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PO-36

Clinical impact of virological failure and resistance analysis definitions used in pivotal clinical trials of initial antiretroviral treatment: a systematic review.

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Background.

- There are no standardised criteria for defining confirmed virological failure (PDVF) nor the inclusion criteria for the resistance analysis population (RAP) in phase III randomised clinical trials (RCT) of initial antiretroviral therapy (ART).
- Current guidelines define VF as a confirmed viral load >200 copies/ml, a threshold that eliminates most cases of apparent viremia caused by viral load blips or assay variability. [1]
- Recent analyses have shown a valid genotype amplification with results predictive of future virological outcomes in samples with HIV-1 RNA 51-199 copies/mL.[2,3]

Aim.

We assessed the clinical impact of mismatching between virological non-response (HIV-1 RNA ≥ 50 copies/mL), confirmed PDVF and RAP definition in studies with the newest first-line ART, at 48 weeks.

1.Lalama CM., et al. J Clin Microbiol. 2015;53(8):2659–66.
2.Gonzalez-Serna A., et al. Clin Infect Dis. 2014;58(8):1165–73.
3.Hermans LE., et al. Lancet Infect Dis. 2018;18(2):188–97.

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Week 48, phase III, RCT of once-daily first-line ART: main characteristics

Methods.

Systematic review of phase III RCTs including preferred once-daily ART (European AIDS guidelines) or recently approved by the FDA.

PRISMA guidelines

Third drug	Clinical Trial	Arm size (n)	NRTIs	Comparator arm	VL> 10^5 cp/mL (%)	CD4 <200 cells/mcL (%)	Efficacy: <50 cp/mL at 48 weeks
DTG	SINGLE	414	3TC/ABC	EFV	32.0	14.0	88% vs 81%; 7 (2 to 12)
	SPRING-2	411	2NRTIs	RAL	28.0	13.0	88% vs 85%; 2.5 (-2.2 to 7.1)
	FLAMINGO	242	2NRTIs	DRV/r	25.0	10.0	90% vs 83%; 7.1 (0.9 to 13.2)
	ARIA	248	3TC/ABC	ATV/r	28.0	26.0	82% vs 71%; 10.5 (3.1 to 17.8)
	GS-US-380-1489	315	3TC/ABC	BIC/FTC/TAF	16.0	10.0	93% vs 92%; -0.6 (3.6 to -4.8)
	GS-US-380-1490	325	FTC/TAF	BIC	17.0	10.0	93% vs 89%; -3.5 (1 to -7.9)
BIC	GS-US-380-1489	314	FTC/TAF	DTG/3TC/ABC	17.0	11.0	92% vs 93%; -0.6 (-4.8 to 3.6)
	GS-US-380-1490	320	FTC/TAF	DTG	21.0	14.0	89% vs 93%; -3.5 (-7.9 to 1)
EVG/c	GS-US-292-0104 and 0111	866	FTC/TAF	FTC/TDF	23.0	13.0	92% vs 90%; 2 (-0.7 to 4.7)
RAL QD	ONCEMRK	531	FTC/TDF	RAL 400mg BID	28.0	13.0	90% vs 90%; -0.4 (-4.9 to 4)
DRV/c	AMBER	362	FTC/TAF	FTC/TDF	16.6	6.1	91% vs 88%; 2.7 (-1.6 to 7.1)
RPV	ECHO	346	FTC/TDF	EFV	48.0	33.0	83% vs 83%; -0.4 (-5.9 to 5.2)
	THRIVE	340	2NRTIs	EFV	45.0	33.0	86% vs 82%; 3.9 (-1.6 to 9.5)
	STaR	394	FTC/TDF	EFV	34.0	13.0	86% vs 82%; 4.1 (-1.1 to 9.2)
DOR	DRIVE-AHEAD	364	3TC/TDF	EFV	20.0	12.0	84% vs 81%; 3.5 (-2 to 9)
	DRIVE-FORWARD	383	2NRTIs	DRV/r	22.0	11.0	84% vs 80%; 3.9 (-1.6 to 9.4)

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Results.

-16 treatment arms (14 RCTs) with 6,175 participants.

-Plasma HIV-1 RNA thresholds for PDVF or RAP ranged from 40 to 50, 200, 400 and 500 copies/mL.

-Only **8 treatment arms genotyped all participants with PDVF**. Most of the remaining eight arms genotyped roughly ≤50% of those with PDVF.

-Overall, 85/296 (29%) patients with PDVF were not genotyped. We found a strong evidence of a **linear correlation** between the **higher HIV-1 RNA threshold for genotyping** and **increasing rates of participants with PDVF that were not genotyped.**

VL	n	N	%	p
50	0	110	0,0	<0,001 *
200	13	32	40,6	
400	50	118	42,4	
500	22	36	61,1	
Total	85	296	28,7	

n= participants not genotyped N=participants with PDVF * Cochran-Armitage test

-**No resistance was selected against the third drug or the backbone NRTIs in any participant in the studies with dolutegravir, bictegravir or darunavir/cobicistat.**

-Elvitegravir/cobicistat, raltegravir and rilpivirine, showed selection of HIV-1 resistance against both the third drug and the NRTIs used in the backbone in approximately 50% of the participants with PDVF and genotypes successfully performed.

