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

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

France ; [14] CHU de Strasbourg, Strasbourg, France ; [15] CHU de Nice, Nice, France ; [16] CHU de Rouen, Université de Rouen Normandie UNIRouen, France ; [17] INSERM U1052, CRCL, Université de Lyon, Laboratoire de Virologie; [18] Laboratoire de Virologie, CHU de Rennes, Rennes, France ; [19] Laboratoire de Virologie, CHRU de Nancy Brabois, Vandoeuvre-lès-Nancy ; [20] CHU Henri Mondor, Laboratoire de Virologie, Créteil, France ; [21] CHU d'Amiens, Amiens, France ; [22] Service de virologie, CHU de Martinique, Fort de France, Martinique; [23] CHU Grenoble-Alpes, Grenoble, France ; [24] Normandie Univ, UNICAEN, UNIROUEN, GRAM 2.0, Caen University Hospital Department of Virology, F14000, France; [25] Laboratoire de Virologie, CHRU de Brest, Brest, France ; 26 INSERM U1259, Université de Tours et Laboratoire de Virologie, CHRU de Tours, Tours, France ; [27] INSERM-Sorbonne Universités, UPMC Univ Paris 06, UMR_S 1136, Paris, France.

* Corresponding author

Mailing address: Department of Virology, Pitié-Salpêtrière Hospital, 83 Boulevard de l'Hôpital, 75013 Paris, France. Phone : 33142177401, Fax : 33142177411.

e-mail: cathia.soulie-ext@aphp.fr

† Members are listed in the Acknowledgement section

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ABSTRACT

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

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

Results: 1104 patients failing to any INSTI-containing regimen (2DR=207 and 3DR=897) were analysed. 577 (52.3%) patients were infected with a B subtype and 527 (47.3%) with non-B subtypes. Overall, 644 (58%) patients showed no known integrase resistance mutations at failure. In multivariate analysis, factors associated with the emergence of at least one integrase mutation were high VL at failure (OR = 1.24 per 1 $\log_{10}$ copies/mL increase), non-B *versus* B subtype (OR = 1.75), low genotypic sensitivity score (GSS) (OR = 0.10 for GSS=2 *versus* GSS = 0-0.5), dolutegravir *versus* raltegravir (OR = 0.46). Although 3DR *versus* 2DR reach statistical significance in univariate analysis (OR = 0.59, p=0.007), the variable is not retained in the final model.

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

INTRODUCTION

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

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

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

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

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

PATIENTS AND METHODS

Patients and antiretroviral regimens

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

Ethics

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

Genotypic resistance testing

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

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

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

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

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

Statistical analysis

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

RESULTS

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

first-line ART. Patients on 2DR were slightly older (median 52 versus 47 years-old, p<0.001), had an older history of HIV infection (median 20.6 versus 12.8 years, p<0.001), had a higher median of baseline CD4 cell count (460 versus 360 cells/mm^3, p<0.001) and a higher median of duration of the current INSTI regimen (20.2 versus 13.5 months, p<0.001). As expected, the median GSS score was higher for patients in 3DR than patients in the 2DR group (median 2 versus 1, p<0.001). A majority (62%) of patients were male with and subtype B was the predominant HIV-1 clade (52%). In 2DR group, the INSTI was preferentially associated with one PI in 53% of cases or with one NNRTI in 35% of cases. In the 3DR group, 87% of patients received a combination of two NRTIs in association with the INSTI. At failure, median VL was 2.9 log_{10} copies/mL (IQR: 2.3-4.0) with higher median levels in patients with lower GSS (3.4, 3.2 and 2.9 log_{10} copies/mL in patients with GSS of [0-0.5], [1-1.5] and [2], respectively).

