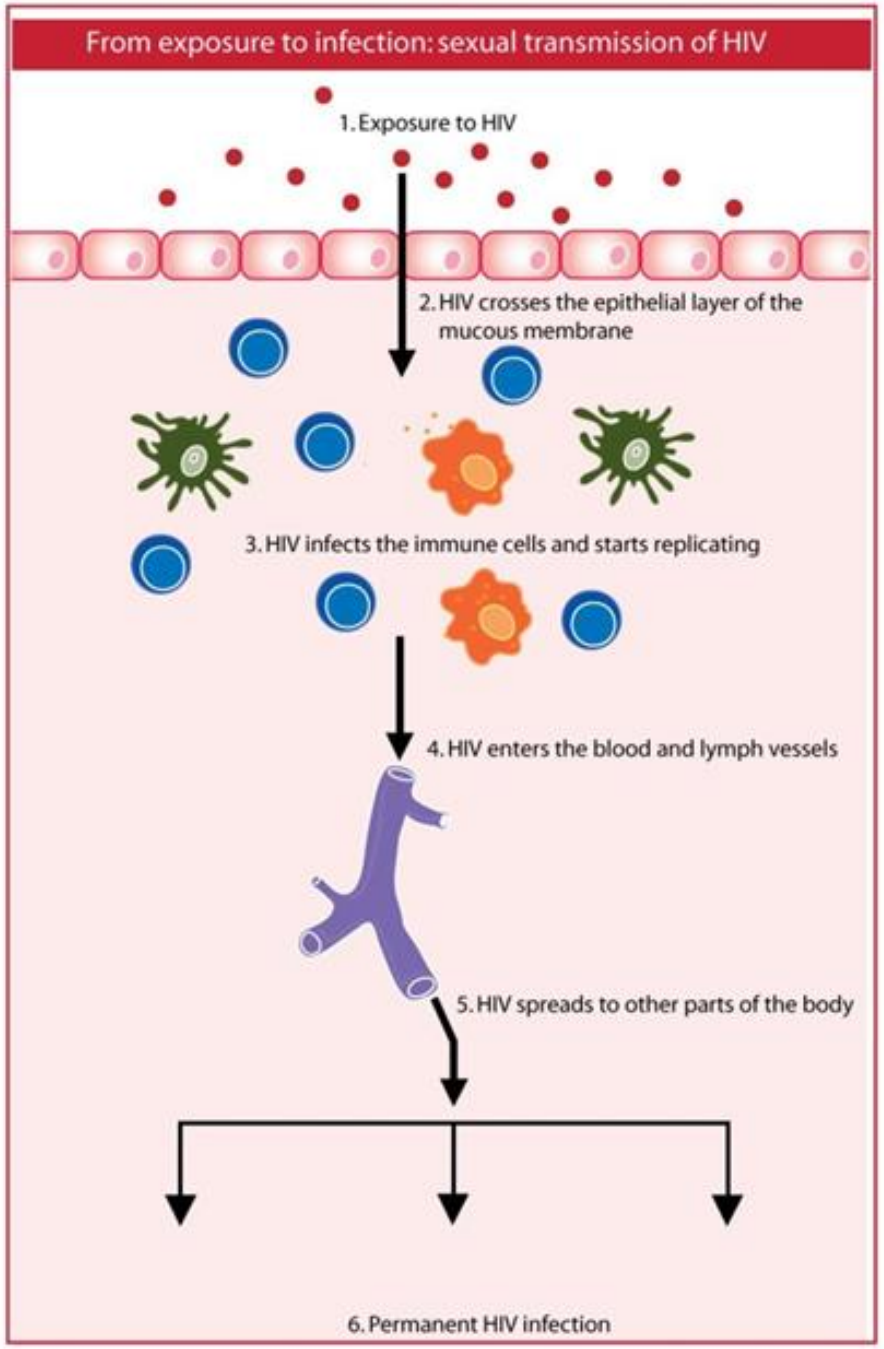
Adult: 32.8 million
Women: 15.9 million
Child (<15 y): 2.5 million

World map according to the HIV infected people in different countries.

UNAIDS

HIV'in bulaşında ve artışındaki temel neden cinsel temastır.

HIV, genital mukoza ile temas eder, epitel katmanını geçer ve burada bağışıklık (dendtritik) hücreleri ile karşılaşır ve çoğalmaya başlar.
Bağışıklık hücreleri onu kan ve lenf dolaşımına taşır ve böylece HIV, derin doku/organlara ulaşır.



Kaynak: http://www.catie.ca/en/pif/fall-2011/exposure-infection-biology-hiv-transmission

Transmission

Infection is transmitted in the same way as hepatitis B, but is much less infectious.

1.) Sexual intercourse:

This is the most common route of transmission world wide. The receptive partner is at greatest risk

There is an increased risk of transmission if partners have other sexually transmitted diseases and during primary HIV infection.

2.) Vertical Transmission:

In the absence of ARV prophylaxis, 10-40% of HIV-exposed babies will acquire the infection from their mothers. This is the second most common route of transmission world wide.

Infection may occur in utero

during birth (commonest)

post-natally, through breast feeding

3.) Exposure to blood:

Intra-venous drug abusers - sharing of needles

Needle-stick injuries - risk approximately 0.3% (depends on extent of the injury)

muco-cutaneous exposure - risk approximately 0.1%

HIV, CD4 + hücreyi enfekte eder ve proviral DNA'sı ile konak genomuna entegre olur.

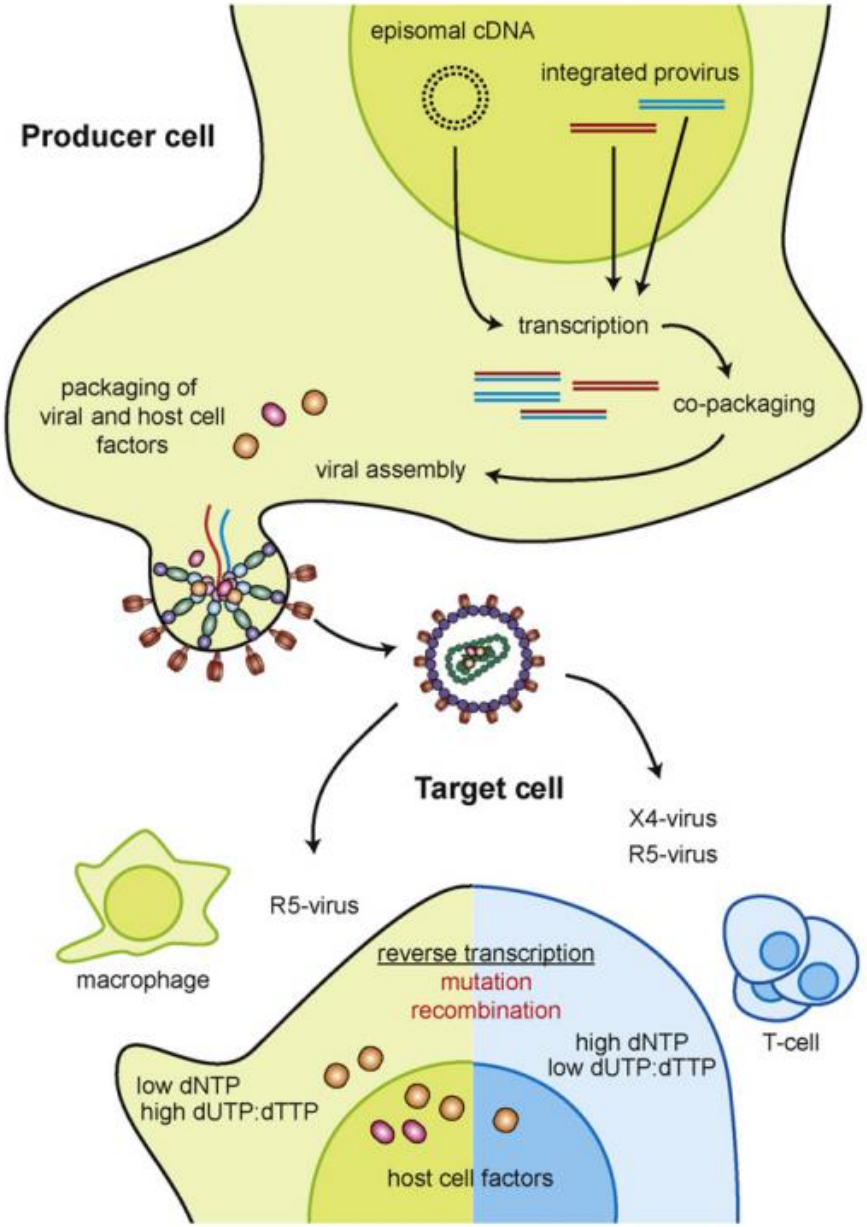


Fig. 1. Viral diversity through the HIV replication cycle. The viral quasispecies is shaped at almost every stage of the virus life cycle. The viral genome is first

doi.org/10.1016/j.virusres.2012.06.015

Eğer kişide CCR5 Δ32 mutasyonu varsa HIV, CD4 + hücreyi enfekte edemez.

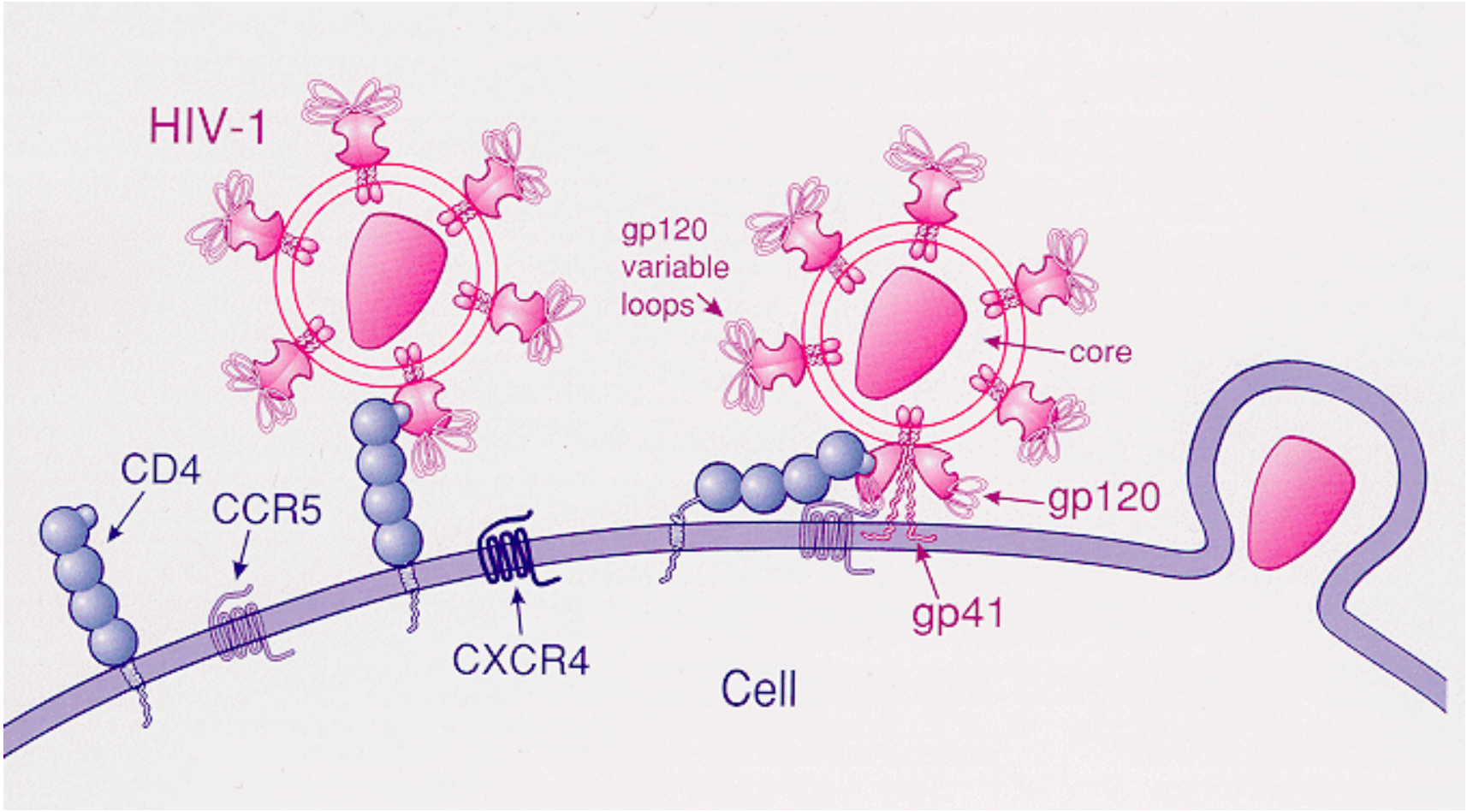
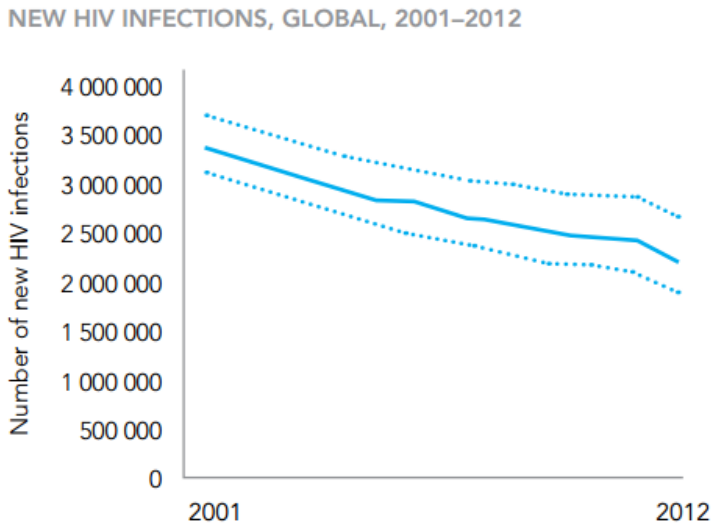
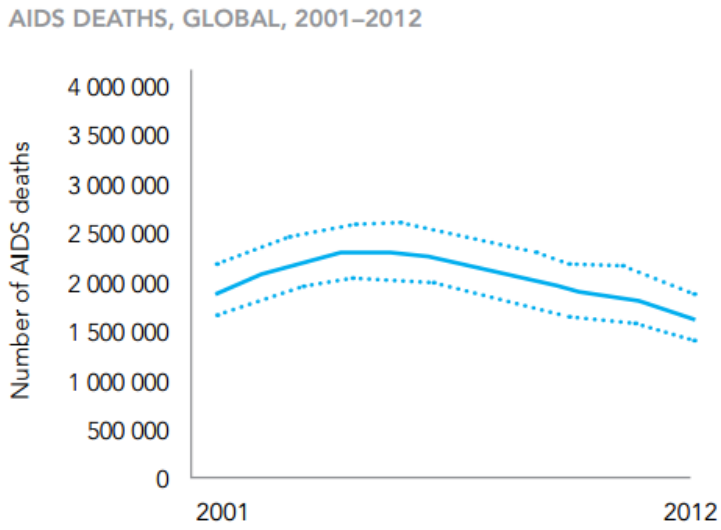
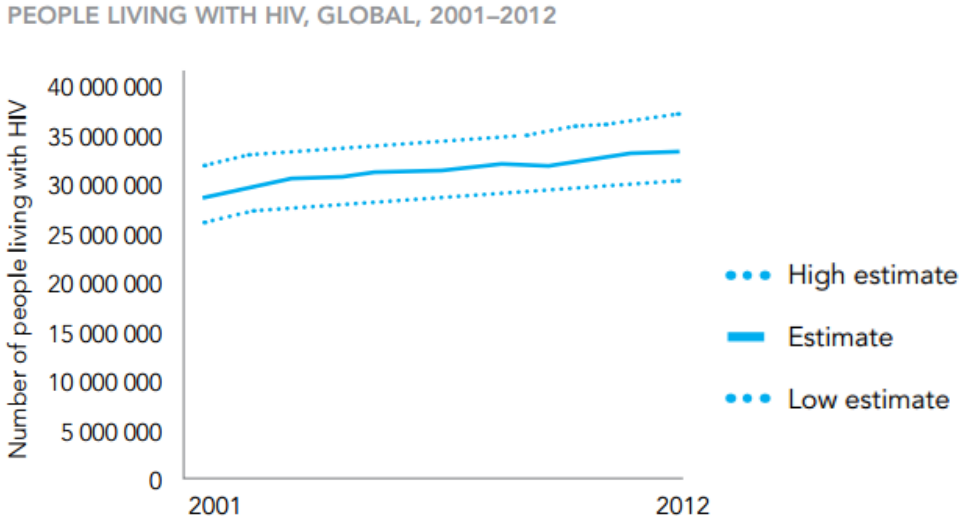


