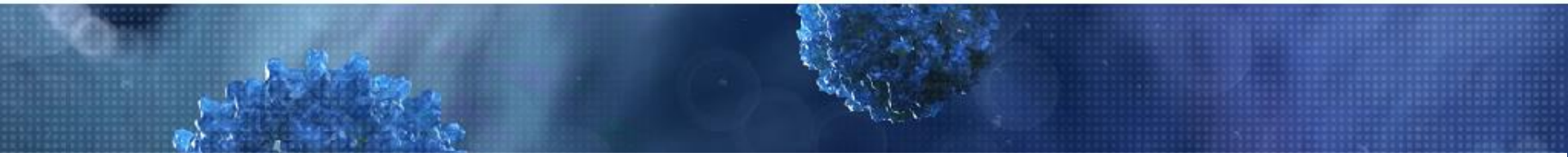
Erasmus MC

Viroscience lab

WHERE SKILLS MEET TO STUDY & PROTECT



Transmission of integrase resistance HIV

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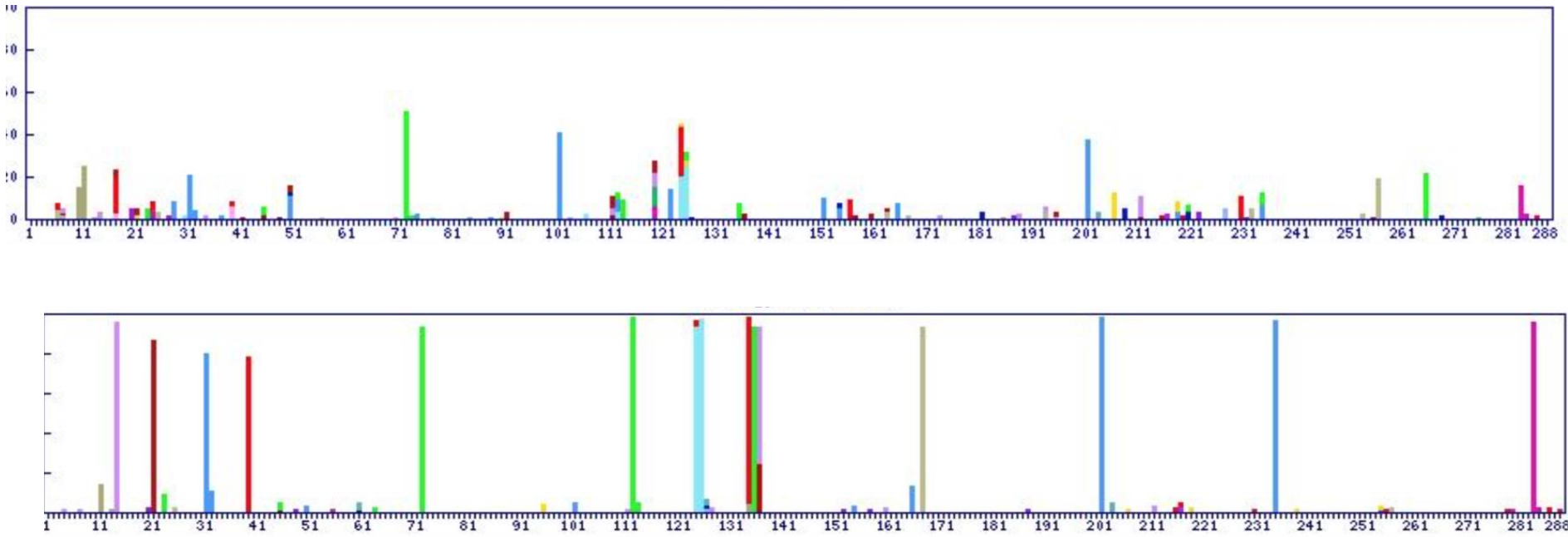
Major resistance mutations (Stanford) 15000 sequences INI naïve, all subtypes

