Storia terapeutica, resistenza genotipica e fitness virale nelle strategie di semplificazione

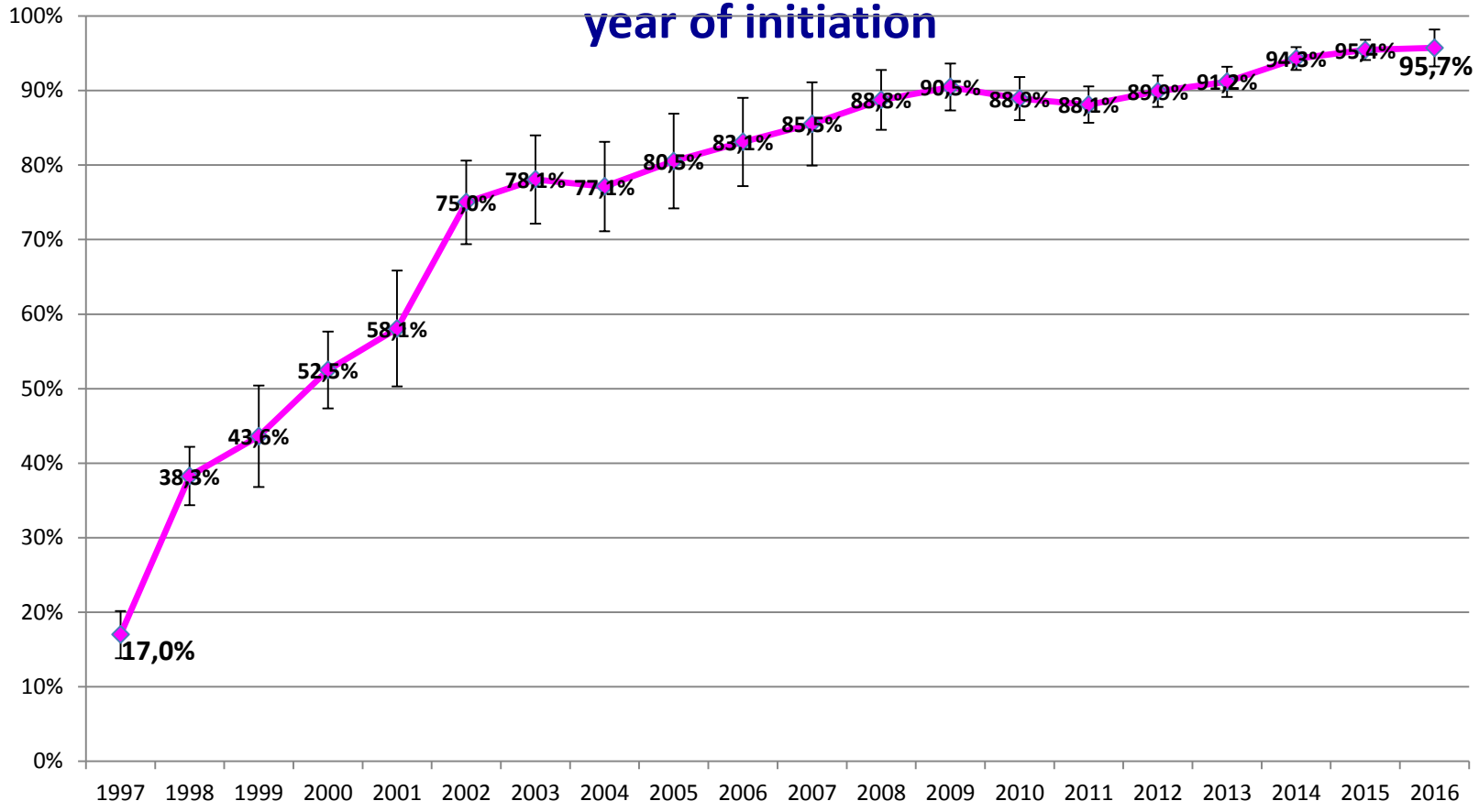
Andrea De Luca
Dipartimento Biotecnologie Mediche Università di Siena
UOC Malattie Infettive
AOU Senese

Conflitti di interesse

- Research grants from:
  - ViiV Healthcare
  - Gilead (Fellowship Program)
  - Merck, Sharp and Dohme
- Paid consultancies:
  - ViiV Healthcare
  - Gilead Sciences
  - Merck, Sharp and Dohme
  - Janssen
  - Abbvie

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Proportion of patients with a VL<=80 copies/mL at 12 months from starting their first ART regimen by calendar year of initiation



June 2017

SIMIT
Società Italiana
di Malattie Infettive
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Devono quindi essere accuratamente valutati, bilanciati e discussi i potenziali rischi e i benefici di *schemi personalizzati di trattamento, modulati sulla base delle preferenze e delle esigenze cliniche del singolo paziente*.

Le principali ragioni che possono portare alla scelta dell'ottimizzazione sono:

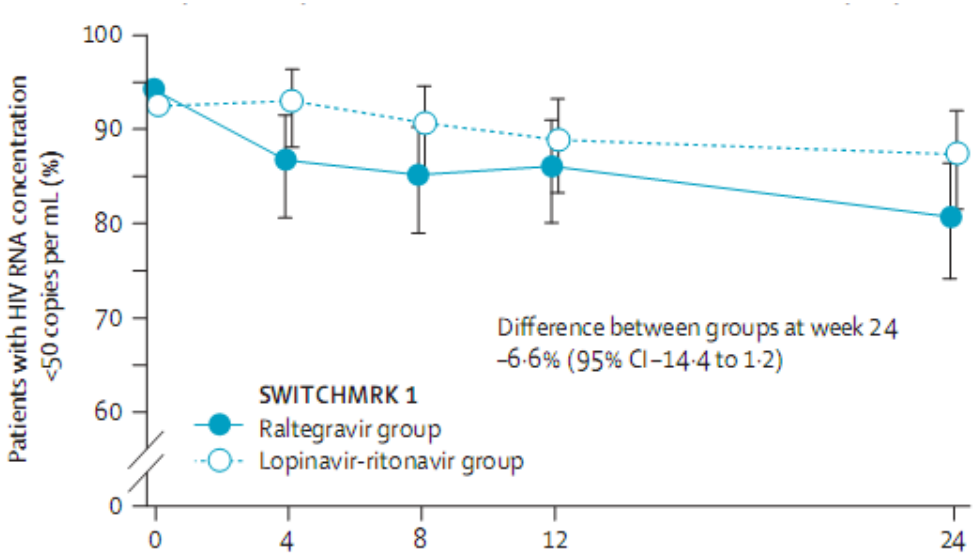
- Intolleranza al regime in atto (effetti indesiderati, documentata tossicità);
- Regime in atto che possa aggravare comorbosità presenti;
- Prevenzione di tossicità a lungo termine (*pre-emptive switch*);
- Regime in atto non più raccomandato;
- Interazioni con altri farmaci, inclusa necessità di cura di altre infezioni (TB, HBV, HCV, ecc.);
- Necessità di migliorare l'aderenza del paziente alla terapia.

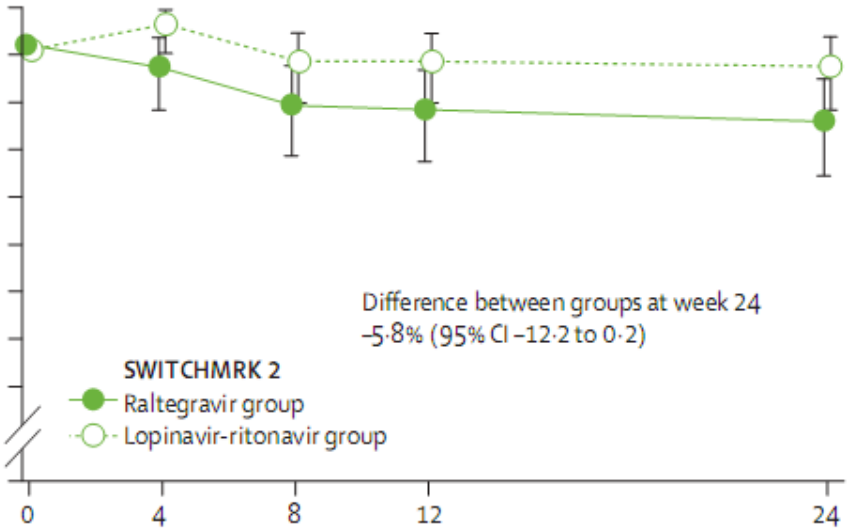
Abandoning boosted PI at simplification in pretreated patients

JournalWATCH® SPECIALTIES

SWITCHMRK: An Avoidable Raltegravir Disaster

Somewhat predictably, treatment-experienced patients on stable regimens who switched from lopinavir/r to raltegravir did not fare as well as those who remained on lopinavir/r.