FIGURE A

Numbers of people living with HIV, new HIV infections, and AIDS deaths, 2001-2012, globally

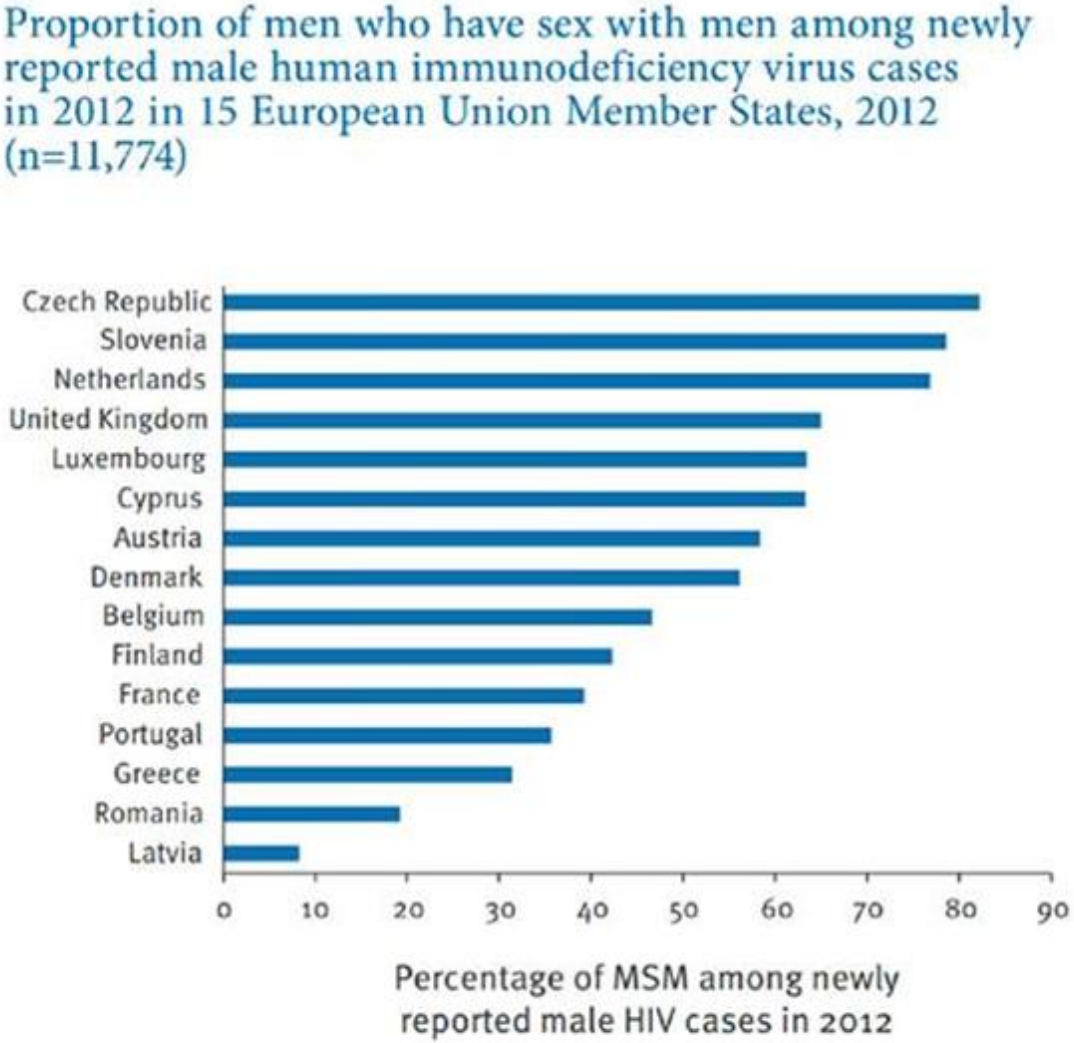






HIV Avrupa'da, erkek eşcinsel bireyler (MSM) arasında hızla yayılıyor. Yeni HIV enfeksiyonlarında artış %36 oranında ve daha çok 20 - 29 yaş arasında.

- HIV danışmanlığının ve test hizmetlerinin daha çok ve sürekli teşvik edilmesi,
- HIV tanısının erkenden konulması,
- Yüksek risk altındaki bireylerin HIV bakım ve tedavisinin arttırılması gerekiyor



Kaynak: http://www.eurosurveillance.org/images/dynamic/EE/V18N48/Janiec_fig1.jpg

FIG. 4

Global HIV Prevention R&D Investments 2005–2012

HIV PREVENTION OPTION	TOTAL INVESTMENT 2005 – 2012
Preventive Vaccines	US$7 billion
Microbicides	US$1.8 billion
Pre-Exposure Prophylaxis	US$0.3 billion
Adult Male Circumcision	US$0.1 billion
Treatment as Prevention	US$0.2 billion
Total 2005 – 2012	US$9.4 billion

Preventive Vaccines
Microbicides
Pre-Exposure Prophylaxis
Adult Male Circumcision
Treatment as Prevention*

* The Working Group began tracking funding for treatment as prevention in 2010.

HIV'i önleme stratejilerinin arasında antiretroviral ilaçların payı hızla artmaktadır..

Course of disease

HIV establishes a persistent infection in its host and only causes death many years later.

Primary infection

Most individuals experience a febrile illness about 2-4 weeks after exposure. This illness co-incides with sero-conversion (development of antibodies) and so is often referred to as the sero-conversion illness. The symptoms are similar to those of glandular fever, namely fever, sore throat, night sweats, lymphadenopathy, diarrhoea. The illness is self limiting.

Asymptomatic phase

Following the primary infection, the patient enters a stage of clinical latency. During this time the patient feels fine, but they are infectious as they have on-going viral replication. They also have HIV antibodies in their blood (and will test positive in HIV tests). This healthy state may last many years.

Prodromal phase

As the CD4 counts drop, there is a gradual onset of a variety of prodromal disorders, such as weight loss, fever, persistant lymphadenopathy, oral candidiasis and diarrhoea. These symptoms precede the progression to AIDS.

Acquired Immunodeficiency Syndrome (AIDS)

Syndrome with the following features:

1) **Constitutional disease:** fever, diarrhoea, weight loss, skin rashes
2) **Neuro-cognitave defects**: dementia, myelopathy, peripheral neuropathy
3) **Immunodeficiency:** Increased susceptibility to opportunistic infections:
4) **Rare malignancies**: Kaposi sarcoma, oral hairy leukoplakia, lymphomas.

1987 FDA approval for zidovudine is granted, making it the first antiretroviral therapy to be used as a treatment for HIV/AIDS. The FDA establishes the treatment investigational new drug (IND) mechanism.

THE LANCET

The Lancet, Volume 382, Issue 9903
doi:10.1016/S0140-6736(13)61809-7

Review

The end of AIDS: HIV infection as a chronic disease

Steven G Deeks, Sharon R Lewin, Diane V Havlir

The success of antiretroviral therapy has led some people to now ask whether the end of AIDS is possible. For patients who are motivated to take therapy and who have access to lifelong treatment, AIDS-related illnesses are no longer the primary threat, but a new set of HIV-associated complications have emerged, resulting in a novel chronic disease that for many will span several decades of life. Treatment does not fully restore immune health; as a result, several inflammation-associated or immunodeficiency complications such as cardiovascular disease and cancer are increasing in importance. Cumulative toxic effects from exposure to antiretroviral drugs for decades can cause clinically-relevant metabolic disturbances and end-organ damage. Concerns are growing that the multimorbidity associated with HIV disease could affect healthy ageing and overwhelm some health-care systems, particularly those in resource-limited regions that have yet to develop a chronic care model fully. In view of the problems inherent in the treatment and care for patients with a chronic disease that might persist for several decades, a global effort to identify a cure is now underway.

Published Online
October 21, 2013
http://dx.doi.org/10.1016/S0140-6736(13)61809-7

Department of Medicine, University of California, San Francisco, CA, USA (Prof S G Deeks MD, Prof D V Havlir MD); **Department of Infectious Diseases, Monash University and Alfred Hospital, Melbourne, VIC, Australia**

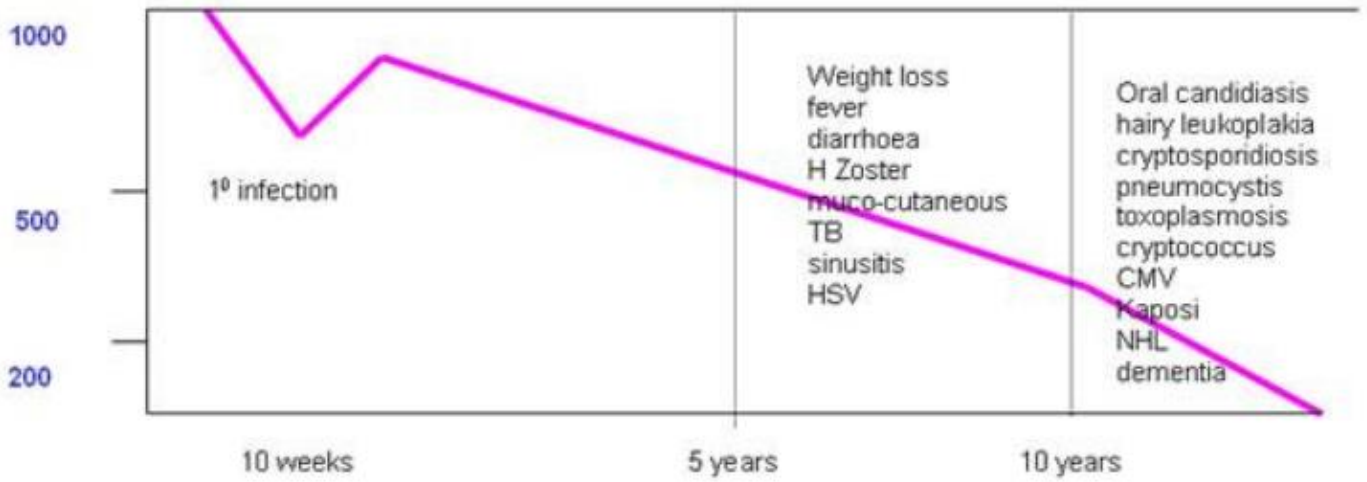
Pathogenesis

When a new infection is established, the first cells to be exposed are the dendritic cells. These cells are resident in the skin and genital mucosa. It is their job to take up antigen in the tissues and to transport it to regional lymph nodes where they present it to T cells. Dendritic cells express a receptor called DC SIGN to which HIV can attach. HIV particles remain attached to the surface of the cell and are passively transported to the very cells that HIV most likes to infect, namely CD4+ T cells. Cycles of infection are set up in the CD4 cells in the lymphoid tissue.

Helper T cells are the primary target of HIV. They are cytokine secreting cells that provide the signals to control the immune response. Without them the immune response cannot function

In the early days after infection, HIV is able to replicate to very high levels while the immune system learns to deal with it. CD4 + levels in the blood fall and virus levels peak at approximately 21 days post infection. The CD4 cell population in the gut is particularly severely affected early on. However, an immune response to the virus does develop after a while and virus levels in the blood fall to a steady state level. Unfortunately, the immune response is not able to control the infection completely and virus replication continues in the lymphoid tissue. As time passes, the antiviral immunity begins to fail and virus levels begin to rise again and the person succumbs to the infection.

Deterioration is linked to the loss of CD4+ cells:



Laboratory diagnosis and monitoring

Serology

The mainstay of diagnosis is the detection of HIV specific antibody. IgG develops 4-6 weeks post exposure and remains detectable for life. As all individuals become chronically infected, the presence of HIV specific antibody indicates infection. There are two situations where further tests may be necessary to confirm a diagnosis:
(a) **Early infection** - the period after exposure before antibody becomes detectable, (sometimes termed the "window" period).
(b) **Infants of HIV positive mothers:** all have passively acquired HIV-specific antibody, but only 10-40% are infected. This antibody may take 12 to 18 months to disappear.

Direct detection of virus

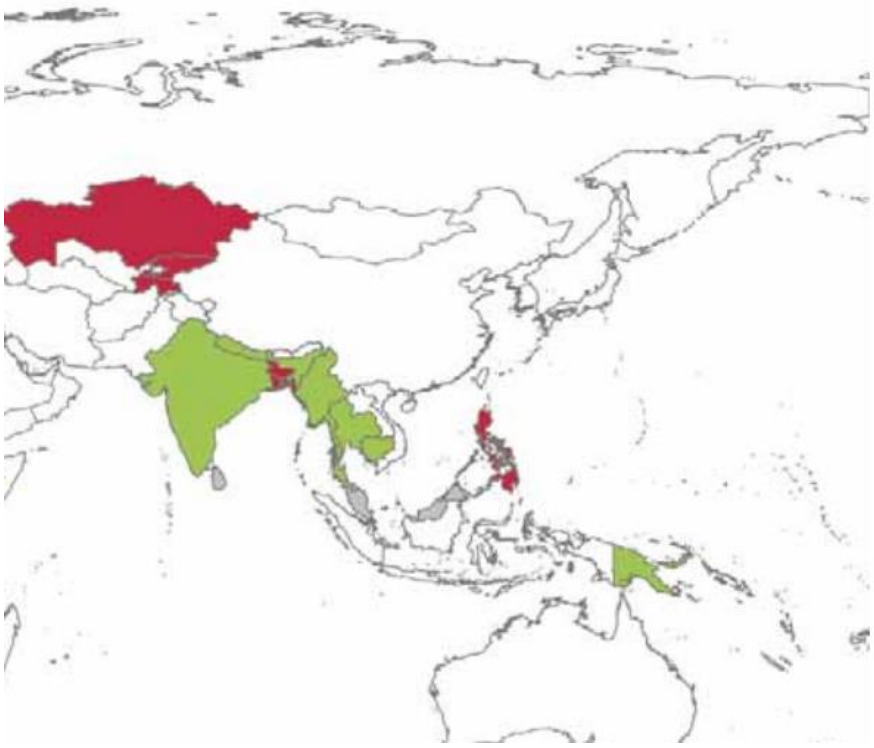
1. Viral **p24 antigen** in serum - This is a useful marker of early infection. It appears in the blood 3-5 weeks post exposure and becomes detectable approximately 6 days before antibody (during the so called window period.) Once antibody appears, the p24 antigen is usually cleared.
Blood donors, source patients of needle-stick injuries and organ donors are routinely screened for both p24 Antigen as well as HIV antibody. These days many laboratories (including our own) use a combination HIV antibody/antigen test as the primary HIV screening test.

