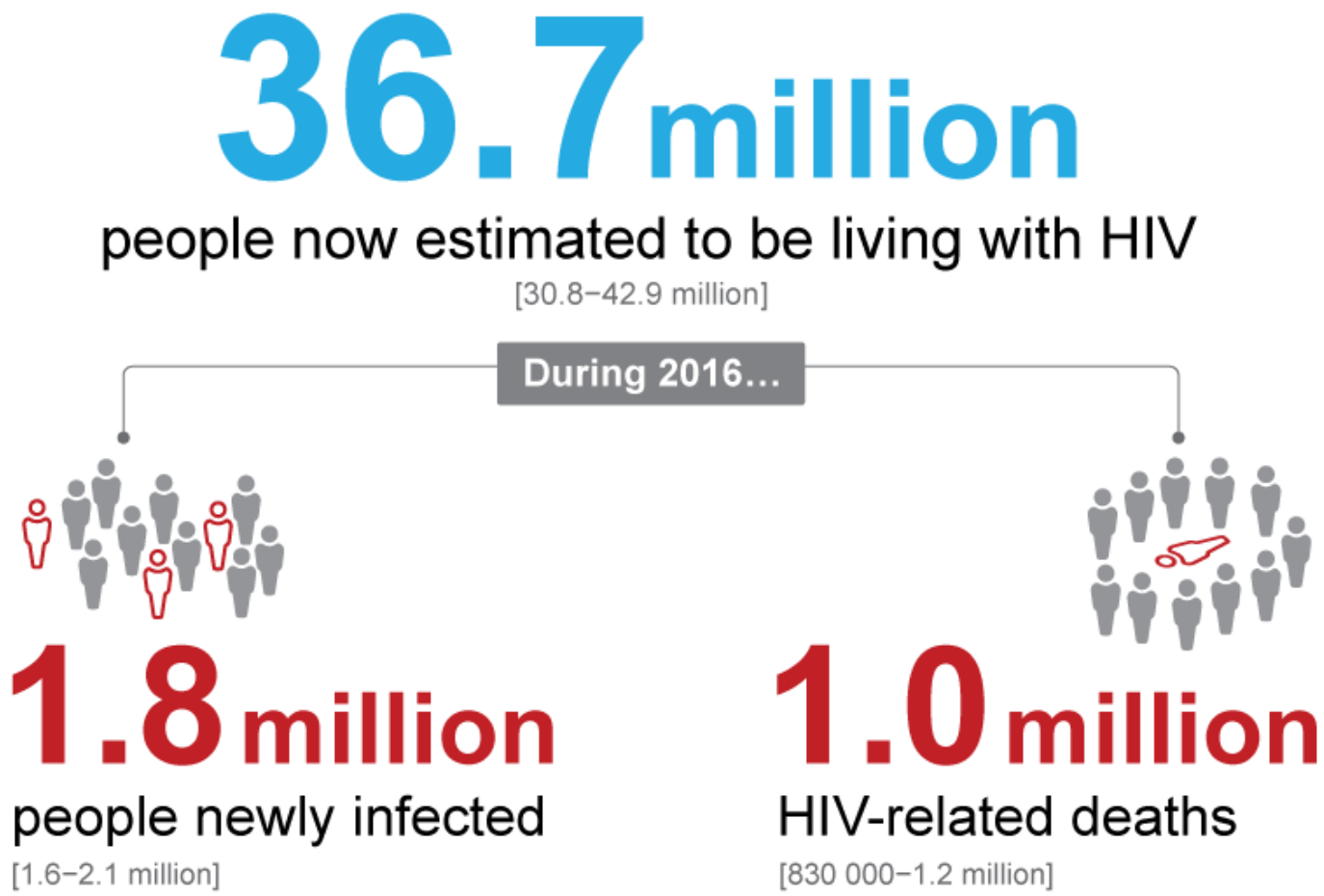
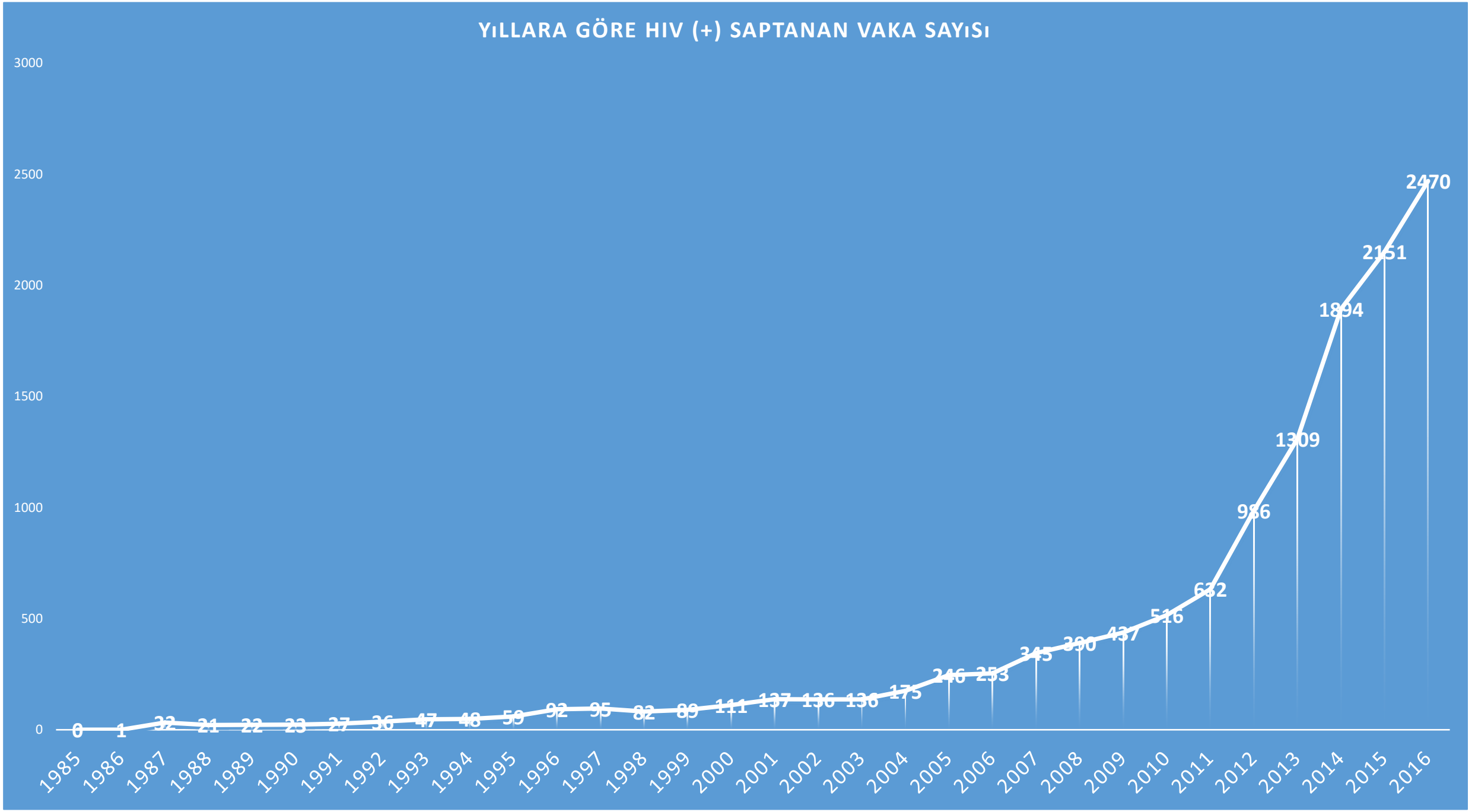
Tanısal Testler ve Direnç

Dr. Mert Ahmet KUŞKUCU
İ.Ü. Cerrahpaşa Tıp Fakültesi
Tıbbi Mikrobiyoloji Anabilim Dalı

Dünya Sağlık Örgütü Verileri (2016)




YıLLARA GÖRE HIV (+) SAPTANAN VAKA SAYıSı
3000
2500
2000
1500
1000
500
0
0
1
32
21
22
23
27
36
47
48
59
92
95
82
89
111
137
136
136
175
246
253
345
390
437
516
632
986
1309
1894
2151
2470
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016

90%

diagnosed

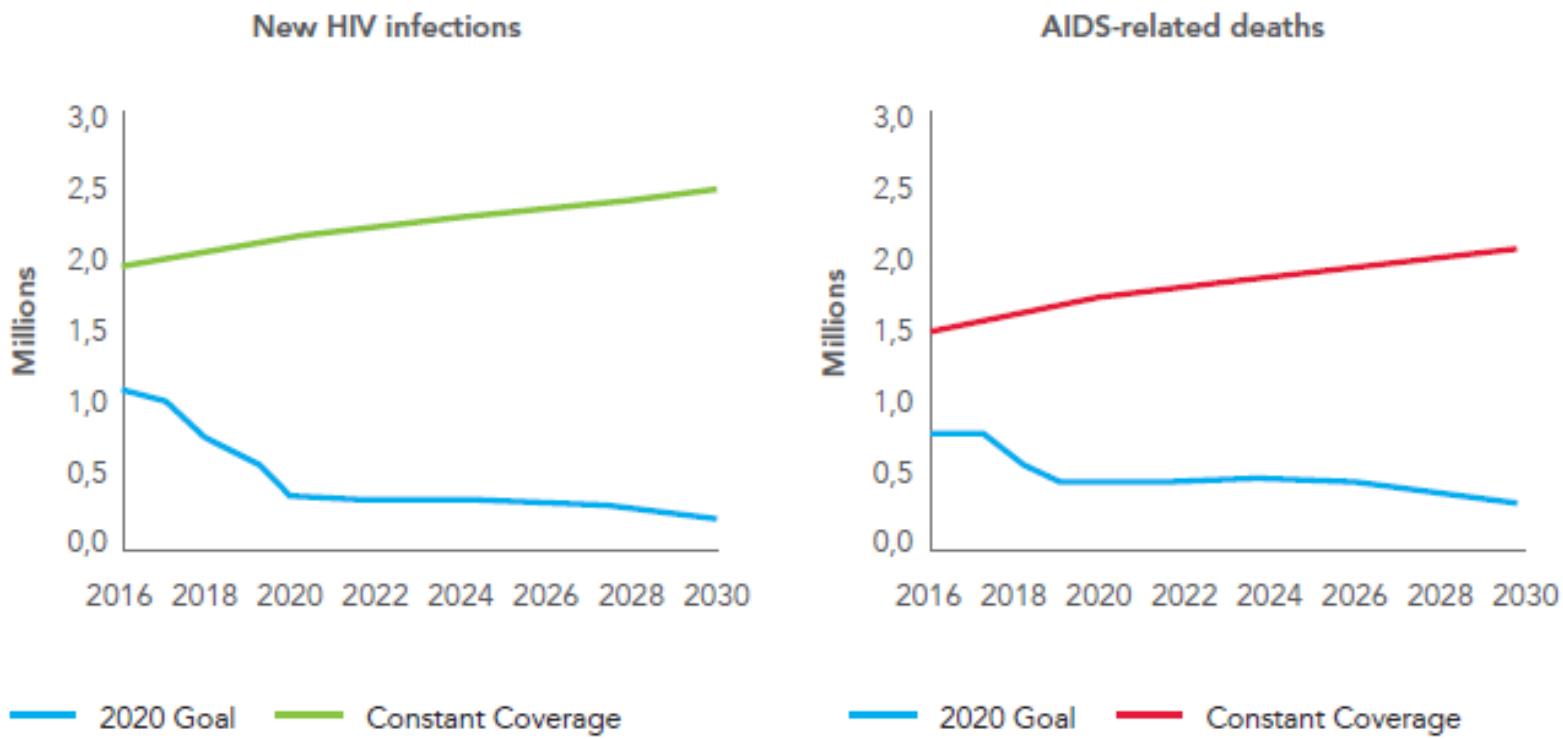
90%

on treatment

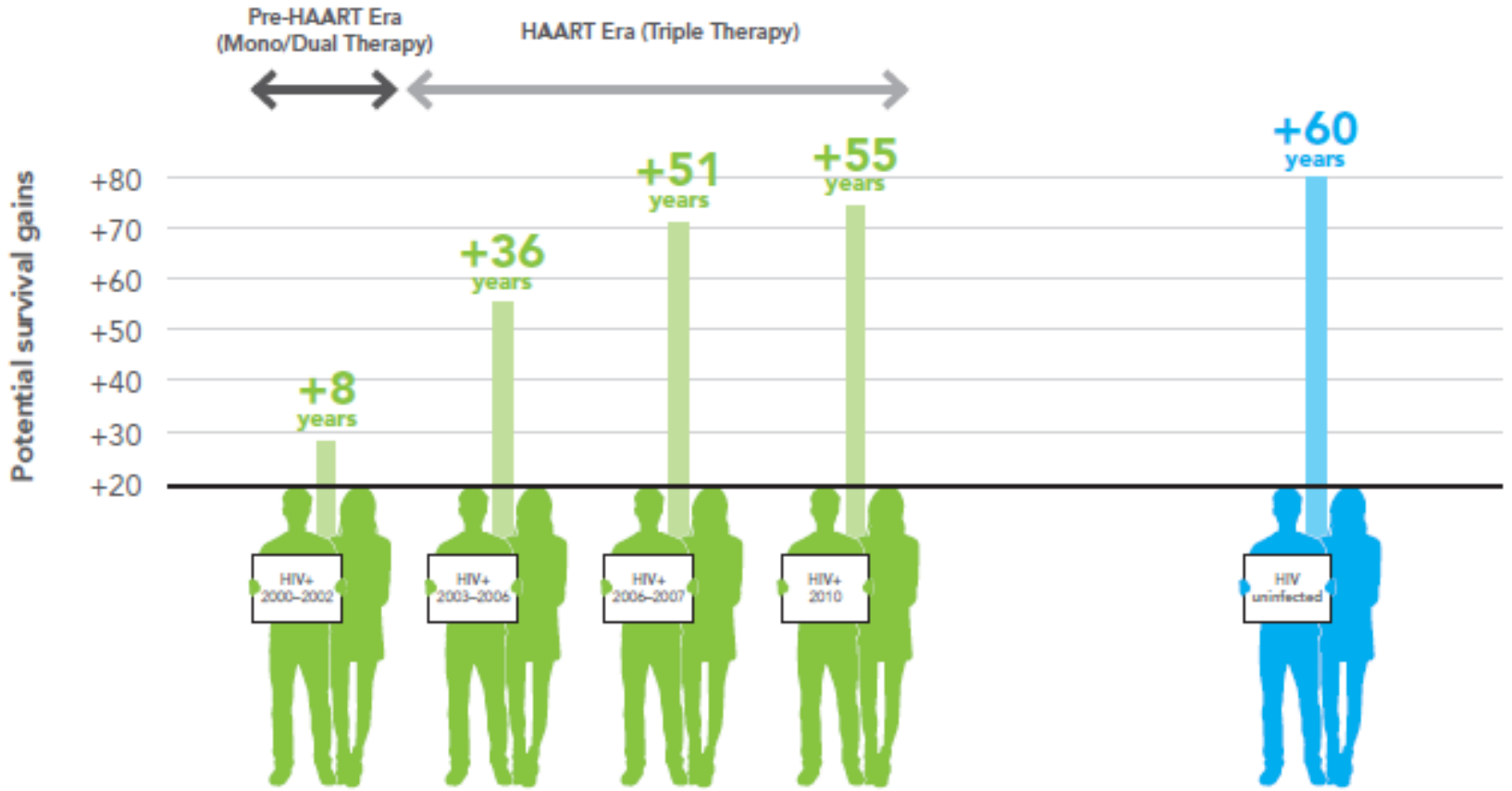
90%

virally suppressed

IMPACT OF THE 90-90-90 TARGET ON HIV INFECTIONS AND AIDS-RELATED DEATHS, 2016-2030



Test Et & Tedavi Et
’’TEST AND TREAT’’ STRATEJİSİ



HIV TARAMA ve TANI TESTLERİ

- Testler farklı amaçlarla uygulanabilir:
  - ➔ Tanı, tarama, doğrulama, izleme,…

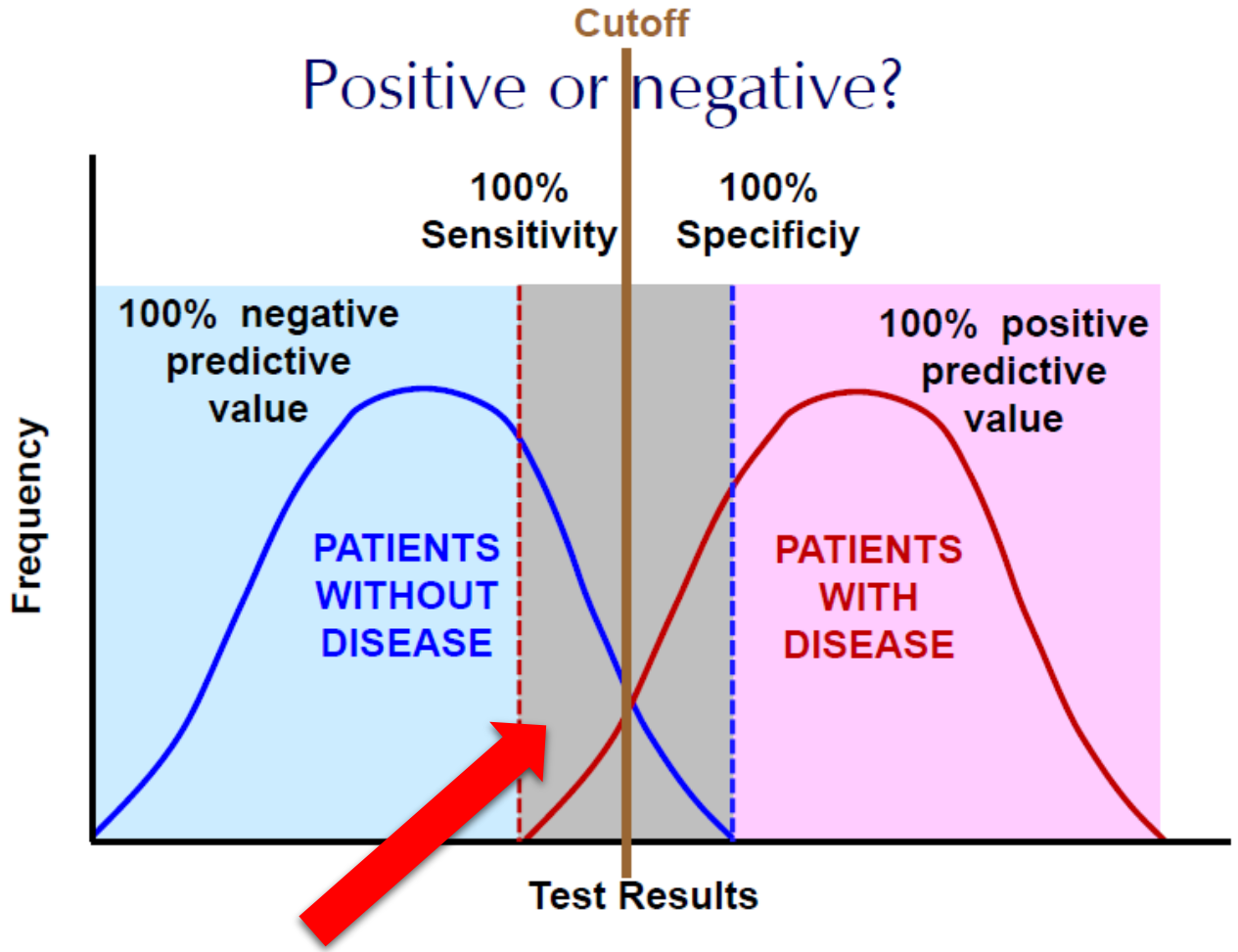
- **Test algoritması**

➔HIV infeksiyonunun varlığını ya da yokluğunu belirlemek için uygulanacak testlerin sırasının adım adım planlanması

HEDEF: İnfekte kişileri atlamamak

- Hastalığın atlanmasının sonuçları ağır olacaksa:

Duyarlılığı yüksek; özgüllük sınırı düşük tutulmalıdır.

