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Integrase strand transfer inhibitor-based regimen is related with a limited HIV-1 V3 loop evolution in clinical practice

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Abstract

Integrase-strand-transfer inhibitors (INSTIs) are known to rapidly reduce HIV-1 plasma viral load, replication cycles, and new viral integrations, thus potentially limiting viral evolution. Here, we assessed the role of INSTIs on HIV-1 V3 evolution in a cohort of 89 HIV-1-infected individuals starting an INSTI- ($N=41$, [dolutegravir: $N=1$; elvitegravir: $N=3$; raltegravir: $N=37$]) or a non-INSTI-based ($N=48$) combined antiretroviral therapy (cART), with two plasma RNA V3 genotypic tests available (one before [baseline] and one during cART). V3 sequences were analysed for genetic distance (Tajima-Nei model) and positive selection (dN/dS ratio). Individuals were mainly infected by B subtype (71.9%). Median (interquartile-range, IQR) plasma viral load and CD4 + T cell count at baseline were 4.8 (3.5–5.5) $\log_{10}$ copies/mL and 207 (67–441) cells/mm^3, respectively. Genetic distance (median, IQR) between the V3 sequences obtained during cART and those obtained at baseline was 0.04 (0.01–0.07). By considering treatment, genetic distance was significantly lower in INSTI-treated than in non-INSTI-treated individuals (median [IQR]: 0.03[0.01–0.04] vs. 0.05[0.02–0.08], $p=0.026$). In line with this, a positive selection (defined as dN/dS ≥ 1) was observed in 36.6% of V3 sequences belonging to the INSTI-treated group and in 56.3% of non-INSTI group ($p=0.05$). Multivariable logistic regression confirmed the independent correlation of INSTI-based regimens with a lower probability of both V3 evolution (adjusted odds-ratio: 0.35 [confidence interval (CI) 0.13–0.88], $p=0.027$) and positive selection (even if with a trend) (adjusted odds-ratio: 0.46 [CI 0.19–1.11], $p=0.083$). Overall, this study suggests a role of INSTI-based regimen in limiting HIV-1 V3 evolution over time. Further studies are required to confirm these findings.

Keywords HIV-1 · Integrase inhibitors · V3 · HIV-1 evolution · HIV-1 tropism

Introduction

HIV-1 co-receptor usage is of central pathological importance due to its strict correlation with the rate of disease progression in HIV-1-infected individuals [1, 2]. Among the different HIV-1 gp120 domains, the V3-loop is recognized as the primary determinant for co-receptor tropism [3, 4], and its evolution may consequently determine a switch from the less pathogenic CCR5-using- to the more pathogenic CXCR4-using virus [5, 6]. This phenomenon was frequently observed both in untreated patients, before the advent of combined antiretroviral therapy (cART), and in patients under cART [7–9].

Integrase strand transfer inhibitors (INSTIs) are the newest and most frequently used class of antiretroviral agents [10, 11] both for treatment-naïve patients and for simplification strategies [12, 13].

The preferential use in clinical practice of INSTIs compared to other drug classes partly derives from their ability to promote a faster HIV-1 viral load decay [14–20] favouring long-term efficacy of treatment [21]. Consistently with

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these data, findings suggest that INSTI-based regimens may also significantly reduce total HIV-1 DNA in virologically suppressed HIV-1-infected patients [22], and limit HIV-1 evolution and drug resistance development [23, 24].

This proof of concept study was aimed at defining the impact of INSTIs on HIV-1 V3 evolution and, as consequence, co-receptor modification in clinical practice.