2. Detection of **viral genome** (proviral DNA or viral RNA) by **PCR:** This is a very sensitive indicator of infection. PCR becomes positive about 2 weeks after infection and remains positive throughout the course of the infection. This is the test of choice for confirming infection in infants of HIV positive mothers

3. Culture of virus from peripheral blood mononuclear cells (PBMCs). This is difficult and not routinely done.

Markers of disease progression:
These give an idea of the stage of infection and are also useful for monitoring response to antiviral drugs:
CD4 count, total lymphocyte count
plasma viral RNA levels

WHO report; global HIV infection status



Increasing >25%

Armenia
Bangladesh
Georgia
Kazakhstan
Kyrgyzstan
Philippines
Tajikistan

Stable

Angola
Argentina
Belarus
Benin
Cameroon
Democratic Republic of the Congo
Djibouti
France
Germany
Ghana
Haiti
Kenya
Lesotho
Lithuania
Malaysia
Niger
Nigeria
Panama
Republic of Moldova
Senegal
Sri Lanka
Uganda
United States of America

Decreasing >25%

Belize
Botswana
Burkina Faso
Cambodia
Central African Republic
Congo
Côte d'Ivoire
Dominican Republic
Eritrea
Ethiopia
Gabon
Guinea
Guinea-Bissau
India
Jamaica
Latvia
Malawi
Mali
Mozambique
Myanmar
Namibia
Nepal
Papua New Guinea
Rwanda
Sierra Leone
South Africa
Suriname
Swaziland
Thailand
Togo
United Republic of Tanzania
Zambia
Zimbabwe

Sıra	Merkez	Naif	Tedavi	Toplam
1	Kocaeli Üniv. + Diğer	79	24	103
2	Göztepe EAH	180	50	230
3	Erciyes Üniv.	10	15	25
4	AnDeva Antalya	8	*	8
5	Haydarpaşa Num.	54	25	79
6	Haseki EAH	40	19	59
7	Kartal EAH	5	4	9
8	Marmara Üniv.	65	10	75
9	Vakıf Gureba	11	5	16
10	Samatya EAH	23	7	30
11	Cerrahpaşa Tıp	17	5	22
12	Okmeydanı EAH	35	16	51
13	Çapa Tıp	67	17	84
14	Trabzon KTÜ	3	10	13
15	Bursa Uludağ Üniv.	30	11	41
16	Antalya Akdeniz Üniv.	61	18	79
17	Edirne Trakya Tıp	6	1	7
18	Urfa Harran Tıp	10	3	13
19	İzmir Atatürk EAH	23	10	33
20	Ankara EAH	3	*	3
21	Haydarpaşa GATA	1	*	1
22	Çanakkale 18 Mart	2	*	2
23	Ege Üniv	2	1	3
24	Amerikan Hast.	1	*	1
25	Sakarya Üniv., EAH	5	2	7
26	Ankara Numune	40	12	52
27	Gaziantep Üniv.	34	15	49
28	Samsun 19 Mayıs	47	15	62
29	Semra Çalangu	7	1	8
30	Şişli Etfal EAH	118	7	125
31	Bolu İzzet Baysal Üniv.	4	4	8
32	Artvin Devlet Hast.	6	3	9
33	Ordu Özel Hast.	*	1	1
34	Behçet Uz Hast.	1	1	2
35	Giresun Devlet Hast.	3	*	3
36	Samsun EAH	2	*	2
37	İstanbul Adli Tıp	5	*	5
38	Bakırköy EAH	8	3	11
39	Pamukkale Üniv	4	*	4
40	Diyarbakır Dicle Üniv	20	2	22
41	Ankara Dış Kapı	*	*	*
42	Yeditepe Üniv. Hast.	1	*	1
43	Mersin Üniv.	5	1	6
44	Florence Nightingale	1	*	1
45	Trabzon Kanuni EAH	1	*	1
46	Başkent Üniv	1	*	1
	Toplam	**1049**	**318**	**1367**

Tablo 1. Kocaeli Üniv, Arş Uyg.Hast. Merkez Lab.,PCR ünitesine 2010 yılından beri HIV-1 ilaç direnci analizi için başvuran hastaların merkez ve klinik durumlarına göre dökümü: 7 Mart 2014 itibariyle

Antiretroviral (HAART) tedavinin hedefleri
Kandaki HIV-RNA düzeyini azami seviyede ve sürekli baskılamak
HIV ile ilişkili başka patolojileri azaltmak/engellemek
Yaşam süresini uzatmak ve kalitesini arttırmak
Bağışıklık sisteminin fonksiyonlarını iyileştirmek ve korumak
HIV bulaşını önlemek

Önce

Şimdi

Survival in HIV infected people

1985: months

1995: years

2005: decades

Despite successfuly antiretroviral drugs failure in treatment possible

Compliance in treatment

Compliance in chronical diseases (virological failure)

Kronik hastalıklarda uyum (ortalama);

HIV…%60

Gastroözafajial reflü…%68

Statin…%70

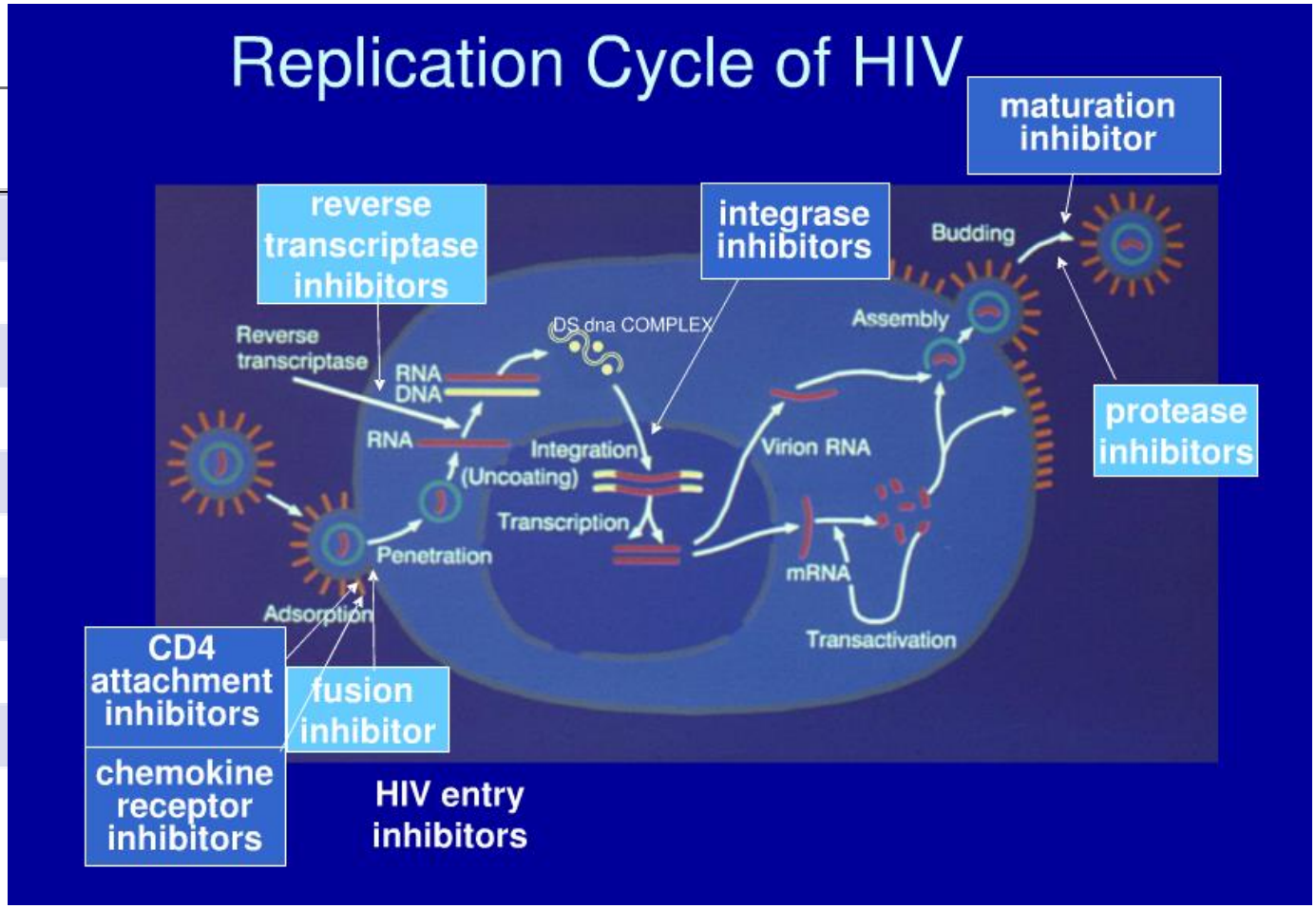
HBV…%81-99

HCV…%74-100

Ann Hepatol. 2013 May-Jun;12(3):380-91.

We have to many drugs and gene targets for the treatment of the HIV infections

Class
NRTIs
NNRTIs
PIs
Fusion inhibitors
CCR5 antagonists
Integrase inhibitors



Why we detect the antiretroviral drug resistance

- Turnover of the HIV population is rapid (type 1/2, approximately every day)
- Error prone (mutation rate, ca. 3×10^{-5} mutations/base/replication cycle)
- and resulting in large and genetically diverse in vivo populations, which are prone to resistance

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

The drug resistance anaylsis: When?

" In a population, genotypic resistance testing is considered costeffective for HIV-1 infection when level of transmitted drug resistance is >5%. ".

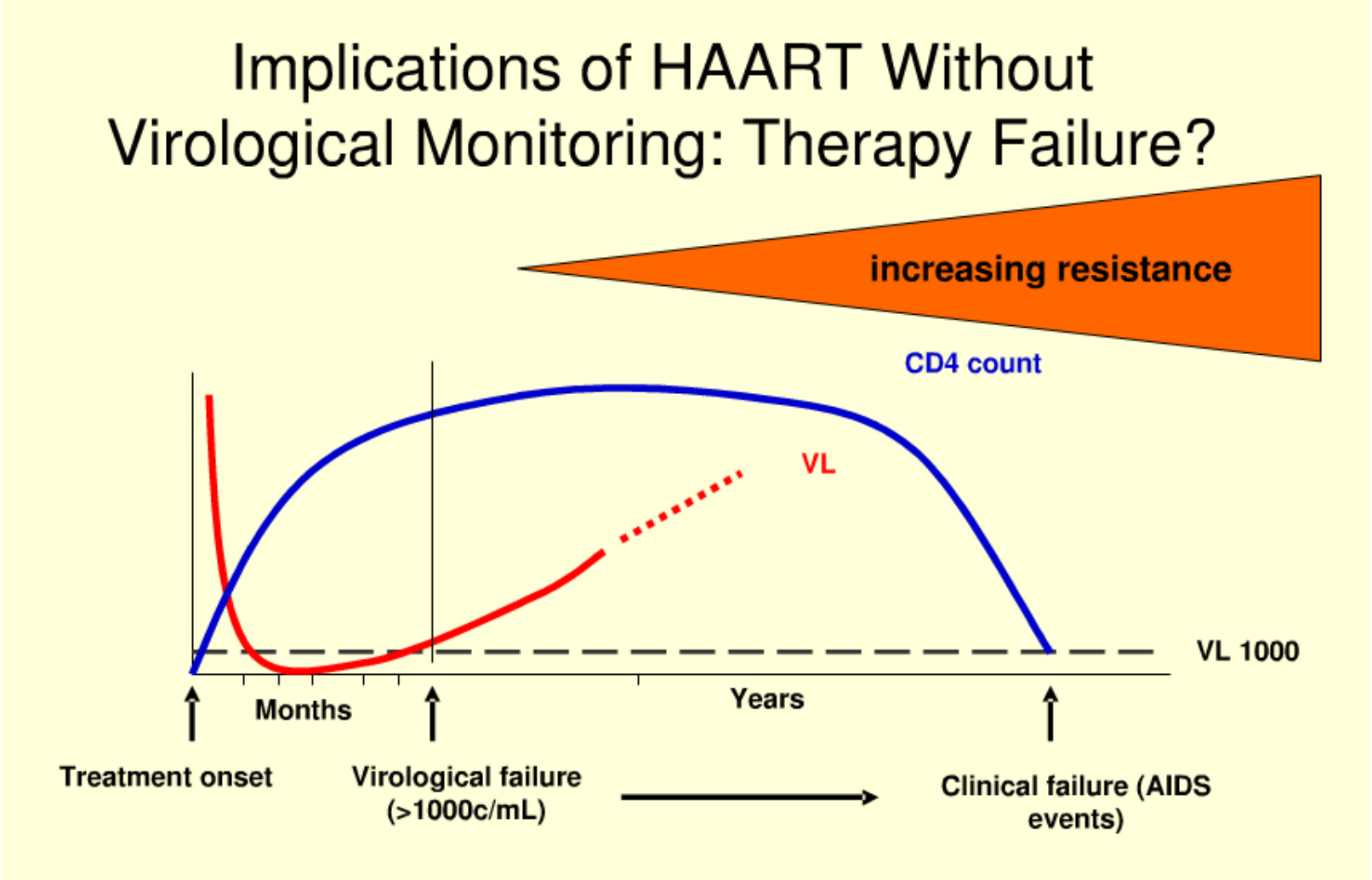
WHO, EACS, UK guidelines

1. In the new cases; for the transmitted drug resistance detection
2. In the start of the treatment; for choice of the drugs
3. In the swithce of the therapy
4. In the lower compliance
5. If viral rebound developed
6. Emergence of the blips
7. In pregnancy

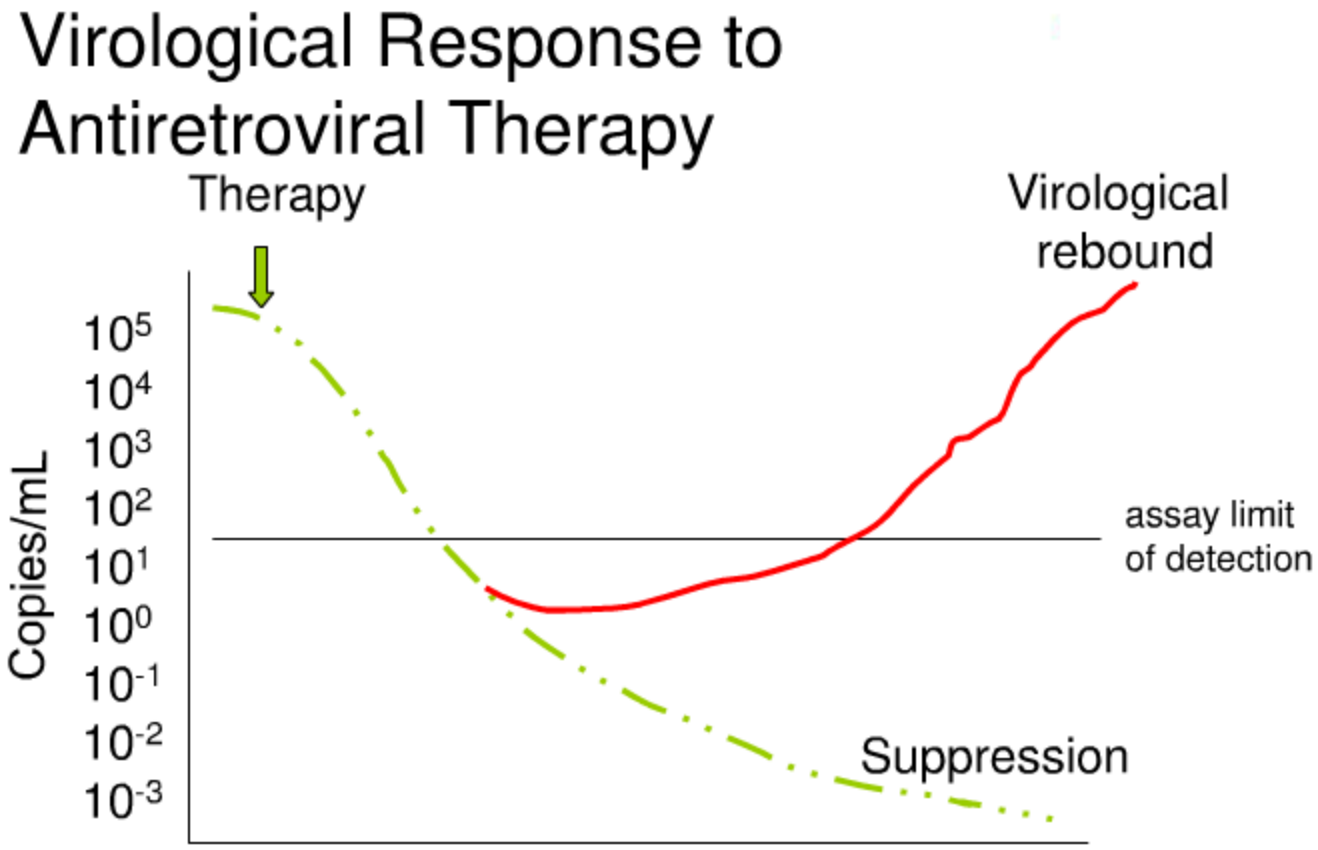
In 2004, the European HIV Drug Resistance Guidelines Panel (EACS) presented recommendations for the use of initial HIV-1 drugresistant testing for the management of the treatment for HIV-1 infection (96% recommendation level)

Transmitted HIV-1 drug resistance is classified in the three categories according to this surveillance: low prevalence (<5%), moderate prevalence (5% - 15%) and high prevalence (>15%) (8).