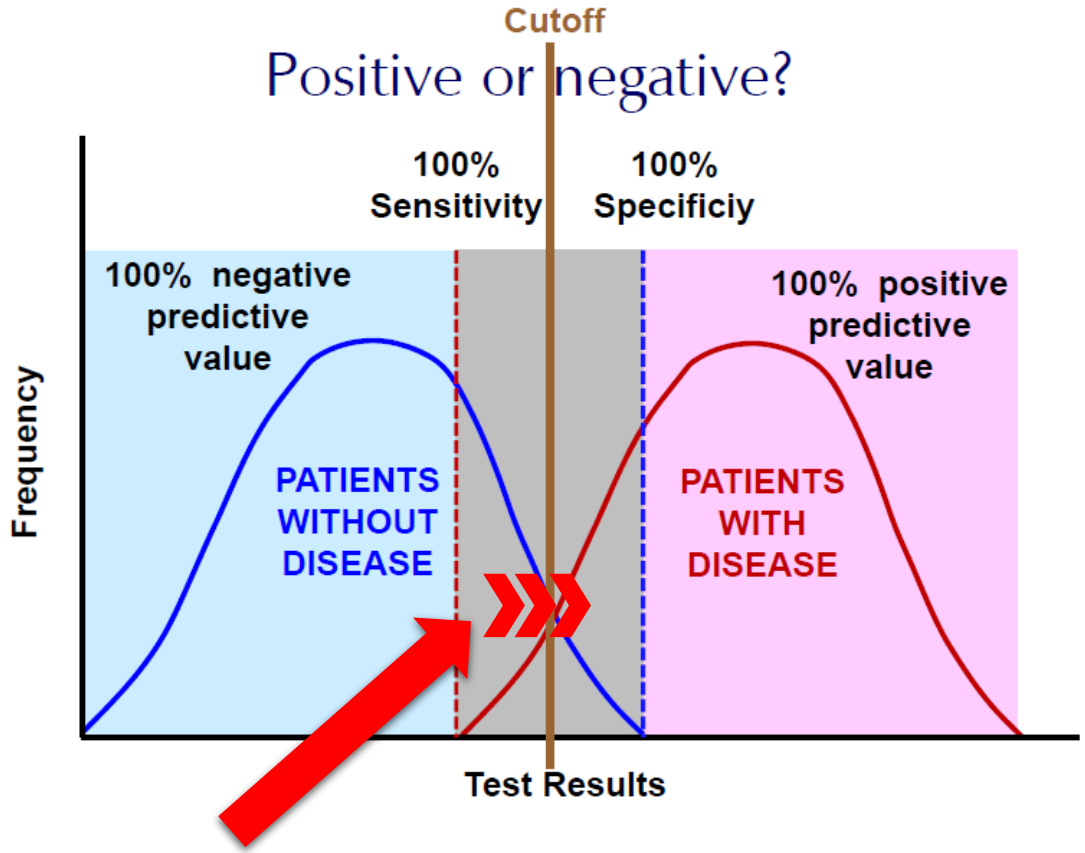


Sorun: Yalancı Pozitiflikler

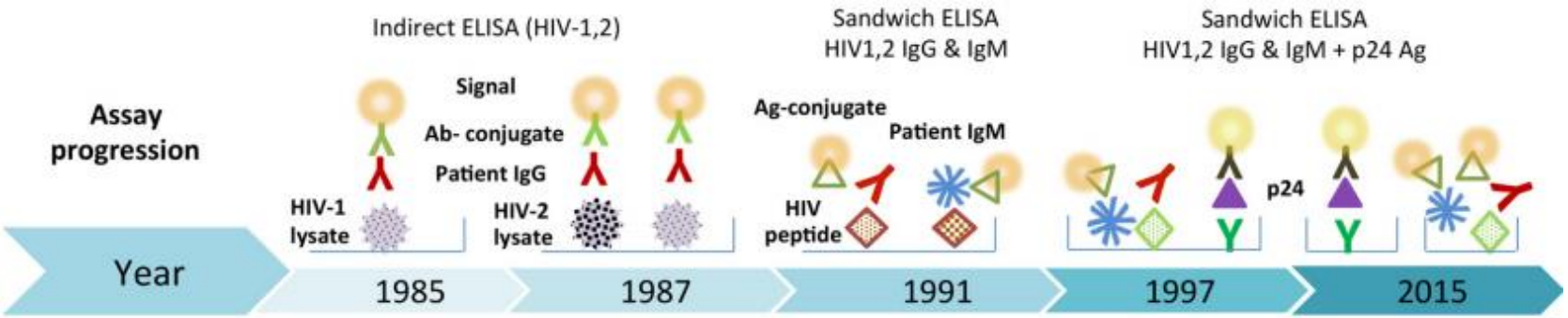
Çözüm:
Ardışık 2 test uygulaması ve net özgüllük:

Net özgüllük= (Özgüllük 1 + Özgüllük 2) – (Özgüllük 1 x Özgüllük 2)

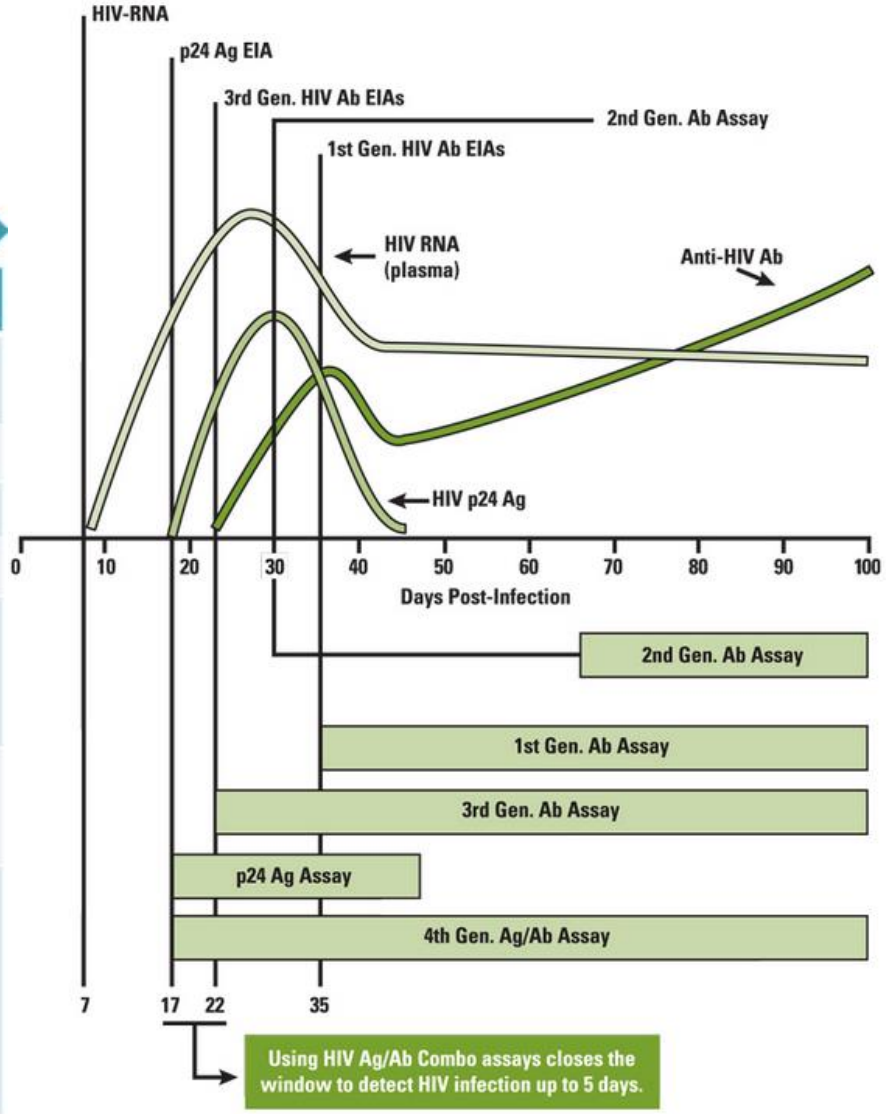
Özgüllük 1= 0.996	**Özgüllük 2= 0.998**
Özgüllük 1 + Özgüllük 2 = 1.994 Özgüllük 1 x Özgüllük 2 = 0.994	
Net Özgüllük = 1.994 - 0.994 **= 1.00**	



Mevcut Testler; Genel Bakış

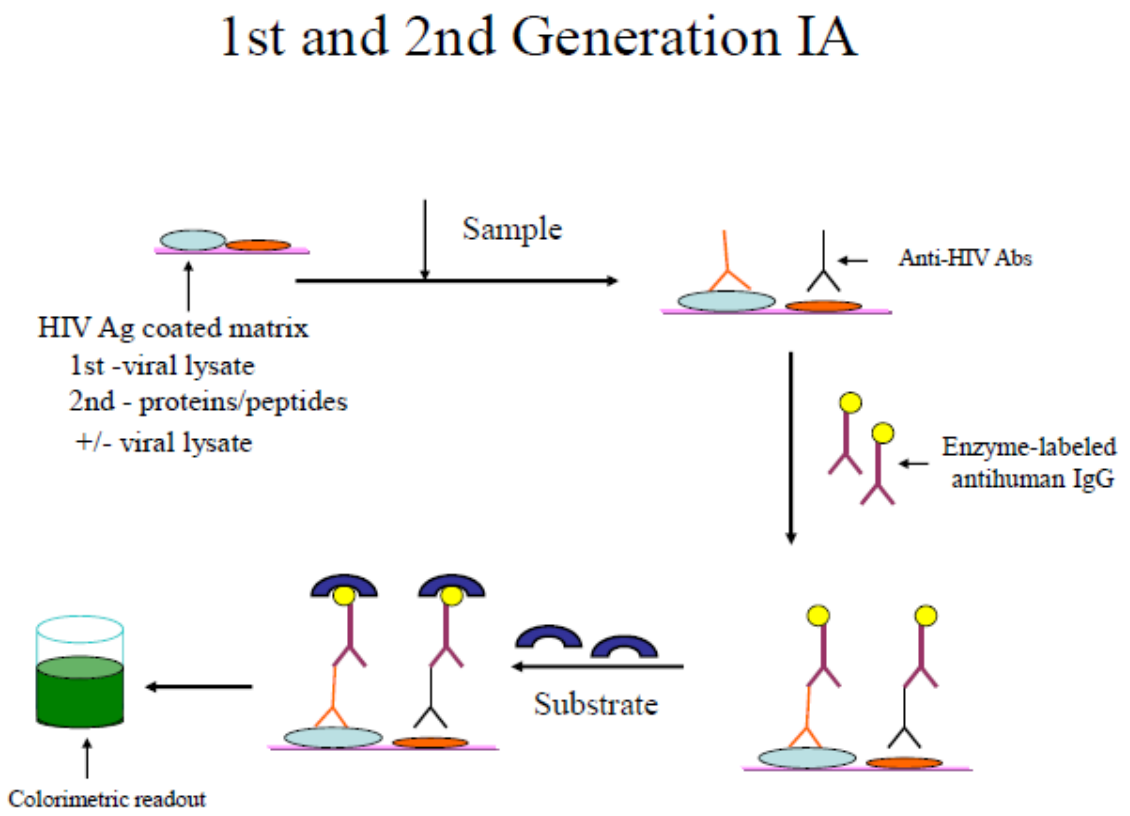


Generation	1st	2nd	3rd	4th	5th
Antigen (Ag) Source	Virus Infected Cell Lysate	Lysate & Recombinant	Recombinant & Synthetic peptides	Recombinant & Synthetic peptides	Recombinant & Synthetic peptides
Specificity	95-98%	>99%	>99.5%	99.5%	99.5%
Sensitivity	99%	>99.5%	>99.5%	>99.8%	100%
Negative Window	8-10 weeks	4-6 weeks	2-3 weeks	2 weeks	2 weeks
Detects Antibody (Ab) and Ag	IgG Anti HIV-1	IgG anti HIV-1 and IgG anti HIV-2	IgG and IgM anti HIV-1, HIV-2 and Group O	IgG and IgM anti HIV-1, HIV-2 and Group O. Also detects HIV-1 p24 Ag	IgG and IgM anti HIV-1, HIV-2 and Group O. Also detects HIV-1 p24 Ag
Results	Single result	Single result	Single result	Single result; does not differentiate Ab from Ag positivity	Separate HIV-1 and HIV 2 Ab and Ag results
Confirming Tests	HIV-1 western blot (WB) or immunofluorescence (IFA)	HIV-1 WB or IFA, HIV-2 ELISA and WB if HIV-1 confirm is negative	HIV-1 WB or IFA, HIV-2 ELISA and WB if HIV-1 confirm is negative	HIV-1.2 differentiation Assay followed by qualitative HIV-1 RNA PCR if differentiation assay is negative	Not determined at the time of this writing



1 ve 2. kuşak testler:

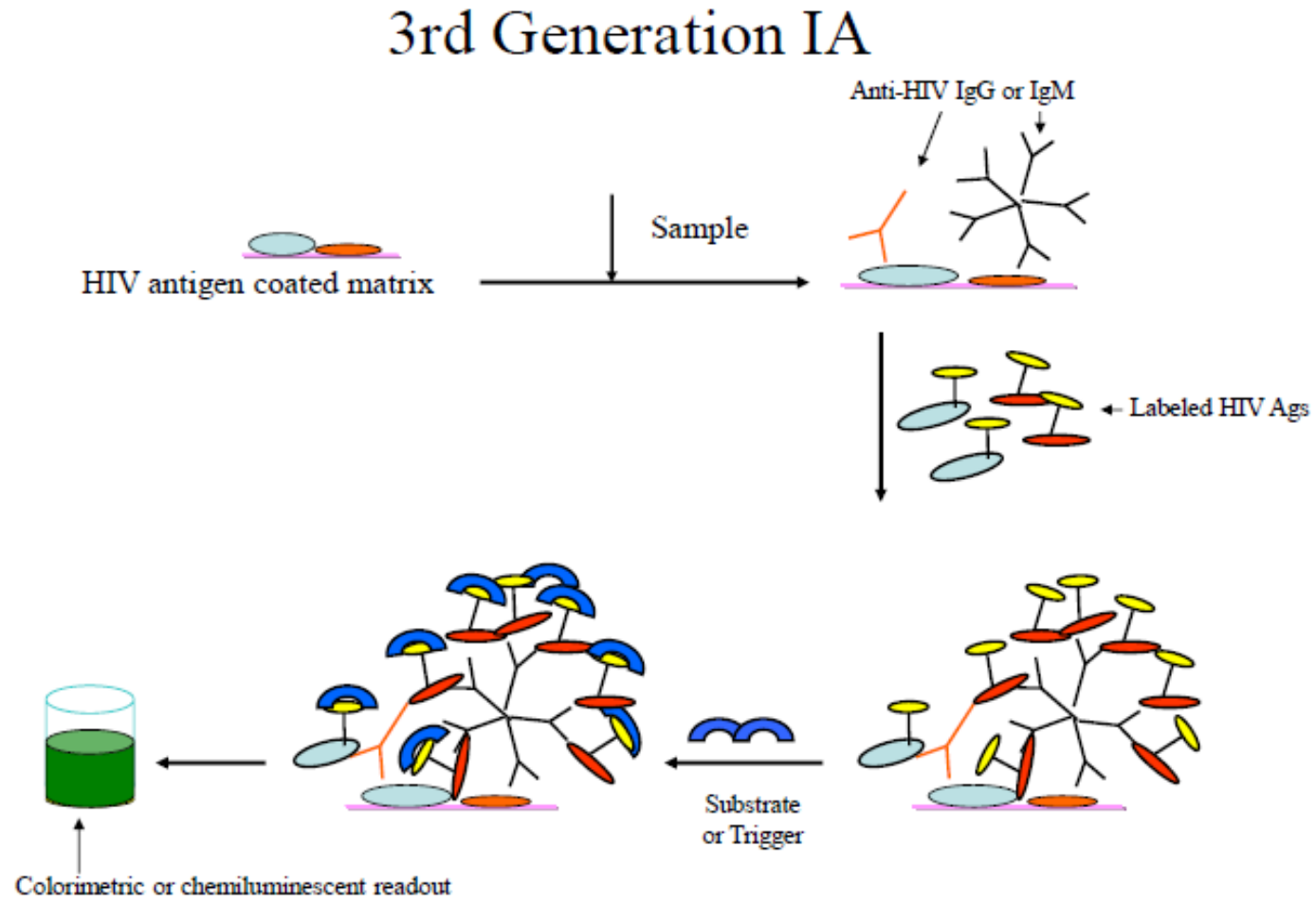
- İlk geliştirilen testler
- Sadece IgG sınıfı antikorları saptıyorlar
- Duyarlılık sorunları
- Doğrulamada hala kullanılmakta olan WB ve IFA gibi testler 1. kuşak testler



3. Kuşak testler

- IgG ve IgM sınıfı antikorları

saptayabiliyorlar

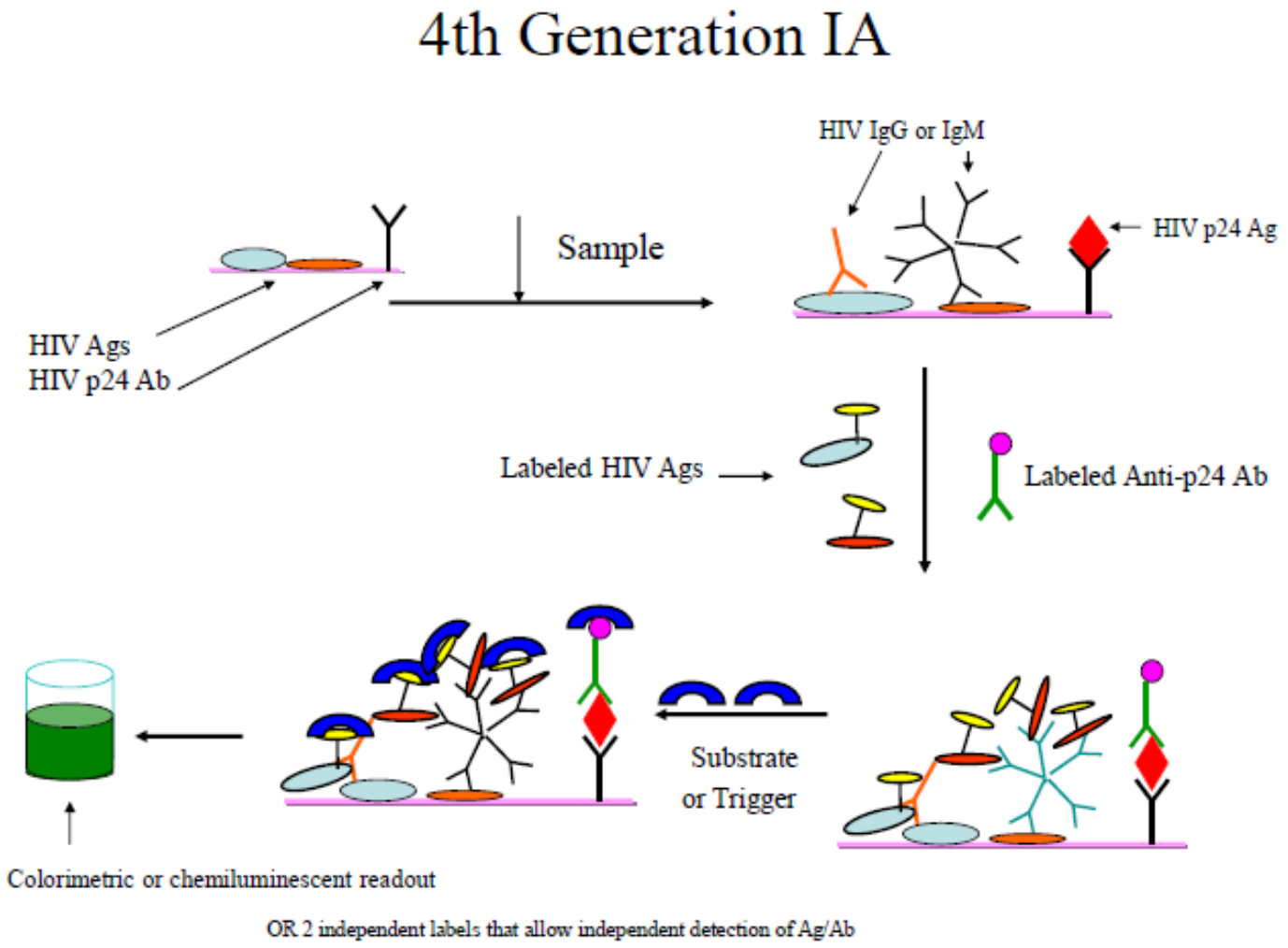


4. Kuşak testler

- Hem antikor hem da antijeni aynı

anda saptıyorlar → Combo test

- Duyarlılık ve özgüllükleri yüksek



5. Kuşak testler

- Hem antikor hem da antijeni aynı anda saptıyorlar; *ayrı ayrı raporluyorlar* → Combo test

