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Resistance to integrase inhibitors: A National Study in HIV-1-Infected Naïve and Experienced Patients

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Summary: This work described the resistance patterns in a large population of patients failing an integrase inhibitor-based regimen. We showed that dolutegravir exhibited the highest robustness regarding resistance selection in case of virological failure in real world clinical setting.

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Synopsis

Introduction: It is of importance to describe integrase strand transfer inhibitors (INSTIs) resistance profiles and factors associated with, in naïve- and experienced-patients failing an INSTI-based regimen in clinical practice.

Methods: Data were collected from patients failing an INSTI-containing regimen in a multicentre french study between 2014 and 2017. Failure was defined by 2 consecutive plasma viral load (VL) > 50 copies/mL. Reverse transcriptase, protease and integrase genes were sequenced at baseline and failure. INSTIs resistance-associated mutations (RAMs) included in the ANRS genotypic algorithm were investigated.

Results: Among the 674 patients, 359 were failing raltegravir, 154 elvitegravir and 161 dolutegravir. Overall, 389 (58%) patients showed no INSTI RAMs at failure. At failure, 36% of patients failing raltegravir exhibited viruses considered genotypically resistant to raltegravir, 44% of patients failing elvitegravir exhibited viruses resistant to elvitegravir, 14% and 7% of patients failing dolutegravir exhibited viruses resistant to dolutegravir once per day and twice daily, respectively. Patients with high VL at failure and low Genotypic Sensitivity Score had a higher risk to select at least one INSTI RAM. Patients failing dolutegravir had significantly less INSTI RAMs at failure than patients failing raltegravir (OR=0.57, p = 0.02) or elvitegravir (OR=0.45, p = 0.005). Among the sixty eight patients failing a first-line regimen: 11/41 (27%) patients failing raltegravir had at failure viruses with emergent INSTI RAMs, 7/18 (39%) with elvitegravir and 0/9 with dolutegravir.

Conclusions: These results confirmed the robustness of dolutegravir regarding resistance selection in case of virological failure in routine clinical care.

Introduction

Integrase strand transfer inhibitors (INSTIs), which actively block the integration of the HIV genome into the host DNA, represent the latest antiretroviral (ARV) class to be approved for treatment of HIV-infected individuals¹. There are currently four INSTIs approved for the treatment of HIV infection: raltegravir, elvitegravir, dolutegravir and more recently bictegravir. Although highly efficacious in the management of HIV, both raltegravir and elvitegravir are susceptible to the development of resistance mutations in case of virological failure. The main resistance pathways that have been reported as selected both *in vitro* and *in vivo* with raltegravir are Y143, Q148 and N155.² It is evident now that raltegravir and elvitegravir share both the Q148 and N155 major resistance pathways.³ However, T66 and E92 pathways are predominantly selected by elvitegravir.⁴ In contrast to raltegravir and elvitegravir that share a common resistance profile, dolutegravir has a markedly distinct resistance profile and appears to have a higher genetic barrier to resistance. Indeed, in clinical trials it has not been shown to select for any resistance-associated mutations in treatment naïve patients when used in triple therapy.^{5,6,7} However, one case of emergence of integrase resistance mutation (Q148K + M184V) during virologic failure in a treatment-naïve man who initiated tenofovir disoproxil fumarate/emtricitabine plus dolutegravir has been recently published.⁸ In addition, there have been some cases of treatment failure with resistance mutations in treatment-experienced but INSTI-naïve patients, in particular with the emergence of the R263K mutation.⁹ Finally, in the particular setting of dolutegravir monotherapy in treatment-experienced patients, the selection of other substitutions at positions E92, Q148, N155 and S230 have been reported.¹⁰ Bictegravir is the most recent INSTI and there is few information available in regard to resistance against this drug. Given its similar chemical structure with dolutegravir and the fact that bictegravir selected for 263K during *in vitro* passages, we can assume that bictegravir share similar resistance profile as dolutegravir.¹¹

Although INSTIs mutation pathways have extensively been studied, most of existing data arises from *in vitro* experiments or clinical trials with a limited number of patients and specific inclusion criteria. In this study, we focused on integrase genotypic resistance tests performed in real world clinical setting by the French national ANRS network in order to better characterize the profile of INSTI resistance among specimens obtained for clinical decision making and to identify factors associated with the selection of integrase resistance mutations.

