Session 3 | Subtypes, Gender, and Ethnicity: Do They Impact HIV Care

HIV Subtypes - Virologic and Resistance Implications

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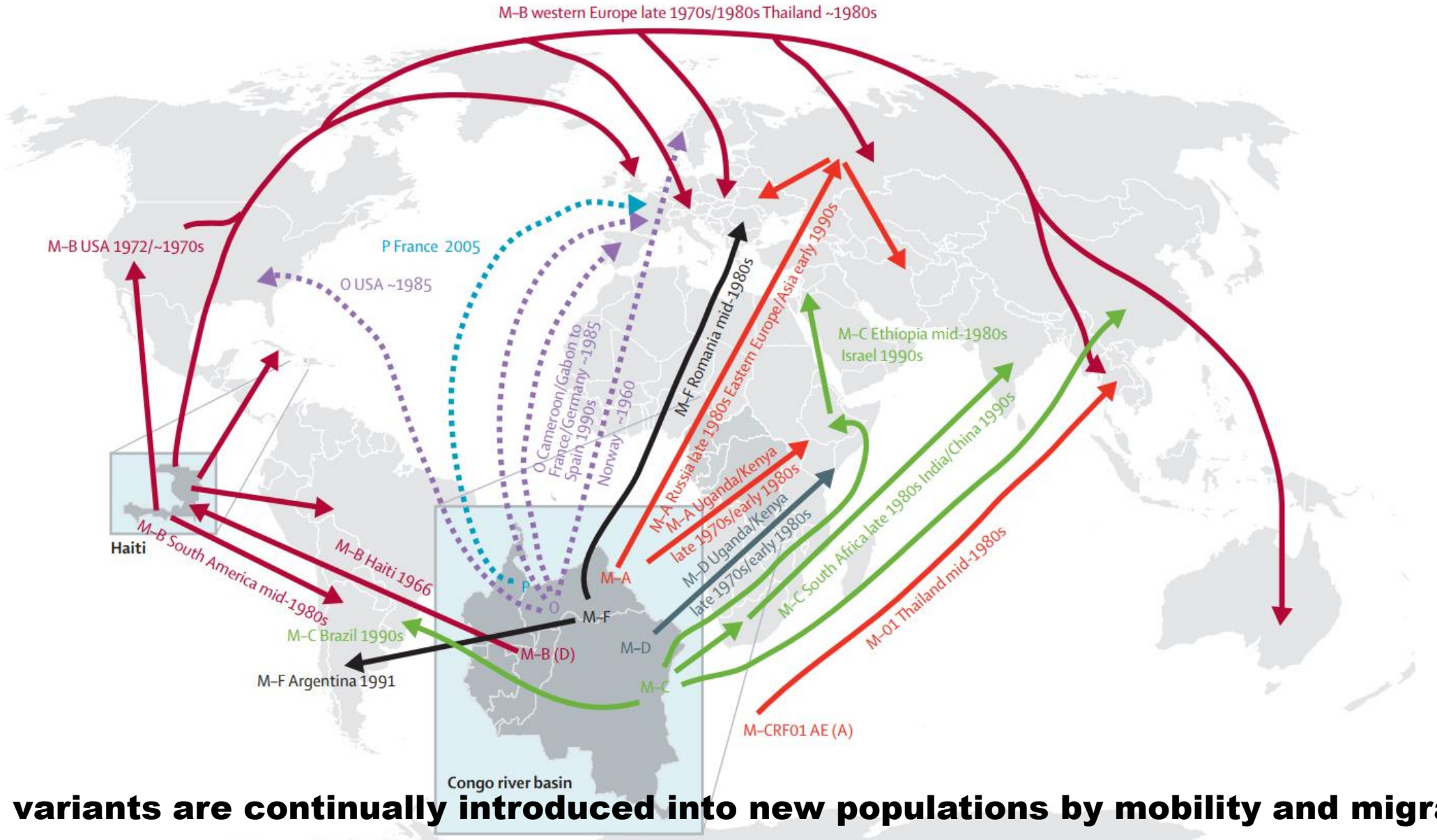
Disclosures

Opass Putcharoen, MD.

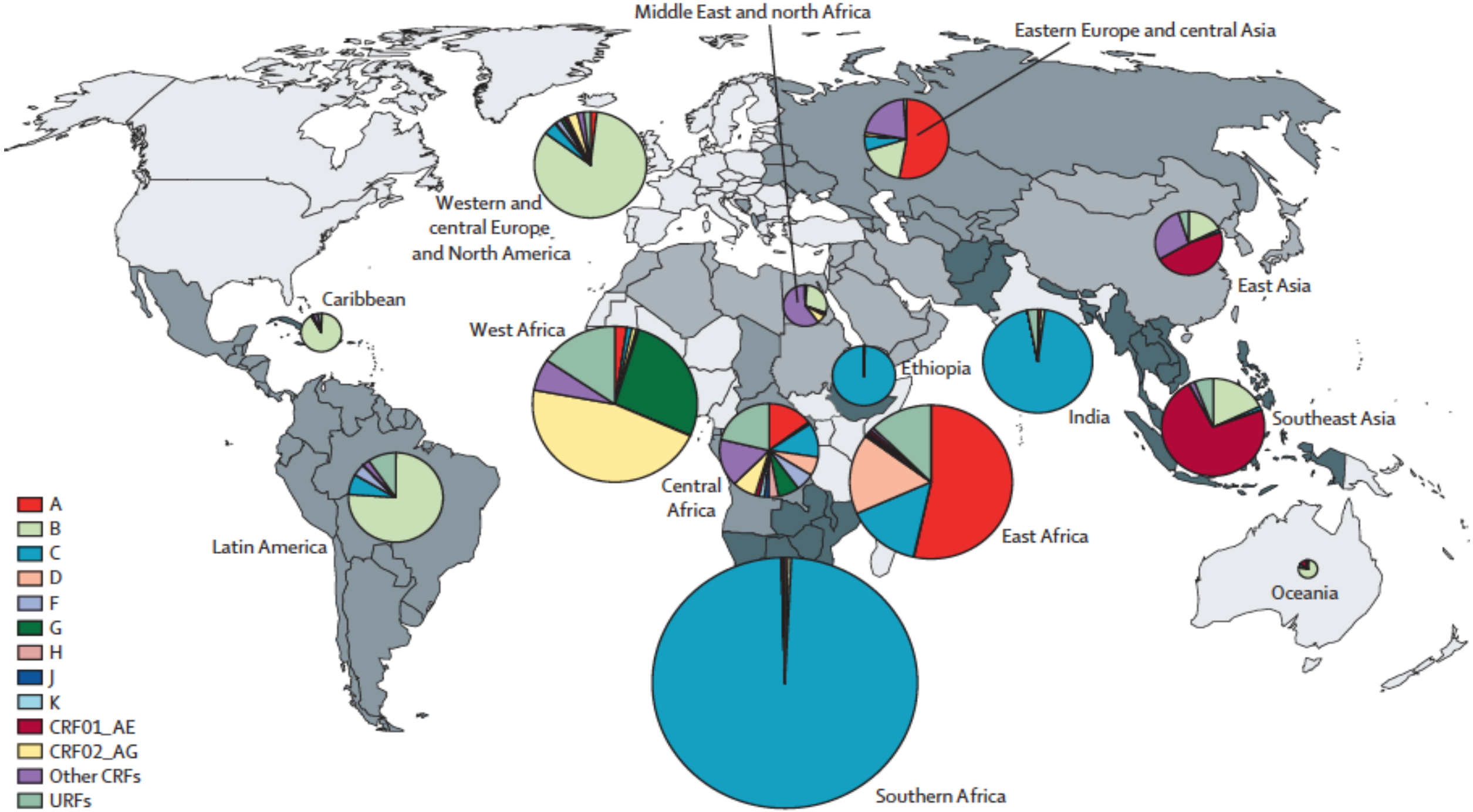
- Consulting fees from BMS
- Non-CME/CE services from Gilead Sciences, BMS, Merck, and Mylan Healthcare Siam Pharmaceutical and Mylan