Abandoning boosted PI at simplification in pretreated patients

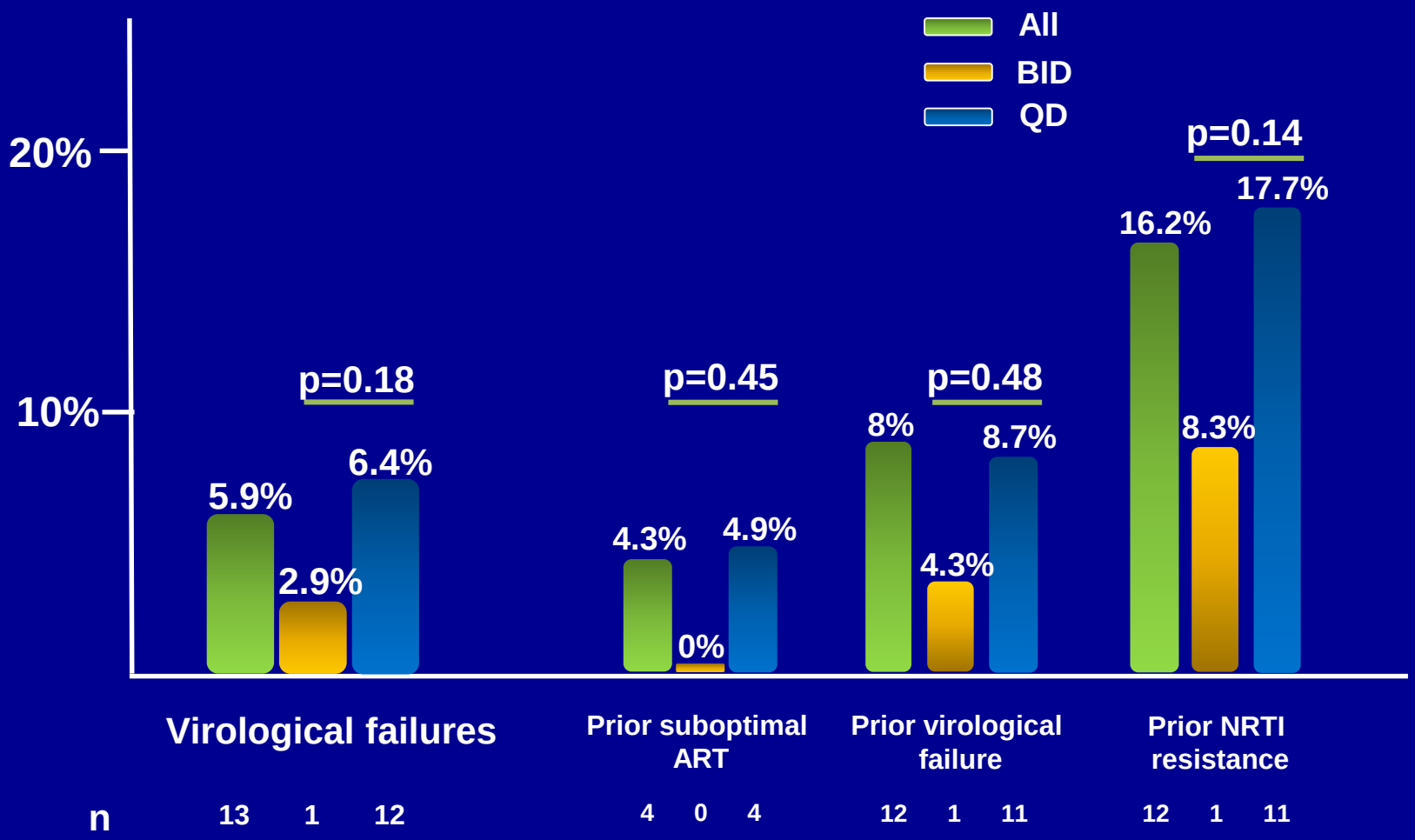
SWITCHMRK

- Heterogeneous patient enrolment
  - 1/3 receiving first HIV treatment before the study
  - 1/3 had had virological failure on other drug regimens

- Trial designs did not require detailed intensive records about previous treatment to be kept
  - Supplementary data collection and later ad-hoc analyses

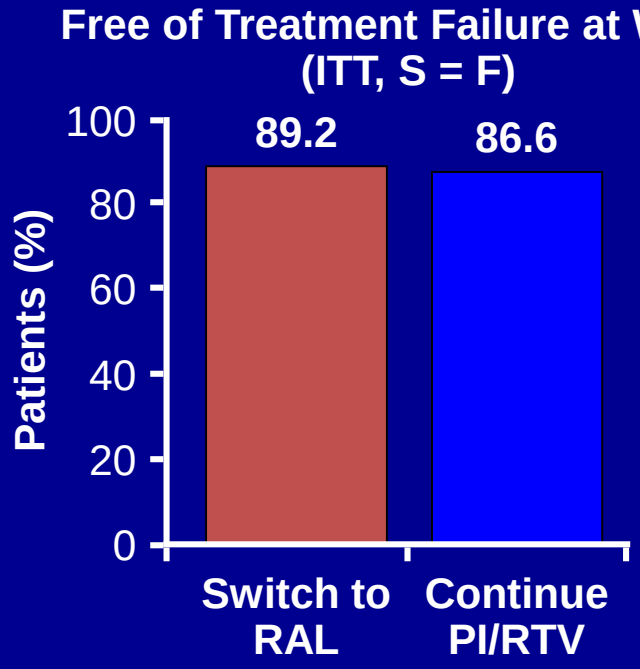
Differences in the virological endpoint were fully accounted for in patients with previous therapeutic failures
(i. e. previous drug resistance)

ODIS - Proportion of patients experiencing virological failure after switching PIs to RAL



The rate of virological failure was 16.2% in patients with prior NRTI resistance compared to 0.7% in the rest (p<0.001)

SPIRAL: Switch to RAL Noninferior to Maintaining PI/RTV Regimens



Patients With VF	RAL (n = 4)	PI/RTV (n = 6)
Prior VF	1	3
Prior suboptimal ART	2	3
Prior resistance mutations	1	5
Resistance test at VF	1	4
- Mutations	0	3 (PR, RT)

Mean Change From Baseline to Wk 48, %	Switch to RAL	Continue PI/RTV	*P* Value
Triglycerides	-22.1	+4.7	< .0001
TC	-11.2	+1.8	< .0001
LDL-C	-6.5	+3.0	< .001
HDL-C	-3.2	+5.8	< .0001
Total to HDL-C ratio	-4.9	-1.3	< .05

Median duration of virologic suppression before switch: 6.6 yrs

Martinez E, et al. AIDS. 2010;24:1697-1707.

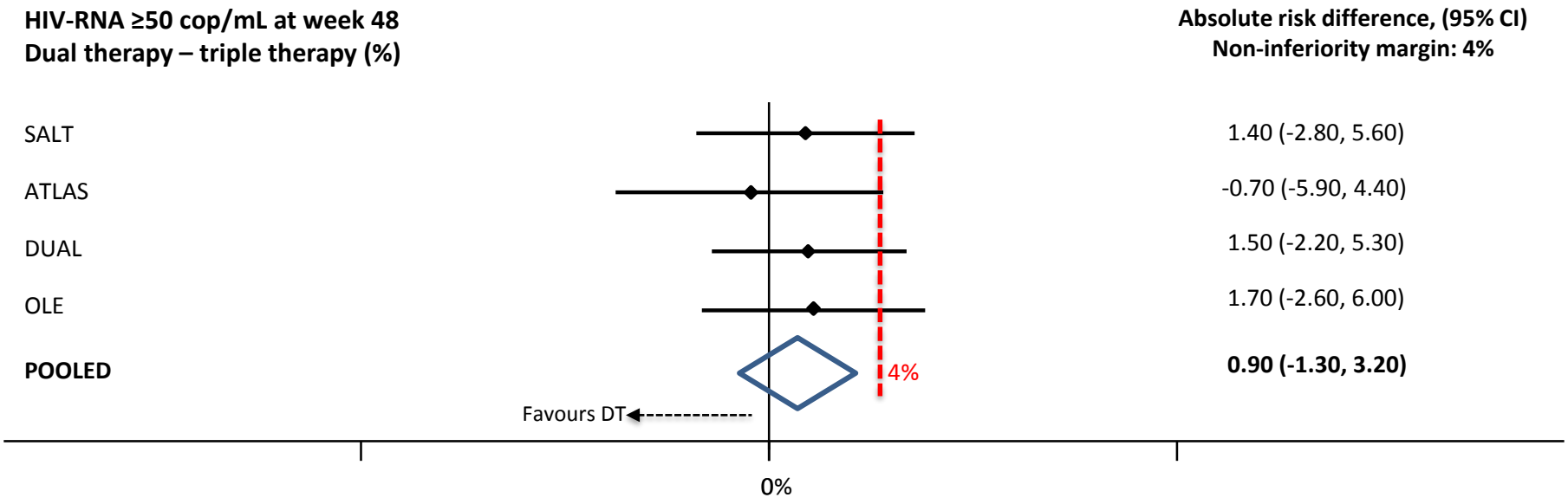
Statement

1. La soppressione virologica in pazienti in terapia efficace con regimi a tre farmaci può essere mantenuta con il cambio verso alcuni regimi a due farmaci con i seguenti livelli di raccomandazione:
   a. DTG + RPV [AI];
   b. ATV/r + 3TC, DRV/r + 3TC [AI per switch da PI con booster, BI per switch da altri regimi;
   c. DRV/r + RAL, DRV/r + RPV [CI];
   d. DTG + 3TC [BII].
2. Pur in assenza di studi randomizzati specifici, ma in ragione della equivalenza delle due coformulazioni, si ritiene che sia ATV/r che DRV/r possono essere sostituiti da ATV/c e DRV/c (rispettivamente) [AIII].
3. Negli studi di switch a DTG + RPV la non inferiorità in termini di mantenimento della soppressione virologica è dimostrata indipendentemente dal regime triplice di provenienza, mentre nello switch a PI/r + 3TC è dimostrata per lo più in caso di provenienza da regimi basati su PI/r (infatti solo il SALT includeva un 33% di pazienti provenienti da NNRTI).
4. I regimi a 2 farmaci hanno in generale documentato una riduzione della tossicità ossea e renale attribuibile a TDF.
5. Rispetto alle altre modalità di switch, quello a DTG + RPV consente di evitare sia la tossicità dovuta a PI che le interazioni farmacologiche dovute all'utilizzo di booster.
6. Pressoché tutti gli studi di switch a duplice terapia riportano un numero di eventi avversi di grado 3 e 4, nonché di eventi avversi severi, simile a quello rilevato nel braccio di confronto (triplice standard).
7. La qualità della vita negli studi di switch a regimi duplici è stata raramente indagata; laddove indagata (negli switch a DTG+RPV), la soddisfazione del paziente e la valutazione dello stato di stato di salute sono risultati simili nei due bracci di terapia [14].
8. Per quanto riguarda lo switch verso una duplice terapia con DRV/r (o DRV/c) + RAL, vi è un solo trial randomizzato, ma confrontato con LPV/r e con end-point primario sulla tossicità renale; tale studio non ha documentato alcun beneficio dello switch su eGFR. Tuttavia, va considerato che un importante studio in pazienti naive [18] ha confermato l'efficacia virologica di questa combinazione rispetto al braccio standard (DRV/r+TDF/FTC), ad

Primary endpoint

At 48w, 4% of patients on DT vs. 3.04% on TT had HIV-RNA ≥50 cop/mL

Difference 0.9% (95%CI, -1.3% to 3.2%)



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Resistance mutations

Only 3 patients developed resistance mutations:

- 1 in DT group (0.19%)
- 2 in TT group (0.38%)

Patient	Clinical Trial	Treatment	Mutation
1	SALT	TT	M184V, L63P
2	DUAL	TT	L10I, A71T, L76W
3	OLE	DT	K103N, M184V