Patients and methods

Patients and antiretroviral regimens. HIV-1-infected patients who experienced virologic failure to an INSTI-containing regimen between 2014 and 2017 were allowed to be included in the study. Patients were treated with raltegravir, elvitegravir or dolutegravir with a background regimen comprising mainly NRTIs, NNRTIs, and/or PIs. Virological failure was defined as two consecutive HIV-1 viral loads (VL) > 50 copies/mL. Clinical data and treatment histories were collected for all patients recruited. Inclusion criteria and all data were checked by the study monitor. The 21 participating laboratories belong to the Agence Nationale de Recherches sur le SIDA et les hépatites virales (ANRS) AC43 network and participate in the annual ANRS quality control assessment of HIV-1 drug resistance sequencing.¹² The study was approved by the scientific committee of the ANRS AC43.

Genotypic resistance testing. The sequences of the protease (PR), reverse transcriptase (RT) and integrase (IN) genes were determined at baseline and failure (on confirmation plasma failure) in each laboratory using the ANRS consensus technique (<http://www.hivfrenchresistance.org/>), the Abbott ViroSeq kit, or an in-house method. For resistance interpretation, we used RT, PR and IN mutations present in the ANRS algorithm (Version 28) to determine whether patients receiving a particular NRTI, NNRTI or PI, had resistant, intermediate or susceptible virus strains. (www.hivfrenchresistance.org). List of INSTIs associated mutations used in the study is: T66AIK, L74FIM, V75I, E92Q, T97A, G118R, F121Y, E138AKT, G140ACS, Y143ACGHRS, P145S, S147G, Q148EGHKR, V151L, S153FY, N155HST, E157Q, S230R, R263K.

The genotypic sensitivity score (GSS) of the current regimen (without INSTI) was calculated according to the ANRS resistance algorithm. For each antiretroviral drug, patients with drug-susceptible viruses were assigned a GSS of 1, and those with intermediate-level and high-level resistance were assigned scores of 0.5 and 0, respectively.

Statistical analysis.

Quantitative variables are described by use of median and Interquartil Range (IQR) while categorical variables are described in percent. HIV-1 RNA at failure, viral subtype (B versus CRF02_AG and other non-B), baseline CD4 cell count, CD4 cell count at failure, nadir CD4, age, duration of infection, duration of INSTI treatment, the ongoing treatment (dual therapy, triple therapy and four and more therapy) and GSS were investigated as potential factors of occurrence of INSTIs mutations by the use of Cochran-Armitage test. A logistic regression model was also used to investigate whether previous variables were independent predictors of occurrence of INSTIs resistance associated mutations (RAMs). All variables tested with a P-value <0.10 in the univariate analysis were retained for the construction of the multivariate model. The latter only keeps the variables significantly associated with the occurrence of INSTIs mutation with a p-value <0.05 .

Results

Overall 674 patients failing an INSTI-containing regimen were included in the study from 21 French centres of the ANRS network. Patients were failing while receiving raltegravir (n = 359), elvitegravir (n = 154) or dolutegravir (n = 161) containing regimen and 10% of them were failing their first-line treatment. The main characteristics of the global study population are presented in Table 1. The average age was 48.5 years (IQR: 39.9-55.4 years) and the majority (65%) of patients were male. Regarding HIV-1 subtypes, 55.8% harboured subtype B and the most frequent non-B subtype was CRF02_AG (18%). The most prescribed combinations with INSTI were 2 NRTIs (55%) and 1 NRTI + 1 PI (13%). Patients were receiving 1, 2, 3 and more than 3 antiretrovirals including the INSTI in 1%, 17%, 66% and 15%, respectively.