Estimated timeline of global evolution and spread of HIV types, groups, and subtypes



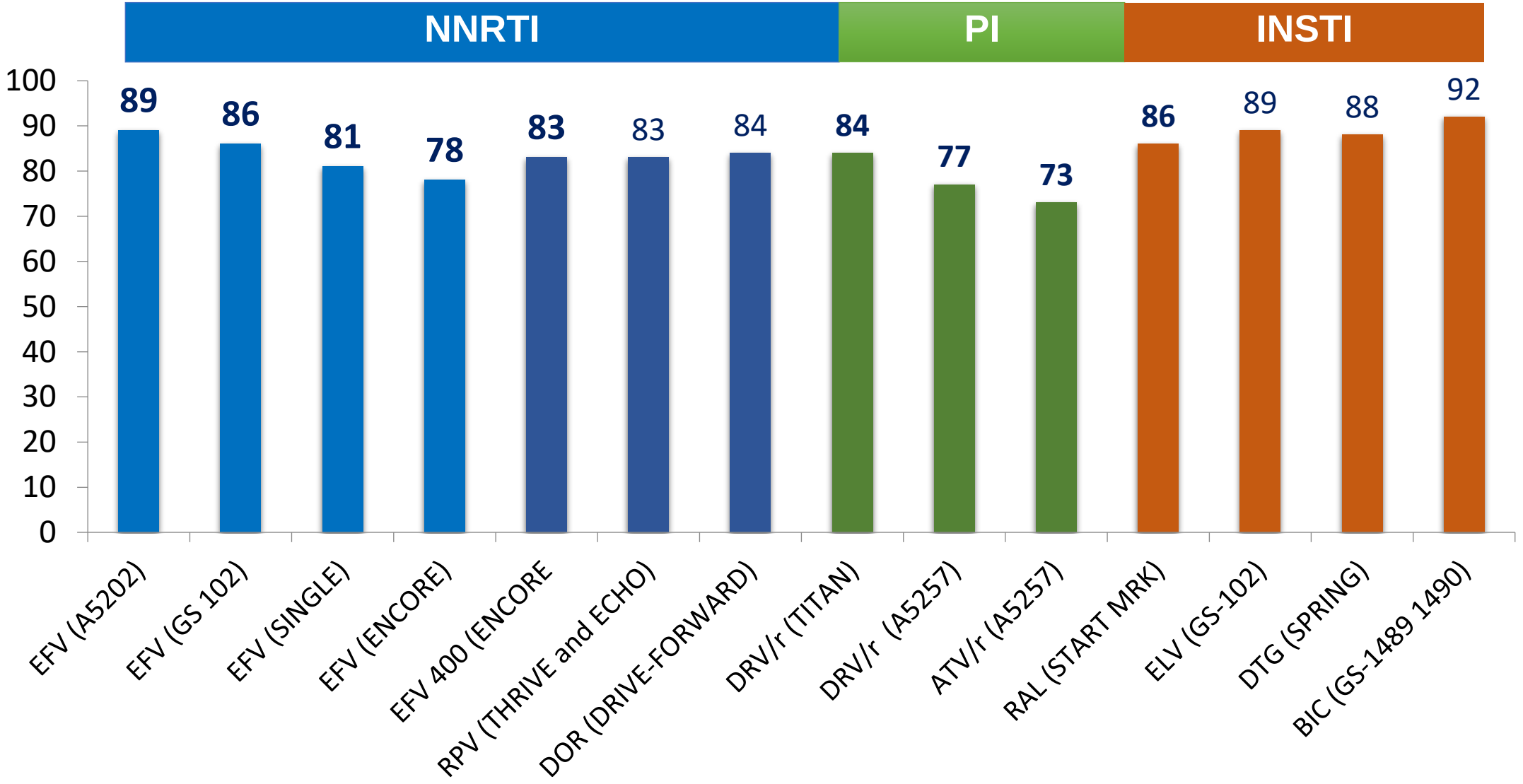
HIV-1 variants are continually introduced into new populations by mobility and migration

Lancet Infectious Diseases. 2011; 11:45–56.


Middle East and north Africa
Eastern Europe and central Asia
Western and central Europe and North America
East Asia
Caribbean
West Africa
Ethiopia
India
Southeast Asia
Central Africa
East Africa
Latin America
Oceania
Southern Africa
A
B
C
D
F
G
H
J
K
CRF01_AE
CRF02_AG
Other CRFs
URFs

Efficacy of Once-daily Regimens

based on controlled trials (48 weeks results, NS=F)



