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Cross-resistance to elvitegravir and dolutegravir in 502 patients failing on raltegravir: a French national study of raltegravir-experienced HIV-1-infected patients

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Objectives: The objectives of this study were to determine the prevalence and patterns of resistance to integrase strand transfer inhibitors (INSTIs) in patients experiencing virological failure on raltegravir-based ART and the impact on susceptibility to INSTIs (raltegravir, elvitegravir and dolutegravir).

Patients and methods: Data were collected from 502 treatment-experienced patients failing a raltegravir-containing regimen in a multicentre study. Reverse transcriptase, protease and integrase were sequenced at failure for each patient. INSTI resistance-associated mutations investigated were those included in the last ANRS genotypic algorithm (v23).

Results: Among the 502 patients, at failure, median baseline HIV-1 RNA (viral load) was 2.9 $\log_{10}$ copies/mL. Patients had been previously exposed to a median of five NRTIs, one NNRTI and three PIs. Seventy-one percent harboured HIV-1 subtype B and the most frequent non-B subtype was CRF02_AG (13.3%). The most frequent mutations observed were N155H/S (19.1%), Q148G/H/K/R (15.4%) and Y143C/G/H/R/S (6.7%). At failure, viruses were considered as fully susceptible to all INSTIs in 61.0% of cases, whilst 38.6% were considered as resistant to raltegravir, 34.9% to elvitegravir and 13.9% to dolutegravir. In the case of resistance to raltegravir, viruses were considered as susceptible to elvitegravir in 11% and to dolutegravir in 64% of cases. High HIV-1 viral load at failure ($P<0.001$) and low genotypic sensitivity score of the associated treatment with raltegravir ($P<0.001$) were associated with the presence of raltegravir-associated mutations at failure. Q148 mutations were selected more frequently in B subtypes versus non-B subtypes ($P=0.004$).

Conclusions: This study shows that a high proportion of viruses remain susceptible to dolutegravir in the case of failure on a raltegravir-containing regimen.

Keywords: integrase, inhibitors, mutations, patterns

Introduction

Advances in ART have markedly improved the prognosis of HIV infection. However, with increasing survival comes the need for new drugs that are well tolerated, efficacious and durable, and can salvage prior treatment failures. Integrase strand transfer inhibitors (INSTIs), that actively block the integration of the HIV genome into the host DNA, represent the most recent antiretroviral (ARV) class. Raltegravir and elvitegravir are first-generation INSTIs that have been used for HIV-infected patients. Despite the potency and tolerability of first-generation INSTIs, resistance mutations are detected in up to 60% of patients with virological failure in clinical trials studying highly treatment-experienced patients, and up to 8% in studies of initial therapy.[1,2] Recently, dolutegravir has been approved as a next-generation INSTI. In contrast to raltegravir and elvitegravir, which share a common resistance profile, dolutegravir has a resistance profile markedly distinct from those of first-generation INSTIs.[3]

There are three primary mutation pathways described for raltegravir: Y143, Q148 and N155.[4–6] E92Q is the most common initial mutation to arise during failure of elvitegravir-based regimens, followed by N155H and Q148R.[7] The broad cross-resistance profile between raltegravir and elvitegravir precludes their sequential use in individuals failing either of them. An accumulation of other secondary mutations under raltegravir or elvitegravir pressure over time can reduce susceptibility to dolutegravir. In two studies of dolutegravir among patients who failed raltegravir (VIKING and VIKING-3), the greatest reduction in dolutegravir susceptibility occurred when Q148 was accompanied by at least two other major mutations.[8,9]

Although INSTI mutation pathways have been extensively studied, most existing data arise from *in vitro* experiments or clinical trials with a limited number of patients and specific inclusion criteria. In this report, we focus on integrase genotypic resistance tests performed in a clinical setting from 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 raltegravir resistance mutations [genotypic sensitivity score (GSS), viral load and ARVs associated with raltegravir].

