Ospedale Luigi Sacco
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Regione Lombardia
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UNIVERSITAS STUDIORUM MEDIOLANENSIS

Le determinazione della resistenza è ancora necessaria per impostare la prima linea di trattamento?

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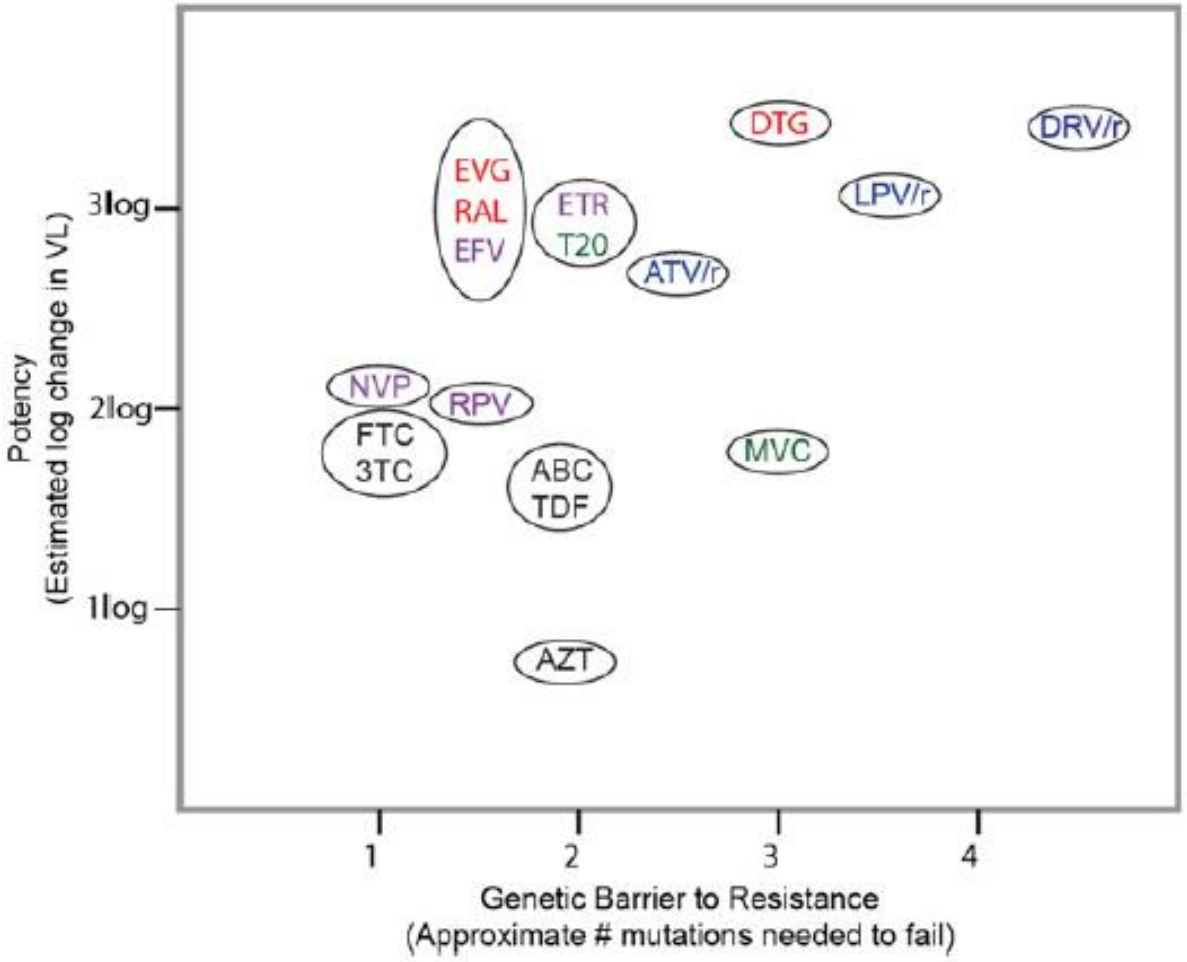
GIORNATE INFETTIVOLOGICHE "LUIGI SACCO"
14-15 giugno 2018

i miei conflitti di interesse

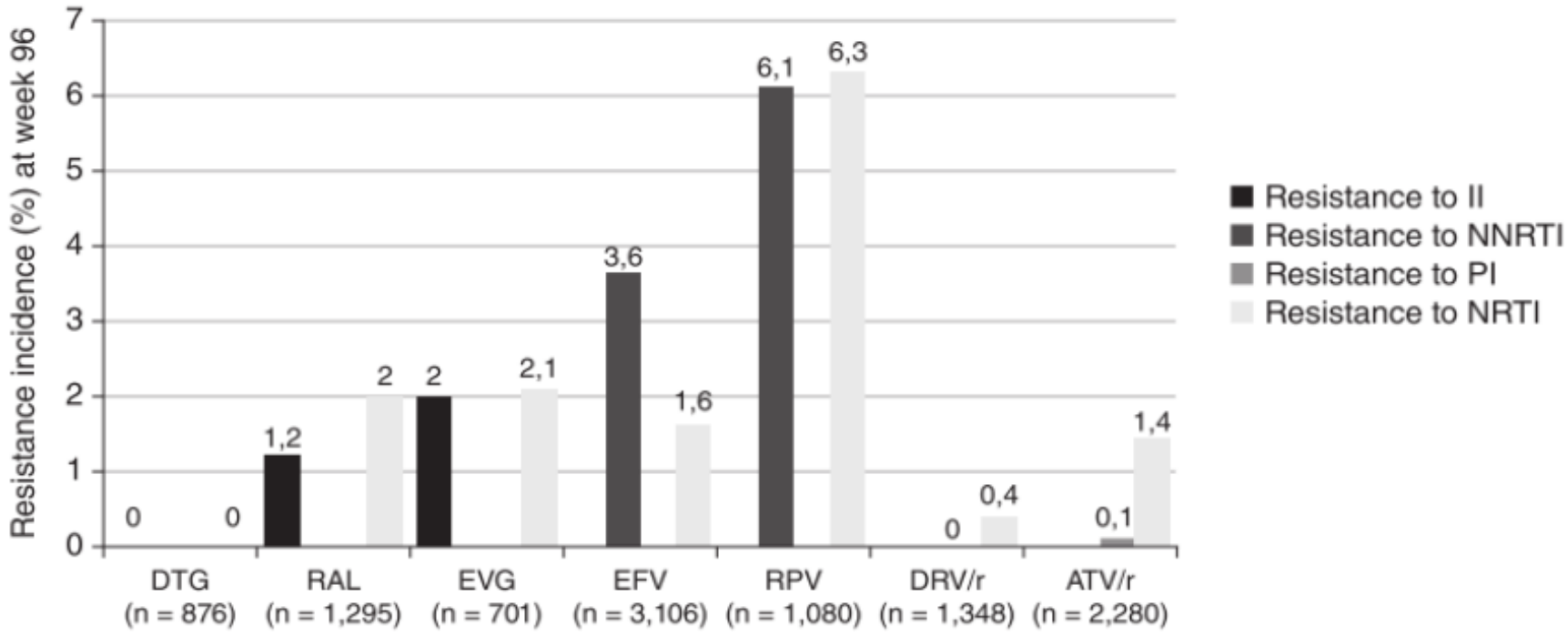
BMS, Gilead, Janssen, MSD, ViiV/GSK

ARV potency versus genetic barrier to resistance



DS Clutter et al. Infection, Genetics and Evolution 2016

Genetic Barrier to Resistance



Libre JM et al. AIDS Rev. 2015

Global HIV-1 transmitted drug resistance in the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial

JD Baxter,[1] D Dunn,[2] E White,[2] S Sharma,[3] AM Geretti,[4] MJ Kozal,[5] MA Johnson,[6] S Jacoby,[7] JM Llibre[8] and J Lundgren[9] for the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) START Study Group

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Objectives

HIV-1 transmitted drug resistance (TDR) in treatment-naïve individuals is a well-described phenomenon. Baseline genotypic resistance testing is considered standard of care in most developed areas of the world. The aim of this analysis was to characterize HIV-1 TDR and the use of resistance testing in START trial participants.

Methods

In the Strategic Timing of AntiRetroviral Treatment (START) trial, baseline genotypic resistance testing results were collected at study entry and analysed centrally to determine the prevalence of TDR in the study population. Resistance was based on a modified 2009 World Health Organization definition to reflect newer resistance mutations.

Results

Baseline resistance testing was available in 1946 study participants. Higher rates of testing occurred in Europe (86.7%), the USA (81.3%) and Australia (89.9%) as compared with Asia (22.2%), South America (1.8%) and Africa (0.1%). The overall prevalence of TDR was 10.1%, more commonly to nonnucleoside reverse transcriptase inhibitors (4.5%) and nucleoside reverse transcriptase inhibitors (4%) compared with protease inhibitors (2.8%). The most frequent TDR mutations observed were M41L, D67N/G/E, T215F/Y/I/S/C/D/E/V/N, 219Q/E/N/R, K103N/S, and G190A/S/E in reverse transcriptase, and M46I/L and L90M in protease. By country, the prevalence of TDR was highest in Australia (17.5%), France (16.7%), the USA (12.6%) and Spain (12.6%). No participant characteristics were identified as predictors of the presence of TDR.

Conclusions

START participants enrolled in resource-rich areas of the world were more likely to have baseline resistance testing. In Europe, the USA and Australia, TDR prevalence rates varied by country.

Keywords: antiretroviral therapy, drug resistance, HIV

Accepted 21 November 2014

Pretreatment HIV-drug resistance in Mexico and its impact on the effectiveness of first-line antiretroviral therapy: a nationally representative 2015 WHO survey

*Santiago Ávila-Ríos, Claudia García-Morales, Margarita Matías-Florentino, Karla A Romero-Mora, Daniela Tapia-Trejo, Verónica S Quiroz-Morales, Helena Reyes-Gopar, Hezhao Ji, Paul Sandstrom, Jesús Casillas-Rodríguez, Juan Sierra-Madero, Eddie A León-Juárez, Marisol Valenzuela-Lara, Carlos Magis-Rodríguez, Patricia Uribe-Zuñiga, Gustavo Reyes-Terán, for the HIVDR MexNet Group**

Summary

Background WHO has developed a global HIV-drug resistance surveillance strategy, including assessment of pretreatment HIV-drug resistance. We aimed to do a nationally representative survey of pretreatment HIV-drug resistance in Mexico using WHO-recommended methods.

Methods Among 161 Ministry of Health antiretroviral therapy (ART) clinics in Mexico, the largest, including 90% of ART initiators within the Ministry of Health (66 in total), were eligible for the survey. We used a probability-proportional-to-size design method to sample 25 clinics throughout the country. Consecutive ART-naive patients with HIV about to initiate treatment were invited to participate in the survey; individuals with previous exposure to ART were excluded. We assessed pretreatment HIV-drug resistance by Sanger sequencing and next-generation sequencing of viruses from plasma specimens from eligible participants with Stanford University HIV Drug Resistance Database methods. We obtained follow-up data for a median of 9·4 months (range 6–12) after enrolment. We investigated possible relations between demographic variables and pretreatment drug resistance with univariate and multivariate logistic regression.

Findings Between Feb 3 and July 30, 2015, we screened 288 patients in 25 clinics, from whom 264 provided successfully sequenced viruses with no evidence of current exposure to antiretroviral drugs. With the Sanger method, of these 264 participants, 41 (15·5%, 95% CI 11·4–20·5) had pretreatment resistance to any antiretroviral drug and 28 (10·6%, 7·2–15·0) had pretreatment resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs). At least low-level pretreatment resistance (Stanford penalty score ≥15) was noted in 13 (4 · 9%) of participants to efavirenz and in 23 (8·7%) to the combination tenofovir plus emtricitabine plus efavirenz. With next-generation sequencing, of 264 participants, 38 (14·4%, 95% CI 10·4–19·2) had pretreatment resistance to any antiretroviral drug and 26 (9·8%, 6·5–14·1) had pretreatment resistance to NNRTIs. After median follow-up of 8 months (IQR 6·5–9·4, range 5–11) after ART initiation, 97 (72%) of 135 NNRTI initiators achieved viral suppression (<50 copies per mL) compared with ten (40%) of 25 individuals who started with protease inhibitor-based regimens (p=0·0045). After multivariate regression considering pretreatment resistance and initial ART regimen as composite variables, people starting NNRTIs with pretreatment drug resistance achieved significantly lower viral suppression (odds ratio 0·24, 95% CI 0·07–0·74; p=0·014) than patients without NNRTI resistance.

Interpretation High levels of pretreatment drug resistance were noted in Mexico, and NNRTI pretreatment drug resistance significantly reduced the effectiveness of first-line ART regimens based on these drugs. Baseline HIV-drug resistance testing for initial ART follow-up and decision making should be considered.

Lancet HIV 2016; 3: e579–91

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See Comment page e553

*Members listed at the end of the report

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doi:10.1093/jac/dkw343 Advance Access publication 28 September 2016

Journal of Antimicrobial Chemotherapy

HIV-1 drug resistance mutations emerging on darunavir therapy in PI-naive and -experienced patients in the UK

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Background: Darunavir is considered to have a high genetic barrier to resistance. Most darunavir-associated drug resistance mutations (DRMs) have been identified through correlation of baseline genotype with virological response in clinical trials. However, there is little information on DRMs that are directly selected by darunavir in clinical settings.

Objectives: We examined darunavir DRMs emerging in clinical practice in the UK.

Patients and methods: Baseline and post-exposure protease genotypes were compared for individuals in the UK Collaborative HIV Cohort Study who had received darunavir; analyses were stratified for PI history. A selection analysis was used to compare the evolution of subtype B proteases in darunavir recipients and matched PI-naive controls.

Results: Of 6918 people who had received darunavir, 386 had resistance tests pre- and post-exposure. Overall, 2.8% (11/386) of these participants developed emergent darunavir DRMs. The prevalence of baseline DRMs was 1.0% (2/198) among PI-naive participants and 13.8% (26/188) among PI-experienced participants. Emergent DRMs developed in 2.0% of the PI-naive group (4 mutations) and 3.7% of the PI-experienced group (12 mutations). Codon 77 was positively selected in the PI-naive darunavir cases, but not in the control group.