Virologic failure occurred after a median time of 10.7 months (IQR: 5.7-30) following administration of INSTI-containing regimen. At failure, median viral load was 2.9 log₁₀ copies/mL (IQR: 2.3-4). Overall, viruses harboured no known INSTIs RAMs and were thus considered as fully genotypically susceptible to all INSTIs in 58% (n = 389) of cases. Thus, 42% of viruses harboured at least 1 INSTI RAM: 1, 2 and at least 3 mutations in 25% (n = 170), 10% (n = 71) and 6.5% (n = 44) of cases, respectively.

Regarding INSTIs RAMs in our dataset, the most frequent observed integrase mutations were N155H/S/T (n = 112; 16.6%), L74F/I/M (n = 82; 11.9%), Q148H/K/R (n = 54; 8.0%) and T97A (n = 53; 7.9%). The other detected INSTIs mutations were in less than 5% of cases: T66A/I/K (n = 15 ; 2.1%), V75I (n = 6 ; 0.9%), E92Q (n = 26 ; 3.9%), E138A/K/T (n = 22 ; 3.3%), G140A/C/S (n = 33 ; 4.9%), Y143A/C/G/H/R/S (n = 25 ; 3%), P145S (n = 3 ; 0.5%); S147G (n = 10; 1.5%), V151L (n = 1 ; 0.2%), S153F/Y (n = 2 ; 0.3%), E157Q (n = 22 ; 3.3%), S230G/R (n = 7 ; 0.6%) and R263K (n = 2 ; 0.3%). Q148H/K/R mutations were selected significantly more frequently in B subtypes versus non-B subtypes (p = 0.0135). In

patients harboring viruses with 2 or 3 INSTIs RAMs, the most common combinations were G140S/Q148H (12%), T97A/G140S/Q148H (6%) and L74I/E92Q (5%).

Interpretation of resistance to the different INSTIs is described in Figure 1. At failure, 36% of patients failing raltegravir exhibited plasma viruses considered genotypically resistant to raltegravir, 44% of patients failing elvitegravir exhibited plasma viruses considered resistant to elvitegravir, 14% and 7% of patients failing dolutegravir exhibited plasma viruses considered resistant to dolutegravir once per day (OD) and twice daily (BID), respectively.

We aimed to characterize clinical and virological factors associated with the emergence of INSTIs RAMs (Table 2). The final multivariate model shows a higher risk of occurrence of at least one INSTI RAM associated with a higher level of VL at failure (Odd Ratio (OR) = 1.2 per 1 log₁₀ copies/mL increase) (Figure 2) and a lower risk of occurrence of at least one INSTI RAM with a higher level of GSS (OR = 0.29 for GSS = 1-1.5, OR= 0.12 for GSS = 2-2.5 and OR = 0.08 for GSS>3 versus GSS = 0-0.5). In addition, patients failing dolutegravir had viruses with significantly less INSTIs RAMs at failure than patients failing raltegravir (OR = 0.57, p = 0.02) and patients failing elvitegravir (OR = 0.45, p = 0.005).

Among the 674 patients, 68 were failing a first-line INSTI-based regimen: 41 containing raltegravir, 18 elvitegravir and 9 dolutegravir. Among the 41 patients failing to a raltegravir-based regimen, 11 (27%) harboured INSTI RAMs on their genotypic resistance test at failure: 4 with emergent mutations (1 L74I/M, 1 T97A, 1 Y143R, 1 V75I) and 7 for whom no baseline test was available: 3 L74I, 1 T97A, 1 E138K, 1 N155H, 1 E92Q + N155H, 1 T97A + N155H + E157Q. Among the 18 patients failing to an elvitegravir-based regimen, 7 (39%) harboured INSTI RAMs on their genotypic resistance test at failure: 5 with emergent mutations (1 T66I, 2 N155H, 1 E92Q + E157Q, 1 E92Q + S153Y + N155H) and 2 for whom no baseline test was available: 1 L74I + P145S, 1 N155H + S230R. Among the 9 patients

