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► To cite this version:

Anne-Genevieve Marcelin, Charlotte Charpentier, Pantxika Bellecave, Basma Abdi, Marie-Laure Chaix, et al.. Factors associated with the emergence of integrase resistance mutations in patients failing dual or triple-integrase inhibitors-based regimen in a French national survey. *Journal of Antimicrobial Chemotherapy*, 2021, 76 (9), pp.2400-2406. 10.1093/jac/dkab193 . hal-03388629

HAL Id: hal-03388629

<https://hal.sorbonne-universite.fr/hal-03388629>

Submitted on 20 Oct 2021

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1 **Factors associated with the emergence of integrase resistance mutations in patients failing**
2 **dual or triple-integrase inhibitors-based regimen in a French national survey**

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43 **Running title:** HIV resistance to integrase inhibitors

44 **Prior presentation:** European Meeting on HIV and Hepatitis 2020 (oral presentation n°4).

45 **Word count:** 2166

46

47 **ABSTRACT**

48 **Objectives:** Successful 2 drug regimens (DR) were made possible by the availability of drugs
49 combining potency and tolerability with high genetic barrier to resistance. How these approaches
50 would deal with resistance development/re-emergence, compared with 3DR, is thus of paramount
51 importance.

52 **Material and Methods:** A national survey including patients failing either naive or experienced (2
53 consecutive plasma viral load (VL) > 50 copies/mL) to any 2DR or 3DR integrase inhibitors
54 (INSTI)-containing regimens was conducted between 2014 and 2019. Genotypic resistance tests
55 were interpreted with the v28 ANRS algorithm.

56 **Results:** 1104 patients failing to any INSTI-containing regimen (2DR=207 and 3DR=897) were
57 analysed. 577 (52.3%) patients were infected with a B subtype and 527 (47.3%) with non-B
58 subtypes. Overall, 644 (58%) patients showed no known integrase resistance mutations at failure.
59 In multivariate analysis, factors associated with the emergence of at least one integrase mutation
60 were high VL at failure (OR = 1.24 per 1 log₁₀ copies/mL increase), non-B *versus* B subtype (OR =
61 1.75), low genotypic sensitivity score (GSS) (OR = 0.10 for GSS=2 *versus* GSS = 0-0.5),
62 dolutegravir *versus* raltegravir (OR = 0.46). Although 3DR *versus* 2DR reach statistical significance
63 in univariate analysis (OR = 0.59, p=0.007), the variable is not retained in the final model.

64 **Conclusions:** This study is one of the largest studies characterizing integrase resistance in patients
65 failing to any INSTI-containing 2DR or 3 DR regimen in routine clinical care and reveals factors
66 associated with emergence of integrase resistance that should be taken into consideration in clinical
67 management. No difference was evidenced between patients receiving 2DR or 3DR.

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71 INTRODUCTION

72 For approximately 20 years, triple therapy has been the dogma of antiretroviral therapy (ART) for
73 naive HIV-1 patients, and also in the switch context for previous antiretroviral-treated HIV-1
74 patients. Nowadays, considering the lifelong ART and the need to decrease the potential adverse
75 effects of drug exposure, some alternative strategies have been introduced and especially 2 drugs
76 regimen (DR).

77 Some clinical trials have demonstrated a similar proportion of virological HIV suppression between
78 2DR and 3/4DR for switch strategies, especially with an integrase strand transfer inhibitor (INSTI):
79 dolutegravir and lamivudine (ASPIRE, LAMIDOL, TANGO), dolutegravir and rilpivirine
80 (SWORD), cabotegravir and rilpivirine (LATTE, FLAIR, ATLAS).¹⁻⁷ Then, the GEMINI clinical
81 trial (dolutegravir and lamivudine) has been conducted in antiretroviral naive HIV-1 patients and
82 evidenced a similar efficacy of the 2DR and 3DR (dolutegravir and tenofovir disoproxil
83 fumarate/emtricitabine) as in the NEAT001/ANRS143 (raltegravir and darunavir) clinical trial.⁸⁻¹⁰
84 However, in this latter trial, emergence of resistance mutations was higher in the raltegravir and
85 darunavir/ritonavir group.¹¹