GESIDA Study 9717

Pérez Molina EACS 2017

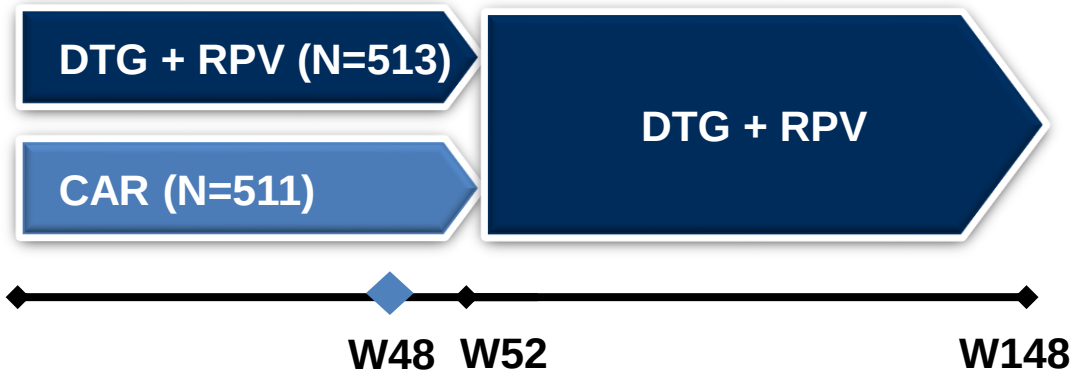
Study Design and Virological Outcomes at W48

Two randomised, multicenter, open-label studies

HIV Suppressed Adults
HIV-1 RNA <50 c/mL
x 12 months

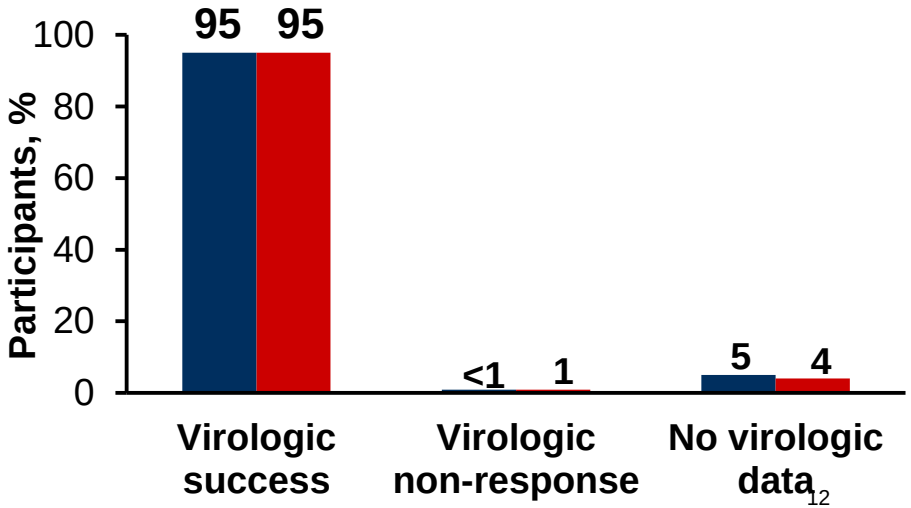
Stable ART x 6 months
INSTI / NNRTI / PI + 2 NRTIs
1st or 2nd ART with no change due to VF

HBV negative



Primary Endpoint[1]

- Non-inferiority established for DTG + RPV vs CAR in virologic suppression (VL < 50 c/mL) at W48 using Snapshot margin of 8% for pooled studies[1]
  - Difference (95%CI): -0.2 (-3.0, 2.5)*
- Non-inferiority was also demonstrated regardless of 3rd agent class[2]



CAR: Continue ART
* Adjusted for age and baseline 3rd agent

1. Llibre JM, et al. CROI 2017; Seattle, WA. Abstract 2421
2. Orkin C, et al. EACS 2017. Milan, Italy. Poster BPD 1/5

Risk–Benefit Trade-Offs: Efficacy, Resistance, Safety Profile, Patient Satisfaction

Parameter	DTG+RPV* vs CAR	Week 48 Results DTG + RPV vs continuing Triple ART
Efficacy[1]	**Similar**	**Non-inferiority by VL < 50 c/mL** • 95% vs 95%; difference (95%CI): -0.2 (-3.0, 2.5)
Resistance[1]	**Relatively worse**	**DTG+RPV: 1 subject had NNRTI resistance (K101K/E)†** • Triple ART: No resistance
Bone Safety[1,4,5]	**Better**	**Greater increase in BMD** (difference: +1.3 for hip and spine) **Reduced bone turnover markers** (73% switched from TDF)
Renal Safety[4]	**Similar**	**No change in renal tubular markers & eGFR** • Despite 73% previously on TDF-based regimen
Lipids, Inflammation, & Atherogenesis[4]	**Similar**	**No change and no difference between arms** • Select markers evaluated
Patient Reported Outcomes[6]	**Similar**	**No difference in symptom bothersome rating and quality of life; very small changes in satisfaction**
Neuropsychiatric Adverse Events[1-3]	**Worse**	**Higher rates of neuropsychiatric adverse events** • DTG+RPV: range 11%-16%; 92% mild-moderate severity **Small, numerically higher discontinuations** 2% vs 0.2%

CAR: Continue ART
* Dosed with food
† Subject resuppressed with continued therapy

1. Llibre JM, et al. CROI 2017; Seattle, WA. Abstract 2421
2. Orkin C, et al. EACS 2017. Milan, Italy. Poster BPD 1/5
3. Walmsley S, et al. ID Week 2017. San Diego, CA. Poster #1382
4. Orkin C, et al. EACS 2017 . Milan, Italy. BPD 2/10
5. McComsey G, et al. IAS 2017. Paris, France. TUPDB0205LB
6. Oglesbey A, et al. EACS 2017. Milan, Italy. Poster BPD 1/2

Impact of M184V on Virologic Efficacy of Switch to 3TC-Based Dual ART

- Retrospective observational study comparing efficacy of 3TC-based dual ART for pts with or without M184V history in Antiretroviral Resistance Cohort Analysis database (N = 436)
  - Inclusion criteria: HIV RNA ≤ 50 copies/mL, switching to dual therapy (3TC + either PI/RTV or INSTI), ≥ 1 prior genotyping
  - M184V determined in historic genotypic resistance tests and last genotyping
  - Primary endpoint: time to virologic failure in M184V-positive vs M184V-negative pts

Dual Therapy Initiated, %	Pts (N = 436)
DRV/RTV + 3TC	36
DTG + 3TC	29
ATV/RTV + 3TC	24
LPV/RTV + 3TC	10
RAL + 3TC	1

Gagliardini R, et al. CROI 2018. Abstract 498.

M184V and Switch to 3TC-Based Dual ART

	M184V- (n=349)	M184V+ (n=87)	p
lamivudine + RAL	2 (1%)	2 (2%)	
Pre-BL ART:			
2NRTI+PI	176 (50%)	44 (51%)	0.081
2NRTI+INI	26 (7%)	7 (8%)	
2NRTI+NNRTI	45 (13)	3 (3%)	
DT	79 (23%)	23 (26%)	
Other	23 (7%)	10 (12%)	
Calendar year*	2014 (2013; 2015)	2014 (2012; 2015)	0.121
GSS of the 2nd drug **	0.99 (0.07)	0.91 (0.20)	**<0.001**
Major PI resistance mutations***	13 (4%)	30 (34%)	**<0.001**

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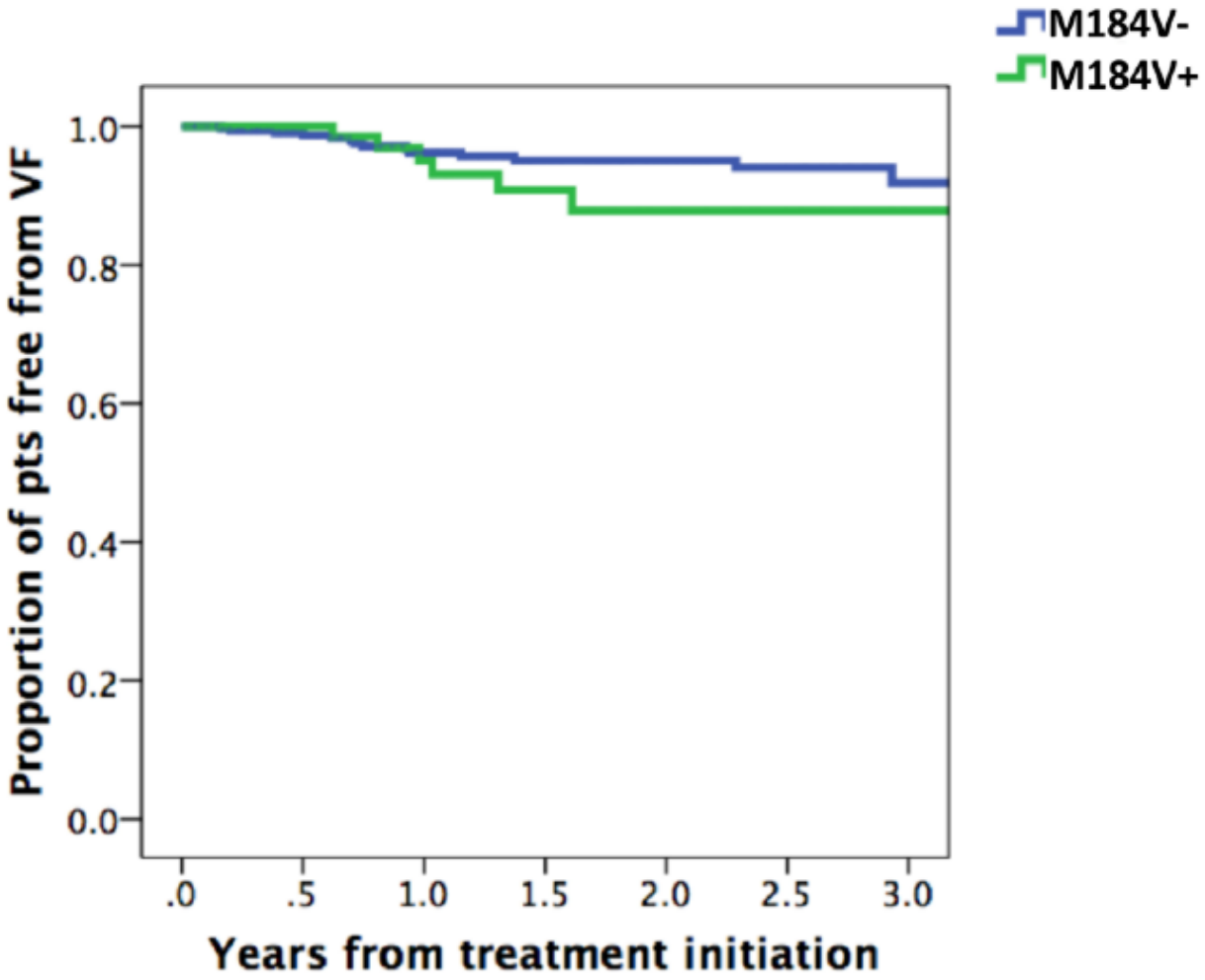
Figure 1a: Estimated probability of being free from virological failure (VF) with dual therapy (M184V groups based on the hGRT)



