HIV Drug Resistance: New Mutations and Cross Resistance

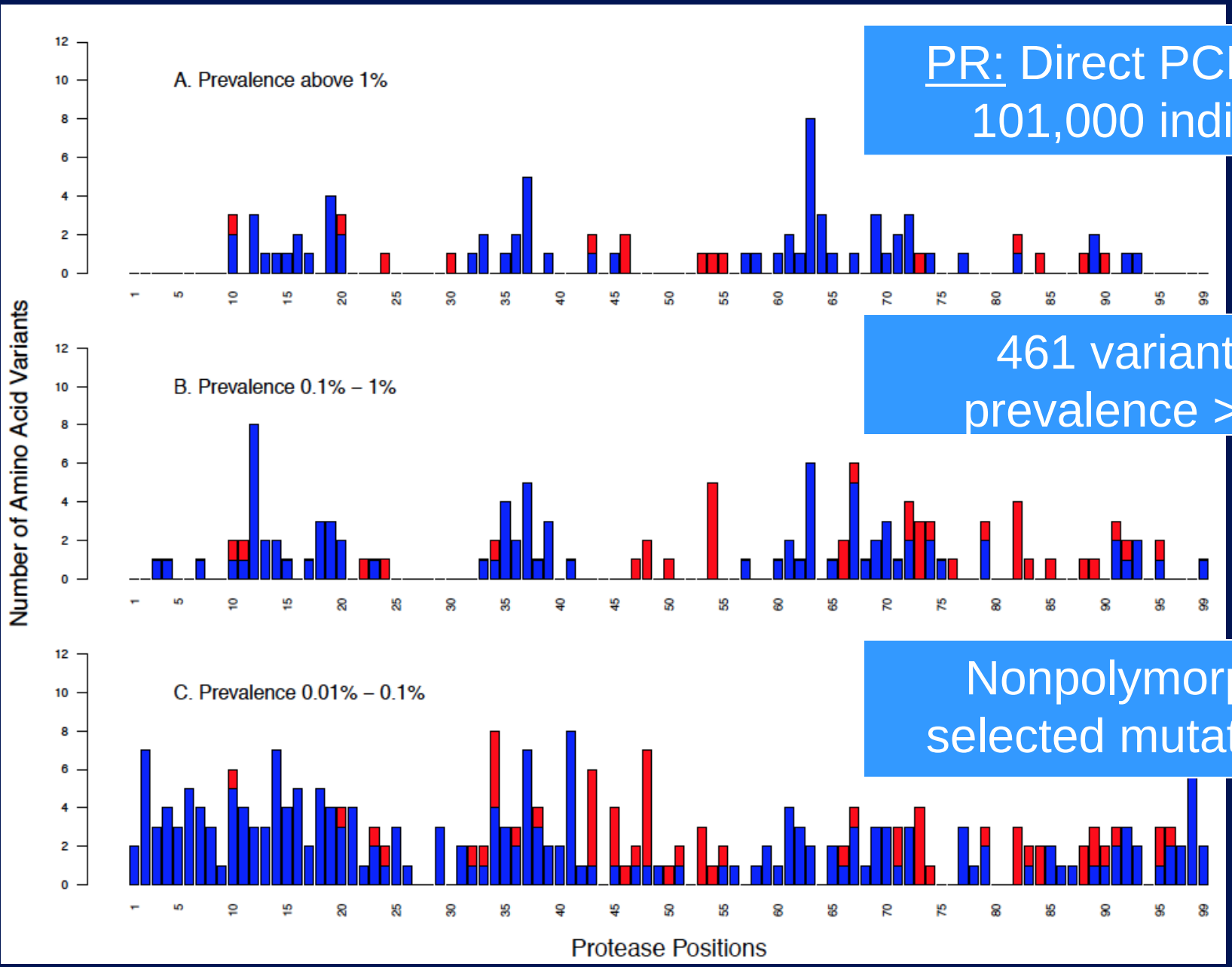
Bob Shafer, MD
Stanford University

Disclosures

- Research grants from Gilead Sciences, Merck, Bristol Myers Squibb
- Consulting for Viiv, Celera

Outline

- Effect of treatment and subtype on RT, PR, and IN variation (7 slides)
- TDR and cross-resistance (4 slides)
- ADR and cross-resistance including slides on TDF, DTG resistance (7 slides).