Conclusions: Our findings suggest that although emergent darunavir resistance is rare, it may be more common among PI-experienced patients than those who are PI-naive. Further investigation is required to explore whether codon 77 is a novel site involved in darunavir susceptibility.

Poster 485

ARV RESISTANCE MUTATIONS IN PATIENTS RECEIVING A WHO TDF-CONTAINING 1ST-LINE REGIMEN

Rhee SY[1], Gupta RK[2], Shafer RW[1] and TenoRes Study Group

[1]Division of Infectious Diseases, Stanford University; [2]UCL, Department of Infection, London, UK

Figure 1: Prevalence of NRTI-associated TDF-regimen associated mutations (TRAMs)*

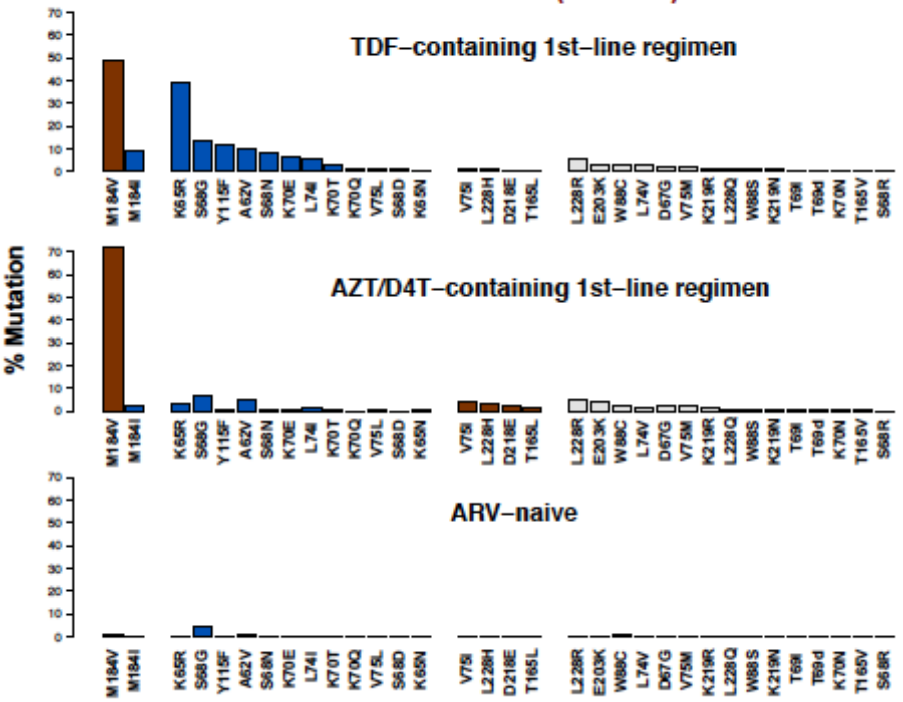


Table 1. Summary of 2,873 study individuals with virological failure on a first-line TDF-containing regimen according to treatment regimen, region and subtype

Characteristics	Percentage (n) In 2,873 individuals
NRTI received	
FTC	36% (1,047)
3TC	64% (1,826)
NNRTI received	
NVP	21% (611)
EFV	79% (2,262)
LMIC resident	
Sub-Saharan Africa	56% (1,617)
South/Southeast Asia	15% (436)
Latin America	1% (18)
UIC resident	
Europe	22% (637)
North America	6% (165)
Subtype	
C	53% (1,524)
B	20% (561)
CRF01_AE	13% (365)
G	5% (135)
A	4% (110)
Other	6% (178)

13 TDF-associated mutations, the most commonly occurring mutations included K65R (occurring in 40% of individuals), S68G/N (21%), Y115F (12%), K70E/Q/T (11%), A62V (10%), and L74I (6%).

CROI 2017 seattle

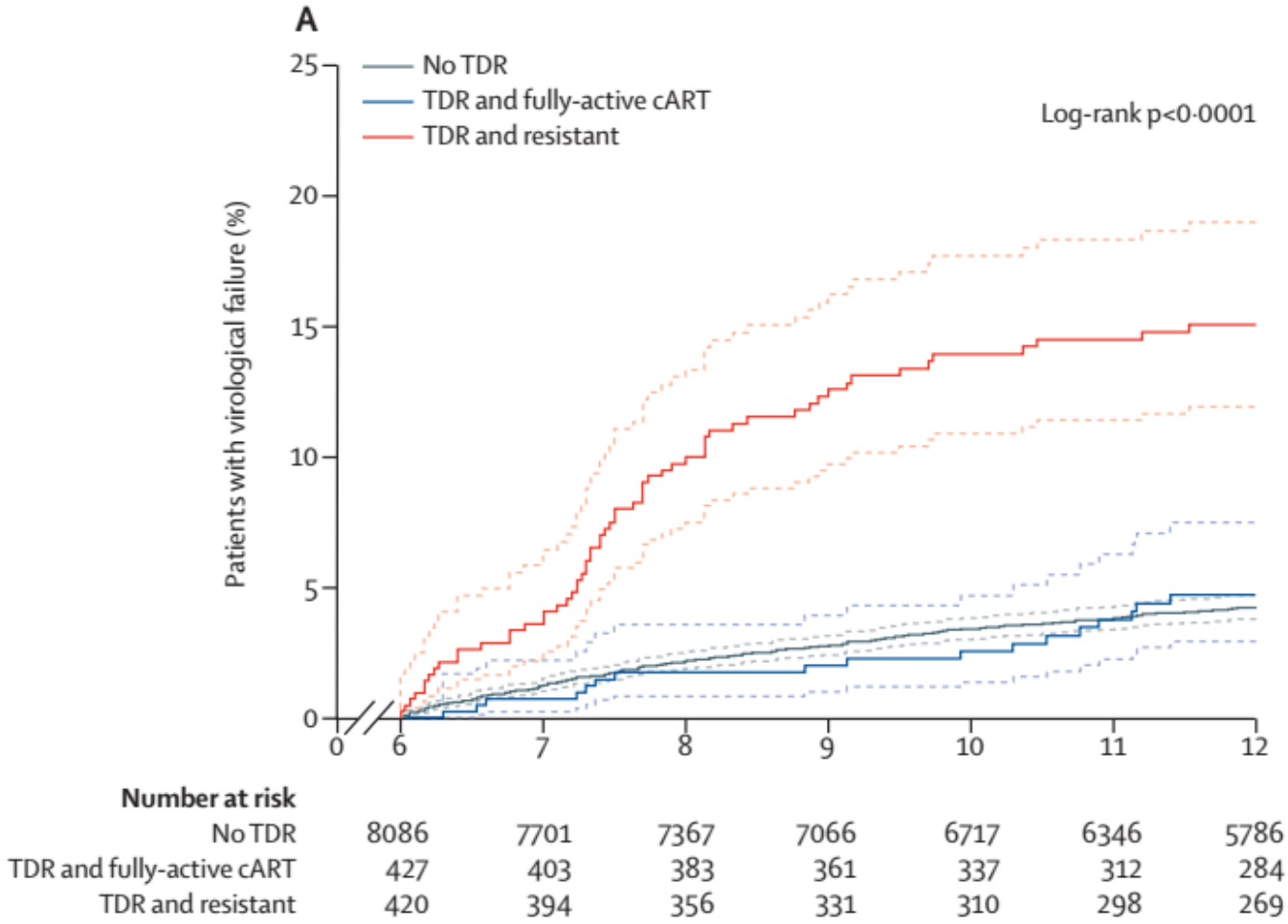
Drug naïves

Baseline characteristics and efficacy results of main ARV studies in HIV naive pts

		pVL (median)	VL>5 log	CD4 median	CD4<200
CASTLE	ATV/r	5.0	51%	205	47%
	LPV/r	5.0	47%	204	48%
ACTG5202	ATV/r	4.6	43%	230	44%
	EFV	4.7	43%	230	42%
ARTEMIS	DRV/r	4.9	34%	228	41%
	LPV/r	4.8	34%	218	42%
STARMRK	RAL	5.1	55%	212	47%
	EFV	5.0	51%	204	48%
102	EVG/c	4.7	34%	391	12%
	EFV	4.8	33%	382	14%
103	EVG/c	4.9	43%	364	15%
	ATV/c	4.9	40%	375	11%
SINGLE	DTG	4.7	32%	335	14%
	EFV	4.7	31%	339	14%
SPRING-2	DTG	4.5	28%	359	13%
	RAL	4.6	28%	362	12%
FLAMINGO	DTG	4.5	25%	390	10%
	DRV/c	4.5	25%	400	10%
ACTG5257	RAL	4.7	32%	304	31%
	ATV/c	4.6	32%	309	29%
	DRV/c	4.6	28%	310	29%

A Antinori, ICAR 2016

Why ARV resistance testing in ARV-naïve patients

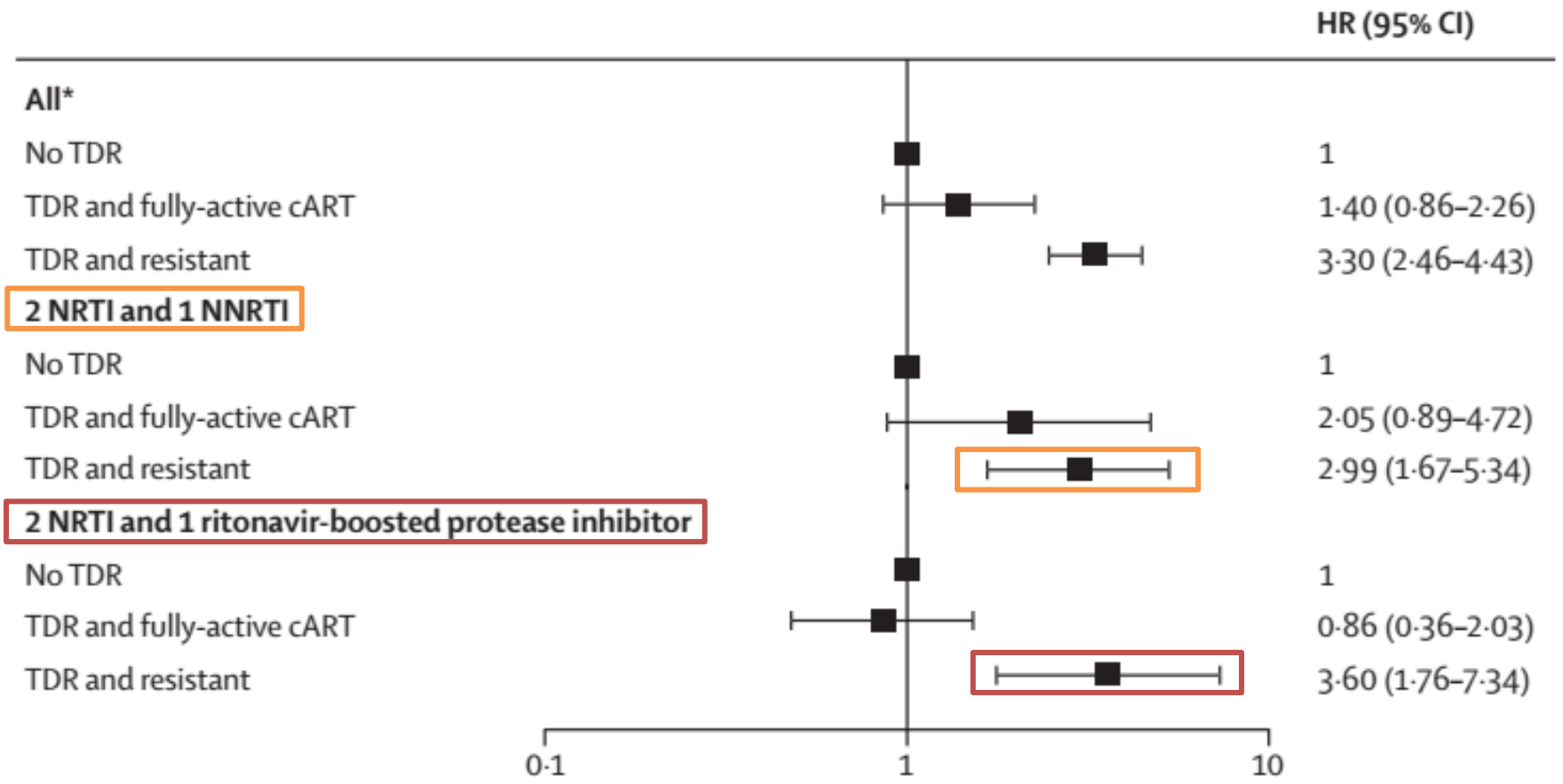


- First cART started from 1998 onward
- 10,056 patients from 25 cohorts
  - 90·5% had HIV without TDR
  - 4·7% had at least one mutation but received fully-active cART
  - 4·8% had at least one mutation and resistance to at least one drug

Risk of virological failure according to patient groups

Wittkop, Lancet Infec Dis 2011

Why ARV resistance testing in ARV-naïve patients



Adjusted HRs in all patients and patients starting a regimen containing two NRTIs plus either one NNRTI or one ritonavir-boosted protease inhibitor

Wittkop, Lancet Infec Dis 2011

Journal of Medical Virology 86:1648–1655 (2014)

The Role of Baseline HIV-1 RNA, Drug Resistance, and Regimen Type as Determinants of Response to First-Line Antiretroviral Therapy