86 The European AIDS Clinical society (EACS) and US-based guidelines have recommended now the
87 2 and 3DR with INSTI for both antiretroviral naive and experienced HIV patients. In the case of
88 2DR for initiation of ART, dolutegravir and lamivudine were approved in patients without hepatitis
89 B antigen, HIV viral load < 500 000 copies/mL.^{12,13}

90 All these studies focused on the virological efficacy of the 2DR versus 3DR, but few data are
91 available on the HIV-1 resistance in case of virological failure and the factors associated with. Our
92 aim was to identify the emergence of INSTI resistance associated mutations (RAM) in failing
93 patients receiving an INSTI-based dual or a triple therapy. In these patients, we investigated baseline
94 variables and the level of viral load at failure associated to at least one INSTI RAM. The aim was,

95 in particular to distinguish between the effect of the following factors (i) receiving a dual or triple
96 therapy, (ii) the genotypic sensitivity score (GSS) associated to the non INSTI drugs in the regimen,
97 and (iii) the INSTI received (raltegravir, elvitegravir or dolutegravir).

98

99 **PATIENTS AND METHODS**

100

101 Patients and antiretroviral regimens

102 HIV-1-infected patients followed in the 21 participating virology laboratories labelled ANRS-MIE
103 AC43 and who experienced virologic failure, defined as two consecutive HIV-1 viral loads (VL) >
104 50 copies/mL, to an INSTI-containing regimen between 2014 and 2019 were included in the study.
105 All data were checked by a study monitor.

106

107 Ethics

108 Individual antiretroviral agents were recorded along with their dates of initiation and
109 discontinuation, if applicable. All patients gave written informed consent that a de-identified,
110 electronic version of their medical chart could be used for research purposes. The study was
111 approved by the scientific committee of the ANRS-MIE AC43.

112

113 Genotypic resistance testing

114 The virology laboratories belonging to the ANRS-MIE AC43 network have participated annually
115 in the ANRS-MIE quality control assessment of HIV-1 drug resistance sequencing.¹⁴

116 The HIV protease (PR), reverse transcriptase (RT) and integrase (IN) sequences were determined
117 in each participating laboratory on plasma obtained to confirm virological failure. Three different
118 methods were used: the ANRS-MIE consensus technique (<http://www.hivfrenchresistance.org/>), the

119 Abbott ViroSeq kit, or an in-house method. For resistance interpretation (resistant, intermediate or
120 susceptible), the ANRS algorithm (Version 28) was used (www.hivfrenchresistance.org).

121 The GSS of the current regimen (without INSTI) was calculated according to the ANRS algorithm
122 as follows: susceptible GSS=1, intermediate GSS=0.5, resistance GSS=0.

123 The studied INSTI RAM were: T66A/I/K, L74F/I/M, V75I, E92Q, T97A, G118R, F121Y,
124 E138A/K/T, G140A/C/S, Y143A/C/G/H/R/S, P145S, S147G, Q148EG/H/K/R, V151L, S153F/Y,
125 N155H/S/T, E157Q, S230R, R263K.

126

127 Statistical analysis

128 Quantitative variables are described by median and Interquartile Range (IQR) while categorical
129 variables are described in percent. HIV-1 RNA at baseline and at failure, viral subtype (B versus
130 non-B), baseline CD4 cell count, CD4 nadir, age, duration of infection, duration of INSTI treatment,
131 type of ongoing treatment (dual versus triple therapy), GSS and INSTI molecule received were
132 investigated as potential factors of occurrence of at least one INSTIs mutation by a logistic
133 regression model. All variables tested with a P-value <0.10 in the univariate analysis were retained
134 for building the final multivariate model using a stepwise selection. Comparison between groups of
135 patients were carried out using either Fisher's exact test for categorical variables or Kruskal-Wallis
136 test for continuous variables.

