
Kirby Institute

Can we use sequential regimens in lieu of HIV drug resistance testing?

The SECOND-LINE resistance substudy

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Boyd et al. Lancet HIV E-pub 20 Jan 2015.

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Disclosures

AbbVie: *research grants, honoraria*

Bristol Myers Squibb: *honoraria*

Boehringer-Ingelheim: *honoraria*

Gilead: *research grant, honoraria*

Janssen-Cilag : *honoraria*

Merck: *research grants, honoraria*

ViiV Healthcare: *honoraria*

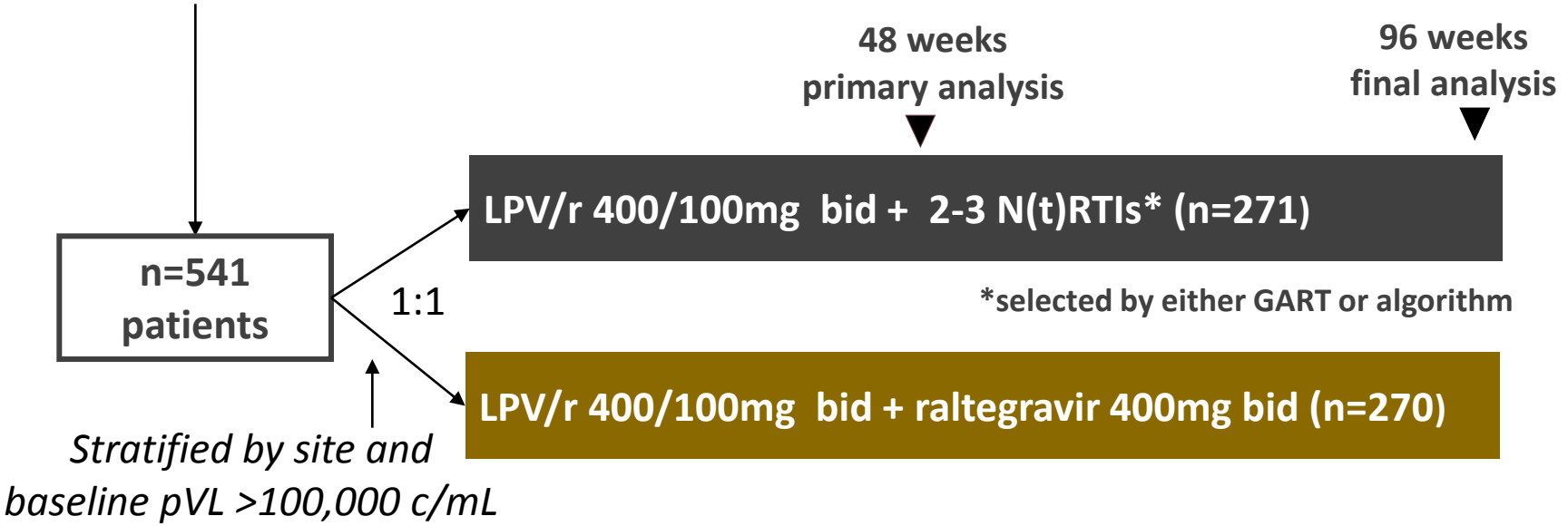
SECOND-LINE resistance substudy

Background

- ART failure is associated with drug resistance
- WHO recommends using a boosted-PI + 2N(t)RTIs after 1st line NNRTI+2N(t)RTI failure
- There is interest in implementing wider access to genotypic testing to optimise N(t)RTI selection

SECOND-LINE main study

Adults ≥16 years old
Confirmed virological failure of NNRTI+2N(t)RTIs (pVL >500 copies/mL)
No prior PI or InSTI exposure



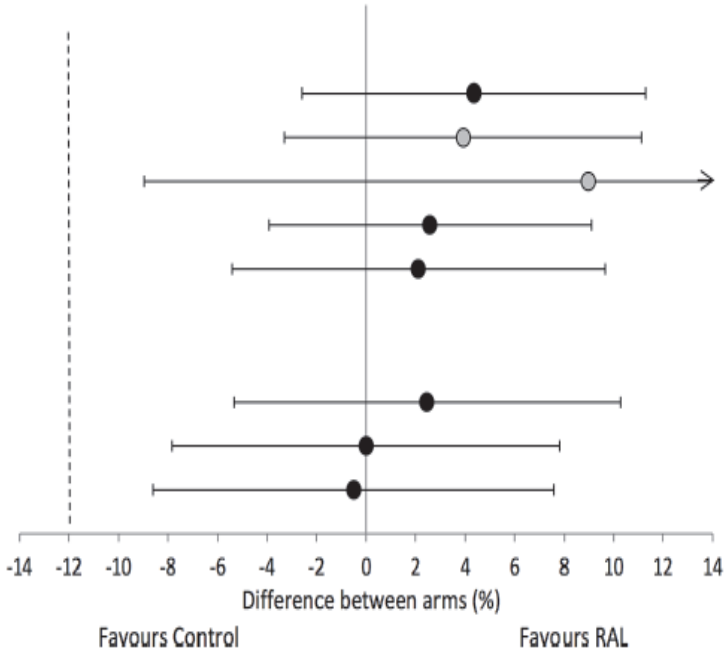
Primary objective

- compare proportions with plasma viral load <200 copies/mL at week 48

SECOND-LINE main study

96 week results

	RAL arm n/N (%)	Control arm n/N (%)	Difference (RAL-Control) %	(95%CI)	p-value
Plasma viral load <200 copies/mL					
Intention to treat	217/270 (80.4)	206/271 (76.0)	4.4	(-2.6, 11.3)	0.22
≤100000 copies/mL*	177/210 (84.3)	176/219 (80.4)	3.9	(-3.3, 11.1)	0.30
>100000 copies/mL*	40/60 (66.7)	30/52 (57.7)	9.0	(-8.9, 26.9)	0.33
Per protocol	200/232 (86.2)	194/232 (83.6)	2.6	(-3.9, 9.1)	0.44
Non-completion=failure	198/270 (73.3)	193/271 (71.2)	2.1	(-5.4, 9.7)	0.58
Plasma viral load <50 copies/mL					
Intention to treat	189/270 (70.0)	183/271 (67.5)	2.5	(-5.3, 10.3)	0.54
Per protocol	175/232 (75.4)	175/232 (75.4)	0.0	(-7.8, 7.8)	1.00
Non-completion=failure	173/270 (64.1)	175/271 (64.6)	-0.5	(-8.6, 7.6)	0.90