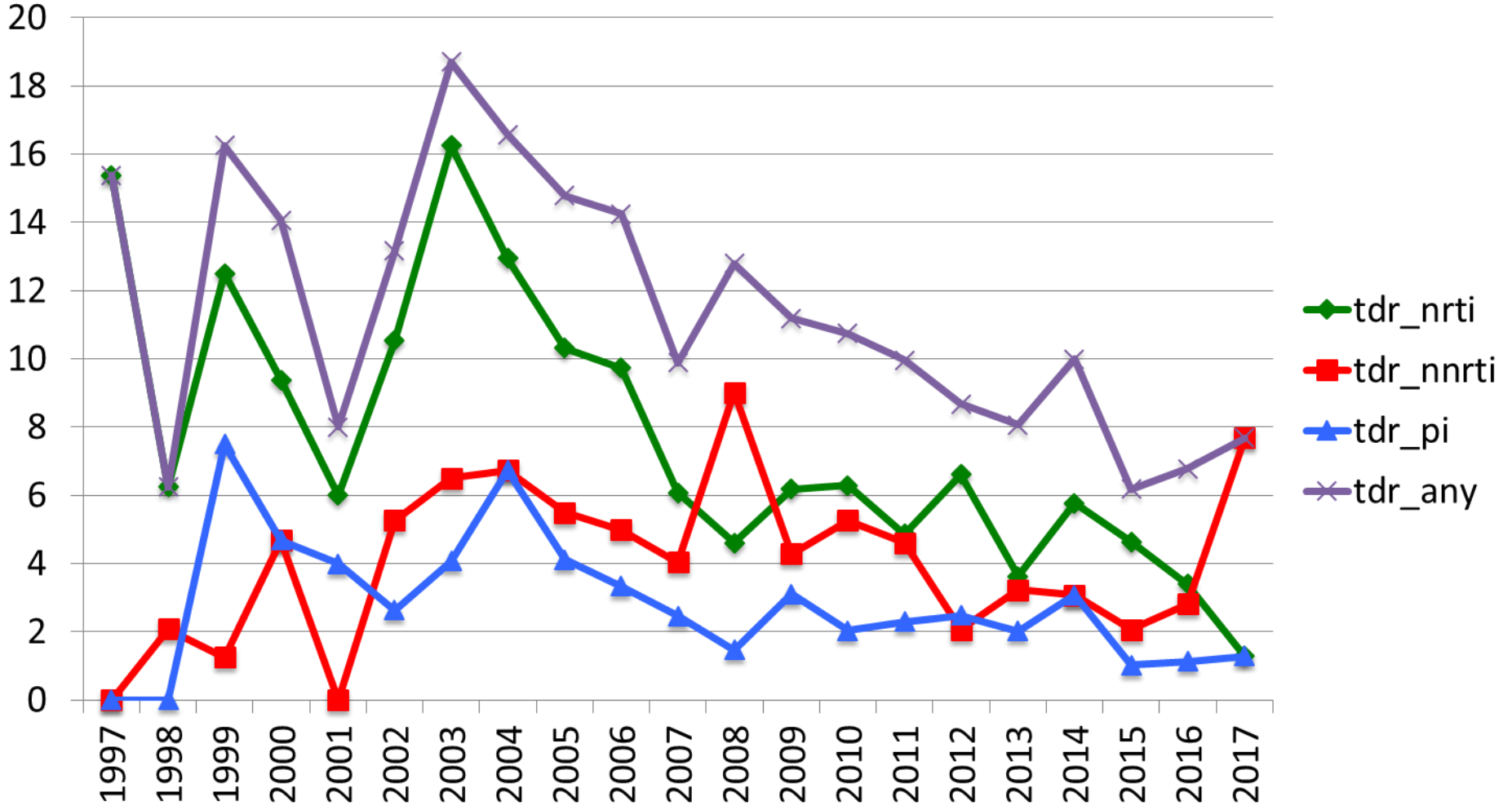
Antonio Di Biagio,[1] Stefano Rusconi,[2]* Angela Marzocchetti,[3] Alessio Signori,[4] Irene Schiavetti,[4] Bianca Bruzzone,[5] Laura Monno,[6] Grazia Punzi,[6] Maria Grazia Colao,[7] Giovanni Penco,[8] Maurizio Zazzi,[9] Andrea De Luca,[3,10] and on behalf of the ARCA Collaborative Group

TABLE II. Variables Associated With Virological Success

	Univariate		Multivariate*	
	HR (95 % CI)	*P*-value	HR (95% CI)	*P*-value
Baseline HIV RNA (copies/ml)				
<100,000	1.00 (Ref)	<0.001	1.00	<0.001
100,000–499,999	0.73 (0.64–0.83)		0.76 (0.65–0.88)	
≥500,000	0.67 (0.56–0.79)		0.52 (0.42–0.64)	
wGSS				
≥3	1.00 (Ref)	0.05	1.00 (Ref)	0.003
<3	0.74 (0.54–1.00)		0.58 (0.40–0.83)	
NRTI backbone of initial regimen				
TDF/FTC	1.00 (Ref)	0.021	1.00 (Ref)	0.73
ABC/3TC	1.17 (0.98–1.39)		1.07 (0.88–1.30)	
ZDV/3TC	0.91 (0.79–1.04)		1.04 (0.84–1.28)	
Other	0.86 (0.71–1.03)		1.16 (0.88–1.54)	
Gender				
Male vs. female	0.84 (0.73–0.96)	0.008	0.76 (0.64–0.90)	0.001
3rd drug of initial regimen				
bPI	1.00 (Ref)	0.038	1.00	<0.001
NNRTI	0.96 (0.85–1.09)		0.98 (0.83–1.14)	
INI	2.02 (1.23–3.31)		3.23 (1.84–5.68)	
Other	1.02 (0.80–1.32)		1.32 (0.96–1.82)	

Time to achieve HIV RNA <50 copies/ml. Univariate and multivariate Cox regression (N = 1,305).
Ref, reference category for interpretation of odds-ratios (OR); wGSS, weighted genotypic susceptibility score; NRTI, nucleoside reverse transcriptase inhibitors; TDF/FTC, tenofovir/emtricitabine; ABC/3TC, abacavir/lamivudine; ZDV/3TC, zidovudine/lamivudine; bPI, boosted protease inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; INI, integrase inhibitor.
*Variables were mutually adjusted in the multivariate model that also included transmission mode, presence of transmitted drug resistance, baseline $CD4^+$ and viral subtype.

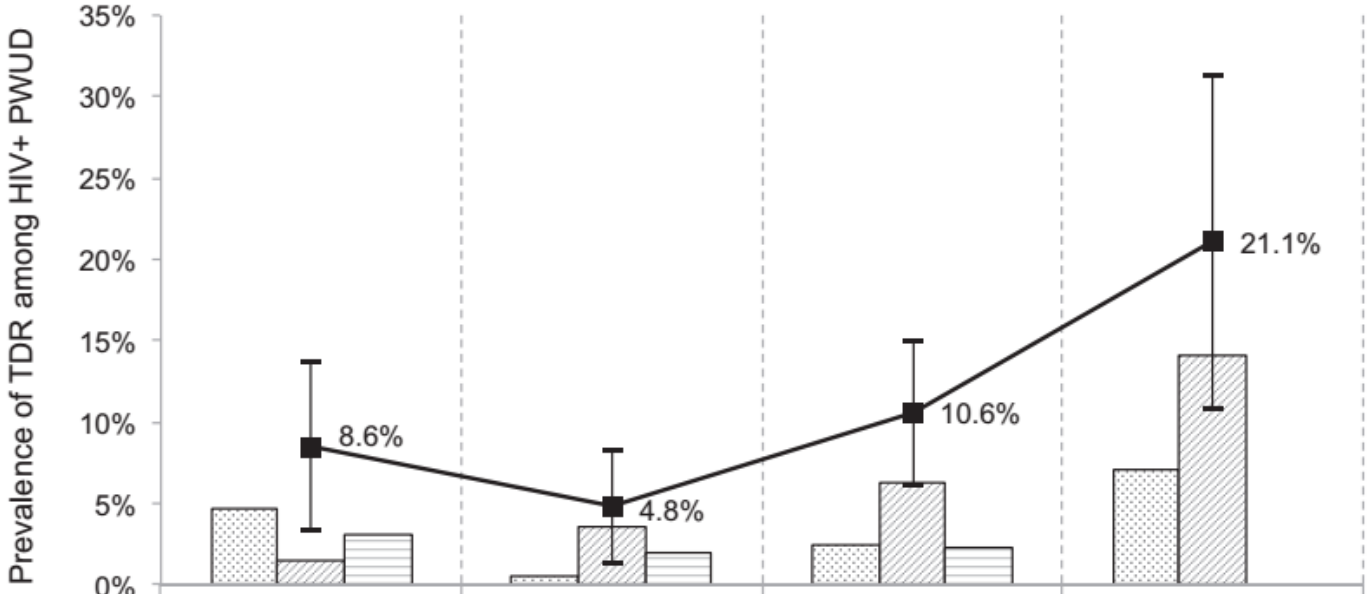
Andamento resistenze primarie nel database ARCA



N pts. 13 48 80 64 50 76 123 193 291 421 445 477 420 493 391 242 243 260 194 177 78

Courtesy of Maurizio Zazzi, 2017

HIV DR mainly involves NNRTIs



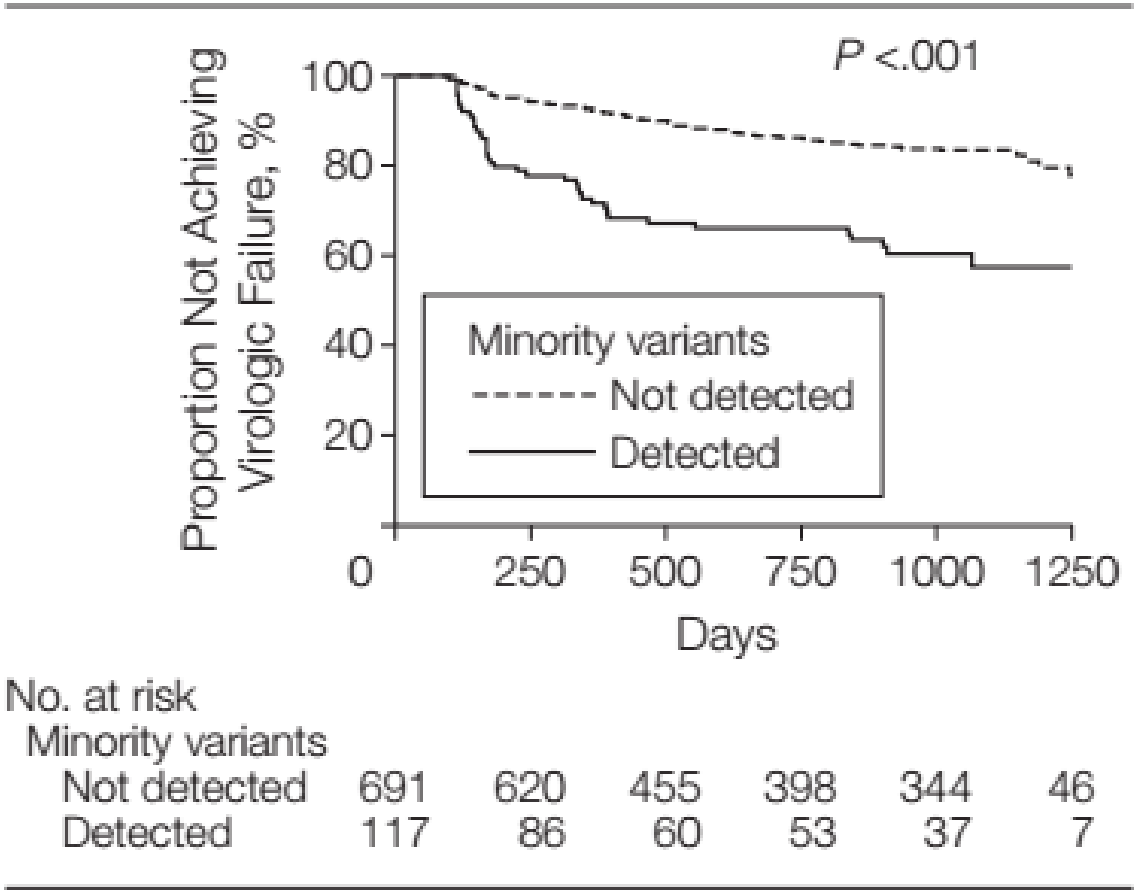
	1996-1999 (128)	2000-2005 (167)	2006-2009 (207)	2010-2015 (71)
NRTI	4.7%	0.6%	2.4%	7.0%
NNRTI	1.6%	3.6%	6.3%	14.1%
PI	3.1%	1.9%	2.4%	0.0%
Any TDR	8.6%	4.8%	10.6%	21.1%
lower CI any TDR	3.4%	1.3%	6.2%	10.9%
upper CI any TDR	13.8%	8.3%	15.0%	31.3%

Based on 2 prospective cohorts of IDUs in Vancouver followed 1996-2015

N=573 (18% with recent HIV infection)

Socias, CID 2017

Low-Frequency HIV-1 Drug Resistance Mutations and Risk of NNRTI-Based Antiretroviral Treatment Failure – *A systematic review and pooled analysis*