Tedavide başarısızlık, ilaç direnci yaratır.
İlaç direnci aktarılabilirdir/bulaşıcıdır.
Tedavi düzenli bir şekilde monitörize edilmelidir.



Tedavide viral rebound gelişebilir.

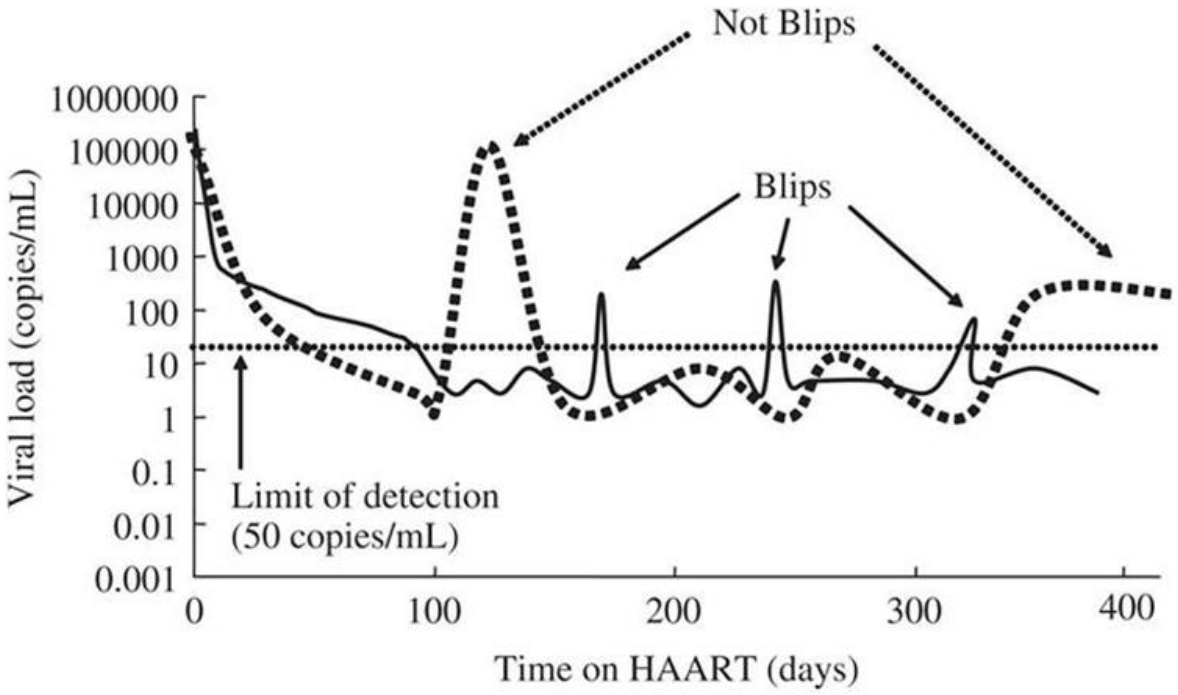


HAART tedavisinde blipler

Blip

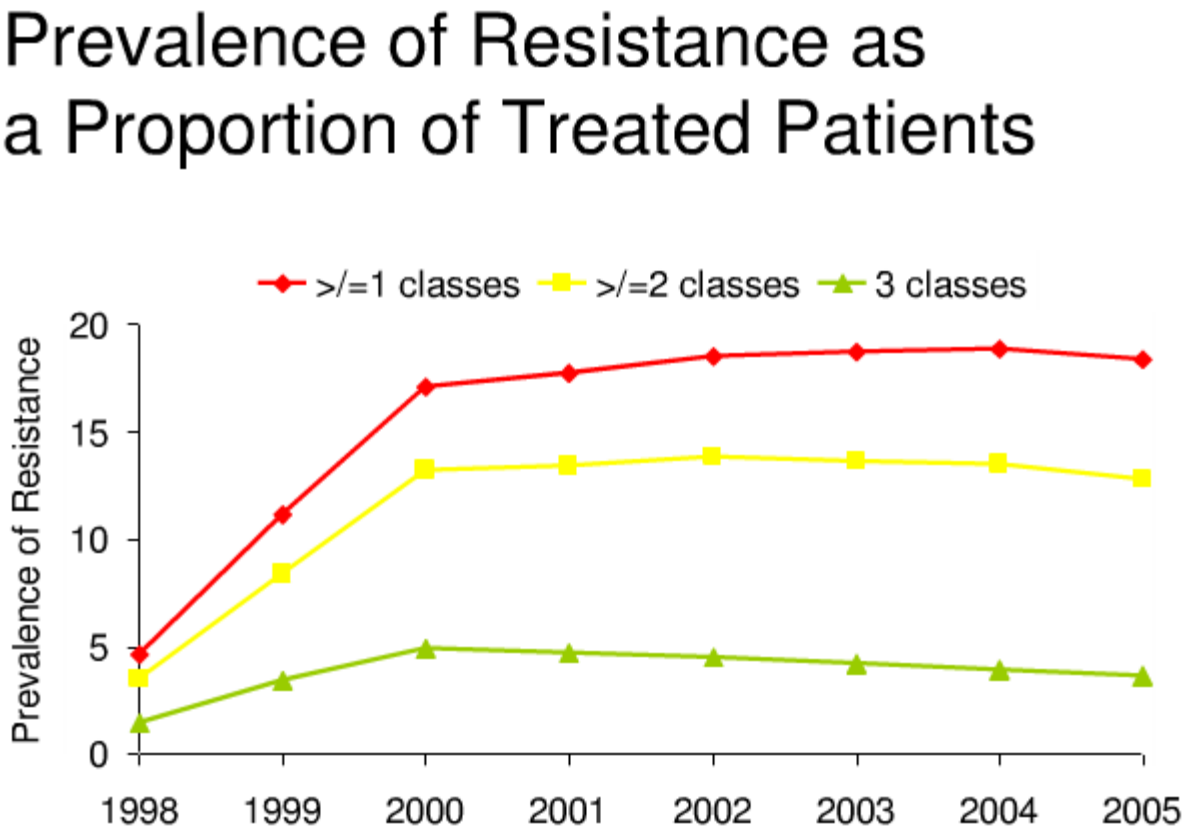
- Viral yükte **bir defalık** 1000 kopya/ml'nin altında tespit edilen yükselme,
- **Blipler (blips);** düşük, tekrar eden, ölçülebilir plazma düzeylerinden ayırdedilmelidir.

DHHS,2012



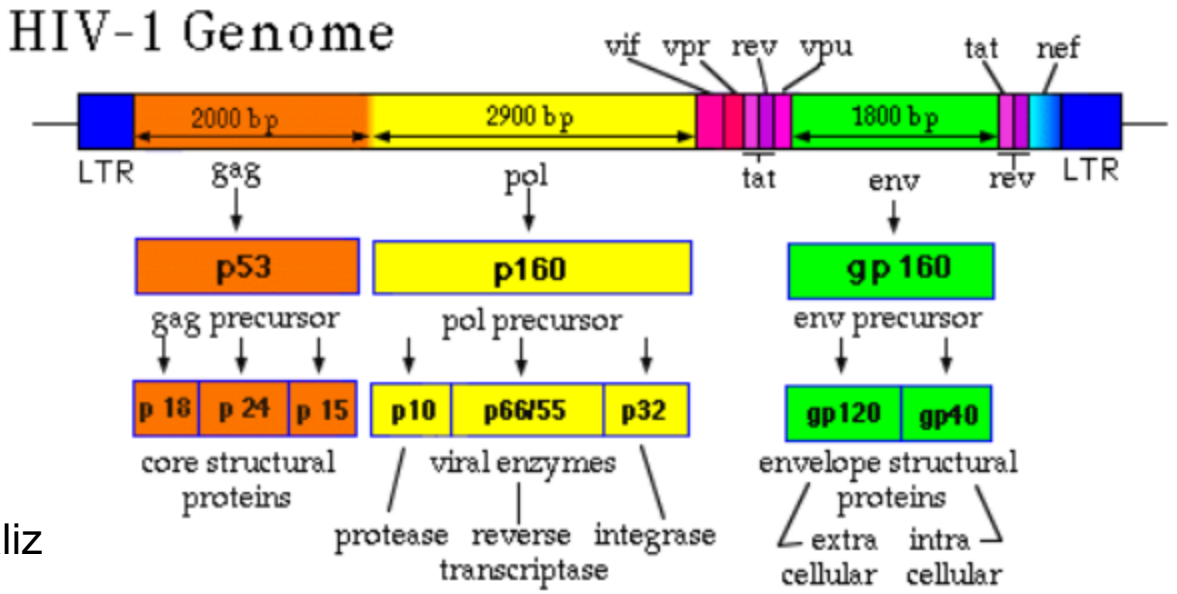
Kaynak;http://jac.oxfordjournals.org/content/57/5/803/F1.expansion.html

HAART tedavisinde direnç daha az gelişmektedir.



Pillay et al. JID 2005;192:967-73.

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



- Klasik HIV-1 ilaç direncinde RT (NRTI ve NNRTI) ve Proteaz inhibitörleri (PI) analiz edilir.
- Ancak Integraz inhibitörleri (INI)'de kullanıma girmiş bulunmaktadır.

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

Tablo 3. HIV ilaç direnci analiz panelinde ele aldığımız antiretroviral grup ve ilaçlar

1.Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Eczanede	**Antiretroviral**	**Üretici**
Combivir	lamivudine, zidovudine	GSK
Emtriva	emtricitabine	Gilead
Epivir	lamivudine	GSK
Epzicom,Kivexa	abacavir and lamivudine	GSK, ViiV
Retrovir	zidovudine, azidothymidine	GSK
Trizivir	abacavir, zidovudine, lamivudine	GSK
Truvada	tenofovir, emtricitabine	Gilead
Videx	didanosine	BMS
Viread	tenofovir	Gilead
Zerit	stavudine	BMS
Ziagen	abacavir	GSK

2. Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Edurant	rilpivirine	Tibotec
Intelence	etravirine	Tibotec
Sustiva	efavirenz	BMS
Viramune	nevirapine	Boehringer Ing.

3. Protease Inhibitors (PIs)		
Aptivus	tipranavir	Boehringer Ing.
Crixivan	indinavir	Merck
Fortovase	saquinavir	H-La Roche
Kaletra	lopinavir/r	Abbott Lab.
Lexiva	fosamprenavir	GSK
Prezista	darunavir	Tibotec, Inc.
Reyataz	atazanavir	BMS
Viracept	nelfinavir	Agouron Pharma

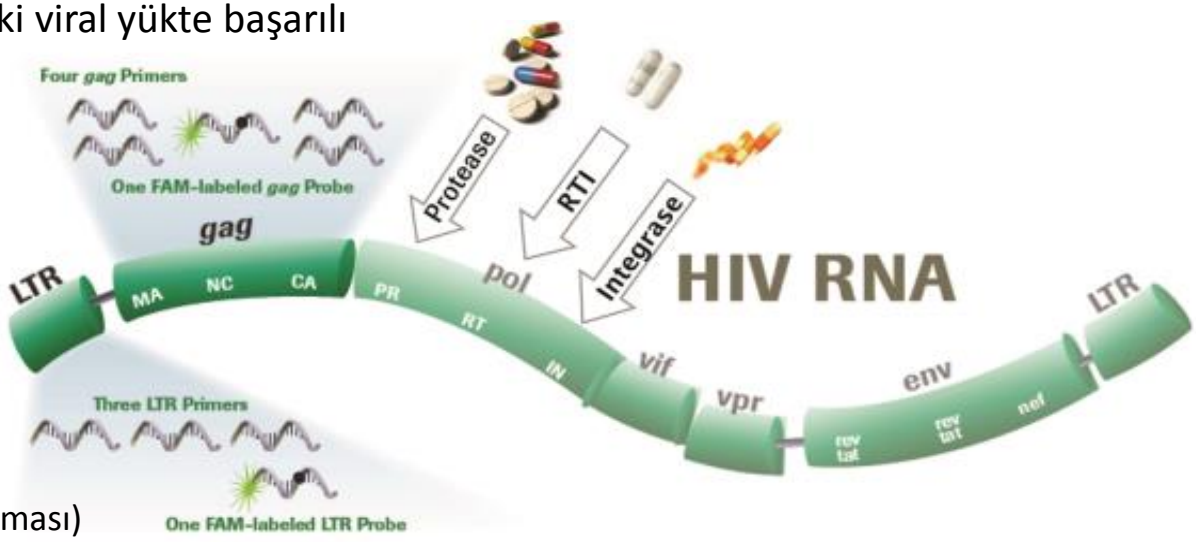
4. Integrase strand transfer inhibitors (INIs)		
Isentress	raltegravir	Merck & Co.
Vitekta	elvitegravir	Gilead
Tivicay	dolutegravir	GSK

Analiz yöntemleri

1. Genotipik testler; Stanford Drug Resistance Database (en sık kullanılan)

- * **Populasyon sekanslama tekniği (Applied Biosystem…)**
  - Integraz analizi mümkün
  - Uygun maliyet
  - Yoğun işçilik
  - Esnek rutin çalışma dizaynı
  - 500 kopya/ml üzerindeki viral yükte başarılı
- **Hazır ticari sistemler; Trugene, ViroSeq (Bayer/Siemens, Celera/Abbott)**
  - Integraz analizi bulunmuyor
  - Çok yüksek maliyetli
  - Numune biriktirmek gerekiyor
  - 500 kopya/ml üzerindeki viral yükte başarılı

2. Fenotipik testler



*bizim kullandığımız (Fransız ANRS algoritması)