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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Members of the ANRS AC43 Resistance Study Group by location

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

Members of the ANRS Clinical Centres by location

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

A. Martin, V. Noyou; Clermont-Ferrand, C. Jacomet; Créteil, J.D. Lelièvre, J.L. Lopez-Zaragoza.; Dijon, B. Lorcerie; Fort de France, A. Cabié; Genève, S. Yerly; Grenoble, P. Leclercq, M. Blanc; Le Kremlin-Bicêtre, C. Goujard; Lille–Tourcoing, O. Robineau; Limoges, P. Weinbreck; Lyon, L. Cotte; D. Makhloufi; Marseille, I. Poizot-Martin, I. Ravaud; Montpellier, J. Reynes; Nancy, H. Fenaux; Nantes, F. Raffi; Nice, E. Cua, J. Durant, P. Pugliese; Orléans, L. Hocquelloux, T. Prazuck; Paris-Bichat Claude Bernard, Y. Yazdanpanah, R. Landman, S. Legac; Paris-HEGP, L. Weiss, M. Karmochkine; Paris-Jean-Verdier, S. Tassi; Paris-Necker-Enfants Malades, C. Duvivier ; HU Paris-Sud, C. Bolliot, M. Malet, D. Vittecoq, M. Raho-Moussa, M. Mole; Paris-Pitié-Salpêtrière, C. Katlama, A. Simon; Paris-Saint Antoine, P. M. Girard, J. L. Meynard; Paris-Saint Louis, J. M. Molina; Paris-Tenon, V. Berrebi, G. Pialoux; Pointe à Pitre, I. Lamaury, Fort de France , A. Cabié; Poitiers, G. Le Moal, D. Plainchamp; Rennes, F. Benezit, J.Vivent, C. Morlat, M. Poisson-Vannier; Rouen, F. Caron, Y. Debab, G. Unal Strasbourg, M. Partisani, D. Rey, P. Fischer; Toulouse, B. Marchou, P. Massip, P Delobel; Tours, G. Gras, G. Fajole; Versailles, A. Greber Belan, Ruel, O. Beletry, F. Granier.

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The authors have no conflict of interest.

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373 **Table 1. Characteristics of patients included in the study population.**
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	Regimen				
	Dual Therapy N=207		**Triple Therapy N=897**		**P value**
	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%)	
PI used				
LPV	6		6	
ATV	21		0	
DRV	83		76	
FPV	0		2	
ATV	0		14	
SQV	0		2	
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%)	

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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	
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.