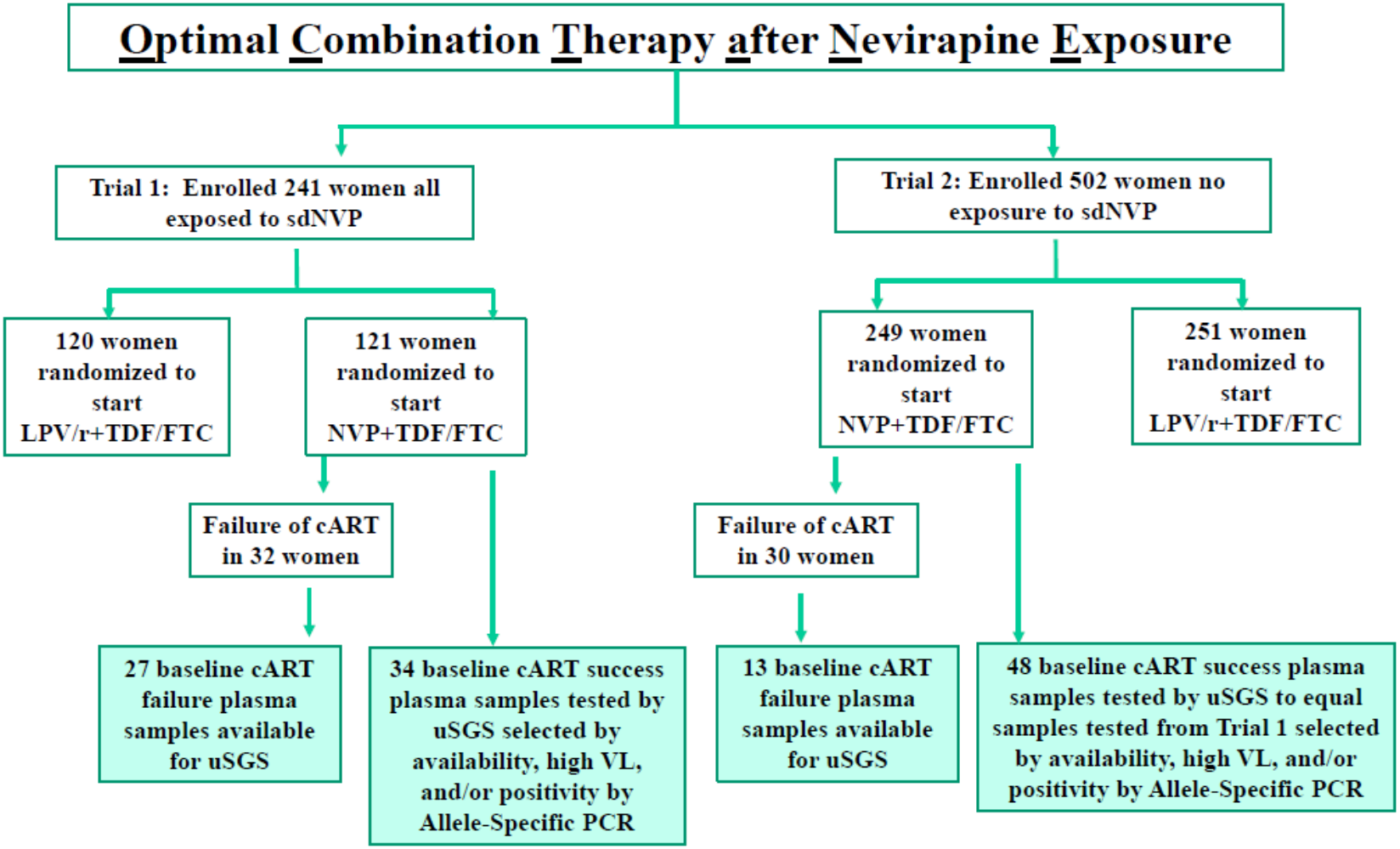
Kaplan-Meier Curves for Proportion of Patients Without Virologic Failure by Presence of Drug-Resistant HIV-1 Minority Variants

- 10 studies, 985 patients, 187 with minority drug resistance mutations (mDRMs)
- mDRMs associated with an increased risk of virologic failure (HR = 2.3; 95% CI 1.7-3.3; P<.001) after controlling for medication adherence, race/ethnicity, baseline CD4 cell count, and plasma HIV-1 RNA levels
- **Risk most strongly associated with NNRTI mDRMs**
- Dose-dependent increased risk of virologic failure found in participants with a higher proportion or quantity of mDRMs

Li, JAMA 2011

Rare HIV variants with linked dual-class resistance are associated with ART failure

Study Design/Sample Collection



Valerie F Boltz et al., CROI 2018 - Boston, poster 536

Rare HIV variants with linked dual-class resistance are associated with ART failure

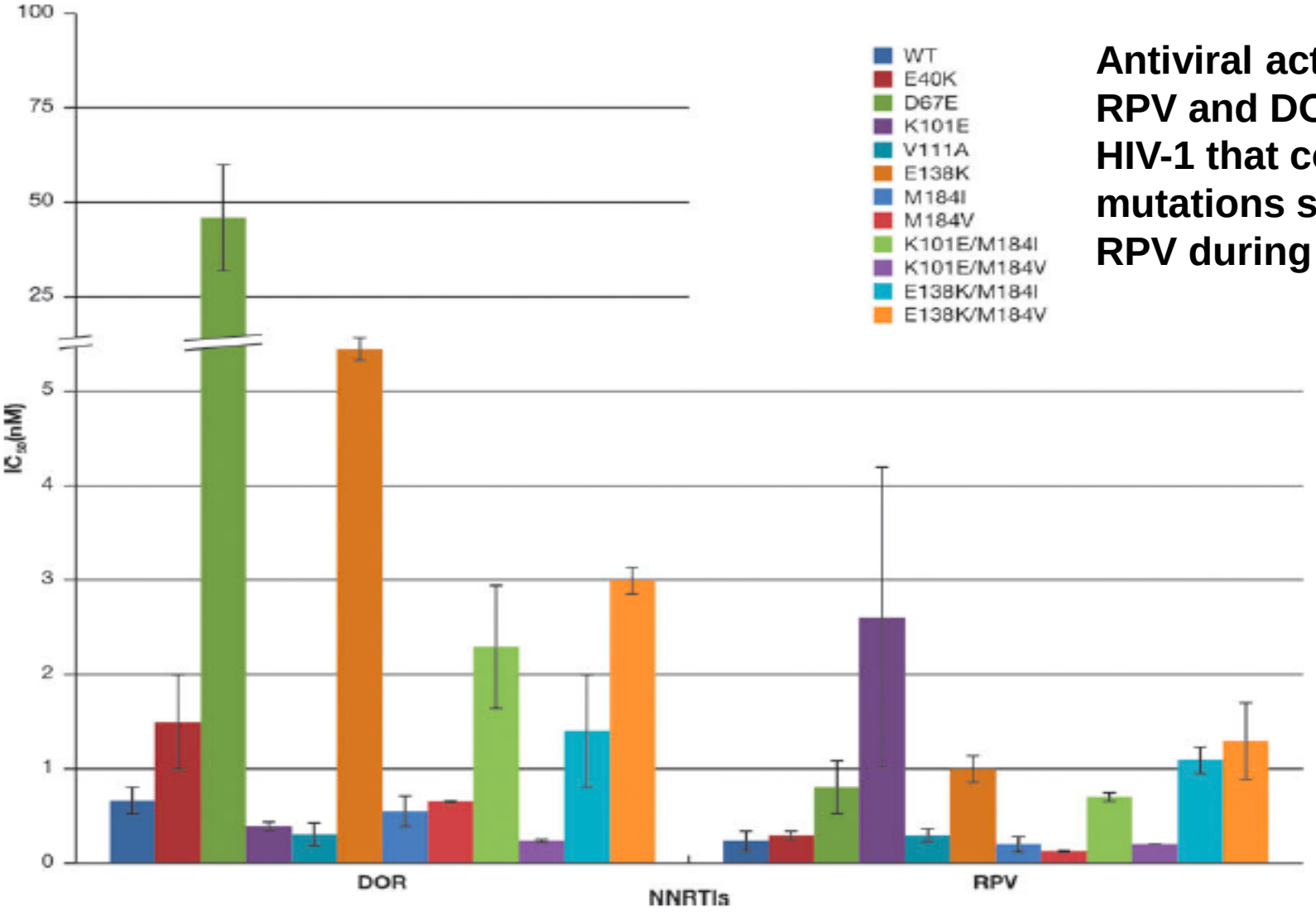
Trial	Donor ID	sdNVP	cART outcome	Total # genomes obtained	Linked mutations conferring dual-class resistance (% frequency)	Linked mutations conferring single-class resistance (% frequency)	Population genotype at failure
1	T1F03	Yes	Failure	4,687	65R/181C (0.04), 184I/103N (0.02)	101E/103N(0.02), 103N/190E (0.02)	181C, 184V
	T1F04			13,747	184I/190E (0.007)	none	65R, 103N, 181C, 184V
	T1F05			20,327	none	103N/190A (0.005)	103N, 181C, 184V, 190A
	T1F07			31,531	184I/103N (0.003), 184V/103N (0.003)	181C/103N (0.003), 103N/190A (0.006)	103N, 181C, 184V
	T1F08			27,132	184I/103N (0.004)	none	103N, 106M, 184I
	T1F09			16,373	none	100I/103N (0.006), 103N/190E (0.006)	181C, 184V
	T1F18			12,692	65R/103N (0.008)	none	Not Done
	T1F23			12,155	103N/184I (0.008), 184I/190E (0.008)	none	103N
	T1F44			44,124	103N/184I (0.002), 184I/190E (0.005)	none	65R, 103N, 181C
	T1F47			57,278	184I/190E (0.002)	none	181C, 184V
	T1S12		Success	6,080	none	101E/190A (0.03)	Not applicable
	T1S26			13,861	184I/190E (0.007)	none	Not applicable
	T1S39			2,496	none	101E/190A (0.04)	Not applicable
	T1S40			4,998	103N/184I (0.02)	none	Not applicable
	T1S58			20,085	none	100I/190E (0.005)	Not applicable
2	T2F17	No	Failure	18,214	184I/190E (0.005)	none	65R, 106M, 181C, 184V
	T2F23			5,819	103N/184I (0.02)	103N/190A (0.16)	65R, 103N, 181C
	T2S43		Success	25,918	184I/190E (0.004)	none	Not applicable
	T2S48			36,814	184I/190E (0.003)	none	Not applicable

Valerie F Boltz et al., CROI 2018 - Boston, poster 536

HIV DR mainly involves NNRTIs

- Reasons why NNRTI PDR still remains at >5% level
  - NNRTI widely used for years
  - Low genetic barrier, except for the rarely used etravirine
  - Limited to no loss of fitness for most NNRTI mutants

Rilpivirine and Doravirine have complementary efficacies against NNRTI-Resistant HIV-1 mutants



Antiviral activities of RPV and DOR against HIV-1 that contains mutations selected by RPV during cART

J Acquir Immune Defic Syndr. 2016 August 15; 72(5): 485–491

Transmitted INSTI resistance cases

Case report	Age/sex	Country	Risk group	IN muts	Other muts
Boyd 2011	47/F	US	Heterosexual	N155H	PR: L33F M36L Q58E T74P RT: K103N
Young 2011	53/M	US	MSM	Q140S Q148H	PR: V32I M46I V82A L90M RT: K70KR K103N V106A
Volpe 2015	40/M	US	?	Q148H	PR: V82A RT: M41L D67N L74V K101E Y181C G190S
Zoufaly 2016	30/M	Austria	?	F121Y	None
Rafiei 2017	28/F	Australia	Heterosexual	Y143HY	None

9°CONGRESSO NAZIONALE
12-14 GIUGNO 2017

POSTER DISCUSSION

Basic science and virology

Is transmitted drug resistance to integrase inhibitors becoming a concern in Italy? A new case report

Maria M. Santoro, PhD

University of Rome "Tor Vergata", Italy

Resistance mutations

PI: L63P

NRTI: T215S

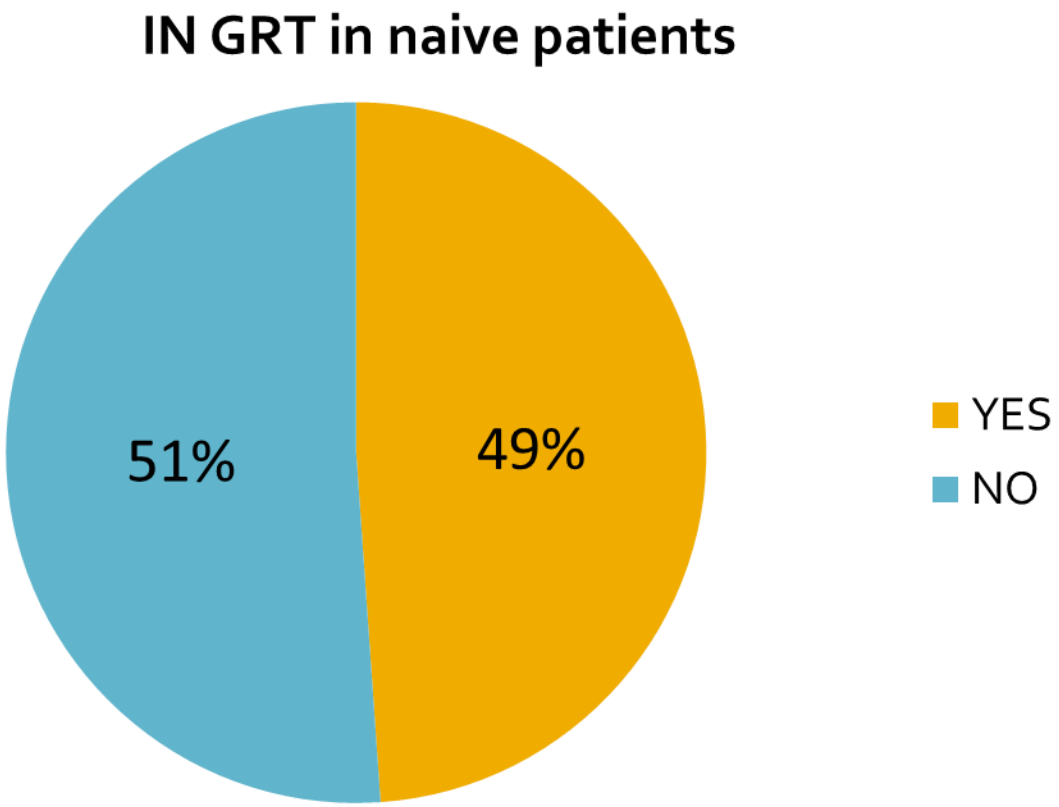
NNRTI: V108VI E138G H221Y M230L

INT: G140S Q148H

Università di Roma Tor Vergata

ICAR Italian Conference on AIDS and Antiviral Research

Integrase DR testing in ARV-naïves



- Survey on HIV drug resistance testing in Italy
- 131 centers, 95 (72.5%) responses
- **14/95 (14.7%) centers do not request resistance tests**