137

138 **RESULTS**

139 Overall, 1104 patients failing an INSTI-containing regimen and receiving either 2DR (n=207) or
140 3DR (n=897) were included in the study from 21 French centers of the ANRS-MIE network.
141 Patients' characteristics are displayed in Table 1. Patients were failing while receiving raltegravir
142 (n = 430), elvitegravir (n = 323) or dolutegravir (n = 351) containing regimen. Overall, 782 (71%)
143 patients were failing their first line of INSTI-containing regimen of whom 160 patients were on their

144 first-line ART. Patients on 2DR were slightly older (median 52 versus 47 years-old, $p < 0.001$), had
145 an older history of HIV infection (median 20.6 versus 12.8 years, $p < 0.001$), had a higher median of
146 baseline CD4 cell count (460 versus 360 cells/mm³, $p < 0.001$) and a higher median of duration of
147 the current INSTI regimen (20.2 versus 13.5 months, $p < 0.001$). As expected, the median GSS score
148 was higher for patients in 3DR than patients in the 2DR group (median 2 versus 1, $p < 0.001$). A
149 majority (62%) of patients were male with and subtype B was the predominant HIV-1 clade (52%).
150 In 2DR group, the INSTI was preferentially associated with one PI in 53% of cases or with one
151 NNRTI in 35% of cases. In the 3DR group, 87% of patients received a combination of two NRTIs
152 in association with the INSTI. At failure, median VL was 2.9 log₁₀ copies/mL (IQR: 2.3-4.0) with
153 higher median levels in patients with lower GSS (3.4, 3.2 and 2.9 log₁₀ copies/mL in patients with
154 GSS of [0-0.5], [1-1.5] and [2], respectively).

155 Among the 1104 failing patients, 460 (42%) patients had viruses carrying INSTI RAM: 1, 2, 3 and
156 at least 4 mutations in 286 (26%), 110 (10%), 44 (4%) and 20 (2%) patients, respectively. The
157 repartition of patients with at least one INSTI RAM was as follow: 52% in the 2DR group and 39%
158 in the 3DR group. Overall, N155H/S/T and L74F/I/M were the most commonly mutations observed
159 in 15% and 14% of patients, respectively (Figure 1). The largest difference was observed for the
160 N155H/S/T mutation which was found in 105 (24%), 49 (15%) and 10 (3%) of patients receiving
161 raltegravir, elvitegravir and dolutegravir, respectively. To note, INSTI RAM were distributed
162 differently according to the HIV-1 subtype in our population as L74F/I/M and E157Q were over-
163 represented in HIV-1 non-B subtype versus B subtype patients (21.1% versus 8.5% and 4.7% versus
164 2.1%) while G140C/H/S and Q148EG/H/K/R were higher in HIV-1 B subtypes (5.5% versus 1.3%
165 and 8.0 versus 3.6%). Figure 2 shows the genotypic interpretation of integrase resistance to different
166 INSTIs among the 1104 patients failing an INSTI-containing regimen. Overall, resistance to INSTI
167 was lower for patients failing dolutegravir (8%) in comparison with patients failing raltegravir
168 (41%) and elvitegravir (37%).

169 We aimed to characterize clinical and virological factors associated with the emergence of at least
170 one INSTI RAM (Table 2). Several factors were retained for the multivariable analysis: 3DR versus
171 2DR ($p=0.007$), HIV RNA viral load at failure ($p<0.0001$), duration of INSTIs treatment ($p=0.003$),
172 duration of infection ($p=0.09$), HIV subtype ($p=0.10$), GSS ($p<0.0001$), and antiretroviral treatment:
173 dolutegravir versus raltegravir ($p<0.0001$); elvitegravir versus raltegravir ($p=0.08$). The final
174 multivariate model showed that a higher risk of occurrence of INSTI RAM was associated with a
175 higher VL at failure (OR = 1.24 per 1 \log_{10} copies/mL increase) and with HIV-1 non-B subtype
176 (OR=1.75 versus B subtype). A lower risk was observed with a higher GSS level (OR=0.32 for
177 GSS=1-1.5 and OR= 0.10 for GSS=2 versus GSS=0-0.5) and dolutegravir-containing regimen
178 (OR=0.46 versus raltegravir). To note, if the L74F/I/M and E157Q RAMs were removed from the
179 analysis, the HIV subtype hasn't longer remained as an associated factor of the emergence of the
180 INSTI RAM (Table S1).