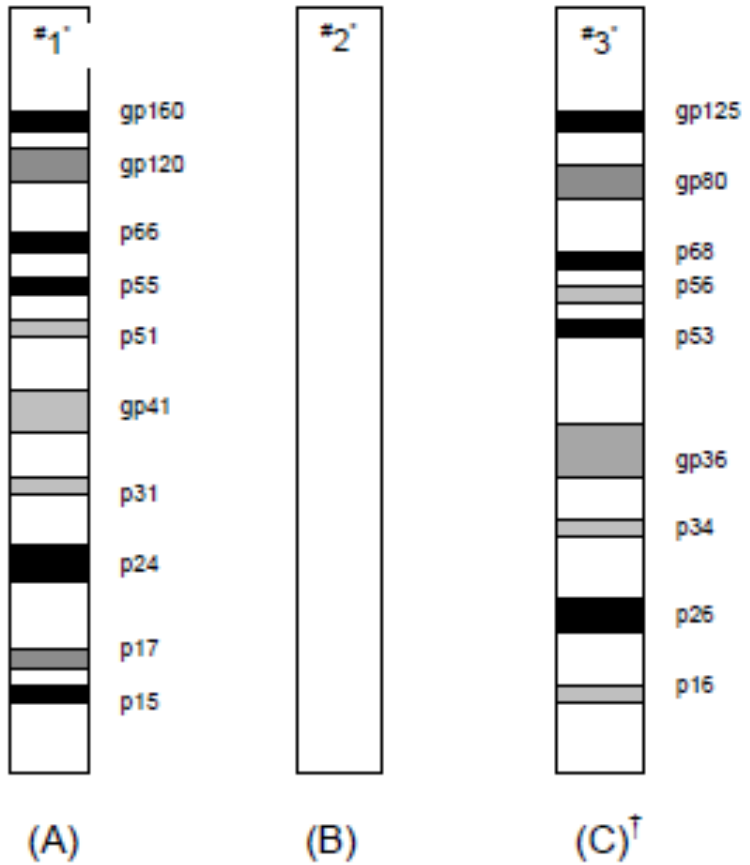
- Duyarlılık ve özgüllükleri yüksek

- BioPlex® 2200 HIV Ag-Ab Assay (HIV-1/2 antigen/antibody combination immunoassay)

Boyalı boncukların antikor ya da antijenle kaplanmasına dayalı, FDA onayı:2015.

- «Multiplex flow immunoassay»: p24 Ag, HIV-1 antikorları (M ve O grupları) ve HIV-2 antikorlarını aynı anda saptayıp ayırabilen bir sistem

Western blot



Line IA (LIA)

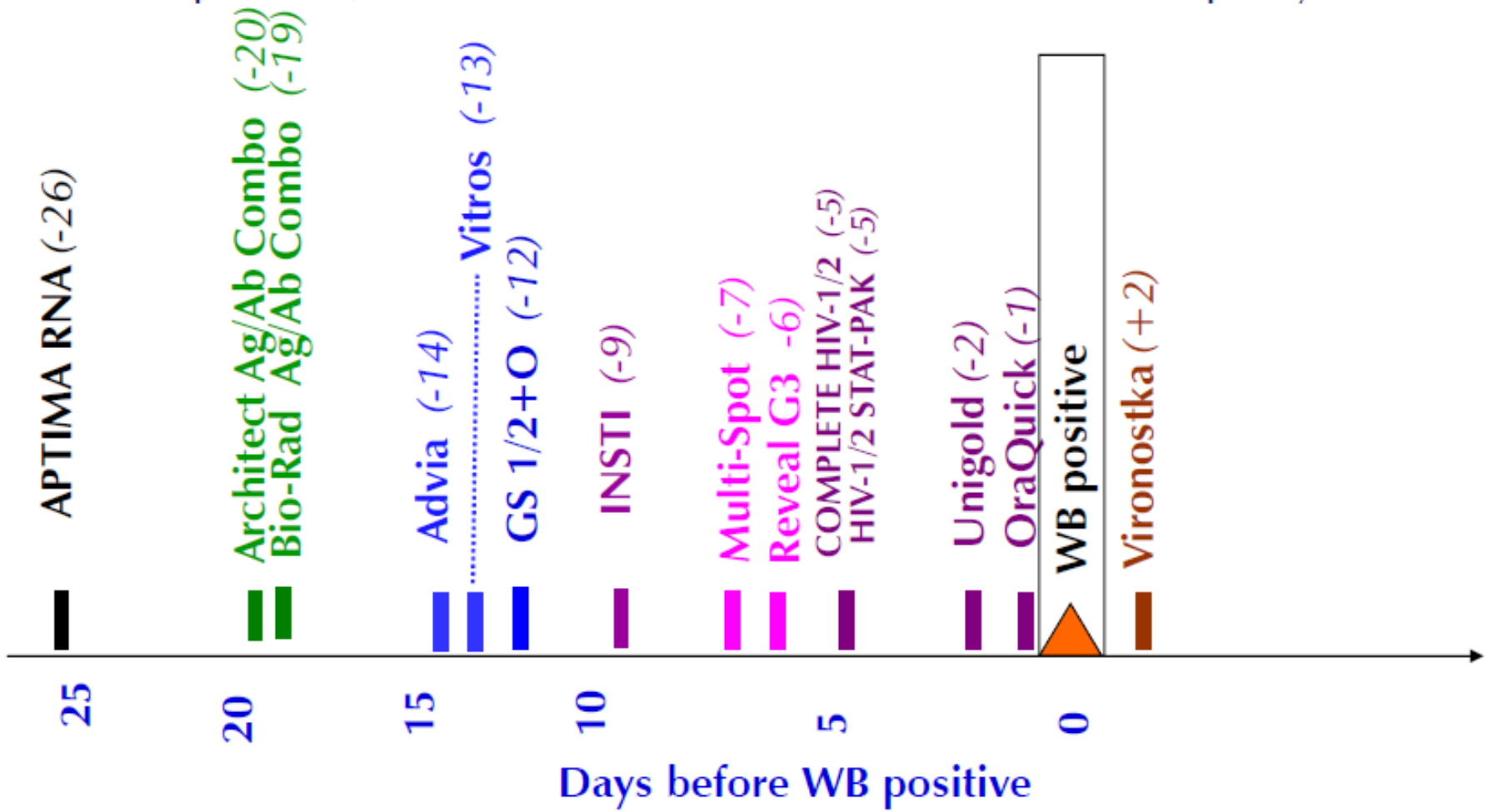

01
02
03
04
05
06
07
08
09
10
11
12
13
14
15
16
17
18
19
20
Streptavidin
*----- 3+
1+
+/-
sgp120
gp41
p31
p24
p17
sgp105
gp36

Multispot EIA doğrulama testi

Multispot HIV-1/HIV-2

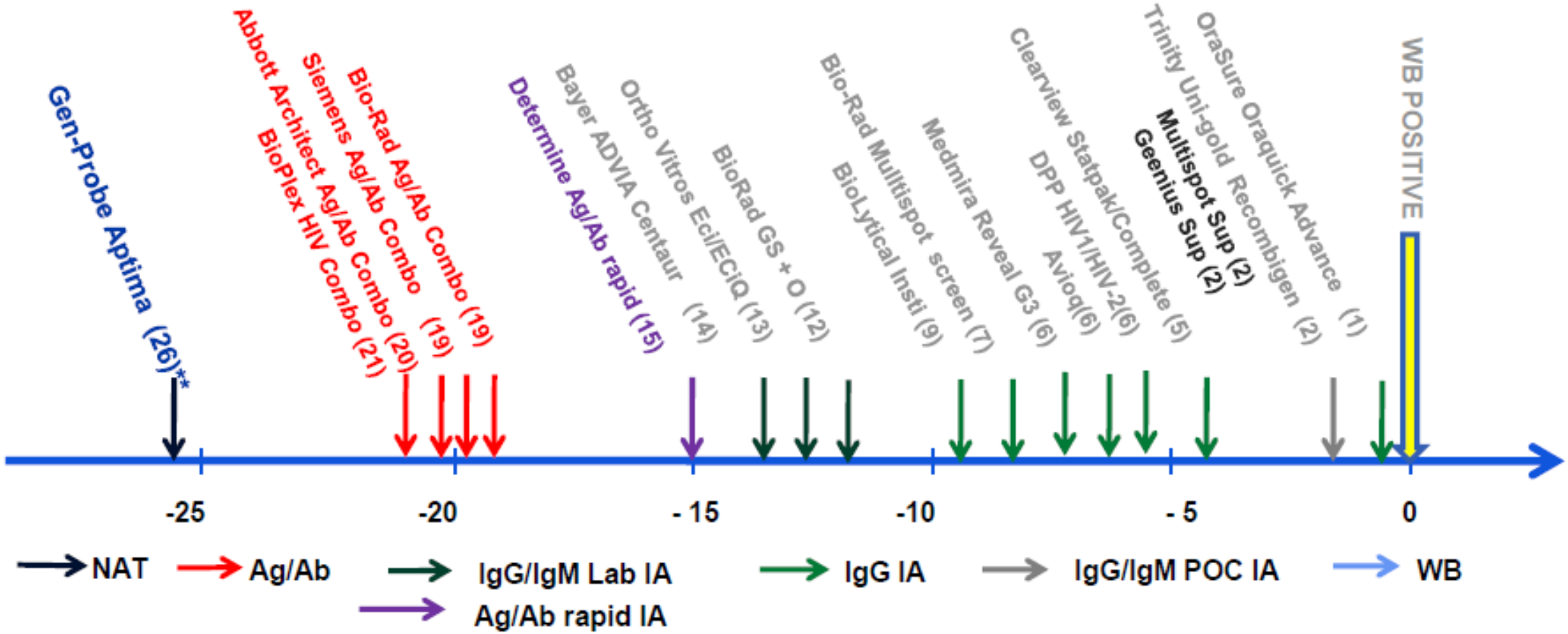
Geenius HIV-1/HIV-2

166 specimens, 17 Seroconverters - 50 % Positive Cumulative Frequency



Modified from *Masciotra et al, J Clin Virol 2011* and *Owen et al, J Clin Micro 2008*

Sequence of HIV Assay Reactivity During Early HIV Infection Relative to Western Blot*



	Method	Sensitivity[a] (range)	Result Output
Abbott ARCHITECT HIV Ag/Ab Combo Assay (Abbott Diagnostics)	CMIA	18.39 (17.80-19.68) pg/mL	Nonreactive Reactive
GS HIV Combo Ag/Ab EIA (Bio-Rad Laboratories)	EIA	14.78 (13.22-15.89) pg/mL	Nonreactive Reactive
ADVIA Centaur HIV Ag/Ab Combo (Siemens)	CMIA	9.04 (6.1-11.4) pg/mL	Nonreactive Reactive
BioPlex 2200 HIV Ag-Ab (Bio-Rad Laboratories)	Multiplex flow IA	5.2 (5.0- 5.4) pg/mL	Nonreactive Reactive for HIV Ag-Ab *with* Reactive for HIV-1 Ag *and/or* Reactive for HIV-1 Ab *and/or* Reactive for HIV-2 Ab *or* Reactive, Undifferentiated
Determine HIV-1/2 Ag/Ab Combo[b] (Alere)	Lateral flow, single-use device	25 pg/mL	Nonreactive Ab Reactive Ag Reactive Ab Reactive & Ag Reactive

	MultiSpot (Bio-Rad Laboratories)	Geenius (Bio-Rad Laboratories)
HIV-1 peptides HIV-1 recombinant (r) proteins	gp41 (ENV) r-gp41 (ENV)	p31 (POL), gp41 (ENV) r-gp160(ENV), r-p24 (GAG)
HIV-2 peptides	gp36 (ENV)	gp36 (ENV), gp140 (ENV)
Possible Results for each assay	Nonreactive	Nonreactive
	Reactive: HIV-1 positive	Reactive: HIV-1 positive
	Reactive: HIV-2 positive	Reactive: HIV-2 positive
	No Equivalent	Reactive: HIV-2 positive with HIV-1 cross reactivity
	Reactive: HIV positive (undifferentiated)	Reactive: HIV positive untypable (undifferentiated)
	Indeterminate: HIV-1 indeterminate	Indeterminate: HIV-1 indeterminate
	No Equivalent	Indeterminate: HIV-2 indeterminate
	No Equivalent	Indeterminate: HIV indeterminate
	Invalid	Invalid
Reading & interpretation of result	Manual reading and interpretation	Geenius Reader and automatic interpretation on Geenius Software
Data Input to LIS/LIMS	Manual	Bi-directional connection to LIS/LIMS
Possible resolution of undifferentiated results	Dilution protocol (PI)	No Equivalent
Specimen type	Serum or plasma	Serum, plasma, fingerstick or Venous whole blood
Intended use	Differentiation of HIV-1 and HIV-2 antibodies in multi-test algorithm	Confirmation and differentiation of HIV-1 and HIV-2 antibodies

- **Multispot *vs* Geenius:**

- Duyarlılıkları: %100 *vs* %100
- Özgüllükleri: %96.3 *vs* %99.1% (NS)
- HIV-1'i ayırtedebilme performansları: %99.2 *vs* %100
- HIV-2 'i ayırtedebilme performansları: %98.1*vs* %98.1

- **INNOLIA *vs* Geenius:**

- Duyarlılık: %83 *vs* %86
- Özgüllük: %91*vs* %99

4. Kuşak Hızlı Testler

- Alere HIV Combo
- SD Bioline HIV Ag/Ab Combo

Kendi Kendine Test 'SELF TEST (ST)'

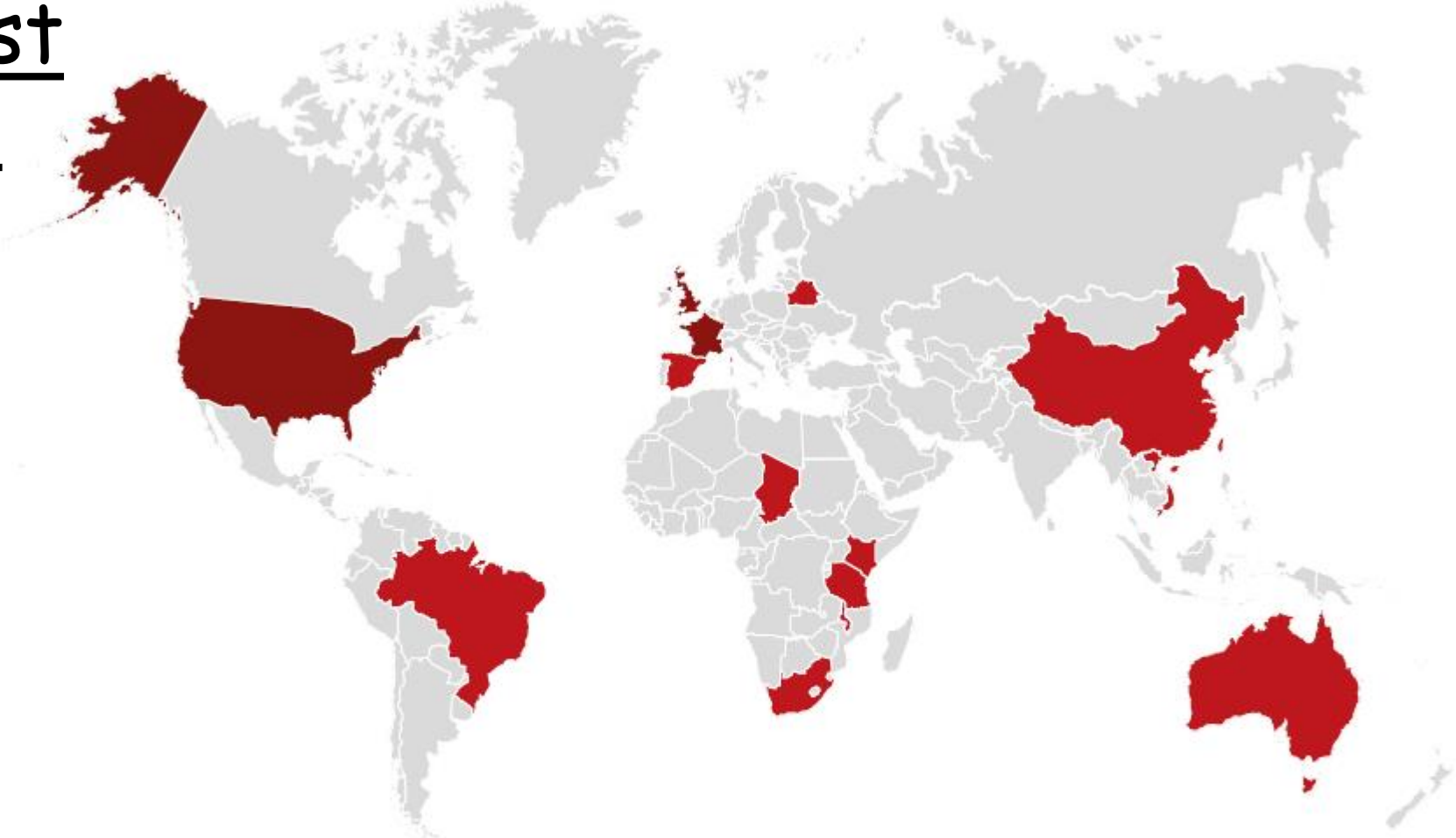
Fingerstick/whole blood-based HIV RDTs for self-testing on the market

Assay name (manufacturer)	Generation	Sensitivity	Specificity	Approval status	Approximate price per test (US$)
autotest VIH® (AAZ Labs, France)	2nd generation	100%	99.8%	CE marked; submitted WHO PQ	25–28 (to consumer)
Private sector version BioSURE HIV Self Test (BioSURE, United Kingdom)	2nd generation	99.7%	99.9%	CE marked	42–48 (to consumer)
Public sector version BioSURE HIV Self Test (BioSURE, United Kingdom)	2nd generation	99.7%	99.9%	CE marked	7.50–15 (to public sector)
INSTI HIV Self Test (bioLytical Laboratories, Canada)	3rd Generation	100%	99.8%	CE marked	36 (to consumer)

Oral fluid-based HIV RDTs for self-testing on the market

Assay name (manufacturer)	Generation	Sensitivity	Specificity	Approval status	Approximate price per test (US$)
OraQuick® In-Home HIV Test (OraSure Technologies Inc., USA)	2nd generation	91.7%	98.7%	FDA	40 (to consumer)
OraQuick® In-Home HIV Test (OraSure Technologies Inc., USA)	2nd generation	100%	99.8%	Completed CE procedure, pending CE certificate	NA

Kendi Kendine Test
'SELF TEST (ST)'



Countries with Policy Supporting HIVST
Australia, Belarus, Chad, China, Kenya, Lesotho, Malawi, Rwanda, South Africa, Spain, United Republic of Tanzania

Countries with Policy Supporting HIVST & Products Approved For HIVST
France, United Kingdom, United States Of America

Unitaid

World Health Organization

psi

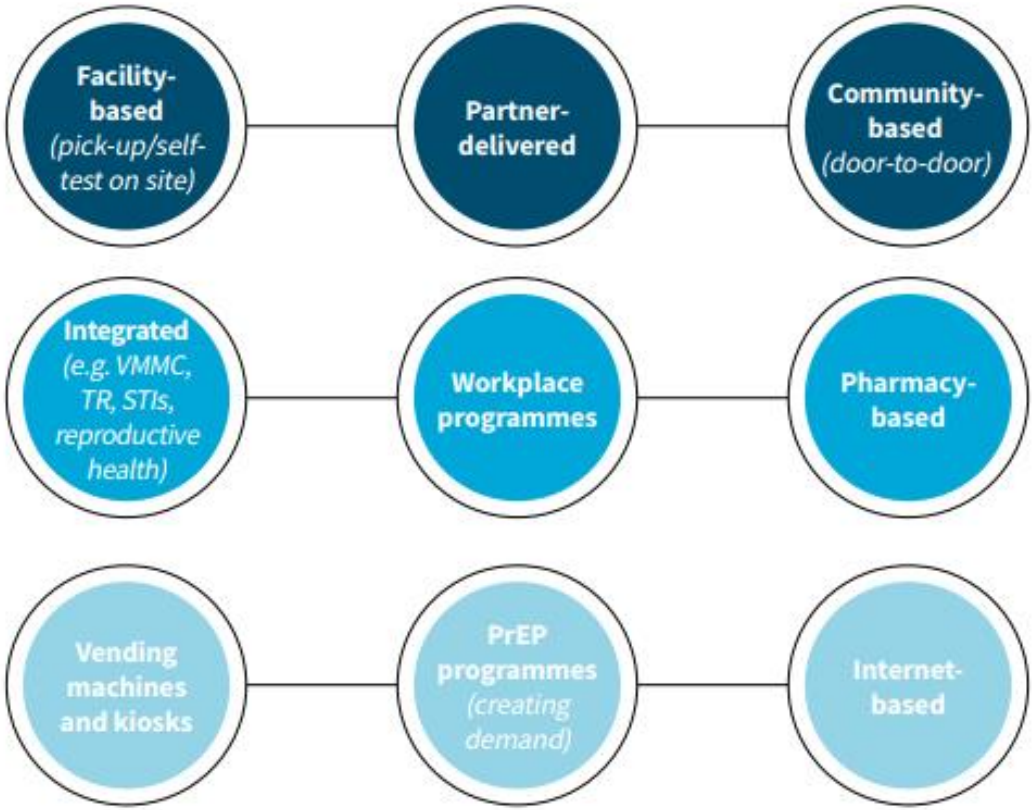
MARKET AND TECHNOLOGY LANDSCAPE

HIV RAPID DIAGNOSTIC TESTS FOR SELF-TESTING

3rd EDITION

FIGURE 1.