Lo Caputo et al., ICAR 2017 Siena

Two ph. III trials in naïve pts: BIC/FTC/TAF vs DTG/ABC/3TC or DTG+FTC/TAF

Screening Visit RT/PR Genotype

	Drug		GENESEQ™	ASSESSMENT*	
	Generic Name	Brand Name	Drug Resistance Associated Mutations Detected	Drug	
NRTI	Abacavir	Ziagen	K70R	ABC	Sensitive
	Didanosine	Videx	None	ddI	Sensitive
	Emtricitabine	Emtriva	K70R	FTC	Sensitive
	Lamivudine	Epivir	K70R	3TC	Sensitive
	Stavudine	Zerit	K70R	d4T	Sensitive
	Tenofovir	Viread	K70R	TFV	Sensitive
	Zidovudine	Retrovir	K70R	ZDV	Resistance Possible
NNRTI	Delavirdine	Rescriptor	K103N	DLV	Resistant
	Efavirenz	Sustiva	K103N	EFV	Resistant
	Etravirine	Intelence	None	ETR	Sensitive
	Nevirapine	Viramune	K103N	NVP	Resistant
	Rilpivirine	Edurant	K103N	RPV	Sensitive
PI	Atazanavir	Reyataz	None	ATV	Sensitive
		Reyataz / r‡	None	ATV/r	Sensitive
	Darunavir	Prezista / r‡	None	DRV/r	Sensitive
	Fosamprenavir	Lexiva / r‡	None	AMP/r	Sensitive
	Indinavir	Crixivan / r‡	None	IDV/r	Sensitive
	Lopinavir	Kaletra	None	LPV/r	Sensitive
	Nelfinavir	Viracept	None	NFV	Sensitive
	Ritonavir	Norvir	None	RTV	Sensitive
	Saquinavir	Invirase / r‡	None	SQV/r	Sensitive
	Tipranavir	Aptivus / r‡	None	TPV/r	Sensitive

Baseline Visit RT/PR Genotype and Phenotype

	Drug			PHENOSENSE™ SUSCEPTIBILITY		Evidence of Susceptibility		Net Assessment
	Generic Name	Brand Name	Cutoffs (lower – upper)	Fold Change	Increasing Drug Susceptibility Decreasing (1 – 10 – 100)	Pheno Sense	Gene Seq	
NRTI	Abacavir	Ziagen	(4.5 – 6.5)	0.73		Y	Y	Sensitive
	Didanosine	Videx	(1.3 – 2.2)	0.83		Y	Y	Sensitive
	Emtricitabine	Emtriva	(3.5)	0.86		Y	Y	Sensitive
	Lamivudine	Epivir	(3.5)	0.95		Y	Y	Sensitive
	Stavudine	Zerit	(1.7)	0.88		Y	Y	Sensitive
	Zidovudine	Retrovir	(1.9)	1.89		Y	P	Partially Sensitive
	Tenofovir	Viread	(1.4 – 4)	1.06		Y	Y	Sensitive
	NRTI Mutations		K70K/R					
NNRTI	Delavirdine	Rescriptor	(6.2)	143		N	N	Resistant
	Efavirenz	Sustiva	(3)	20		N	N	Resistant
	Etravirine	Intelence	(2.9 – 10)	1.04		Y	Y	Sensitive
	Nevirapine	Viramune	(4.5)	107		N	N	Resistant
	Rilpivirine	Edurant	(2)	1.01		Y	Y	Sensitive
	NNRTI Mutations		K103N					
PI	Atazanavir	Reyataz	(2.2)	0.85		Y	Y	Sensitive
		Reyataz / r‡	(5.2)	0.85		Y	Y	Sensitive
	Darunavir	Prezista / r‡	(10 – 90)	0.59		Y	Y	Sensitive
	Fosamprenavir	Lexiva / r‡	(4 – 11)	0.85		Y	Y	Sensitive
	Indinavir	Crixivan / r‡	(10)	0.84		Y	Y	Sensitive
	Lopinavir	Kaletra‡	(9 – 55)	0.79		Y	Y	Sensitive
	Nelfinavir	Viracept	(3.6)	0.96		Y	Y	Sensitive
	Ritonavir	Norvir	(2.5)	0.90		Y	Y	Sensitive
	Saquinavir	Invirase / r‡	(2.3 – 12)	0.70		Y	Y	Sensitive
	Tipranavir	Aptivus / r‡	(2 – 8)	0.77		Y	Y	Sensitive
	PI Mutations		none					

K White et al., CROI 2018 - Boston, poster 532

Two ph. III trials in naïve pts: BIC/FTC/TAF vs DTG/ABC/3TC or DTG+FTC/TAF

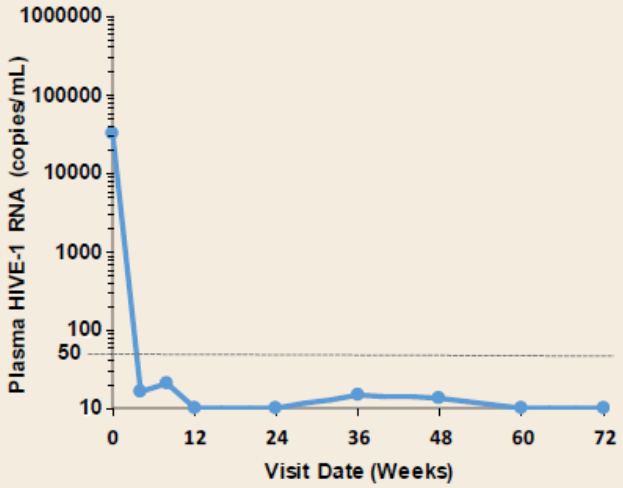
Baseline Visit IN Genotype and Phenotype

	Drug		GENESEQ™	ASSESSMENT*	
	Generic Name	Brand Name	Drug Resistance Associated Mutations Detected	Drug	
INI	Dolutegravir	Tivicay	G140S, Q148H	DTG	Resistance Possible
INI	Elvitegravir	Vitekta	G140S, Q148H	EVG	Resistant
INI	Raltegravir	Isentress	G140S, Q148H	RAL	Resistant

	Drug			PHENOSENSE™ SUSCEPTIBILITY		Assessment	
	Generic Name	Brand Name	Cutoffs (lower - upper)	Fold Change	Increasing Drug Susceptibility Decreasing (1, 10, 100)	Drug	
INI	Bictegravir	Bictegravir	(2.5)	2.14		BIC	Sensitive
INI	Dolutegravir	Tivicay	(4 – 13)	4.45		DTG	Partially Sensitive
INI	Elvitegravir	Vitekta	(2.5)	>MAX		EVG	Resistant
INI	Raltegravir	Isentress	(1.5)	>MAX		RAL	Resistant

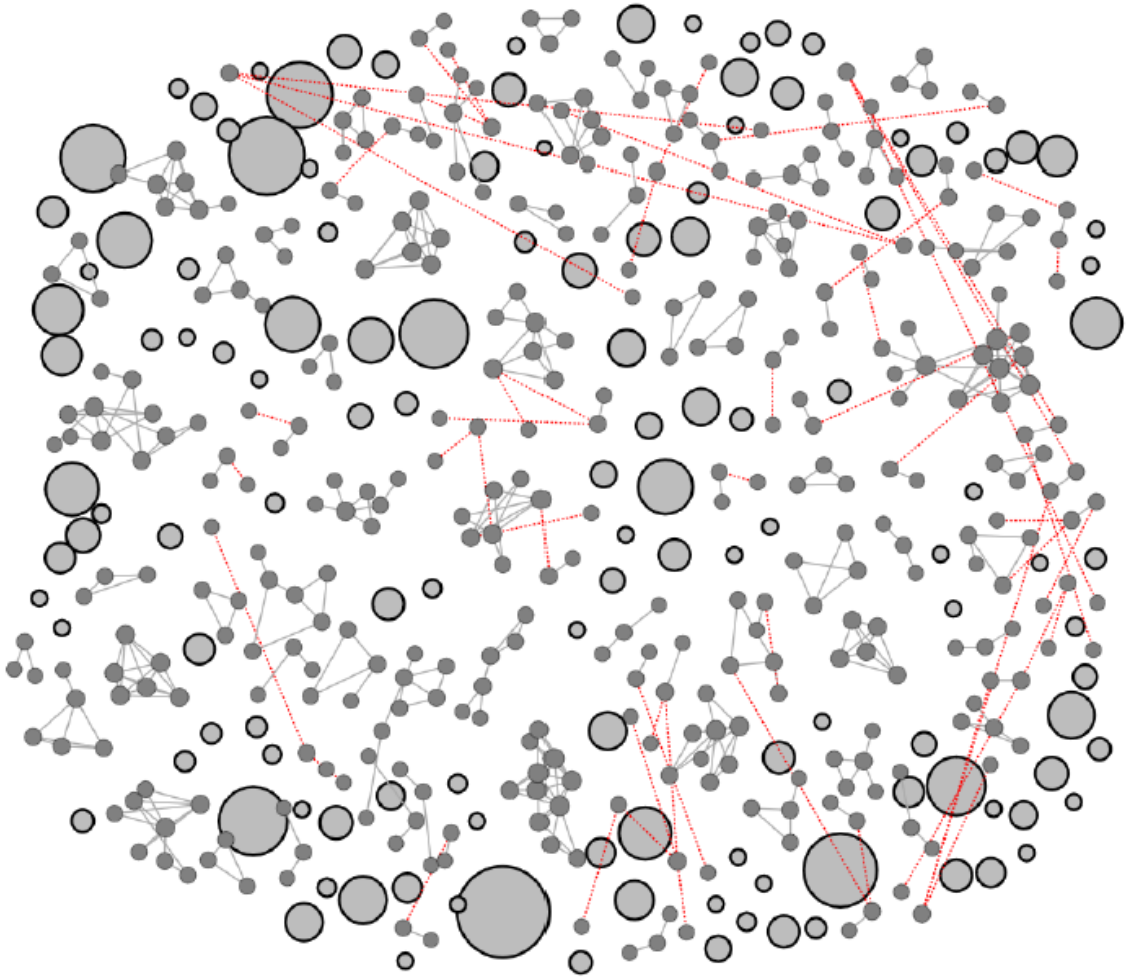
N Lower Clinical Cutoff (in bold)
N Upper Clinical Cutoff (in bold)
Biological Cutoff
Hypersusceptibility Cutoff
Sensitive
Partial Sensitivity
Resistance

HIV-1 RNA Results for Participant with G140S/Q148H INSTI Genotypic Resistance at Baseline Treated with B/F/TAF



K White et al., CROI 2018 - Boston, poster 532

211 TCs, involving **1,626** (31.2%) **newly diagnosed individuals**, were identified. **24 TCs** (11.4%) **involved individuals from both North and Central Italy**, suggesting an **intermixing** between individuals belonging from different areas.



Clusters analysis by HIV-1 TRACE

Of note, **a significant increase of individuals over time** was found in both **B** and **non-B subtype TCs**

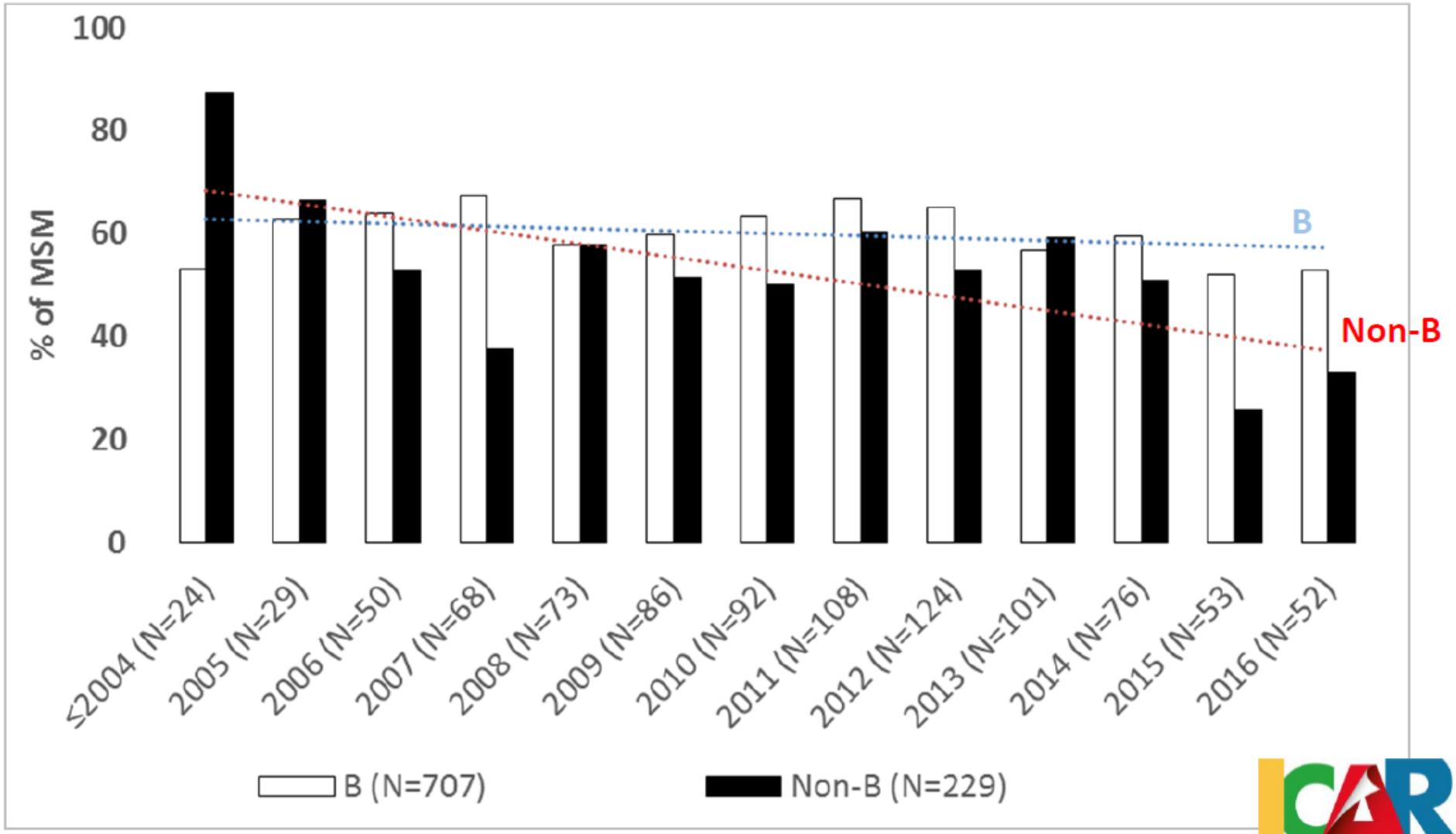
- **B subtype**:
2004-2016: 12.5%-41.6%

- **Non-B subtypes**:
2004-2016: 13.3%-35.9%

p<0.0001

Fabeni, ICAR 2017

The contribution of **MSM in TCs** significantly **decreased for non-B** subtypes (**2004-2016: 87.5%-33.3%, p<0.001**), while remained **stable for B subtype** (**2004-2016: 53.1%-52.8%, p=0.072**)



Fabeni, ICAR 2017

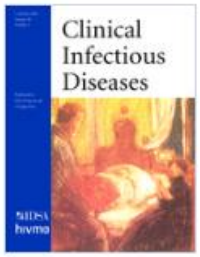
Logistic regression confirmed that **more recent diagnosis** and **higher CD4+ T cells** were both **positive predictors of TCs.**

Variables	Predictors of Transmission Clusters (N=211)			
	Crude		Adjusted[a]	
	OR (95% C.I.)	p-value	OR (95% C.I.)	p-value
Age (per 1 year increase)	0.98 (0.97-0.98)	5.05E-13	0.98 (0.97-0.98)	9.77E-10
Gender (male vs female)	3.06 (2.56-3.67)	7.20E-34	1.71 (1.37-2.14)	2.00E-06
Subtype (B vs non-B)	1.30 (1.14-1.48)	5.96E-05	1.20 (1.03-1.40)	2.10E-02
Risk factor:				
MSM[b]	1		1	
BISEX	1.19 (0.84-1.70)	3.20E-01	1.03 (0.70-1.51)	0.87
HET	0.47 (0.34-0.67)	1.77E-05	0.78 (0.63-0.97)	0.025
IDU	0.33 (0.20-0.55)	1.66E-05	0.44 (0.28-0.68)	2.49E-04
Other/unknown	0.84 (0.59-1.19)	0.32	-	-
Nationality (Italian vs foreign)	2.88 (2.49-3.33)	2.14E-45	2.90 (2.44-3.44)	1.15E-33
Year of diagnosis (per 1 year increase)	1.07 (1.05-1.09)	6.33E-16	1.07 (1.05-1.10)	5.19E-12
Viral load at GRT (per 1 $\log_{10}$ increase)	0.98 (0.92-1.05)	0.56	-	-
CD4 at GRT (per 50 cells increase)	1.06 (1.05-1.07)	2.10E-30	1.04 (1.03-1.05)	6.08E-12

[a] Adjusted for factors with p<0.100 in univariate analysis: age and subtype. [b] Reference group (dummy). OR: odds ratio.

