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Evaluation of integrase resistance in individuals who failed a regimen containing dolutegravir in French and Italian clinical settings

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Background: This work aims to evaluate integrase resistance and its predictors in HIV-1 infected combined antiretroviral therapy (cART) experienced individuals failing a dolutegravir-based regimen.

Methods: Major resistance mutations (MRM) and genotypic susceptibility score (GSS) of dolutegravir companion drugs were evaluated on plasma genotypic resistance test (GRT) performed at dolutegravir failure. Logistic regression was used to evaluate factors associated to the risk of integrase strand-transfer inhibitors (INSTI)-resistance at dolutegravir failure.

Results: We retrospectively analysed 467 individuals. At failure GRT, individuals had been under dolutegravir for a median (IQR) time of 11 (5–20) months; around half of them had never been exposed to INSTI (52%) and 10.7% were at first-line regimen. Fifty-eight (12.4%) individuals showed ≥1 INSTI MRM. Among them, people INSTI-exposed showed significantly higher prevalence of INSTI resistance compared to those who were INSTI naïve [46 (21.2%) versus 9 (3.9%), $P < 0.001$].
N155H was the most prevalent MRM (5.4%), followed by G140S (4.5%) and Q148H (4.3%). These MRM were more probably present in INSTI-experienced individuals compared to those INSTI naïve. Despite failure, 89.5% of individuals harboured viral strains fully susceptible to dolutegravir and bictegravir and 85.0% to all INSTI. No INSTI exposure before receiving dolutegravir [OR: 0.35 (0.16–0.78), $P < 0.010$] and a GSS for companion drugs ≥2 (OR: 0.09 [0.04–0.23], $P < 0.001$) were negatively associated with INSTI resistance at failure.

Conclusions: In a large set of individuals failing dolutegravir in real-life, INSTI resistance was low and mainly related to previous first-generation INSTI exposure. Surveillance of integrase resistance remains crucial to preserve efficacy of INSTI class in the future.

Background

The introduction of integrase strand-transfer inhibitors (INSTI) in the antiretroviral drug armamentarium was a milestone in the management of HIV-1 infection.[1] These drugs, for their potency and tolerability, saved many individuals without treatment options, and they are currently taking over non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI) based first-line treatments improving the quality of life of newly HIV-1 infected individuals.[2] Despite this, first-generation INSTI did not show a robust genetic barrier, and, even though they performed better than NNRTI, concerns about integrase resistance soon emerged.[3] However, the approval of dolutegravir (DTG) as a second-generation INSTI weakened those concerns because of its extraordinary genetic barrier.[3,4] In fact, previous studies (both registrational and observational) evaluating factors associated with the emergence of integrase resistance mutations demonstrated that DTG usage is associated with a lower risk in acquiring INSTI resistance.[5–9]

After a decade of wide usage of DTG in clinical practice, with the only exception regarding DTG monotherapy,[10] virological failures under this INSTI have been rarely recorded and most of the individuals failing DTG do not acquire new resistance mutations.[11,12] This phenomenon was so intriguing that several studies were performed to identify potential genomic areas outside HIV-1 integrase, such as the 3′-polypurine tract (3′-PPT), in which

atypical resistance to DTG[13–15] might arise. However, the analysis of these potential new resistance target areas is still not implemented in clinical routine. Moreover, the collection of a consistent number of genotypic resistance tests (GRT) at DTG failure is difficult due to the rarity of failure events often observed in a context of low-level viremia. On the basis of these considerations, a large international surveillance of INSTI resistance observed under DTG is, at present, the only way to have a clearer picture of DTG resistance from clinical practice. Thus, this work aims to evaluate integrase resistance and its predictors in HIV-1 infected individuals who failed a DTG-based regimen in real-life settings in France and Italy.

Materials and methods

Study population

This is a retrospective observational study including several clinical and virological centres involved in HIV care in France and Italy.

Adult individuals (age ≥18 years) who experienced virological failure under a DTG-containing regimen for whom a plasma HIV-1 RNA GRT was performed at the moment of virological failure were included. Virological failure was defined as two consecutive plasma HIV-RNA >50 copies/mL under DTG treatment.

Ethics

This study was approved by the scientific committee of the ANRS-MIE AC43 and ethics committee of Tor Vergata Hospital (Ethics Approval No. 119/16, 12 July 2016). The research was conducted on anonymous samples in accordance with the principles of the Declaration of Helsinki and the Italian Ministry of Health. All information, including virological and clinical data, was recorded in an anonymized database.