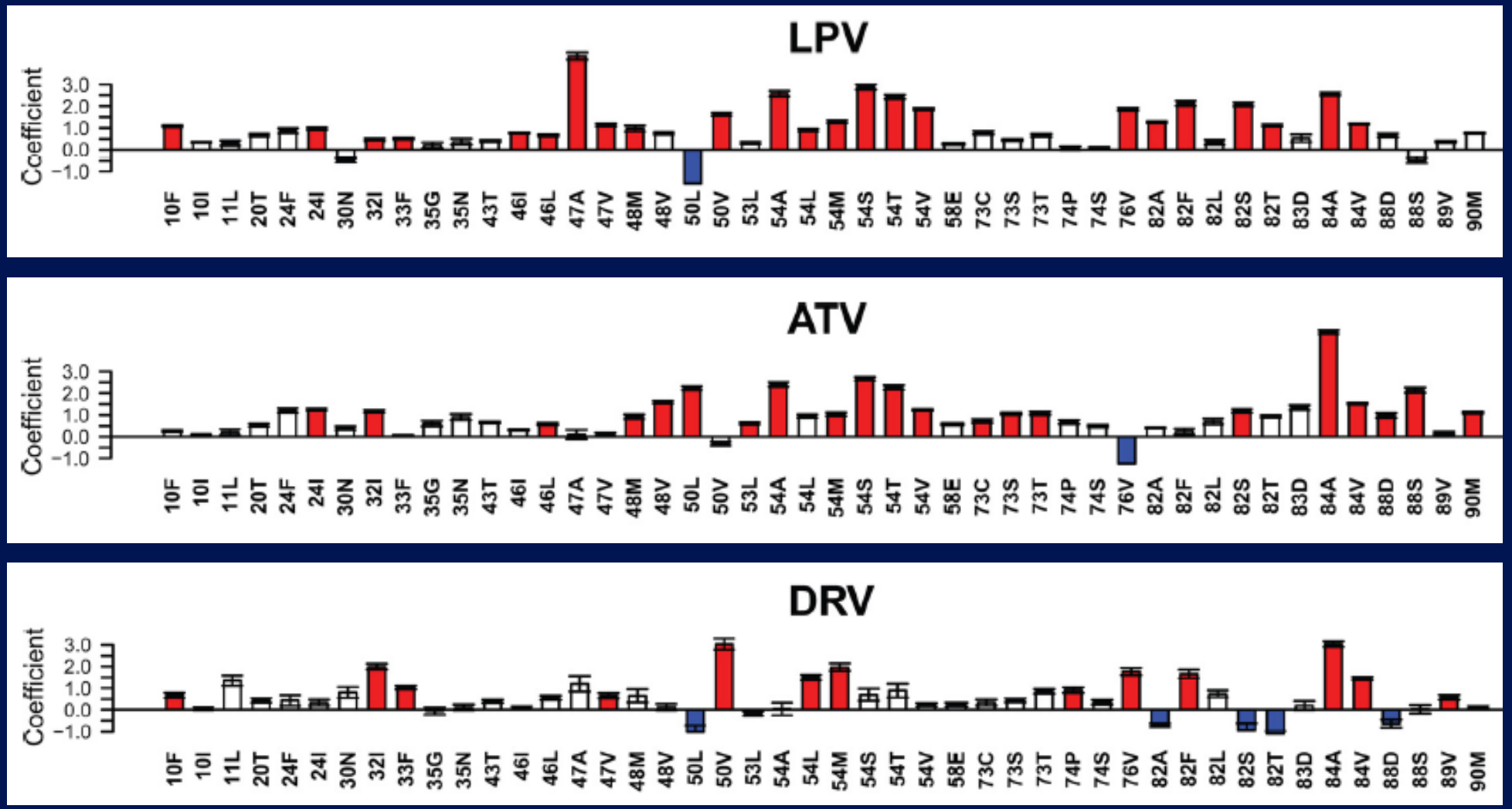
PR: Direct PCR plasma
101,000 individuals