HIVST service-delivery approaches



Source: WHO, 2016 [20].

'Point of Care' Testler ve Mobil Sağlık Teknolojileri;

Cheap Smartphone Dongle Diagnoses HIV And Syphilis In 15 Minutes

İKİLİ YA DA ÇOKLU TESTLER

Accelerating introduction of dual syphilis & HIV rapid diagnostic tests

A simple, proven, and inexpensive dual test for syphilis and HIV, combined with a web-linked hand-held optical reading device, could improve the quality, acceptability, and uptake of testing and treatment in rural areas to accelerate elimination of MTCT of syphilis and HIV.

Why do we care?

- Globally, syphilis caused 300,000 stillbirths and neonatal deaths in 2008, and 390,000 children were newly infected with HIV in 2010
  - These are preventable deaths
- Newborns in Zambia are at great risk
  - 5.3% of antenatal attendees are seropositive for syphilis
  - 12.3% of antenatal attendees are seropositive for HIV
  - Syphilis-positive pregnant women are ***two*** times more likely to be seropositive for HIV
- We have an opportunity to make a difference in Zambia
  - 94% of antenatal attendees were tested for HIV
  - Only 43% of antenatal attendees were tested for syphilis
- Innovative strategies are needed to ensure that all pregnant women are tested for syphilis ***and*** HIV in early pregnancy

What will we do?

- Assess laboratory performance of newly available dual rapid diagnostic tests (RDTs) for syphilis & HIV
- Field test the highest performing RDT along with a web-linked handheld optical reader offering patient-tailored care algorithms

What will we learn?

- Dual RDT performance
- Acceptability of dual testing by patients and staff
- Effect of optical reader on improving testing quality and data management
- Feasibility of web-based surveillance to improve program and procurement
- Acceptability of patient-tailored care algorithms
- Changes in utilization of health services

What difference will this innovation make?

- We can help eliminate mother-to-child transmission of syphilis ***and*** HIV in 600,000 infants born in Zambia each year
- Improved data can provide evidence for informed public health decision-making
- Generic protocol can be used for other countries interested in scaling up integrated antenatal services

For more information: Dr. Lori Newman, newmanl@who.int

- HIV+SY
- HIV+SY+HCV/HBV

'We can help eliminate mother-to-child transmission of syphilis and HIV in 600,000 infants born in Zambia each year'

NAT TESTLERİ

Cepheid GeneXpert® System

Beckman Coulter Veris

Hologic Panther

Liat™ Analyzer Roche

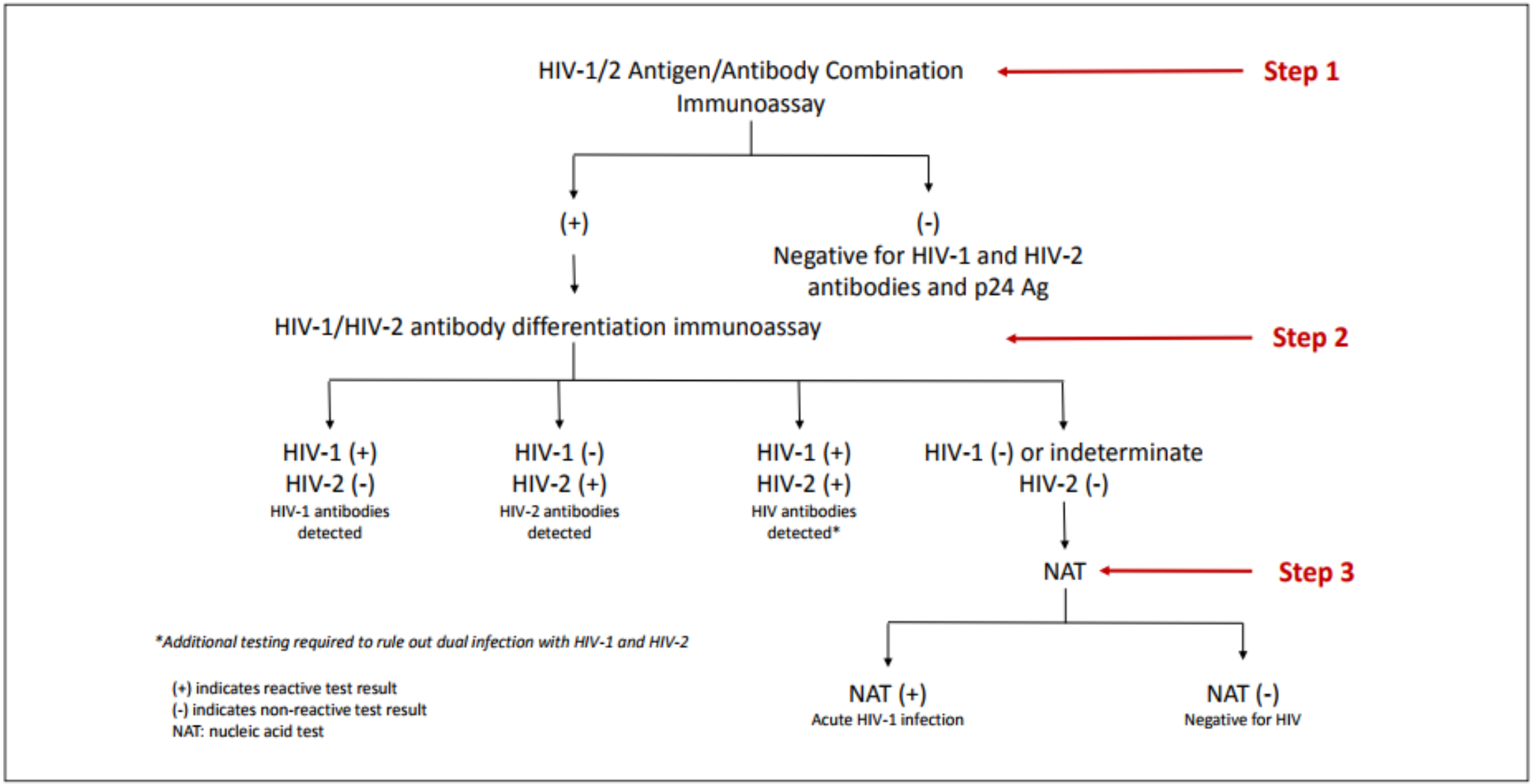
Diagnostics for the Real World SAMBA

Alere™ Q System

HIV İNFEKSİYONUN EDİNİLMESİ İLE GÜVENİLİR BİR ŞEKİLDE SAPTANABİLİMESİ ARASINDAKİ SÜRE → PENCERE DÖNEMİ

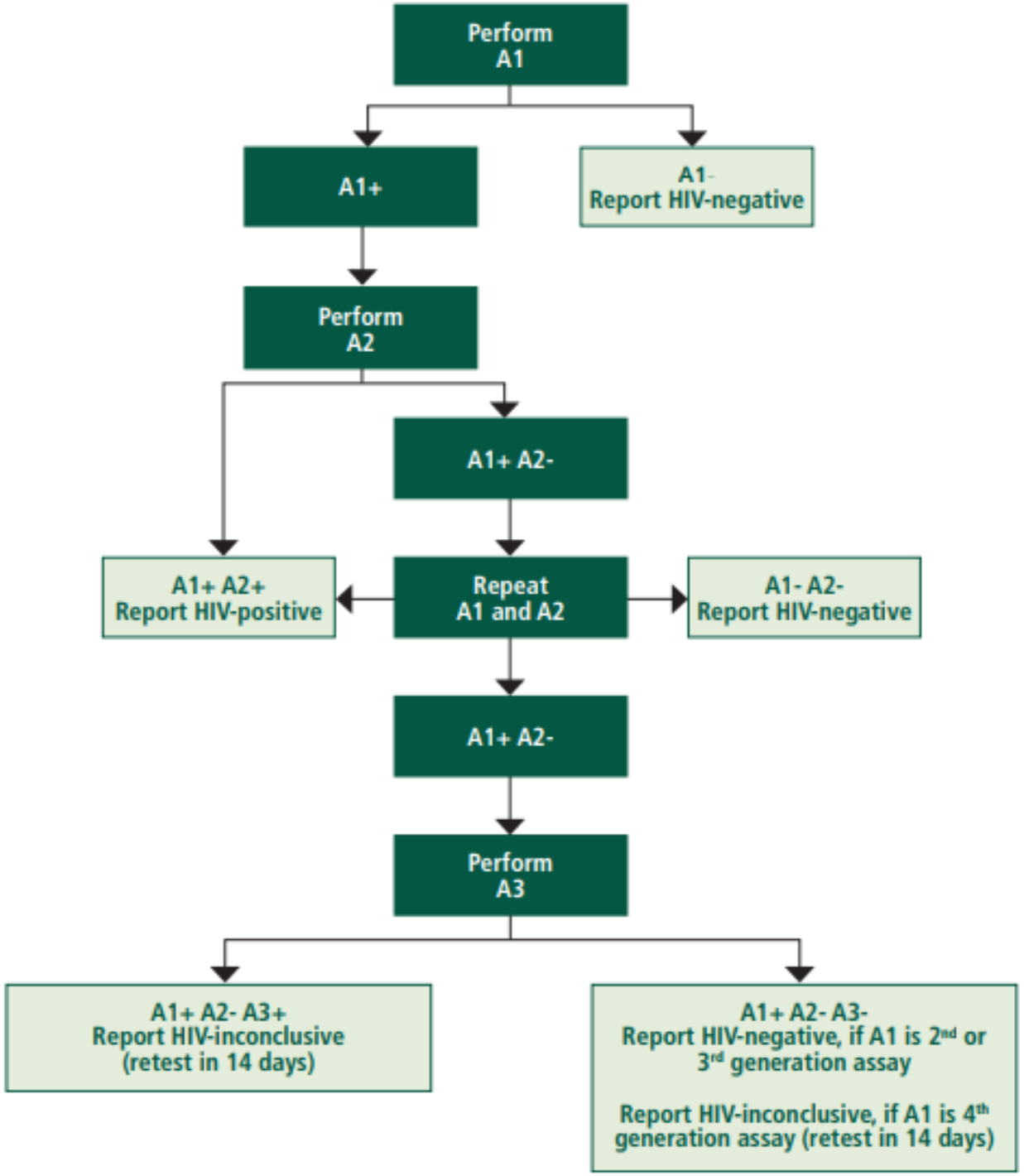
TEST	Pencere dönemi (hafta)	Pencere dönemini kısaltma (gün)
1. kuşak	≈ 6	-----
2. kuşak	≈ 4-6	10
3. kuşak	≈ 3-4	6
4. kuşak	≈ 2	5
NAT		
Tek tek	< 1-2	3
Havuzlanarak	< 1-2	3

HIV Laboratory Diagnostic Testing Algorithm (adapted from CDC and APHLLaboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations. 2014)



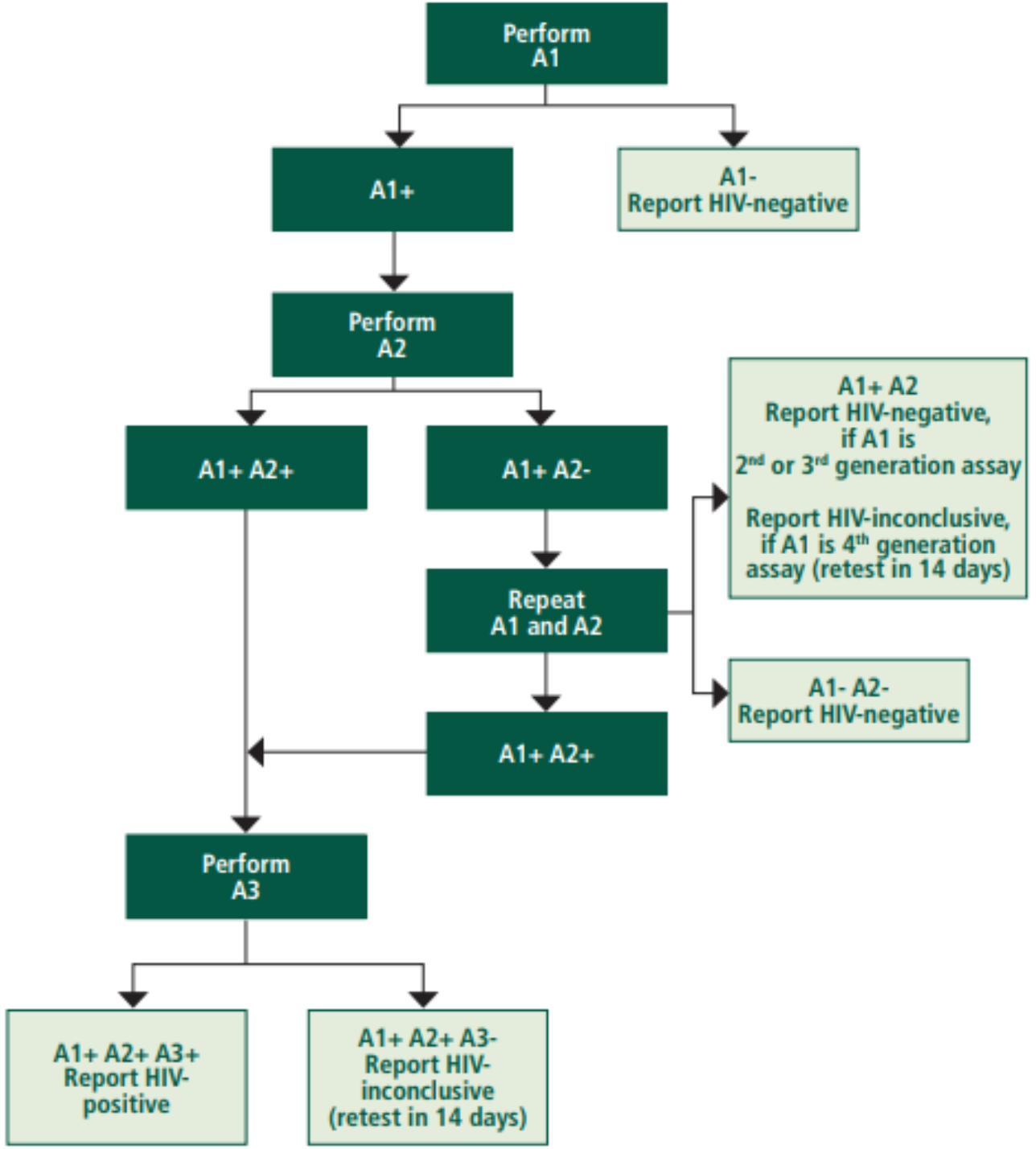
World Health Organization

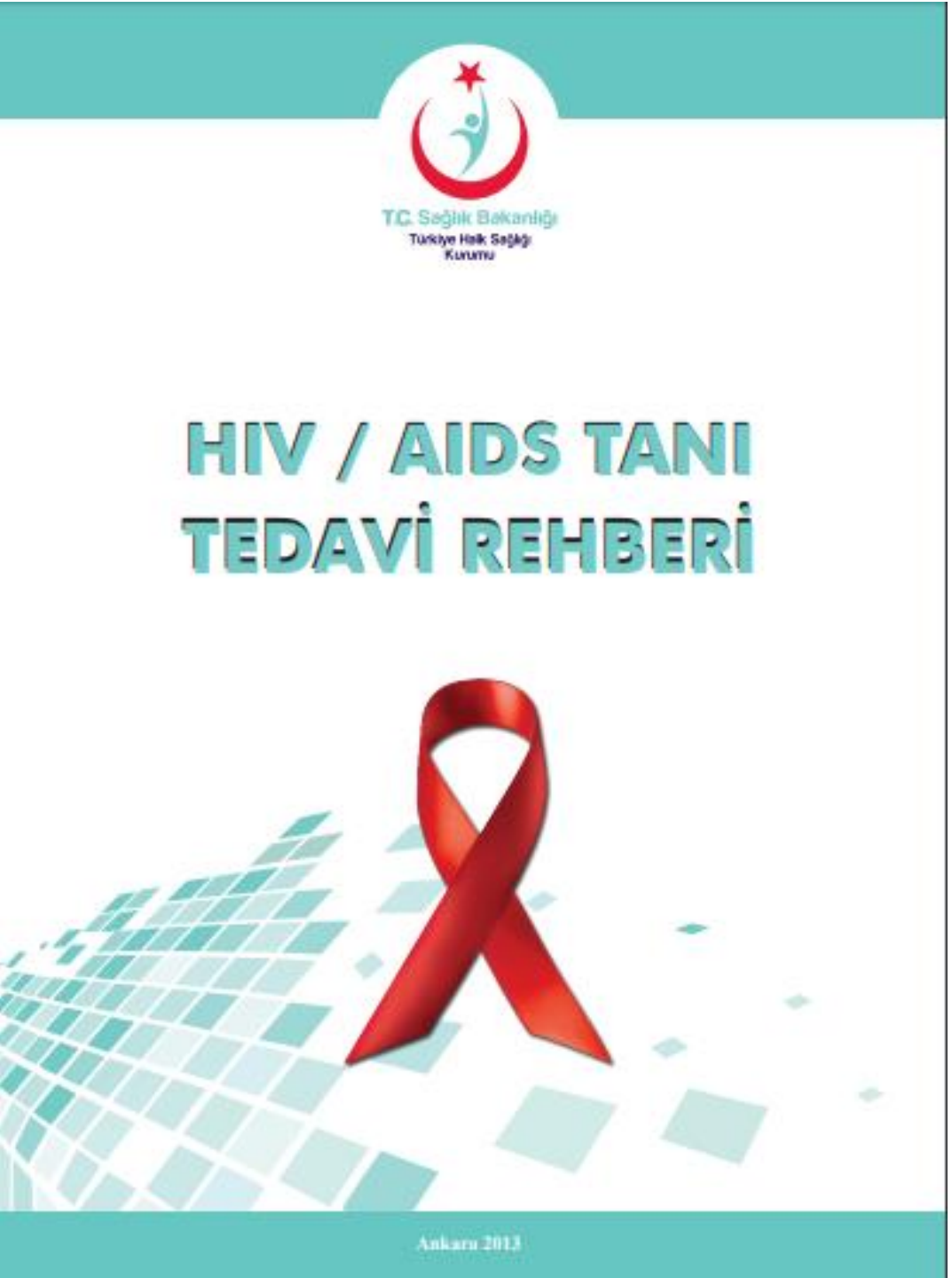
Testing strategy for HIV diagnosis in high prevalence settings