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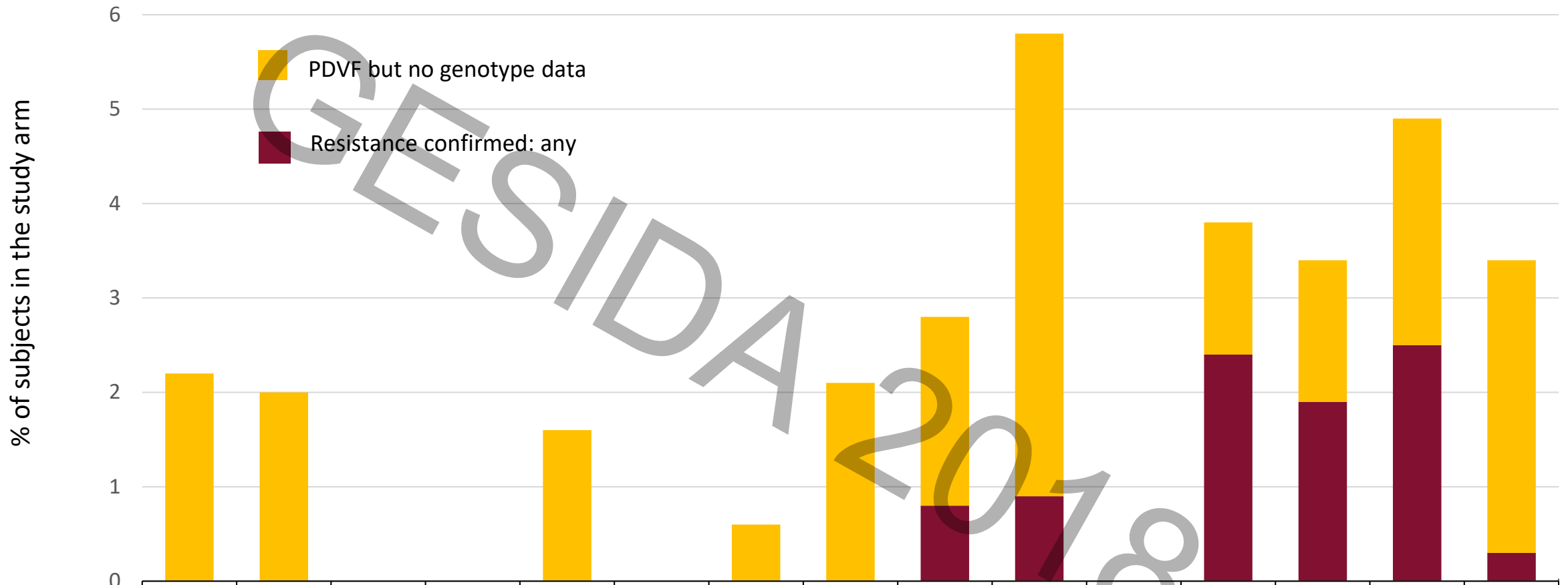
Week 48, phase III, RCT of once-daily first-line ART: VF and resistance selection



	SINGLE (n=414)	SPRING-2 (n=411)	FLAMINGO (n=242)	ARIA (n=248)	GS-US-380-1489 (n=315)	GS-US-380-1490 (n=325)	GS-US-380-1489 (n=314)	GS-US-380-1490 (n=320)	GS-US-292-0104 (n=866)	ONCEMRK (n=531)	AMBER (n=362)	ECHO and THRIVE (n=368)	STaR (n=260)	DRIVE-AHEAD (n=364)	DRIVE-FORWARD (n=383)
PDVF but no genotype data	2,2	2	0	0	1,6	0	0,6	2,1	2	4,9	0	1,4	1,5	2,4	3,1
Resistance confirmed: any	0	0	0	0	0	0	0	0	0,8	0,9	0	2,4	1,9	2,5	0,3
	DTG						BIC		EVG/c	RAL	DRV/c	RPV*		DOR	

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* For **RPV**, data shown include only participants with viral load less than or equal to 100,000 HIV-1 RNA copies/mL

Conclusions.

1- The absence of standardised definitions of VF and criteria for resistance testing in pivotal phase III RCTs of first-line ART leads to the possibility of **underreporting of resistance mutations** when genotypes are only performed at higher viral load cut-offs.

2- Stringent homogeneous criteria should be defined to ensure that all participants with PDVF (confirmed HIV RNA $\geq$ 50 copies/mL and the second >200 copies/mL) undergo genotyping.