Fabeni, ICAR 2017

DR & Low-Level Viremia



Volume 39, Issue 7
1 October 2004

Genotypic Resistance in HIV-1–Infected Patients with Persistently Detectable Low-Level Viremia while Receiving Highly Active Antiretroviral Therapy

Richard E. Nettles,[1] Tara L. Kieffer,[1] Rachel P. Simmons,[1] Joseph Cofrancesco, Jr.,[1] Richard D. Moore,[1] Joel E. Gallant,[1] Deborah Persaud,[2] and Robert F. Siliciano[1,3]

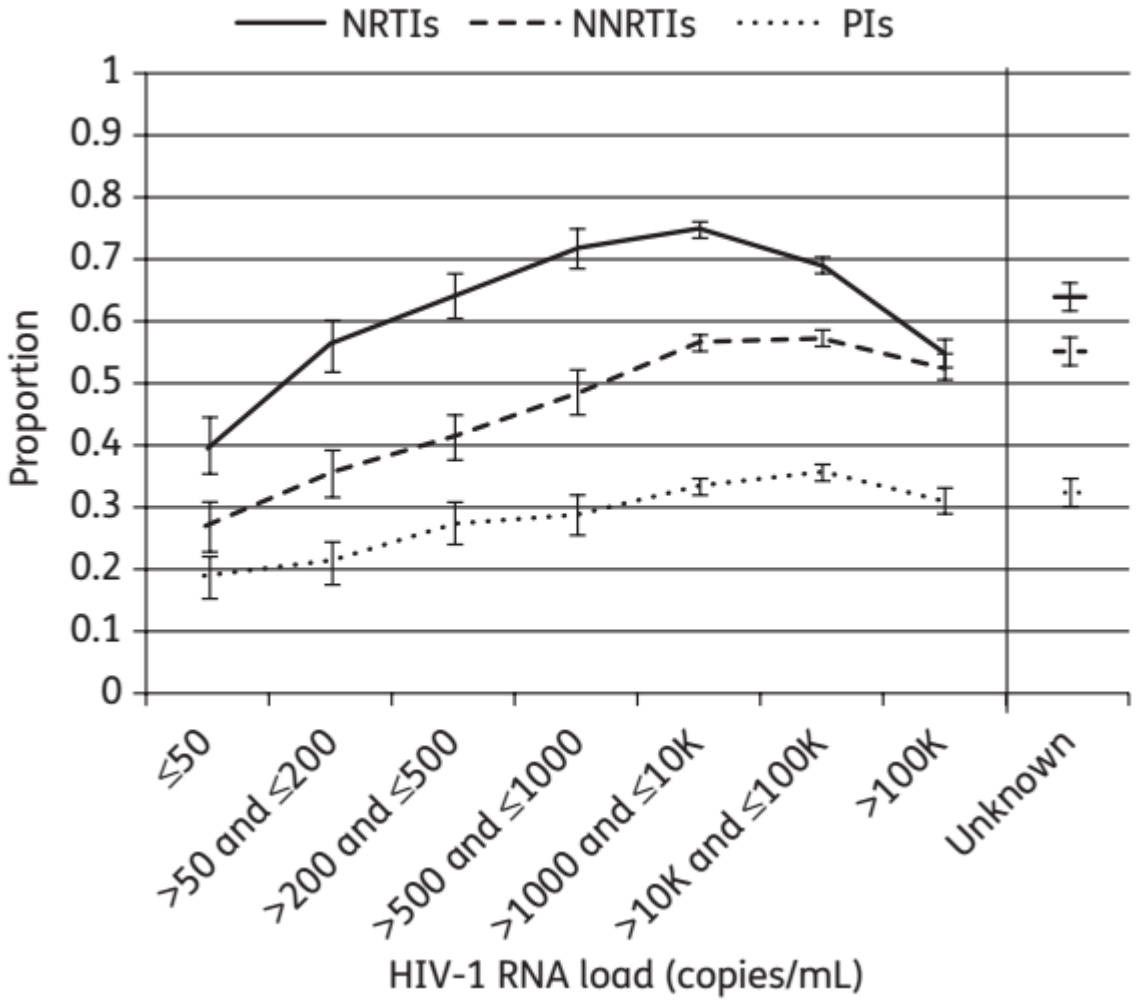
Departments of [1]Medicine and [2]Pediatrics, Johns Hopkins University School of Medicine, and [3]Howard Hughes Medical Institute, Baltimore, Maryland

Background. Technical limitations in the sensitivity of commercial genotyping methods may prevent clinicians from determining whether drug-resistant human immunodeficiency virus type 1 (HIV-1) is present in patients with low-level viremia. We performed ultrasensitive HIV-1 genotyping for patients with persistent plasma virus loads of 50–400 copies/mL to better define the prevalence of drug resistance and the most common resistance mutations during persistently detectable low-level viremia.

Methods. Genotyping of HIV-1 was performed with an ultrasensitive clonal genotyping method.

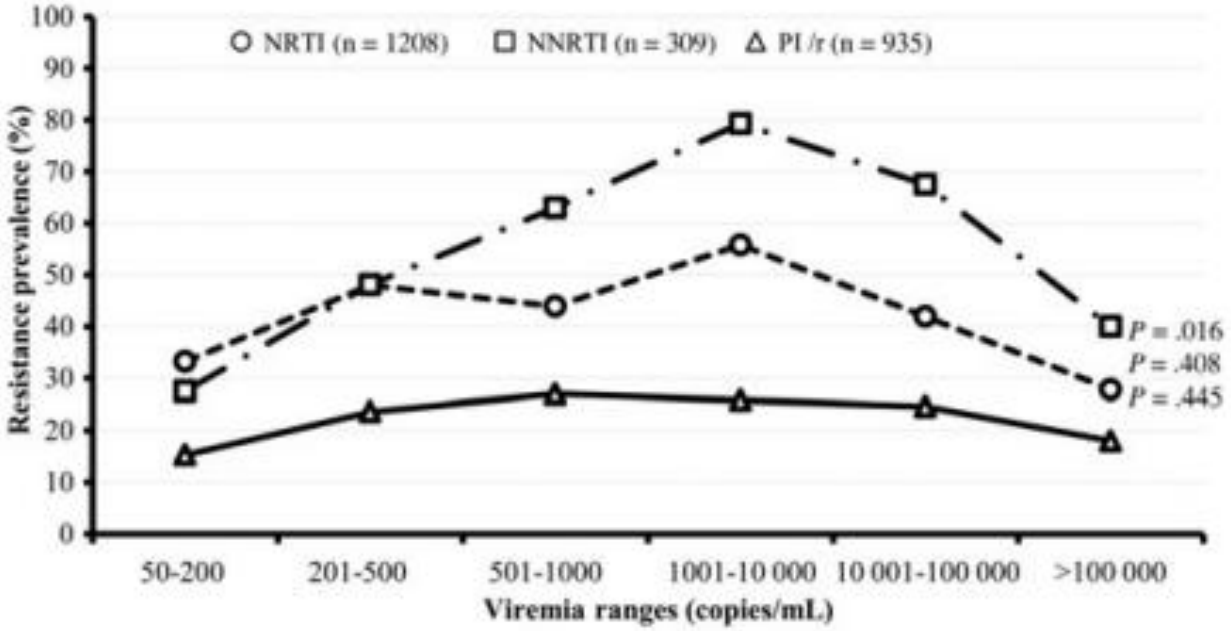
Results. We studied 21 patients who had persistent, detectable, low-level viremia for a median of 11 months. Nine (43%) of 21 patients had HIV-1 isolates with significant resistance mutations. The most common mutations were M184V, K65R, and M41L/T215Y.

Conclusions. The finding that clinically significant resistance mutations were present in some but not all patients with persistent viremia (range, 50–400 copies/mL) highlights the need to improve the sensitivity of current clinical assays for detection of drug resistance.



- SEHERE consortium (I, UK, P, D, B, E, S)
- 16,511 PR/RT sequences from 11,492 treatment-experienced patients
- 2,500/16,511 (15.14%) test results were obtained at a viral load <1,000 copies/mL

