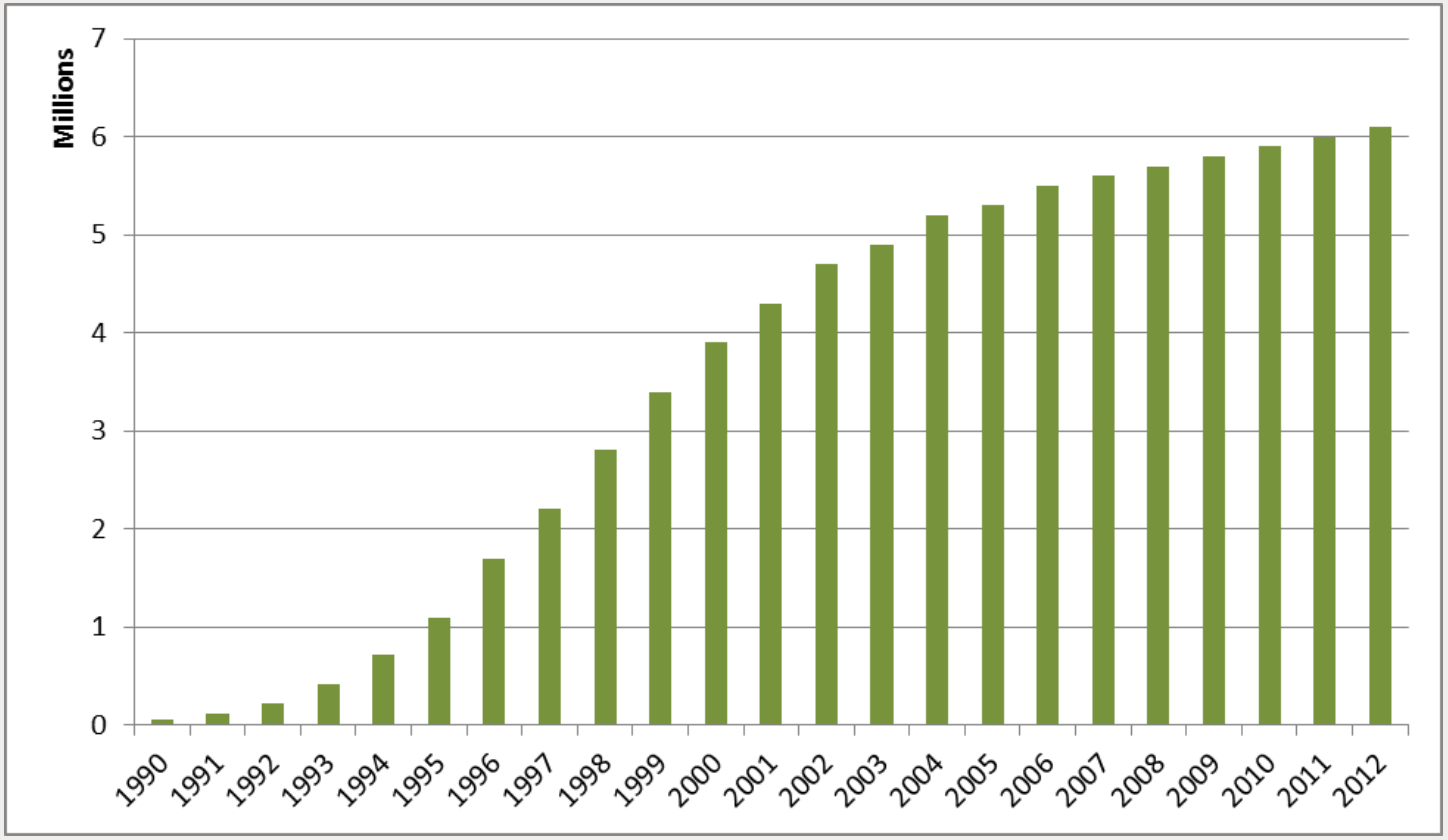
Increasing Prevalence of Protease Inhibitor Resistance Mutations in South African Adults Failing a Boosted PI-based Regimen

K. Steegen, L. Hans, E. Shoul, M. Papathanasopoulos, S. Carmona and WS. Stevens

National Health Laboratory Services
University of the Witwatersrand
Johannesburg, South Africa