World Health Organization

Testing strategy for HIV diagnosis in low prevalence settings





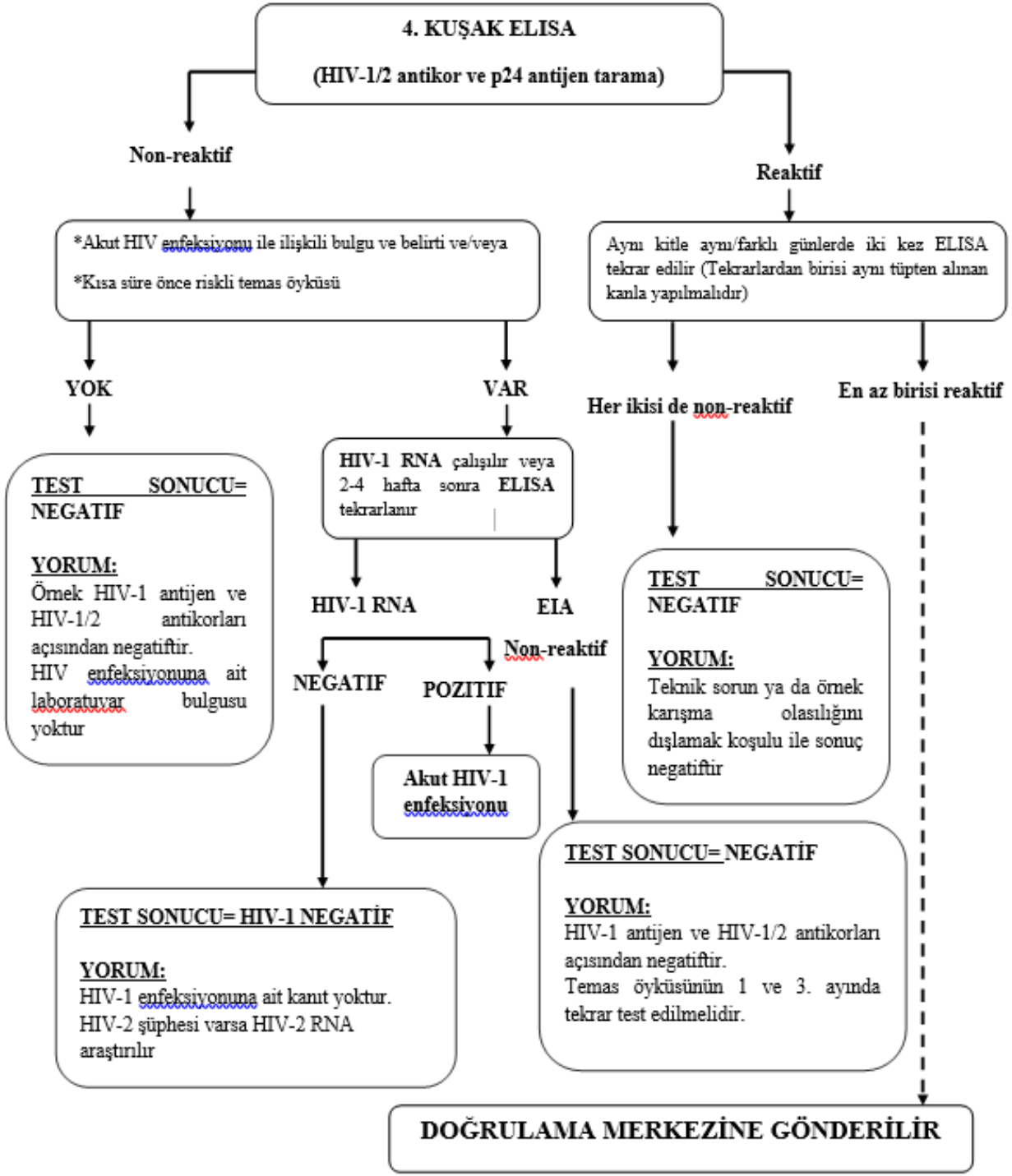
T.C. SAĞLIK BAKANLIĞI

HALK SAĞLIĞI GENEL MÜDÜRLÜĞÜ

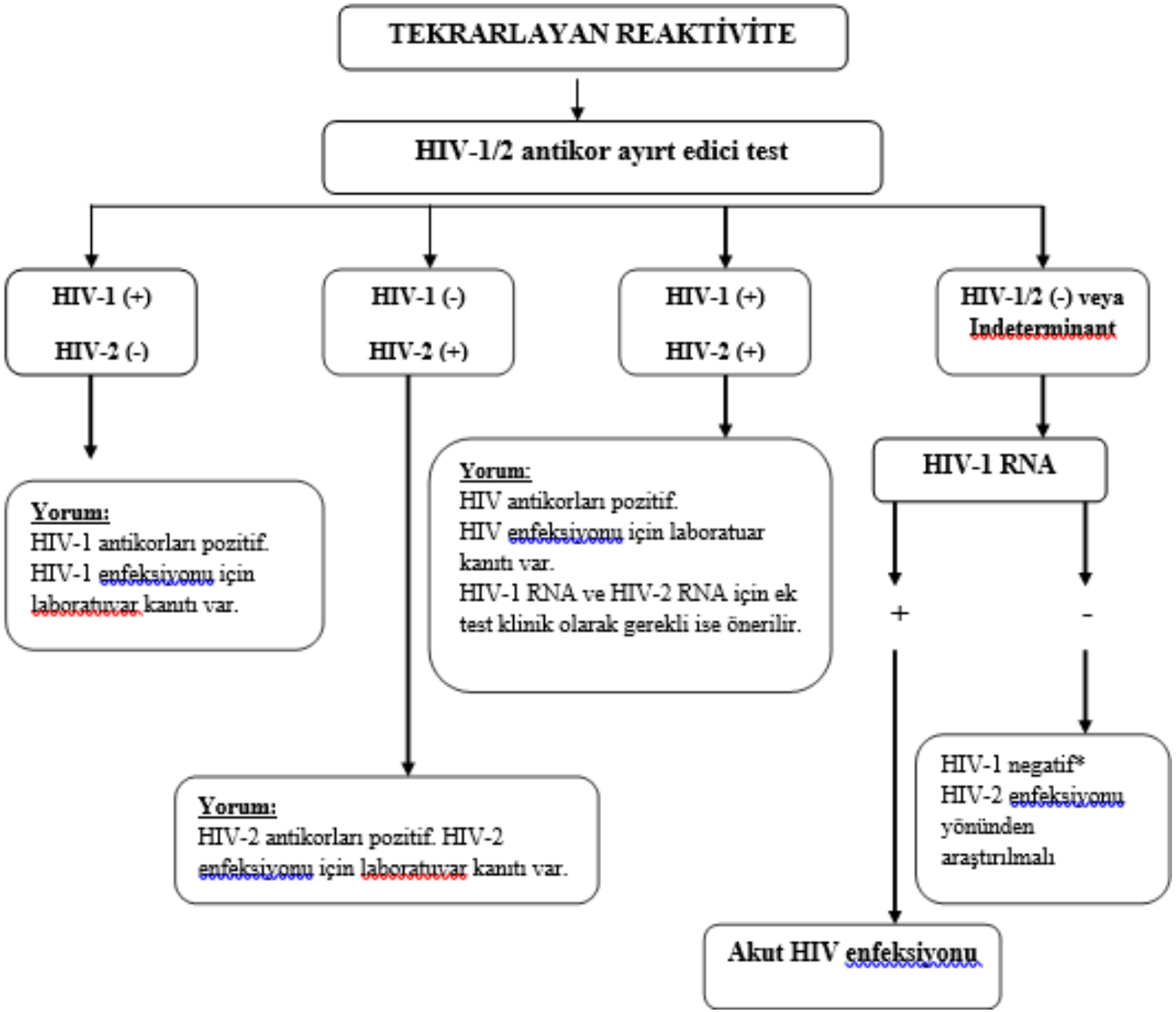
HIV/AIDS TANI REHBERİ-2018

ANKARA 2018

Erişkinlerde ve 18 aydan büyük çocuklarda HIV tarama algoritması



18 aydan büyük çocuk ve erişkinlerde önerilen doğrulama testi tanı algoritması



Yenidoğanda ve 18 Aylıktan Küçükler İçin Önerilen Algoritma

Anne gebeliği sırasında ***DOĞRU*** antiretroviral tedavi almış ve viral baskılanma sağlanmış ise:

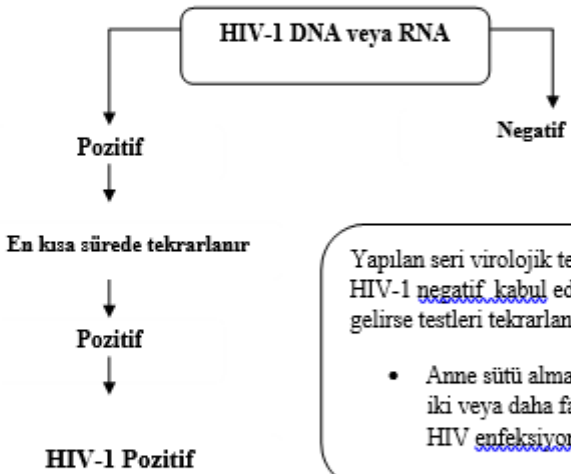
HIV enfeksiyonu riski **DÜŞÜK**

1. Test: 14-21 gün arası
2. Test: 1-2 ay arası
3. Test: 4-6 ay arası

Anne gebeliği sırasında doğru antiretroviral tedavi almamış veya viral baskılanma sağlanmamış ise:

1. Test: Doğumu* takiben hemen
2. Test: 14-21 gün arası
3. Test: 1-2 ay arası
4. Test: 4-6 ay arası

*Kordon kanı önerilmez



Yapılan seri virolojik test sonuçları NEGATİF ise bebek HIV-1 negatif kabul edilir. Süt çocuğu semptomatik hale gelirse testleri tekrarlanır

- Anne sütü almayan, altı aydan büyük bebeklerde iki veya daha fazla HIV antikor testi negatifliği ile HIV enfeksiyonu dışlanır*

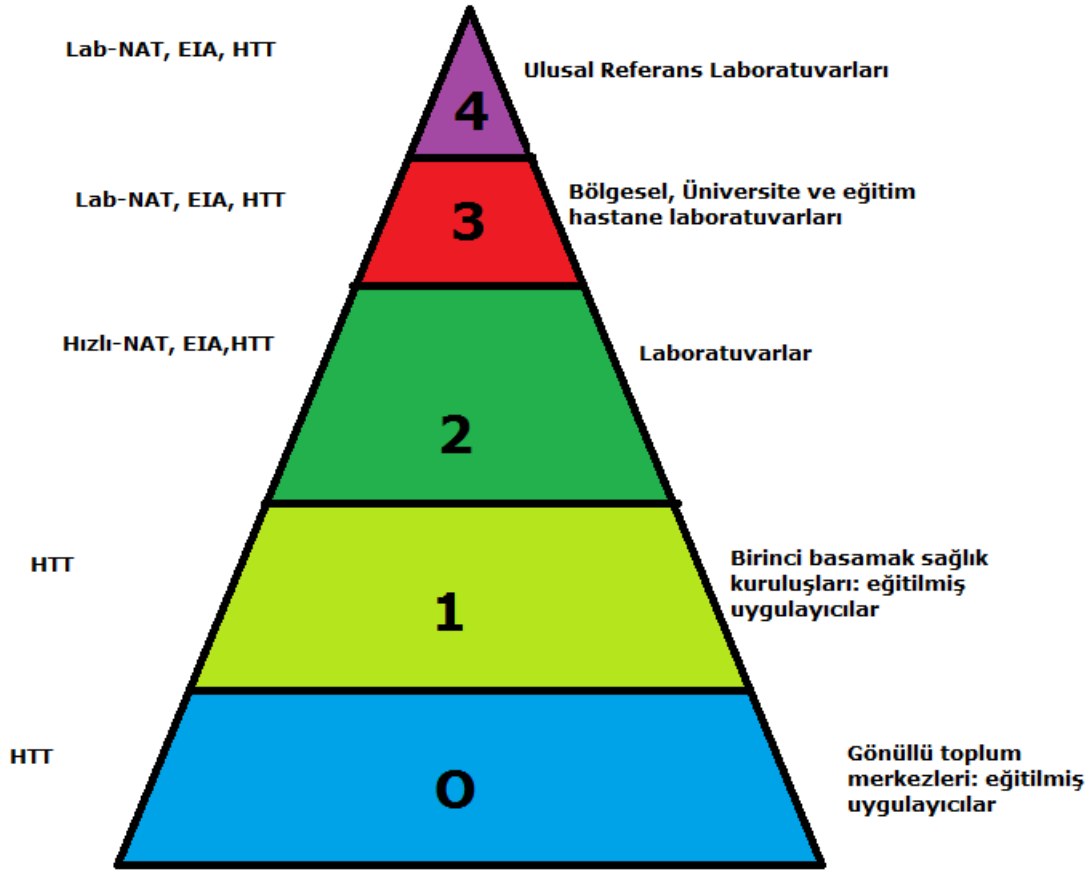
*Bebeğin anne sütü aldığı sürece risk altında olduğu göz önünde bulundurulmalıdır.

*ART'nin serolojik test sonuçlarını etkileyeceği unutulmamalıdır. Profilaksi tamamlandıktan 2-4 hafta sonra serolojik testler tekrarlanmalıdır.

HIV Test Sonucu Raporu Açıklamaları

Uygulanan test	Sonuç	Yorumlama	Bildirim
1. HIV-1/2 Ag/Ab ELISA	1. Nonreaktif	HIV-1 antijen HIV-1/2 antikorları açısından negatif. HIV enfeksiyonuna ait laboratuvar bulgusu yok. Eğer akut HIV enfeksiyonu şüphesi varsa HIV-1 RNA önerilir.	Negatif
1.HIV-1/2 Ag/Ab ELISA **2. HIV-1/2 ayırt edici test**	1. Reaktif 2. HIV-1 reaktif, HIV-2 nonreaktif	HIV-1 antikorları pozitif. HIV-1 enfeksiyonu için laboratuvar bulgusu var.	1. ve 2. test sonuçları rapor edilir
1. HIV-1/2 Ag/Ab ELISA **2. HIV-1/2 ayırt edici test**	1. Reaktif 2. HIV-1 nonreaktif ,HIV-2 reaktif	HIV-2 antikorları pozitif. HIV-2 enfeksiyonu için laboratuvar bulgusu var.	1. ve 2. test sonuçları rapor edilir
1. HIV-1/2 Ag/Ab ELISA **2. HIV-1/2 ayırt edici test** **3. HIV-1 RNA**	1. Reaktif 2. Nonreaktif veya indeterminant 3. RNA saptandı	HIV-1 pozitif. Akut HIV-1 enfeksiyonu için laboratuar bulgusu var	1, 2 ve 3. test sonuçları rapor edilir
1. HIV-1/2 Ag/Ab ELISA **2. HIV-1/2 ayırt edici test**	1. Reaktif 2. HIV-1 ve HIV-2 reaktif	HIV antikorları açısından pozitif. HIV enfeksiyonu için laboratuvar bulgusu var. HIV-1 ve HIV-2 RNA için ek test klinik olarak gerekli ise önerilir.	1. ve 2. test sonuçları rapor edilir
1. HIV-1/2 Ag/Ab ELISA **2. HIV-1/2 ayırt edici test**	1. Reaktif 2. Nonreaktif veya indeterminant	HIV-1 antikorları konfirme edilmemiştir. HIV-1 RNA testi uygulanmamıştır. Örneğin test süreci tamamlanmamıştır. HIV antikorları açısından takibi ve HIV-1 RNA testinin en kısa sürede tamamlanması gerekir.	1. ve 2. test sonuçları rapor edilir.

Desantralizasyon



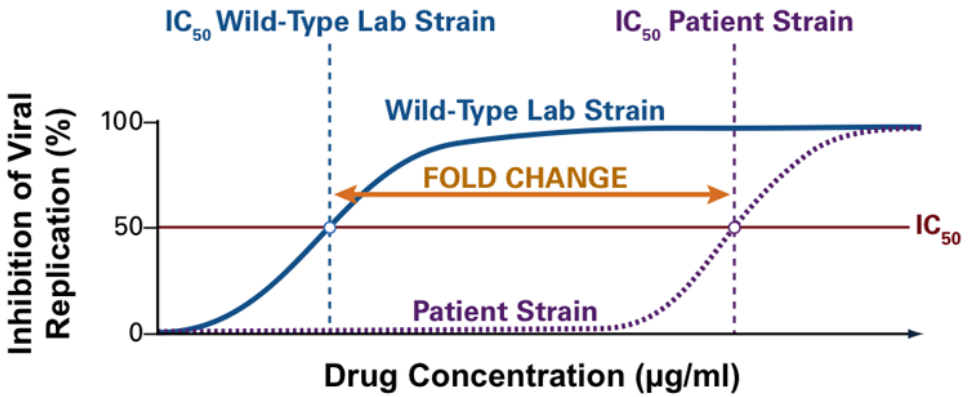
Doğrulama yapılmadan istekte bulunan hekime reaktif sonucun bildirilebileceği durumlar:

- Doğum eylemi başlamış ve antiretroviral tedaviden yarar görebilecek gebeler
- Mesleki kazalardan sonra yapılan incelemeler
- HIV ile ilişkili olabilecek klinik belirtileri/bulguları, HIV'i tanımlayıcı hastalıkları olan kişilerin acil tedavisi
- Doğrulama sonuçları henüz alınmadan taburcu edilecek hastalar
- Takibi yapılamayacak kişiler

Direnç: Virusun mutasyon yeteneği ile birlikte antiretroviral ilaç varlığında virusun replike olabilmesi

