



**HAL**  
open science

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

Anne-Genevieve Marcelin, Charlotte Charpentier, Pantxika Bellecave, Basma Abdi, Marie-Laure Chaix, Virginie Ferre, Stephanie Raymond, Djeneba Fofana, Laurence Bocket, Audrey Mirand, et al.

### ► 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

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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**

3  
4 Anne-Genevieve MARCELIN<sup>1</sup>, Charlotte CHARPENTIER<sup>2</sup>, Pantxika BELLECAVE<sup>3</sup>, Basma  
5 ABDI<sup>1</sup>, Marie-Laure CHAIX<sup>4</sup>, Virginie FERRE<sup>5</sup>, Stephanie RAYMOND<sup>6</sup>, Djeneba FOFANA<sup>7</sup>,  
6 Laurence BOCKET<sup>8</sup>, Audrey MIRAND<sup>9</sup>, Helene LE GUILLOU-GUILLEMETTE<sup>10</sup>, Brigitte  
7 MONTES<sup>11</sup>, Corinne AMIEL<sup>12</sup>, Coralie PALLIER<sup>13</sup>, Samira FAFI-KREMER<sup>14</sup>, Anne DE  
8 MONTE<sup>15</sup>, Elodie ALESSANDRI-GRADT<sup>16</sup>, Caroline SCHOLTES<sup>17</sup>, Anne MAILLARD<sup>18</sup>,  
9 Helene JEULIN<sup>19</sup>, Magali BOUVIER-ALIAS<sup>20</sup>, Catherine ROUSSEL<sup>21</sup>, Georges DOS SANTOS<sup>22</sup>,  
10 Anne SIGNORI-SCHMUCK<sup>23</sup>, Julia DINA<sup>24</sup>, Sophie VALLET<sup>25</sup>, Karl STEFIC<sup>26</sup>, Cathia  
11 SOULIÉ<sup>1\*</sup>, Vincent CALVEZ<sup>1</sup>, Diane DESCAMPS<sup>3</sup>, Philippe FLANDRE<sup>27</sup>, on behalf of the  
12 ANRS-MIE AC43 group†.

13  
14 <sup>1</sup> Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-  
15 HP, Hôpitaux Universitaires Pitié Salpêtrière - Charles Foix, laboratoire de virologie, F75013, Paris,  
16 France; <sup>2</sup> Service de Virologie, Université de Paris INSERM, IAME, UMR 1137, AP-HP, Hôpital  
17 Bichat,-Claude Bernard, F-75018 Paris, France; <sup>3</sup> CHU de Bordeaux, Laboratoire de Virologie,  
18 Univ. Bordeaux, CNRS UMR 5234, F-33076 Bordeaux, France ; <sup>4</sup> INSERM U941, Université de  
19 Paris, Laboratoire de Virologie, AP-HP, Hôpital Saint-Louis, Paris, France; <sup>6</sup> INSERM UMR 1291  
20 Toulouse, F-31300 France and Laboratoire de Virologie, CHU Toulouse Purpan, Toulouse, F-31300  
21 France; <sup>7</sup> AP-HP, CHU Saint Antoine, INSERM-Sorbonne Universités, UPMC Univ Paris 06,  
22 UMR\_S 1136, Paris, France; <sup>8</sup> Univ. Lille, CHU Lille, Laboratoire de Virologie, Lille, France; <sup>9</sup>  
23 CHU de Clermont-Ferrand, France ; <sup>10</sup> Laboratoire de Virologie, CHU Angers and HIFIH  
24 Laboratory EA 3859, LUNAM, Angers, France ; <sup>11</sup> Laboratoire de Virologie, CHU Montpellier,  
25 Univ Montpellier, France ; <sup>12</sup> AP-HP, CHU Tenon, Paris, France ; <sup>13</sup> CHU Paul Brousse, Villejuif,

