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OC 16 Do low-frequency drug-resistant HIV-1 variants have a role on first-line INSTI-containing regimens? A case-control study from the ICONA cohort

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ABSTRACT

Background: Little is still known about the impact of INSTI minority resistant variants detected through next generation sequencing (NGS) on virological response to first-line regimens based on second-generation INSTI.

Material and methods: This is a case-control study involving ART-naïve individuals from the ICONA cohort with an available plasma HIV-1 RNA before ART start (baseline, BL), who received a second-generation INSTI-containing regimen. Cases were individuals who experienced virological failure (VF: two consecutive HIV-1 RNA >50 copies/mL or one >1000 copies/mL after achieving HIV-1 RNA ≤50 copies/mL) after first-line regimen start. They were matched with controls who never experienced VF according to type of INSTI-containing regimen. NGS data obtained through the HIV-1 Solution v2 kit (Arrow Diagnostics, Illumina MiSeq platform) were evaluated by HIVdb algorithm (version 9.5.1). INSTI resistance associated mutations listed as Major (MRM), Accessory (AMR) and Other (ORM) were analysed setting NGS at 5%, 10%, 20% cut-offs. The impact of pre-existing INSTI resistance and Genotypic Susceptibility Score (GSS) of the regimen on VF was evaluated by conditional logistic regression analysis (CLR).

Results: The study included 254 individuals (89 cases; 165 controls; Table1). Cases experienced VF with a median (IQR) viremia of 300 (93-5,884) copies/mL in a median (IQR) time of 14 (8-28) months after ART start. At BL, most of individuals harboured a fully susceptible viral strain, regardless NGS setting (Figure 1A).

Concerning resistance, the presence of ≥1 MRM (G140R, S147G, Q146P/R) was detected in 2%, 0.8% and 0.4% of individuals at NGS set at 5%, 10% or 20%, respectively. Regardless the NGS setting used, prevalence of ARM (L74M, T97A, S153A, E157Q, G163K,) was moderate (cut-off 5%, 10% and 20%: 7.5%, 7.1%, 6.3%) and of ORM (M50I, L74I, S119R, E138D, V151I, S230N) was considerably high (50.8%, 45.3%, and 42.5%).

The presence of ≥1 MRM, ARM or ORM was not significantly different among cases and controls (Figure 1B). When NGS was set at 5%, the proportion of individuals harbouring ≥2 ORM (mostly L74I plus M50I or S230N polymorphisms) was significantly higher among cases compared to controls (P=0.008, Figure 1B). These results were independent from subtype (cases with ≥2 ORM in B vs. non-B subtypes: 5, 11.9% vs. 7, 14.9%, P=0.680). By CLR multivariate model, ≥2 ORM detected as minority variants (NGS set at 5% or 10%) were an independent predictor of experiencing VF (Table 2).

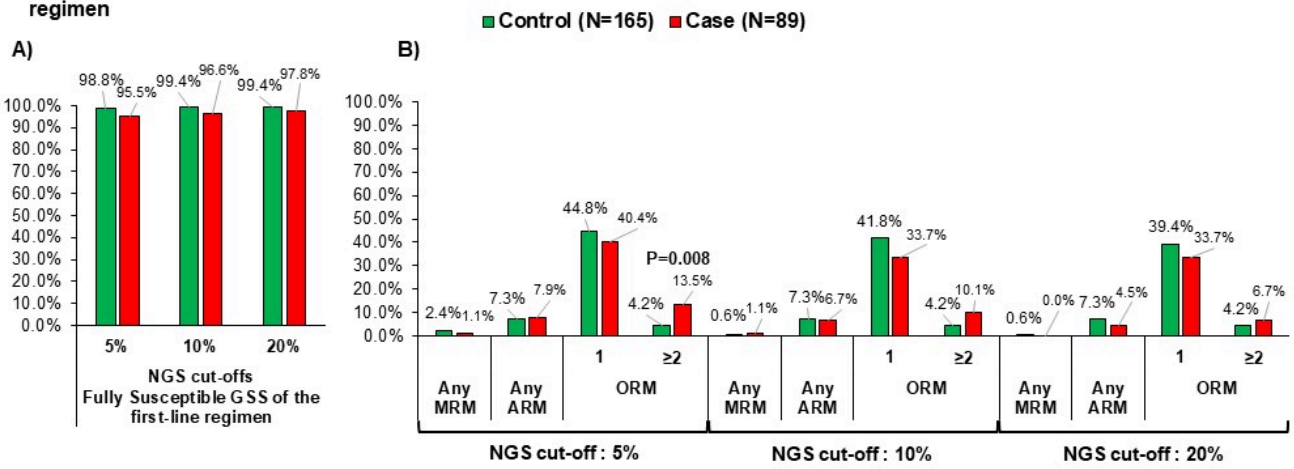
Conclusions: This case control study shows that pre-existing INSTI resistance is rare and does not relate to virological failures to first-line regimens based on second generation INSTI, often observed only as low-level viremia rebound events. The combination of polymorphic mutations associated to INSTI detected as minority variants through NGS seems to identify individuals more prone to lose virological control.