184 failing to a dolutegravir-based regimen, 3 harboured INSTI RAMs on genotypic resistance
185 test at failure but none were considered as emergent: 2 mutations were already present at
186 baseline (1 L74I and 1 E157Q) and 1 E138K for which no baseline test was available.
187 Interestingly, 7/41 (17%) of the patients failing a first-line raltegravir-based regimen had
188 plasma viruses with M184V (4 M184V alone and 3 with INSTI mutation). Among the 18
189 patients failing of a first-line elvitegravir-based regimen, 7 (39%) had INSTI RAMs and all of
190 them also displayed a M184V mutation, while it was 0/9 in patients failing a dolutegravir fist-
191 line regimen. However, the Fisher test did not show a significant association between the
192 emergence of the M184V mutation and INSTI treatment ($p = 0.07$).

193

194

Discussion

The development and expanding use of integrase inhibitors in ARV-naïve and ARV-experienced patients makes it increasingly important to survey INSTIs resistance in the context of large clinical settings.¹³ Here, we provide one of the largest data that characterizes INSTI resistance among INSTI failing patients obtained for clinical indications and in which collection of clinical and virological parameters were available.

Overall, our results show that 42% of patients' viruses experiencing failure to INSTI harbor viruses with at least one INSTI RAM. This rate is higher compared to a study that aimed to characterize INSTI resistance among integrase resistance testing obtained for clinical indications in the United States in which the investigators found that only 15.6% of viruses harbored INSTI major mutations.¹⁴ However, our results are similar to a more recent study showing that 39% of patients' viruses at time of failure to raltegravir harbor at least one INSTI resistance mutation.¹⁵ Methodological differences between studies can be noticed, as the predefined list of INSTI RAMs has evolved with the inclusion of new mutations over time. In addition, in the present study, we have analyzed failures to 3 different INSTIs and not only to raltegravir, as compared in the French study¹⁵ and in another study where the laboratory did not obtain data on the patient's treatment status (naïve or experienced) or history of prior ARV exposures.¹⁴ This point is crucial as INSTIs have different resistance profile and genetic barrier. Indeed, second-generation INSTIs, including dolutegravir display a more robust resistance profile than either raltegravir or elvitegravir and offer a higher barrier to resistance compared to the first-generation class.¹⁶ The resistance profile of dolutegravir has been extensively characterized during the past few years and high-level dolutegravir resistance requires multiple INSTI first-generation resistance mutations.³ This is supported by our results showing that at failure, only 14% and 7% of patients failing dolutegravir exhibited viruses considered genotypically resistant to dolutegravir OD and BID, respectively,

220 whereas 36% of patients failing raltegravir exhibited viruses considered resistant to raltegravir
221 and 44% of patients failing elvitegravir exhibited viruses considered resistant to elvitegravir.
222 Indeed, dolutegravir efficacy has been initially investigated in the VIKING Phase IIB study
223 where antiretroviral-experienced patients, with raltegravir and/or elvitegravir resistant viruses,
224 received DTG 50 mg either OD (Cohort I) or BID (Cohort II).¹⁷ In spite of the positive
225 results, the VIKING-3 study also highlighted how the dolutegravir response was most reduced
226 in subjects carrying viruses with resistance-associated mutations at position G140 and Q148.
227¹⁸ This mutation complex is known to cause up to a 10620-fold reduced susceptibility to
228 dolutegravir and, furthermore, subjects harboring viruses with Q148 + × 2 mutations have
229 96% lower odds of achieving VL <50 copies/mL at week 24 if compared with those with no
230 Q148 mutations.^{19,20} In addition, our results reinforce the robustness of dolutegravir
231 regarding selection of resistance in clinical practice as patients failing dolutegravir had
232 significantly less INSTI resistance mutations at failure as compared to patients failing
233 raltegravir or elvitegravir.