Virological response at week 96 by randomised arm, study population and baseline VL

SECOND-LINE resistance substudy

Objectives

Examine the contribution of baseline N(t)RTI-resistance as well as other potential predictive variables to virological failure (VF) in SECOND-LINE

- demographics, HIV history, ART history, ART adherence

SECOND-LINE resistance substudy

Hypothesis

That the gGSS would predict an adequate response to therapy defined as a plasma viral load <200 copies per mL at week 96 in the N(t)RTI group

i.e.

- that the higher the score the more likely a patient in the N(t)RTI group would achieve and sustain a fully suppressed VL
- that baseline N(t)RTI resistance would have no association with outcome in the N(t)RTI-sparing arm

SECOND-LINE resistance

Methods

Analysis population

- Modified intention to treat (mITT)

Virological failure (VF)

- plasma viral load (pVL) ≥200 copies/ml
  - central laboratory

Genotypic antiretroviral testing (GART)

- Viroseq HIV-1 type genotyping system for RT/PI and InSTI

Adherence

- Validated 7 day recall instrument
  - '**all ART taken**' *versus* '**most, half, very few or no ART taken**'
  - conducted at week 4 and week 48

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Methods

Global Genotypic Sensitivity Score (gGSS)*

- combined GSS for lamivudine/emtricitabine, abacavir, zidovudine, stavudine, didanosine, and tenofovir for each viral isolate (max score = 6)
  - *scores for each N(t)RTI = 0, 0.25, 0.50, 0.75, and 1 for high-level, intermediate, low-level, potential low-level resistance and susceptible respectively*

Specific Genotypic Sensitivity Score (sGSS)*

- GSS for the N(t)RTIs used by each participant
- N(t)RTI arm only (max score = 2 or 3)

Multivariate logistic regression

- assess predictors of VF

*Stanford algorithm HIV database version 6.3.1 (http://hivdb.stanford.edu)