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

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

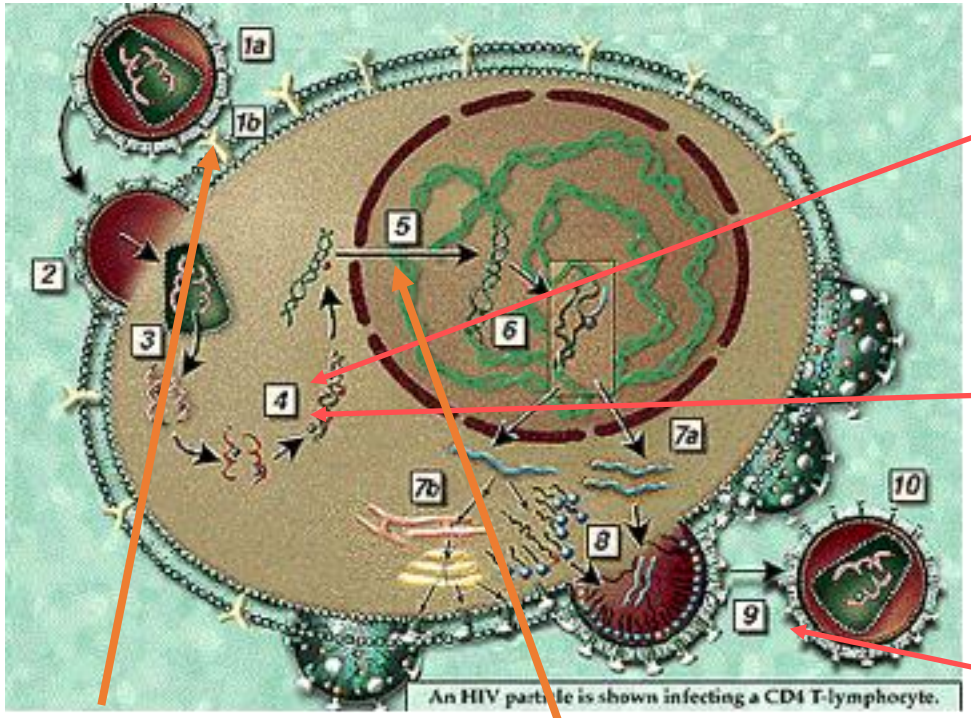


Direnç gelişimi viruslar arasında farklılık gösterir

- RNA'lı viruslarda daha hızlı
- Direnç mutasyonlarının evrim hızı değişken
- Bazen tek bir mutasyon yüksek düzeyde R kazandırabilir
- Bazı ilaç sınıflarına karşı R mutasyonların aşamalı bir biçimde birikimi sonucu gelişir
- R ile ilişkili bazı mutasyonlar virusun *fittness* ini düşürür → ilave mutasyonlar *fittness* i restore edebilir

David H. Spach, MD. Features of Genotypic and Phenotypic Resistance Assays. HIV Web Study (www.hivwebstudy.org)

HIV'in Yaşam Döngüsü ve Anti-HIV İlaçların Hedefleri



İlaç sınıfları:

Nükleosid Revers Transkriptaz İnhibitörleri (NRTI)
AZT, ddI, d4T, 3TC, FTC, ABC,TDF, (TAF)

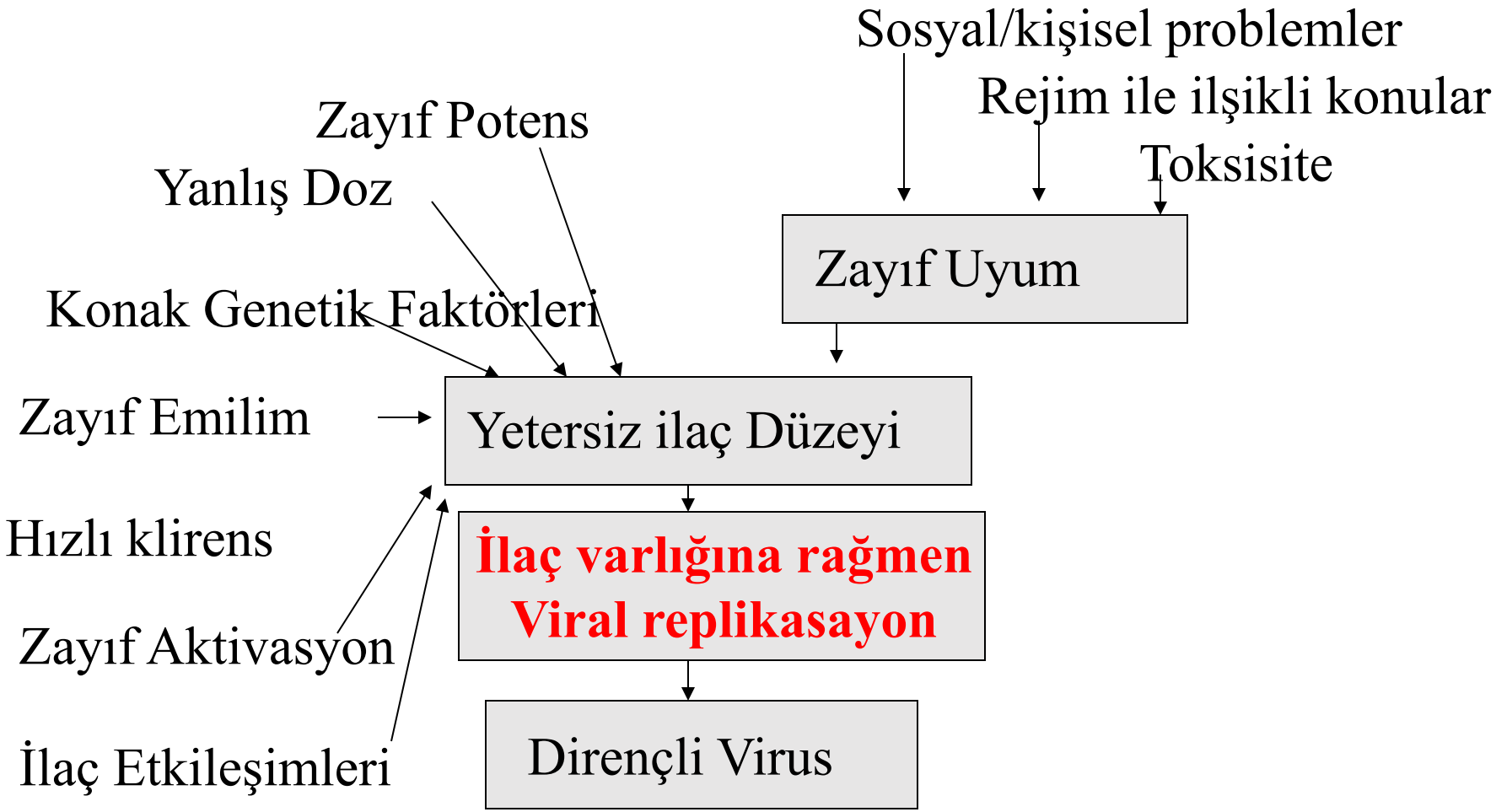
Non-Nükleosid Revers Transkriptaz İnhibitörleri (NNRTI)
EFV, NVP, ETR, RPV

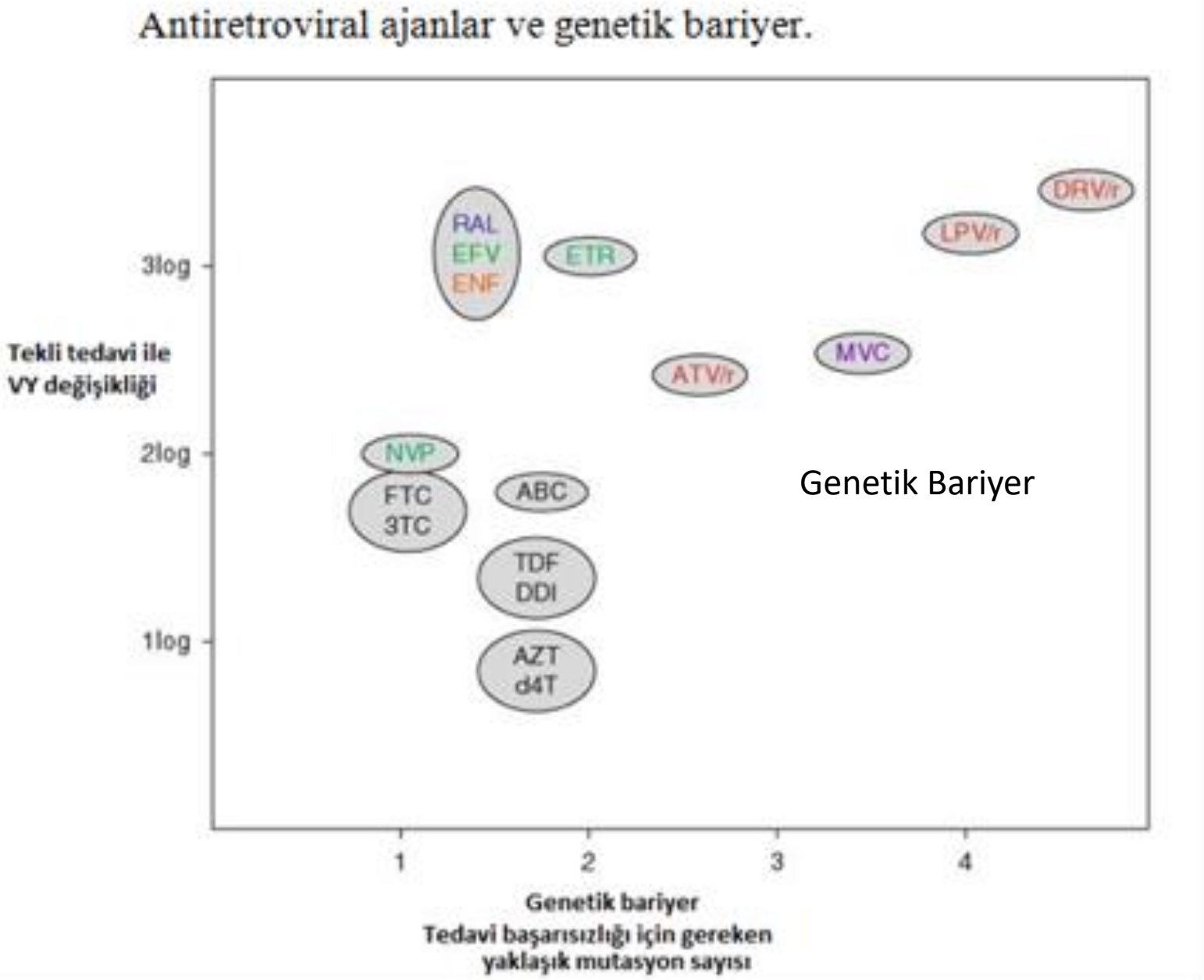
Proteaz İnhibitörleri (PI)
SQV, IDV, RTV, NFV, fAPV, LPV, ATV, TPV, DRV

Giriş İnhibitörleri (EI)
T20, Maraviroc/MVC, Cinicriviroc/CNC) (AMD3100 AMD 070)

İntegraz İnhibitörleri(INI)
RAL, EVG, DTG

Direnç Nasıl Gelişir?





Genetik Bariyer

Bir virus bir AV tarafından inhibe edilirken bir yandan da direnç mutasyonları gelişen suşlar seçilir. Bu olayın ne kolaylıkla gerçekleşeceği, gelişecek olan olası mutasyonların virusun *fittness* ini azaltmaksızın direnç kazandırabilmesine bağlıdır. Bu olgu «**genetik bariyer**» olarak bilinmektedir.

ARV direnç testleri

- **Genotipik testler:**

- RT-PCR sonrası: - Dizi analizi
  - Revers hibridizasyon
  - OLA (Oligonükleotid ligation assay)

- **Fenotipik testler:** Ticari

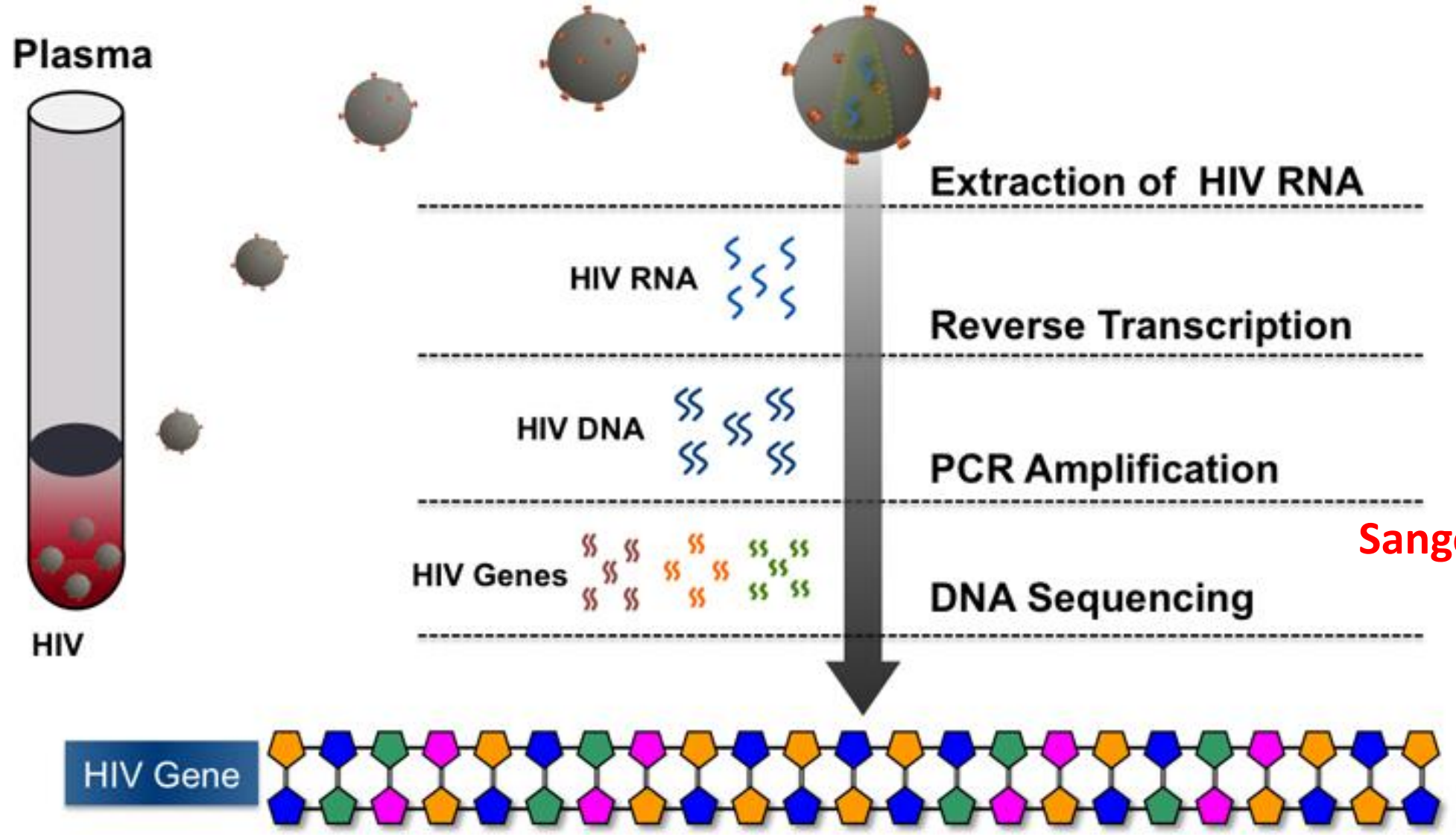
Direnç Saptamada Yeni Yaklaşımlar:

- Droplet (digital) PCR
  - Tek bir moleüklün çoğaltılması ve saptanması olanaklı,
  - Mutant kökenlerin daha hasas saptanmasını sağlayabilecek

- Ultra-Deep Sequencing
  - Klasik dizilemede popülasyonu oluşturan kökenlerin oran %20'nin üzerinde ise saptanabiliyor.
  - Ultra-deep dizileme ile %1 gibi minör varyantları bile saptamak mümkün

Direnç Testleri Uygulama Zamanı

- İlk tanı konduğunda (tedavi kararından bağımsız olarak)
- Tedavi başarısızlıklarında: İlaç altında iken ya da tercihen ilaç kesildikten sonra ilk 4 hafta içersinde
- Tedaviye başlarken
- Viral yük > 500 kopya/ml olmalı



Sanger Sequencing
YND

Örnek:
PLAZMA

- APOBEC3

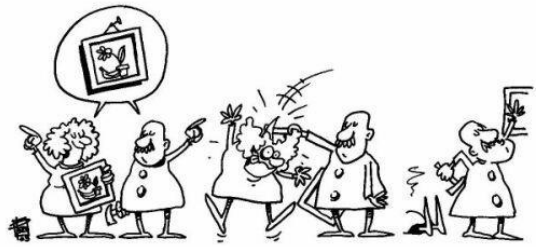
David H. Spach, MD. Features of Genotypic and Phenotypic Resistance Assays. HIV Web Study (www.hivwebstudy.org)

Direnç Analizinde İzlenecek Ana Yollar

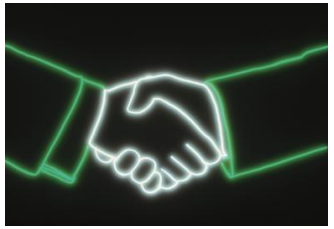
Kurala Dayalı Sistemler

	L	G	K	L		V	L	E		M
Atazanavir +/- ritonavir[5]	10	16	20	24		32	33	34		36
	I	E	R	I		I	I	Q		I
	F		M				F			L
	V		I				V			V
	C		T							
			V							

Uzman Grup



Tartışma

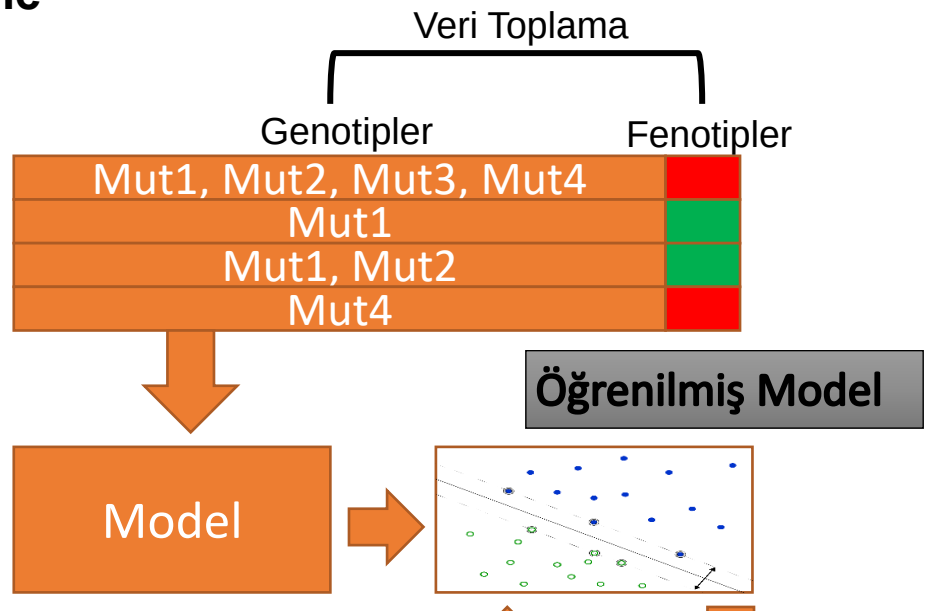


Uzlaşı

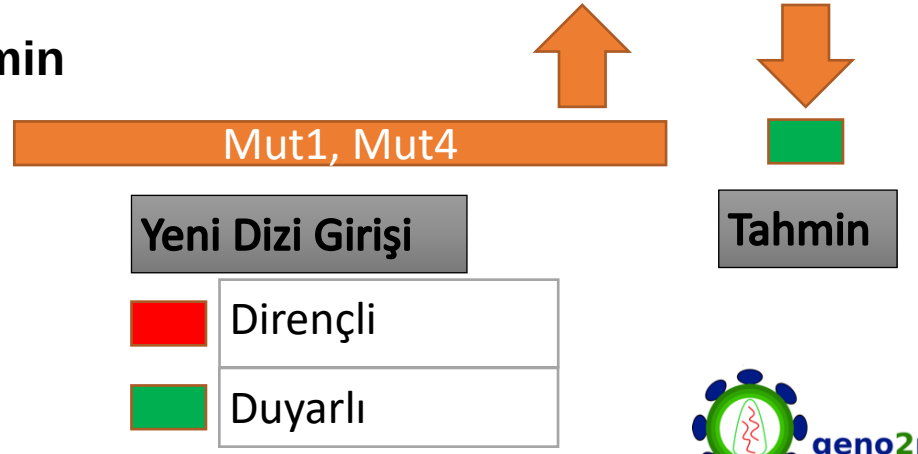
STANFORD UNIVERSITY
HIV DRUG RESISTANCE DATABASE
A curated public database designed to represent, store, and analyze the divergent forms of data underlying HIV drug resistance.