26 France ; <sup>14</sup> CHU de Strasbourg, Strasbourg, France ; <sup>15</sup> CHU de Nice, Nice, France ; <sup>16</sup> CHU de  
27 Rouen, Université de Rouen Normandie UNIRouen, France ; <sup>17</sup> INSERM U1052, CRCL, Université  
28 de Lyon, Laboratoire de Virologie; <sup>18</sup> Laboratoire de Virologie, CHU de Rennes, Rennes, France ;  
29 <sup>19</sup> Laboratoire de Virologie, CHRU de Nancy Brabois, Vandoeuvre-lès-Nancy ; <sup>20</sup> CHU Henri  
30 Mondor, Laboratoire de Virologie, Créteil, France ; <sup>21</sup> CHU d'Amiens, Amiens, France ; <sup>22</sup> Service  
31 de virologie, CHU de Martinique, Fort de France, Martinique; <sup>23</sup> CHU Grenoble-Alpes, Grenoble,  
32 France ; <sup>24</sup> Normandie Univ, UNICAEN, UNIROUEN, GRAM 2.0, Caen University Hospital  
33 Department of Virology, F14000, France; <sup>25</sup> Laboratoire de Virologie, CHRU de Brest, Brest,  
34 France ; <sup>26</sup> INSERM U1259, Université de Tours et Laboratoire de Virologie, CHRU de Tours,  
35 Tours, France ; <sup>27</sup> INSERM-Sorbonne Universités, UPMC Univ Paris 06, UMR\_S 1136, Paris,  
36 France.

37  
38 \* Corresponding author  
39 Mailing address: Department of Virology, Pitié-Salpêtrière Hospital, 83 Boulevard de l'Hôpital,  
40 75013 Paris, France. Phone : 33142177401, Fax : 33142177411.  
41 e-mail: [cathia.soulie-ext@aphp.fr](mailto:cathia.soulie-ext@aphp.fr)

42 † Members are listed in the Acknowledgement section

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 log<sub>10</sub> 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.

68

69

70

## 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).<sup>1-7</sup> 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.<sup>8-10</sup>  
84 However, in this latter trial, emergence of resistance mutations was higher in the raltegravir and  
85 darunavir/ritonavir group.<sup>11</sup>

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.<sup>12,13</sup>

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.<sup>14</sup>

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](http://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/mm<sup>3</sup>,  $p < 0.001$ ) 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 log<sub>10</sub> copies/mL (IQR: 2.3-4.0) with  
153 higher median levels in patients with lower GSS (3.4, 3.2 and 2.9 log<sub>10</sub> 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.<sup>15-18</sup> 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.<sup>19-21</sup> 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.<sup>17,18,22,23</sup>  
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.<sup>15</sup> This could be explained by a higher affinity of  
205 dolutegravir for its target and therefore a higher genetic barrier to resistance.<sup>24-26</sup> 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.<sup>27</sup> 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.<sup>16</sup> 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.<sup>28</sup>

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 <sup>16,23</sup> 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. <sup>3,8,29</sup> 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**

243

244 Members of the ANRS AC43 Resistance Study Group by location

245 Amiens, C. Roussel; Angers, H. Le Guillou-Guillemette, A. Ducancelle ; Argenteuil, L.  
246 Courdavault; Avicenne, C. Alloui, P. Honore; Besançon, Q. Lepiller, D. Bettinger; Bordeaux, P.  
247 Bellecave, P. Pinson-Recordon, C. Tumiotto, S. Reigadas; Brest, S. Vallet, C Payan, JC. Duthe;  
248 Caen, M. Leroux, J. Dina, A. Vabret; Clermont-Ferrand, A. Mirand, C. Henquell; Créteil-Henri  
249 Mondor, M. Bouvier-Alias; Dijon, A. Simohamed ; Fort de France, G. Dos Santos; Genève, S.  
250 Yerly, C. Gaille, W. Caveng, S. Chapalay, A. Calmy; Grenoble, A. Signori-Schmuck, P Morand;  
251 HU Paris Sud, C. Pallier, M. Raho-Moussa, M. Mole, M-J. Dulucq; Lille–Tourcoing, L. Bocket,  
252 K.Alidjinou; Limoges, S. Ranger-Rogez; Lyon, M. A. Trabaud, V Icard, J.C. Tardy; Marseille, C.  
253 Tamalet; Metz/Thionville, C. Delamare; Montpellier, B. Montes; Nancy, E. Schvoerer, H. Fenaux;  
254 Nantes, A. Rodallec, E. André-Garnier, V. Ferré; Nice, A. De Monte; Orléans, A. Guigon, J.  
255 Guinard; Paris-Bichat Claude Bernard, D. Descamps, C. Charpentier, B Visseaux, G. Peytavin;  
256 Paris-Necker, M. Fillion; Paris-Pitié-Salpêtrière, C. Soulié, I. Malet, M. Wirden, A. G. Marcelin,  
257 V. Calvez, P. Flandre, L. Assoumou, D. Costagliola; Paris-Saint Antoine, L. Morand-Joubert, S.  
258 Lambert-Niclot, D. Fofana; Paris-Saint Louis, C. Delaugerre, ML Chaix, N. Mahjoub; Paris-Tenon,  
259 C. Amiel; Poitiers, G. Giraudeau, A. Beby-Defaux, D. Plainchamp; Rennes, A. Maillard; Rouen, E.  
260 Alessandri-Gradt, M. Leoz, J. C. Plantier; Strasbourg, P. Gantner S. Fafi-Kremer, P. Fischer ;  
261 Toulouse, S. Raymond, J. Izopet, J Chiabrande; Tours, F. Barin, G. Fajole, O. Burgault; Versailles,  
262 S. Marque Juillet.