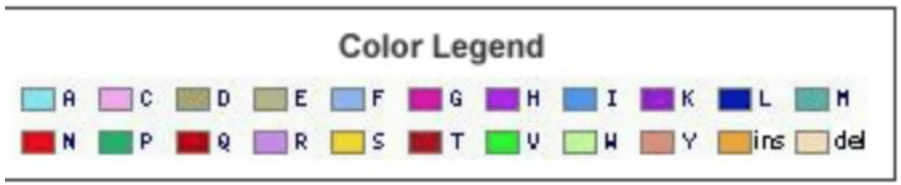
Consensus	66 T	92 E	118 G	138 E	140 G	143 Y	147 S	148 Q	155 N	263 R
Bictegravir (BIC)	K	Q	R	KAT	SAC			**HRK**	H	K
Dolutegravir (DTG)	K	Q	R	KAT	SAC			**HRK**	H	K
Elvitegravir (EVG)	**AIK**	**Q**	**R**	**KAT**	**SAC**		**G**	**HRK**	**H**	**K**
Raltegravir (RAL)	AI**K**	**Q**	**R**	**KAT**	**SAC**	**RCH**		**HRK**	**H**	K

66 no
92 no
118 no
138 0,2 % K
139 no
140 no
143 no
147 no
148 no
155 no
263 0,1 % K

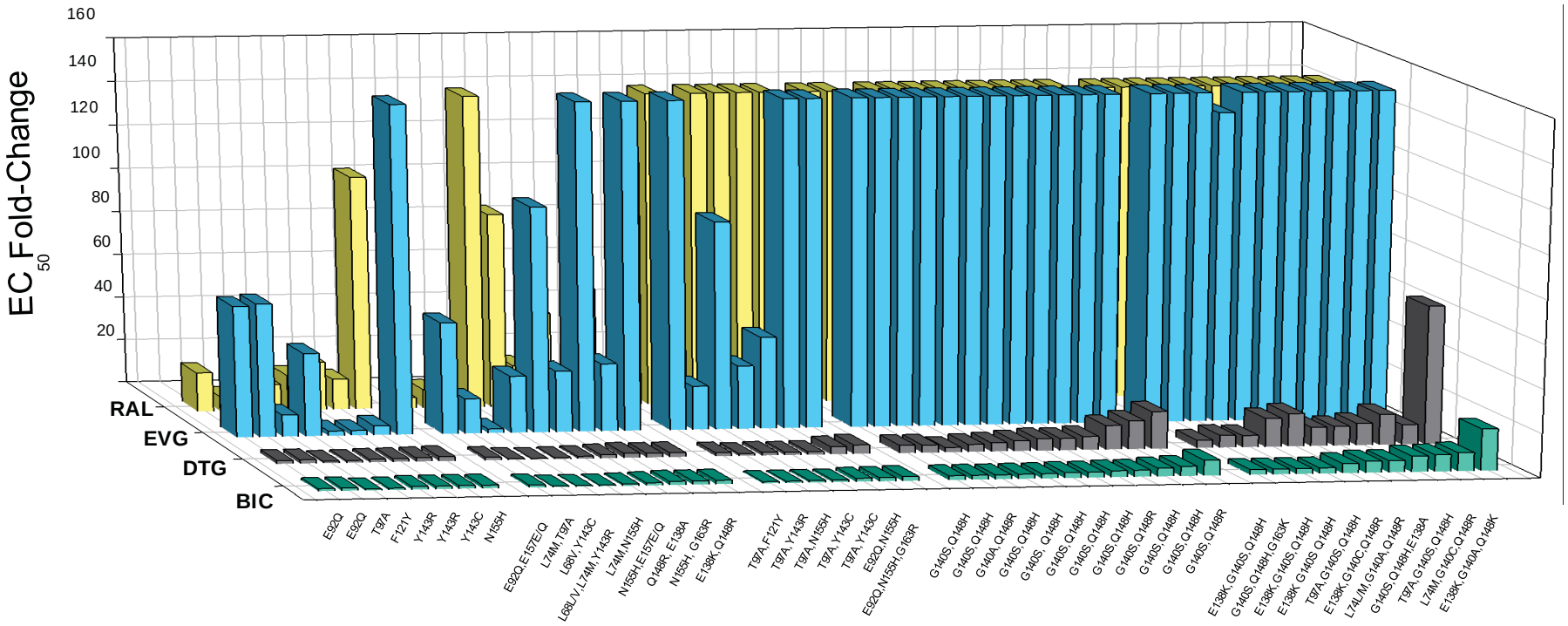
Additional integrase mutations
H51Y, L74M, Q95K, T97A, F121Y, Y143G/K/S/A, P145S, Q146P, V151A/L, S153F/Y, N155S/T, E157Q, G163 K/R, S230R