Table 1. Participants' characteristics at baseline

Variables	Overall (N=254)	Case (N=89)	Control (N=165)	P-value
Age, years, Median (IQR)	40 (31-51)	40 (30-51)	39 (31-50)	0.877
Male, n (%)	**212 (83.5)**	**66 (74.2)**	**146 (88.5)**	**0.003**
Ethnicity, n (%)				
Caucasian	**203 (79.9)**	**64 (71.9)**	**139 (84.2)**	**0.001**
Hispanic	**24 (9.5)**	**8 (9.0)**	**16 (9.7)**	
African	**23 (9.1)**	**17 (19.1)**	**6 (3.6)**	
Asian	**2 (0.8)**	**0 (0.0)**	**2 (1.2)**	
Unknown	**2 (0.8)**	**0 (0.0)**	**2 (1.2)**	
Italian nationality, n (%)	**186 (73.2)**	**57 (64.0)**	**129 (78.2)**	**0.015**
Mode of HIV transmission, n (%)				
Men who have sex with men	**137 (53.9)**	**38 (42.7)**	**99 (60.0)**	**0.026**
Heterosexual	**85 (33.5)**	**41 (46.1)**	**44 (26.7)**	
Drug abuse	**7 (2.8)**	**1 (1.1)**	**6 (3.6)**	
Transgender	**3 (1.2)**	**1 (1.1)**	**2 (1.2)**	
Unknown	**22 (8.7)**	**8 (9.0)**	**14 (8.5)**	
Subtype, n (%)				
B	**156 (61.4)**	**42 (47.2)**	**114 (69.1)**	**0.003**
CRF02_AG	**20 (7.9)**	**13 (14.6)**	**7 (4.2)**	
*A**	**14 (5.5)**	**8 (9.0)**	**6 (3.6)**	
C	**12 (4.7)**	**5 (5.6)**	**7 (4.2)**	
Other	**52 (20.5)**	**21 (23.6)**	**31 (18.8)**	
CD4+ T cell count, cells/mm^3, Median (IQR)	**281 (80-473)**	**158 (52-391)**	**326 (100-523)**	**0.005**
HIV RNA, log$_{10}$ copies/mL, Median (IQR)	**5.1 (4.6-5.5)**	**5.3 (4.7-5.7)**	**5.0 (4.5-5.5)**	**0.003**
Calendar year of ART start, Median (IQR)	2017 (2016-2019)	2017 (2016-2019)	2017 (2016-2019)	0.729
Time between sampling and ART start, days, Median (IQR)	5 (0-21)	4 (0-18)	6 (0-23)	0.587
Type of first-line regimen, n (%)				
*Triple DTG***	216 (85.0)	76 (85.4)	140 (84.8)	0.985
Triple BIC	21 (8.3)	7 (7.9)	14 (8.5)	
Dual DTG	17 (6.7)	6 (6.7)	11 (6.7)	

*A subtype: A1 (n=7, 50.0%); A3 (n=3, 21.4%); A6 (n=4, 28.6%); ** Triple DTG: 3TC, ABC, DTG (n=102, 47.2%); FTC, TAF, DTG (n=38, 17.6%); FTC, TDF, DTG (n=76, 35.2%).

Figure 1. Baseline resistance detected through NGS in case and control individuals who started an INSTI-based first-line regimen



GSS: genotypic susceptibility score (HIVdb ver 9.5.1). ARM: accessory resistance mutations; MRM: major resistance mutations; ORM: other resistance mutations.

Table 2. Predictive value of baseline resistance on virological failure under INSTI-based first-line regimen according to conditional regression model

Variables	Unadjusted				Adjusted			
	P value	OR	95.0% CI		P value	AOR	95.0% CI	
			Lower	Upper			Lower	Upper
≥ 1 MRM NGS set at 5%[a]	0.568	0.563	0.078	4.047	0.797	0.766	0.100	5.849
≥ 1 MRM NGS set at 10%[a]	0.724	1.427	0.198	10.261	0.792	1.323	0.166	10.544
≥ 1 MRM NGS set at 20%[b]	-	-	-	-	-	-	-	-
≥ 2 ORM NGS set at 5%[c]	**0.034**	**1.941**	**1.051**	**3.585**	**0.014**	**2.249**	**1.181**	**4.283**
≥ 2 ORM NGS set at 10%[c]	0.141	1.687	0.841	3.386	**0.045**	**2.098**	**1.017**	**4.328**
≥ 2 ORM NGS set at 20%[c]	0.485	1.349	0.582	3.128	0.120	2.025	0.832	4.932

[a]Adjusted for: calendar year of ART start, viral load at ART start, CD4 cell count at ART start, sex, ethnicity and HIV-1 subtype. [b] Model not performed since MRM were present in only 1 case at NGS set at 20%. [c]Adjusted for: calendar year of ART start, viral load at ART start, CD4 cell count at ART start, genotypic susceptibility score of regimen, sex, ethnicity and HIV-1 subtype.