234 The most common resistance pathways identified in the present study were N155H/S/T,
235 L74F/I/M, Q148A/C/G/H/R/S and T97A. In addition, our findings corroborate previous
236 observations, indicating the unique propensity of subtype B to the development of the
237 Q148+G140 mutation pathway.²¹ A glycine to serine substitution at integrase position 140
238 requires only one nucleotide change in subtype B and two nucleotide changes in all non-B
239 clades, thus raising the genetic barrier to the emergence of G140 mutants. As mutations at
240 codon 140 play a key role in restoring the fitness of Q148 mutants, their occurrence can also
241 influence the emergence of Q148H/R/K, thus explaining the reduced prevalence of Q148
242 mutants observed in non-B subtypes. In the present study, some rare mutations have been also
243 evidenced, as the R263K mutation in two cases. The R263K mutation was the first mutation
244 rarely found selected at time of virological failure in experienced patients failing a first-line

dolutegravir -based treatment.⁹ Further *in vitro* studies on R263K mutants showed a moderate increase in phenotypic resistance level and a drastic reduction in viral replicative capacity. More recently, it has been shown that in both single and multiple rounds of HIV-1 infections, bictegravir and cabotegravir, two more recent INSTIs remained active against R263K mutant.²² Other mutations (i.e G118R and F121Y), rarely described in patients failing on raltegravir,²³ have been also shown to induce broad cross-resistance to dolutegravir *in vitro*.²⁴ However, we did not see evidence of either G118R or F121Y in this study.

Another interesting mutation is the E157Q mutation that is polymorphic, found between 1.7% and 5.6% of viral sequences issued from ART-naïve patients depending on the viral subtype; as well as acquired resistance emerging at failure of a raltegravir-based regimen in two case reports.²⁵ Data on phenotypic resistance level of E157Q mutants and virological response of patients harboring an E157Q virus initiating an INSTI-based regimen, showed that dolutegravir might be the most recommended INSTI in such patients.^{26,27} However, in the present study, 1/9 patients who failed DTG had a virus already harbouring a E157Q at baseline, thus it is difficult to give strong recommendations.

In clinical practice, it has been shown that after previous exposure to first-generation INSTIs, treatment with dolutegravir showed long durability and that subjects infected with a non-B HIV-1 subtype had a greater risk of having detectable VL at the last observation.²⁸ It is also important to determine, in case of virological failure, which factors are associated with the development of resistance mutations. In a previous study, we showed that a low GSS was associated with the presence of raltegravir-associated mutations and that a high HIV-1 VL level at failure (>1000 copies/mL) was associated with the presence of raltegravir-associated mutations.¹⁵ Here we reinforce this message showing that patients with high VL (> 3 log cp/mL) at failure and low GSS have a higher risk to select at least one INSTI RAM. This has

clinical consequences suggesting that careful attention should be paid to patients with detectable viral load under an INSTI regimen.

In this study we have made a special focus on failures in treatment-naïve patients. At failure, 27% of patients receiving raltegravir had emergent or not previously evidenced INSTI RAMs, 39% with elvitegravir and none with dolutegravir. In addition, 17% of patients failing raltegravir had plasma viruses with a M184V mutation (4 alone and 3 with INSTI mutation), 39% of patients failing elvitegravir (always associated with INSTI mutation) and none in patients failing dolutegravir. Our results corroborate data from clinical trials showing that raltegravir and elvitegravir have relatively low genetic barrier to the development of resistance with an overlapping resistance profile and do not protect NRTI backbone.²⁹ In treatment-naïve patients, data from clinical trial showed neither resistance mutation to INSTIs nor to NRTIs in the rare patients experiencing virological failure in the dolutegravir arm up to 96 weeks.⁶ Thus our data corroborate that the use of dolutegravir as first-line therapy in clinical practice should also prevent the development of INSTI and associated-NRTI drug resistance. However, this should be carefully monitored because despite a high barrier to resistance, no ARV agent is impervious to resistance and even it is extremely rare to date, dolutegravir failure and resistance in treatment naïve patients is possible.⁸

Overall, this paper describes one of the largest studies characterizing INSTI resistance among resistance testing obtained for clinical indications from naïve and experienced patients failing to raltegravir, elvitegravir and dolutegravir and reveals factors associated with resistance to INSTIs that should be taken into consideration in clinical management. The results confirmed the robustness of dolutegravir regarding resistance selection in case of virological failure in routine clinical care.