Percent natural variation at positions in subtype B and AE (Stanford)





Integrase Inhibitor (INSTI) Resistance Mutations



Adapted from White K et al, 14th Euro Workshop, May 2016, Rome

Year	Antiretroviral class and agent[a]					Event
	NRTI	NNRTI	PI	EI	InSTI	
1986	ZDV	–	–	–	–	Yarchoan *et al.* [33] publish first clinical trial
1987	ZDV	–	–	–	–	FDA approval [34]
1993	ZDV	–	–	–	–	Erice *et al.* [13] report TDR
	–	NVP	–	–	–	Cheeseman *et al.* [17] publish first clinical trial
1995	–	–	SQV	–	–	Kitchen *et al.* [21] publish first clinical trial
	–	–	SQV	–	–	FDA approval [34]
1996	–	NVP	–	–	–	FDA approval [34]
1997	–	NVP	–	–	–	Imrie *et al.* [18] report TDR
1998	–	–	SQV	–	–	Hecht *et al.* [20] report TDR
2002	–	–	–	ENF	–	Kilby *et al.* [35] publish first clinical trial
2003	–	–	–	ENF	–	FDA approval [34]
2006	–	–	–	–	RAL	Markowitz *et al.* [36] publish first clinical trial
2007	–	–	–	–	RAL	FDA approval [34]
	–	–	–	ENF	–	Peuchant *et al.* [37] report TDR
2010	–	–	–	–	RAL	Young *et al.* [11] and Boyd *et al.* [12] report TDR

EI, entry inhibitor; ENF, enfuvirtide (T-20); FDA, US Food and Drug Administration; InSTI, integrase strand-transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RAL, raltegravir; SQV, saquinavir; TDR, transmitted drug resistance; ZDV, zidovudine.

Table 1. Date of first clinical trial publication, US FDA approval and initial report of TDR for selected antiretrovirals

The transmission of resistance to Integrase inhibitors (INSTIs) is still a rare event.