HIV Epidemic in South Africa

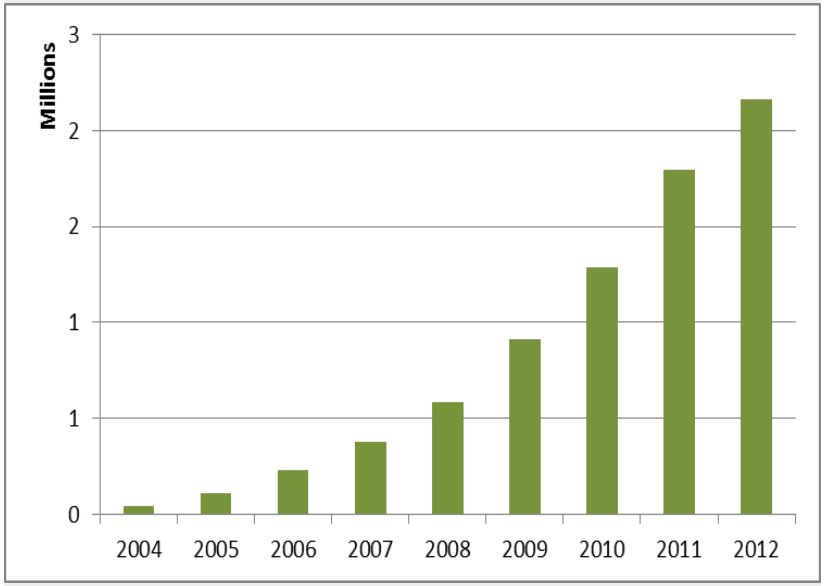
Estimated number of South Africans living with HIV



Adapted from UNAIDS 2013

cART program in South Africa

Estimated number of South Africans receiving antiretroviral treatment



2.2 million people on cART in 2012

Adapted from Johnson et al. 2012 SAJHIVMED

Public health approach to cART

2004:
d4T+3TC+EFV or NVP → AZT+ddI+LPV/r

2010:
TDF+3TC or FTC+EFV or NVP → AZT+3TC+LPV/r

d4T+3TC+EFV or NVP → TDF+3TC or FTC+LPV/r
AZT+3TC+EFV or NVP → TDF+3TC or FTC+ LPV/r

2013:
TDF+FTC+EFV (FDC) → AZT+3TC+LPV/r

TDF+FTC+NVP → AZT+3TC+LPV/r
AZT+3TC+EFV or NVP → TDF+3TC+LPV/r

HIVDR testing recommended after 2nd-line failure
3rd-line: RAL+DRV/r+ETR (after expert advice)

Adapted from NDoH cART guidelines

Study Population

- Retrospective analysis of resistance profiles in adults failing a 2nd-line PI-based regimen at the public Charlotte Maxeke Johannesburg Academic Hospital between 2012-2013 (n=58)

- Virological failure defined as two consecutive VL measurements >1000 cp/ml

- Resistance testing was requested at clinician's discretion *(no HIVDR testing guidelines at the time)*

Methods

- Demographic and clinical characteristics were retrieved from laboratory request forms and patient files.
- *Pol* sequences were derived from plasma specimens using in-house methods covering PR 1-99 and RT 1-400*.
- Sequences were submitted to Stanford HIVdb v 6.3.1 for genotypic resistance predictions.
- Results were compared with those obtained between 2009-2010 from the same region**.