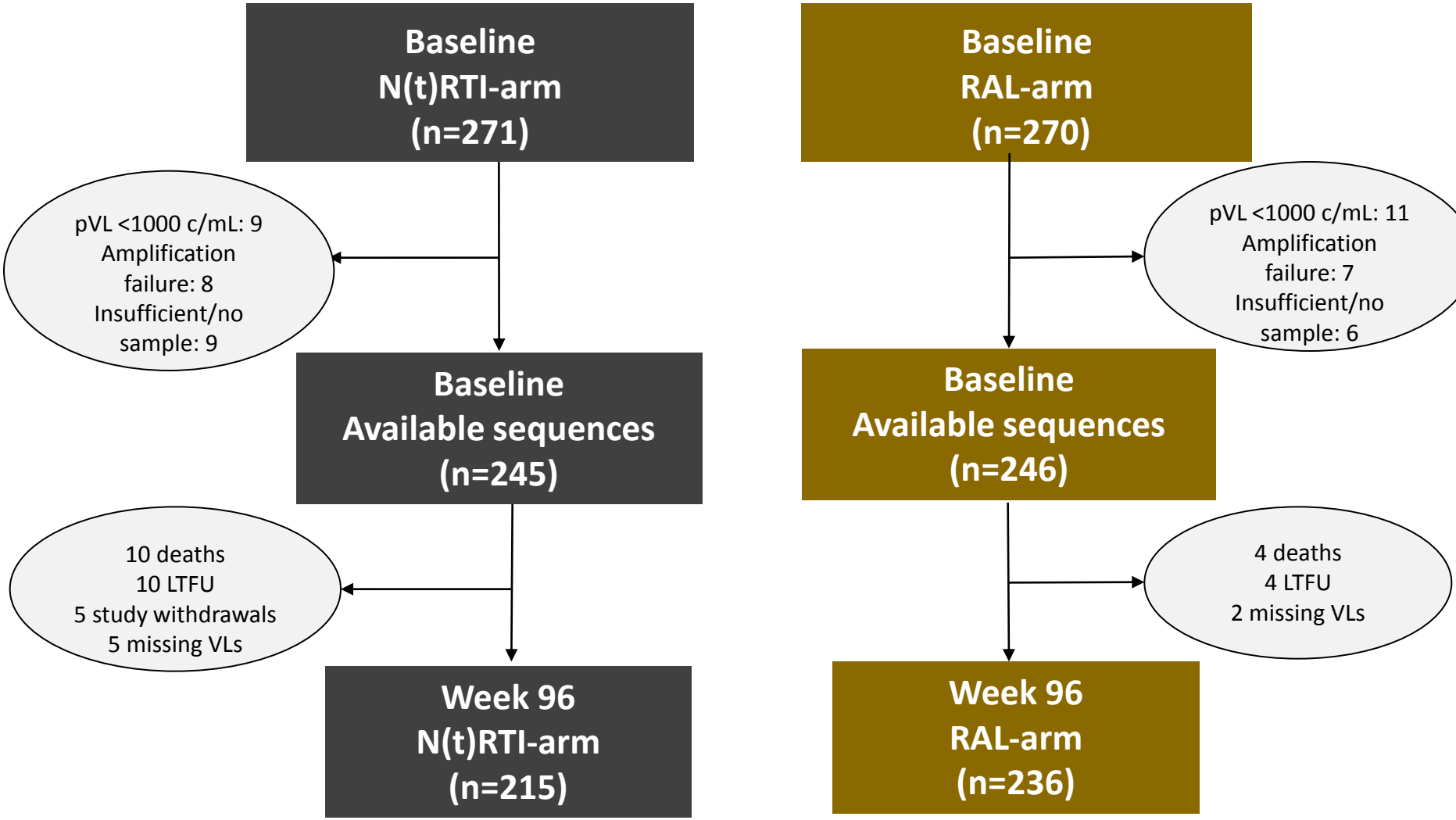
SECOND-LINE baseline characteristics

Characteristics		N(t)RTI-arm (n=271)	RAL-arm (n=270)
Median age (years)		38.5 (3-46)	38.4 (32-44)
Men		156 (57.6%)	142 (52.6%)
Population	Caucasian Asian Hispanic African	6.6% 43.2% 14% 36.2%	8.5% 41.5% 13.7% 35.9%
HIV disease stage	C	46.5%	47.4%
Median CD4+ T-cell count (cells/µL)		189 (80-289)	190 (104-307)
Median Log_{10} plasma HIV RNA		4.3 (3-7-4.9)	4.2 (3.6-4.8)
Median duration of first-line ART (yrs)		3.3 (1.8-5.4)	3.5 (2.0-5.7)

SECOND-LINE N(t)RTI-arm drug selection

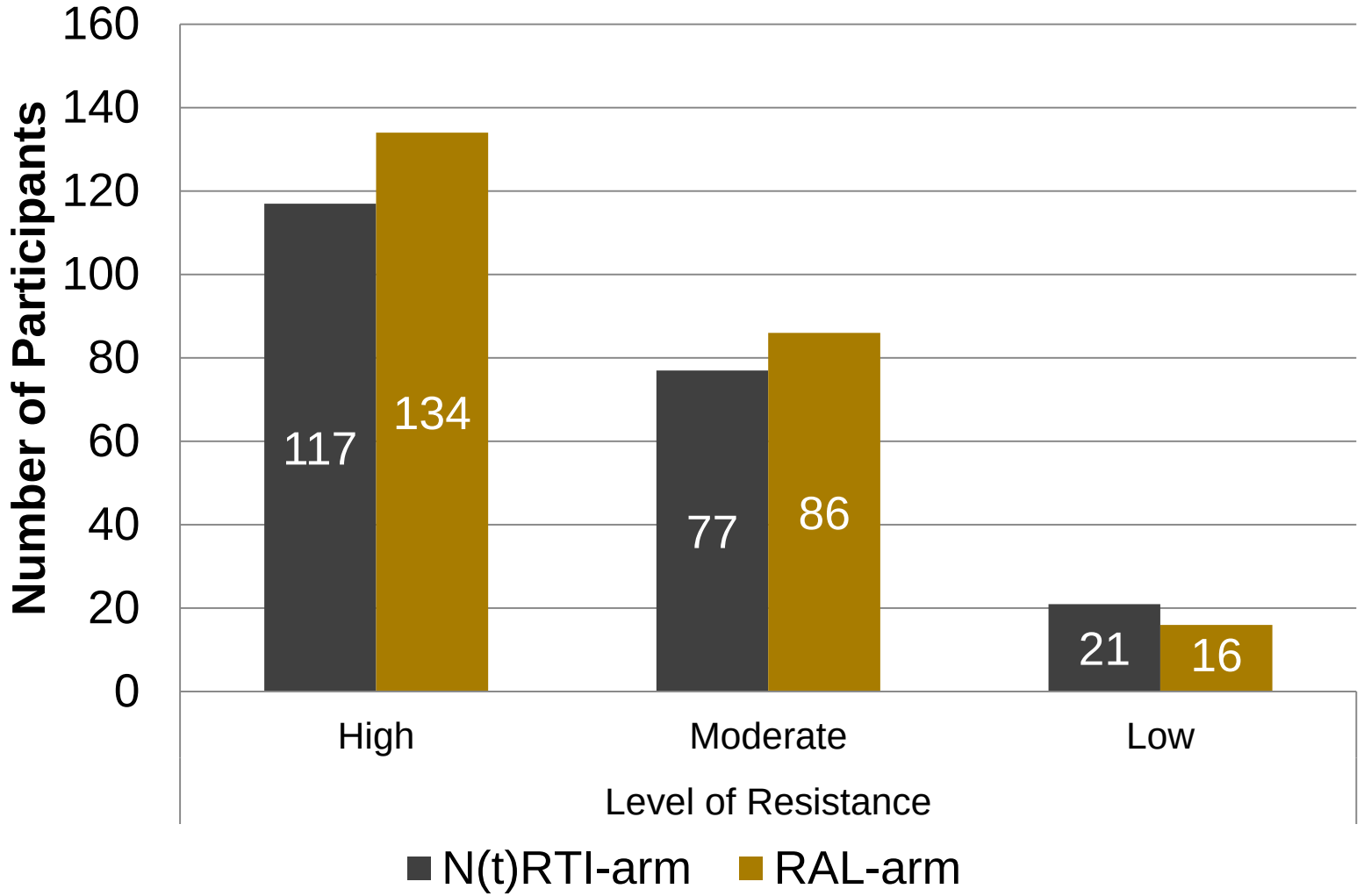
GART for N(t)RTI-selection	198 (73%)
Algorithm for N(t)RTI selection	73 (27%)
2N(t)RTIs in 2nd line ART	208 (77%)
3N(t)RTIs in 2nd line ART	63 (23%)
TDF in 2ndline N(t)RTI-regimen	220 (81%)
3TC/FTC in 2nd line N(t)RTI-regimen	236 (87%)
AZT in 2nd line N(t)RTI-regimen	123 (45%)