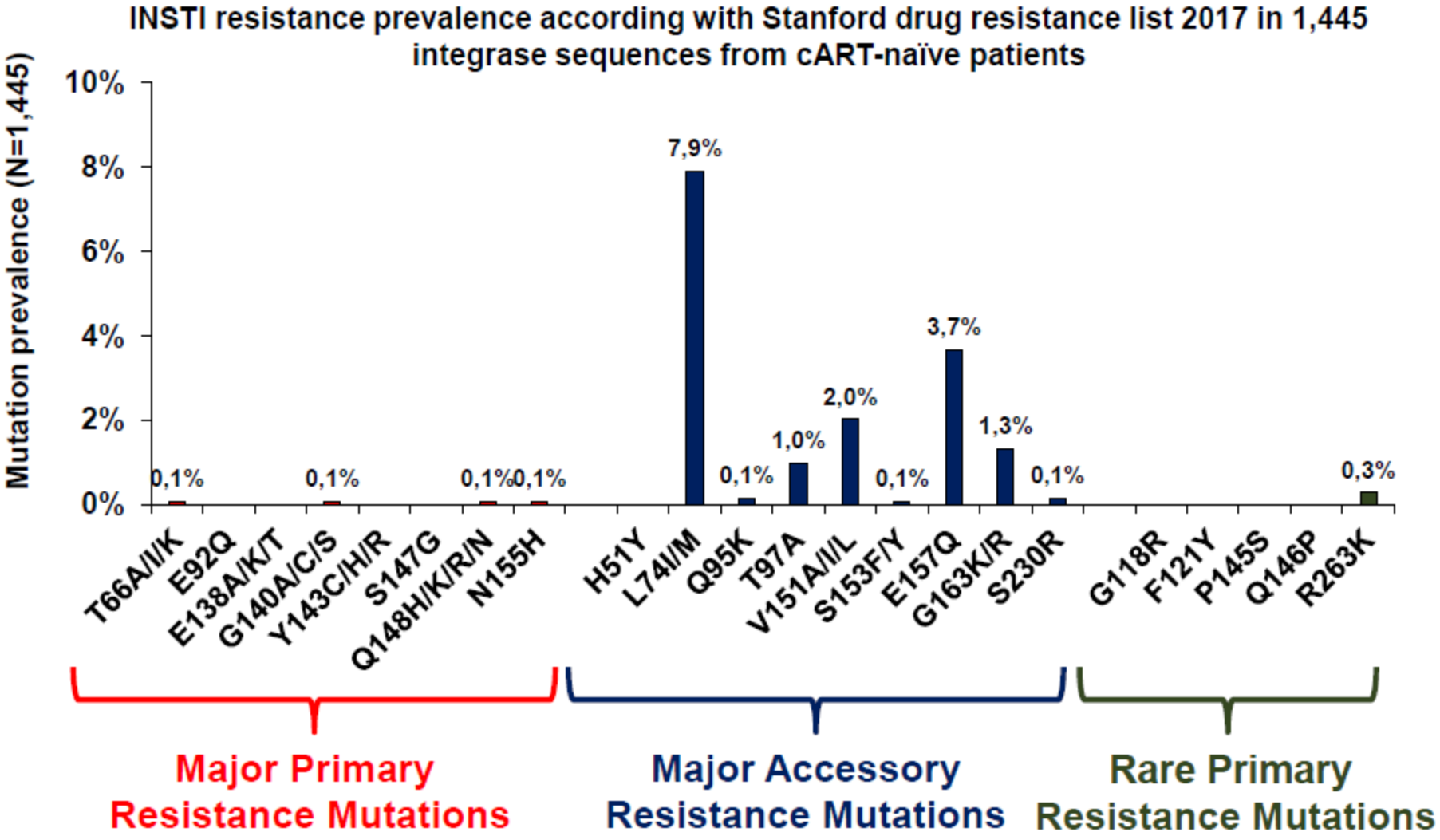
- *Young B, Fransen S, Greenberg K, et al. Transmission of integrase strand-transfer inhibitor, multidrug resistant HIV-1: Case report and natural history of response to raltegravir-containing antiretroviral therapy. Antivir Ther. 2011; 16(2):253–256.*
- *Boyd S, Maldarelli F, Sereti I, et al. Transmitted raltegravir resistance in an HIV-1 CRF_Ag infected patient. Antivir Ther. 2011; 16(2):257–261.*
- *Hurt CB. Transmitted resistance to HIV integrase strand-transfer inhibitors: right on schedule. Antivir Ther. 2011;16(2):137-40.*
- *Bertoli A, Armenia D, Santoro MM, et al. An Italian case of transmitted integrase inhibitor resistance in a drug-naïve patient: a refined analysis by ultra-deep-454 pyrosequencing. European HIV clinical forum 2016.*
- *Hernandez AL, Ocfemia MCB, Saduvala N, et al. HIV Integrase Genotypic Testing and Resistance in the United States - 9 U.S. Jurisdictions. CROI 2017. Abstract N° 478.*

Transmitted INSTI resistance is rarely found

- Few large series of genotype studies looking in large recent cohorts at base line published

- In those studies transmittion of INSTI resistance major mutations remain rare events.

In our experience, among 1,445 sequences from drug-naïve patients the presence of INSTI primary resistance is very rare



Sui-Yuan Chang, et al
2016 Nature scientific reports

- To determine the prevalence of INSTI-related genetic mutations in Taiwan before its increasing use as the first-line regimen
- Raltegravir introduced in 2009

Materials and methods

- Genotypic resistance assays were performed on the HIV-1 strains obtained from ARV-naïve patients (N=948) and ARV-experienced patients without exposure to INSTI (N=359), and raltegravir-experienced patients (N=63) from 2006 to 2015.