*Bronze et al. ASLM Conference 2012
Lukhwareni et al. Pathpoint Conference 2012

**Wallis et al. 2011, AIDS Res Treat

ART regimens at time of resistance testing

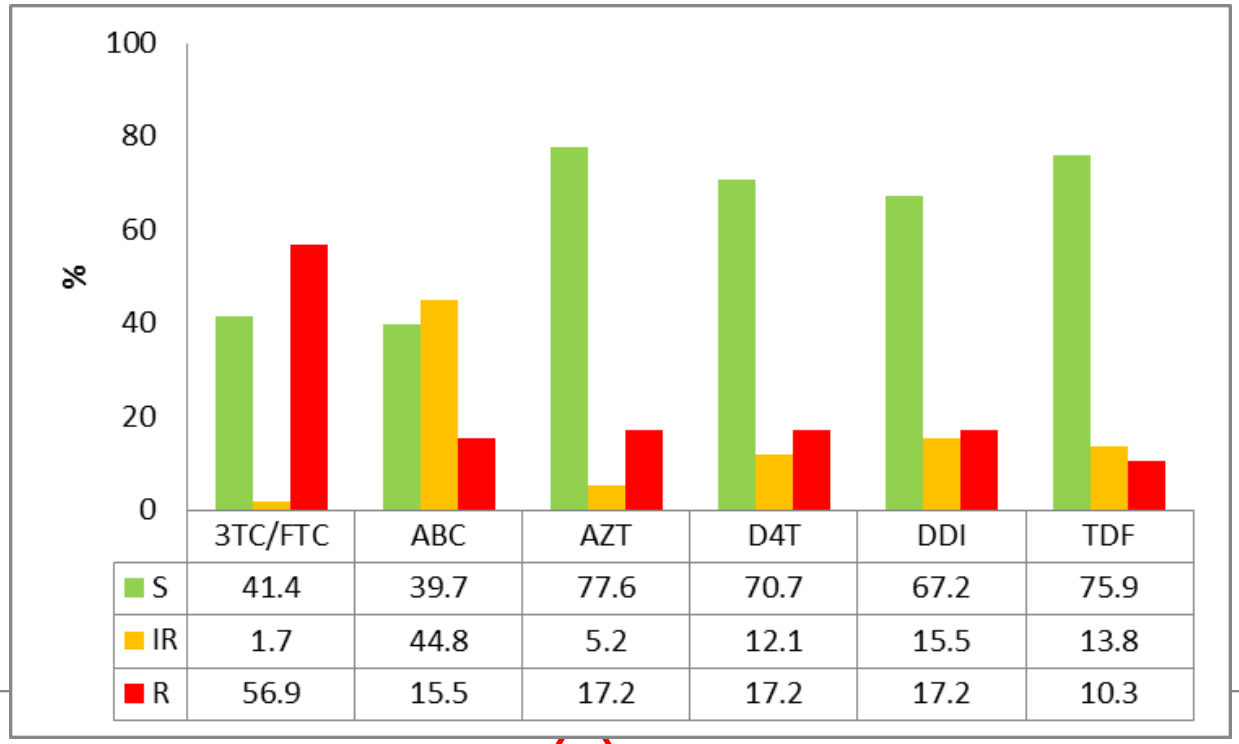
Current regimen	Number of patients	% of patients
AZT+3TC+LPV/r	24	41.4
TDF+3TC+LPV/r	24	41.4
ABC+3TC+LPV/r	2	3.4
AZT+ddI+LPV/r	1	1.7
3TC+EFV+ATV/r	1	1.7
TDF+3TC+AZT+LPV/r	1	1.7
TDF+3TC+EFV+LPV/r	1	1.7
TDF+AZT+3TC+LPV/r	1	1.7
TDF+ABC+3TC+LPV/r	1	1.7
TDF+ABC+3TC+LPV/r+ATV/r	2	3.4
TOTAL	**58**	

Patient Characteristics

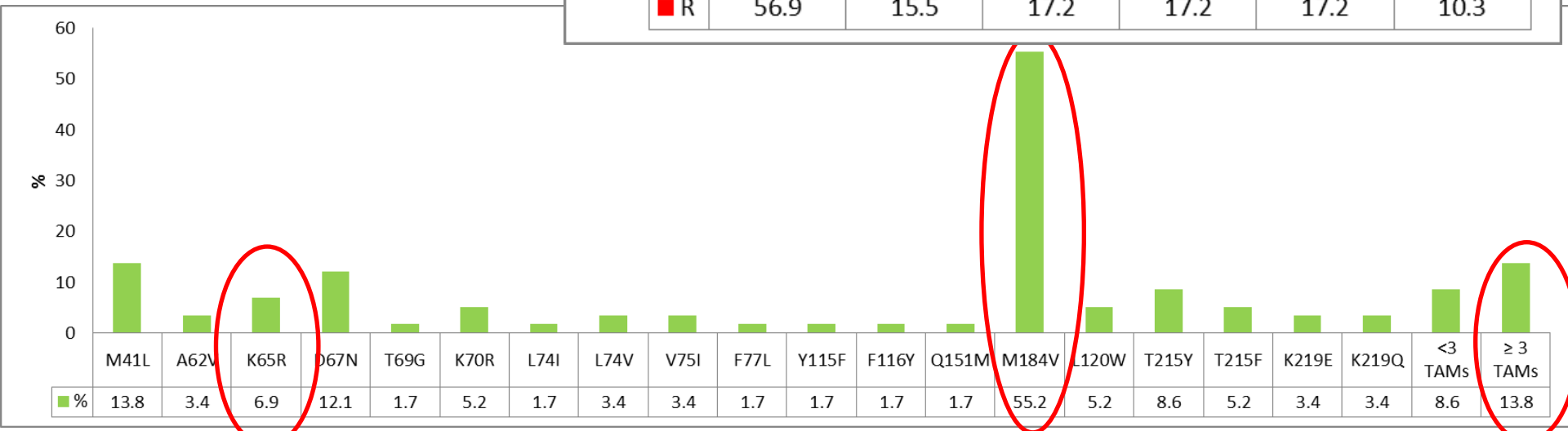
	Current Study (n=58)			Wallis et al. 2011* (n=75)			p-value
	N (%)	Median	IQR	N (%)	Median	IQR	
Gender (Female)	36 (62.1)			52 (69.3)			0.4604
Age (years)		38	34-44		34	29-40	NA
Viral Load (log RNA copies/ml)		4.2	3.8-4.8		5.3	4.0-5.2	NA
Total Time on Rx (months)		61	35-89		NA	NA	NA
Time on current Rx (months)		29	18-46		16	4-54	NA
Subtype C	56 (96.6)			72 (96.0)			1.0000
No HIV Drug Resistance	15 (25.9)			29 (38.7)			0.1394
NNRTI and NRTI mutations	20 (34.5)			22 (29.3)			0.5752
Major PI mutations	14 (24.1)			5 (6.7)			0.0057
Extensive Triple-class resistance	10 (17.3)			0 (0.0)			0.0002