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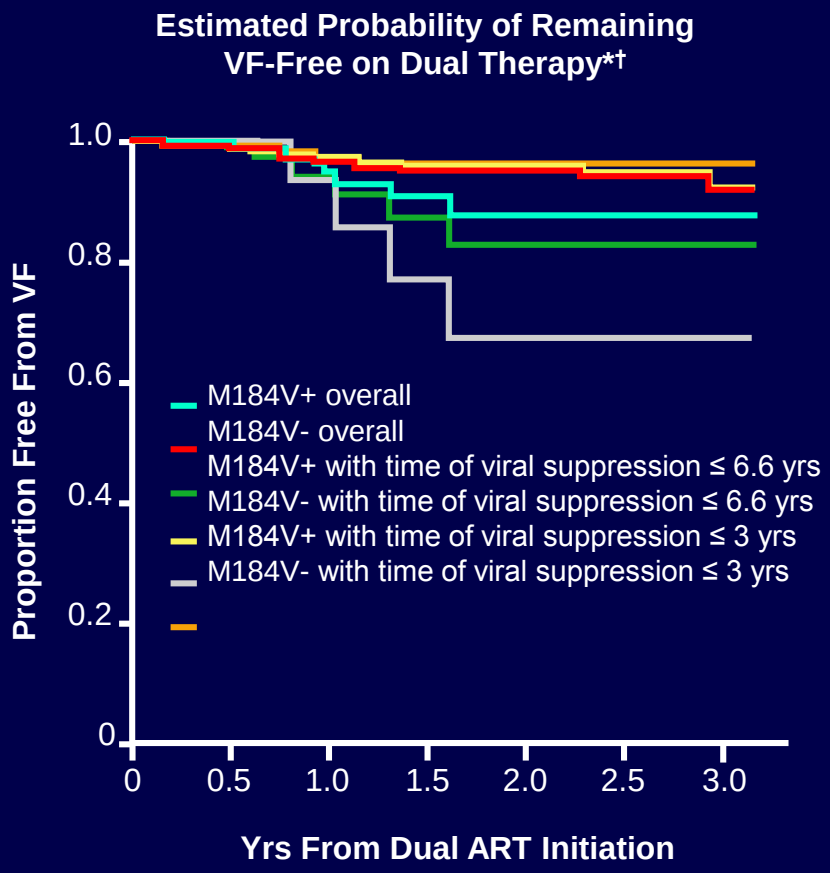
M184V and Switch to 3TC-Based Dual ART: Efficacy



- Significantly higher 3-yr probability of remaining free from viral blip‡ without vs with M184V (log-rank *P* = .016)
  - M184V: 79.8% (95% CI: 67.8% to 91.8%)
  - No M184V: 90.1% (95% CI: 84.0% to 96.2%)

*VF: 2 HIV-1 RNA findings > 50 c/mL or 1 finding ≥ 200 c/mL. †No VF in 21 pts on DTG + 3TC over median f/u of 10 mos.
‡Viral blip: single HIV-1 RNA finding 51-199 c/mL, not confirmed.

Gagliardini R, et al. CROI 2018. Abstract 498. Reproduced with permission.

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M184V and Switch to 3TC-Based Dual ART:

Predictors of VF:
GSS of the 2nd drug better predicts VF as M184V
Implications for DTG+3TC?

	Univariate analysis		Multivariable analysis 1		Multivariable analysis 2	
Variables	HR (95% CI)	p value	aHR (95% CI)	p value	aHR (95% CI)	p value
M184V in hGRT	1.56 (0.64;3.76)	0.327	1.23 (0.46;3.31)	0.684	1-11 (0.38; 3.23)	0.847
Type of DT (PI vs INI)	0.42 (0.10;1.85)	0.251				
Age (+ 10 years)	1.17 (0.83;1.65)	0.381			1.11 (0.73; 1.69)	0.625
Gender (male vs female)	0.66 (0.29;1.50)	0.320			0.61 (0.25; 1.51)	0.284
Ethnicity (Caucasian vs other)	0.60 (0.14; 2.54)	0.483				
Risk factor (ref. sexual)						
IDU	2.40 (0.85; 6.75)	0.098				
Other/unknown	1.51 (0.57; 4.02)	0.411				
HCV infection (ref. absent)						
present	1.85 (0.78; 4.37)	0.163				
Unknown	0.16 (0.02; 1.19)	0.073				
HBsAg (ref. negative)						
Positive	8.85 (2.25; 31.5)	**0.001**			**12.53 (2.15; 72.9)**	0.005
Unknown	0.50 (0.15; 1.71)	0.269			1.67 (0.46; 5.96)	0.437
Previous AIDS-defining events	1.34 (0.46: 3.93)	0.594				
Duration of virological suppression before baseline (+ 1 year)	0.97 (0.86; 1.16)	0.965	0.95 (0.81;1.1)	0.95	0.92 (0.79;1.08)	0.306
Baseline CD4+ counts (+100 cells/µl)	0.99 (0.86;1.14)	0.922				
Nadir CD4+ counts (+100 cells/µl)	0.86 (0.64; 1.16)	0.319				
Peak HIV-RNA (+1 log_{10} copies/mL)	1.91 (1.06; 3.42)	**0.030**	1.91 (1.05; 3.49)	0.035	1.61 (0.89; 2.91)	0.116
GSS of the 2nd drug (+0.5)	0.36 (0.16; 0.84)	**0.018**	0.41 (0.16; 1.03)	0.058	0.41 (0.15;1.19)	0.082

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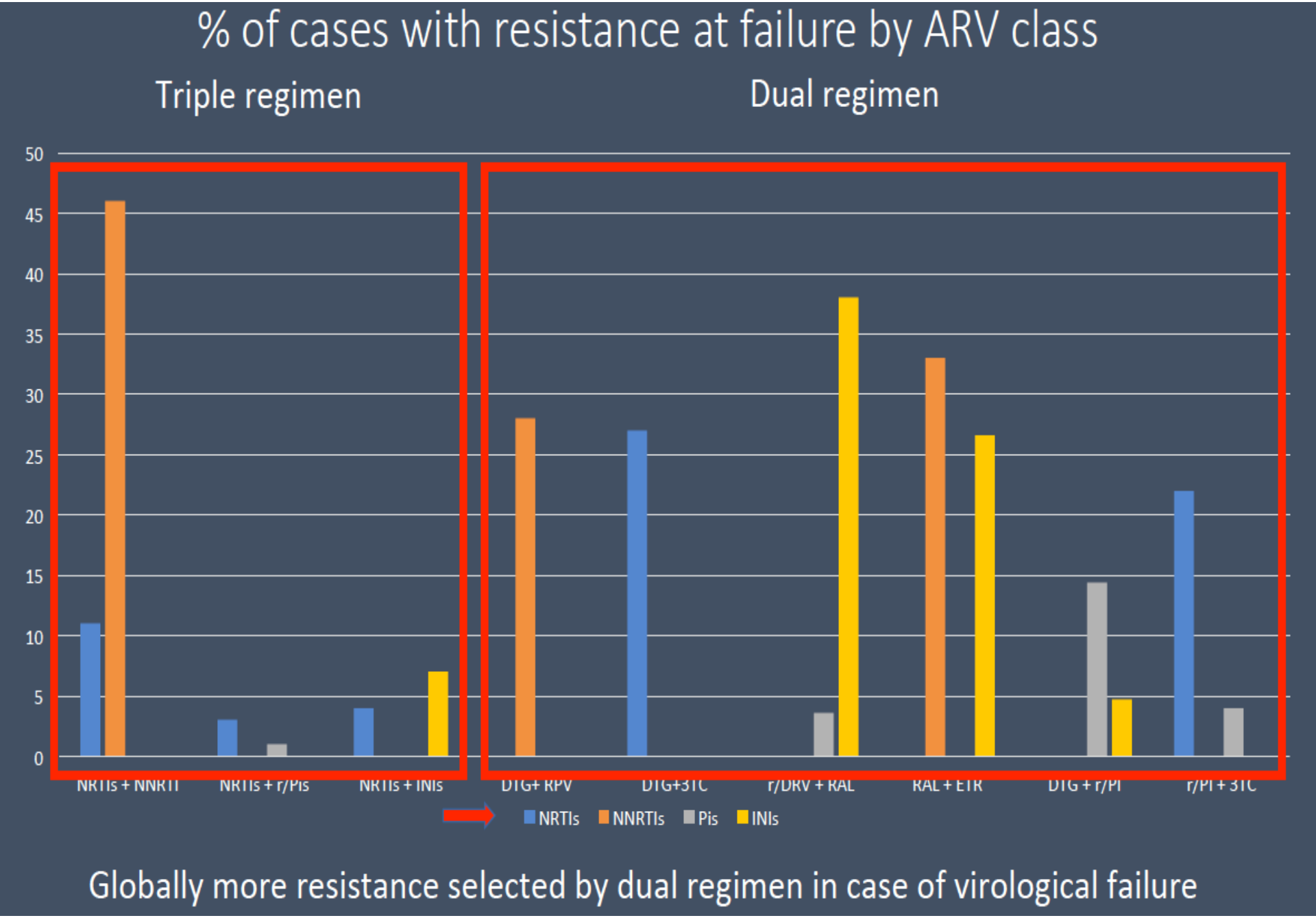
Antiretroviral resistance selected at failure in HIV+ treated with triple or dual regimens