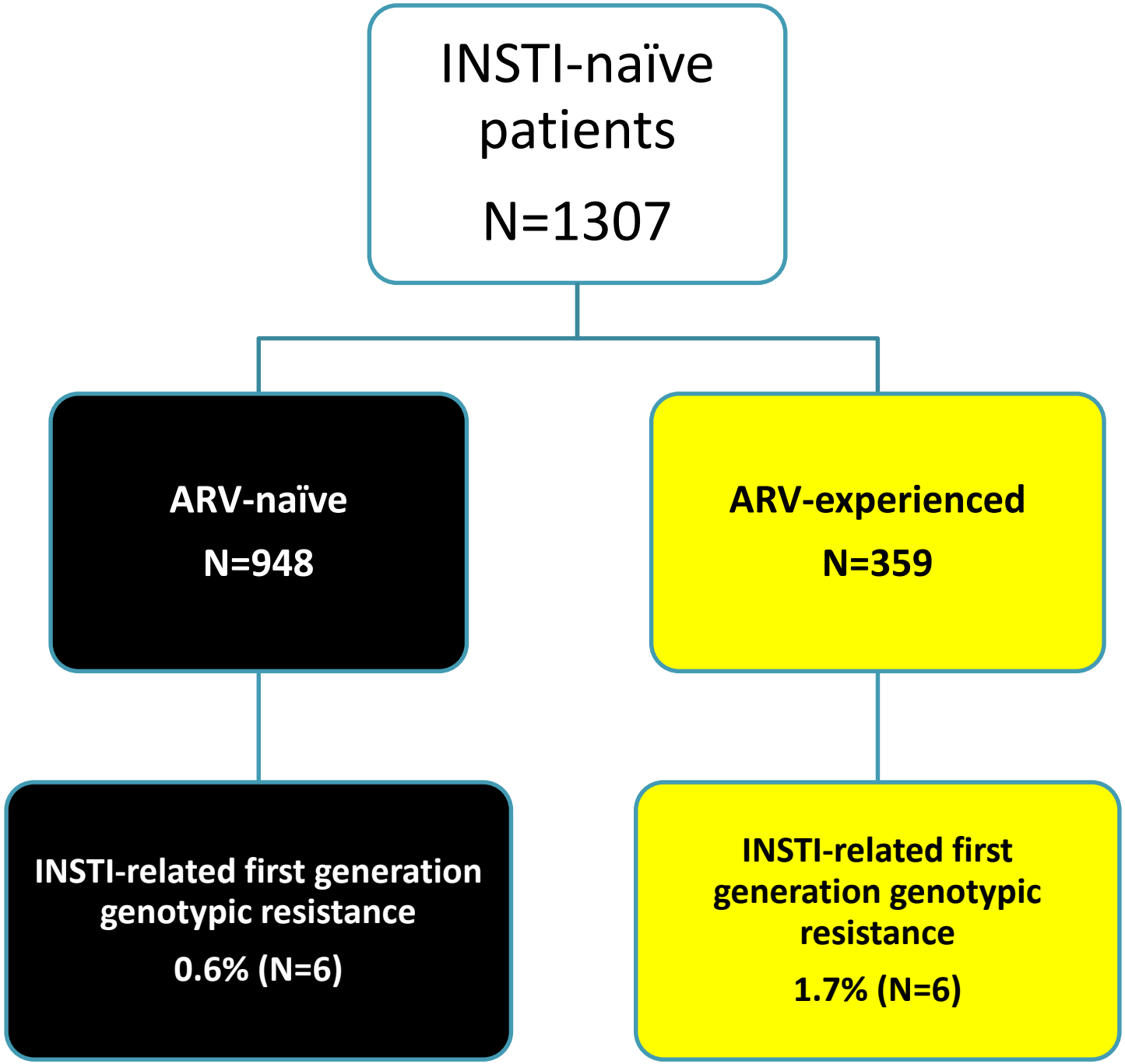
- Signature INSTI mutations were defined according to the IAS-USA list.
  - Y143C/H/R, Q148H/K/R, and N155H