Study disposition



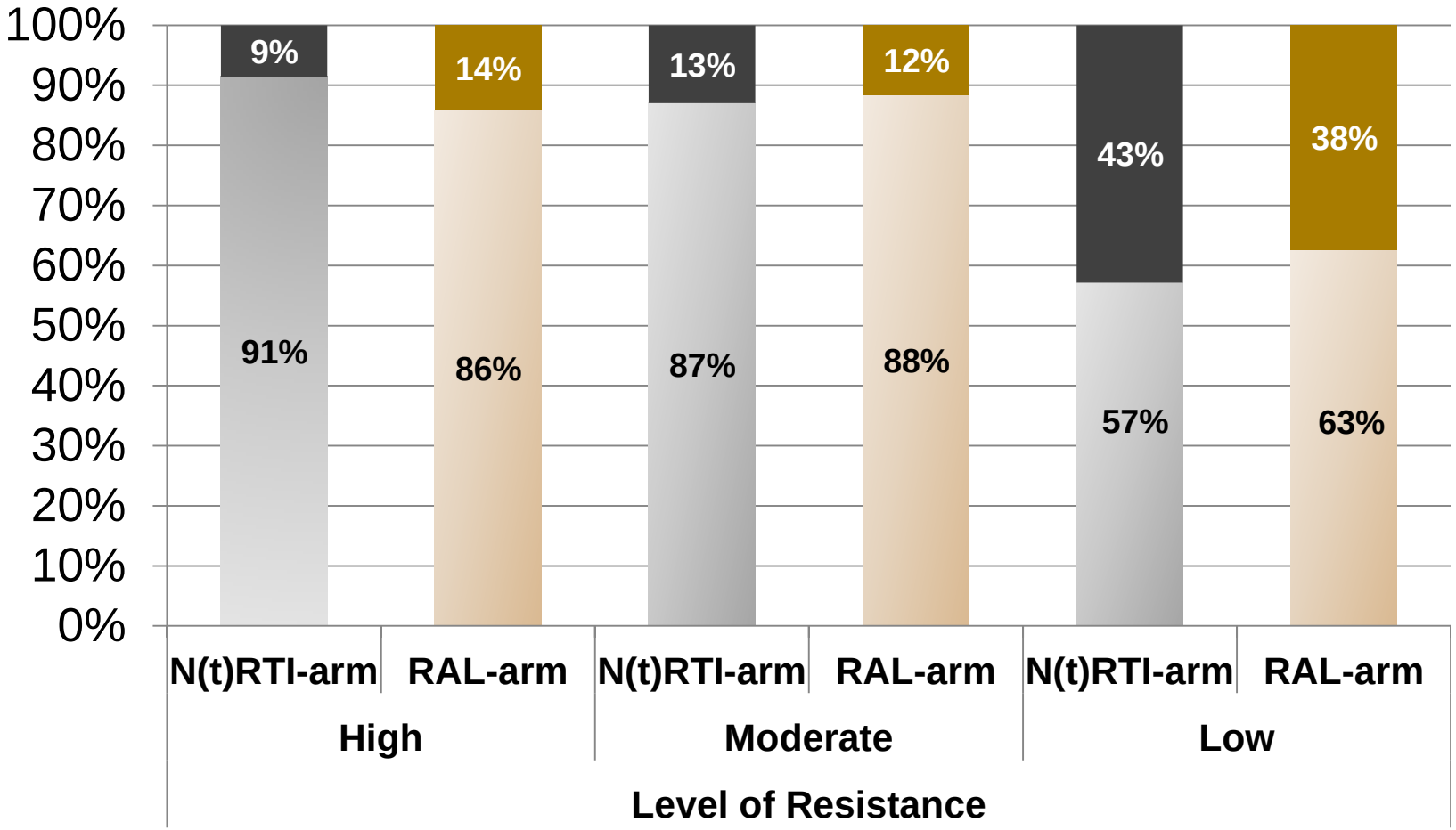
SECOND-LINE resistance study

Distribution of baseline global GSS by treatment arm



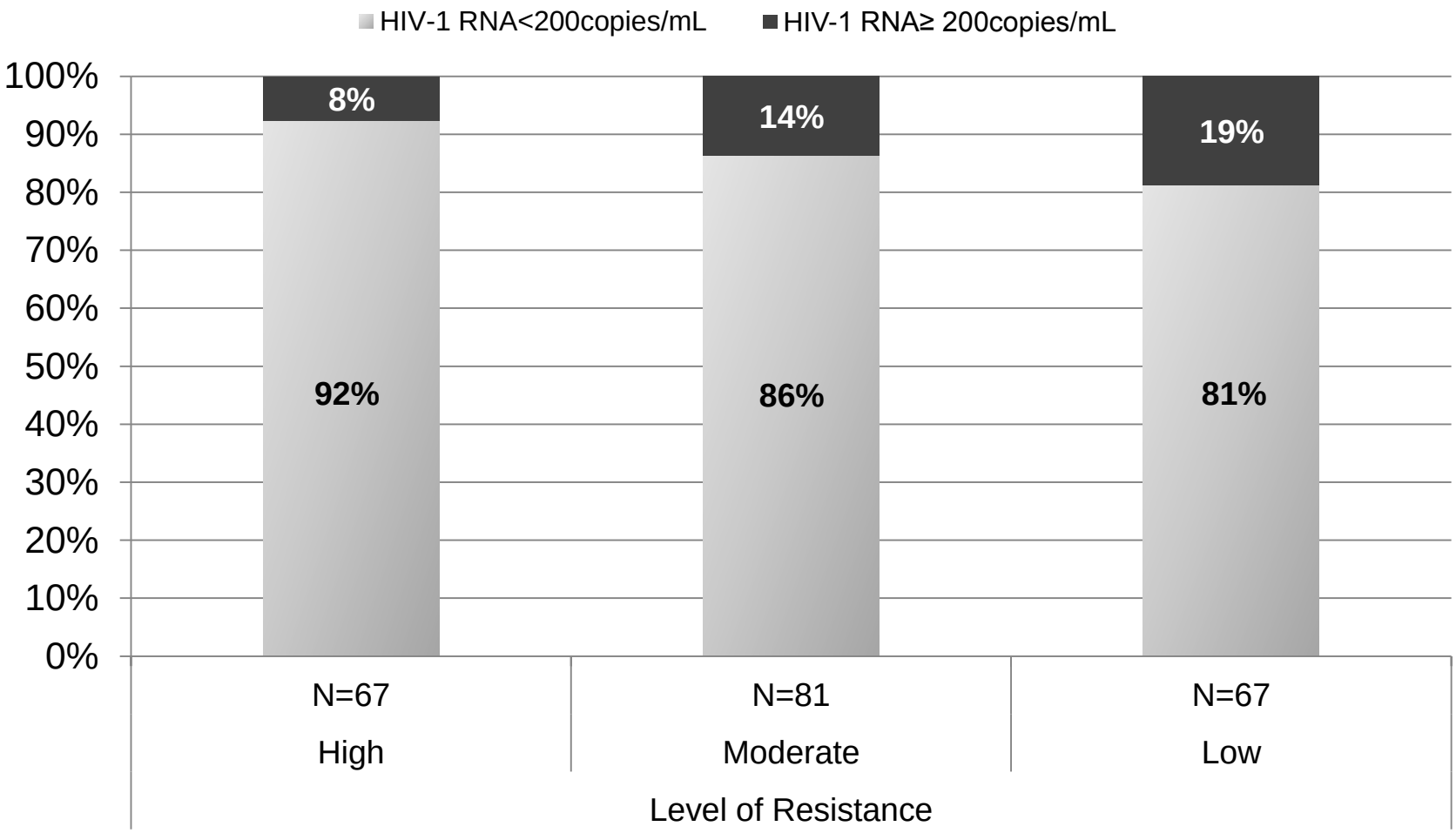
SECOND-LINE resistance study

VF at W96 by gGSS at baseline by treatment arm



SECOND-LINE resistance study

VF at W96 by sGSS at baseline in the N(t)RTI-arm



Predictors of VF over 96 weeks

Predictors	Multivariate OR	95% CI	p-value overall
Population			
Asian *(n=212, VF=19)*	1		
Caucasian *(n=34, n=4)*	2.28	0.65, 8.02	
Hispanic *(n=66, VF=13)*	3.13	1.21, 9.13	
African *(n=182, VF=31)*	3.49	1.68, 7.28	0.007
Baseline VL			
≤100,000 c/mL (n=399, VF=45)	1		
>100,000 c/mL (n=96, VF=23)	3.43	1.70, 6.94	<0.001

Predictors of VF over 96 weeks

Predictors	MVA OR	95% CI	p-value
Adherence at W4			
All ART in last 7 d (n=419, VF=50)	1		
<All ART in last 7 d (n=70, VF=18)	2.18	1.07, 4.47	0.032
Adherence at W48			
All ART in last 7 d (n=434, VF=51)	1	0.65, 8.02	
<All ART in last 7 d (n=45, VF=13)	3.43	1.09, 5.69	0.03
gGSS			
High resistance (n=251, VF=29)	1		
Moderate resistance (n=163 , VF=20)	1.03	0.52, 2.03	
Low resistance (n=37, VF=15)	4.73	1.04, 11.46	0.002

ACTG 5273 (SELECT): impact of baseline resistance on risk of virological failure