Aim of the study

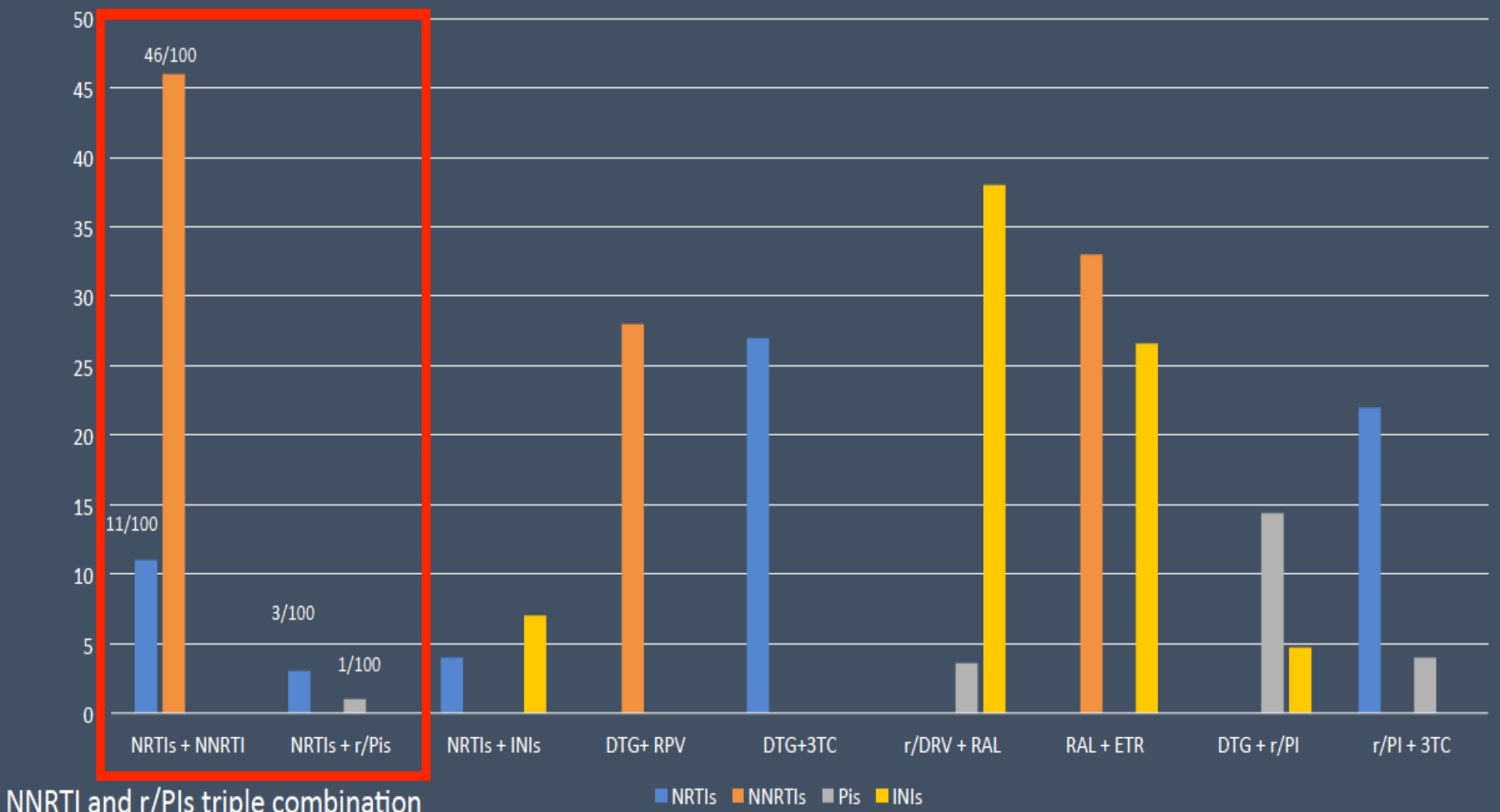
- To measure resistance selected in patients treated by triple and dual regimen experiencing virologic failure
- 465 patients were studied (> 30 centers in Italy and France)
  - 300 receiving standard NRTI based triple combinations initiation or switch
    - NRTIs + NNRTI (EFV or RPV) (n=100)
    - NRTIs + INI (RAL or c/EVG or DTG) (n=100)
    - NRTIs + r/PI (r/DRV or r/ATV) (n=100)
  - 165 receiving DTG, RAL or r/PI based dual switch combinations
    - DTG based regiment: DTG + RPV (n=14) ; DTG + 3TC (n= 11); DTG + r/PI (n = 21)
    - RAL based regiment: RAL + r/DRV (n= 55); RAL + ETR (n= 15)
    - r/Pis based regiment: r/PI + 3TC (n= 49)
- None of these patients have failed to drugs of these classes in their therapeutic histories
- Definition of VF was: 2 consecutive VL > 50 copies/ml
- Resistance testing on the second plasma sample

Calvez V, EACS 2017



Calvez V, EACS 2017

% of cases with resistance at failure by ARV class

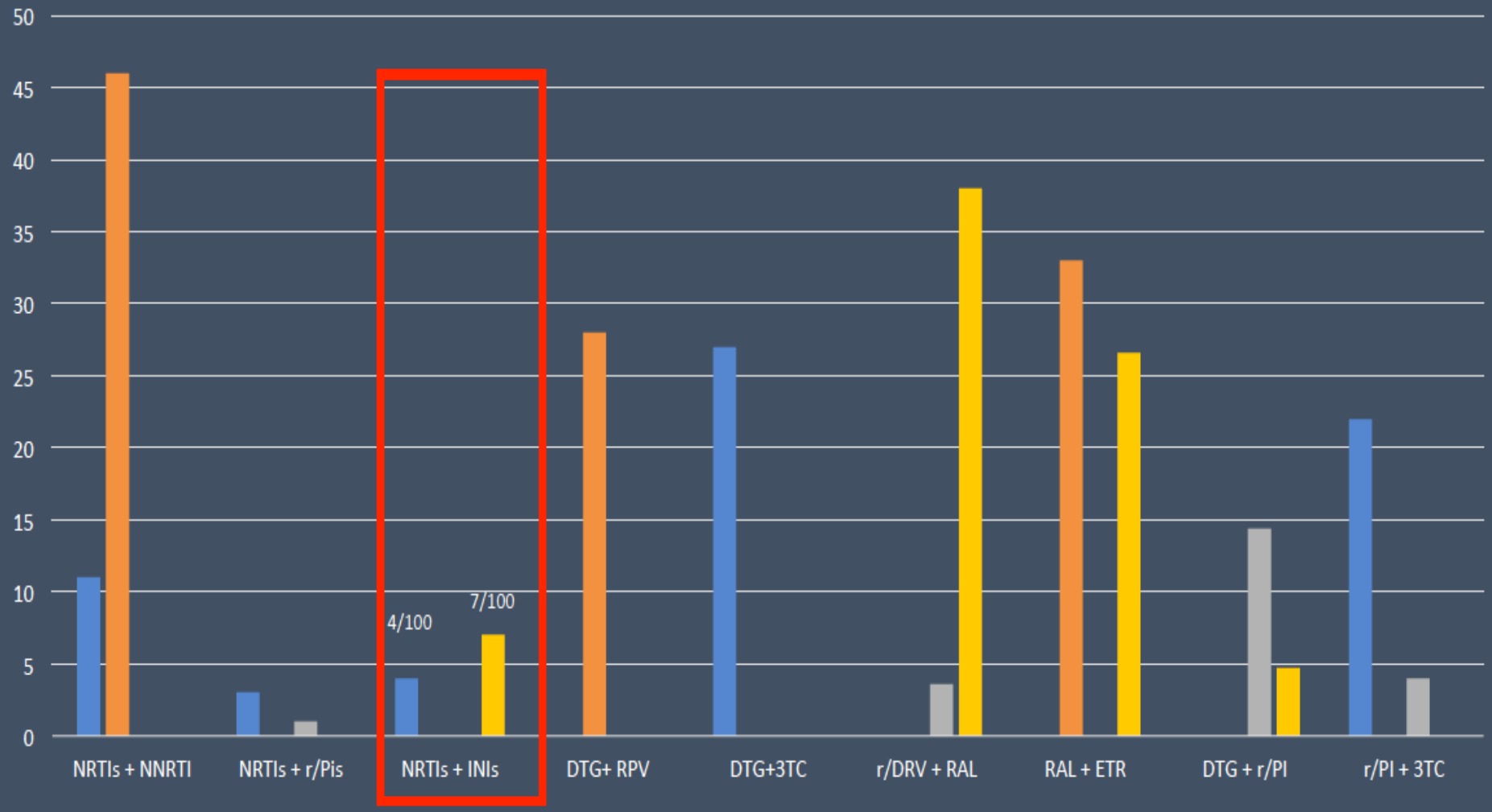


NNRTI and r/PIs triple combination

- High rate of NNRTI resistance
- Very low rate of PI resistance
- Protection of the NRTI backbone with r/PIs

Calvez V, EACS 2017

% of cases with resistance at failure by ARV class

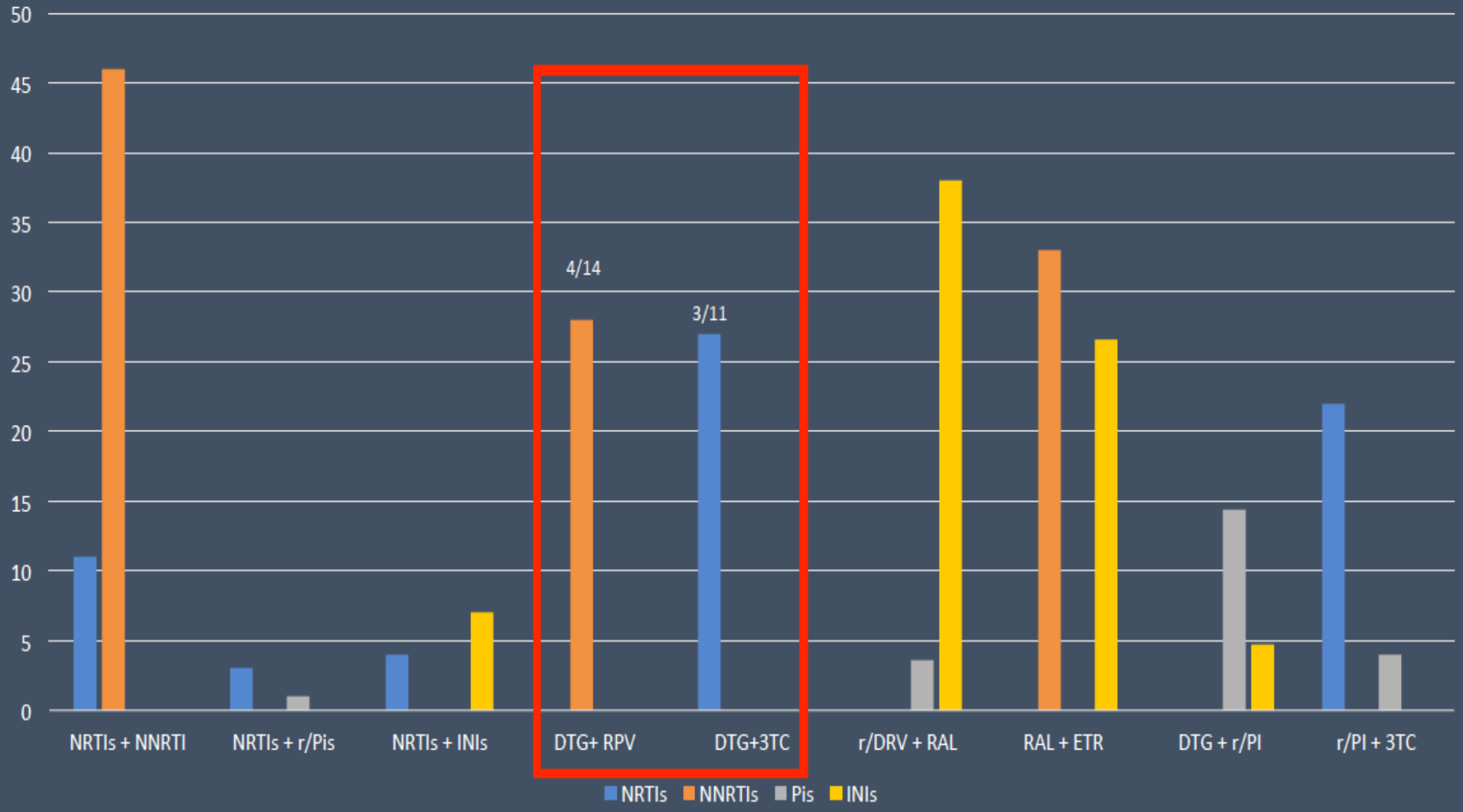


INIs used in triple combinations:

- No DTG resistance when used in triple combination
- Resistance selected only with RAL (n=2) and c/EVG (n=5) use in triple combination

Calvez V, EACS 2017

% of cases with resistance at failure by ARV class

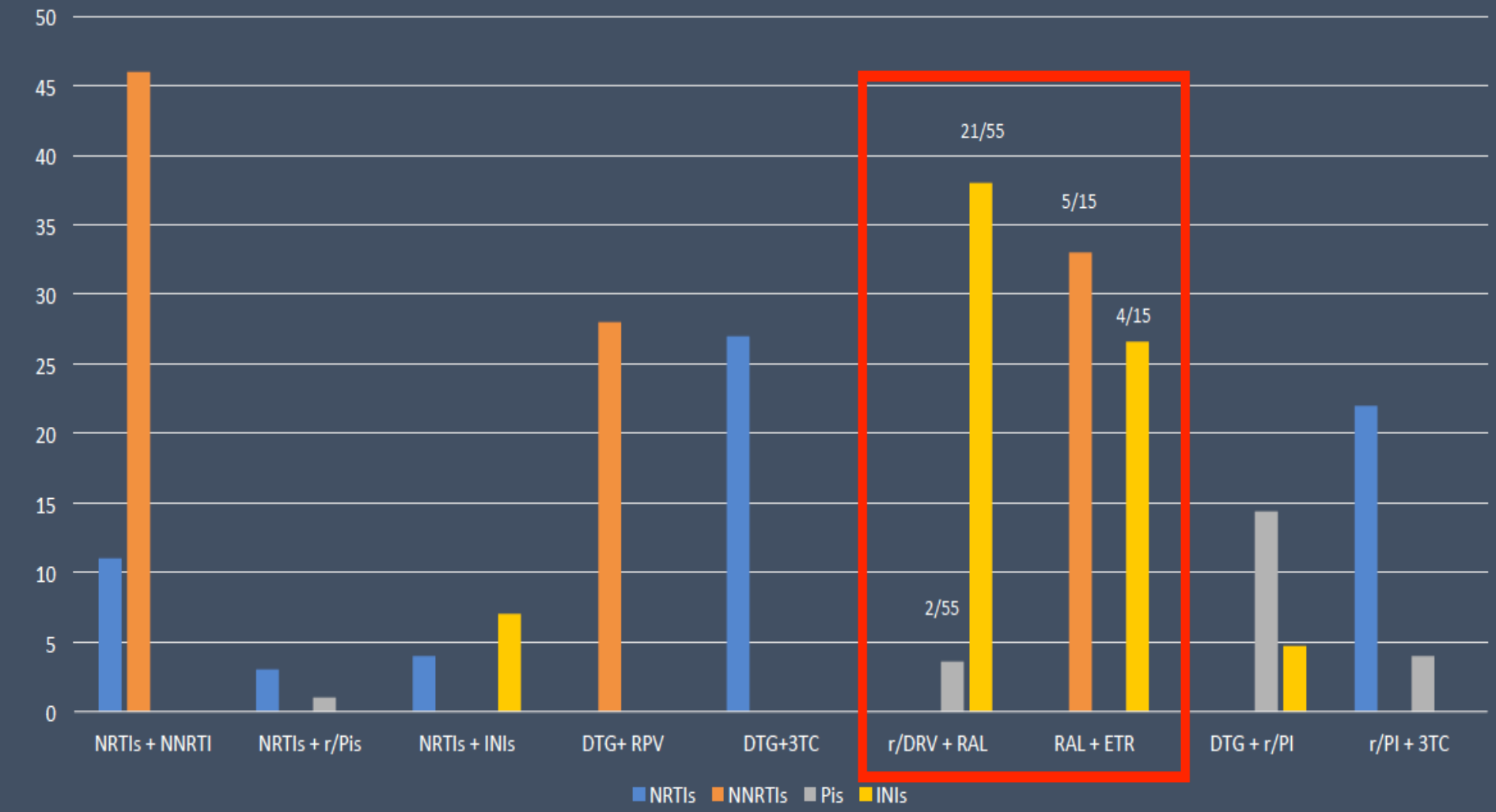


DTG dual combination with 3TC or RPV

- No DTG resistance
- DTG does not always protect for RPV or 3TC resistance in case of failure

Calvez V, EACS 2017

% of cases with resistance at failure by ARV class



RAL dual combinations

- r/DRV does not protect for RAL resistance
- No cross protection for resistance between RAL and ETR

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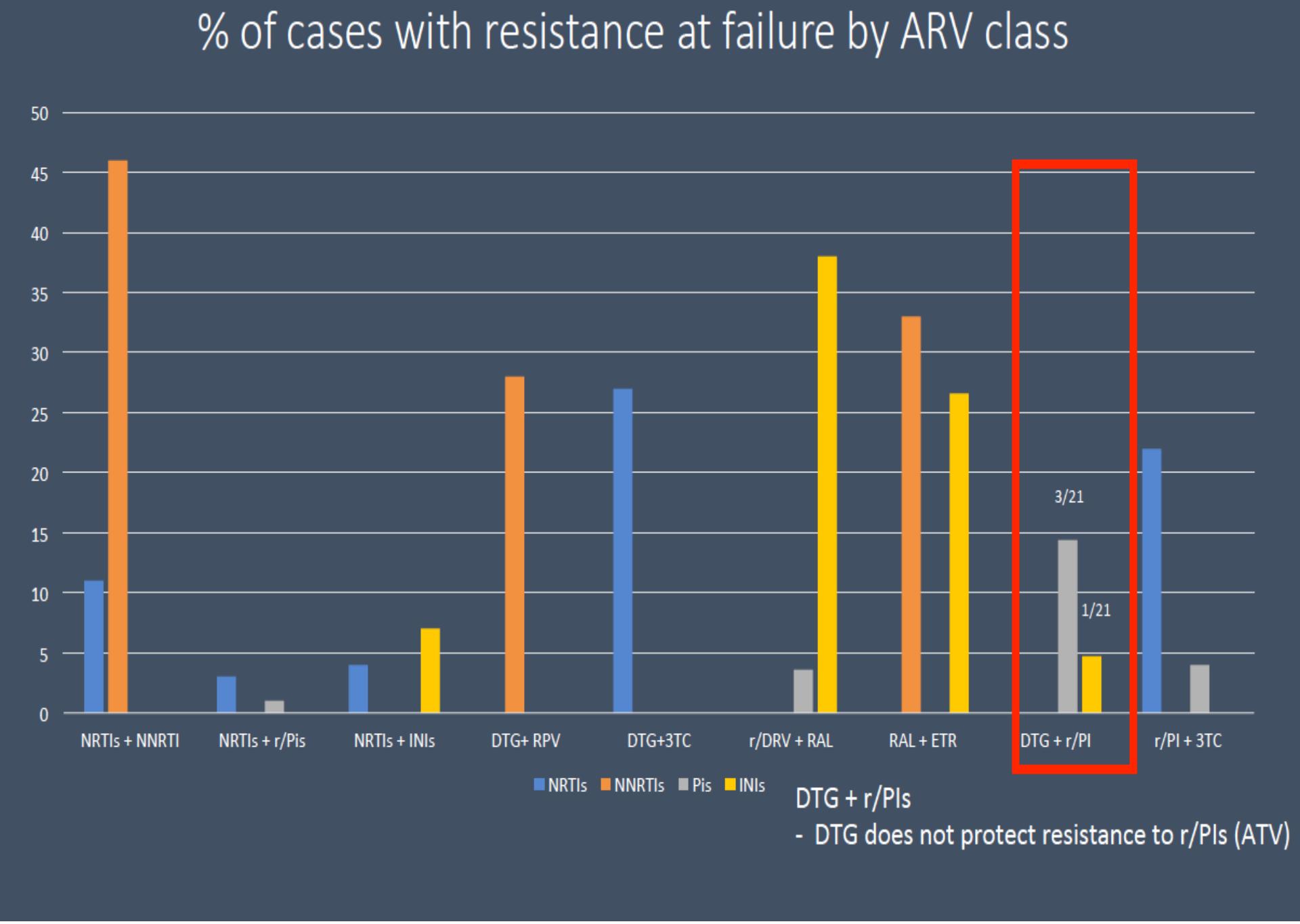