Materials and methods

- The integrase substitutions with a Stanford HIVdb score ≧10 to at least one INSTI was included for analysis.
  - H51Y, T66A/I/K, L74M, E92G/Q/V, Q95K, T97A, F121Y, E138A/K, G140S/C/A, Y143G/K/S/A, P145S, Q146P, S147G, V151A/L, S153F/Y, N155S/T, E157Q, G163 K/R, S230R, and **R263K**

Clinical characteristics of 1307 HIV-positive patients who were InSTI-naive

Characteristics		INSTI-naïve N=1307
Male, n (%)		1211/1263 (95.8)
Age, mean (SD), years		33.0 (9.7)
Risk behavior, n (%)	MSM	1035/1230 (84.1)
	IDU	104/1230 (8.5)
	Heterosexual	84/1230 (6.8)
	Others	7/1230(0.6)
HIV subtypes, n (%)	B	1120 (85.7)
	C	117 (9.0)
	CRF01_AE	64 (4.9)
	Others	6 (0.5)
PVL, mean (SD) log_{10} copies/mL		5.43 (6.05)
PVL> 5 log_{10} copies/mL, n (%)		427/1290 (33.1)
CD4 count, mean (SD), cells/µL		299 (198)
CD4 count <200 cells/µL, n (%)		405/1277(31.7)
Genotypic INSTI resistance, n (%)		12 (0.9)


INSTI-naïve patients
N=1307
ARV-naïve
N=948
ARV-experienced
N=359
INSTI-related first generation genotypic resistance
0.6% (N=6)
INSTI-related first generation genotypic resistance
1.7% (N=6)

Summary of ARV-related genotypic mutations detected in 12 INSTI-naive patients all with subtype B

Case Number	Date of specimen collected	ART-naive	INSTI		NRTI	nNRTI	PI
			Major mutations	Minor mutations	major mutations	major mutations	major mutations
3992	2006/11	1	Q148QR				
930	2013/1	1	Q148QR				
947	2013/1	1	Q148QR				
1043	2013/3	1	Q148QR				
1323	2013/5	1	P145PR, Q148QR				
1800	2013/8	1	Y143R	T97A, G163R	M184V		
608	2012/6	0	Q148QR		K70R, M184V		M46I, I50L, V82A
965	2013/1	0	Q148QR		K65KR	Y181CY, F227CF	
1035	2013/3	0	Q148QR		M184I	V108I, Y181C	
1066	2013/3	0	Q148QR, N155NS	S230R		G190A	
1312	2013/5	0	P145PR, Q148QR	L74V	T215S		
4562	2015/6	0	Q148QR	H51HR			

Numbers of RAL-experienced patients having INSTI signature mutations and combination of INSTI-related mutations

		Q148			N155H	Y143R
		H	K	R		
Concomitant major mutations	N155H			1		
Concomitant minor mutations	H51R			1	1	
	L74I				3	
	T97A					2
	G140S	11		1		
	V151I				1	
	T97A+G140S	1				
	T97A+E157Q					1
	E138K+G140A		2			
	V151I+E157Q				1	
No minor mutations				1	1	2

Summary

- Of the 1307 HIV-1 strains from patients never exposed to INSTI, the overall prevalence of resistance mutations to INSTI was 0.9% (n=12), with an increase to 1.2% (9/766) in 2013.
- Of these 12 strains, 11 harboured Q148H/K/R, one Y143R, and none N155H.
- E92V, E138AK (2X), Y143S, N155S, S230R, R263K

Scherrer JID 2016
Between 2008-2014 in 1 of 1316 sequences (0,1%) in Switzerland a major INSTI mutations was detected.
The first year after introduction of INSTI only 85 0f 2571 failed, vs PI 1543 0f 5923 9 18,2 times, 609 of 4347 NNRTI 7,2 times