Analiz yöntemleri

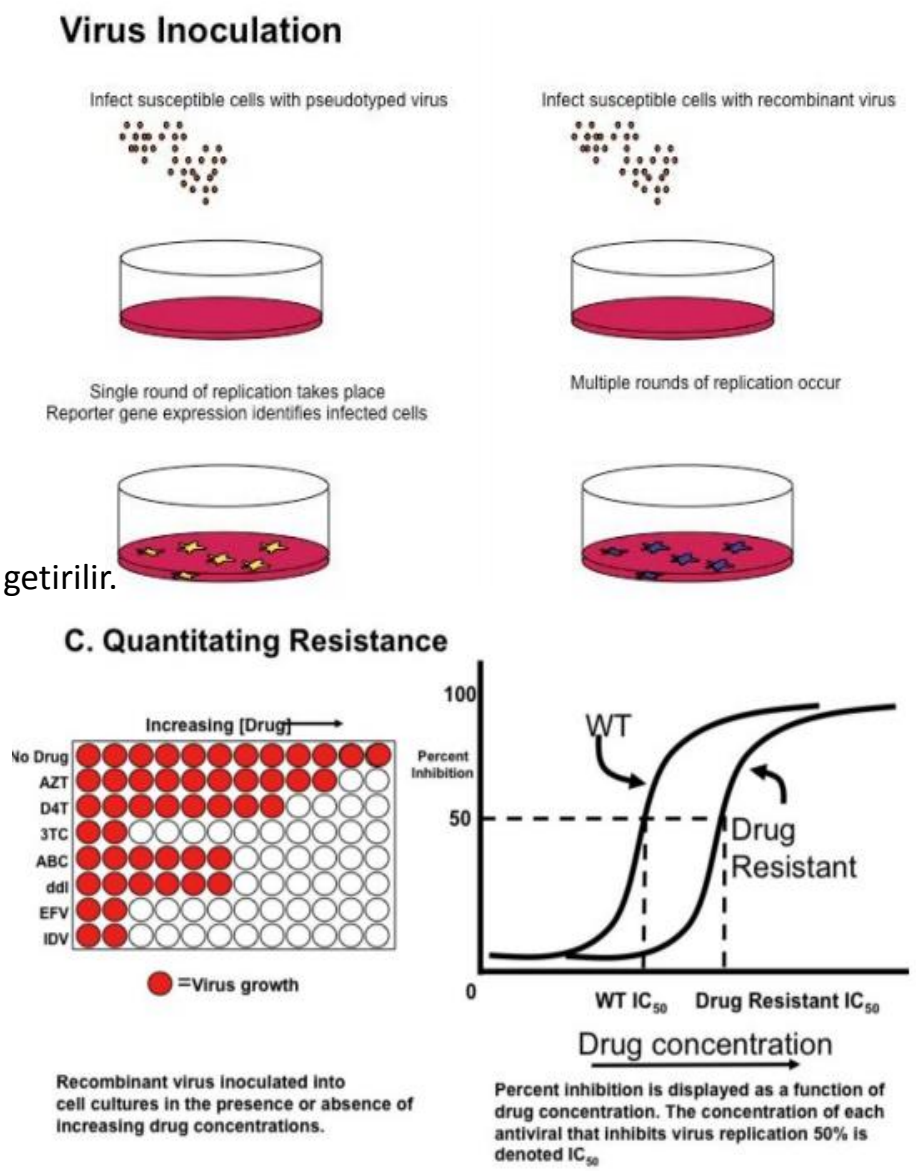
Genotipik testler; Stanford Drug Resistance Database

- **Populasyon sekanslama tekniği (Applied Biosystem…)**
  - Integraz analizi mümkün
  - Uygun maliyet
  - Yoğun işçilik
  - Esnek rutin çalışma dizaynı
- **Hazır ticari sistemler; Viroseq (Abbott Laboratories)**
  - Integraz analizi bulunmuyor
  - Oldukça maliyetli
  - Numune biriktirmek gerekiyor

Fenotipik testler

- Hücre kültürü ortamında virus ve ilaç bir araya getirilir.
- Rutin kullanıma uygun değiller
- Çok pahalı tekniklerdir*
- Zaman alıcıdır
- Değerlendirmesi zordur

*Maliyet: 350 -500 Euro / örnek başına



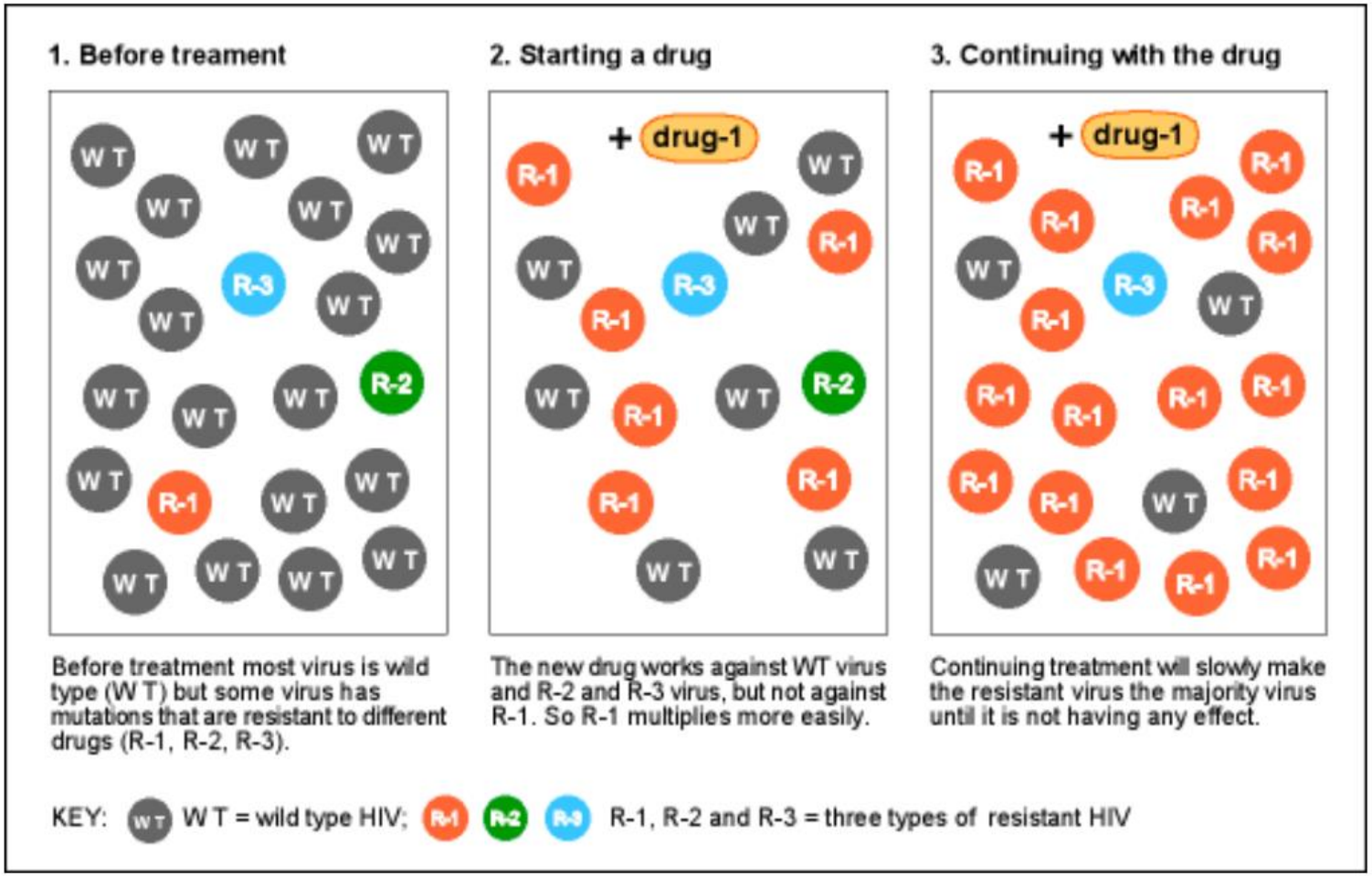
Genotipik / fenotipik analiz metodlarının kıyaslanması

Table 1
Advantages and disadvantages of genotypic and phenotypic HIV resistance assays

	Genotypic assay	Phenotypic assay
Measure of susceptibility	Indirect	Direct
Availability	Good	Restricted
Time to result	Days	Usually weeks
Required resources	Expertise available in large molecular diagnostic laboratory	Available only in purpose built facilities
Interpretation of result	Needs complex algorithm and/or expert	Relatively simple
Knowledge of genomic mutation conferring resistance	Required	Not required
Cost	Less expensive (~ $AUD800)	More expensive (~ $AUD2,000)

Ammaranond P, Journal Clin Virol 2003; 26:153-161

Antiretroviral ilaçların seçici baskısı; düzensiz tedaviler, dirence yol açar.



- İlaç direnci bulaşıcıdır.
- HIV'in reenfeksiyonu tedaviyi başarısız kılabilir.

- Bazı ilaç direnci mutasyonları 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.

Farklı antiretroviral ilaç sınıflarında direnç gelişimi; Genetik bariyer.

Table 1. Simplified overview of the genetic barrier to resistance offered by different antiretroviral drugs

Class	ARVs	Genetic barrier
NRTIs	ZDV/3TC, d4T/3TC	++
	ABC/3TC, TDF/3TC	+
	TDF/FTC	++
NNRTIs	Efavirenz, nevirapine, rilpivirine	+
	Etravirine	+/++
PIs	Boosted by ritonavir	+++/++++
Fusion inhibitors	T20 (enfuvertide)	+
CCR5 antagonists	Maraviroc	++ (for R5 virus)
Integrase inhibitors	Raltegravir, elvitegravir	+

3TC, lamivudine; ABC, abacavir; ART, antiretroviral; d4T, stavudine; FTC, emtricitabine; NRTIs, nucleoside/nucleotide reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors, PIs, protease inhibitors; TDF, tenofovir; ZDV, zidovudine.

- Düşük genetik bariyer (tek bir mutasyon yeterli)
    - M184V: LAM, Emtrisitabin
    - K103N: Efavirenz
    - D30N: Nelfinavir

Genetik bariyer ve viral fitness restorasyonu

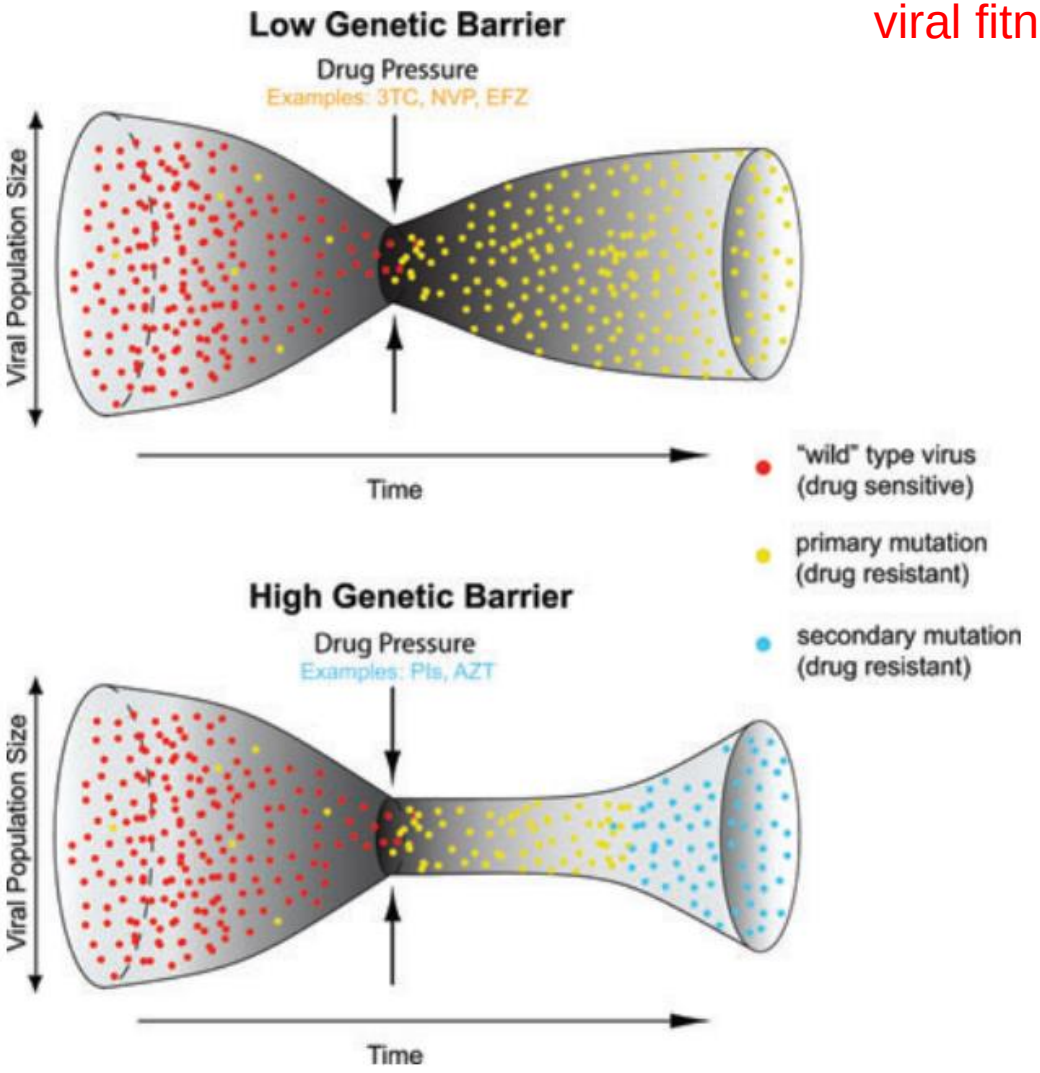


Figure 3. Figure showing the development of resistance focusing on low and high genetic barrier drugs. Low genetic barrier: selection of previously existing variants. High genetic barrier: selection as well as *de novo* mutations and evolution. Red: "wild" type virus. Yellow: primary mutations—strong 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.

Ann. N.Y. Acad. Sci. 2011;230:108–118

Prezista'nın genetik bariyeri yüksektir. Direnç çok zordur.

Ülkemizde *******hastada saptadık?????????????