461 variants with
prevalence > 0.01%

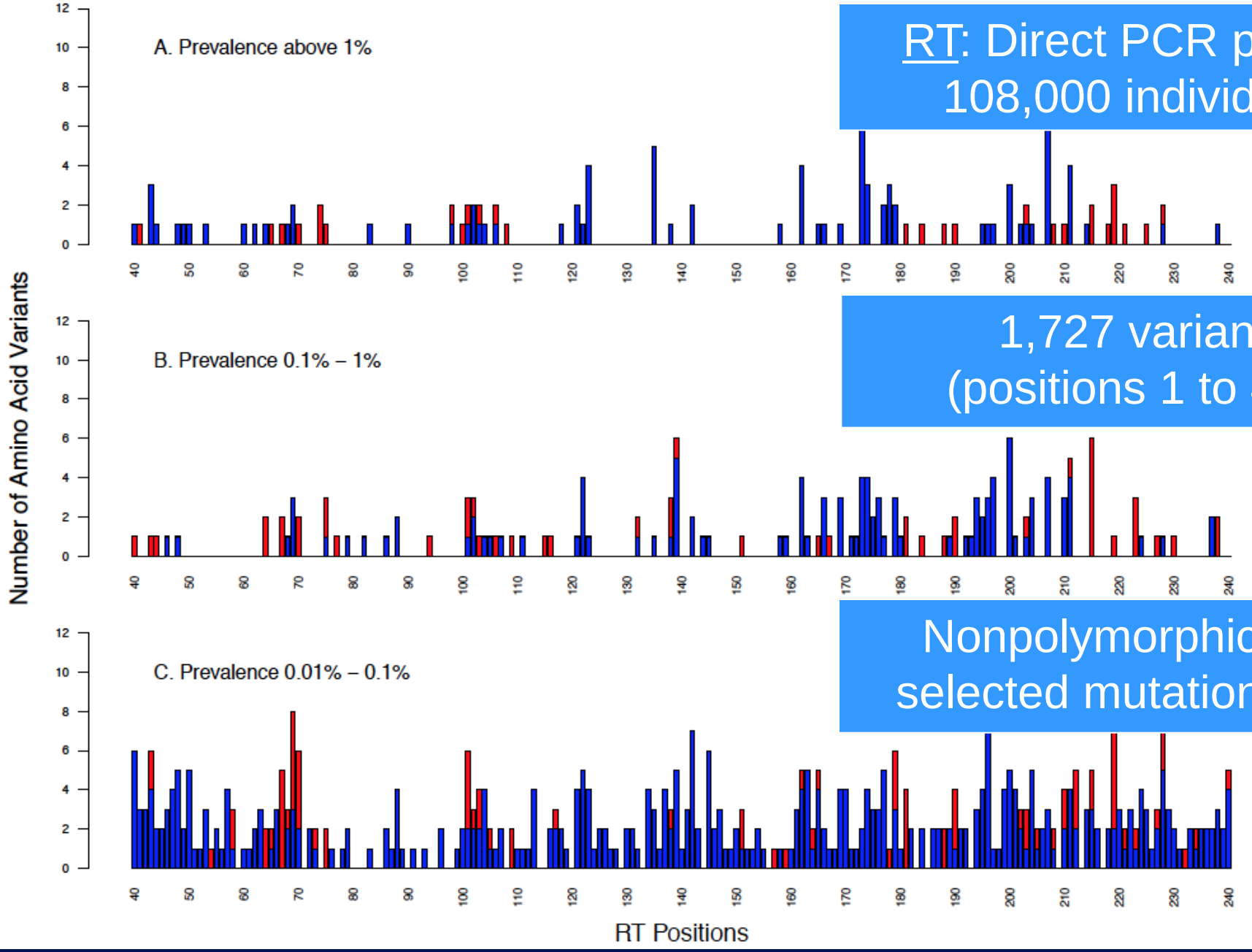
Nonpolymorphic PI-
selected mutations: 111

Rhee SY et al. HIV-1 protease, reverse transcriptase, and integrase variation. J Virol 2016

Phenotypic Effects of PI-Resistance Mutations



Rhee SY et al. HIV-1 protease mutations and protease inhibitor cross-resistance. AAC 2010



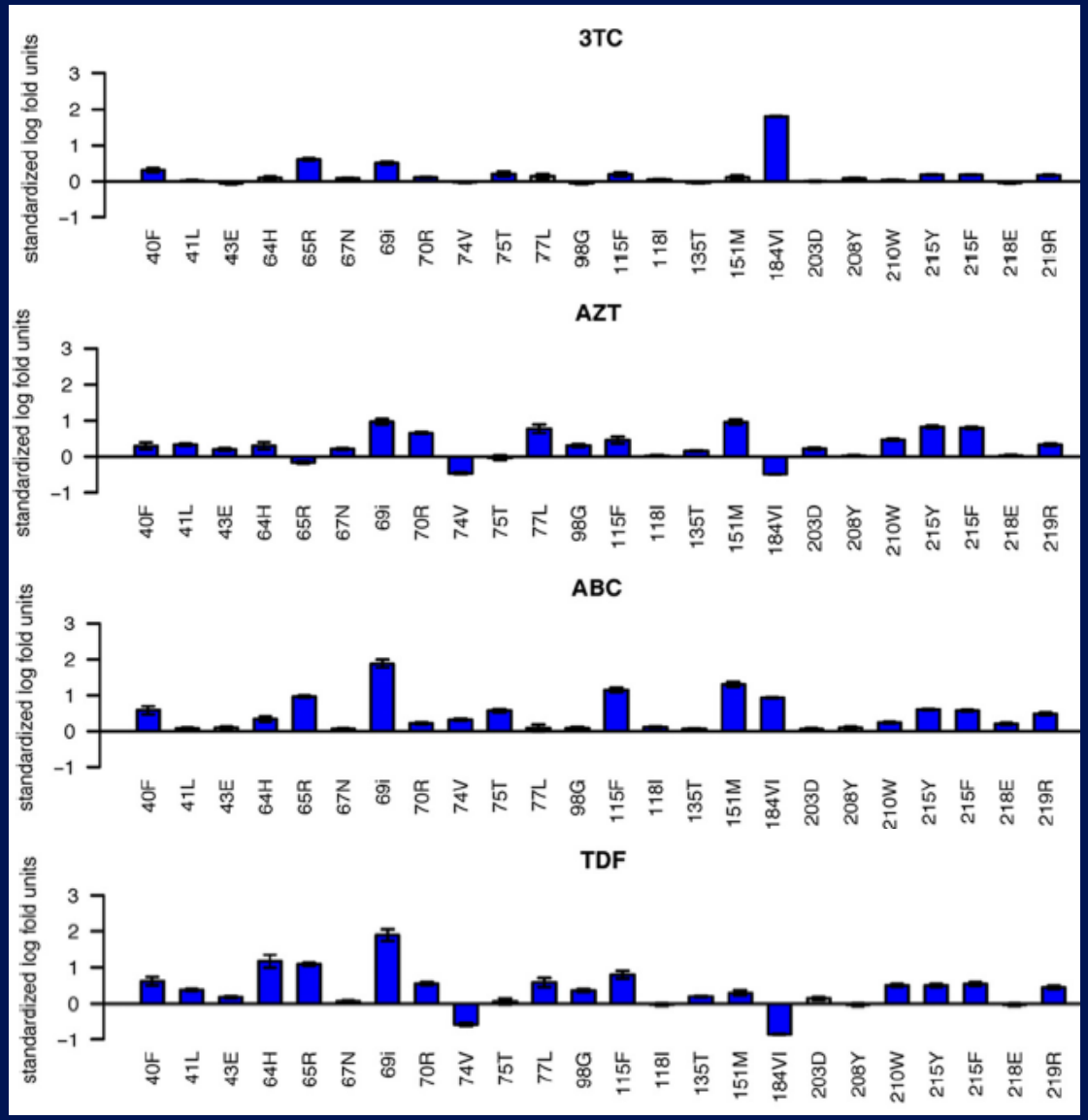
RT: Direct PCR plasma
108,000 individuals