*Included data from two large hospitals in Johannesburg

NRTI Mutation Profiles



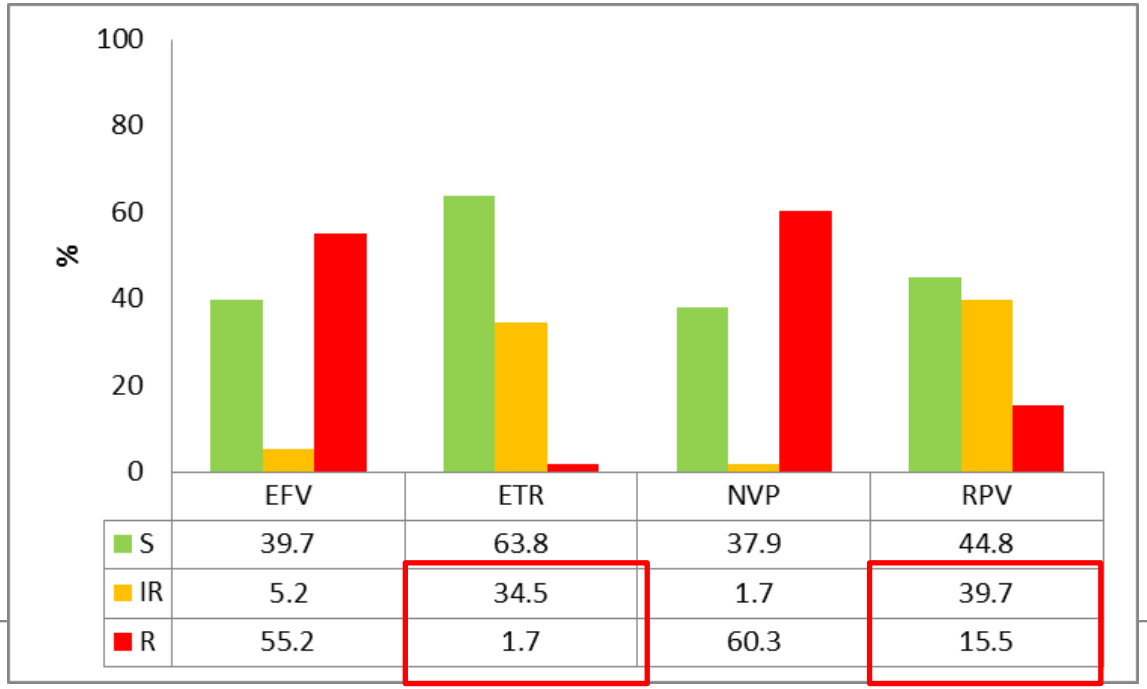
	3TC/FTC	ABC	AZT	D4T	DDI	TDF
S	41.4	39.7	77.6	70.7	67.2	75.9
IR	1.7	44.8	5.2	12.1	15.5	13.8
R	56.9	15.5	17.2	17.2	17.2	10.3