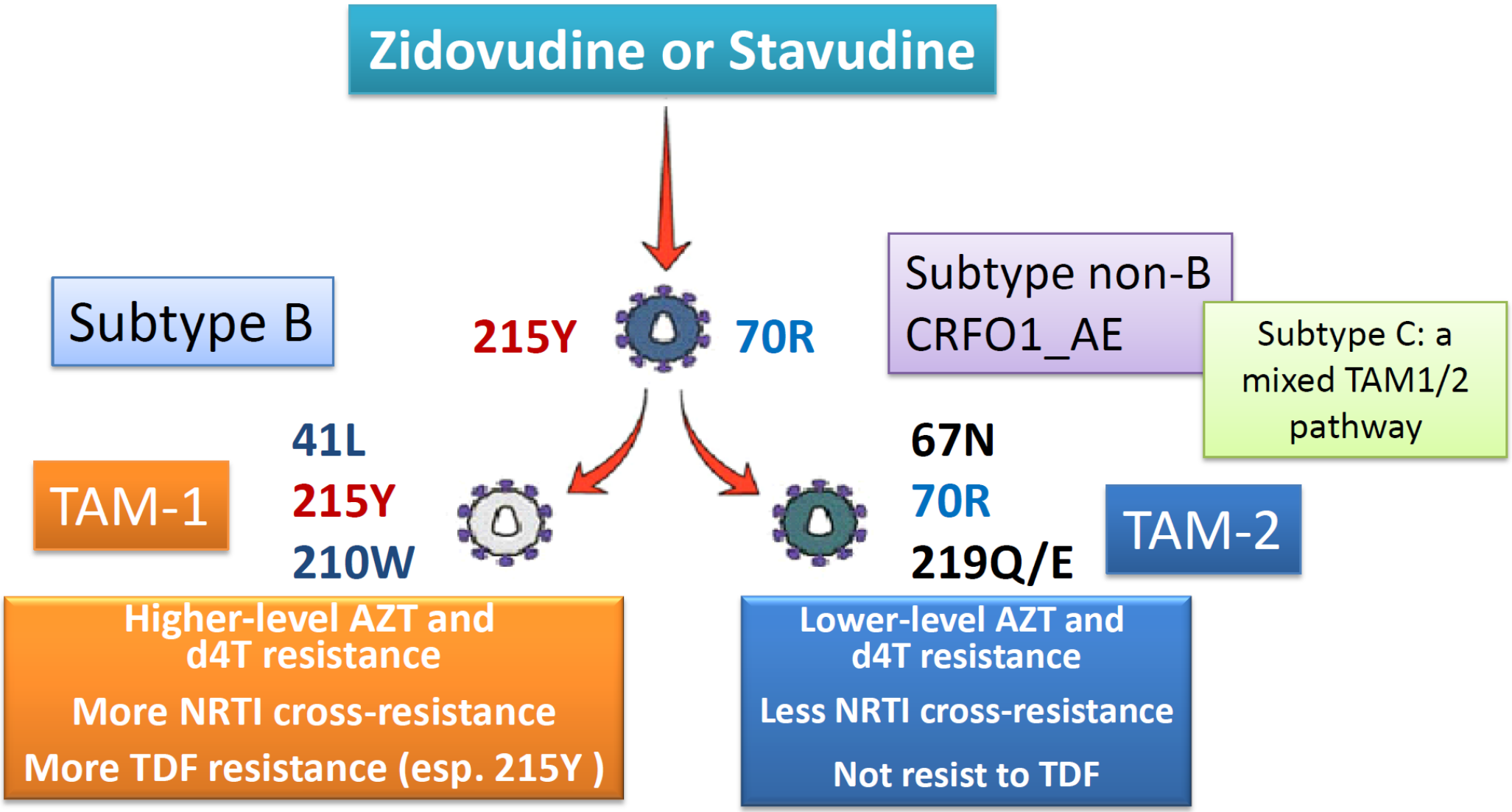
Permpalung N, Putcharoen O, Avihingsanon A, Ruxrungtham K. Expert Opin. Pharmacother. (2012) Early Online:1-17

Virological outcomes with specific antiretroviral drugs across different HIV-1 subtype

ART	Study	Subtype	Response
RPV	ECHO, THRIVE	▪ 30% non-B subtypes ▪ 11% subtype C	▪ 84 % subtype B ▪ 86% non-B subtypes
LPV	ARTEMIS	▪ 42% non-B subtypes ▪ 14% subtype C	▪ 78% subtype B ▪ 78-82% non-B subtypes
DRV	ARTEMIS	▪ 39% non-B subtypes ▪ 11% subtype C	▪ 84% subtype B ▪ 87-88% non-B subtypes
RAL	STARTMARK	▪ 19% non-B subtypes ▪ 7% subtype C	▪ 89% subtype B ▪ 95% non-B subtypes

Adapted from Curr Opin Virol 2012;2(5): 636-643

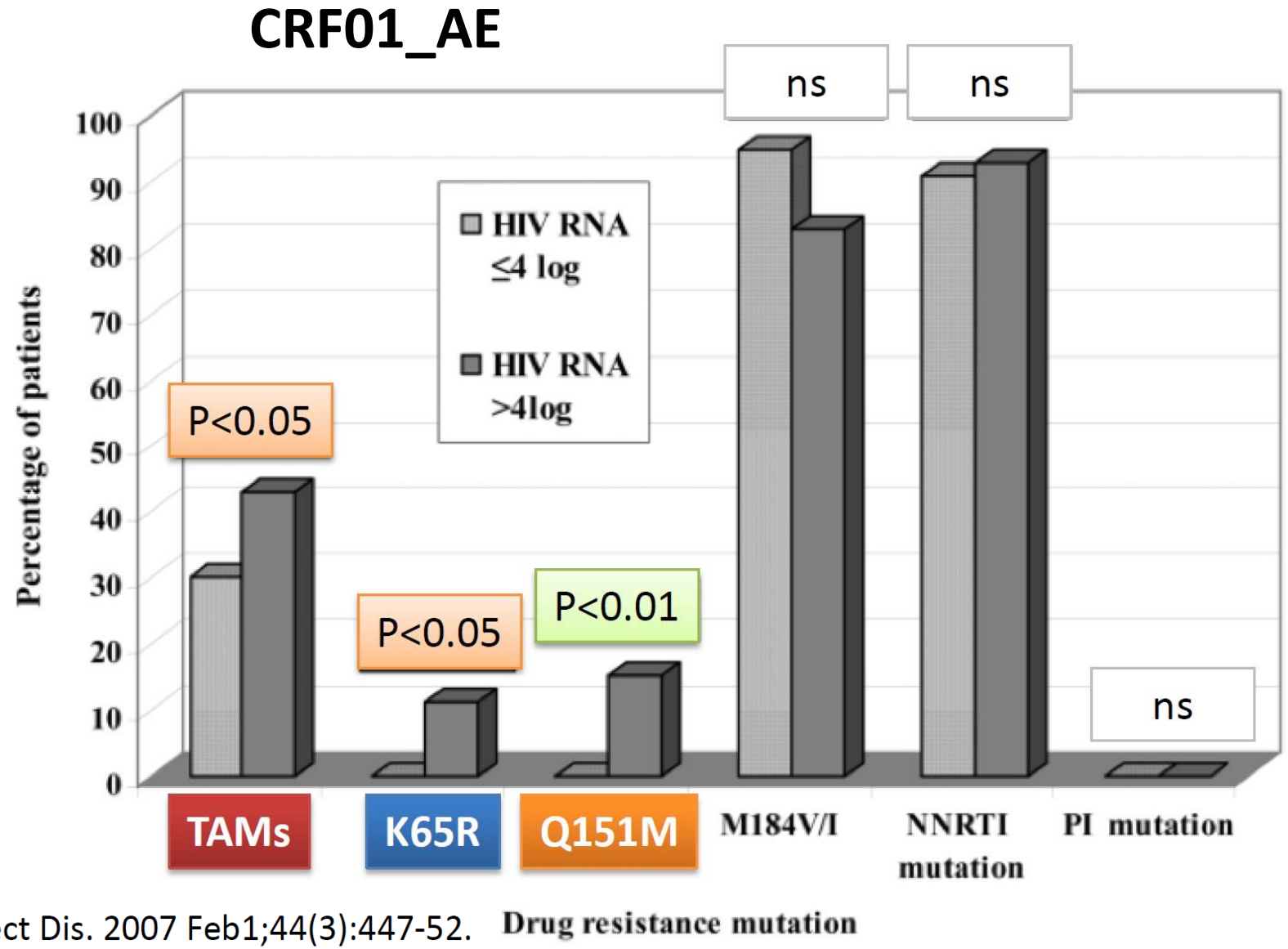
Dichotomous Pathways in the Evolution of TAMs