1,727 variants
(positions 1 to 400)

Nonpolymorphic RTI-selected mutations: 185

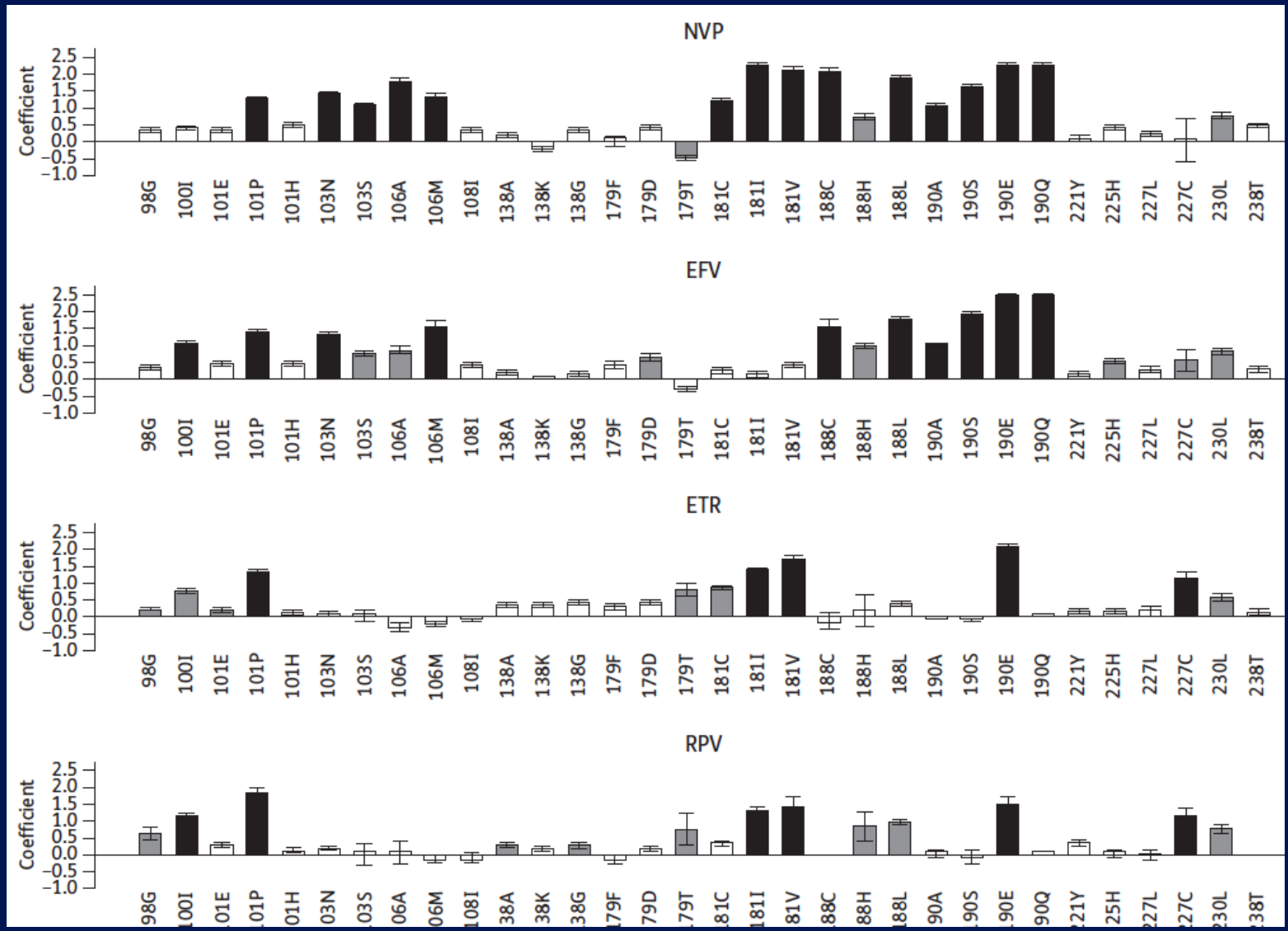
Rhee SY et al. HIV-1 protease, reverse transcriptase, and integrase variation. J Virol 2016