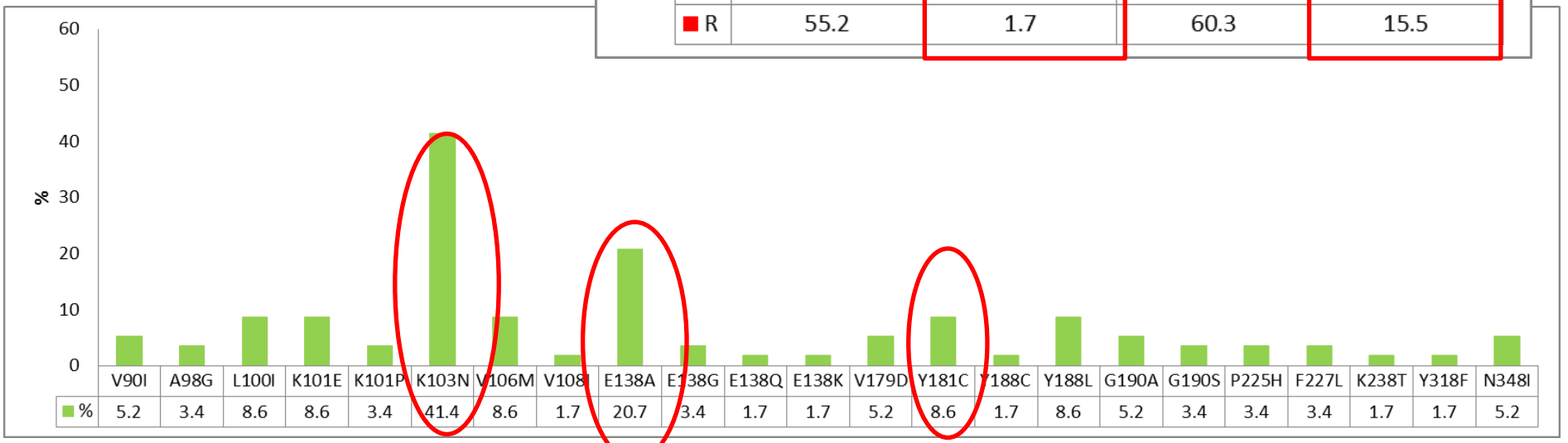
	M41L	A62V	K65R	D67N	T69G	K70R	L74I	L74V	V75I	F77L	Y115F	F116Y	Q151M	M184V	L120W	T215Y	T215F	K219E	K219Q	<3 TAMs	≥ 3 TAMs
%	13.8	3.4	6.9	12.1	1.7	5.2	1.7	3.4	3.4	1.7	1.7	1.7	1.7	55.2	5.2	8.6	5.2	3.4	3.4	8.6	13.8

NNRTI Mutation Profiles

More than one third of patients present with high-level or intermediate resistance to 2nd-generation NNRTIs