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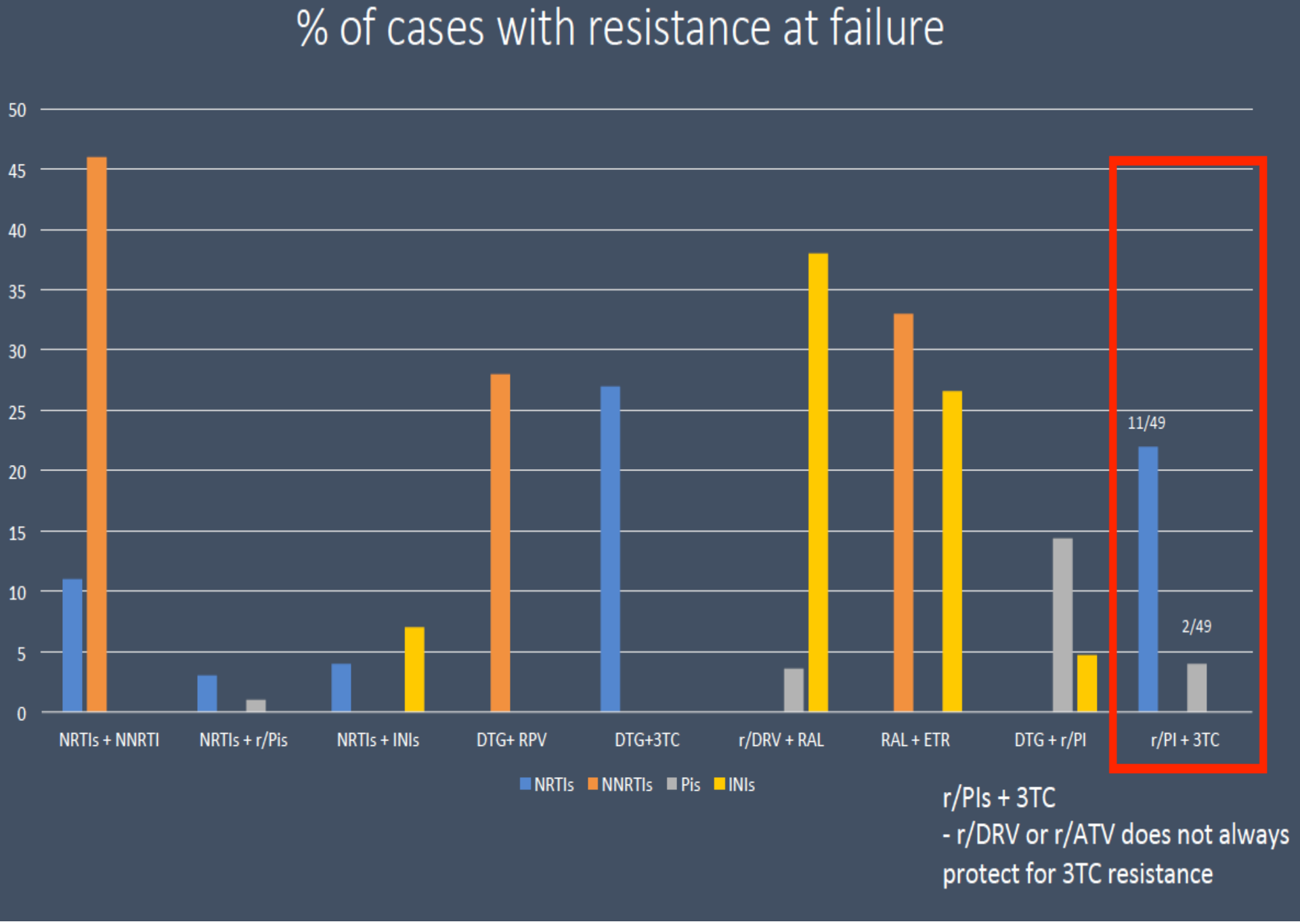
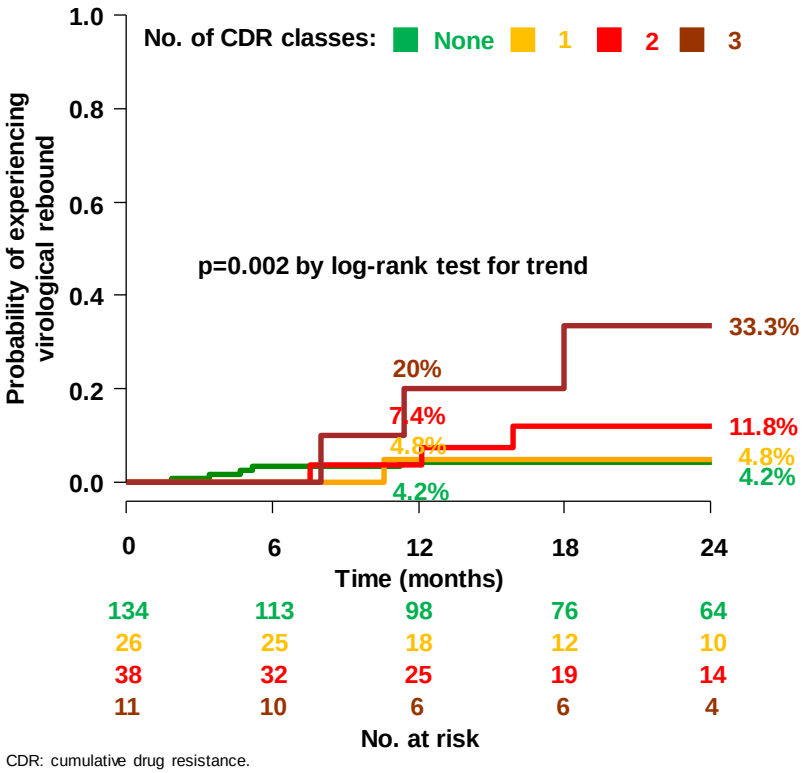


Calvez V, EACS 2017

Drug resistance and virological rebound with DRV or ATV/r+3TC



CDR: cumulative drug resistance.

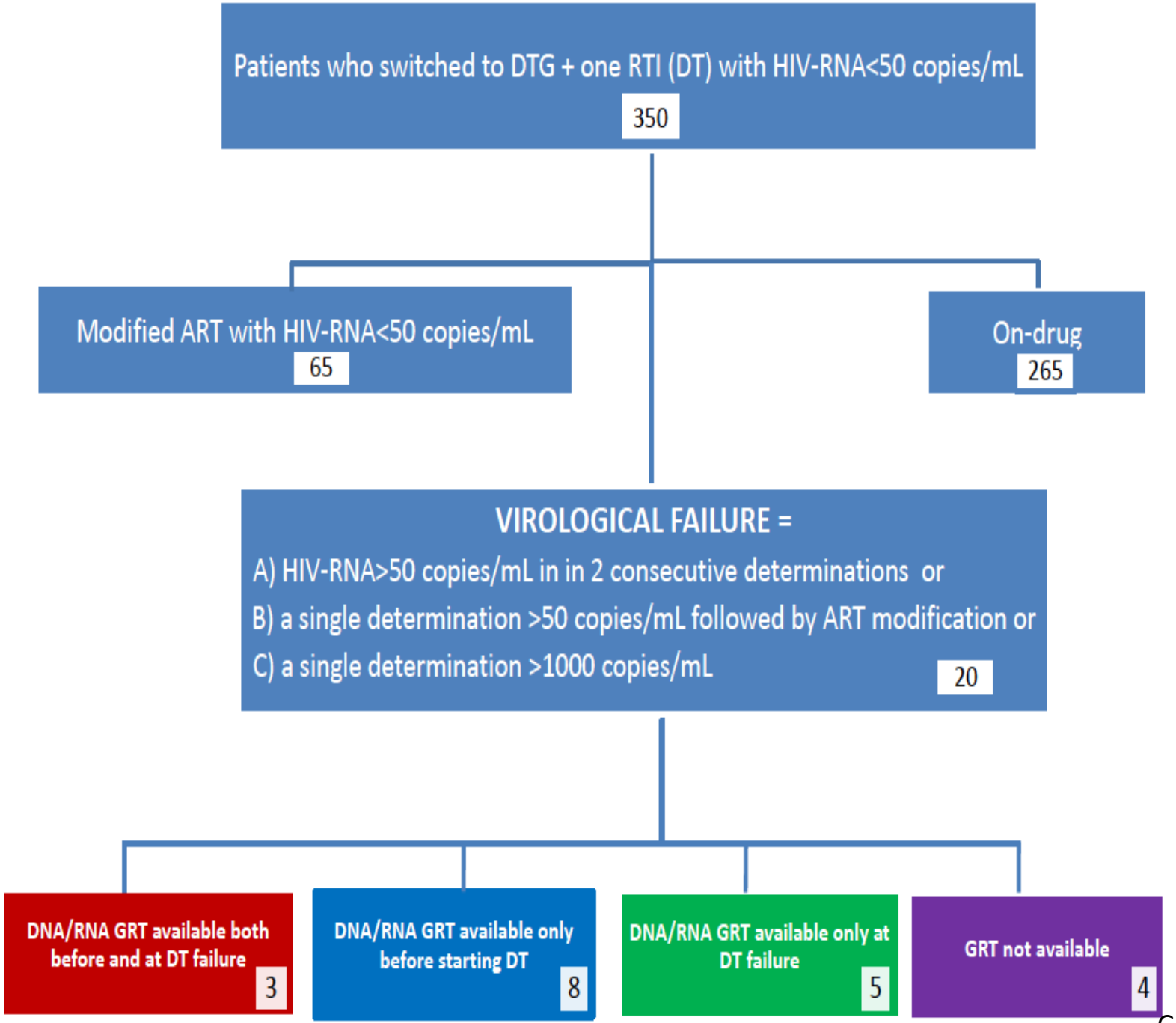
ID Patient	HIV-1 subtype	Regimen	Exposure to regimen (days)	Plasma HIV-1 RNA at GRT (log_{10} copies/mL)	No. of previous GRTs	No. of previous regimens
GEV-GE03038	CRF01_AE	3TC+ATV/r	343	5.6	1	16
MOV-MO-0372	B	3TC+ATV/r	1385	2.9	1	11

/r: boosted ritonavir. 3TC: lamivudine. ATV: atazanavir. GRTs: genotypic resitance tests.

ID Patient	Cumulative RAMs prior to switch			RAMs at 3TC+ATV/r failure		
	PI	NRTI	NNRTI	PI	NRTI	NNRTI
GEV-GE03038	M46I, I54V, L76V, V82F	A62V, K65R, K70R, V75I, Y115F, F116Y, Q151M, M184V	Y188L, G190A	M46I, I54V, L76V, V82F	A62V, K65R, K70R, V75I, Y115F, F116Y, Q151M, M184V	Y188L, G190A
MOV-MO-0372	None	M41L, D67N, K70R, T215Y, K219Q	K101E, E138Q, G190A	**V32I**, **M46L**, **I50L**, **V82A**	M41L, D67N, K70R, **M184V**, T215Y, K219Q	K101E, G190A

Boldface represent acquired mutations compared to cumulative RAMs prior to switch. /r boosted ritonavir. 3TC: lamivudine. ATV: atazanavir. NNRTI: non-nucleoside reverse transcriptase inhibitor. NRTI: nucleos(t)ide reverse transcriptase inhibitor. PI: protease inhibitor. RAMs: resistance associated mutations.