Protease Resistance

Inhibitor	L10F/I/C/V	V11I	I13V	G16E	K20M/R*	L24I	D30N	V32I	L33F/V*	E35G	M36I	K43T	M46I	I47V	G48V	I50V	I50L	F53L	I54V/T/M/L	Q58E
Indinavir																				
Ritonavir																				
Saquinavir																				
Nelfinavir																				
Fosamprenavir																				
Atazanavir																				
Lopinavir																				
Tipranavir																				
Darunavir																				

Inhibitor	D60E	I62V	L63P*	I64L/M/V	H69K	A71V/T	G73S	T74P	L76V	V77I*	V82A	V82S/F/T	N83D	I84V	N88D	N88S	L89V	L90M	T91S	I93L/M
Indinavir																				
Ritonavir																				
Saquinavir																				
Nelfinavir																				
Fosamprenavir																				
Atazanavir																				
Lopinavir																				
Tipranavir																				
Darunavir																				

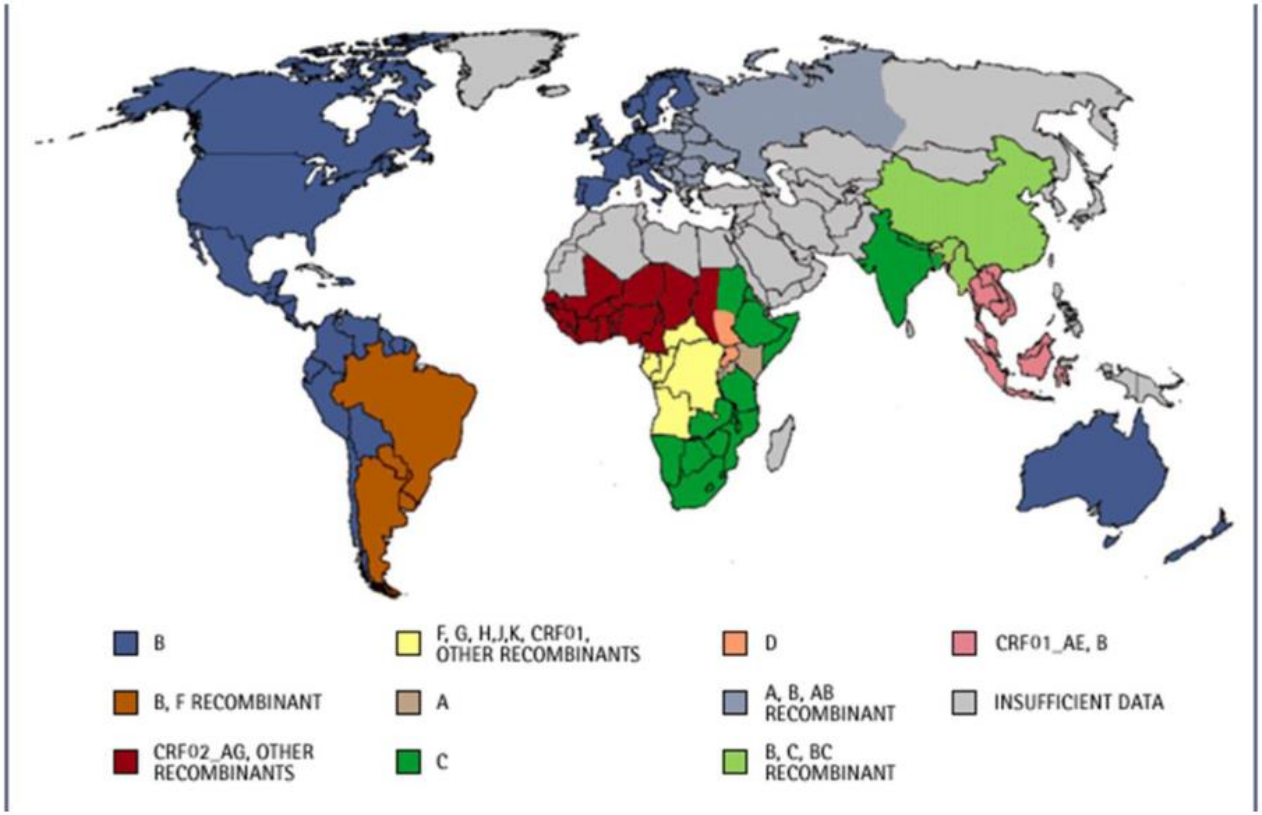
Primary Resistance
Secondary Resistance
Hypersusceptibility

DRV/RTV

600/100 mg BID

- **At least 4 mutations among: V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V**

Türkiye'yi " yetersiz data " bölgesinden çıkardık.



Global HIV-1 subtip ve CRF dağılımı

Dolaşımdaki HIV-1 subtipleri giderek karmaşık bir hal almaktadır.

HIV-1 CRF subtiplerin 12'si komplex (cpx)'dir.

HIV-1 CRF cpx subtiplerinin coğrafik dağılım, tipi ve kompozisyonuna bakıldığında;

- Yunanistan ve Kıbrıs'da CRF04_cpx (A, G, H, K, U)
- Orta/Batı Afrika ve Estonya'da **CRF06_cpx (A, G, J, K)**
- Orta/Batı Afrika'da CRF09_cpx (A, G, U)
- Orta Afrika'da CRF11_cpx (A, G, J, CRF01_AE) ve **CRF13_cpx (A, G, J, U, CRF01_AE, CRF11_cpx)**
- Küba ve Orta Afrika'da CRF18_cpx (A1, F, G, H, K, U) ve CRF19_cpx (A1, D, G)
- Suudi Arabistan ve Orta Afrika'da CRF25_cpx (A, G, U)
- Kongo'da CRF27_cpx (A, E, G, H, J, K, U)
- Kamerun'da CRF36_cpx (A, G, CRF01_AE, CRF02_AG)
- Kamerun ve Mozambik'de CRF37_cpx (A, G, CRF01_AE, CRF02_AG, U)
- Gambia'da CRF49_cpx (A, C, J, K, U)

Kaynak: Hemelaar J. The origin and diversity of the HIV-1 pandemic. Trends Mol Med 2011; 25(5): 679-89.

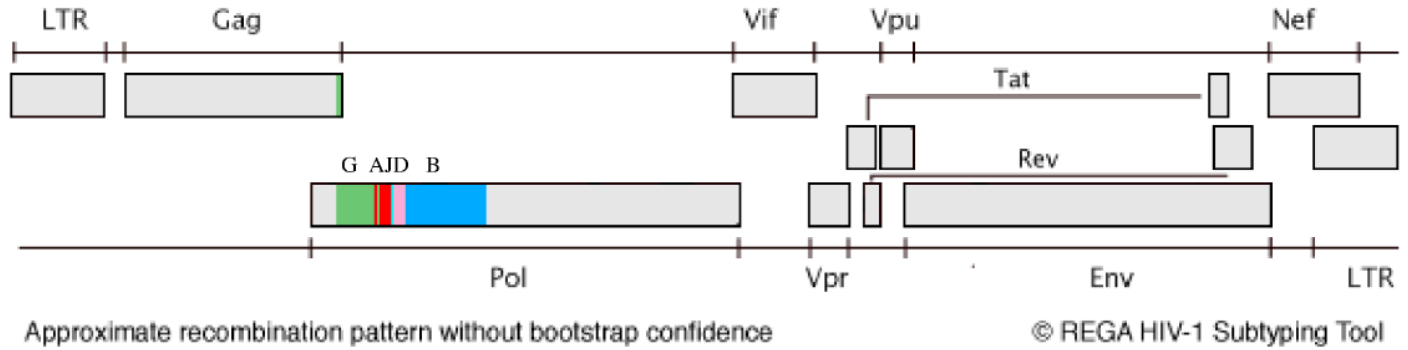
Türkiye'de saptanan komplex rekombinant HIV-1 CRF06_cpx subtipinin moleküler karakterizasyonu

Murat Sayan[1], Figen Kaptan[2], Bahar Örmen[2], Nesrin Türker[2]

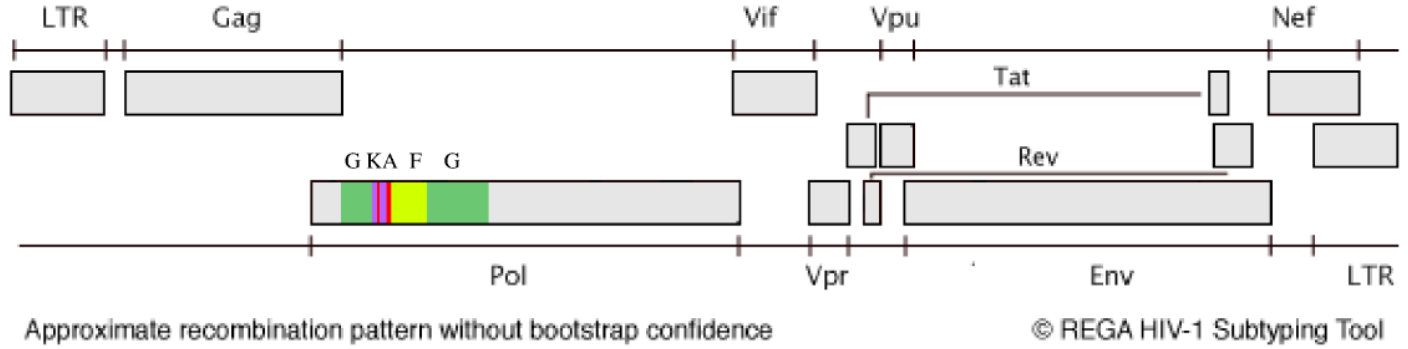
[1] Kocaeli Üniversitesi, Arş. ve Uyg. Hast., Merkez Lab., Kocaeli.

[2] Katip Çelebi Üniversitesi, Atatürk Eğt. ve Arş. Hast. Enf. Hast. Kliniği, İzmir.

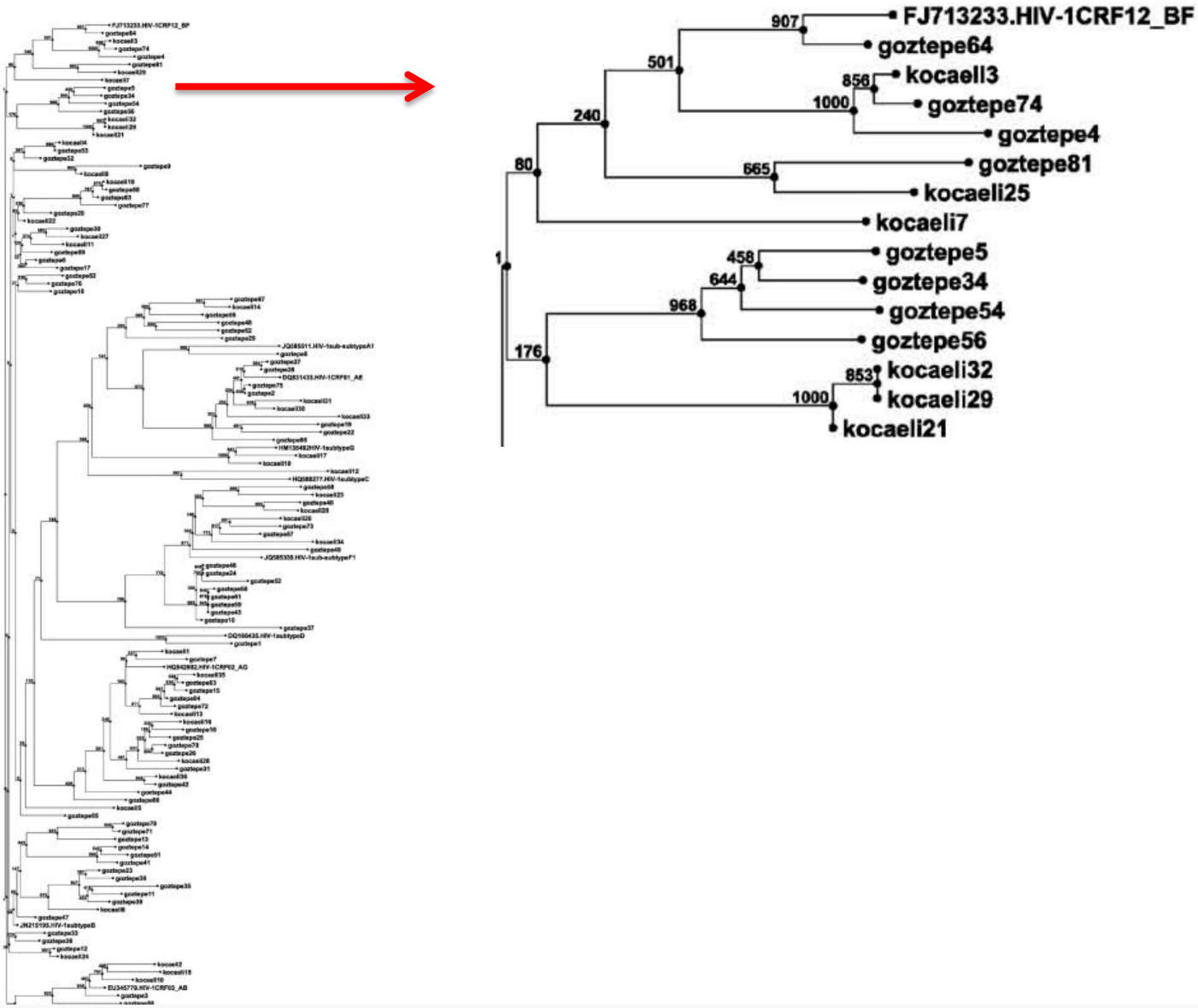
A.



B.



Sekil 2. HIV-1 CRF06_cpx ile enfekte erkek (A) ve kadin (B) hastada rekombinasyon paternleri.



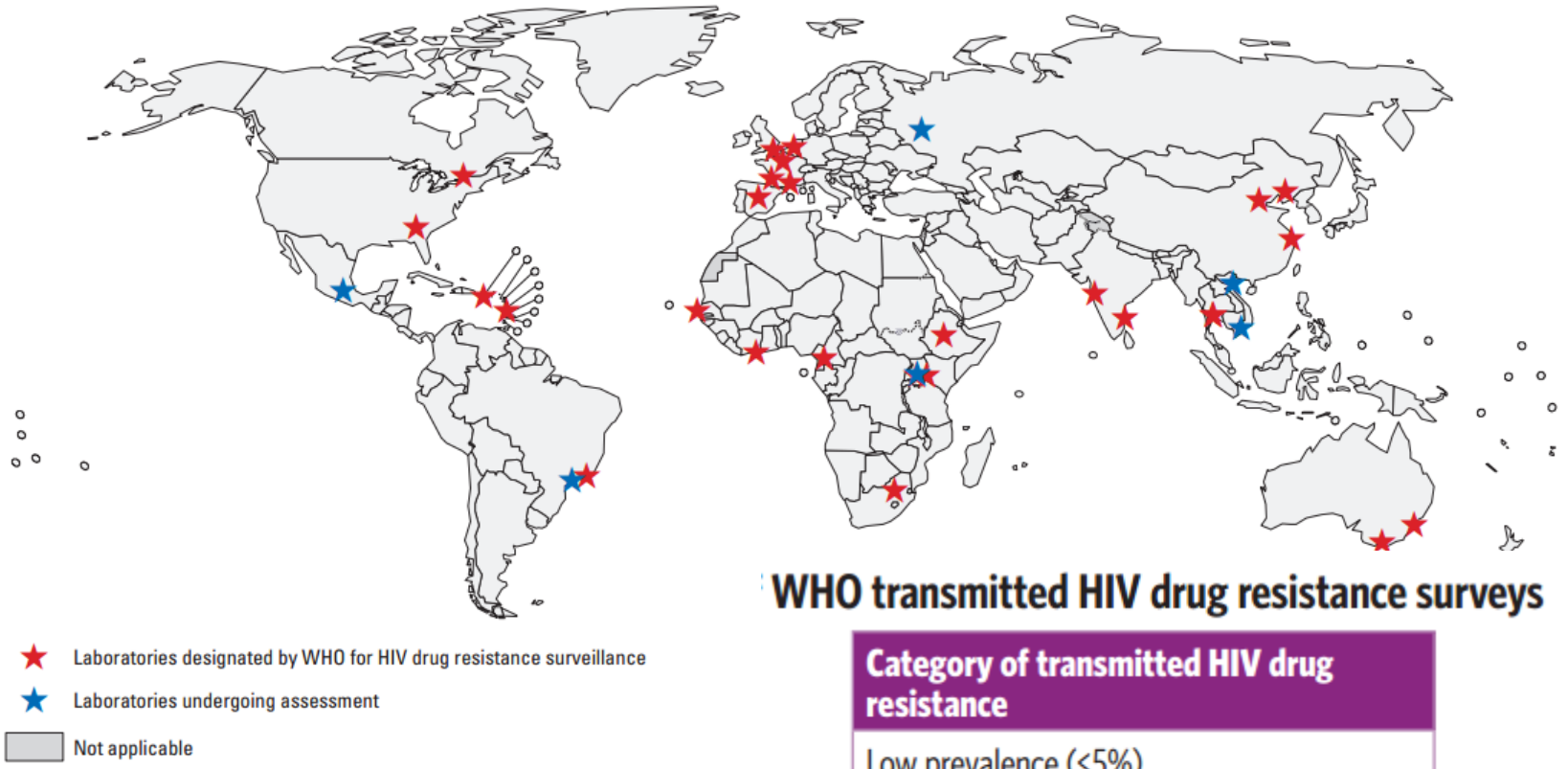
HIV-1 Subtypes and Primary Antiretroviral Resistance Mutations in Antiretroviral Therapy Naive HIV-1 Infected Individuals in Turkey

By: Sayan, M.; Willke, A.; Ozgunes, N.; et al.