263 Members of the ANRS Clinical Centres by location

264 Angers, P. Abgueuen, V. Rabier, Y.M. Vandamme; Besançon, B. Hoen; Bordeaux, M. Dupon, P.  
265 Morlat, D. Neau; Brest, M. Garré, V. Bellein; Caen, R. Verdon, A. De la Blanchardière, S. Dargère,

266 A. Martin, V. Noyou; Clermont-Ferrand, C. Jacomet; Créteil, J.D. Lelièvre, J.L. Lopez-Zaragoza.;  
267 Dijon, B. Lorcerie; Fort de France, A. Cabié; Genève, S. Yerly; Grenoble, P. Leclercq, M. Blanc;  
268 Le Kremlin-Bicêtre, C. Goujard; Lille–Tourcoing, O. Robineau; Limoges, P. Weinbreck; Lyon, L.  
269 Cotte; D. Makhloufi; Marseille, I. Poizot-Martin, I. Ravaud; Montpellier, J. Reynes; Nancy, H.  
270 Fenaux; Nantes, F. Raffi; Nice, E. Cua, J. Durant, P. Pugliese; Orléans, L. Hocquelloux, T. Prazuck;  
271 Paris-Bichat Claude Bernard, Y. Yazdanpanah, R. Landman, S. Legac; Paris-HEGP, L. Weiss, M.  
272 Karmochkine; Paris-Jean-Verdier, S. Tassi; Paris-Necker-Enfants Malades, C. Duvivier ; HU Paris-  
273 Sud, C. Bolliot, M. Malet, D. Vittecoq, M. Raho-Moussa, M. Mole; Paris-Pitié-Salpêtrière, C.  
274 Katlama, A. Simon; Paris-Saint Antoine, P. M. Girard, J. L. Meynard; Paris-Saint Louis, J. M.  
275 Molina; Paris-Tenon, V. Berrebi, G. Pialoux; Pointe à Pitre, I. Lamaury, Fort de France , A. Cabié;  
276 Poitiers, G. Le Moal, D. Plainchamp; Rennes, F. Benezit, J.Vivent, C. Morlat, M. Poisson-Vannier;  
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