Materials and methods

Study population

The study included 89 HIV-1-infected individuals selected from a large Italian anonymous database collecting data for HIV-1-infected patients followed at several clinical centres in Central Italy and from the ARCA database (http://www.dbarca.net). Eligible individuals were those for whom two plasma HIV-1 RNA V3 sequences were available, one at baseline of INSTI- or non-INSTI based regimen (defined as current cART; range: 0–18 weeks before) and one during current cART (range: 3–210 weeks after). Of these individuals, 41 started treatment with an INSTI-based regimen (dolutegravir: $N=1$; elvitegravir: $N=3$; raltegravir: $N=37$) and 48 with a non-INSTI-based regimen (2 nucleos(t)ide reverse transcriptase inhibitors [NRTIs] + 1 non-NRTI [NNRTI]: $N=12$; 2 NRTIs + 1 protease inhibitor [PI]: $N=35$; 1 NNRTI + 1 PI: $N=1$). Maraviroc-containing regimens were excluded from the study.

All V3 sequences were obtained using a national recognized protocol for Sanger sequencing, characterized by a high rate of efficiency and sensitivity, designed in the framework of the OSCAR programme [25].

Analysis of HIV-1 V3 sequences

V3 evolution was evaluated by estimating both genetic distance (based on Tajima Nei model, Mega6 [26]) and non-synonymous/synonymous substitution rate (dN/dS, based on Nei and Gojobori method, SNAP [27]) between the V3 sequences during cART and V3 sequences at baseline.

For each HIV-1 V3 sequence, HIV-1 tropism was assessed using the Geno2pheno algorithm available at http://coreceptor.bioinf.mpi-inf.mpg.de/ [28].

Statistical analyses

Fisher's exact test (for categorical variables) and Mann–Whitney test (for quantitative variables) were used to define statistically significant differences between V3 sequences derived from INSTI- and non-INSTI treated individuals ($p<0.05$).

Multivariable logistic regression analysis was performed to evaluate the impact of INSTI on pronounced V3 evolution (defined as a genetic distance higher than the median overall value, >0.04), and positive selection (defined as a $dN/dS \geq 1$) (for further details please refer to Supplementary Text).

All these analyses were performed using the statistical software package SPSS (version 19.0) for Windows (SPSS Inc., Chicago, IL, USA) and R for Windows (version 3.4.2).

Results and discussion

Patient characteristics

The population was mainly composed by males (68.5%) with a median (IQR) age of 40 (33–50) years (Table 1). The majority of individuals were infected by HIV-1 subtype B (71.9%).

Looking at the differences between INSTI- and non-INSTI-treated groups, only 5 INSTI-treated patients (12.2%) were at their first-line regimen with respect to 31 (64.6%) of non-INSTI treated individuals ($p<0.001$). In line with this, the cumulative duration of cART was longer in INSTI-treated individuals compared to the non-INSTI group (13.2 [5.6–17.9] vs. 4.1 [1.9–6.4] years, $p<0.001$). INSTI-treated individuals were characterized by a lower plasma viral load both at baseline (4.3 [2.5–5.0] vs. 5.0 [4.3–5.6] $\log_{10}$ copies/mL, $p=0.013$) and at zenith during cART (3.0 [2.3–4.8] vs. 4.2 [3.0–5.1] $\log_{10}$ copies/mL, $p=0.010$), compared to non-INSTI treated individuals. No significant differences were observed in percentage of individuals experiencing viral failure, CD4 + T cell count, resistance to at least one drug, genotypic susceptibility score (GSS) and false-positive rate (FPR) neither at baseline nor during cART between the two groups.

Detailed information regarding time points of viral load measurements, V3 sequencing and co-administrated drugs are present in Supplementary Fig. 1.

Impact of INSTI on V3 evolution and FPR change

Overall genetic distance (median [IQR]) between the V3 sequences at baseline and those obtained during cART was 0.04 (0.01–0.07). Genetic distance was lower in INSTI-treated than in non-INSTI treated individuals (median [IQR]: 0.03 [0.01–0.04] vs. 0.05 [0.02–0.08], $p=0.026$) (Fig. 1a). In line with these results, 15 (36.6%) V3 sequences belonging to the INSTI-treated group evolved towards a positive selection (defined as a $dN/dS \geq 1$) with respect to 27 (56.3%) in the non-INSTI group ($p=0.05$) (Fig. 1b). Looking at delta viral load and delta CD4 + T cell count between the V3 sequences at baseline and those obtained