JAPANESE JOURNAL OF INFECTIOUS DISEASES Volume: 66 Issue: 4 Pages: 306-311 Published: JUL 2013

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

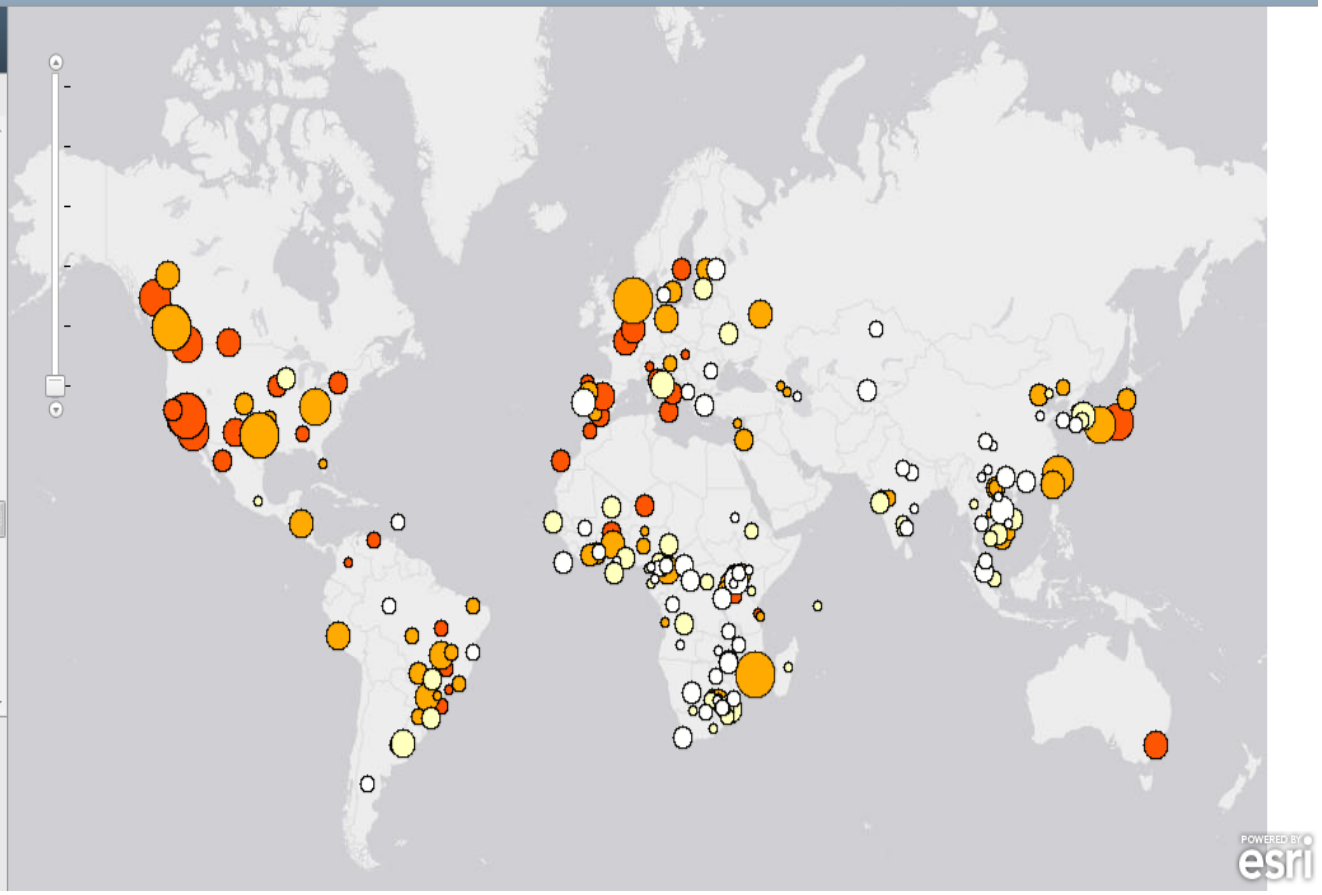
Continent	Country	Publication	%SDRM	n
	AND THE GRENADIN			
Europe	ALBANIA	Ciccozzi05	1.5	66
Europe	AZERBAIJA	Saad06	0	41
Europe	BELGIUM	Vercauteren08	10.1	298
Europe	BYELORUS SSR,RUSSI FEDERATIC	Vazquez de Parga05	9.8	246
Europe	CYPRUS	Kousiappa09	5.4	37
Europe	DENMARK	Jorgensen03	2.1	97
Europe	ESTONIA	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

n

- < 50
- 50 - < 100
- 100 - < 200
- 200 - < 400
- 400 - < 800
- 800 - < 1600
- >= 1600

% SDRM

- < 2.5
- 2.5 - < 5
- 5 - < 10
- >= 10



Laboratuvar sorunu

HIV (+) bireyler, HIV RNA negatif olduklarında motivasyonları ve tedaviye bağlılıkları artıyor.

CD4 + hücre sayımı,
HIV RNA miktarı ve
HIV ilaç direnci analizlerinde bu tüp kullanılmalıdır.

Ulusal HIV-1 ilaç direnci surveyansı:
Kocaeli deneyimi

HIV-1 ilaç direnci analizi: komplex, pahalı, uzmanlık gerektiren ve emek yoğun bir analiz.

- Klinisyenlere ilaç direnci analizi sağlanması
- Hasta tedavisinin hızlı bir şekilde planlanması
- Rasyonel tedavi seçeneklerinin oluşturulması
- Klinik merkezlerle ortak uluslar arası makale yazımı
- Uluslar arası toplantılarda sunum
- Global örgüt/sistemlere entegre olunması ve gerçek yaşam verilerinin sağlanması
- Ulusal politikaların geliştirilmesine zemin hazırlanması
- HIV'in toplumsal dinamiğinin (sirkülasyonu) anlaşılması
- Hastaların tedaviye bağlı tutulması
- Sosyal medya ile hasta-doktor bağının sürekli hale gelmesi
- HIV (+) hastanın sürekli kontrol altında tutulması
- Yaşayan HIV (+) hasta veri tabanı oluşturulması

HIVdb: Genotypic Resistance Interpretation, Date: 07-Jun-2013

Seq ID: G.A

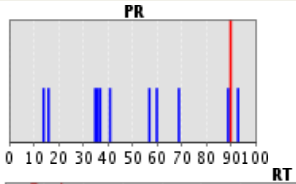
Sequence includes PR: codons: 1 - 99

Sequence includes RT: codons: 40 - 223

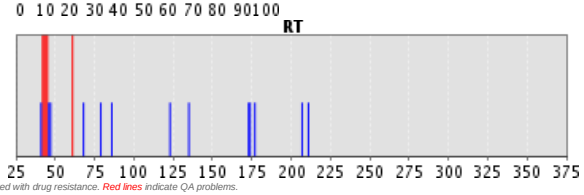
There are no insertions or deletions

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:	42, 43, 44, 45, 61



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, G16A, E35D, M36I, N37D, R41K, R57K, D60E, 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)	Susceptible
saquinavir/r (SQV/r)	Susceptible
tipranavir/r (TPV/r)	Susceptible

Drug Resistance Interpretation: RT

NRTI Resistance Mutations: None
NNRTI Resistance Mutations: None
Other Mutations: M41T, E42V, K43P, E44S, G45N, K46N, I47F, F61L, S68G, E79G

Nucleoside RTI

lamivudine (3TC)	Susceptible
abacavir (ABC)	Susceptible
zidovudine (AZT)	Susceptible
stavudine (D4T)	Susceptible
didanosine (DDI)	Susceptible
emtricitabine (FTC)	Susceptible
tenofovir (TDF)	Susceptible

Non-Nucleoside RTI

efavirenz (EFV)	Susceptible
etravirine (ETR)	Susceptible
nevirapine (NVP)	Susceptible
rilpivirine (RPV)	Susceptible

Hastada HIV-1 ilaç direnci yok.

HIVdb: Genotypic Resistance Interpretation, Date: 19-Jul-2013

Seq ID: O.Y

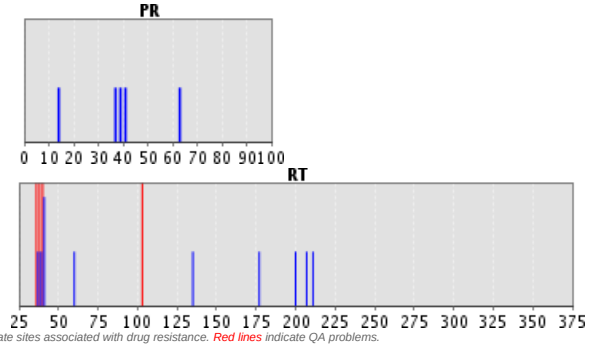
Sequence includes PR: codons: 1 - 99

Sequence includes RT: codons: 34 - 222

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:	36, 38, 40



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, N37S, P39Q, R41K, 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: E36L, I37L, C38K, T39L, E40Y, V60I, I135V, D177E, T200A

Nucleoside RTI

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

Non-Nucleoside RTI

efavirenz (EFV)	Susceptible
etravirine (ETR)	Susceptible
nevirapine (NVP)	Susceptible
rilpivirine (RPV)	Susceptible

Hastada Timidin Analoğu mutasyonu var.

HIVdb: Genotypic Resistance Interpretation, Date: 01-Jul-2013

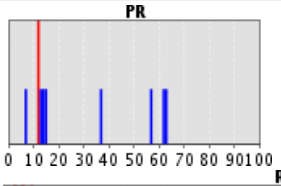
Seq ID: P.Ç.

Sequence includes PR: codons: 1 - 99

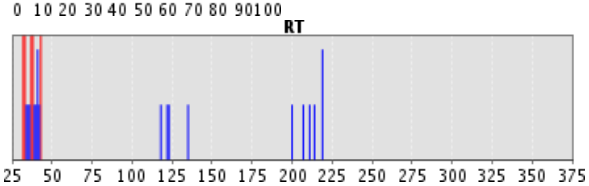
Sequence includes RT: codons: 31 - 221

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:	32, 33, 37, 38



*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:	Q7R, I13V, K14R, I15V, N37D, R57K, I62V, L63A

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, K219N**
NNRTI Resistance Mutations:	None
Other Mutations:	K32S, A33P, L34I, V35E, E36T, I37V, C38P, T39V, E40K, E42K

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

Hastada ikili Timidin Analoğu mutasyonu var.

HIVdb: Genotypic Resistance Interpretation, Date: 24-Dec-2012

Seq ID: M.N.T.

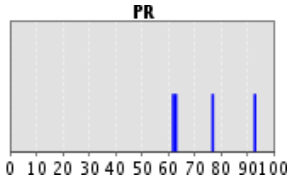
Summary Data

Sequence includes PR: codons: 1 - 99

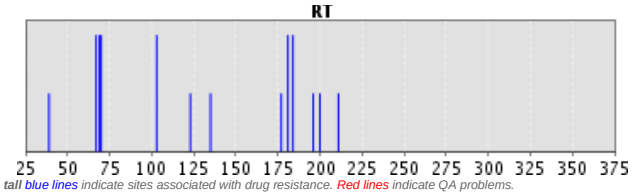
Sequence includes RT: codons: 39 - 213

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: I62V, L63A, 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

Drug Resistance Interpretation: RT

NRTI Resistance Mutations: D67N, T69N, K70R, M184V

NNRTI Resistance Mutations: K103N, Y181C

Other Mutations: T39S, D123E, I135T, D177N, G196E, T200N, R211K

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

Hasta Tenofovir'e duyarlı, Emtrisitabin'e dirençli.

HIVdb: Genotypic Resistance Interpretation Date: 12-Nov-2013

Seq ID: M.F.

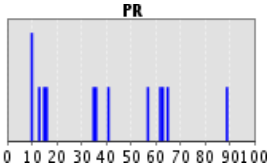
Summary Data

Sequence includes PR: codons: 1 - 99

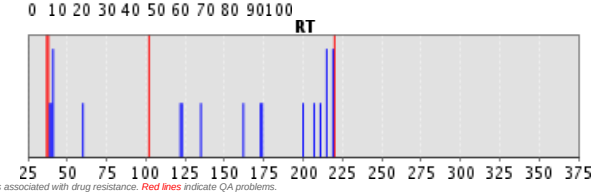
Sequence includes RT: codons: 37 - 222

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:	37, 38



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**
Other Mutations:	I13V, I15V, G16E, E35D, M36I, R41K, R57K, I62V, 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, T215N, K219Q**
NNRTI Resistance Mutations:	None
Other Mutations:	I37V, C38L, T39L, E40K, V60I, K122E, D123E, I135L, S162C

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

Hasta Emtristabin'e duyarlı, Tenofovir'e dirençli.

HIVdb: Genotypic Resistance Interpretation Date: 23-Sep-2013

Seq ID: N.A.

Summary Data

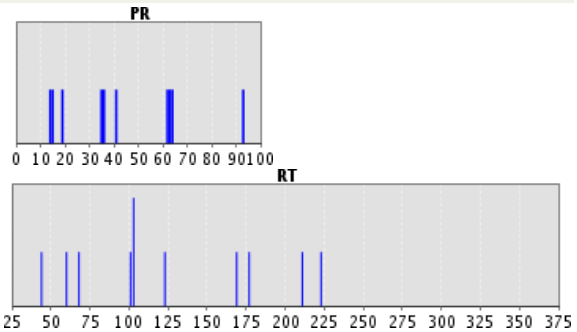
Sequence includes PR: codons: 1 - 99

Sequence includes RT: codons: 44 - 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:	*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, I15V, L19F, E35D, M36I, R41K, I62V, L63P, I64L

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: None

NNRTI Resistance Mutations: **K103N**

Other Mutations: E44K, V60I, S68G, K101Q, D123E, E169D, D177E, R211K, K223Q

Nucleoside RTI	
lamivudine (3TC)	Susceptible
abacavir (ABC)	Susceptible
zidovudine (AZT)	Susceptible
stavudine (D4T)	Susceptible
didanosine (DDI)	Susceptible
emtricitabine (FTC)	Susceptible
tenofovir (TDF)	Susceptible

Non-Nucleoside RTI	
efavirenz (EFV)	High-level resistance
etravirine (ETR)	Susceptible
nevirapine (NVP)	High-level resistance
rilpivirine (RPV)	Susceptible

Hasta Stocrin ve Viramun'a dirençli.

HIVdb: Genotypic Resistance Interpretation, Date: 09-Oct-2012

Seq ID: N.D.