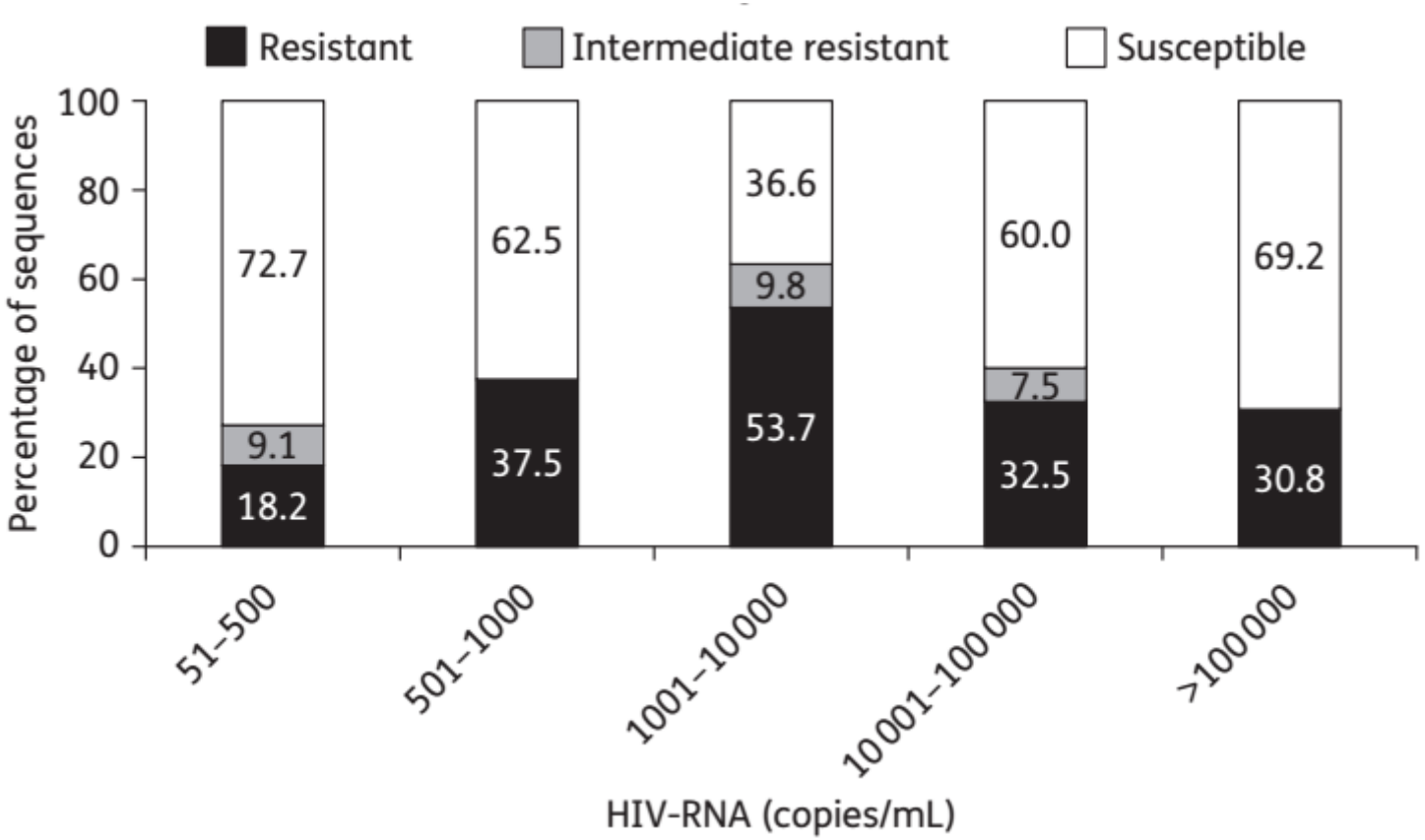
Prosperi, JAC 2011



NRTI	196	123	82	283	315	209
NNRTI	40	27	27	87	83	45
PI/r	150	106	63	209	240	167

Detection of DR in plasma RNA stratified by viremia levels

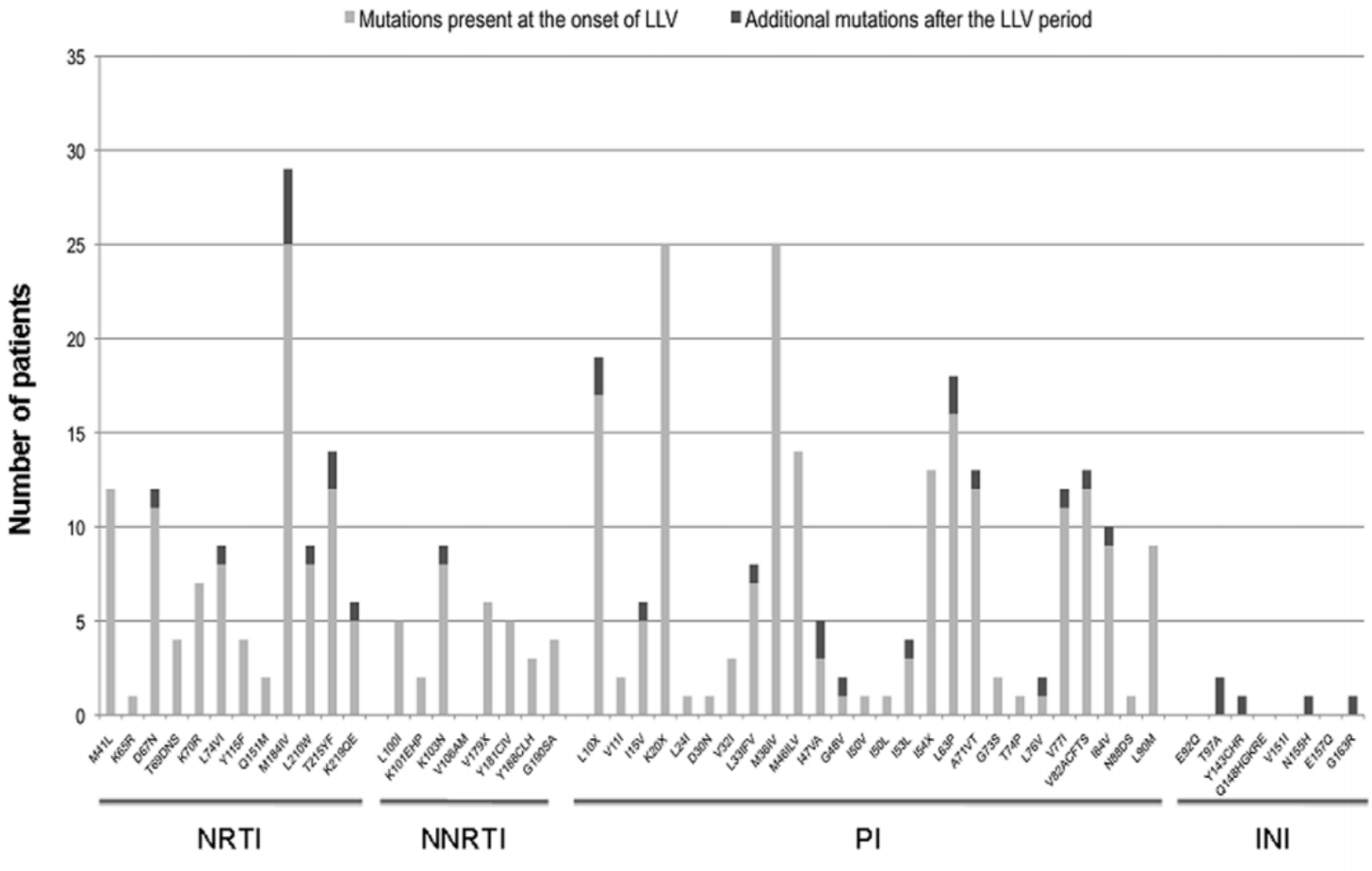
Santoro, CID 2014



Raltegravir genotypic susceptibility scores (GSS) according to viraemia level in samples from patients failing a raltegravir-containing regimen

Armenia, JAC 2015

Drug resistance can emerge <u>during</u> persistent low-level viremia



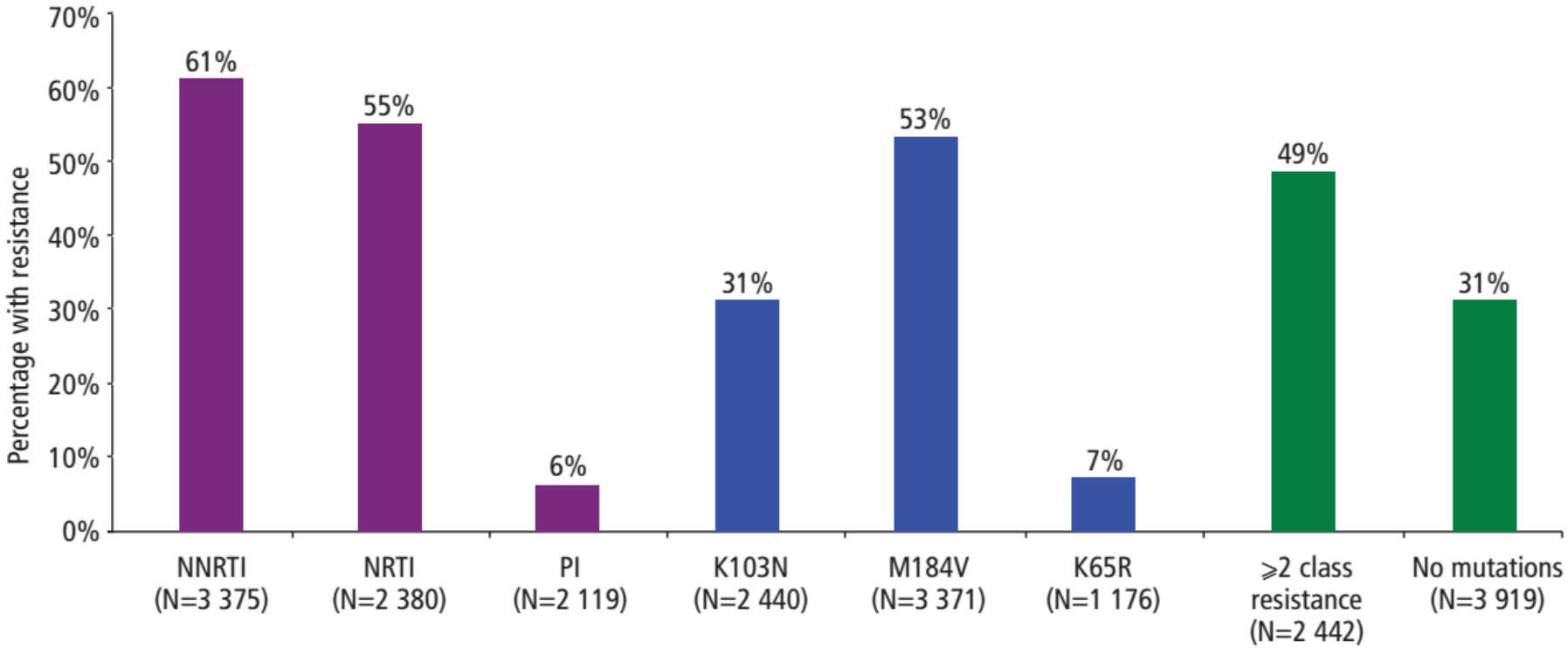
- 48 patients (4 naive and 44 pretreated) with LLV episode with a median duration of 11 months
- Successful resistance testing at both onset and end of the LLV episode obtained for 37 patients (77%)
- 11 (30%) acquired at least 1 DRAM during the LLV period: for NRTI in 6, for NNRTI in 1, for PI in 4, and for raltegravir in 2

Delaugerre, PLoS ONE 2012

Virological failures

HIV ADR in low/middle income countries

Fig. 15: Acquired HIV drug resistance among individuals on ART (systematic literature review, 2014–2017)



Genotype data were available for a total of 3919 individuals from both “viral load and genotype cohorts” and “genotyping only cohorts”. In this subgroup, the pooled estimates using a random effects model show that 70.7% were found to have any DRM.

WHO HIV drug resistance report - 2017

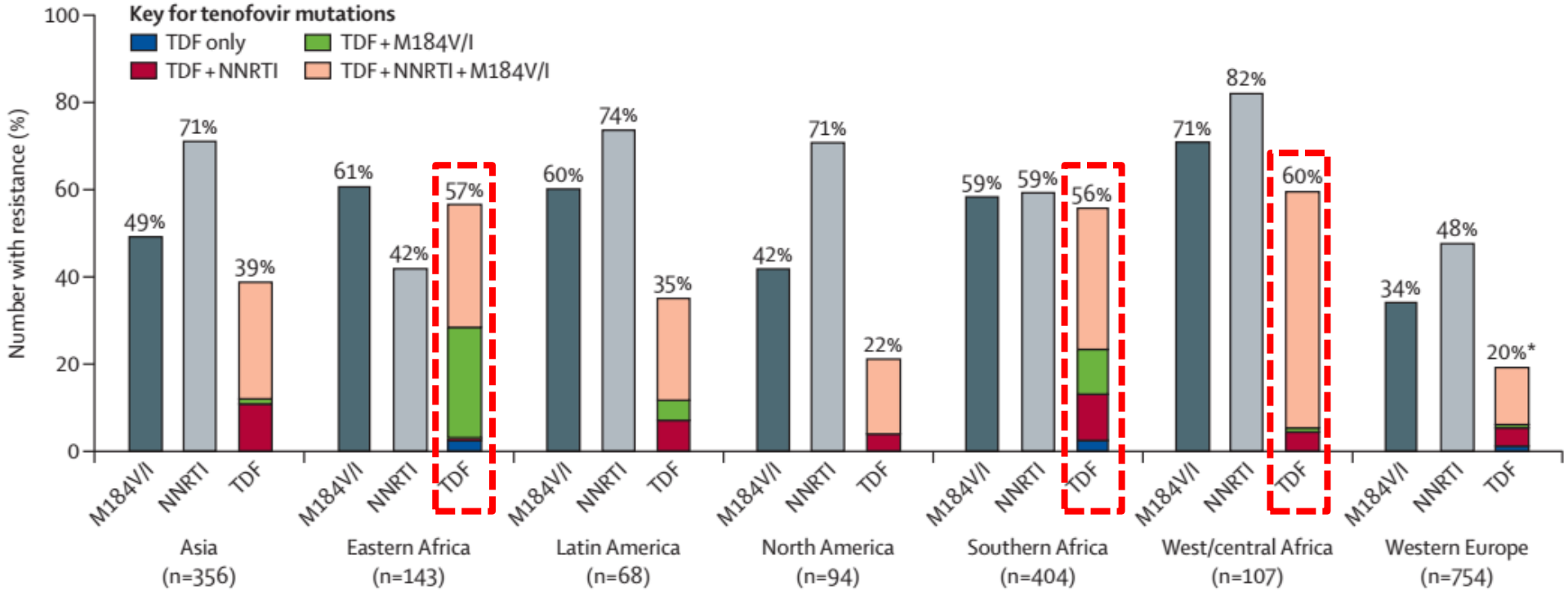
HIV Drug Resistance Mutations in Non-B Subtypes After Prolonged Virological Failure on NNRTI-Based First-Line Regimens in Sub-Saharan Africa

Cissy Kityo, MSc, Jennifer Thompson, MSc,† Immaculate Nankya, PhD,* Anne Hoppe, PhD,† Emmanuel Ndashimye, PhD,* Colin Warambwa, MD,‡ Ivan Mambule, MBChB,§ Joep J. van Oosterhout, MD,‖¶ Kara Wools-Kaloustian, MD,# Silvia Bertagnolio, MD,** Philippa J. Easterbrook, MD,** Peter Mugyenyi, FRCP,* A. Sarah Walker, PhD,† and Nicholas I. Paton, MD,†‡‡ for the Europe Africa Research Network for Evaluation of Second-line Therapy (EARNEST) Trial Team*

- Drug resistance mutation (DRM) patterns in patients failing NNRTI-based first-line antiretroviral therapy regimens in programs without routine viral load (VL) monitoring
- Examine intersubtype differences in DRMs
- Sequences from 787 adults/adolescents who failed an NNRTI-based first-line regimen
- DRMs were more common in subtype-C than in subtype-A and/or subtype-D
- **Higher rates of etravirine and rilpivirine resistance in subtype-C may limit their potential utility in salvage regimen**

J Acquir Immune Defic Syndr • Volume 75, Number 2, June 1, 2017

Resistance to TDF(/TAF) at first-line TDF/XTC/NNRTI treatment failure

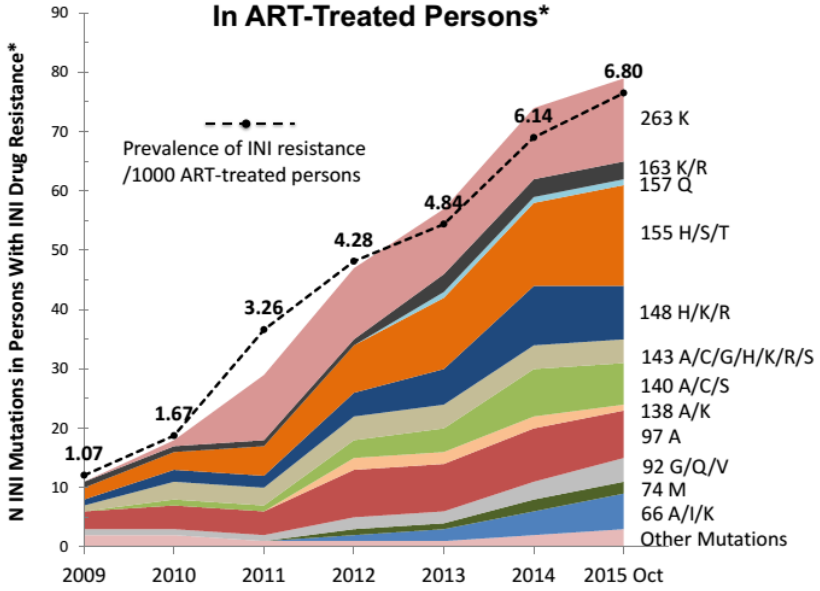


Based on analysis of 1926 patients from 36 countries with treatment failure between 1998 and 2015

TENORES, Lancet Infect Dis 2016

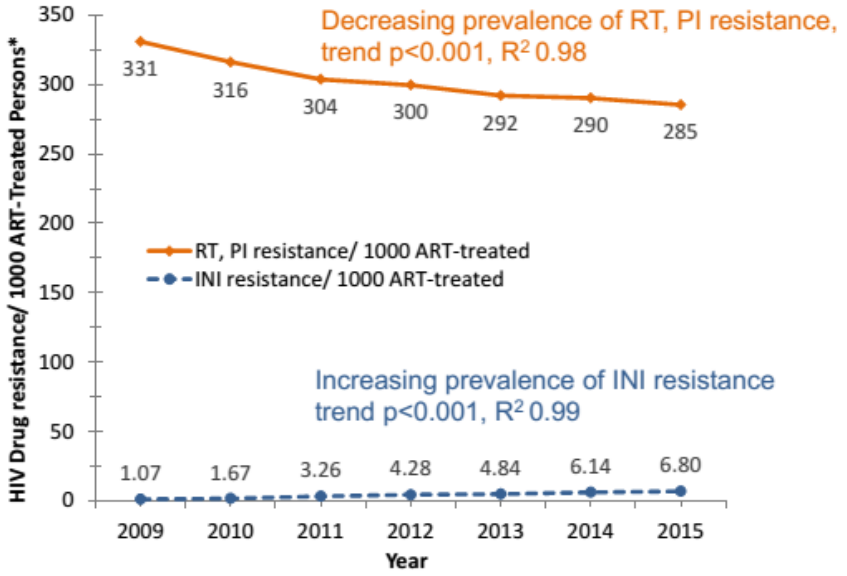
Time trends of INSTI resistance in treatment failing patients

Fig. 2: Prevalence of Integrase Drug Resistance Mutations In ART-Treated Persons*



* Persons with drug resistance mutations conferring a total score ≥30 (Stanford HIV Drug Resistance Algorithm v.7.0.1) for at least one INI. For each person, cumulative INI mutations were reported in the first and each subsequent year following detection of drug resistance.