Sanger sequencing and drug resistance evaluation

Sanger sequencing for protease, reverse transcriptase (RT) and integrase was performed at each reference laboratory during the standard follow-up of patients. Resistance interpretation was made according to the Stanford algorithm (HIVdb v.9.1, https://hivdb.stanford.edu/). For each individual, resistance to PI, nucleos(t)ide RT inhibitors (NRTI), NNRTI and INSTI was evaluated by considering major resistance mutations (MRM) detected in the GRT performed at DTG failure. Accessory resistance mutations (ARM) to INSTI were also considered. Genotypic susceptibility score for companion drugs (GSS) included in the current regimen containing DTG was carried out using the Stanford algorithm (https://hivdb.stanford.edu/hivalg/by-mutations/). Individuals with GSS ≥ 2 and GSS < 2 were considered as harbouring viral strains fully and partially susceptible to companion drugs, respectively.

Moreover, GSS to each INSTI was also calculated to evaluate resistance to DTG and cross-resistance to bictegravir, elvitegravir and raltegravir at DTG failure.

Statistical analysis

A descriptive analysis was performed on the overall population. Quantitative variables were described as median and interquartile range (IQR) whereas categorical variables were described as a percentage. Comparison between groups of patients was carried out using either Fisher's exact test or Chi-Squared test. Sex, age, HIV-1 subtype, nadir CD4 count, CD4 count and plasma HIV-1 RNA at DTG start and failure, time under DTG at failure, time since HIV-1 diagnosis, drug-naïve status at DTG start, previous INSTI exposure and GSS were investigated as potential factors in the occurrence of at least one INSTI MRM 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.

All analyses were executed using SAS v.9.4 (Cary, NC, USA). For all the analyses, $P < 0.05$ were considered significant.

Results

Patients' characteristics at DTG start

Overall, 467 individuals composed mainly of males (61.9%) with a median (IQR) age of 49 (39–55) were analysed (Table 1). They had a long history of HIV-1 infection with a median (IQR) of 15 (5–22) years since HIV diagnosis and low median (IQR) CD4 cell count nadir [129 (35–273) cell/mm^3]; 24.6% had viremia ≤50 copies/mL at DTG start. Around half of the individuals were infected with non-B subtype (44.2%), mainly with CRF02_AG and heterogenous recombinant forms. Before DTG failure, around half of the individuals were never exposed to INSTI, whereas, among those who were INSTI-experienced, individuals received mainly raltegravir and DTG. At failure, 330 (70.7%) individuals were receiving DTG in a triple regimen, in particular DTG plus two NRTI (62.7%), followed by heterogeneous combinations of three or more drugs in the DTG-containing regimen (19.0%). Concerning regimens containing fewer than three drugs, 72 individuals (15.4%) experienced failure to DTG-based dual therapy and 13 (2.8%) to DTG monotherapy.

Viro-immunological parameters and resistance at DTG failure.

At failure, individuals were under DTG for a median (IQR) time of 11.2 (5.4–20.3) months with a median (IQR) viremia and CD4 count of 2.8 (2.2–4.1) $\log_{10}$ copies/mL and 380 (191–625) cells/mm^3, respectively (Table 1). Overall, 58 (12.4%) individuals showed at least one INSTI MRM. The proportion of individuals showing integrase resistance at DTG failure was significantly higher in people previously exposed to INSTI compared to those who were INSTI naïve [46 (21.2%) versus 9 (3.9%), $P < 0.001$]. A detailed overview of viro-immunological parameters, resistance detected and previous ARVs received in individuals harbouring INSTI resistance is reported in Supplementary Tables S1 and S2 (available as Supplementary data at *JAC* Online) for the 46 INSTI-experienced individuals and in Table 3 for the nine INSTI-naïve individuals.

Patients who received a regimen containing three drugs showed a lower prevalence of INSTI resistance [24/330 (7.3%)] at DTG failure compared to those who failed a DTG-based dual therapy [13/72 (18.1%), $P = 0.01$]. This difference was more prominent among those who failed an NNRTI-containing regimen (triple therapy 7.2%; dual therapy 33.3%, $P = 0.001$), whereas the comparison was not significant in patients receiving PI-containing regimens (triple therapy 7.2%; dual therapy 13.1%, $P = 0.203$).