Novitsky V, et al. AIDS Res Hum Retroviruses. 2007; 23:868-78.
Clavel F and Hance AJ. HIV Drug Resistanc. N Engl J Med 2004; 350:1023-35.

Resistance profiles in NNRTI-based failure

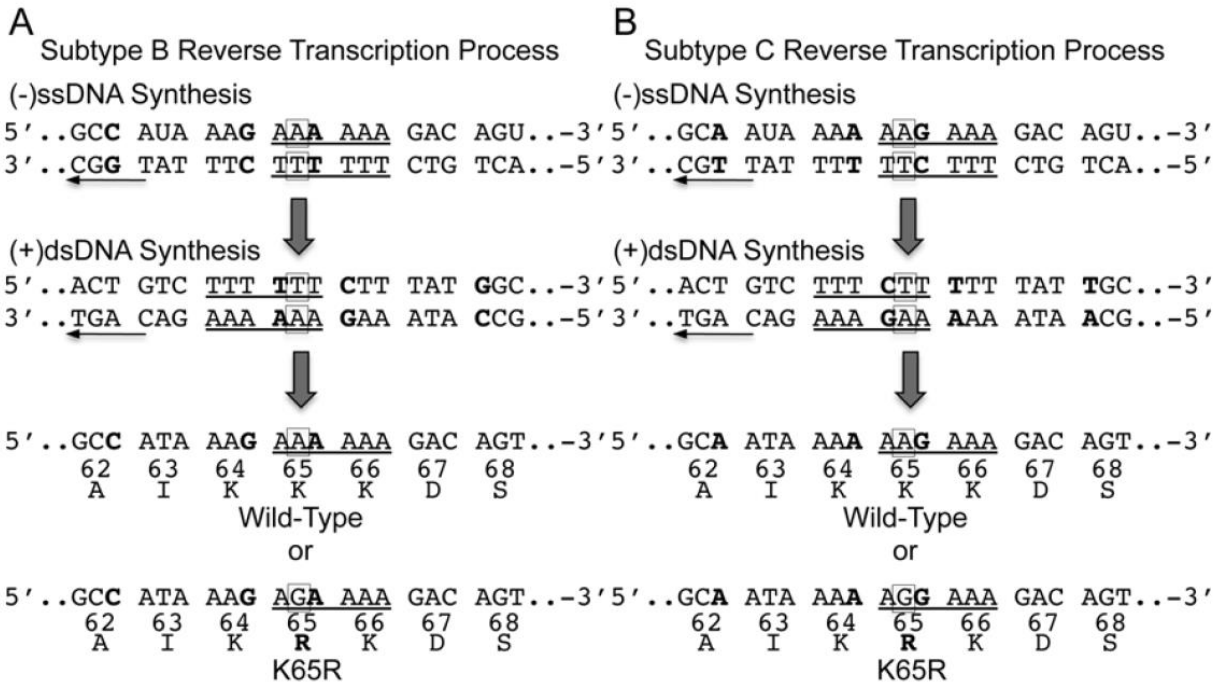
Higher VL (>4 log) was associated with more TAMs, MDR and K65R