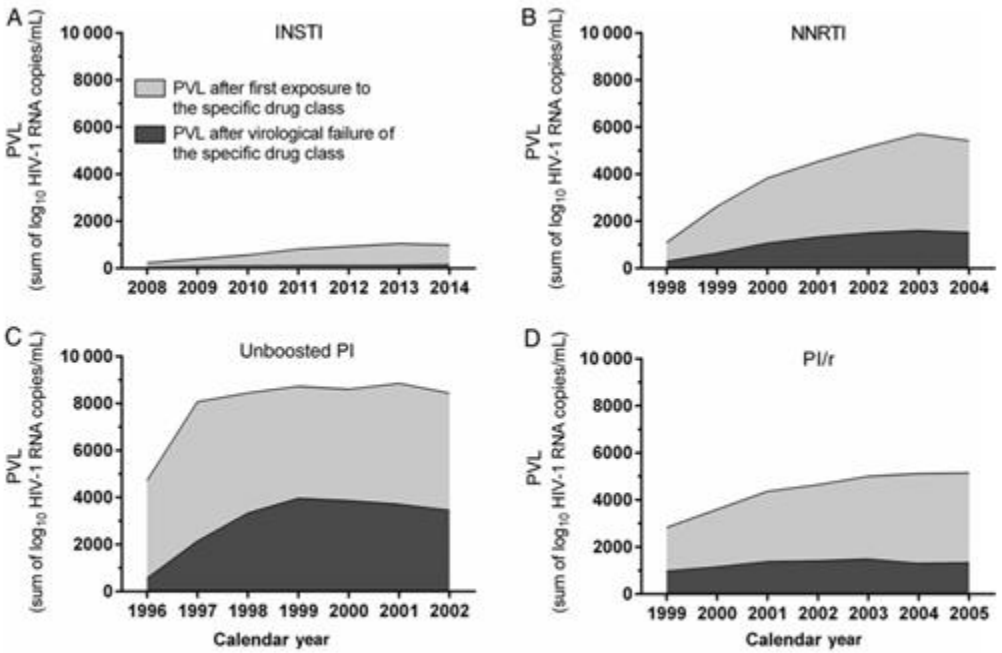


Figure 1. *A–D*, Population viral load (PVL) of patients treated with integrase strand transfer inhibitor (INSTIs; *A*), nonnucleoside reverse transcriptase inhibitors (NNRTIs; *B*), unboostsed protease inhibitors (PIs; *C*), and ritonavir-boosted PI (PI/r; *D*) in the 7 years after introduction of each drug class. The areas represent the PVL after first exposure to the specific drug class (light gray) and the PVL after virological failure of the specific drug class (dark gray). Abbreviation: HIV-1, human immunodeficiency virus type 1.