Among specific INSTI MRM, N155H was the most prevalent mutation observed, followed by G140S and Q148H. MRM R263K and G118R, specifically related to DTG, showed a prevalence <2% [Figure 1(a)]. Concerning ARM to INSTI, L74I was the most prevalent mutation (9.2%) mainly observed in individuals infected by heterogeneous subtypes (CRF02_AG 27.9%; A 23.3%;

Table 1. Patients' characteristics

Variables	Overall ($n=467$)
Male gender, *n* (%)	289 (61.9)
Age	49 (39–55)
Subtype, *n* (%)	
B	248 (53.1)
CRF02_AG	82 (17.6)
G	17 (3.6)
F	13 (2.8)
A1	11 (2.4)
Unknown	13 (2.8)
Others[a]	83 (17.8)
Time since HIV Infection, years, median (IQR)	15 (5–22)
Nadir CD4 cell count (cells/mm^3), median (IQR)	129 (35–273)
Baseline CD4 cell count (cells/mm^3), median (IQR)	358 (170–632)
Baseline Viremia (log_{10} copies/mL), median (IQR)[b]	2.6 (1.6–4.6)
Baseline Viremia, copies/mL (%)[b]	
≤50 copies/mL	115 (24.6)
51–1000 copies/mL	122 (26.1)
1001–100 000 copies/mL	101 (21.6)
>100 000 copies/mL	68 (14.6)
Unknown	61 (13.1)
Previous INSTI experience	
INSTI naïve, *n* (%)	233 (50.0)
RAL	142 (30.0)
EVG	38 (8.1)
DTG	85 (18.2)
Unknown	17 (4.0)
First-line regimen, *n* (%)	47 (10.1)
Type of regimen and DTG companion drugs	
Monotherapy	13 (2.8)
Dual therapy	72 (15.4)
With NRTI[c]	12 (2.6)
With NNRTI[d]	21 (4.5)
With PI	38 (8.1)
Other	1 (0.2)
Triple therapy	330 (70.7)
With NRTIs	293 (62.7)
With NRTI + PI	12 (2.6)
With NRTI + NNRTI	3 (0.6)
With NNRTI + PI	9 (1.9)
With PIs	2 (0.4)
Other	11 (2.4)
Therapy based on four or more drugs	52 (11.1)
CD4 cell count (cells/mm^3) at failure, median (IQR)	380 (191–625)
Viremia (log_{10} copies/mL) at failure, median (IQR)	2.8 (2.2–4.1)
Time under DTG before failure, months, median (IQR)	11.2 (5.4–20.3)

[a]CRF06_cpx, A, C, CRF11_cpx, D, CRF12_BF, CRF22, A6, CRF01_AE, CRF14_BG, CRF42_BF, F1, H, A3, CRF09, CRF13_cpx, CRF17_BF, CRF18_CPX, CRF28_BF, CRF40_BF, CRF45_CPX, CRF46_BF, CRF51_01B, CRF71_BF1, CRF94, F2.

[b]Available for 406 individuals.

[c]Lamivudine, $n=10$; abacavir, $n=1$; tenofovir, $n=1$.

[d]Rilpivirine, $n=16$; etravirine, $n=3$; nevirapine, $n=2$.

B 20.9%; G 9.7%; other CRF 18.6%), followed by T97A (6.9%). All the other INSTI ARM showed a prevalence <4% [Figure 1(c)].

By stratifying the prevalence of INSTI-resistance mutations according to previous INSTI experience, the most prevalent MRM N155H, G140S, Q148H, E138K, S147G and the ARM T97A and G163R were significantly more likely to be observed in those individuals who previously experienced an INSTI before DTG failure compared to those who were never exposed to INSTIs [Figure 1(b–d)].

Despite DTG failure, 89.5% of individuals harboured viral strains fully susceptible to DTG and bictegravir and 85.0% to all INSTI. Concerning cross-resistance to first-generation INSTI, 85.4% and 85.2% of individuals harboured viral strains fully susceptible to raltegravir and elvitegravir, respectively.

By multivariable logistic regression, individuals who were INSTI naïve before DTG failure and those receiving fully active companion drugs showed a significantly decreased risk in developing INSTI resistance at DTG failure (Table 2). No factors were positively associated with resistance development.

An overview of resistance observed in the nine INSTI-naïve individuals is reported in Table 3. At DTG start, most of them (six, 66.6%) were combined antiretroviral therapy (cART)-experienced. Two of them who showed exclusively INSTI resistance, had received a DTG monotherapy (ID 1 and 2). Among the remaining four individuals, nobody showed complex resistance patterns. They had baseline viremia <500 copies/mL and showed resistance to one or two classes at failure.