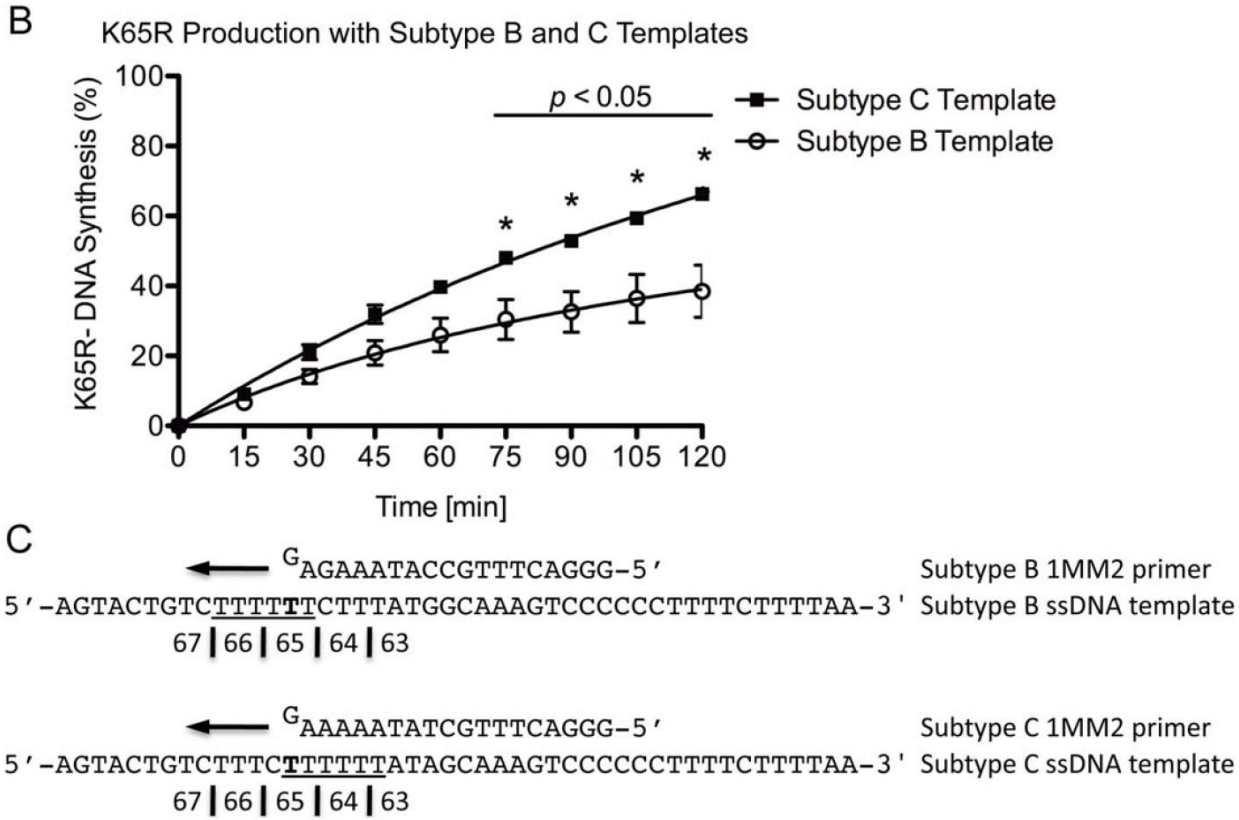


Sungkanuparph S, et al. Clin Infect Dis. 2007 Feb1;44(3):447-52.

Development of K65R in subtype C

A Template-Dependent Dislocation Mechanism Potentiates K65R Reverse Transcriptase Mutation Development in Subtype C Variants of HIV-1





High rate of K65R for ART naïve patients with subtype C HIV infection failing a TDF-containing first-line regimen in South Africa

- **Very high rates (>65%) of K65R for patients failing TDF-based first-line regimens at McCord hospital with few additional NRTI mutations compared to subtype B. These rates may reflect faster in vivo selection, longer time on a failing regimen, or transmitted DR.**

AIDS. 2012 August 24; 26(13): 1679–1684.

No Evidence That HIV-1 Subtype C Infection Compromises the Efficacy of Tenofovir-Containing Regimens: Cohort Study in the United Kingdom

Ellen White,[1] Erasmus Smit,[6] Duncan Churchill,[7] Simon Collins,[4] Clare Booth,[5] Anna Tostevin,[1] Caroline Sabin,[2] Deenan Pillay,[3,8] and David T. Dunn[1]; on behalf of the UK HIV Drug Resistance Database and UK Collaborative HIV Cohort Study

[1]MRC Clinical Trials Unit at UCL, [2]Department of Infection and Population Health, [3]Division of Infection and Immunity, University College London, [4]HIV i-Base, [5]Health Service Laboratories, Royal Free Hospital, London, [6]Public Health England, Birmingham Heartlands Hospital, and [7]Brighton and Sussex Hospitals NHS Trust, United Kingdom; and [8]Africa Centre for Population Health, University of KwaZulu-Natal, Durban, South Africa

J Infect Dis. 2016 Nov 1; 214(9): 1302–1308.

Drug resistance mutations between HIV-1 subtypes and CRFs and impact on antiretroviral drug resistance and susceptibility

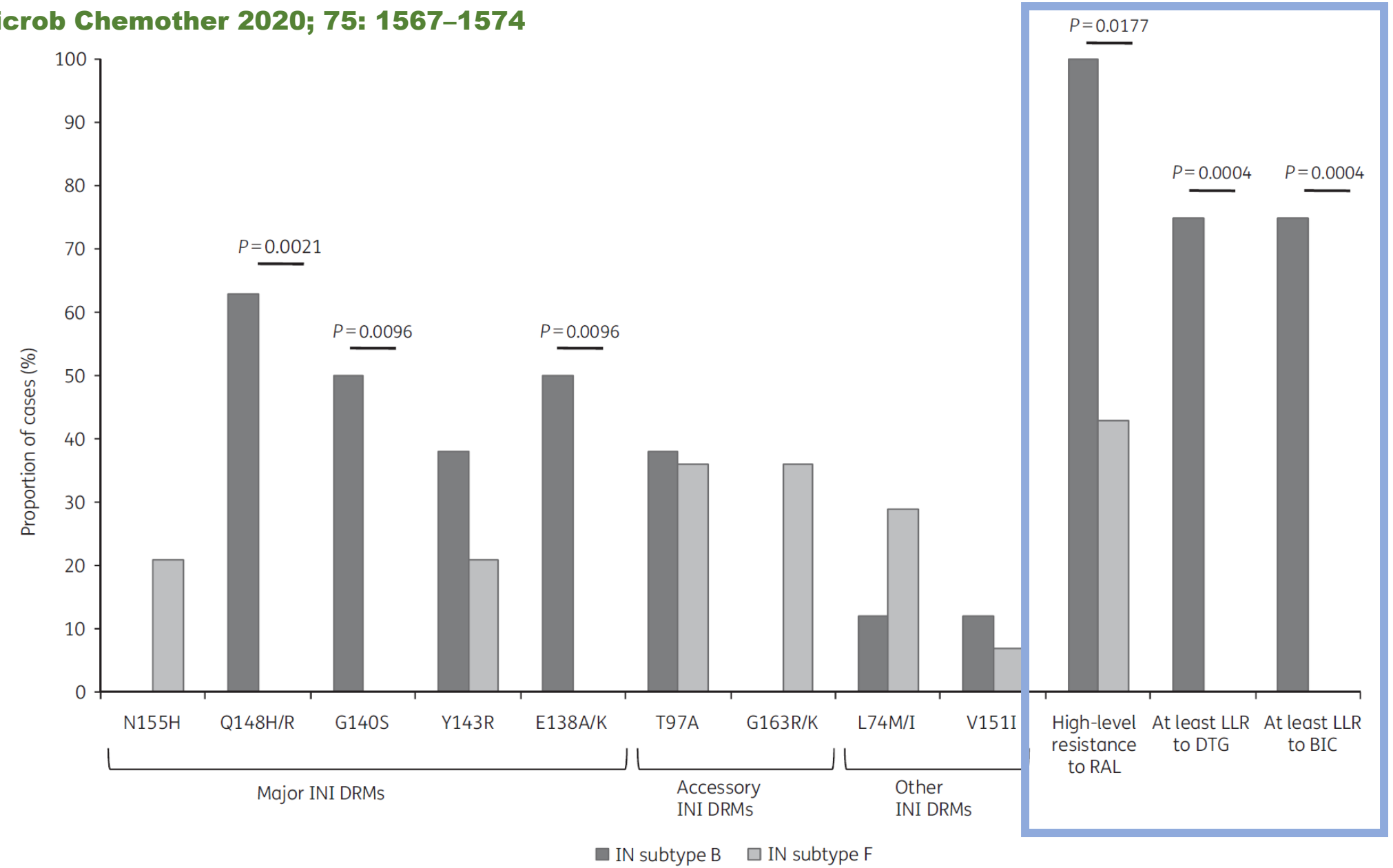
Enzyme	Position	Findings	Reference(s)
RT	**K65R**	**Subtype C** – AAG (K); subtype B – AAA (K): preferential pausing of reverse transcription, related to homopolymeric stretch of adenine bases	Antiviral Chemistry and Chemotherapy. 2010; 20:117–131.
	E138K	E138K the first mutation to emerge in **subtype C** during **ETR** therapy	Antimicrobial Agents and Chemotherapy. 2011; 55:600–607
	Y181C	Preferential selection of Y181C for **subtype A and B** during etravirine therapy	Antimicrobial Agents and Chemotherapy. 2010; 54:4812–4824
	N348I	Reduces susceptibility to etravirine in subtypes A, B and C. **High prevalence in subtype C samples from patients failing first-generation NNRTIs**	Antimicrobial Agents and Chemotherapy. 2011; 55:1806–1809.
PR	G17E	**CRF2_AG** hypersusceptibility to nelfinavir, atazanavir and indinavir	Antimicrobial Agents and Chemotherapy. 2012; 56:2719–2725
	M36I	**Subtype C – ATA (I); subtype B – ATG (M)**: affects susceptibility to protease inhibitors and viral replication capacity	Antimicrobial Agents and Chemotherapy. 2010; 54:2878–2885
	I64M	**CRF2_AG** hypersusceptibility to nelfinavir, atazanavir and indinavir	Antimicrobial Agents and Chemotherapy. 2012; 56:2719–2725
	M89T	**Subtype C** – ATG (M); subtype B – CTG (L): leads to preferential emergence of M89T in subtype C	Journal of Antimicrobial Chemotherapy. 2012; 67:988–994.