289 **REFERENCES**

- 290 1. Taiwo BO, Marconi VC, Berzins B, *et al.* Dolutegravir Plus Lamivudine Maintains Human  
291 Immunodeficiency Virus-1 Suppression Through Week 48 in a Pilot Randomized Trial. *Clin Infect*  
292 *Dis* 2018; **66**: 1794–7.
- 293 2. Joly V, Burdet C, Landman R, *et al.* Dolutegravir and lamivudine maintenance therapy in HIV-1  
294 virologically suppressed patients: results of the ANRS 167 trial (LAMIDOL). *J Antimicrob*  
295 *Chemother* 2019; **74**: 739–45.
- 296 3. Aboud M, Orkin C, Podzamczar D, *et al.* Efficacy and safety of dolutegravir-rilpivirine for  
297 maintenance of virological suppression in adults with HIV-1: 100-week data from the randomised,  
298 open-label, phase 3 SWORD-1 and SWORD-2 studies. *Lancet HIV* 2019; **6**: e576–87.
- 299 4. Margolis DA, Gonzalez-Garcia J, Stellbrink H-J, *et al.* Long-acting intramuscular cabotegravir  
300 and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-  
301 label, phase 2b, non-inferiority trial. *Lancet* 2017; **390**: 1499–510.
- 302 5. Swindells S, Andrade-Villanueva J-F, Richmond GJ, *et al.* Long-Acting Cabotegravir and  
303 Rilpivirine for Maintenance of HIV-1 Suppression. *N Engl J Med* 2020; **382**: 1112–23.
- 304 6. Orkin C, Arasteh K, Górgolas Hernández-Mora M, *et al.* Long-Acting Cabotegravir and  
305 Rilpivirine after Oral Induction for HIV-1 Infection. *N Engl J Med* 2020; **382**: 1124–35.
- 306 7. van Wyk J, Ajana F, Bisshop F, *et al.* Efficacy and Safety of Switching to  
307 Dolutegravir/Lamivudine Fixed-Dose Two-Drug Regimen Versus Continuing a Tenofovir  
308 Alafenamide-Based Three- or Four-Drug Regimen for Maintenance of Virologic Suppression in  
309 Adults With HIV-1: Phase 3, Randomized, Non-inferiority TANGO Study. *Clin Infect Dis* 2020.
- 310 8. Cahn P, Madero JS, Arribas JR, *et al.* Dolutegravir plus lamivudine versus dolutegravir plus  
311 tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naïve adults with HIV-1 infection  
312 (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-  
313 inferiority, phase 3 trials. *Lancet* 2019; **393**: 143–55.
- 314 9. Cahn P, Madero JS, Arribas JR, *et al.* Durable Efficacy of Dolutegravir Plus Lamivudine in  
315 Antiretroviral Treatment-Naïve Adults With HIV-1 Infection: 96-Week Results From the GEMINI-  
316 1 and GEMINI-2 Randomized Clinical Trials. *J Acquir Immune Defic Syndr* 2020; **83**: 310–8.
- 317 10. Raffi F, Babiker AG, Richert L, *et al.* Ritonavir-boosted darunavir combined with raltegravir or  
318 tenofovir–emtricitabine in antiretroviral-naïve adults infected with HIV-1: 96 week results from the  
319 NEAT001/ANRS143 randomised non-inferiority trial. *The Lancet* 2014; **384**: 1942–51.
- 320 11. Lambert-Niclot S, George EC, Pozniak A, *et al.* Antiretroviral resistance at virological failure  
321 in the NEAT 001/ANRS 143 trial: raltegravir plus darunavir/ritonavir or tenofovir/emtricitabine  
322 plus darunavir/ritonavir as first-line ART. *J Antimicrob Chemother* 2016; **71**: 1056–62.
- 323 12. EACS AIDS Clinical Society. *EACS guidelines version 10.0 (Nov. 2019)*. 2020. Available at:  
324 <https://eacs.sanfordguide.com>.