Among the three individuals who failed their first-line DTG treatment, two individuals showed resistance only to INSTI (ID 4 and 6 with E138K), while one to INSTI and NRTI (ID10: R263K + M184V). E138K and R263K are mutations rarely observed in naïve individuals and their constitutive presence cannot be excluded.

Discussion

Considering the rarity of failure events under regimens containing DTG, as far we know, this study is one of the largest international surveys of DTG resistance in clinical practice. We confirmed the high genetic barrier of DTG, observing INSTI resistance in 12% of cART experienced individuals who failed a DTG-based regimen.

To our knowledge, estimating the rate of acquired DTG resistance in observational settings is still challenging. In fact, observational studies evaluating INSTI resistance in individuals who failed a DTG-containing regimen are very few and often resistance information is difficult to extrapolate due to the small number of failures.[5,9,16–18] In this regard, in one Italian study, a considerable proportion (42.9%) of individuals under INSTI showed at least low-level resistance to any INSTI, but among the subgroup of 51 individuals who failed DTG it was not possible to extrapolate the rate of acquired INSTI resistance.[16]

Nevertheless, recent systematic reviews indicated that development of resistance to DTG remains rare.[6,19]

In the present study, we found that INSTI resistance increased in individuals who failed dual therapies containing DTG, mainly when in combination with an NNRTI. On this point, it is already known that, even though dual therapy based on DTG plus an

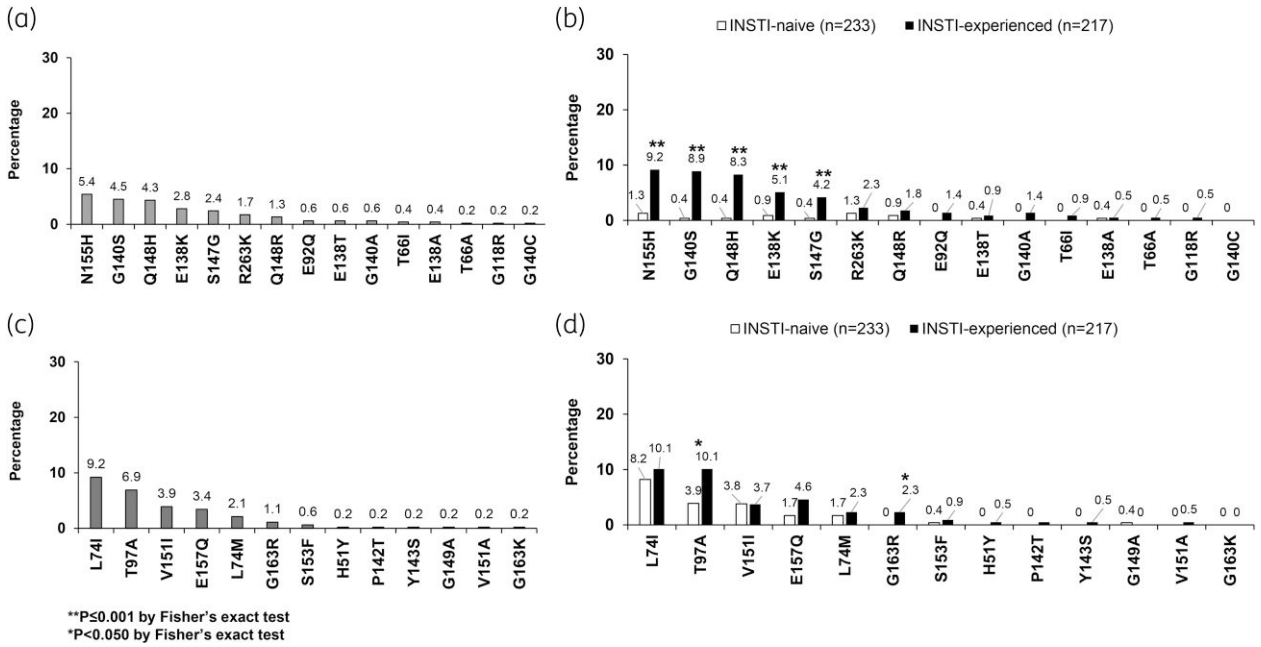

Figure 1. Prevalence of resistance mutations associated to INSTI detected in the GRT performed at failure under a dolutegravir containing regimen. (a) Prevalence of MRM in the overall population. (b) Prevalence of MRM stratified according to previous exposure to INSTI. (c) Prevalence of ARM in the overall population. (d) Prevalence of ARM stratified according to previous exposure to INSTI. *P* values were calculated by using the Fisher's exact test or chi-squared test, when appropriate. $P < 0.05$ was considered statistically significant. $^{**}P \leq 0.001$; $^{*}P < 0.05$.