Table 1 Patients' characteristics

Variables	Overall ($N=89$)	INSTI-based regimen ($N=41$)	Non-INSTI-based regimen ($N=48$)	p value[a]
Male, *n* (%)	61 (68.5)	29 (70.7)	32 (66.7)	0.429
Italians, *n* (%)	69 (77.5)	37 (90.2)	32 (66.7)	0.010
Age (years), median (IQR)	40 (33–50)	46 (36–52)	38 (31–48)	0.016
HIV-1 subtype, *n* (%)				
B	64 (71.9)	31 (75.6)	33 (68.7)	0.316
CRF02_AG	8 (9.0)	2 (4.9)	6 (12.5)	0.279
F1	7 (7.9)	4 (9.8)	3 (6.3)	0.699
Other subtypes	10 (11.2)	4 (9.8)	6 (12.5)	0.748
Risk factor, *n* (%)				
Heterosexual	37 (41.6)	14 (34.1)	23 (47.9)	0.026
Homosexual	16 (18.0)	4 (9.8)	12 (25.0)	0.095
Other/unknown	36 (40.4)	23 (56.1)	13 (27.1)	0.009
First-line cART, *n* (%)	36 (40.4)	5 (12.2)	31 (64.6)	< 0.001
Co-administered drugs, *n*(%)				
NRTI	72 (80.9)	25 (61.0)	47 (97.9)	< 0.001
NNRTI	20 (22.5)	7 (17.1)	13 (27.1)	0.314
PI	70 (78.7)	34 (82.9)	36 (75.0)	0.441
Year of current cART start, median (IQR)	2011 (2010–2012)	2011 (2010–2014)	2011 (2010–2012)	0.313
Duration of current cART (weeks)[b], median (IQR)	76.3 (38.6-131.5)	68.7 (38.1-121.4)	81.1 (39.9-137.4)	0.573
Cumulative duration of cART (years), median (IQR)	5.6 (2.6–14.9)	13.2 (5.6–17.9)	4.1 (1.9–6.4)	< 0.001
Patients achieving VS under current cART, *n* (%)	47 (52.8)	21 (56.8)	26 (54.2)	0.493
Time to achieve VS under current cART (weeks), median (IQR)	20 (11–30)	16 (10–55)	20 (13–24)	0.966
Patients with VF under current cART, *n* (%)	38 (42.7)	14 (34.1)	24 (50.0)	0.141
Plasma viral load zenith under current cART (Log_{10} copies/mL), median (IQR)	3.5 (2.6–4.9)	3.0 (2.3–4.8)	4.2 (3.0–5.1)	0.010
CD4 + T cell count nadir under current cART (cells/mm^3), median (IQR)	238 (85–412)	270 (99–425)	203 (78–395)	0.497
At first V3 sequence (baseline)				
Plasma viral load (Log_{10} copies/mL), median (IQR)	4.8 (3.5–5.5)	4.3 (2.5–5.0)	5.0 (4.3–5.6)	0.013
CD4 + T cell count (cells/mm^3), median (IQR)	207 (67–441)	278 (84–496)	176 (66–404)	0.372
Resistance to at least one available drug[c], *n* (%)	26 (29.2)	14 (41.2)	12 (27.3)	0.147
Resistance to PIs, *n* (%)	10 (11.2)	3 (6.8)	7 (20.6)	0.072
Resistance to NRTIs, *n* (%)	18 (20.2)	11 (32.4)	7 (15.9)	0.076
Resistance to NNRTIs, *n* (%)	12 (13.5)	9 (26.5)	3 (6.8)	0.019
Resistance to INSTIs, *n* (%)	5 (5.6)	1 (6.3)	4 (16.0)	0.341
GSS[c], *n* (%)				
Fully susceptible	69 (77.5)	29 (85.3)	40 (90.9)	0.337
Intermediate or fully resistant	9 (10.1)	5 (14.7)	4 (9.1)	
FPR, median (IQR)	27.1 (8.5–64.8)	23.6 (11.8–69.7)	33.8 (6.9–63.5)	0.941
FPR < 10%, *n* (%)	25 (28.1)	9 (21.9)	16 (33.3)	0.249
FPR > 60%, *n* (%)	26 (29.2)	11 (26.8)	15 (31.2)	0.815
At second V3 sequence (during cART)				
Plasma viral load (Log_{10} copies/mL), median (IQR)	2.6 (1.8–4.3)	2.5 (1.8–3.3)	2.9 (2.0–4.5)	0.287
CD4 + T cell count (cells/mm^3), median (IQR)	295 (144–575)	356 (178–623)	268 (143–522)	0.490
Resistance to at least one available drug[d], *n* (%)	31 (34.8)	17 (51.5)	14 (38.9)	0.209
Resistance to PIs, *n* (%)	7 (7.9)	6 (18.2)	1 (2.8)	0.041
Resistance to NRTIs, *n* (%)	18 (20.2)	8 (24.2)	10 (27.2)	0.477
Resistance to NNRTIs, *n* (%)	18 (20.2)	7 (21.2)	11 (30.6)	0.272