181

182 **DISCUSSION**

183 The current expanding use of integrase inhibitors and 2DR for both naive and suppressed HIV-1
184 patients evidence the need for large clinical routine care studies to evaluate the integrase resistance
185 in case of virological failure and the factors associated with. This study evidenced that less than half
186 of HIV patients failing an INSTI regimen harbored viruses with at least one integrase RAM. Two
187 factors were independently associated with a higher risk of occurrence of integrase RAM, HIV-1
188 RNA VL at failure and HIV-1 non-B subtype. On the contrary, a lower risk was associated with a
189 higher GSS and a dolutegravir based regimen. Furthermore, there was no difference regarding the
190 antiretroviral strategy, 2DR versus 3DR, on the emergence of integrase RAM.

191 Overall, among this large cohort of HIV-1 patients failing INSTI based regimen and followed in the
192 hospital clinical care, about less than half of rebound viruses carried INSTI RAM. These results are

193 in accordance with those of our previous national studies and some cohorts.¹⁵⁻¹⁸ However, these
194 rates may seem higher than described in other cohorts, but this could be explained by several factors
195 as the defined list of INSTI mutations (major mutations or polymorphisms), the INSTI studied (first
196 and/or second generation), the patients' characteristics (immunological and virological factors) and
197 the time under INSTI treatment.¹⁹⁻²¹ Furthermore, in comparison with the first studies on INSTI
198 resistance, some patients had been receiving INSTI for several years.

199 The most common INSTI RAM found in our study were L74F/I/M and N155H/S/T. This higher
200 prevalence of N155H/S/T was also evidenced in Italian, English and Argentinian cohorts.^{17,18,22,23}
201 The prevalence of this mutation was different according to the INSTI, with a lower prevalence for
202 patients failing dolutegravir. Overall, the level of INSTI genotypic resistance was lower for patients
203 failing dolutegravir than for patients failing raltegravir and elvitegravir regimen and this is in
204 accordance with our previous national survey.¹⁵ This could be explained by a higher affinity of
205 dolutegravir for its target and therefore a higher genetic barrier to resistance.²⁴⁻²⁶ In general, it is
206 now admitted that emerging resistance during dolutegravir failure is rare and observed mostly in
207 ARV-experienced patients in comparison to the first generation of INSTIs.²⁷ The results of our
208 multivariate analysis were consistent as the use of dolutegravir in the antiretroviral treatment was
209 associated to a lower risk of RAM acquisition.

210 Considering the occurrence of at least one INSTI RAM, the multivariate analysis showed a higher
211 risk with a higher level of HIV-1 VL at failure and a lower risk with a higher level of GSS. In a
212 previous study focusing on raltegravir, a lower GSS and a higher HIV-1 VL level at failure (>1000
213 copies/mL) were associated with the presence of raltegravir RAM.¹⁶ Usually, a higher VL and/or a
214 lower CD4 count at baseline were associated with more treatment failures in a cohort of HIV-1
215 patients with first line integrase inhibitor based antiretroviral treatment, but in this study the link
216 between treatment failure and resistance mutations emergence was not evaluated or established.²⁸

217 Overall, HIV-1 subtype seemed also to influence the occurrence of at least one integrase RAM with
218 a higher risk of non-B subtypes. However, the HIV-1 subtype was no longer associated with the
219 emergence of INSTI RAM when L74F/I/M and E157Q were removed of the analysis. Indeed, the
220 distribution of INSTI RAM was different according to the HIV-1 subtype, as L74F/I/M and E157Q
221 were mostly present for HIV-1 non-B subtypes although G140C/H/S and Q148EG/H/K/R for B
222 subtype. Two previous studies demonstrating a higher prevalence of mutations at positions Q148
223 for HIV-1 B subtype for patients only receiving raltegravir as INSTI in their antiretroviral treatment.
224 ^{16,23} Two limitations of our study appeared concerning the HIV subtype leverage: the absence of
225 HIV-1 baseline genotypes and the lack of adherence data or pharmacological measurements of the
226 patients to explore the hypothesis of an adherence difference according to the HIV-1 subtype.