Yapay Zekaya Dayalı – Makine Öğrenmesine Dayalı(Zahiri)

1. Öğrenme



2. Tahmin



Matthias Döring
Max Planck Institute for Informatics,**ESCV Workshop "Techniques in Clinical Virology"**
December 4, 2015

geno2pheno [resistance]

HIV-Db mutasyon sınıflamaları

PR mutasyonları:

- Majör DRM
- Aksesuar DRM
- Diğer

RT Mutasyonları:

- NRTI DRM
- NNRTI DRM
- Diğer

IN mutasyonları:

- Majör DRM
- Aksesuar DRM
- Diğer

- None: Yukardaki sınıflamalara girmeyenler

Primer ya da Majör Mutasyonlar: Tek başlarına olsalar bile duyarlılığı doğrudan azaltırlar, M184 mutasyonları gibi

Aksesuar (Secondary, minör) Muutasyonlar: Virusun fitness'ını düzeltir. Duyarlılığı azaltır.

İmza (Signature) Mutasyonları: Özel ilaç için ilişkili mutasyonlar **(M184V ➘ Lamivudin, Emtircitabin, I50L➘atazanavir Direnci)**

Mutasyon Skorları

- (1) **0–9: Duyarlı**
- (2) **10–14: Olası düşük düzey direnç** → Büyük olasılıkla tam duyarlı, fakat değerlendirilen dizide daha önce ARV ile karşılaşmış olduğuna işaret eden mutasyonlar söz konusu
- (3) **15-30: Düşük düzeyde direnç**: Suboptimal virolojik yanıt
- (4) **30-59 (ortya düzeyde direnç):** İlaç illa kullanılmak isteniyorsa, ilacın genetik bariyerinin yüksek olması ya da fazla ilaç seçeneğinin bulunmaması gerekir.
- (5) **60 ve üzeri**: Yüksek düzeyde direnç.

Skorlama;

- Tek tek saptanan mutasyonların etkisi ve bunların kombine etkileri göz önünde bulundurulur.

L74I/V skoru 30,

M184I/V'nin skoru 15

L74I/V + M184I/V skoru 15

30 (L74I/V) + 15 (M184I/V) + 15 (L74I/V + M184/V) = 60

Değerlendirme

Mutation Scoring

PR	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	NFV	SQV/r	TPV/r
T74S	0	0	0	0	0	15	0	0
Total:	0	0	0	0	0	15	0	0

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF	EFV	ETR	NVP	RPV
M184V	60	15	-10	-10	10	60	-10	-	-	-	-
Total:	60	15	-10	-10	10	60	-10	0	0	0	0

0 -9 DUYARLI,
10 -14 OLASI DÜŞÜK DÜZEY DİRENÇ,
15-29 DÜŞÜK DÜZEY DİRENÇ,
30-59 ORTA DÜZEYDE DİRENÇ
>60 YÜKSEK DÜZEYDE DİRENÇ

MARVEL on RT mutations at position 184

HIVdb Algorithm: Comments & Scores

- M184V/I cause high-level resistance to 3TC and FTC and low-level resistance to ddI and ABC. However, M184V/I are not contraindications to continued treatment with 3TC or FTC because they increase susceptibility to AZT, TDF and d4T and are associated with clinically significant reductions in HIV-1 replication. In combination with K101E or E138K, M184I synergistically reduces RPV susceptibility.

Mutation	3TC	FTC	ABC	AZT	D4T	DDI	TDF
M184I	60	60	15	-10	-10	10	-10
M184V	60	60	15	-10	-10	10	-10

Footnote: Mutation scores on the left are derived from published literature linking mutations and ARVs (the complete details can be found in the HIVdb Release Notes).

Mutation Scoring

PR	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	NFV	SQV/r	TPV/r
T74S	0	0	0	0	0	15	0	0
Total:	0	0	0	0	0	15	0	0

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF	EFV	ETR	NVP	RPV
M184V	60	15	-10	-10	10	60	-10	-	-	-	-
Total:	60	15	-10	-10	10	60	-10	0	0	0	0

Mutation Patterns	Number of Sequences	AZT fold$_n$	TDF fold$_n$	ABC fold$_n$	3TC fold$_n$
184V	7022	0.5_{124}	0.5_{63}	3.1_{125}	200_{175}
67N,70R,184V	1143	3.7_{32}	1.2_{26}	4.5_{31}	200_{50}
41L,184V,210W,215Y	821	18_{51}	1.6_{38}	6.5_{48}	200_{69}
41L,184V,215Y	798	6.0_{41}	1.1_{24}	5.1_{41}	200_{55}
41L,67N,184V,210W,215Y	795	30_{53}	1.6_{41}	6.5_{46}	200_{72}
70R,184V	697	0.8_{14}	0.7_{7}	3.4_{15}	200_{21}
67N,70R,184V,215F	380	7.7_{7}	1.0_{4}	5.5_{7}	200_{8}
65R,184V	376	0.4_{16}	1.2_{16}	8.4_{16}	200_{27}
74V,184V	371	0.3_{9}	0.4_{7}	5.2_{9}	200_{13}
41L,67N,69D,184V,210W,215Y	359	43_{28}	1.8_{19}	7.8_{26}	200_{38}

Footnote: Mutation patterns were defined by the presence or absence of major NRTI drug resistance mutations ; Sequences containing a mixture at a major drug resistance positions were excluded; For the cutoffs defined by PhenoSense, open the sample report form provided on this page; The full list of all mutation patterns are also available here.

Fold Resistance

AZT	3	10
D4T	1.5	2
TDF	1.5	4
ABC	3	6
DDI	1.5	2
3TC	3	20

THE WORLD HEALTH ORGANIZATION 2009 LIST OF MUTATIONS

For Surveillance of Transmitted Drug Resistant HIV Strains

NRTI	
M41	L
K65	R
D67	N, G, E
T69	D, Ins
K70	R, E
L74	V, I
V75	M, T, A, S
F77	L
Y115	F
F116	Y
Q151	M
M184	V, I
L210	W
T215	Y, F, I, S, C, D, V, E
K219	Q, E, N, R

NNRTI	
L100	I
K101	E, P
K103	N, S
V106	M, A
V179	F
Y181	C, I, V
Y188	L, H, C
G190	A, S, E
P225	H
M230	L

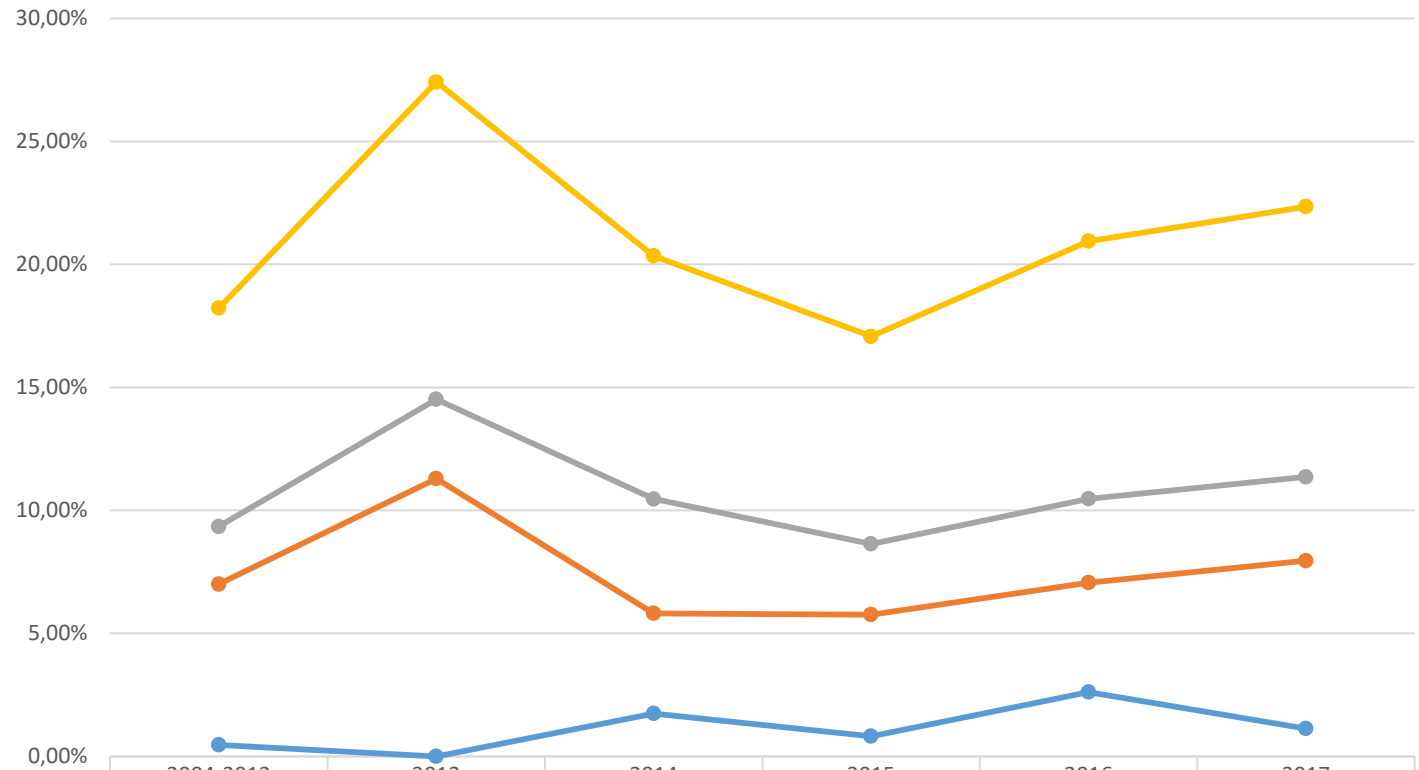
PI	
L23	I
L24	I
D30	N
V32	I
M46	I, L
I47	V, A
G48	V, M
I50	V, L
F53	L, Y
I54	V, L, M, A, T, S
G73	S, T, C, A
L76	V
V82	A, T, F, S, C, M, L
N83	D
I84	V, A, C
I85	V
N88	D, S
L90	M

Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance: 2004-2017

Yıl	n (toplam 1580)	PI	NRTI	NNRTI	Herhangi Bir
2004-2012	214	1	14	5	19
		0.47%	6.54%	2.34%	8.88%
2013	62	0	7	2	8
		0.00%	11.29%	3.23%	12.90%
2014	172	3	7	8	17
		1.74%	4.07%	4.65%	9.88%
2015	486	4	24	14	41
		0.82%	4.94%	2.88%	8.44%
2016	382	10	17	13	40
		2.62%	4.45%	3.40%	10.47%
2017	264	3	18	9	29
		1.14%	6.82%	3.41%	10.98%
Toplam	1580	21	87	51	154
		1.33%	5.51%	3.23%	9.75%

Based on Bennett DE et all. Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance: 2009 Update.DOI: 10.1371/journal.pone.0004724

Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance: 2004-2017 (total 1580)



	2004-2012	2013	2014	2015	2016	2017
Herhangi Bir	8,88%	12,90%	9,88%	8,44%	10,47%	10,98%
NNRTI	2,34%	3,23%	4,65%	2,88%	3,40%	3,41%
NRTI	6,54%	11,29%	4,07%	4,94%	4,45%	6,82%
PI	0,47%	0,00%	1,74%	0,82%	2,62%	1,14%

Based on Bennett DE et all. Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance: 2009 Update.DOI: 10.1371/journal.pone.0004724

Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance: 2016-2017

2016

M46	I50	G73	V82	N83	M41	D67	M184	T215	K219	K101	K103	V106	G190
PI					NRTI					NNRTI			
I, L	V, L	S, T, C, A	A, T, F, S, C, M, L	D	L	N, G, E	V, I	Y, F, I, S, C, D, V, E	Q, E, N, R	E, P	N, S	M, A	A, S, E
2	4	1	2	1	10	1	1	13	1	5	5	1	3
0.524%	1.047%	0.262%	0.524%	0.262%	2.618%	0.262%	0.262%	3.403%	0.262%	1.309%	1.309%	0.262%	0.785%

TAM1: M41L, L210W ve T215Y

TAM2: D67N, K70R, T215F ve K219Q/E

2017

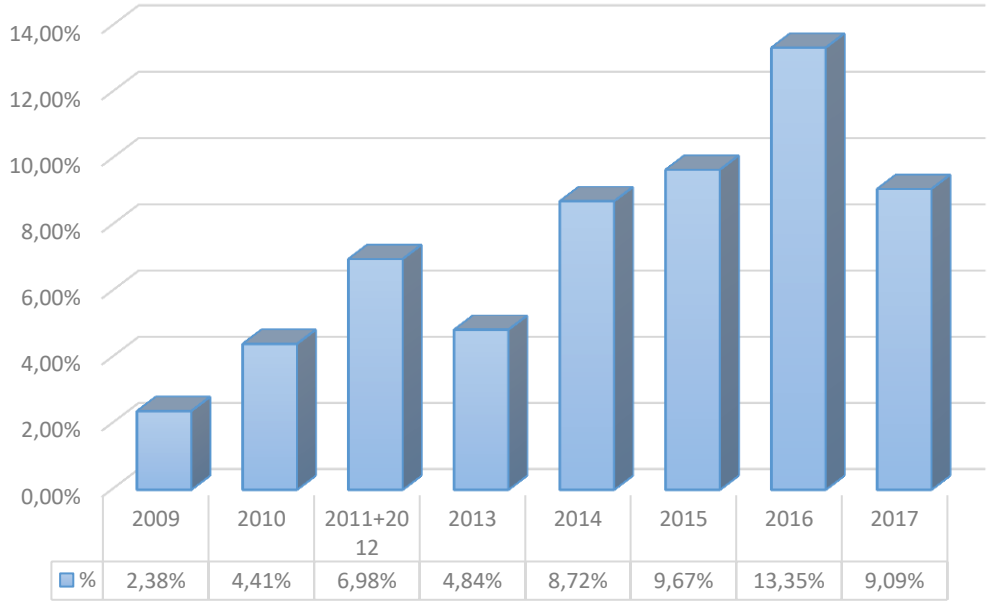
M46	I54	M41	D67	K70	M184	T215	K103	G190	P225
PI		NRTI					NNRTI		
I, L	V, L, M, A, T, S	L	N, G, E	R, E	V, I	Y, F, I, S, C, D, V, E	N, S	A, S, E	H
2	1	10	2	1	3	14	7	1	1
0.758%	0.379%	3.788%	0.758%	0.379%	1.136%	5.303%	2.652%	0.379%	0.379%

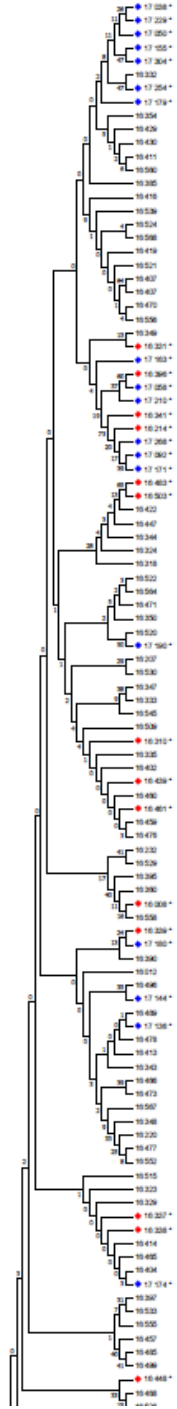
Ülkemizde Genel Durum

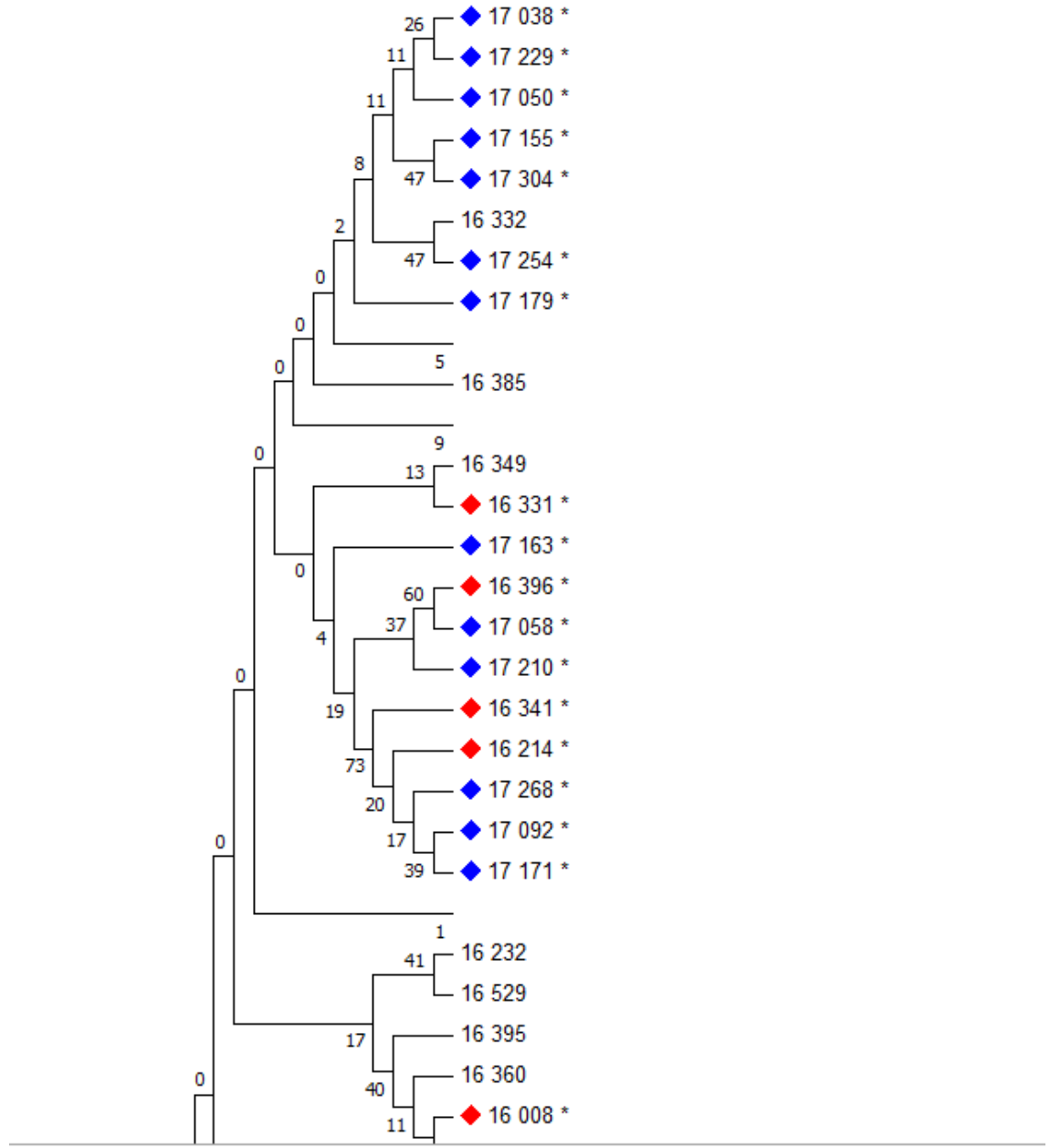
	Korten ve ark.	Sayan ve ark.	Kuskucu ve ark.		Sertöz ve ark.
n	273	1306	590		483
Dönem	2011	2010-2015	2004-2010	2011-2015	2008-2016
NRTI	6,90%	8,10%	5,92%	5,23%	3,0%
NNRTI	0,00%	3,30%	3,55%	4,04%	10,3% (5,0% E138A)
PI	1,70%	2,30%	0,60%	1,60%	1,8 %
Any	8,60%	10,10%	10,00%		15,0%

E138 Mutasyonları

Yıl	n	E138AG	%
2009	42	1	2.38%
2010	68	3	4.41%
2011+2012	43	3	6.98%
2013	62	3	4.84%
2014	172	15	8.72%
2015	486	47	9.67%
2016	382	51	13.35%
2017	264	24	9.09%






17 038 *
17 229 *
17 050 *
17 155 *
17 304 *
16 332
17 254 *
17 179 *
16 385
16 349
16 331 *
17 163 *
16 396 *
17 058 *
17 210 *
16 341 *
16 214 *
17 268 *
17 092 *
17 171 *
16 232
16 529
16 395
16 360
16 008 *

Secure | https://hivdb.stanford.edu/page/surveillance-map/

Stanford University
HIV DRUG RESISTANCE DATABASE
A curated public database to represent, store and analyze HIV drug resistance data.