Table 2. Factors associated with the presence of INSTI resistance at dolutegravir failure

	Risk to have at least one INSTI major resistance mutation at DTG failure					
	Crude			Adjusted		
Variables	OR	95%CI	*P*[a]	OR	95%CI	*P*
Female versus male	0.64	0.35–1.20	0.160			
Age (per 10 years increase)	**1.29**	**1.01–1.60**	**0.040**	1.05	0.78–1.43	0.730
Subtype non-B versus B	0.62	0.35–1.10	0.100			
Baseline CD4 (per 100 cells/mm^3 increase)	0.97	0.88–1.10	0.550			
CD4 at failure (per 100 cells/mm^3 increase)	0.99	0.90–1.10	0.790			
Nadir CD4 (per 100 cells/mm^3 increase)	0.92	0.78–1.10	0.340			
Plasma HIV-RNA at failure (per 1 log increase)	1.17	0.94–1.45	0.170			
Plasma HIV-RNA at baseline (per 1 log increase)	1.10	0.91–1.32	0.330			
Time under dolutegravir (per 1 year increase)	1.10	0.84–1.33	0.640			
Duration since HIV diagnosis (per 5 years increase)	**1.21**	**1.04–1.4**	**0.010**	0.97	0.80–1.18	0.770
First-line therapy	0.48	0.15–1.60	0.240			
INSTI naive	**0.15**	**0.07–0.32**	**<0.001**	**0.25**	**0.10–0.60**	**0.002**
GSS of companion drugs (>2 versus <2)	**0.07**	**0.03–0.17**	**<0.001**	**0.11**	**0.04–0.27**	**<0.001**

[a]$P < 0.05$ are indicated in bold. 95%CI: 95% confidence interval. OR: odds ratio.

NNRTI showed excellent results in clinical trials[20,21] and observational studies,[22–25] signal of increased risk of virological failure was found in the presence of previous NNRTI resistance.[26] According with these considerations, individual candidates to switch to dual therapies containing DTG and NNRTI should be carefully selected to avoid potential resistance selection and need particular attention.

Another important finding related to the present DTG resistance survey, is related to the detection of INSTI resistance in INSTI-naïve individuals at DTG failure. In this regard, excluding

Table 3. Overview of resistance detected at dolutegravir failure in individuals never exposed to INSTI before DTG switch

ID	Viremia at baseline (copies/mL)	Regimen containing DTG	cART naïve at DTG start	ARVs received before DTG start	Subtype	Time under DTG (months)	Viremia at failure (copies/mL)	Resistance detected at DTG failure					GSS for companion drugs	GSS for INSTI			
								PI	NRTI	NNRTI	INSTI	INSTI accessory		RAL	EVG	BIC	DTG
10	1,760,695	*3TC TDF DTG*	Yes	None	C	7.0	432	None	M184V	None	R263K	None	1	I	I	I	I
4	3,231,480	*3TC DTG*	Yes	None	B	0.5	321	Na	Na	Na	E138K	None	Na	I	I	S	S
6	168,149	*ABC 3TC DTG*	Yes	None	CRF94_cpx	7.8	115	None	None	None	E138K	G140E, D232N	2	I	I	S	S
1	<20	*DTG*	No	RPV, ATV, DRV, RTV, XTC	B	8.6	63,000	None	none	None	S147G, N155H	T97A	Na	R	R	I	I
2	<20	*DTG*	No	AZT, DDI, NVP, RPV, IDV, RTV, XTC	B	36.4	1,670,000	Na	Na	Na	N155H, R263K	None	Na	R	R	R	R
3	<20	*RPV DTG*	No	AZT, DDI, NVP, LPV, RTV, XTC	G	44.4	1500	None	None	K103N, E138G,	E92A, N155H	T97A	0	R	R	S	S
8	<50	*ABC 3TC DTG*	No	ABC, AZT, LPV, SQV, RTV, XTC	B	7.4	174	None	None	None	E138T, G140S, Q148H	T97A	2	R	R	R	R
9	<40	*ABC 3TC DTG*	No	ABC, AZT, LPV, RTV, XTC	G	51.5	8128	None	M184V	None	R263K	None	0.5	I	I	I	I
11	316	*ABC 3TC DTG*	No	AZT, LPV, RTV, XTC	CRF02_AG	26.5	12,600	None	None	None	E138A	G149A	2	I	I	S	S