227 Some authors suggested a possible weakness of the 2DR strategy which could allow a viral escape
228 and selection of RAM. In our study, conditionally to other factors such as GSS and INSTI, no
229 difference between 2DR and 3DR was observed in terms of occurrence of RAM. This result
230 confirmed in a large cohort of clinical routine care the robustness of 2DR including an INSTI with
231 no consequence on HIV resistance. Indeed, other studies showed no difference in achieving
232 virological and a limited or no emergence of INSTI RAM in patients failing a 2DR with
233 dolutegravir. ^{3,8,29} However, we cannot generalize this conclusion to every 2DR regimen, as 53% of
234 2DR treated patients were receiving a PI in combination with an INSTI.

235 Overall, this study is one of the largest studies conducted in patients failing to any INSTI-containing
236 2DR or 3DR regimen in routine clinical care, and showing that a higher HIV RNA VL and HIV-1
237 non-B subtypes were associated with a higher risk of emergence of integrase RAM. Conversely the
238 use of dolutegravir was associated with a lower risk of emergence of integrase RAM and no
239 difference was evidenced between patients receiving 2DR or 3DR. These results should be taken
240 into consideration in patients' clinical management.

241

242 **ACKNOWLEDGMENTS**

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277 Rouen, F. Caron, Y. Debab, G. Unal Strasbourg, M. Partisani, D. Rey, P. Fischer; Toulouse, B.
278 Marchou, P. Massip, P Delobel; Tours, G. Gras, G. Fajole; Versailles, A. Greber Belan, Ruel, O.
279 Belety, F. Granier.

280

281 **FUNDING**

282 This work was supported by the Agence Nationale de Recherches sur le SIDA et les Hépatites
283 virales – Maladies Infectieuses Emergentes (ANRS - MIE, AC43) and ViiV Healthcare.

284

285 **TRANSPARENCY DECLARATIONS**

286 The authors have no conflict of interest.

287

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371

372

373 **Table 1. Characteristics of patients included in the study population.**

374

	Regimen				P value
	Dual Therapy N=207		Triple Therapy N=897		
	Median	IQR	Median	IQR	
Age	52.4	43.3-58.2	47.1	38.1-54.1	<0.001
Time since HIV-1 diagnosis, years	20.6	11.1-25.1	12.8	4.5-21.0	<0.001
Duration of current INSTI regimen, months	20.2	9.3-41.9	13.5	6.4-29.9	<0.001
GSS	1.0	0.0-1.0	2.0	1.0-2.0	<0.001
Nadir CD4 cell count/mm ³	162.0	54-268	144.0	44-292	0.81
Baseline CD4 cell count/mm ³	460.0	271-712	360.0	177-626	<0.001
Baseline plasma HIV-1 RNA, log ₁₀ copies/mL	1.7	1.3-3.1	2.5	1.6-4.7	<0.001
CD4 at failure, cell count/mm ³	485.0	294-698	393	211-634	0.001
Plasma HIV-1 RNA at failure, log ₁₀ copies/mL	2.8	2.3-3.8	2.9	2.3-4.0	0.53
	N (%)		N (%)		
Male	126 (61%)		559 (62%)		0.68
Subtype B	120 (58%)		457 (51%)		0.07
Naïve	11 (5.3%)		149 (16.6%)		<0.001
First line containing INSTI	117 (56.5%)		662 (73.8%)		<0.001
CD4 baseline <200 cells count/mm ³	44 (21%)		307 (34%)		<0.001
Baseline VL (copies/ml)					
<50	115 (56%)		351 (39%)		
50-100,000	79 (38%)		395 (44%)		<0.001
>100,000	13 (6%)		151 (17%)		
INSTI treatment					
Raltegravir	144 (70%)		286 (32%)		
Elvitegravir	0		323 (36%)		<0.001
Dolutegravir	63 (30%)		288 (32%)		
INSTI co-treatment					
one NNRTI	73 (35%)	two NRTIs	776 (87%)		