Phenotypic Effects of NRTI-Resistance Mutations



Melikian G et al. Standardized comparison of the relative impacts of HIV-1 reverse transcriptase (RT) mutations on nucleoside RT inhibitor susceptibility. AAC 2012

Phenotypic Effects of NNRTI-Resistance Mutations



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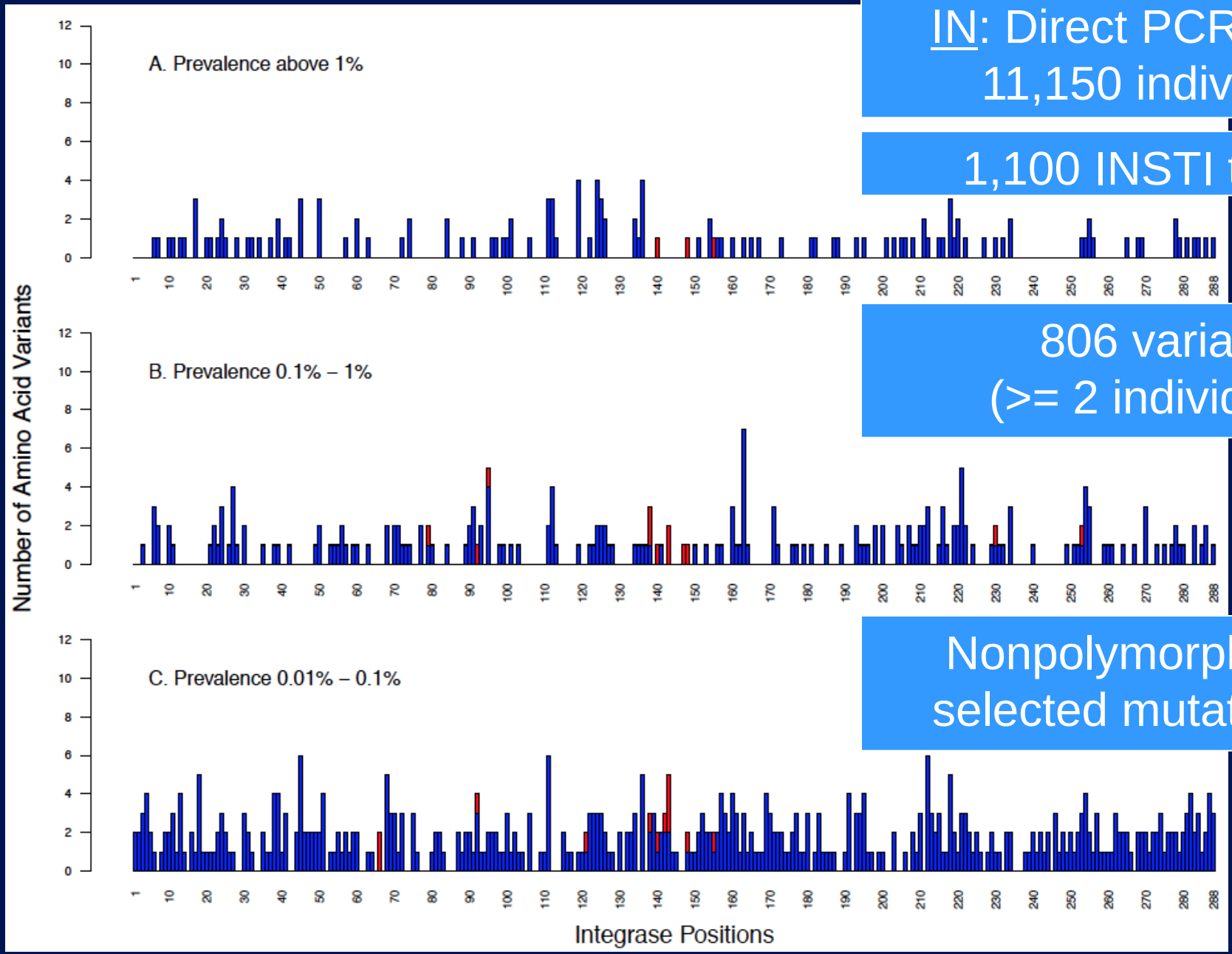


IN: Direct PCR plasma
11,150 individuals

1,100 INSTI treated

806 variants
(>= 2 individuals)

Nonpolymorphic RTI-selected mutations: 30

Rhee SY et al. HIV-1 protease, reverse transcriptase, and integrase variation. J Virol 2016