Drug resistance mutations between HIV-1 subtypes and CRFs and impact on antiretroviral drug resistance and susceptibility

Enzyme	Position	Findings	Reference(s)
IN	E92Q	E92Q/N155H double mutant 10-fold more resistant to raltegravir and elvitegravir in subtype B versus subtype C	AIDS. 2010; 24:2171–2179
	L101I	Present more frequently in non-B subtypes compared to subtype B (both INI-naïve and RAL-experienced)	Antiviral Research. 2011; 90:164–167.
	G118R	Most common resistance pathway during dolutegravir therapy in subtype C	Journal of Virology. 2010; 84:9210–9216
	T124A	Present more frequently in INI-naïve non-B subtypes compared to subtype B	Antiviral Research. 2011; 90:164–167.
	N155H	Subtype B with this mutation more resistant to raltegravir (and elvitegravir) than subtype C	AIDS. 2010; 24:2171–2179.
	R263K	Most common resistance pathway during dolutegravir therapy in subtype B	Journal of Virology. 2012; 86:2696–2705.

Impact of genotypic diversity on selection of subtype-specific drug profiles during RAL-based therapy in individuals infected with B and BF recombinant HIV-1 strains

J Antimicrob Chemother 2020; 75: 1567–1574



Resistance pathway during DTG therapy

Isolation of R263K mutant viruses with DTG in subtype B

	Week 20	Week 37
 Subtype B	R263K	R263K
 Subtype A/G	R263K, G118R	R263K
 Subtype C	G118R	H51Y

Serial passage experiments with CBMCs infected with subtype B, A/G, and C HIV-1 viruses in the presence of increasing concentrations of DTG

J Virol. 2012 Mar;86(5):2696-705.

INSTI for treatment-naïve patients

INSTI	Clinical Trial	Treatment Group	Resistance Analysis Population; n (%) [a]	Emergent INSTI Resistance; n (%)	Emergent Other Resistance; n (%)
RAL	STARTMRK	RAL (BID) + FTC/TDF	9 (3.2%)	4 (1.4%)	3 (1.1%)
		EFV + FTC/TDF	7 (2.5%)	na	3 (1.1%)
	QDMRK	RAL (QD) + FTC/TDF	30 (7.9%)	9 (2.4%)	20 (5.2%)
		RAL (BID) + FTC/TDF	16 (4.1%)	2 (0.5%)	6 (1.5%)
EVG	GS-US-236-0102	EVG/COBI/FTC/TDF	14 (4.0%)	7 (2.0%)	8 (2.3%)
		EFV/FTC/TDF	17 (4.8%)	na	8 (2.3%)
	GS-US-236-0103	EVG/COBI/FTC/TDF	12 (3.4%)	4 (1.1%)	4 (1.1%)
		ATV + RTV + FTC/TDF	8 (2.3%)	0	0
DTG	SPRING-2	DTG + [FTC/TDF or ABC/3TC]	20 (4.9%)	0	0
		RAL + [FTC/TDF or ABC/3TC]	28 (6.8%)	1 (0.2%)	4 (1.0%)
	SINGLE	DTG + ABC/3TC	18 (4.3%)	0	0
		EFV/FTC/TDF	17 (4.1%)	na	4 (1.0%)
	FLAMINGO	DTG + [FTC/TDF or ABC/3TC]	2 (0.8%)	0	0
		DRV + RTV + [FTC/TDF or ABC/3TC]	2 (0.8%)	0	0

Viruses 2014, 6, 2858-2879

Resistance to DTG in treatment-naïve patients

Clinical Infectious Diseases

BRIEF REPORT

Clinical Infectious Diseases® 2018;67(5):791–4

Emergence of Integrase Resistance Mutations During Initial Therapy Containing Dolutegravir

Patient's profile:

OI: PCP

VL= 1 970 000 copies/mL

CD4=78/µL (12%)