Patients and methods

Patients and ARV regimens

HIV-1-infected patients who experienced virological failure on a raltegravir-containing regimen were allowed to be included in the study. Patients were treated with raltegravir with a background regimen comprising mainly NRTIs, NNRTIs and/or PIs. Virological failure was defined as two consecutive HIV-1 viral loads >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 17 participating laboratories belong to the Agence Nationale de Recherches sur le SIDA (ANRS) AC11 network and participate in the annual ANRS quality control assessment of HIV-1 drug resistance sequencing.[10]

Genotypic resistance testing

The sequences of the protease (PR), reverse transcriptase (RT) and integrase (IN) genes were determined at failure in each laboratory using the ANRS consensus technique (http://www.hivfrenchresistance.org/), the Bayer TrueGene kit, the Abbott ViroSeq kit or an in-house method. For resistance interpretation, we used mutations present in the RT and PR genes and the ANRS algorithm to determine whether patients receiving a particular NRTI, NNRTI or PI had resistant, intermediate or susceptible virus strains. Similarly, IN sequences were analysed for the presence of INSTI resistance mutations T66K, L74M, E92Q, G118R, F121Y, E138K, G140A/C/S, Y143A/C/G/H/R/S, Q148E/G/H/K/R, V151L, S153Y/F, N155H/S/T, E157Q and R263K (www.hivfrenchresistance.org; September 2013, version 23).

The GSS of the current regimen (without raltegravir) was calculated according to the ANRS resistance algorithm. For each ARV 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 as medians and IQRs while categorical variables are described as percentages. HIV-1 RNA at failure, viral subtype (B versus non-B), GSS for PI and GSS for NRTI were investigated as potential factors in the occurrence of INSTI mutation by the use of the Cochran–Armitage test. A logistic regression model was also used to investigate whether previous variables were independent predictors of the occurrence of INSTI mutation.

Results

Overall, 502 treatment-experienced patients failing a raltegravir-containing regimen were included in the study from 17 French centres of the ANRS network. The main characteristics of the study population are presented in Table 1. The average age was 47.8 years (IQR=42–53 years) and the majority (74%) of patients were male; patients had previously been exposed to NRTIs (median=5; IQR=3–6), NNRTIs (median=1; IQR=0-1) and PIs (median=3; IQR=1-4) before starting a raltegravir-containing regimen. Twenty-one percent had been exposed to enfuvirtide and 3% to maraviroc. Regarding HIV-1 subtypes, 71% harboured subtype B and the most frequent non-B subtype

Table 1. Baseline characteristics of the study population (n=502)

Male, %	74
Subtype B, %	71
Plasma HIV-1 RNA $\log_{10}$ copies/mL, median (IQR)	2.9 (2.3–3.8)
CD4 cell count/mm^3, median (IQR)	218 (93–337)
Previous ART, median (IQR)	
number of ARV drugs	8 (5–11)
number of NRTIs	5 (3–6)
number of NNRTIs	1 (0–1)
number of PIs	3 (1–4)
Raltegravir co-treatment, %	
NRTIs	28
NRTIs+PIs	22
PIs	13
NRTIs+NNRTIs+PIs	7
NRTIs+PIs+other	6
NNRTIs+PIs	6
other	18

was CRF02_AG (13.3%). In the background regimen associated with raltegravir, patients received a median of two ARVs (IQR=2–3), 28% were receiving two NRTIs, 13% were receiving a PI and 22% were receiving NRTIs in association with a PI. The most frequent NRTIs prescribed were emtricitabine/lamivudine (64%), tenofovir (48%) and abacavir (22%); the most frequent PI was darunavir (35%) and etravirine was associated with raltegravir in 19% of cases. The GSS of the raltegravir-associated treatment was 0 in 11% of cases, 0.5 in 11%, 1 in 32%, 1.5 in 7%, 2 in 26%, 2.5 in 1% and ≥3 in 13%.

Virological failure occurred after a median time of 11 months (IQR=6–22) following administration of raltegravir. At failure, median viral load was 2.9 $\log_{10}$ copies/mL (IQR=2.3–3.8). Overall, viruses harboured no INSTI resistance-associated mutations and were thus considered as fully susceptible to all INSTIs in 61% of cases (n=306) while resistance to raltegravir, elvitegravir and dolutegravir was predicted in 38.6% (n=194), 34.9% (n=175) and 13.9% (n=70) of patients, respectively (Figure 1a). Among the 194 patients having a virus defined as resistant to raltegravir, 21 (11%) were considered genotypically as susceptible to elvitegravir and 124 (64%) to dolutegravir (Figure 1b).

Regarding INSTI resistance-associated mutations in our dataset, Q148 and N155 pathways predominated [observed in 77 (15.4%) and 96 (19.1%) patients, respectively], whereas Y143 was detected in 34 (6.7%) patients. The other INSTI mutations detected were T66A/K (n=3; 0.6%), E92Q (n=9; 1.8%), G118R (n=1; 0.2%), E138K (n=11; 2.2%), G140A/C/S (n=60; 12%), S147G (n=1; 0.2%) and E157Q (n=10; 2%). No patient had the R263K mutation. A mutation at Q148 was accompanied by a G140 mutation in 52 patients and by a E138 mutation in 10 patients. The N155 pathway accompanied Q148R in four patients and E92Q in five other patients (Figure 1b).