Effect of Subtype on Variation and Resistance Mutations

Numbers of Viruses

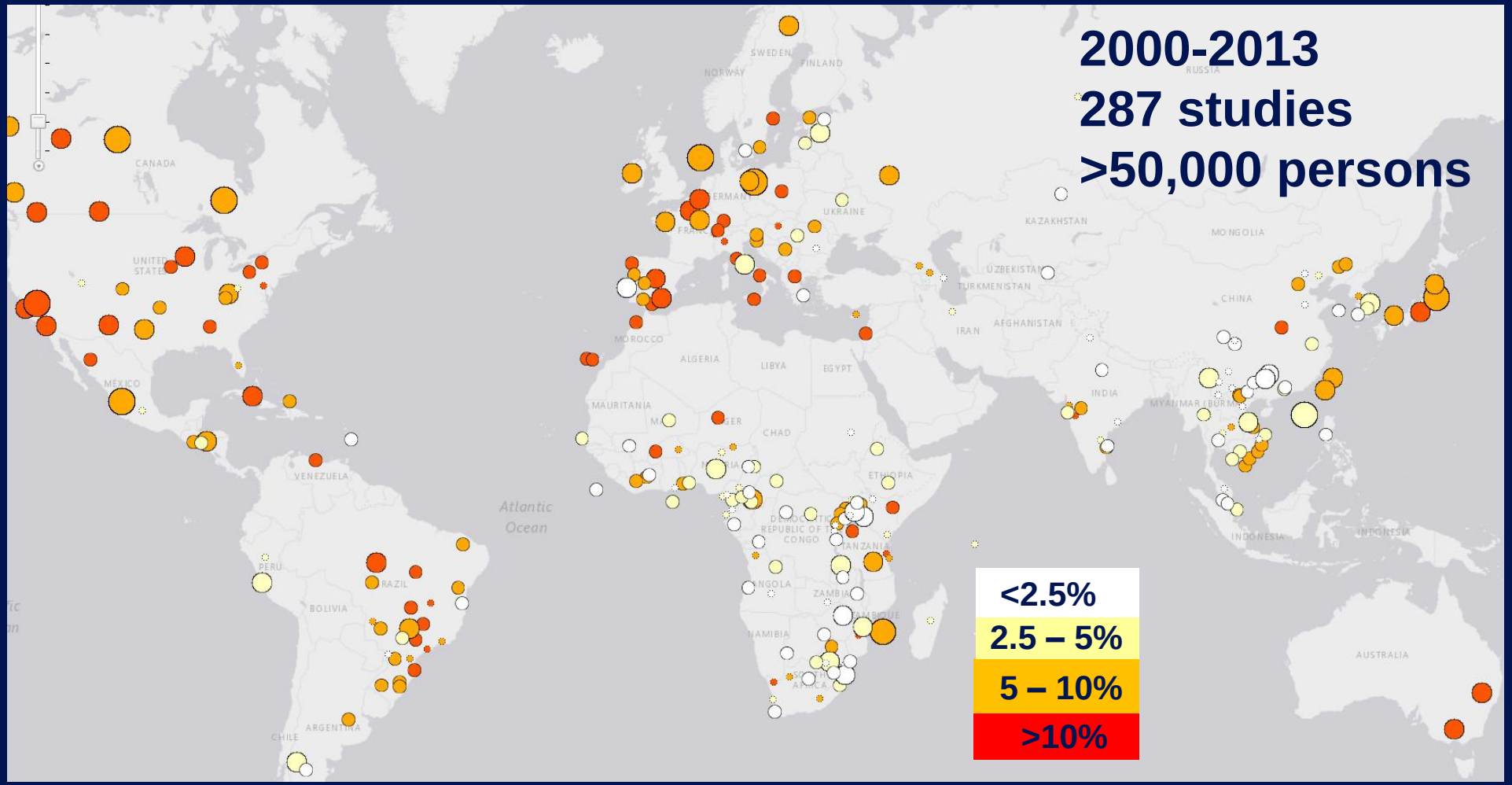
Subtype	Rx-Naïve (1000x)	RTI-Treated (1000x)
B	29	30
C	9.1	8.9
AE	6.2	4.1
A	4.2	1.6
AG	3.1	1.9

- Median intersubtype ratio of mutation prevalences: 1.9 to 2.9
- % of variants that have a prevalence ratio >10-fold between any two subtypes: 2% to 5%

Subtype-specific DRMs

Gene	Pos	AA	Subtype
RT	**106**	**M**	**C**
RT	190	S	A-FSU
RT	75	M	AE
PR	82	M	G
IN	**140**	**S**	**B**