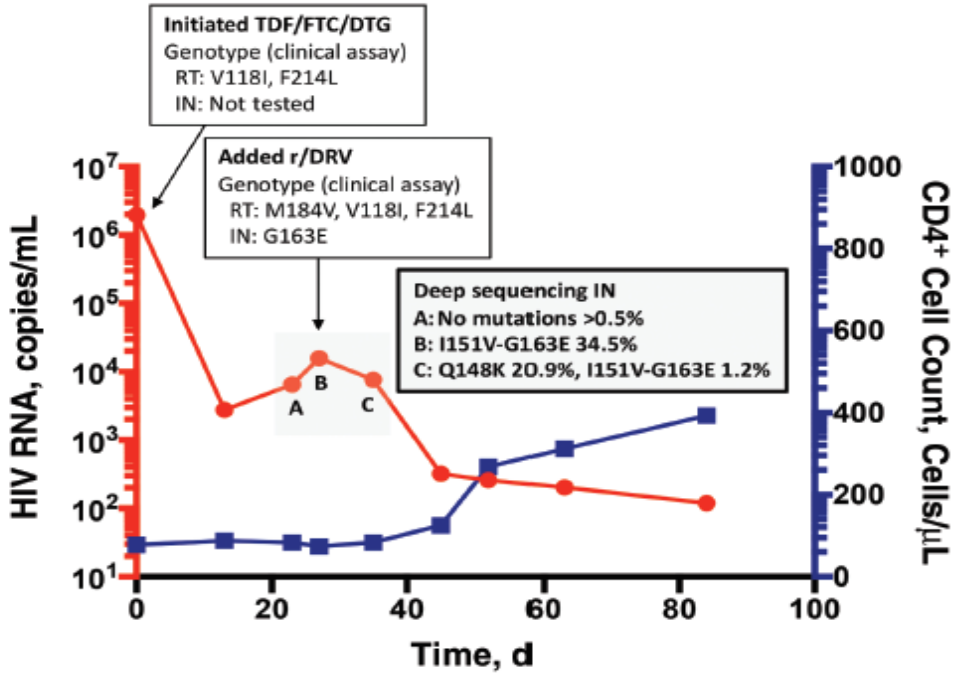
Backbone: TDF/FTC

Genotype Frequencies (%) at Each Time Point

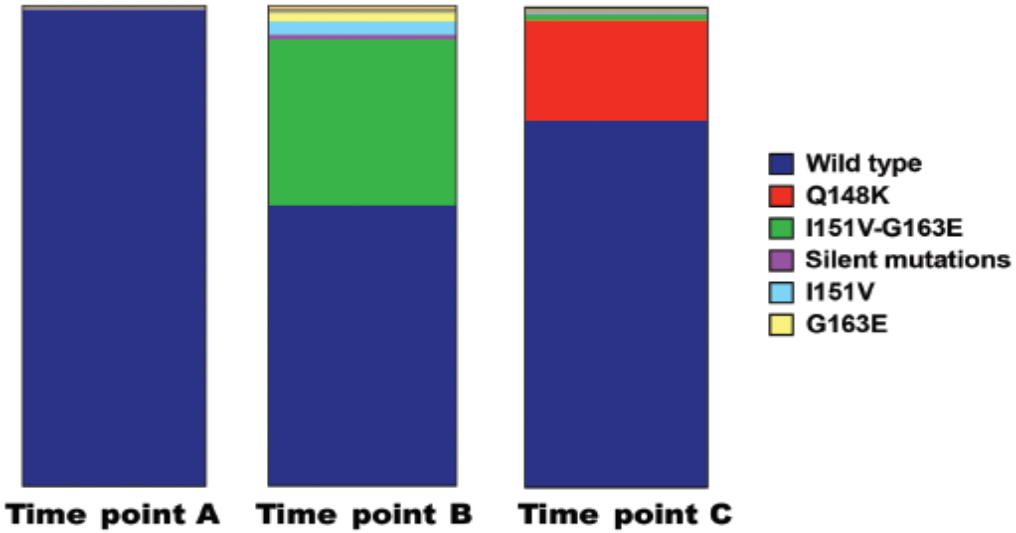
Genotype[a]	Time Point A	Time Point B	Time Point C
Wild type	98.9	58.3	76.3
Q148K	0.0	0.0	20.9
I151V-G163E	0.0	34.5	1.2
Silent mutations	0.3	0.9	0.2
I151V	0.0	2.7	0.2
G163E	0.0	1.9	0.1

[a]Genotypes present at any time point at frequency >0.5%

A



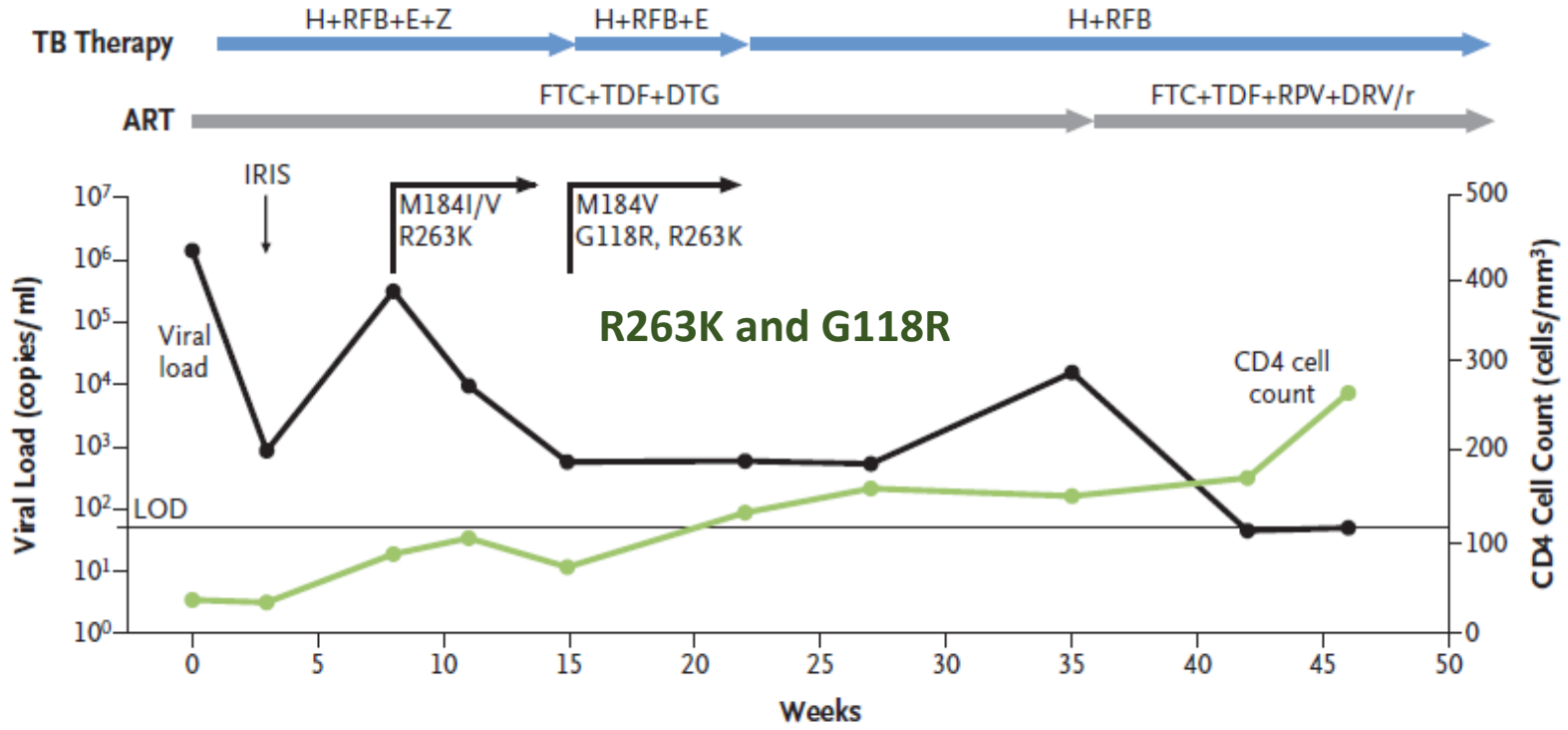
B



Resistance to DTG in treatment-naïve patients

Failure of Dolutegravir First-Line ART with Selection of Virus Carrying R263K and G118R