¶

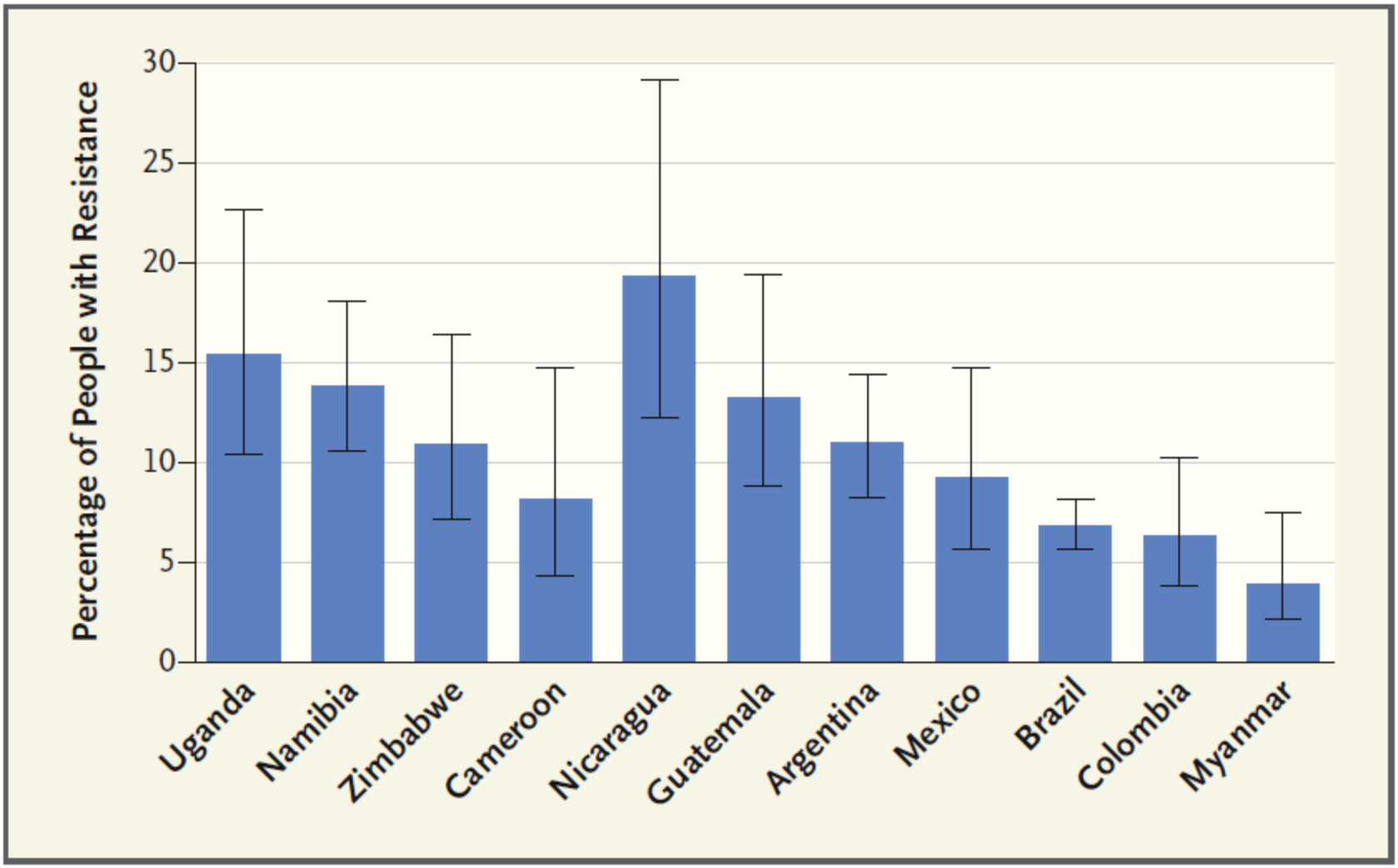
Testing for baseline integrase resistance ?
R Koulias et al CID 2017

- Decision analysis model, 96 weeks clinical outcomes and cost effectiveness of testing versus non testing
- First line use Dolutegravir and a 0,1 % resistance.

- Testing would not improve clinical outcome and would cost more.

DHSS guidelines 2016

- Standard genotypic drug-resistance testing in ARV-naive persons involves testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance ***is a concern***, providers should ensure that genotypic resistance testing also includes INSTI genotype testing **(BIII)**.



Pretreatment HIV Drug Resistance to Nonnucleoside Reverse Transcriptase Inhibitors in 11 Countries.

Shown are the percentages of people tested who had resistance to efavirenz or nevirapine. I bars denote 95% confidence intervals. Data are from the World Health Organization.[1]

In conclusion

- Transmission of INSTI resistant viruses in resource rich countries remains rare.
- Those viruses that are transmitted were selected by first generation insti (raltegravir and elvitegravir) and in most cases wil not be highly resistance to dolutegravir and bictegravir.
- The limited transmission rates can be explained by the low numbers amount of INSTI failures and the short periods of failures.
- Guidelines recommend to test for transmitted insti resistance on indication (cave transmitted (N)NRTI and PI transmitted resistance)
- Under routine conditions when using second generation INSTI first line in a STR with three ARV and proper viral load baseline INSTI resistance testing is most likely of limited value.
- Monitoring for transmitted INSTI resistance remains warranted.

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