We aimed to characterize clinical and virological factors associated with the emergence of raltegravir-associated mutations and to investigate whether some factors might be related to the selection of a specific pathway [three major pathways (Q148, N155 and Y143) were investigated]. Regardless of the INSTI pathway of resistance, high HIV-1 viral load level at failure (P<0.001) and low GSS of the treatment with raltegravir (P<0.001) were associated with the presence of raltegravir-associated mutations (Figure 2). Both variables are independent factors of occurrence of INSTI mutation (logistic regression). Analysing factors associated with the INSTI pathway of resistance, we found that Q148 mutations were selected significantly more frequently in B subtypes versus non-B subtypes (P=0.004).

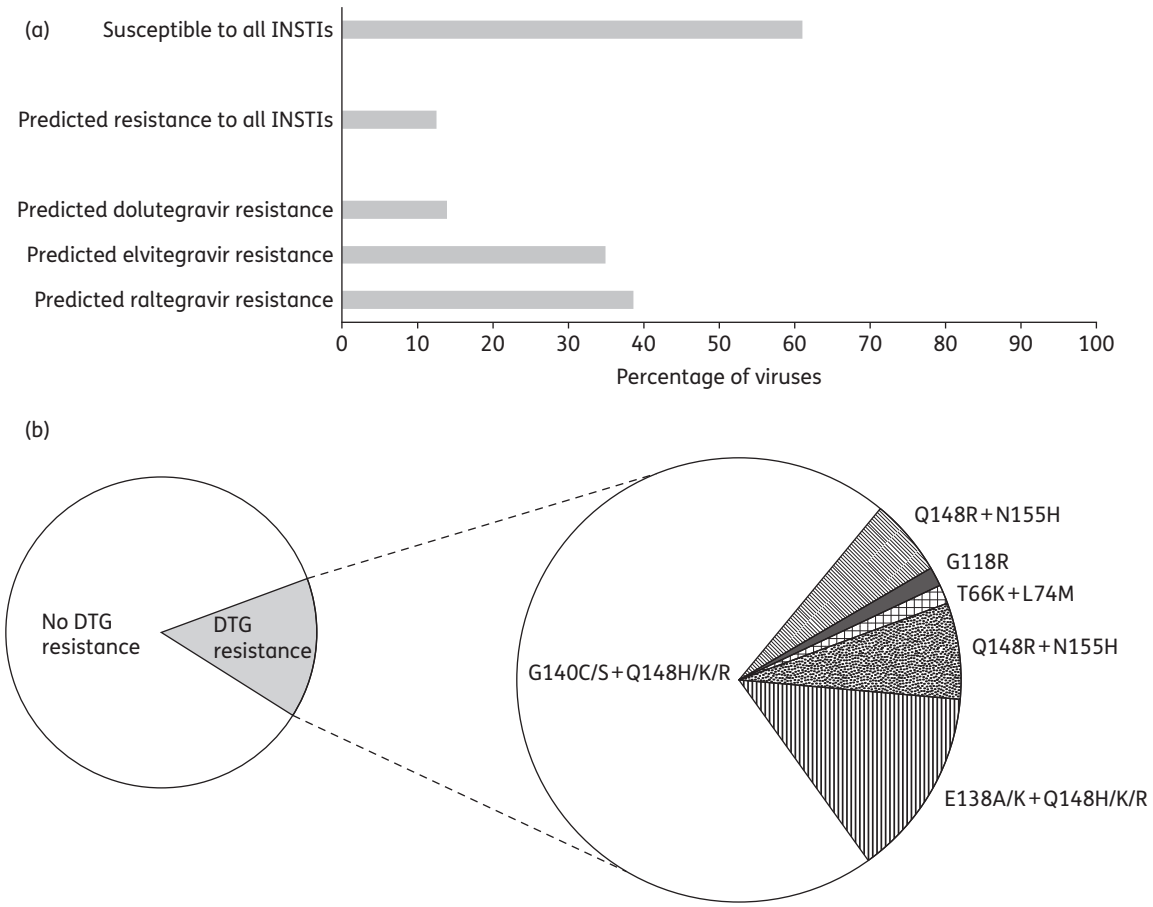

Figure 1. Prevalence of INSTI resistance-associated mutations in sequences from 502 patients failing a raltegravir-containing regimen. (a) Predicted resistance to raltegravir, elvitegravir and dolutegravir according to the last ANRS algorithm. (b) Distribution of mutations associated with dolutegravir resistance. DTG, dolutegravir.