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Table 1. Baseline characteristics of the study population (n = 674)

Male	65 %
Subtype B	56 %
Median time since HIV-1 diagnosis, years (IQR)	15.7 (6.74-22.4)
Median duration of current INSTI regimen, months (IQR)	10.7 (5.7-30)
Median baseline plasma HIV-1 RNA log ₁₀ copies/mL (IQR)	3.1 (1.9-4.9)
Median failure plasma HIV-1 RNA log ₁₀ copies/mL (IQR)	2.9 (2.3-4)
Median baseline CD4 cell count/mm ³ (IQR)	371 (173-649)
Median failure CD4 cell count/mm ³ (IQR)	418 (223-670)
INSTI co-treatment (%):	
NRTIs	55.3 %
NRTIs + PIs	13.2 %
NNRTIs	7 %
PIs	5.6 %
NNRTIs + PIs	4.9 %
NRTIs + NNRTIs	3.8 %
Other	8.7 %
GSS Score (%):	
0-0.5	16.11%
1-1.5	27.22%
2-2.5	44.07%
>=3	12.59%

IQR, interquartile range; NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; INSTI, integrase strand transfer inhibitors, GSS, genotypic sensitivity score.

Table 2. Factors associated with the occurrence of INSTIs resistance associated mutations

		Univariate Analysis			Multivariate Analysis		
		OR	95% IC	P-value	OR	95% IC	P-value
Age (per 10 years increase)		1.115	0.977-1.273	0.1065			
CD4 baseline (per 100 cells/mm3 increase)		1.007	0.960-1.056	0.7764			
CD4 Failure (per 100 cells/mm3 increase)		0.988	0.941-1.038	0.6387			
Nadir CD4 (per 100 cells/mm3 increase)		0.99	0.902-1.087	0.8338			
Duration of Infection (per years increase)		1.018	1.001-1.035	0.0393			
Duration of INSTI treatment (per years increase)		1.052	0.982-1.126	0.1519			
LOG HIV RNA baseline (per 1 log10 copies/ml increase)		0.956	0.850-1.074	0.4478			
LOG HIV RNA Failure (per 1 log10 copies/ml increase)		1.345	1.165-1.553	<0.0001	1.223	1.027-1.456	0.0242
Viral subtype	CFR02 VS B	0.869	0.572-1.319	0.5425			
	NON B VS B	0.971	0.677-1.394	0.8239			
	1 or 1.5 VS 0 or 0.5	0.29	0.156-0.540	0.0715	0.293	0.156-0.551	0.1326
GSS	2 or 2.5 VS 0 or 0.5	0.101	0.056-0.184	<0.0001	0.116	0.063-0.213	<0.0001
	>=3 VS 0 or 0.5	0.075	0.035-0.162	<0.0001	0.079	0.036-0.174	<0.0001
Dual Therapy VS Triple Therapy		0.545	0.361-0.822	0.2545			
Dual Therapy VS Four and more Therapy		0.437	0.253-0.754	0.0235			
DTG VS RAL		0.406	0.270-0.610	<0.0001	0.567	0.345-0.931	0.0251
DTG VS EVG		0.362	0.226-0.581	<0.0001	0.448	0.254-0.789	0.0055

INSTI, integrase strand transfer inhibitors; OR, odds ratio; GSS, genotypic sensitivity score; DTG, dolutegravir; RAL, raltegravir; EVG, elvitegravir

Figure 1. Genotypic interpretation of resistance to different integrase strand transfer inhibitors (INSTIs) among the 674 patients failing an INSTI-containing regimen.
Predicted resistance to raltegravir (RAL), elvitegravir (EVG) and dolutegravir (DTG) once per day (OD) or twice daily (BID) according to the ANRS algorithm.

479 **Figure 2. Association between level of HIV viral load at failure and the selection of**
480 **integrase strand transfer inhibitors (INSTIs) resistance associated mutations (RAMs).**

481