Summary Data

Sequence includes PR: codons: 1 - 99

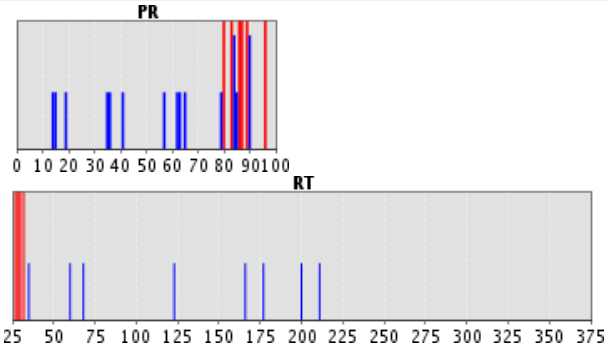
Sequence includes RT: codons: 25 - 223

PR AA Insertion: codon 89 AA: VSNIM NA: GTAAGTAACATCATG

Sequence Quality Assessment

Gene	QA Problem	Codons
PR	Stop Codons, Frame Shifts:	*None*
PR	Ambiguous Positions:	83
PR	Unusual Residues:	80, 86, 87, 89, 90

Gene	QA Problem	Codons
RT	Stop Codons, Frame Shifts:	27
RT	Ambiguous Positions:	*None*
RT	Unusual Residues:	28, 29, 30, 32



Drug Resistance Interpretation: PR

PI Major Resistance Mutations:	**I84V**
PI Minor Resistance Mutations:	**L90C**
Other Mutations:	K14R, I15V, L19F, E35D, M36I, R41K, R57N, I62V, L63N, E65D

Protease Inhibitors

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

Drug Resistance Interpretation: RT

NRTI Resistance Mutations:	None
NNRTI Resistance Mutations:	None
Other Mutations:	T27*, E28I, E29S, K30H, K32S, V35T, V60I, S68G, D123E, K166R, D177E

Nucleoside RTI

lamivudine (3TC)	Susceptible
abacavir (ABC)	Susceptible
zidovudine (AZT)	Susceptible
stavudine (D4T)	Susceptible
didanosine (DDI)	Susceptible
emtricitabine (FTC)	Susceptible
tenofovir (TDF)	Susceptible

Non-Nucleoside RTI

efavirenz (EFV)	Susceptible
etravirine (ETR)	Susceptible
nevirapine (NVP)	Susceptible
rilpivirine (RPV)	Susceptible

Hastada tüm proteaz inhibitörlerine direnç var.

HIVdb: Genotypic Resistance Interpretation, Date: 04-Jan-2013

Seq ID: B.M.

Summary Data

Sequence includes PR: codons: 1 - 99

Sequence includes RT: codons: 39 - 221

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: **M46I, I54V, V82A**
PI Minor Resistance Mutations: **L10I, L24I, K43T**
Other Mutations: T12P, K14R, R41K, K55R, L63A, I64L, V77I, L89M, I93L

Protease Inhibitors

atazanavir/r (ATV/r)	High-level resistance
darunavir/r (DRV/r)	Susceptible
fosamprenavir/r (FPV/r)	Intermediate 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)	Low-level resistance

Drug Resistance Interpretation: RT

NRTI Resistance Mutations: **D67G, K70R, L74I, M184V, K219N**
NNRTI Resistance Mutations: **K103N, Y181C, G190A**
Other Mutations: V60I, S68G, D123E, I135T, K166R, T200I, F214L

Nucleoside RTI

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

Non-Nucleoside RTI

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

Hasta sadece Prezista'ya duyarlı.

Murat Sayan

Murat | Ana Sayfa | Arkadaşlarını Bul

Murat Sayan

Bilgilerini Güncelle

Hareketler Dökümünü Gör ...

Zaman Tüneli | Hakkında | Arkadaşlar | Fotoğraflar | Diğer

Kocaeli Üniversitesi'de Doç.Dr.
2005 - halen

Dokuz Eylül Üniversitesi'de okudu

İzmit'te yaşıyor

3 Ekim 1966 tarihinde doğdu

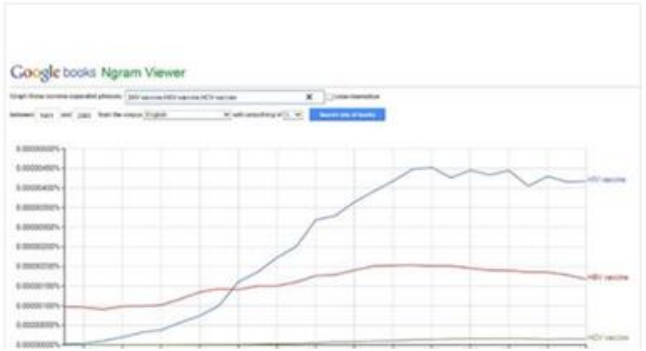
668 kişi takip ediyor

Murat Sayan
30 Ekim 2015

HIV'i Önleyecek Aşıya Neden Hala Uzaktayız?

Bir çok insan HIV'i önleyecek bir aşı konusunda iyimserdir. Bu onlar için mutlaka gerçekleşecek bir hedeftir. Bir çok hastalık etkeni için koruyucu bir aşı vardır ve HIV içinde olabilir. Öyle midir?

Ya da bir çokları " Aşısı var hatta kesin tedavisi bile. Ancak ortaya çıkarmıyorlar. Sürekli ilaç kullanmamız daha karlı bir iş" gibi benzeri fikilere sahiptir. Bu doğru mudur?...
Devamını Oku



No	Klinik	Naif	Therapy	Toplam
1	Kocaeli Üniv. + Kızılay Bölge	155	32	187
2	Göztepe EAH	326	58	384
3	Erciyes Üniv.	22	26	48
4	Pamukkale Üniv	26	5	31
5	Haydarpaşa Num.	172	33	205
6	Samsun 19 Mayıs	96	34	130
7	Marmara Üniv.	108	23	131
8	Bezm-i Alem	19	8	27
9	Samatya EAH	28	9	37
10	Cerrahpaşa Tıp	17	6	23
11	Okmeydanı EAH	55	26	81
12	Çapa Tıp	107	21	128
13	Gaziantep Üniv.	79	27	106
14	Bursa Uludağ	90	17	107
15	Akdeniz Üniv.	135	35	170
16	Dicle Üniv	44	9	53
17	Urfa Harran Tıp	13	3	16
18	İzmir Atatürk EAH	29	13	42
19	Ankara Numune	60	16	76
20	Haydarpaşa GATA	19	4	23
21	Ankara GATA	8	*	8
22	Şişli Etfal EAH	195	19	314
23	Samsun EAH	27	2	29
24	Bakırköy EAH	31	4	35
25	Sakarya Üniv., EAH	19	4	23
26	Trabzon KTÜ, Tıp	12	27	39
27	Mersin Üniv. Tıp	27	13	40
28	İst F.Nightingale	8	1	9
29	Ege Üniv, Tıp Fak.	2	1	3
30	Semra Çalangu	12	2	14
31	Bolu Üniv.	11	4	15
32	Artvin Devlet	7	4	11
33	Ordu Özel Hast.	*	1	1
34	Behçet Uz Hast.	2	3	5
35	Giresun Devlet Hast.	3	*	3
36	Amerikan Hast.	1	*	1
37	İstanbul Adli Tıp	21	*	21
38	Edirne Trakya Tıp	6	1	7
39	Kartal EAH	5	7	12
40	Çanakkale 18 Mart	4	1	5
41	Ankara Dış Kapı	*	*	*
42	Yeditepe Üniv. Hast.	1	*	1
43	Ankara EAH	4	1	5
44	Medstar Antalya	11	1	12
45	Trabzon Kanuni EAH	2	2	4
46	Başkent Üniv	2	1	3
47	Mardin Kızıltepe	2	*	2
48	Antalya Devlet Hast	1	*	1
49	Üsküdar Devlet Hast.	3	*	3
50	İstanbul Kanuni EAH	*	*	*
51	Adana Çukurova Üniv.	1	*	1
52	MedikalPark Göztepe	3	*	3
53	ŞanlıUrfa Çoçuk Hast	*	1	1
54	Medipol Üniv.Tıp Fak.	1	1	2
55	Haseki EAH	42	19	61
56	FSM EAH	13	*	13
57	KKTC, NEU Üniv.	7	*	7
58	Antalya EAH	20	1	21
59	Ümraniye EAH	11	*	11
60	Hacettepe Pediatri	*	3	3
61	Şişli F. Nightingale	1	*	1
62	Ordu Medikal Park	2	*	2
63	Yeni Yüzyıl Üniv, Tıp	2	1	3
64	Gelişim Lab	2	*	2
65	Düzce Tıp	*	1	1
66	Tepecik EAH	1	*	1
67	Koç Üniv. Tıp Fak.	3	*	3
	Total	**2136**	**531**	**2767**

Tablo 1. Türkiye'de HIV-1 ile enfekte 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

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

*T.C. Sağlık Bakanlığı

Tablo 2. HIV-1 ilaç direnci analizi: veritabanımdan*

Dönem	Tedavi naif hasta	Antiretroviral deneyimli hasta	Toplam
2010 - 2015	1678	425	2103**

*Türkiye'de 59 enfeksiyon hastalıkları kliniğine ait hasta analizini içermektedir
** Tekrarlanan ve/veya henüz sonuçlanmamış analizler dahildir.

Veritabanımdan;

(2010 Mart - 2015 Mart, n=1508)

Tedavi naif (yeni tanı) (n=1243)

- Cinsiyet; %90 erkek
- Yaş, ortanca yıl; 36
- CD4+T hücre sayısı; ortanca mm3; 359
- HIV-1 RNA yükü, ortanca IU/ml; 2592000
- Bulaş yolu;
  - **Heterosexual temas; 52% (n=647)**
  - **MSM; 43% (n=530)**
  - **Bisexual temas; 3.5% (n=44)**
  - Kan transfuzyonu; <1% (n=8)
  - IVDU; <1% (n=4)
  - Dövme; <1% (n=4)
  - Dental/medikal girişim; <1% (n=2)
  - Emzirme; <1% (n=2)
  - Vertikal; <1% (n=2)

Tedavi altında (viral rebound) (n=265)

- Cinsiyet; %90 erkek
- Yaş, ortanca yıl; 40
- CD4+T hücre sayısı; ortanca mm3; 233
- HIV-1 RNA yükü, ortanca IU/ml; 1350000
- Acquisition route;
  - **Heterosexual temas; 68% (n=181)**
  - **MSM; 22% (n=59)**
  - **Bisexual temas; 6% (n=16)**
  - Dental/medikal girişim; 1% (n=3)
  - Kan transfuzyonu; <1% (n=2)
  - IVDU; <1% (n=1)
  - Dövme; <1% (n=1)
  - Vertikal; <1% (n=2)

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

Sayan M[1,2], Sargin F[3], Inan D[4], Sevgi DY[5], Celikbas AK[6], Yasar K[7], Kaptan F[8], Kutlu S[9], Fisgin NT[10], Inci A[11], Ceran N[12], Karaoglan I[13], Cagatay A[14], Celen MK[15], Koruk ST[16], Ceylan B[17], Yildirmak T[18], Akalın H[19], Korten V[20], Willke A[21].

Author information

[1]1 Faculty of Medicine, Clinical Laboratory, PCR Unit, University of Kocaeli , Kocaeli, Turkey .
[2]2 Research Center of Experimental Health Sciences, University of Near East , Nicosia, Northern Cyprus .
[3]3 Goztepe Educational and Research Hospital, Clinic of Infectious Diseases, Medeniyet University , Istanbul, Turkey .
[4]4 Faculty of Medicine, Department of Infectious Diseases, University of Akdeniz , Antalya, Turkey .
[5]5 Educational and Research Hospital, Clinic of Infectious Diseases , Sisli Etfal, Istanbul, Turkey .
[6]6 Educational and Research Hospital , Clinic of Infectious Diseases, Ankara Numune, Ankara, Turkey .
[7]7 Educational and Research Hospital, Clinic of Infectious Diseases , Bakırkoy Dr. Sadi Konuk, Istanbul, Turkey .
[8]8 Educational and Research Hospital, Department of Infectious Diseases, University of Katip Celebi , İzmir, Turkey .
[9]9 Faculty of Medicine, Department of Infectious Diseases, University of Pamukkale , Denizli, Turkey .
[10]10 Faculty of Medicine, Department of Infectious Diseases, University of 19 Mayıs , Samsun, Turkey .
[11]11 Educational and Research Hospital, Clinic of Infectious Diseases , Istanbul Kanuni Sultan Süleyman, Istanbul, Turkey .
[12]12 Educational and Research Hospital, Clinic of Infectious Diseases , Haydarpasa Numune, Istanbul, Turkey .
[13]13 Faculty of Medicine, Department of Infectious Diseases, University of Gaziantep , Gaziantep, Turkey .
[14]14 Faculty of Medicine, Department of Infectious Diseases, University of Istanbul , Istanbul, Turkey .
[15]15 Faculty of Medicine, Department of Infectious Diseases, University of Dicle , Diyarbakır, Turkey .
[16]16 Faculty of Medicine, Department of Infectious Diseases, University of Harran , Urfa, Turkey .
[17]17 Faculty of Medicine, Department of Infectious Diseases, University of Bezm-i Alem , Istanbul, Turkey .
[18]18 Educational and Research Hospital, Clinic of Infectious Diseases , Istanbul Okmeydani, Istanbul, Turkey .
[19]19 Faculty of Medicine, Department of Infectious Diseases, University of Uludag , Bursa, Turkey .
[20]20 Faculty of Medicine, Department of Infectious Diseases, University of Marmara , Istanbul, Turkey .
[21]21 Faculty of Medicine, Department of Infectious Diseases, University of Kocaeli , Kocaeli, Turkey .

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)

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

HIV-1 subtype, n (%)	Subtype B	885 (68)	-	-
	Non-subtype B	136 (10)	A1	48 (3.6)
			C	21 (1.6)
			D	3 (0.2)
			F	2 (0.1)
			F1	24 (1.8)
			F2	1 (0.07)
			G	36 (2.7)
			K	1 (0.07)
	Circulating recombinant form (CRF)	285 (22)	CRF01_AE	132 (10.1)
			CRF 02_AG	85 (6.5)
			CRF 03_AB	13 (1)
			CRF 06_cpx	3 (0.2)
			CRF 07_BC	1 (0.07)
			CRF 08_BC	1 (0.07)
			CRF 11_cpx	3 (0.2)
			CRF 12_BF	33 (2.5)
			CRF 13_cpx	3 (0.2)
			CRF 14_BG	11 (0.8)

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

Sampling, region/city of Turkey	Marmara/Kocaeli, İstanbul, Edirne, Bursa, Sakarya, Bolu Black Sea/Samsun, Artvin, Giresun, Trabzon Southeast Anatolia/Urfa, Diyarbakir, Gaziantep Central Anatolia/Ankara, Kayseri Aegean/İzmir, Denizli, Çanakkale Mediterranean/Antalya, Adana, Mersin	
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)**

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

Co-infection status, n (%)	Hepatitis B	35 (2.7)
	Syphilis	18 (1.4)
	Tuberculosis	14 (1.1)
	P. jiroveci pneumonia	11 (0.8)
	Hepatitis C	7 (0.5)
	Kaposi sarcoma	7 (0.5)
	Candida esophagitis	7 (0.5)
	HPV infection	4 (0.3)
	Hepatitis D	3 (0.2)
	Herpes zoster	3 (0.2)
	Toxoplasmosis	3 (0.2)
	Condyloma	2 (0.15)
	CMV retinitis	1 (<0.1)
	Cryptococcal meningitis	1 (<0.1)
	PML	1 (<0.1)
	Total	**117 (8.9)**

Abbreviations: M/F; male/female, MSM; men who have sex with men, HPV; Human papilloma virus, CMV; cytomegalovirus, PML; progressive multifocal leukoencephalopathy

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.