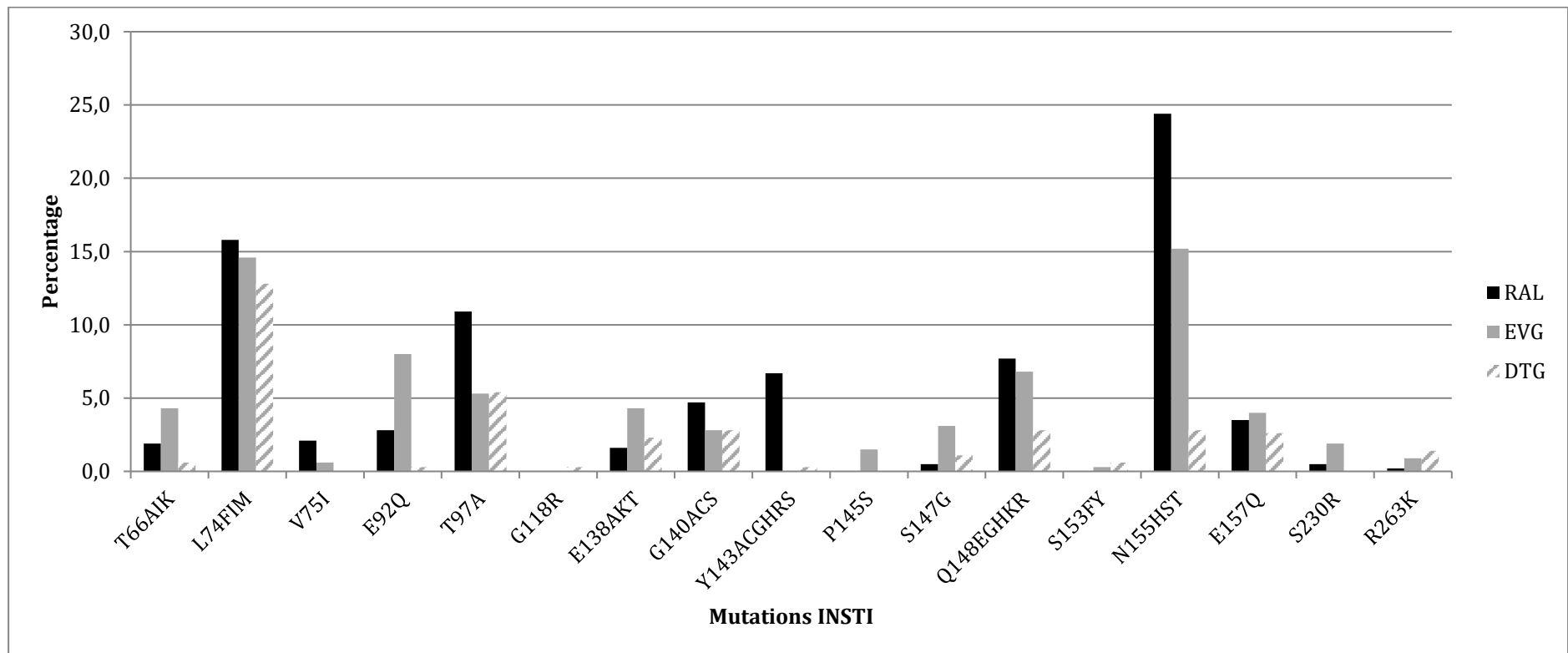
one NRTI	14 (7%)	NRTI+NNRTI	12 (1%)	
one PI	110 (53%)	PI + other	17 (2%)	
Other	10 (5%)	PI+NNRTI	36 (4%)	
		PI+NRTI	39 (4%)	
		2 PIs	4 (0.5%)	
		Other	13 (1%)	
<hr/>				
PI used				
LPV	6		6	
ATV	21		0	
DRV	83		76	
FPV	0		2	
ATV	0		14	
SQV	0		2	
<hr/>				
GSS score				
0	52 (28%)		40 (5%)	
0.5	7 (4%)		78 (10%)	<0.001
1	128 (68%)		191 (24%)	
1.5			12 (2%)	
2			473 (60%)	

Table 2. Factors associated with the occurrence of at least one INSTI resistance associated mutations.