- 325 13. Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of*  
326 *Antiretroviral Agents in Adults and Adolescents with HIV*. Department of Health and Human  
327 Services.; 2020. Available at: [http://www.aidsinfo.nih.gov/ContentFiles/](http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf)  
328 [AdultandAdolescentGL.pdf](http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf).
- 329 14. Descamps D, Delaugerre C, Masquelier B, *et al*. Repeated HIV-1 resistance genotyping external  
330 quality assessments improve virology laboratory performance. *J Med Virol* 2006; **78**: 153–60.
- 331 15. Marcelin A-G, Grude M, Charpentier C, *et al*. Resistance to integrase inhibitors: a national study  
332 in HIV-1-infected treatment-naïve and -experienced patients. *J Antimicrob Chemother* 2019; **74**:  
333 1368–75.
- 334 16. Fourati S, Charpentier C, Amiel C, *et al*. Cross-resistance to elvitegravir and dolutegravir in 502  
335 patients failing on raltegravir: a French national study of raltegravir-experienced HIV-1-infected  
336 patients. *J Antimicrob Chemother* 2015; **70**: 1507–12.
- 337 17. Modica S, Rossetti B, Lombardi F, *et al*. Prevalence and determinants of resistance mutations  
338 in HIV-1-infected patients exposed to integrase inhibitors in a large Italian cohort. *HIV Med* 2019;  
339 **20**: 137–46.
- 340 18. Scutari R, Alteri C, Vicenti I, *et al*. Evaluation of HIV-1 integrase resistance emergence and  
341 evolution in patients treated with integrase inhibitors. *J Glob Antimicrob Res* 2020; **20**: 163–9.
- 342 19. Hurt CB, Sebastian J, Hicks CB, Eron JJ. Resistance to HIV integrase strand transfer inhibitors  
343 among clinical specimens in the United States, 2009-2012. *Clin Infect Dis* 2014; **58**: 423–31.
- 344 20. Lepik KJ, Harrigan PR, Yip B, *et al*. Emergent drug resistance with integrase strand transfer  
345 inhibitor-based regimens. *AIDS* 2017; **31**: 1425–34.
- 346 21. De Francesco MA, Izzo I, Properzi M, *et al*. Prevalence of Integrase Strand Transfer Inhibitors  
347 Resistance Mutations in Integrase Strand Transfer Inhibitors-Naïve and -Experienced HIV-1  
348 Infected Patients: A Single Center Experience. *AIDS Res Hum Retroviruses* 2018; **34**: 570–4.
- 349 22. Cecchini DM, Castillo S, Copertari G, *et al*. Resistance to HIV integrase strand transfer  
350 inhibitors in Argentina: first interim survey. *Rev Esp Quimioter* 2019; **32**: 263–7.
- 351 23. Doyle T, Dunn DT, Ceccherini-Silberstein F, *et al*. Integrase inhibitor (INI) genotypic resistance  
352 in treatment-naïve and raltegravir-experienced patients infected with diverse HIV-1 clades. *J*  
353 *Antimicrob Chemother* 2015; **70**: 3080–6.
- 354 24. Hightower KE, Wang R, Deanda F, *et al*. Dolutegravir (S/GSK1349572) exhibits significantly  
355 slower dissociation than raltegravir and elvitegravir from wild-type and integrase inhibitor-resistant  
356 HIV-1 integrase-DNA complexes. *Antimicrob Agents Chemother* 2011; **55**: 4552–9.
- 357 25. DeAnda F, Hightower KE, Nolte RT, *et al*. Dolutegravir interactions with HIV-1 integrase-  
358 DNA: structural rationale for drug resistance and dissociation kinetics. *PLoS One* 2013; **8**: e77448.
- 359 26. Llibre JM, Pulido F, García F, *et al*. Genetic barrier to resistance for dolutegravir. *AIDS Rev*  
360 2015; **17**: 56–64.

361 27. Raffi F, Jaeger H, Quiros-Roldan E, *et al.* Once-daily dolutegravir versus twice-daily raltegravir  
362 in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a  
363 randomised, double-blind, non-inferiority trial. *Lancet Infect Dis* 2013; **13**: 927–35.

364 28. Pyngottu A, Scherrer AU, Kouyos R, *et al.* Predictors of virological failure and time to viral  
365 suppression of first line integrase inhibitor based antiretroviral treatment. *Clin Infect Dis* 2020. *Clin*  
366 *Infect Dis* 2020 Oct 24;ciaa1614. doi: 10.1093/cid/ciaa1614

367 29. Lagi F, Baldin G, Colafigli M, *et al.* Viro-immunological efficacy and tolerability of  
368 dolutegravir-based regimens compared to regimens based on other integrase strand inhibitors,  
369 protease inhibitors or non-nucleoside reverse transcriptase inhibitors in patients with acute HIV-1  
370 infection: A multicenter retrospective cohort study. *Int J Antimicrob Agents* 2019; **54**: 487–90.