Table 1 (continued)

Variables	Overall ($N=89$)	INSTI-based regimen ($N=41$)	Non-INSTI-based regimen ($N=48$)	p value[a]
Resistance to INSTIs, *n* (%)	7 (7.9)	7 (28.0)	0 (0.0)	0.031
GSS[d], *n* (%)				
Fully susceptible	47 (52.8)	22 (66.7)	25 (69.4)	0.504
Intermediate or fully resistant	22 (24.7)	11 (33.3)	11 (30.6)	
FPR, median (IQR)	20.2 (6.3–63.5)	37.7 (9.6–73.6)	15.9 (5.5–58.2)	0.307
FPR < 10%, *n* (%)	28 (31.5)	11 (26.8)	17 (35.4)	0.493
FPR > 60%, *n* (%)	18 (20.2)	10 (24.3)	8 (16.7)	0.432

cART combined antiretroviral therapy, *FPR* false-positive rate, *GSS* genotypic susceptibility score for current therapy, *INSTI* integrase strand transfer inhibitor, *IQR* interquartile range, *NRTI* nucleoside inhibitor, *NNRTI* non-nucleoside inhibitor, *PI* protease inhibitor, *VS* virological success (defined as 2 consecutive viral load determination < 50 copies/mL during cART), *VF* virological failure (defined as at least one viral load determination > 200 copies/mL after VS, for those patients who achieved VS, or at least one viral load determination > 200 copies/mL after 24 weeks of cART for those patients who did not achieve VS)

[a]Statistically significant differences ($p<0.05$) were assessed by Fisher's exact test for categorical variables and by Mann–Whitney test for quantitative variables

[b]Duration of current cART was defined as the time between the first V3 sequencing and the second V3 sequencing

[c]Data available for 78 POL sequences and 41 integrase sequences

[d]Data available for 69 POL sequences and 39 integrase sequences

during cART, we found that delta values were not significantly different in INSTI-treated and in non-INSTI treated individuals (Fig. 1c, d).

Looking at dN/dS values at single amino acidic positions, we observed an increased positive selection at only two V3 positions (aa: 14 and 18) in the INSTI-group, versus five amino acid positions (aa: 19, 21, 23, 25, 27) in the non-INSTI group (Fig. 1e, f). Of note, most of these positions (such as 14, 19, 21, 25, 27) have a key role for the co-receptor usage determination, and their modifications are strong predictors for CXCR4 tropism [29]. It is important to note that four out of these five CXCR4-related positions underwent positive selection in the non-INSTI group, suggesting a protective role of INSTI in limiting V3 evolution, positive selection, and probably selection of CXCR4-tropic variants.