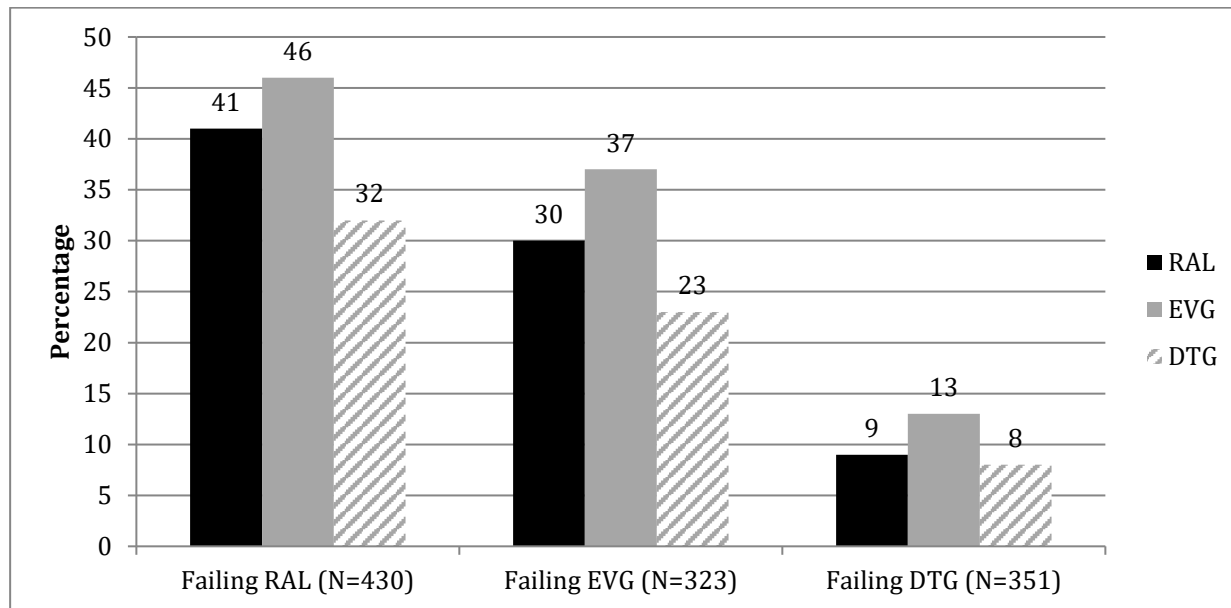
	Univariate			Multivariate		
	OR	95%CI	P-value	OR	95%CI	P-value
Triple vs. Dual therapy	0.59	0.44--0.8	0.0007			
Age (per 10 years increase)	1.02	0.92--1.13	0.69			
CD4 baseline (per 100 cells/mm ³ increase)	1.01	0.97--1.05	0.69			
Nadir CD4 (per 100 cells/mm ³ increase)	0.96	0.90--1.03	0.22			
Log HIV RNA Failure (per 1 log ₁₀ copies/ml increase)	1.31	1.18--1.47	<0.0001	1.24	1.1--1.4	0.001
Log HIV RNA baseline (per 1 log ₁₀ copies/ml increase)	0.96	0.89--1.04	0.29			
Duration of INSTI treatment (per one-year increase)	1.09	1.03--1.16	0.003			
Duration of Infection (per 10 years increase)	1.11	0.98--1.26	0.09			
Subtype Non B vs B	1.22	0.96--1.55	0.10	1.75	1.3--2.3	0.0002
GSS 1-1.5 vs 0-0.5	0.34	0.23--0.51	<0.0001	0.32	0.2--0.5	<0.0001
GSS 2 vs 0-0.5	0.11	0.07--0.16	<0.0001	0.10	0.07-0.2	<0.0001
DTG vs RAL	0.30	0.22--0.41	<0.0001	0.46	0.3--0.7	<0.0001
EVG vs RAL	0.77	0.58--1.03	0.08	1.28	0.9--1.8	0.16

INSTI, integrase strand transfer inhibitors; GSS, genotypic sensitivity score; DTG, dolutegravir; RAL, raltegravir; EVG, elvitegravir
P-value in bold is significant

Figure 1. Prevalence of sequences with at least one INSTIs resistance associated mutations in the total dataset according to the INSTIs in the antiretroviral treatment.



1 **Figure 2. Genotypic interpretation of integrase resistance to different INSTIs among the 1104 patients failing an INSTI-containing**
2 **regimen. Predicted resistance to raltegravir (RAL), elvitegravir (EVG) and dolutegravir (DTG) according to the integrase sequence with**
3 **the ANRS algorithm.**



4