ABC, abacavir; ATV, atazanavir; AZT, zidovudine; DDI, didanosine; DRV, darunavir; IDV, indinavir; LPV, lopinavir; Na, not available; NVP, nevirapina; RPV, rilpivirine; RTV, ritonavir; SQV, saquinavir; XTC, lamivudine/emtricitabine.

those individuals who failed DTG monotherapy, known as suboptimal strategy,[10] seven (3.0%) individuals showed INSTI resistance and among them three were at first-line treatment. Among these three individuals who showed resistance under first-line DTG-based regimen, we observed several surveillance INSTI drug resistance mutations,[27,28] but we could not assess whether resistance had really been acquired under first-line regimen because of the lack of information on genotypic resistance before DTG started.

These results demonstrated that in treatment-naïve people, even though INSTI resistance remains uncommon being observed in only three individuals under first-line DTG-based treatment, it is slightly higher than those observed in metanalyses performed on clinical trials[19] and observational studies,[27,29]

However, we should consider that the findings of our INSTI-resistance survey are retrieved from a large collection of DTG failures from real life. In this context, it is plausible to identify patients at higher risk of treatment failure with DTG resistance. In fact, individuals with severe immunosuppression or poor adherence are usually under-represented in licensing studies;[19] but, in a large observational study such as this, these individuals can be recruited.

At DTG failure, we found that R263K and G118R, specifically related to DTG,[29,30] were rarely observed, whereas the most prevalent MRM detected were mainly those already observed in individuals failing first-generation INSTI.[31]

Besides major resistance, L74I polymorphism, previously described as a risk factor related to failures of the long-acting regimen based on cabotegravir and rilpivirine together with subtype A1/A6 and body mass index.[32,33] showed a considerable presence. However, in the context of this study, with regards to people who failed a DTG-based regimen not being eligible to start a long-acting strategy containing cabotegravir, concerns about L74I are needless.[34,35] Another important natural polymorphism, T97A, was found with a prevalence of 6.9%. As previously described, T97A is a common polymorphic INSTI-resistance mutation. It has a prevalence between 1% and 5% among INSTI-naïve persons depending on subtype.[36,37] Recent studies demonstrated that this mutation, when added in individuals with prior INSTI resistance, can increase DTG resistance[38] and provides a strong selective advantage persisting for months after discontinuing DTG.[39] We could not assess whether in the present cohort T97A emerged under DTG or was previously present; but, due to the fact that we found a non-negligible prevalence of T97A in INSTI-naïve individuals (4.2%), the surveillance of this mutation deserves attention.

Concerning predictors of resistance, we found that they are mainly related to patient's previous history. In fact, among the demographic, viro-immunological and therapeutic parameters evaluated, only to be INSTI naïve and receiving fully active companion drugs with DTG were factors significantly associated with absence of INSTI resistance at failure.

However, these predictors are related to the presence of INSTI MRM in the overall population (mainly represented by individuals receiving DTG as part of triple therapies) and, even though we found resistance in INSTI-naïve individuals, due to the low numbers related to this phenomenon, we still cannot assess its predictors. The full activity of companion drugs, in the case of dual therapies remain.

Further large studies on *ad hoc* populations are necessary to provide more information and fulfil this unmet clinical need.

This study might have some limitations. First, we collected only GRTs performed at DTG failure. In this context we could only hypothesize a relationship with a previous exposure to INSTI drugs and resistance at DTG failure. In this regard, we should underline that, at the moment of DTG start in our cohort, guidelines did not recommend integrase genotyping in INSTI-naïve individuals. Moreover, because this study is retrospective and based on data retrieved from clinical routine, factors such as adherence or biases related to missing data or clinicians' decisions might have affected the analyses performed.

In conclusion, the present study confirms that the number of individuals that fail a DTG-containing regimen with INSTI resistance remains low, and it is mainly related with previous INSTI failures. However, resistance in INSTI-naïve individuals is not absent and suboptimal activity of companion drugs might be a trigger for integrase resistance emergence. These observations reinforce the fact that collecting additional data on the surveillance of INSTI resistance remains crucial for all individuals who need to receive a second-generation INSTI to avoid resistance accumulation and jeopardize efficacy of this drug class in the future.

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Transparency declarations

The authors have nothing to declare.

Supplementary data

Tables S1 and S2 are available as Supplementary data at *JAC* Online.

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