Baseline NRTI Resistance	HR for VF in Both Arms (95% CI)	p-value
K65R, ≥ 3 TAMs, Q151M or 69 ins/del ▪ yes vs no (ref)	0.49 (0.31-0.76)	.001
IAS NRTI mutations ▪ ≥ 3 vs < 3 (ref)	0.45 (0.30-0.70)	< .001
K65R and/or M184V/I ▪ No K65R but M184V/I vs no M184V/1 (ref) ▪ K65R and M184V/I vs no M184V/1 (ref)	0.41 (0.25-0.67) 0.19 (0.08-0.44)	< .001

La Rosa AM, et al. Lancet E-pub 18 April 2016.

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Summary

Virological failure in the SECOND-LINE trial was associated with:

- self-reported non-adherence
- higher baseline gGSS
- baseline pVL >100,000 copies/mL
- study population

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Conclusions

For HIV treatment and care programs the results support:

- greater investment in understanding and implementing effective adherence support and interventions
- greater emphasis on a reliable drug supply
- the use of sequential ART regimens in lieu of HIVDR

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Acknowledgements

Writing Committee: Boyd MA, Moore CL, Molina J-M, Wood R, Madero JS, Wolff M, Ruxrungtham K, Losso M, Renjifo B, Teppler H, Kelleher A, Amin J, Emery S, Cooper DA.

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Study Partners: Merck, AbbVie, amfAR, NHMRC.