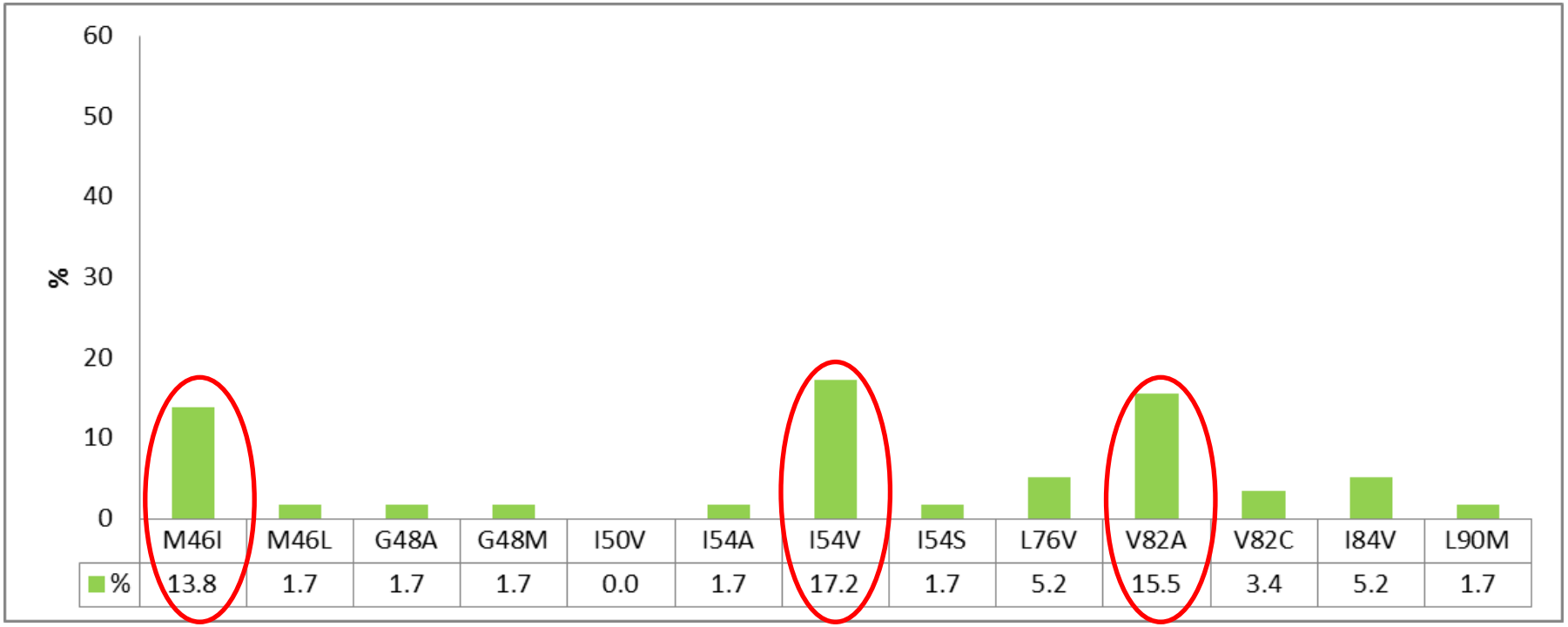
	EFV	ETR	NVP	RPV
S	39.7	63.8	37.9	44.8
IR	5.2	34.5	1.7	39.7
R	55.2	1.7	60.3	15.5



	V90I	A98G	L100I	K101E	K101P	K103N	V106M	V108I	E138A	E138G	E138Q	E138K	V179D	Y181C	Y188C	Y188L	G190A	G190S	P225H	F227L	K238T	Y318F	N348I
%	5.2	3.4	8.6	8.6	3.4	41.4	8.6	1.7	20.7	3.4	1.7	1.7	5.2	8.6	1.7	8.6	5.2	3.4	3.4	3.4	1.7	1.7	5.2

PI Mutation Profiles

- 44 (75.9%) patients did not show any major PI mutations.
- 4 (6.9%) patients presented with 1 or 2 major PI mutations
- 10 (17.2%) patients presented with ≥ 3 major PI mutations



Triple-class resistance

	PI								NRTI						NNRTI			
Patient	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	NFV	SQV/r	TPV/r	3TC/FTC	ABC	AZT	D4T	DDI	TDF	EFV	ETR	NVP	RPV
1	R	S	R	R	R	R	IR	IR	IR	R	R	R	R	R	R	IR	R	IR
2	R	S	R	R	R	R	R	IR	R	R	R	R	R	IR	R	IR	R	R
3	R	IR	R	R	R	R	R	R	R	R	R	R	R	R	R	IR	R	IR
4	R	S	R	R	IR	R	R	R	R	R	IR	IR	R	S	R	IR	R	IR
5	R	S	R	R	R	R	IR	IR	S	IR	R	R	IR	IR	R	S	R	IR
6	R	IR	R	R	R	R	R	IR	R	IR	R	R	IR	IR	R	S	R	S
7	IR	S	IR	IR	IR	R	IR	IR	R	R	R	R	R	IR	R	S	R	S
8	R	S	R	R	R	R	R	IR	R	R	R	R	R	R	IR	IR	R	IR
9	R	S	R	R	R	R	IR	IR	R	IR	S	S	S	S	R	S	R	S
10	IR	IR	R	R	R	R	IR	IR	R	IR	S	S	S	S	R	IR	R	IR

- DRV/r remains a good option as 3rd-line drug in most patients
- ETR might be a good option as well, despite a higher frequency of intermediate resistance due to the presence of E138A

Conclusion

- The frequency of PI resistance is on the rise: 24.1% (2012-2013) versus 6.7% (2009-2010).
- The increasing presence of triple-class resistance in patients presenting with 2nd-line virological failure justifies the introduction of routine HIVDR testing in this population.
- The prevalence of complete susceptible profiles seems to decrease: 25.9% (2012-2013) versus 38.7% (2009-2010).