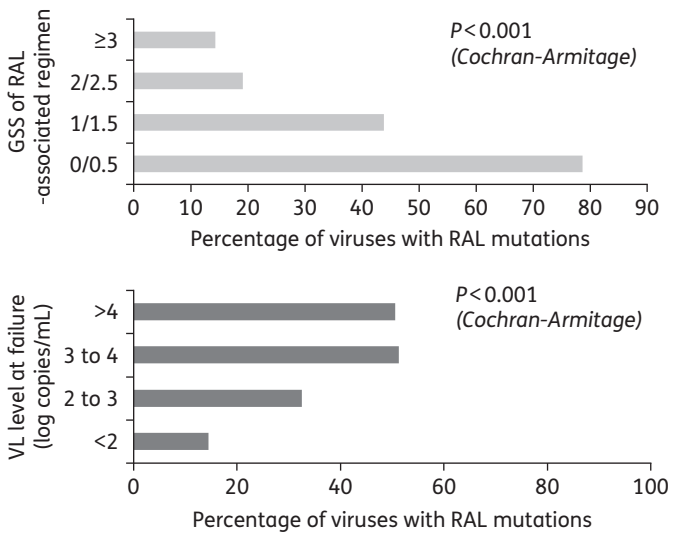

Figure 2. Factors associated with the selection of raltegravir resistance mutations. Three major pathways (N155, Q148 and Y143) were investigated independently or together. Regardless of the resistance pathway, high HIV-1 viral load level at failure ($P<0.001$) and low GSS of the treatment associated with raltegravir ($P<0.001$) were associated with the presence of raltegravir-associated mutations at failure. RAL, raltegravir; VL, viral load.

Discussion

The development and expansion of the use of integrase inhibitors in ARV-naive and -experienced patients makes it increasingly important to re-evaluate INSTI resistance in the context of large clinical settings. While elvitegravir became commercially available in France only a few months before the end of the study period, raltegravir has been used for several years. Several factors can influence the response to raltegravir, e.g. adherence, pharmacological profile, drug–drug interactions and the activity of the background regimen, which can be assessed by the GSS. Here, we provide a large dataset that characterizes INSTI resistance among raltegravir-experienced patients obtained for clinical indications, and in which treatment history, background regimen and viral load at treatment failure were available.

Overall, our results show that 39% of viruses of patients experiencing failure to raltegravir harbour at least one major INSTI resistance mutation. This rate shows a higher rate of resistance compared with a recent similar study that aimed to characterize INSTI resistance among integrase resistance testing obtained for clinical indications in the USA, in which the investigators found that only 15.6% of viruses harboured integrase major mutations.[11] This difference may be explained by different patient characteristics and data interpretation. In the US study, it was not reported whether resistance testing was performed at baseline or after failure to raltegravir, and the algorithms of resistance interpretation were different. In clinical trials, finding integrase mutations in approximately half of successfully genotyped subjects has been very common, especially in experienced subjects.[2] Again, methodological differences are noticed, as raltegravir resistance was investigated only when viral load was >400 copies/mL (our study defined virological failure as two consecutive viral loads >50 copies/mL). Alternatively, these data may underestimate INSTI resistance because mutations may be present as minority variants or could have developed and been archived as proviruses if patients had stopped therapy prior to the resistance testing.

Pathways of resistance to raltegravir involve primary mutations at positions N155, Q148 and Y143. Similarly to other studies,[11] we confirm the predominance of N155 and Q148 pathways observed in 96 (19.1%) and 77 (15.4%) patients, respectively, Y143 being detected in 34 patients (6.7%). Although second-generation INSTIs, including dolutegravir, display a more robust resistance profile than either raltegravir or elvitegravir and offer a higher barrier to resistance compared with the first-generation class,[12,13] we found that 14% of strains at failure were considered as resistant to dolutegravir. Dolutegravir resistance was predicted mainly in the context of G140 and Q148 substitutions. In the case of resistance to raltegravir, 64% of viruses were still considered genotypically susceptible to dolutegravir. These results are in line with VIKING trial results in which dolutegravir was introduced in ARV-experienced adults with historical or current evidence of resistance to raltegravir. VIKING-3 involved 183 patients failing a raltegravir-containing regimen; the proportion of subjects with undetectable viraemia (viral load <50 copies/mL) at week 24 was 69%. Virological response varied according to the genotype pathway of INSTI resistance. In subjects with Q148 pathway mutations, the virological response decreased with an increasing number of secondary mutations.[9] As high-level dolutegravir resistance requires multiple INSTI first-generation resistance mutations, a timely interruption of raltegravir/elvitegravir would prevent accumulation of resistance and should be considered in order to maximize the potential effect of dolutegravir. In our study, the efficacy of the subsequent regimen after the raltegravir-containing regimen failure was not recorded, thus further clinical observational studies would be necessary to evaluate the virological response to a subsequent regimen containing dolutegravir in such patients. However, the population studied here is less advanced than those included in the VIKING-3 study (median CD4 cell count 218 versus 123 cells/mm^3, number of prior ARTs 8 versus 14 and genotypic major INSTI resistance mutation detection 39% versus 67%), thus we assume that the use of dolutegravir would provide a virological response at least as good as in the VIKING-3 study.