Mutations Associated With TDR



http://hivdb.stanford.edu/surveillance/map/

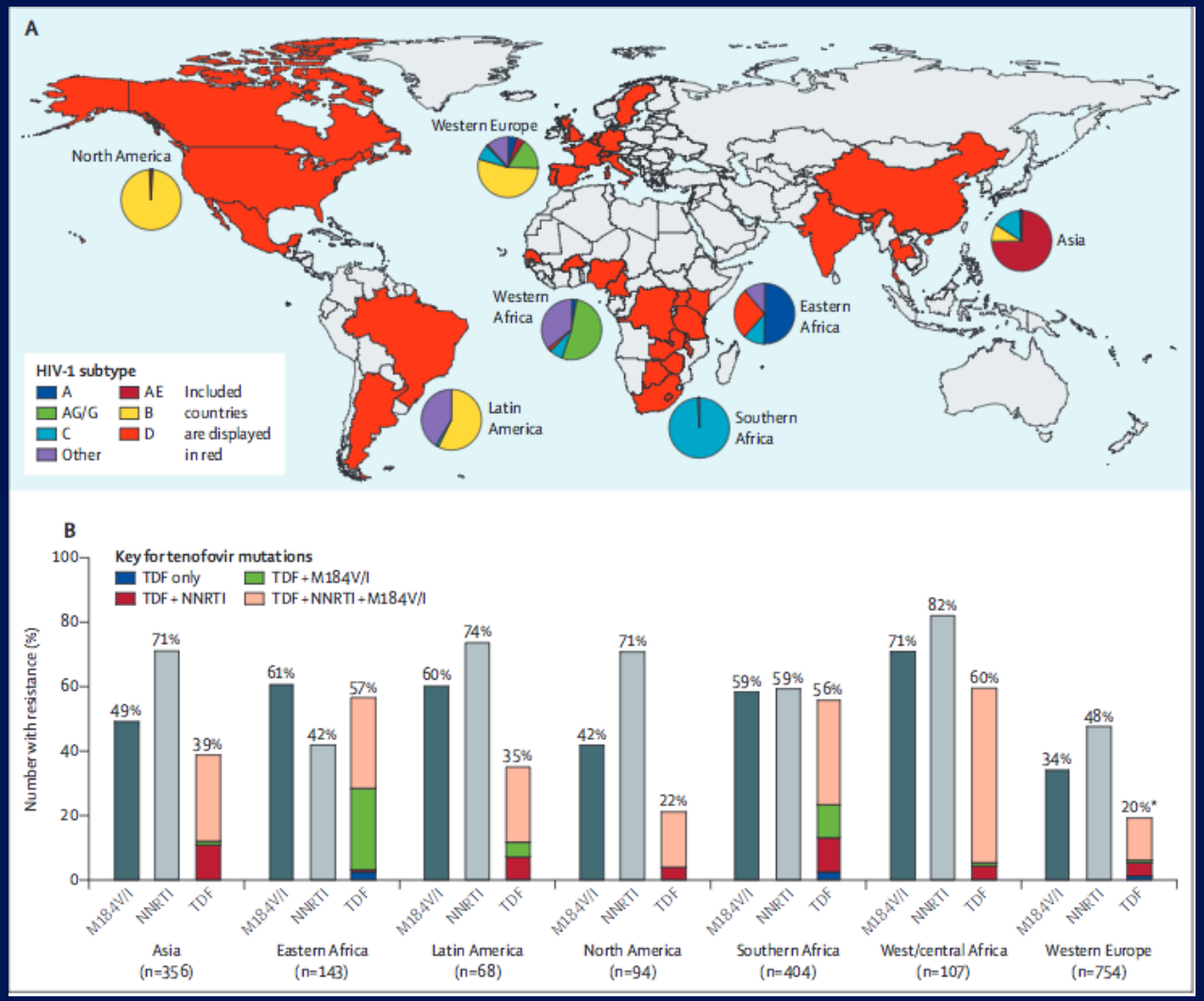
NNRTI-Resistance Mutations Associated With TDR

Sub-Saharan Africa n=11628 361 with major DRMs			South/Southeast Asia n=6830 146 with major DRMs			Latin America n=5715 225 with major DRMs			Upper-income countries n=24898 1089 with major DRMs		
DRM	DRM%	DRM% Sum	DRM	DRM%	DRM% Sum	DRM	DRM%	DRM% Sum	DRM	DRM%	DRM% Sum
K103N	57.5	57.5	Y181C	41.4	41.4	K103N	63.0	63.0	K103N	67.0	67.0
Y181C	20.6	73.7	K103N	37.4	76.8	Y181C	17.3	77.2	Y181C	14.7	78.0
G190A	18.0	86.8	G190A	17.2	84.8	G190A	13.6	85.8	G190A	11.7	86.4
L100I	3.1	89.5	V106M	5.1	88.9	Y188L	6.2	91.4	Y188L	5.1	90.5
G190E	2.2	91.7	V106A	2.0	90.9	G190S	3.7	94.4	K103S	3.4	92.2
K103S	3.1	93.4	K103S	7.1	92.9	K103S	4.3	96.3	Y188H	1.6	93.6
Y188L	1.3	94.7	G190E	2.0	94.9	Y188C	1.2	97.5	Y188C	1.4	94.9
V106M	1.3	95.6	Y188L	2.0	97.0	M230L	4.9	98.8	V106A	1.6	96.0

http://hivdb.stanford.edu/pages/POC_NNRTI_Naive_DRMs_Summary.html/

Rhee SY et al. Geographic and temporal trends in the molecular epidemiology and genetic mechanisms of transmitted HIV-1 drug resistance. PLOS Medicine 2015

Acquired TDF Resistance



M184V/I	53.6%
K65R	31.4%
A62V	6.9%
L74V/I	5.6%
Y115F	6.5%
K70E	3.3%
K70Q/G/T/N	1.3%
K65N	0.8%
T69del	0.6%

TenoRes Study Group: Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection. Lancet Inf Dis 2016