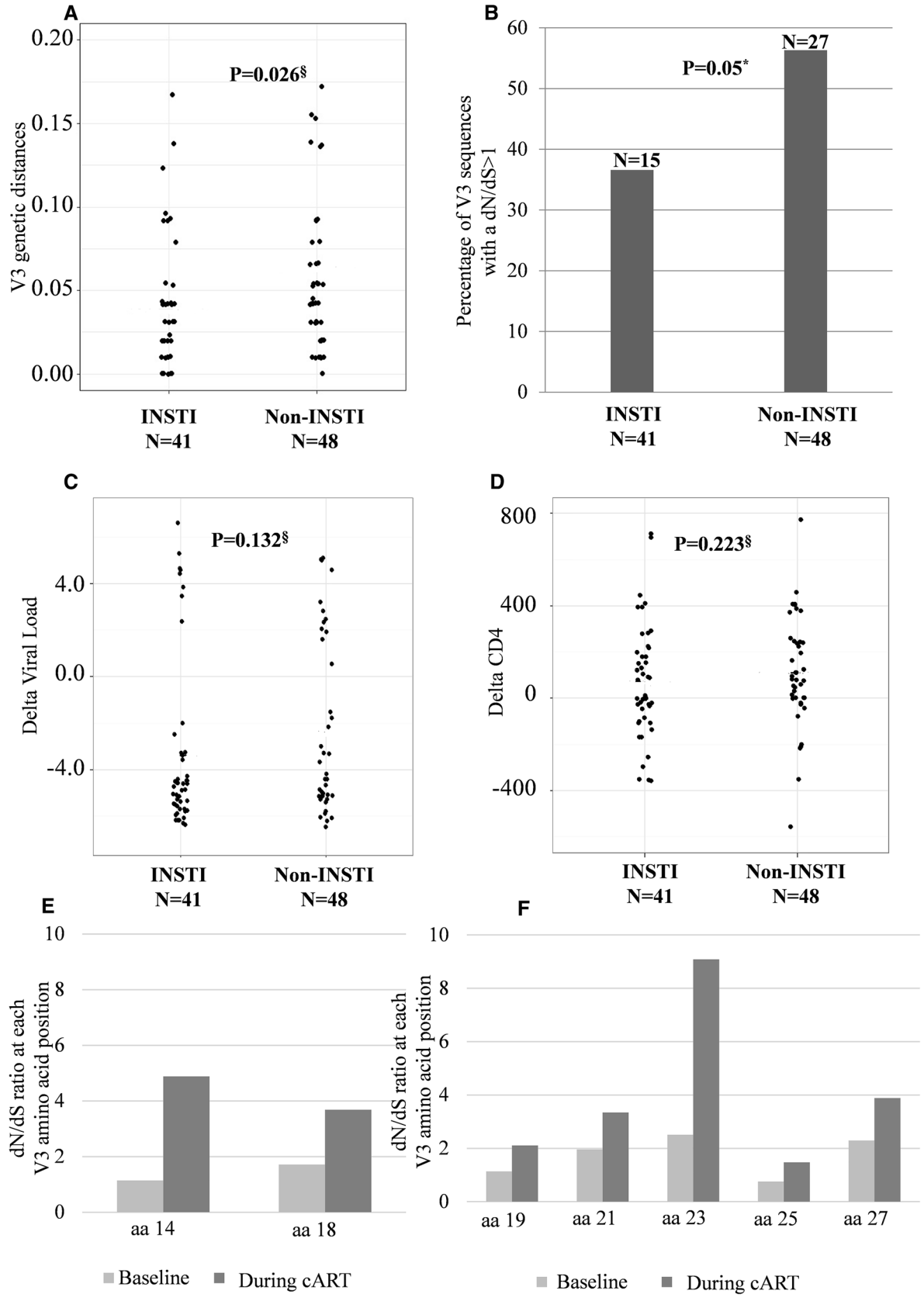
To define whether the lower V3 genetic distance and positive selection observed in INSTI-treated individuals respect to those non-INSTI-treated may be related with FPR changes during cART, we focused the analysis on the subgroup of V3 sequences with a baseline FPR > 60%, characterized by the complete absence of CXCR4-using variants in viral population [30]. Only one sequence belonging to an INSTI-treated individual (9.1%) switched during cART to an FPR < 60%, as compared to seven (46.7%) sequences from non-INSTI treated individuals ($p=0.049$).