Fig. 3: Prevalence of Drug Resistance



* Persons with drug resistance mutations conferring a total score ≥30 (Stanford HIV Drug Resistance Algorithm v.7.0.1) for at least one INI, RT or PI.

- A total of 57 persons with intermediate or high level INI resistance were identified January 2009 to October 2015
- Apparent increase in selection of mutations at integrase codons 66, 140, 148, 155 and 263
- Although the prevalence of INI resistance is increasing, INI resistance remains low in comparison to RT and PI resistance

Lepik, CROI 2016 & AIDS 2017

Time trends of INSTI resistance in treatment failing patients

Fig. 4a: Integrase Inhibitor Use

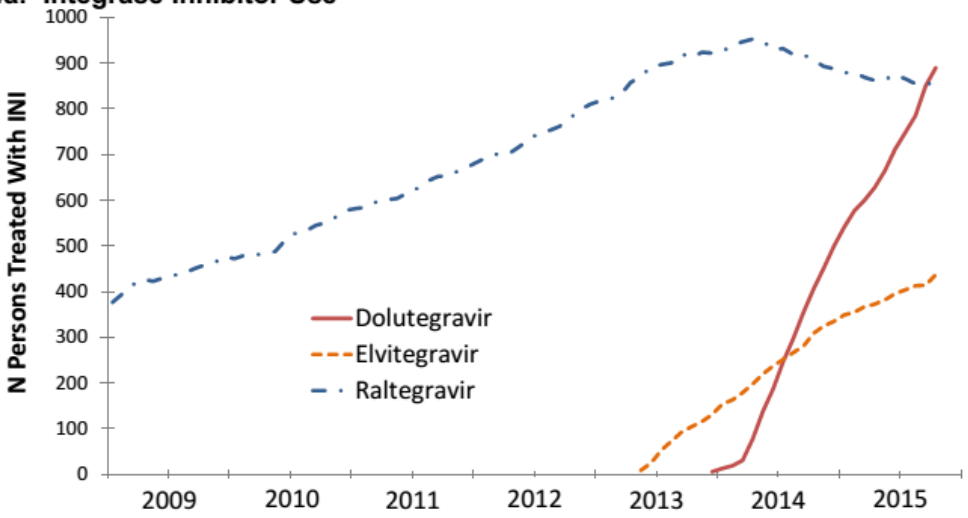


Fig. 4b: Newly Identified Cases of Integrase Resistance*

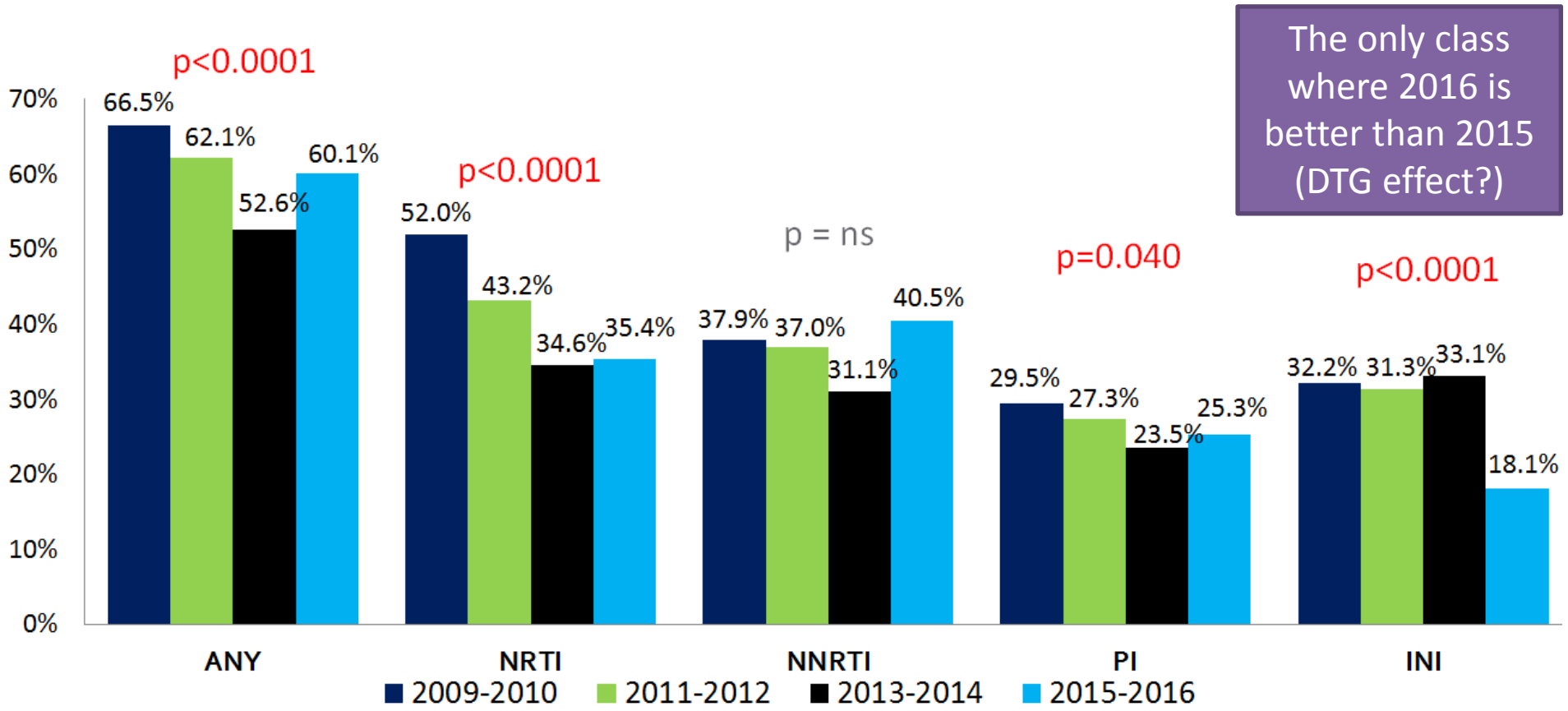
Year	2009	2010	2011	2012	2013	2014	2015
INI associated with resistance	N=6 n	N=4 n	N=12 n	N=8 n	N=8 n	N=11 n	N=8 n
Dolutegravir	-	-	-	-	-	-	3
Elvitegravir	-	-	-	-	-	2	3
Raltegravir	6	3	9	8	7	7	2
Unclassifiable	-	-	3	-	1	2	-

* ART-treated persons contributed data in the first year INI resistance mutations conferring a total score ≥30 (Stanford HIV Drug Resistance Algorithm v.7.0.1) for at least one INI were identified.

- Until 2013, most new cases of INI resistance associated with RAL use
- In 2014 and 2015, 8/19 (42%) new INI resistance cases followed EVG or DTG use
- Five cases were associated with EVG use in treatment-experienced persons (two 66A/I and one each 92Q, 145S, 147G)
- Three cases of emergent INI resistance during DTG therapy
  - 263K in two treatment experienced persons
  - 66I in one treatment-naïve person treated with dolutegravir-abacavir-lamivudine

Lepik, CROI 2016 & AIDS 2017

Time trends in ADR in Italy



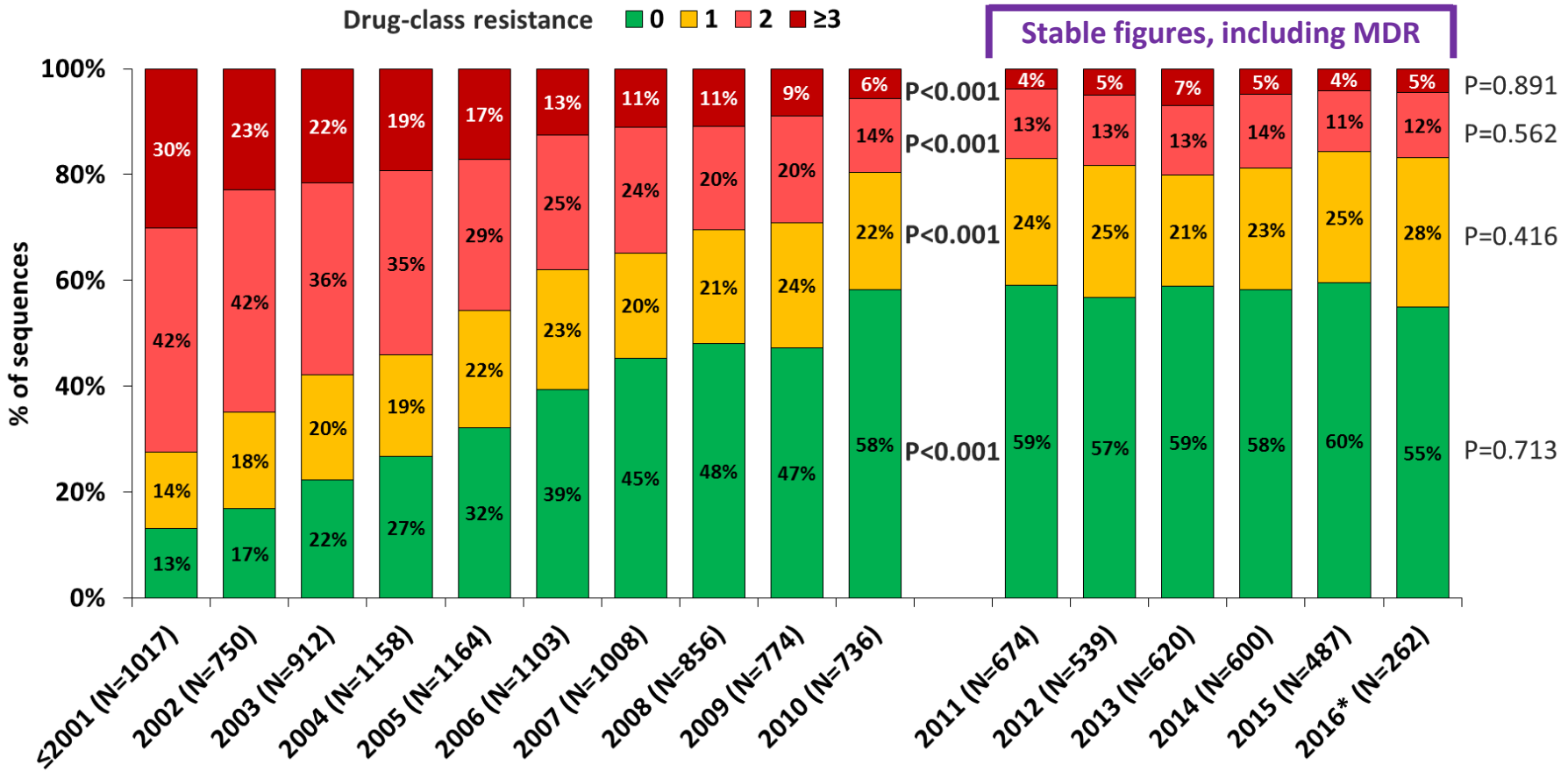
- 2009-2016 observation period
- On treatment at genotyping with HIV-1 viral load >200 copies/ml after >6 months of therapy

Lai, ICAR 2017

Patients with a Multidrug Resistant Virus

HIV MDR in Italy

Prevalence of resistance to any drug-class among ART-experienced HIV-1 infected patients over the years.



Analysis performed on 12660 sequences of protease, reverse transcriptase or integrase, from ART-experienced HIV-1 infected patients (N=6051). P-values by Chi-squared test for trend; statistically significant tests ($p<0.05$) are indicated in boldface. Sequences performed from 1999 to 2001 were grouped. *Update August 2016.

Take home messages

- **DR testing** still necessary at individual and population level in **naïve** patients (beware of **TDR**)
  - Yet, INSTI DR testing is below the 5% cost/benefit threshold. To be considered the incremental use of INSTI, thus the potential increase in INSTI DR, although newer and more potent compounds may limit this phenomenon

- **HIV resistance testing at LLV** is possible and is able to reveal some degree of viral evolution under pharmacological pressure

- Acquired DR testing mandatory at **treatment failure [reservoir]**, advisable at every level of viremia
  - Risk of ADR highly dependent on genetic barrier and adherence

- Resistance testing still valuable in **HTE patients with MDR [reservoir]** to address salvage or holding regimens
  - Room for phenotyping when available

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