Patient's profile:
OI: TB on rifampicin with IRIS
VL= 1 400 000 copies/mL
HIV-1 subtype F
CD4=22/µL (12%)
Backbone: TDF/FTC



Resistance Analysis

Mutation	Wk 0	Wk 3	Wk 8	Wk 11	Wk 15	Wk 22	Wk 27	Wk 35	Wk 36
					%				
M184V	0.17	0.22	85.8	95.6	98.1	98.6	ND	99.4	99.6
M184I	0.09	0.07	13.6	2.9	0.0	0.0	ND	0.0	0.0
G118R	0.01	0.00	0.0	4.0	23.0	0.0	0.0	29.7	45.2
R263K	0.00	0.00	64.1	82.9	69.8	99.4	99.2	69.2	30.4

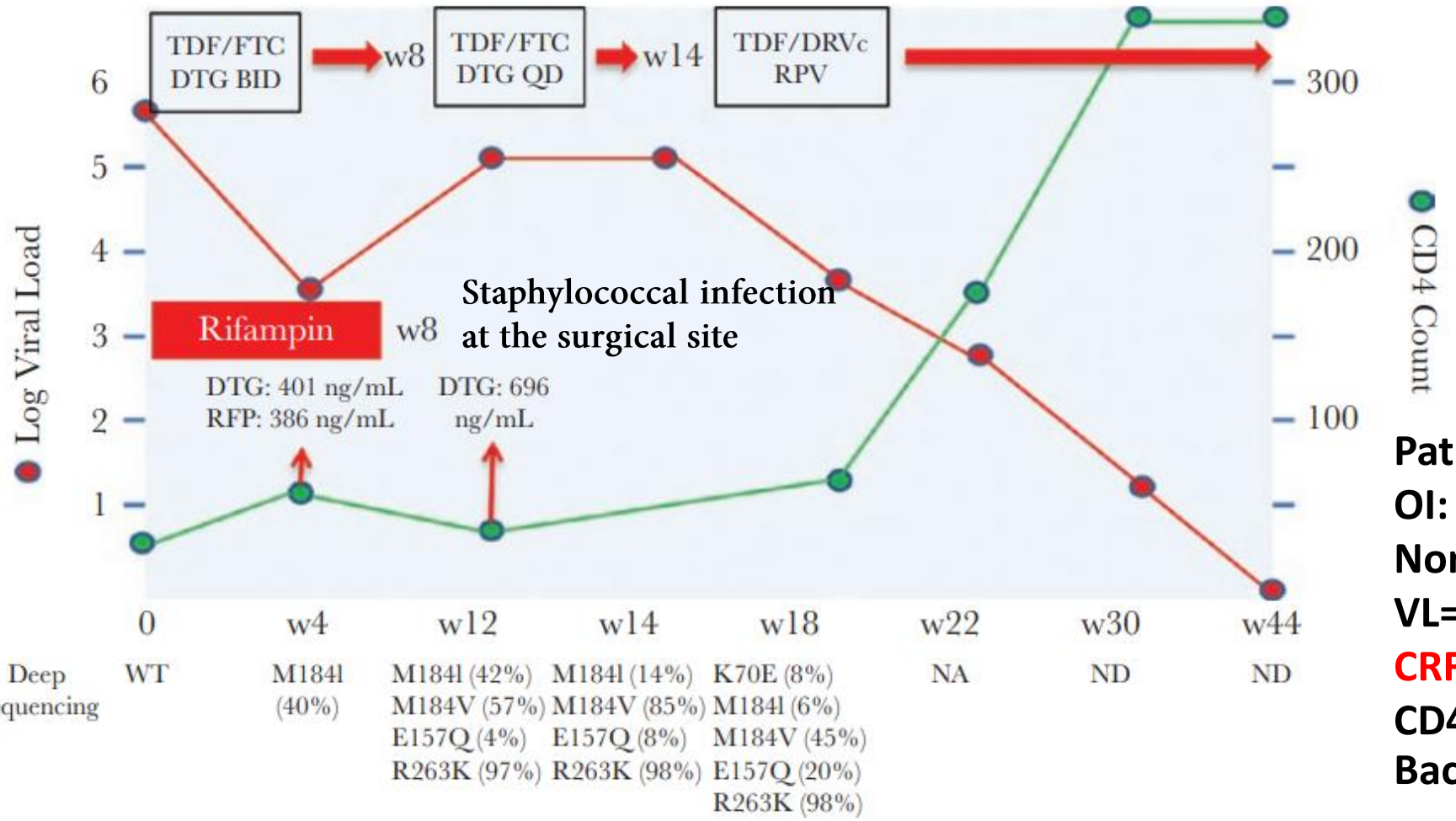
N ENGL J MED 381;9 NEJM.ORG AUGUST 29, 2019

Resistance to DTG in treatment-naïve patients

Open Forum Infectious Diseases

BRIEF REPORT

Virological Failure in HIV to Triple Therapy With Dolutegravir-Based Firstline Treatment: Rare but Possible



Patient's profile:

OI: PCP

Norwegian scabies

VL= 457 000 copies/mL

CRF14_BG

CD4=42/µL (12%)

Backbone: TDF/FTC

DTG failure in treatment-naïve patients

- Very rare but possible
- Risk
  - Advanced HIV infection (low CD4 and high HIV RNA)
  - Concurrent OI
  - Use of rifamycin?
  - Non-subtype B HIV-1
- Likely DR mutation in case report:
  - INSTI DR: R263K E158Q G118R Q148K I151V G163E
  - Backbone (TDF/FTC): M184V

Summary

- The diversity HIV has given rise to multiple subtypes and recombinant strains
- The majority of research into antiretroviral agents and drug resistance has been performed on subtype B viruses, yet non-subtype B strains are responsible for 90% of global infections
- Response to ART in treatment-naïve patients are the same in all subtypes
- There is emerging evidence of subtype differences in drug resistance, relevant to antiretroviral strategies in different parts of the world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Thank you