The negative impact of INSTIs on V3 evolution was also confirmed by a multivariable approach taking into account also baseline plasma viral load, and plasma viral load zenith. In particular, factors negatively associated with a V3 genetic distance > 0.04 were only INSTI-based regimen and CD4 + T cell count nadir (adjusted odds ratio [AOR], confidence intervals [CI] 0.35 [0.13–0.88], $p=0.027$ and 0.88 [0.78–0.99], $p=0.031$, respectively) (Supplementary Table 1). When a similar multivariable model was used to estimate potential factors associated with a dN/dS ≥ 1, again INSTI-based regimen resulted to be negatively correlated with a dN/dS ≥ 1 (even if as a trend) (AOR [CI] 0.46 [0.19–1.11], $p=0.083$) (Supplementary Table 1).

Interestingly, when information of drug resistance to any drug and GSS for the administered regimen at both first and second V3 sequencing was considered in the multivariable models, no significant association was found with both V3 evolution > 0.04 and dN/dS ≥ 1 (Supplementary Tables 1 and 2).

Maraviroc-containing regimens were deliberately excluded from this study because of the role of this drug in

Fig. 1 **a** Distribution of HIV-1 V3 genetic distances, stratified for INSTI-based and non-INSTI-based regimens. **b** Percentage of individuals harbouring HIV-1 V3 sequences characterized by a dN/dS ≥ 1. All the analyses were performed by comparing the HIV-1 V3 sequences obtained during cART with those at baseline. *Statistically significant differences were assessed by Fisher's exact test. §Statistically significant differences were assessed by Mann–Whitney Test. Delta viral load (**c**) and delta CD4 + T cell count (**d**) between the V3 sequences at baseline and those obtained during cART. §Statistically significant differences were assessed by Mann–Whitney test. V3 amino acid positions showing an increased dN/dS value during cART in INSTI-treatment group (**e**) and non-INSTI treatment group (**f**). *cART* combined antiretroviral therapy, *INSTI* integrase strand transfer inhibitor. *Delta Viral Load* delta of plasma viral load for each patient from the first to the second V3 sequence (Log_{10} copies/mL), *delta CD4* delta of CD4 + T cell count for each patient from the first to the second V3 sequence (cells/mm^3)


A
V3 genetic distances
0.20
0.15
0.10
0.05
0.00
P=0.026§
INSTI N=41
Non-INSTI N=48
B
Percentage of V3 sequences with a dN/dS>1
60
50
40
30
20
10
0
N=15
P=0.05*
N=27
INSTI N=41
Non-INSTI N=48
C
Delta Viral Load
4.0
0.0
-4.0
P=0.132§
INSTI N=41
Non-INSTI N=48
D
Delta CD4
800
400
0
-400
P=0.223§
INSTI N=41
Non-INSTI N=48
E
dN/dS ratio at each V3 amino acid position
10
8
6
4
2
0
aa 14
aa 18
Baseline
During cART
F
dN/dS ratio at each V3 amino acid position
10
8
6
4
2
0
aa 19
aa 21
aa 23
aa 25
aa 27
Baseline
During cART

the evolution of V3, and therefore, in the shift of tropism. However, when we analysed separately the V3 sequences belonged to seven maraviroc-treated patients, a positive selection (defined as $dN/dS \geq 1$) was observed in 57.1% of the V3-pairs, a prevalence in line with that observed for non-INSTI group (56.3%), and lower than that observed in INSTI-treated patients (36.6%) (data not-shown). This finding suggests that the limited evolution observed on the V3 loop might be exclusive of INSTI treatment.