Di Carlo D, ICAR 2017 (submitted)



Galizzi N ICAR 2018

Table 1. Patients with DNA/RNA GRT available both before and at DT failure

ID	DNA/RNA GRT BEFORE STARTING DT					FAILING REGIMEN	HIV-RNA AT FAILURE	DNA/RNA GRT AT FAILURE				
	PRIMARY PI	SECONDARY PI	NRTI	NNRTI	INSTI			PRIMARY PI	SECONDARY PI	NRTI	NNRTI	INSTI
5515	None	None	L74V, M184V	K103N, Y181C	N/A	RPV DTG	354; 1127	None	None	L74V, M184V	K103N, Y181C, H221Y, P225H	G118GRS, E138EA, G140GA, Q148QR
8637	None	None	None	None	None	RPV DTG	5044; 20906	None	None	None	None	None
3536	N/A	N/A	T215Y M184V	N/A	N/A	3TC DTG	65; 107	None	N88ND	M41ML, M184MV, T215CNSY	None	None

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Table 3. Patients with DNA/RNA GRT available only at DT failure

ID	FAILING REGIMEN	HIV-RNA AT FAILURE	DNA/RNA GRT AT FAILURE				
			PRIMARY PI	SECONDARY PI	NRTI	NNRTI	INSTI
4311	3TC DTG	107720; 583	None	None	None	None	N/A
5268	3TC DTG	86; 190	N/A	N/A	N/A	N/A	None
2369	3TC DTG	51; 74	None	None	None	E138A	None
5690	3TC DTG	52; 64	None	Q58E	**M41L, M184, L210W, T215Y**	None	N/A
3026	3TC DTG	65	None	None	None	None	N/A

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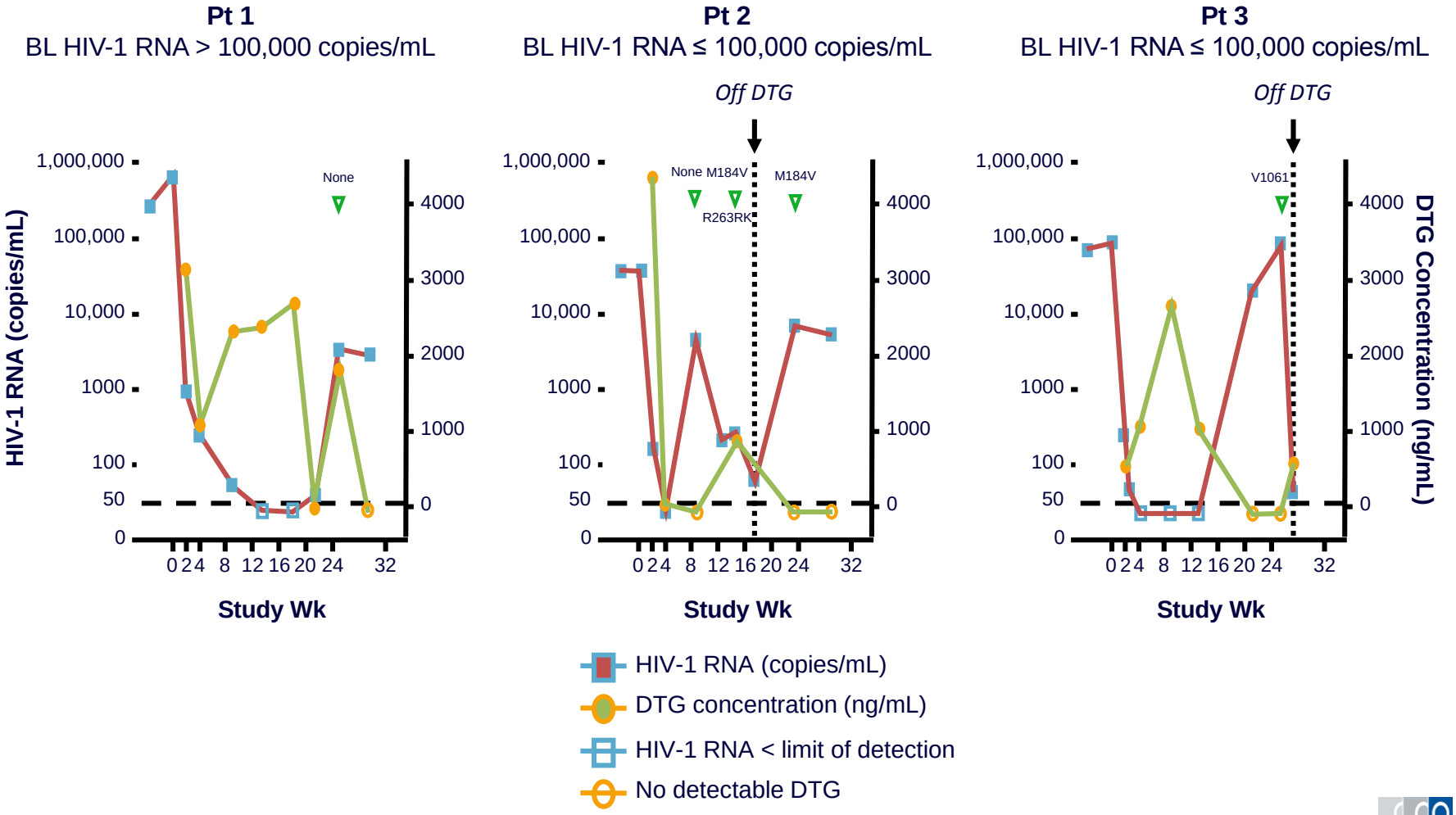
ACTG A5353: HIV-1 RNA Levels and DTG Concentration in Pts Experiencing PDVF



Taiwo BO, et al. IAS 2017. Abstract MOAB0107LB. Reproduced with permission.

VF with DTG+3TC (Odoacre)

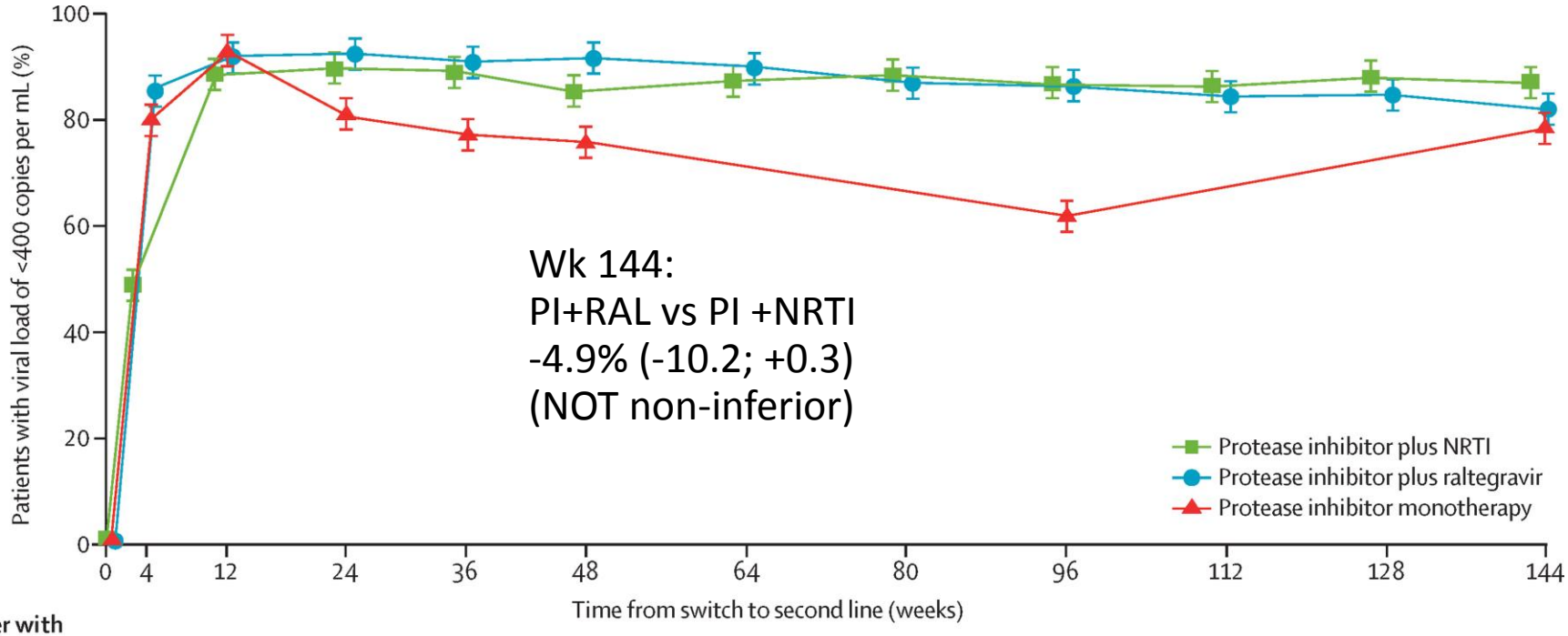
- 206 patients median follow up of 12.8 months:
- 5 virological failures over 216.5 PYFU (2.3 VF per 100 PYFU).
  - Estimated probabilities of maintaining virological suppression
    - 48 weeks 98.2% (95% CI, 96.0%-100%)
    - 96 weeks 95.1% (95%CI 90.4%-99.8%)
  - Peak HIV-1 RNA≥$5x10^5$ copies/mL: 7.8 VF per 100 PYFU:
  - Probabilities of virological suppression in subgroup
    - 48 weeks 95.2% (95%CI 86.2%-100.0%)
    - 96 weeks 86.6% (95%CI 68.4%-100.0%) (vs <$5x10^5$ copies/mL p=0.049)
- lack of adherence 2 of 5 cases
- 1 tested: no resistance

Borghetti A HIV Medicine 2018 and unpublished

RESIDUAL ACTIVITY OF 2 NRTIs DESPITE RESISTANCE

EARNEST: Second-line LPV/RTV in Patients With Virologic Failure: 144wks follow-up

Open label, 14 African sites, all pts failing 2NRTI+NNRTI



Wk 144:
PI+RAL vs PI +NRTI
-4.9% (-10.2; +0.3)
(NOT non-inferior)

Number with viral-load result												
Protease inhibitor plus NRTI	426	374	381	382	386	395	382	370	379	351	342	367
Protease inhibitor plus raltegravir	433	389	394	389	382	400	392	378	391	369	351	383
Protease inhibitor monotherapy	481	374	385	378	379	389			380			375

Paton NI, et al. Lancet HIV. 2017;4:e341-e348.

Considerations

- Consequences of lowering genetic barrier?
- Role of previous resistance in response to PI/DTG+3TC
  - Role of M184V and resistance to the 2nd drug
- Emergence of resistance upon VF with 2DR
  - Resistance to DTG in 2DR very rare (only with RPV or DRV/r: role of previous resistance to the accompanying drugs; one case with 3TC in naive)
  - More than with TT? Role of previous failure and resistance? Residual NRTI activity?
  - What if 2DR only for those without history of VF?