371

372



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

374

	<b>Regimen</b>				<b>P value</b>
	<b>Dual Therapy</b>		<b>Triple Therapy</b>		
	<b>N=207</b>		<b>N=897</b>		
	<b>Median</b>	<b>IQR</b>	<b>Median</b>	<b>IQR</b>	
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 <sup>3</sup>	162.0	54-268	144.0	44-292	0.81
Baseline CD4 cell count/mm <sup>3</sup>	460.0	271-712	360.0	177-626	<0.001
Baseline plasma HIV-1 RNA, log <sub>10</sub> copies/mL	1.7	1.3-3.1	2.5	1.6-4.7	<0.001
CD4 at failure, cell count/mm <sup>3</sup>	485.0	294-698	393	211-634	0.001
Plasma HIV-1 RNA at failure, log <sub>10</sub> copies/mL	2.8	2.3-3.8	2.9	2.3-4.0	0.53
	<b>N (%)</b>		<b>N (%)</b>		
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 <sup>3</sup>	44 (21%)		307 (34%)		<0.001
<b>Baseline VL (copies/ml)</b>					
<50	115 (56%)		351 (39%)		
50-100,000	79 (38%)		395 (44%)		<0.001
>100,000	13 (6%)		151 (17%)		
<b>INSTI treatment</b>					
Raltegravir	144 (70%)		286 (32%)		
Elvitegravir	0		323 (36%)		<0.001
Dolutegravir	63 (30%)		288 (32%)		
<b>INSTI co-treatment</b>					
one NNRTI	73 (35%)	two NRTIs	776 (87%)		

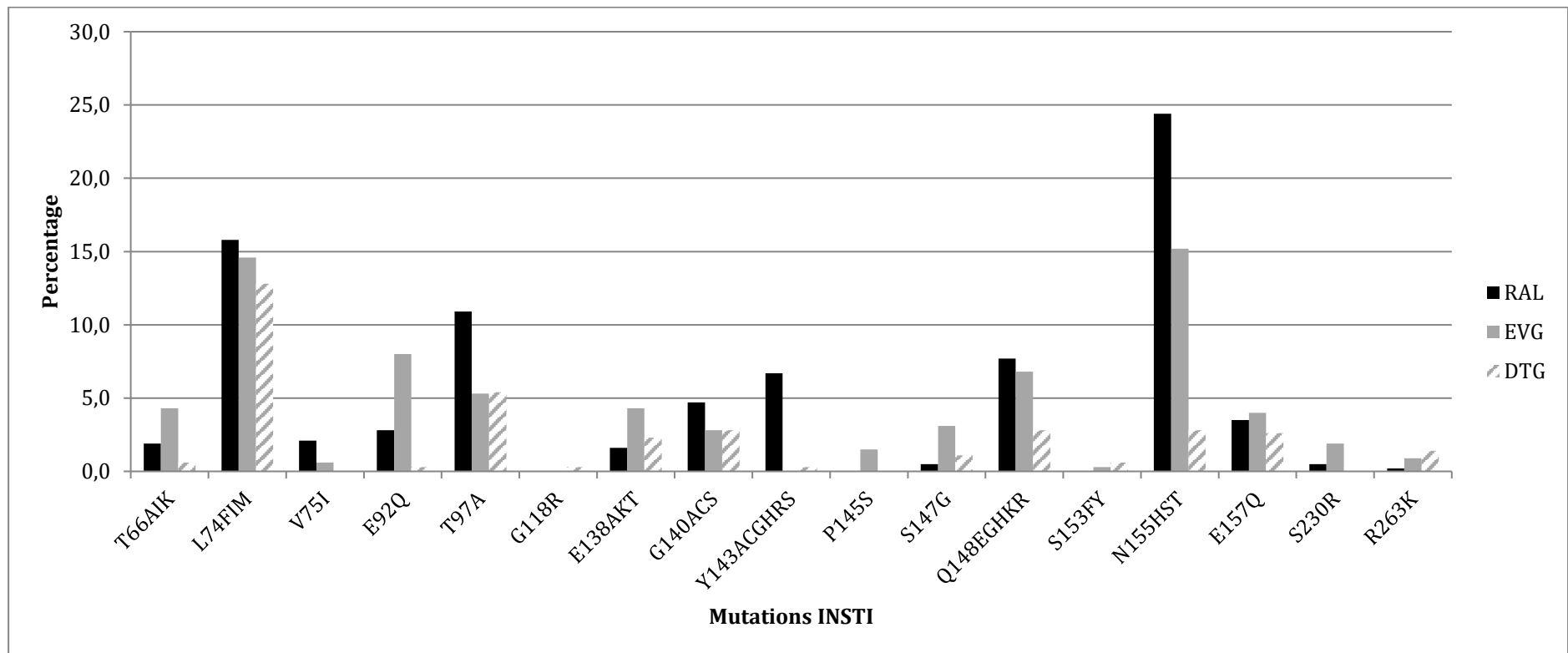
one NRTI	14 (7%)	NRTI+NNRTI	12 (1%)	
one PI	110 (53%)	PI + other	17 (2%)	
Other	10 (5%)	PI+NNRTI	36 (4%)	
		PI+NRTI	39 (4%)	
		2 PIs	4 (0.5%)	
		Other	13 (1%)	
<hr/>				
<b>PI used</b>				
LPV	6		6	
ATV	21		0	
DRV	83		76	
FPV	0		2	
ATV	0		14	
SQV	0		2	
<hr/>				
<b>GSS score</b>				
0	52 (28%)		40 (5%)	
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.**