Other resistance pathways have been identified with regard to dolutegravir in the absence of exposure to first-generation INSTIs. One major pathway involves R263K. This substitution was first selected *in vitro* by Quashie *et al.*[14] during *in vitro* passages under dolutegravir pressure and has been shown to confer low-level resistance to dolutegravir. Additional *in vitro* experiments evidenced secondary mutations to R263K (i.e. H51Y, E138K) that increased resistance to dolutegravir,[15,16] but led to severe attenuation of both viral replicative capacity and integrase strand transfer activity.[17] These findings may explain the fact that extremely rare individuals have progressed to virological failure with dolutegravir resistance mutations in clinical trials with INSTI-naive patients. Specifically, R263K has been observed in a study of ARV-experienced, INSTI-naive patients (SAILING) in only two patients (out of 354) failing a dolutegravir regimen.[18] In our dataset, R263K has never been observed, further confirming the infrequency of this mutation in clinical practice. Other mutations (i.e. G118R and F121Y), rarely described in patients failing on raltegravir,[19] have

also been shown to induce broad cross-resistance to dolutegravir *in vitro*.[20] In our study, G118R was detected in only one patient.

In treatment-naive patients of the SPRING-2 study no resistance mutation to INSTIs or NRTIs was detected in patients receiving dolutegravir even when suboptimal responses or viral rebound occurred up to 96 weeks.[21] Overall, resistance during dolutegravir is rare and probably limited to ARV-experienced patients. While raltegravir and elvitegravir are now among preferred agents as part of an ARV regimen for treatment-naive patients, these INSTIs have a relatively modest genetic barrier to the development of resistance with an overlapping resistance profile. The above-mentioned studies reveal that the use of dolutegravir in first-line therapy should prevent the facile development of drug resistance.

An important development in the analysis of HIV-1 drug resistance is the prediction of the activity of the background regimen as assessed by the GSS. In the context of resistance to a raltegravir-containing regimen, our group has shown that a GSS <2 in the current ARV regimen and HIV-RNA >200 copies/mL at failure are independently associated with the development of raltegravir resistance.[22] In the current study, we confirm that a low GSS is associated with the presence of raltegravir-associated mutations ($P<0.001$) and that a high HIV-1 viral load level at failure (>1000 copies/mL) is associated with the presence of raltegravir-associated mutations, regardless of the INSTI pathway of resistance ($P<0.001$). A similar relationship has been documented recently in the UK showing that the highest level of resistance is observed when the genotypes are determined with viral load between 1000 and 100 000 copies/mL.[23] Genotypes determined at viral loads <1000 copies/mL may represent blips or tests where we are unable to pick up early mutation development with population sequencing.

Regarding HIV-1 subtypes, INSTIs have been shown to be active against both B and non-B variants in culture and in patients.[4,24] However, little is known about differential impact of viral subtypes in INSTI resistance. HIV variability between subtypes at the nucleotide level can influence the genetic barrier, an important determinant for the development of resistance. In this context, our team has previously demonstrated that variability between subtypes B and CRF02_AG affected the genetic barrier for mutations G140C and G140S in the integrase gene. Such mutations often being associated with the Q148 pathway, they could make it more difficult for subtype CRF02_AG versus B to become resistant to raltegravir through the Q148 pathway. In the present dataset, our finding that Q148 mutations were selected more frequently in B subtypes versus non-B subtypes ($P=0.004$) corroborate this hypothesis.

Overall, this paper describes one of the largest studies to characterize INSTI resistance among integrase resistance testing obtained from patients failing on raltegravir for clinical indications and reveals factors associated with resistance to raltegravir that should be taken into consideration in clinical management.

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Transparency declarations

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