Study Participants


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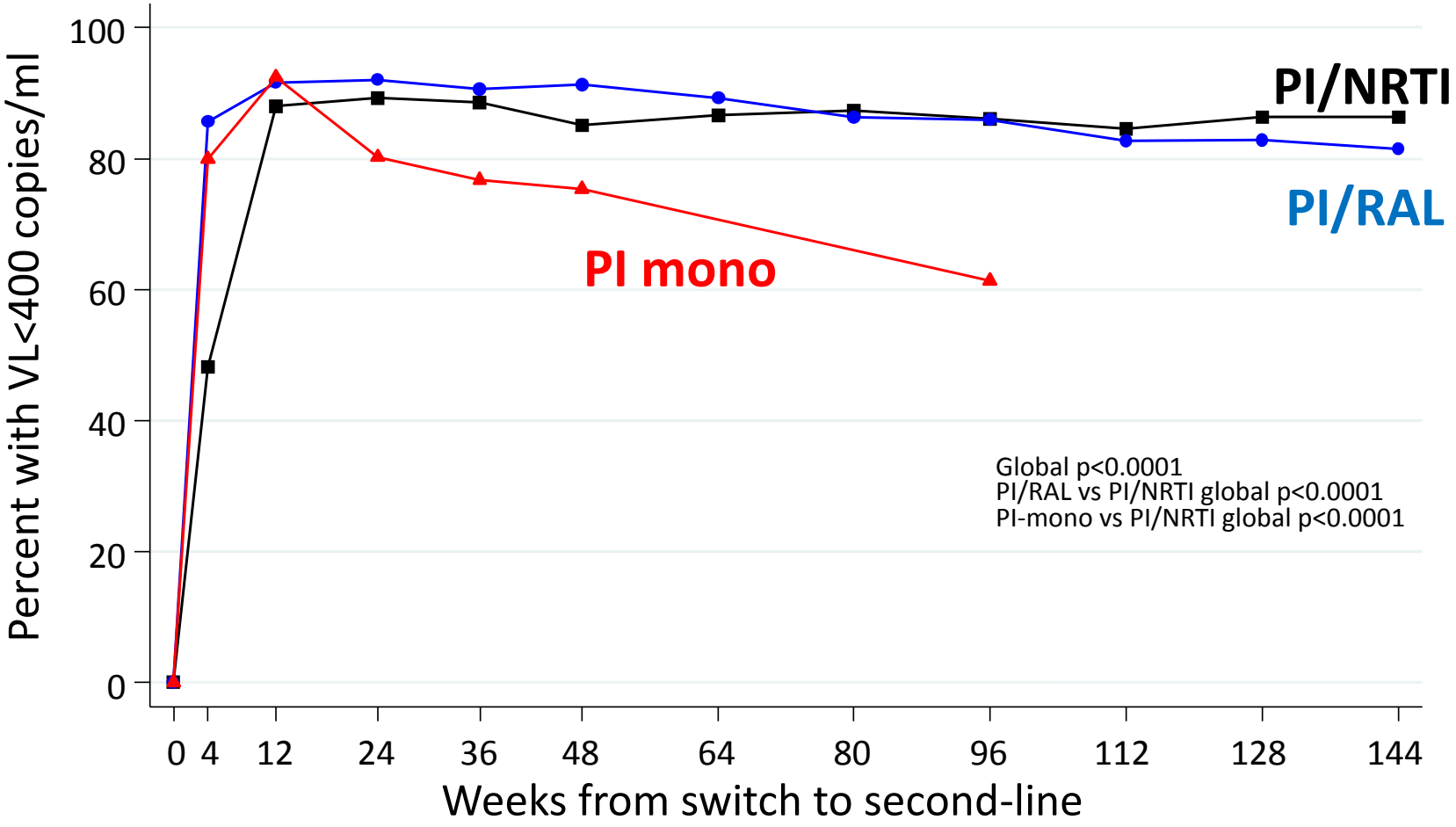
EARNEST