Thus, overall findings support the major role of INSTI-based regimen in limiting V3 evolution, and even if in less extent positive selection. The mechanism underlining the role of INSTIs in limiting HIV-1 evolution might be related to the greater ability of this drug-class in controlling viral replication, as suggested by several scientific papers [14–20], and by the lower plasma viral load at zenith found in the INSTI-treated group compared to non-INSTI group of our study (Table 1).

Few previous studies focused on dolutegravir investigated the effect of INSTI-based regimen on HIV-1 evolution. A first study showed a low genetic and amino acid env diversification with dolutegravir treatment in vitro [31]. Although this study does not adequately reflect HIV genetic evolution within the host, results are quite in line with our findings, even if our study is based mainly on raltegravir, known to have a lower genetic barrier for resistance and to be a less potent drug when compared with dolutegravir [32, 33]. By contrast, a second study [34] suggested that notwithstanding the initiation of a dolutegravir-based regimen, the genetic diversity of the HIV-1 reservoir is reshaped during cART, mainly in chronic individuals.

Before drawing conclusions, a few limitations of our study need to be discussed. First of all, the low number of individuals involved (notwithstanding the data merge from two different Italian databases) and the differences (mainly regarding the percentage of patients in first-line therapy, and cumulative duration of cART) between the INSTI and non-INSTI groups, must be considered. Even if multivariable analysis (adjusted for these major differences) suggests a null or very limited role of these factors in V3 genetic evolution, to definitely confirm the role of INSTIs in HIV evolution, further studies based on larger datasets will be required. This further investigation should take into account other and more extended HIV-1 regions and should be performed through next-generation sequencing methodologies. This should be done also in light of potential added benefit of second-generation dolutegravir, bictegravir and cabotegravir characterized to have a higher genetic barrier to resistance respect to raltegravir.

In conclusion, this proof of concept study suggests that in clinical practice, INSTI-based regimens may limit HIV-1 V3 evolution. This phenomenon results in a weaker positive selection, also at key positions for tropism determination. Confirmation of these results in largest dataset is required to support INSTIs as treatment of choice to limit V3 evolution and potential selection of X4 variants.

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Author contributions C.A. conceived the presented idea and wrote the manuscript. R.S. developed and performed the statistical analyses. D.A. and M.M.S. contributed to perform and interpret the statistical analyses. A.B., C.G., and I.V. determined the V3 sequences. G.F., C.M.M., C.C., A.C., B.B., M.A., and A.A. provided samples. R.S. and M.M.S. contributed to the writing of the manuscript. M.Z., V.S., F.C.S. and C.F.P. contributed to the interpretation of the results and revised the manuscript. All authors reviewed and approved the manuscript.

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Compliance with ethical standards

Conflict of interest The authors have no competing interests that might be perceived to influence the results and/or discussion reported in this paper. However, Francesca Ceccherini-Silberstein reports personal fees from Gilead Sciences, Bristol-Myers Squibb, Abbvie, Roche Diagnostics, Janssen-Cilag, Abbott Molecular, ViiV Healthcare; grants and personal fees from Merck Sharp & Dohme; grants from Italian Ministry of Education, University and Research (MIUR). Carlo Federico Perno reports grants from Italian Ministry of Instruction, University and Research (MIUR), and from Aviralia Foundation; personal fees from Gilead Sciences, Abbvie, Roche Diagnostics, Janssen-Cilag, Abbott Molecular, and grants and personal fees from Bristol-Myers Squibb, Merck Sharp & Dohme, and ViiV Healthcare. All other authors have nothing to declare.

Informed consent This study was conducted on data collected for clinical purposes. All data used in the study were previously anonymized, according to the requirements set by Italian Data Protection Code (leg. decree 196/2003) and by the General authorizations issued by the Data Protection Authority. Written informed consent for medical procedures/interventions performed for routine treatment purposes was collected for each patient included in the ARCA database or from other clinical centers involved in the study, in accordance with the ethics standards of the committee on human experimentation and the Helsinki Declaration (1983 revision).

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