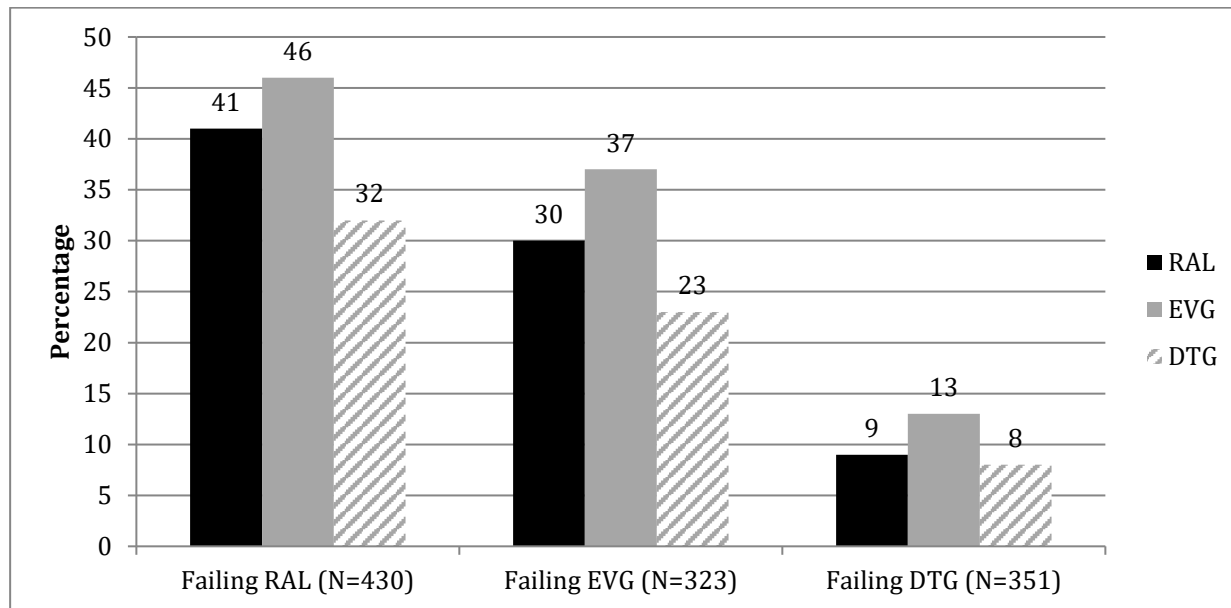
	Univariate			Multivariate		
	OR	95%CI	P-value	OR	95%CI	P-value
Triple vs. Dual therapy	0.59	0.44--0.8	0.0007			
Age (per 10 years increase)	1.02	0.92--1.13	0.69			
CD4 baseline (per 100 cells/mm <sup>3</sup> increase)	1.01	0.97--1.05	0.69			
Nadir CD4 (per 100 cells/mm <sup>3</sup> increase)	0.96	0.90--1.03	0.22			
Log HIV RNA Failure (per 1 log <sub>10</sub> 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 <sub>10</sub> 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