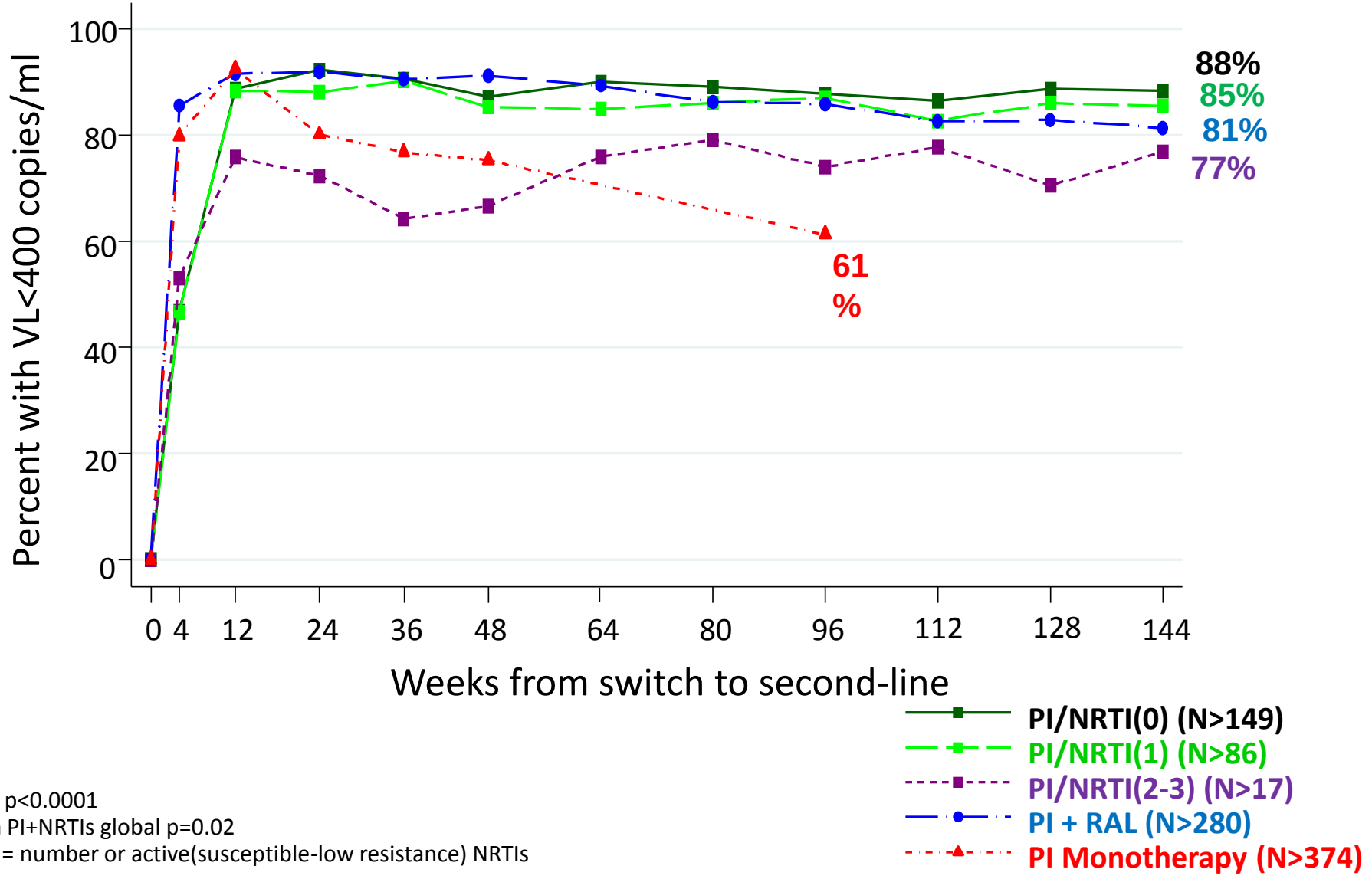
VL responses by randomized arm



Week 96 outcomes: Paton, NEJM 2014; 371; 234-47; Week 144 outcomes: Hakim, Poster 552, CROI 2015

EARNEST

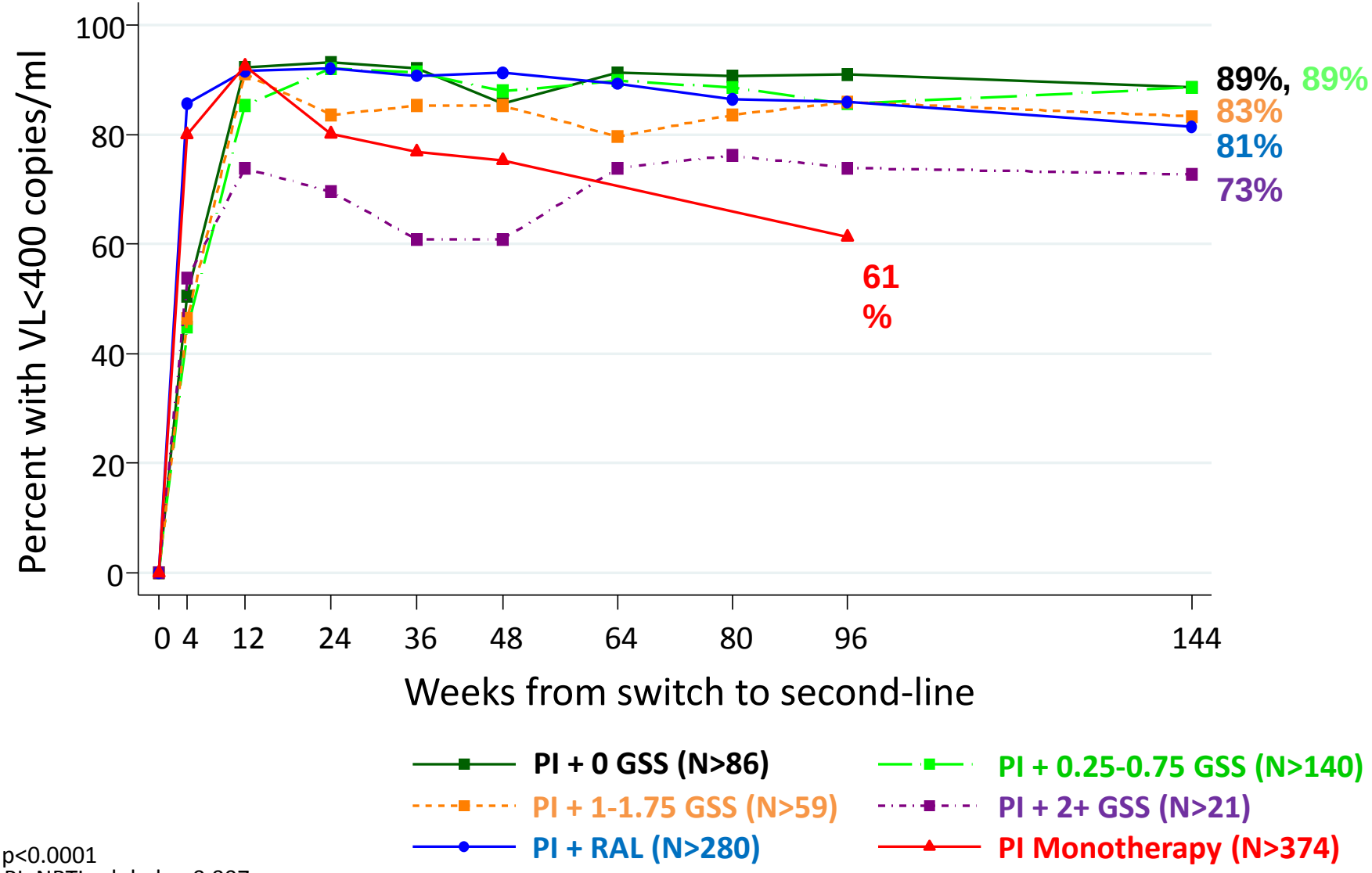
VL response by no. of active NRTIs in the regimen



Global p<0.0001
Within PI+NRTIs global p=0.02
NRTI() = number or active(susceptible-low resistance) NRTIs

EARNEST

VL response by GSS of NRTIs in the regimen



Global p<0.0001
Within PI+NRTIs global p=0.007

Emergent N(t)RTI Mutations, n, (%)