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
85	**V**
N88	D, S
L90	M

New mutations are in **bold**

Future considerations:

- IN resistance mutations
- Additional TDF resistance mutations (K65N, T69del, K70QNT)
- Possibly RPV resistance mutations (E138KGQ)

Bennett DE et al. Drug resistance mutations for surveillance of transmitted HIV-1 drug resistance: 2009 update. PLoS One 2009

NRTI-Associated Cross-Resistance Following First-Line Therapy (Intermediate / High)

NRTIs	# Patients	AZT Resistance	TDF Resistance	ABC Resistance
AZT/3TC	1435	39%	15%	27%
TDF/XTC	1961	5%	40%	50%
ABC/3TC	136	6%	17%	60%

Pooled data from 79 AZT / 49 TDF / 14 ABC publications with available sequences; http://hivdb.stanford.edu

NNRTI-Associated Cross-Resistance Following First-Line Therapy

NNRTI	# Patients	NVP Resistance	EFV Resistance	RPV Resistance	ETR Resistance
NVP	2795	85%	85%	58%	47%
EFV	3753	76%	76%	31%	20%

Pooled data from 96 NVP / 106 EFV publications with available sequences; http://hivdb.stanford.edu

PI-Associated Cross-Resistance Following First PI-Containing Regimen (Intermediate / High)

PI	# Patients	LPV Resistance	ATV Resistance	DRV Resistance
LPV/r	1272	16%	15%	2%
ATV, ATV/r	134	4%	30%	0%

Pooled data from 52 LPV / 13 ATV publications with available sequences; http://hivdb.stanford.edu

INI-Associated Cross-Resistance Following First INI-Containing Regimen (Intermediate / High)

INI	# Patients	RAL Resistance	EVG Resistance	DTG Resistance
RAL	972	76%	67%	32%
EVG	100	29%	36%	4%

Pooled data from 28 RAL / 5 EVG publications with available sequences; http://hivdb.stanford.edu

Novel DTG-Resistance Mutations: R263K

INI	In vitro selection	In vivo selection	In vitro resistance
RAL		N=8; Rhee2016	1x Mesplede2013; 1x Liang2015
EVG	Margot2012		3x Mesplede2013; 4x Liang2015
DTG	Quashie2012 Mesplede2013	N=2; Cahn2013	10x Quashie2012; 2x Mesplede2013; 5x Liang2015

***1. Margot2012**. In vitro resistance selections using elvitegravir, raltegravir, and two metabolites of elvitegravir M1 and M4. Antiviral Res; **2. Quashie2012.** Characterization of the R263K mutation in HIV-1 integrase that confers low-level resistance to the second-generation integrase strand transfer inhibitor dolutegravir. J Virol **3. Mesplete2013** Viral fitness cost prevents HIV-1 from evading dolutegravir drug pressure. Retrovirology. **4. Liang2015**. Substitutions in HIV-1 Integrase Is Incompatible with High-Level Viral Replication and the Development of High-Level Drug Resistance. J Virol; **5. Cahn2013**. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet; **6. Rhee2016.** PR, RT, and IN Variation. J Virol.*

Novel DTG-Resistance Mutations: G118R

INI	In vitro selection	In vivo selection	In vitro resistance
RAL		N=1; Malet2011	7x (Kobayashi2008); 26x (Malet2011); 14x (Quashie2015); 8x (Malet2014); 20x (Munir2015); 1x (Brenner2016)
EVG			2.6x (Kobayashi2008); 9x (Malet2011); 7x (Quashie2015); 3x (Malet2014); 1x (Bremer2016)
DTG	Quashie2015 Brenner2016	N=2; Brenner2016	12x (Quashie2015); 10x (Malet2014); 20x (Munir2015); 1x (Brenner2016)

1. Malet2011*. The HIV-1 integrase G118R mutation confers raltegravir resistance to the CRF02_AG HIV-1 subtype. JAC;* ***2. Kobayashi2008****. Selection of diverse and clinically relevant integrase inhibitor-resistant human immunodeficiency virus type 1 mutants. Antiviral Res.* ***3.*** **Malet2014**. New raltegravir resistance pathways induce broad cross-resistance to all currently used integrase inhibitors. JAC **4. Quashie2015**. Differential effects of the G118R, H51Y, and E138K resistance substitutions in different subtypes of HIV integrase. J Virol. **5. Munir 2015.** G118R and F121Y mutations identified in patients failing raltegravir treatment confer dolutegravir resistance. JAC. 6**. Brenner2016**, Development of a G118R mutation in HIV-1 integrase following a switch to dolutegravir monotherapy leading to cross-resistance to integrase inhibitors.

Conclusions

- There are many novel NRTI, NNRTI, and PI-selected mutations but most are rare and accessory.
- Additional work is needed to identify the full-spectrum of INSTI-resistance mutations.
- Additional work is needed to determine whether transmitted TDF resistance will increase.
- Cross-resistance within the NRTI, PI, and INSTI classes is incomplete, thus providing opportunities for developing more than three lines of therapy even in regions where genotypic resistance testing is not available.