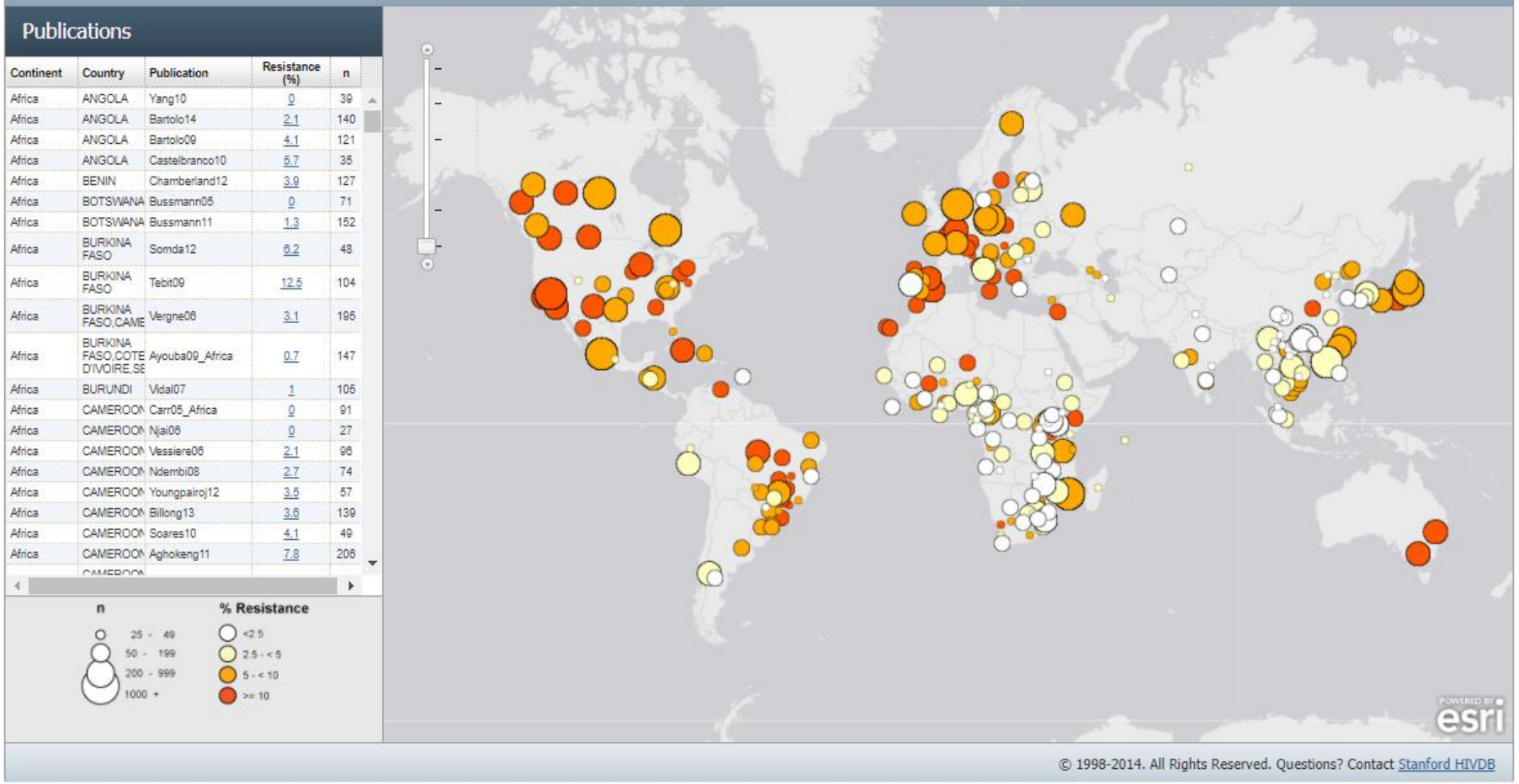
HOME GENOTYPE-RX GENOTYPE-PHENO GENOTYPE-CLINICAL HIVdb PROGRAM ABOUT HIVdb

HIV-1 Drug Resistance in ARV-naive Populations

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

Publications

Continent	Country	Publication	Resistance (%)	n
Africa	ANGOLA	Yang10	0	39
Africa	ANGOLA	Bartolo14	2.1	140
Africa	ANGOLA	Bartolo09	4.1	121
Africa	ANGOLA	Castelbranco10	5.7	35
Africa	BENIN	Chamberland12	3.9	127
Africa	BOTSWANA	Bussmann05	0	71
Africa	BOTSWANA	Bussmann11	1.3	152
Africa	BURKINA FASO	Somda12	6.2	48
Africa	BURKINA FASO	Tebit09	12.5	104
Africa	BURKINA FASO,CAME	Vergne06	3.1	195
Africa	BURKINA FASO,COTE D'IVOIRE,SE	Ayouba09_Africa	0.7	147
Africa	BURUNDI	Vidal07	1	105
Africa	CAMEROON	Carr05_Africa	0	91
Africa	CAMEROON	Njai06	0	27
Africa	CAMEROON	Vessiere06	2.1	96
Africa	CAMEROON	Ndembi08	2.7	74
Africa	CAMEROON	Youngpairoj12	3.5	57
Africa	CAMEROON	Billong13	3.6	139
Africa	CAMEROON	Soares10	4.1	49
Africa	CAMEROON	Aghokeng11	7.8	206



Secure | https://hivdb.stanford.edu/page/surveillance-map/

Stanford University
HIV DRUG RESISTANCE DATABASE
A curated public database to represent, store and analyze HIV drug resistance data.

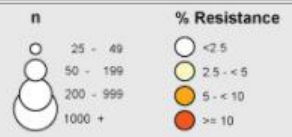
HOME | GENOTYPE-RX | GENOTYPE-PHENO | GENOTYPE-CLINICAL | HIVdb PROGRAM | ABOUT HIVdb

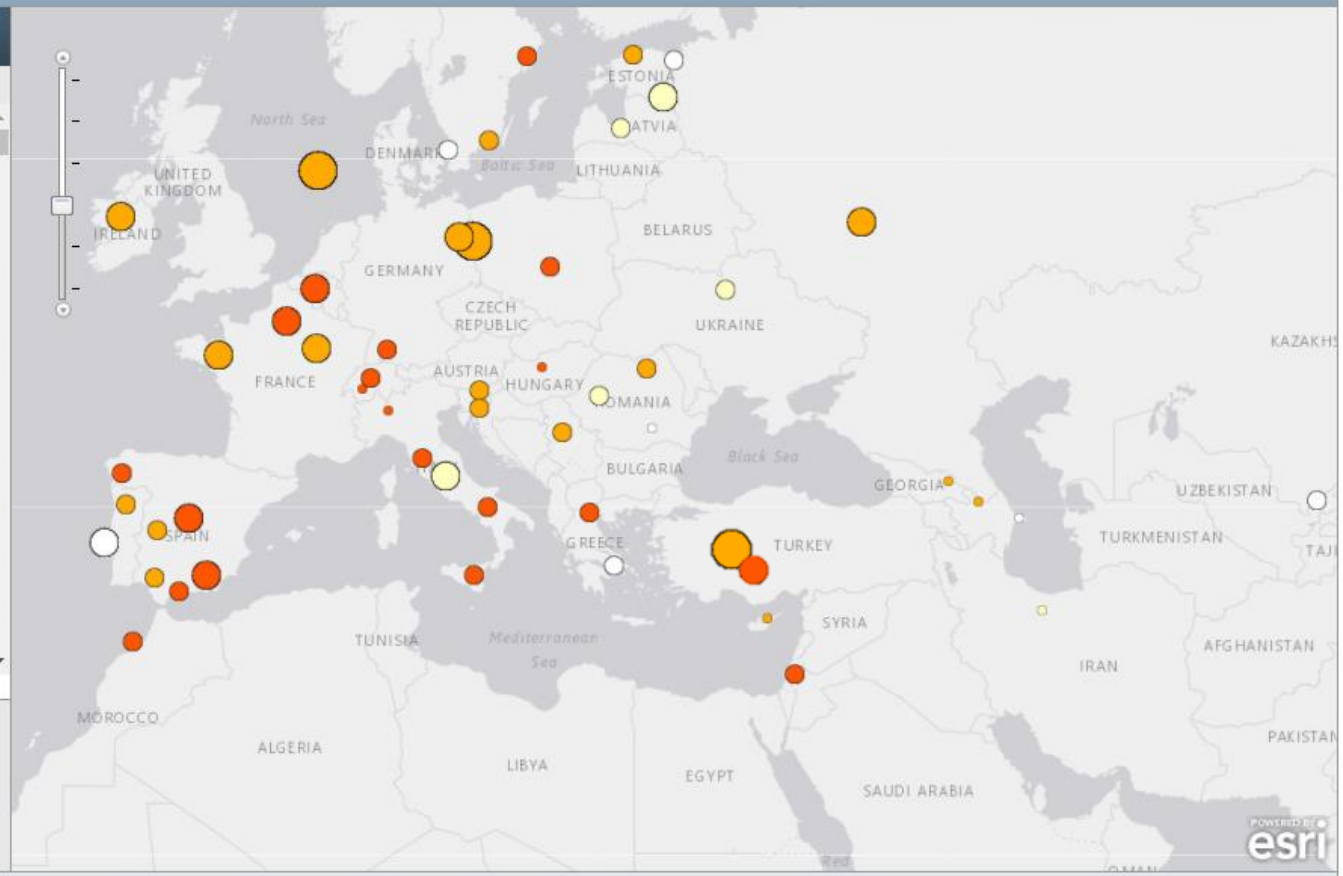
HIV-1 Drug Resistance in ARV-naive Populations

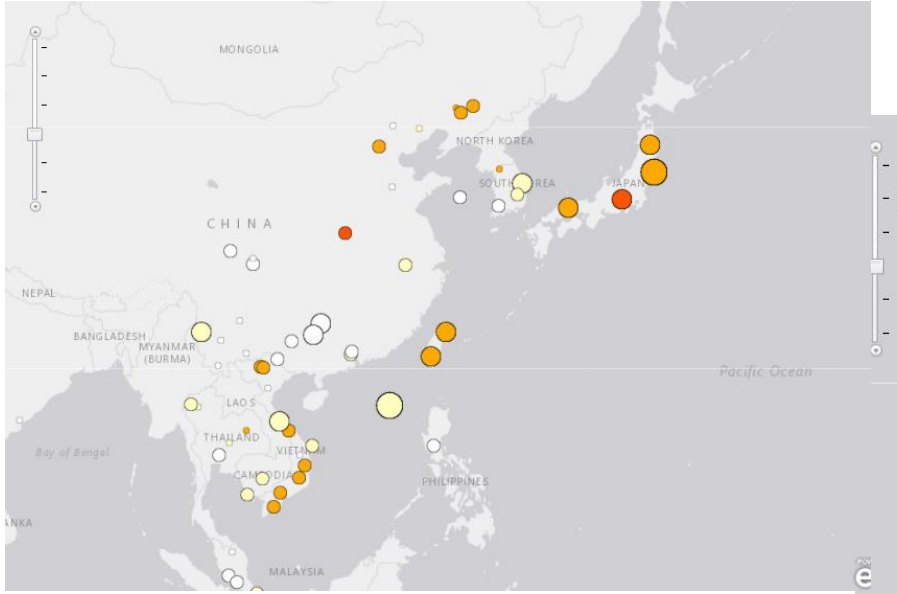
Compendium of published virus sequences from 50,869 persons, 287 studies according to region, year and subtype

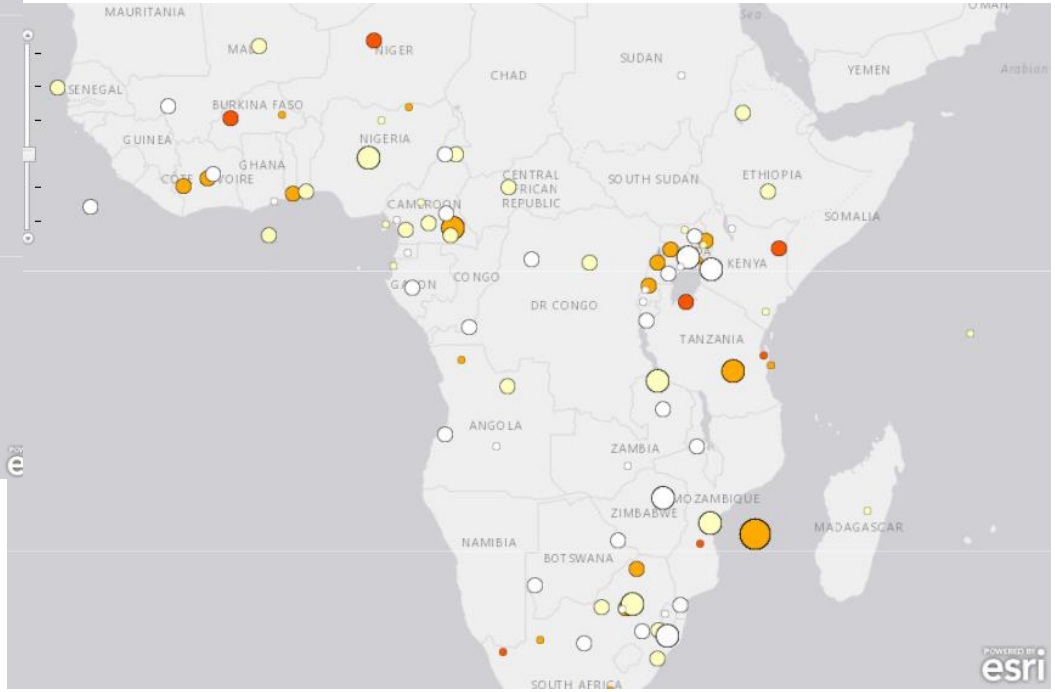
Publications

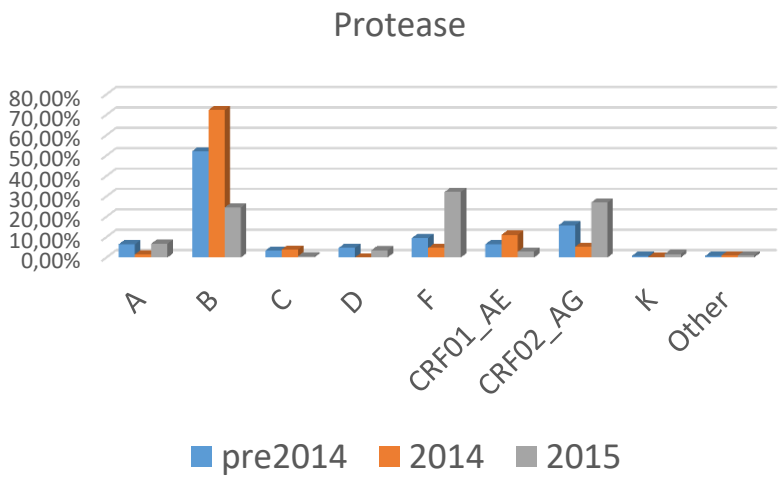
Continent	Country	Publication	Resistance (%)	n
Africa	ANGOLA	Yang10	0	39
Africa	ANGOLA	Bartolo14	2.1	140
Africa	ANGOLA	Bartolo09	4.1	121
Africa	ANGOLA	Castelbranco10	5.7	35
Africa	BENIN	Chamberland12	3.9	127
Africa	BOTSWANA	Bussmann05	0	71
Africa	BOTSWANA	Bussmann11	1.3	152
Africa	BURKINA FASO	Somda12	6.2	48
Africa	BURKINA FASO	Tebit09	12.5	104
Africa	BURKINA FASO,CAME	Vergne08	3.1	195
Africa	BURKINA FASO,COTE D'IVOIRE,SE	Ayouba09_Africa	0.7	147
Africa	BURUNDI	Vidal07	1	105
Africa	CAMEROON	Carr05_Africa	0	91
Africa	CAMEROON	Njai06	0	27
Africa	CAMEROON	Vessiere06	2.1	96
Africa	CAMEROON	Ndembi08	2.7	74
Africa	CAMEROON	Youngpairoj12	3.5	57
Africa	CAMEROON	Billong13	3.6	139
Africa	CAMEROON	Soares10	4.1	49
Africa	CAMEROON	Aghokeng11	7.8	206

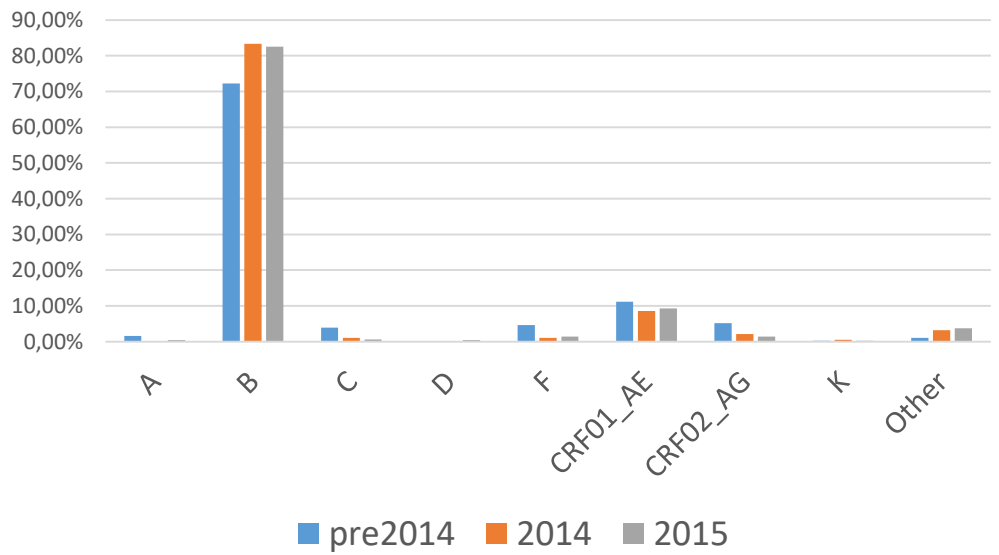





MONGOLIA
NORTH KOREA
SOUTH KOREA
JAPAN
CHINA
NEPAL
BANGLADESH
MYANMAR (BURMA)
LAOS
THAILAND
VIETNAM
CAMBODIA
PHILIPPINES
Pacific Ocean
Bay of Bengal
MALAYSIA


MAURITANIA
MALI
NIGER
CHAD
SUDAN
YEMEN
SENEGAL
BURKINA FASO
GUINEA
NIGERIA
GHANA
CÔTE D'IVOIRE
CENTRAL AFRICAN REPUBLIC
SOUTH SUDAN
ETHIOPIA
SOMALIA
CAMEROON
KENYA
CONGO
GABON
DR CONGO
TANZANIA
ANGOLA
ZAMBIA
MOZAMBIQUE
ZIMBABWE
NAMIBIA
BOTSWANA
MADAGASCAR
SOUTH AFRICA
esri


Protease
80,00%
70,00%
60,00%
50,00%
40,00%
30,00%
20,00%
10,00%
0,00%
A
B
C
D
F
CRF01_AE
CRF02_AG
K
Other
pre2014
2014
2015


90,00%
80,00%
70,00%
60,00%
50,00%
40,00%
30,00%
20,00%
10,00%
0,00%
A
B
C
D
F
CRF01_AE
CRF02_AG
K
Other
pre2014
2014
2015

90–90–90: Treatment for all

There are 36.7 million people living with HIV

But only 60% know they are HIV positive. The rest do not

Less than half of people living with HIV are on antiretroviral therapy

And only 38% have achieved undetectable levels of HIV

Teşekkürler…