	NtRTI-arm	RAL-arm
Total number with amplifiable sequence	64	65
Number of participants with mutations	**8 (12.5)**	**2 (3.1)**
Major mutations	8 (12.5)	2 (3.1)
Number of major mutations	**8**	**2**
M184V	1	0
D69N	3	1*
T69NT	2	0
K219KN	0	1
T215NSTY	1	0
K70G	1	0

*participant switched to TDF/FTC prior to VF

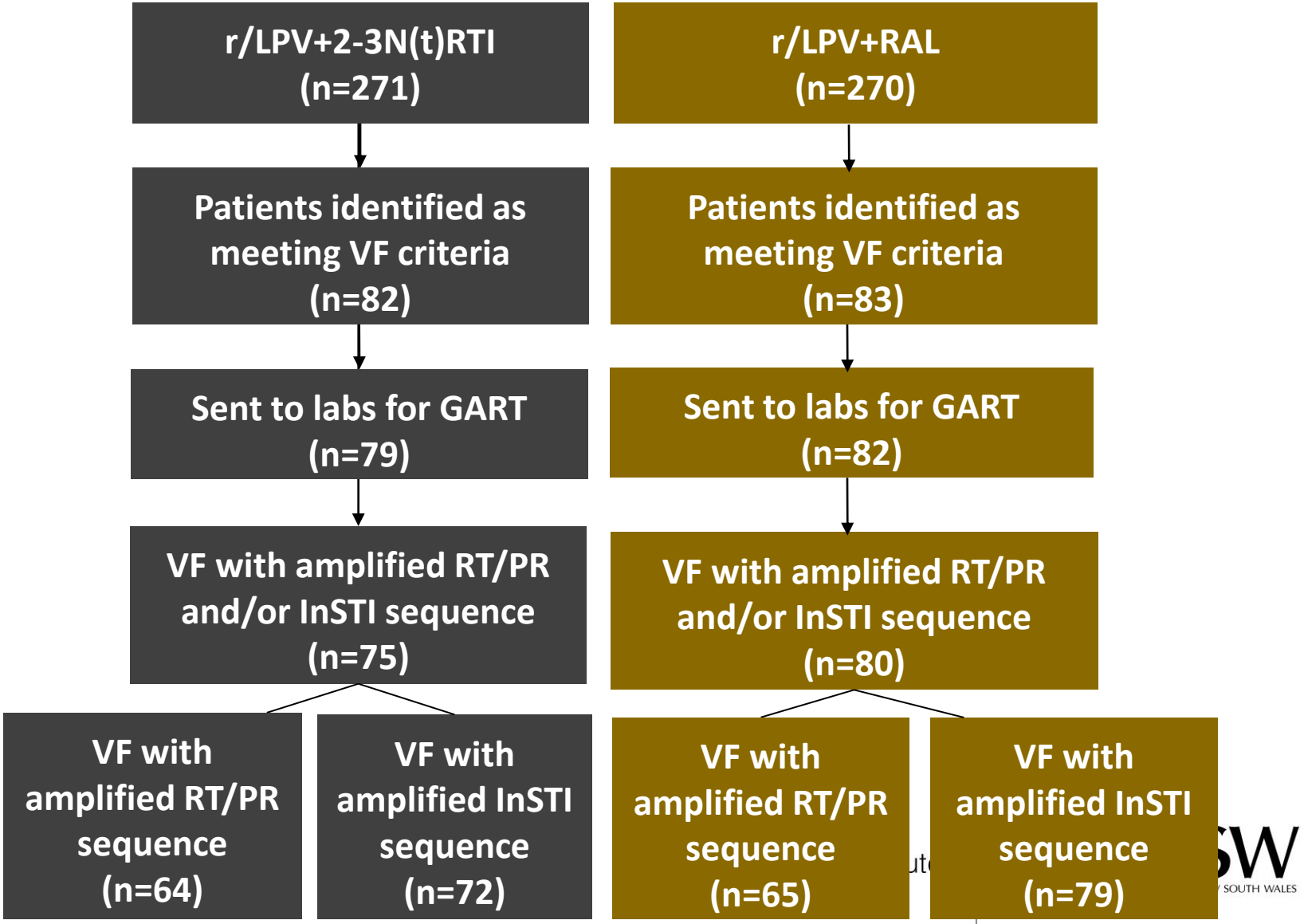
Emergent PI Mutations, n (%)

	NtRTI-arm	RAL-arm
Total number with amplifiable sequence	64	65
Number of participants with mutations	**2 (3.1)**	**0**
Major mutations	1 (1.6)	0
Minor mutations	1 (1.6)	1 (1.6)
Number of major mutations	**2**	**0**
M46I	1	0
V82AV	1	0
Number of minor mutations	1	1
A71V	1	0
L90F	0	1

Emergent InSTI Mutations, n(%)

	NtRTI-arm	RAL-arm
Total number with amplifiable sequence	72	79
Number of participants with mutations	**1 (1.4)**	**20 (25.3)**
Major mutations	0	16 (20.3)
Minor mutations	1 (1.4)	4 (5.1)
Number of major mutations	**0**	**19**
N155HN	0	14
Q148QR	0	2
T66AST	0	2
Y143SY	0	1
Number of minor mutations	1	5
L74ILM	1	2
T97AT	0	2

Study Flow


r/LPV+2-3N(t)RTI (n=271)
r/LPV+RAL (n=270)
Patients identified as meeting VF criteria (n=82)
Patients identified as meeting VF criteria (n=83)
Sent to labs for GART (n=79)
Sent to labs for GART (n=82)
VF with amplified RT/PR and/or InSTI sequence (n=75)
VF with amplified RT/PR and/or InSTI sequence (n=80)
VF with amplified RT/PR sequence (n=64)
VF with amplified InSTI sequence (n=72)
VF with amplified RT/PR sequence (n=65)
VF with amplified InSTI sequence (n=79)