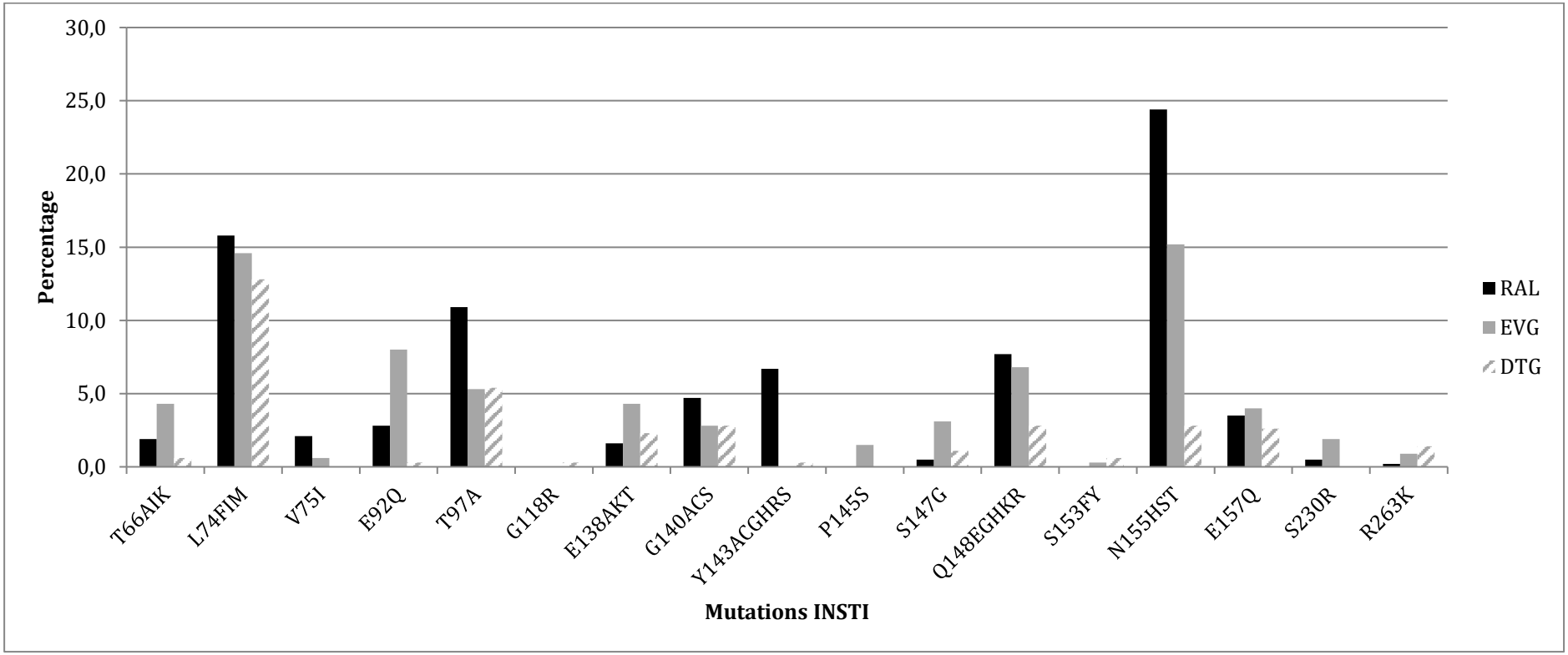
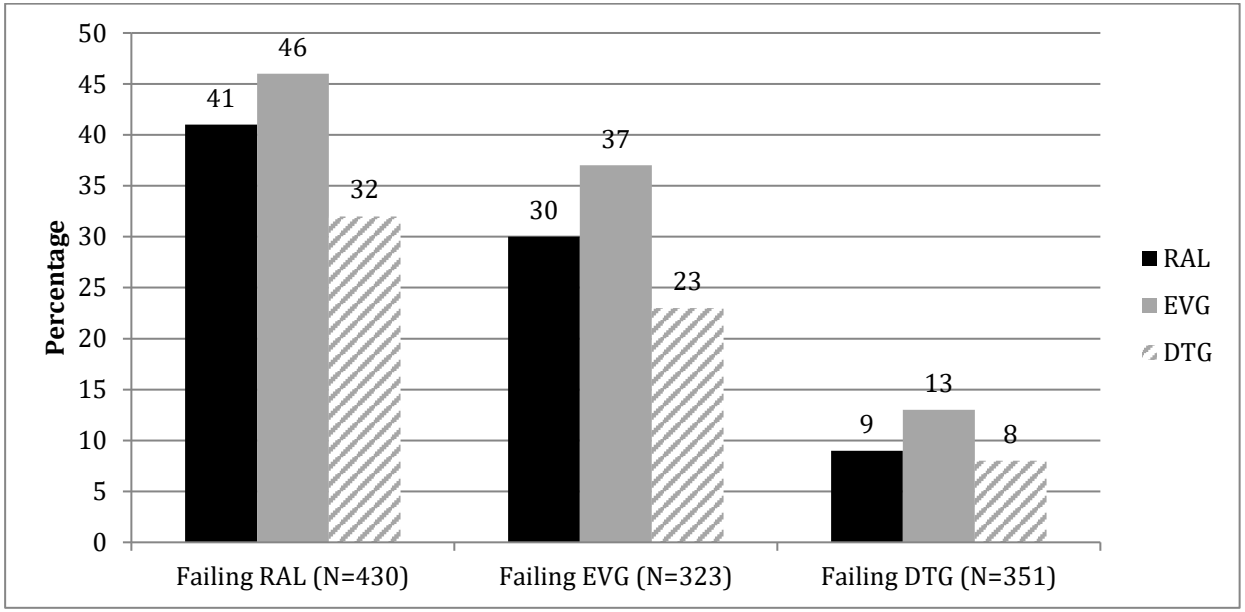


Figure 2. Genotypic interpretation of integrase resistance to different INSTIs among the 1104 patients failing an INSTI-containing regimen. Predicted resistance to raltegravir (RAL), elvitegravir (EVG) and dolutegravir (DTG) according to the integrase sequence with the ANRS algorithm.



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