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Primary Resistance to Integrase Strand-Transfer Inhibitors in Europe

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Background

Primary HIV-1 resistance can compromise the efficacy of antiretroviral therapy (ART).

The prevalence of primary resistance to integrase strand-transfer inhibitors (INSTI) in recently HIV-1-infected subjects remains unknown.

Methods

This was a multicenter cross-sectional study within the European SPREAD surveillance programme which continuously collects data from a representative set of newly diagnosed patients.

A representative set of 300 samples from 1950 untreated patients diagnosed in 2006/2007 was selected from the main cohort. The prevalence of INSTI resistance was evaluated using quality controlled baseline population sequencing of integrase (IN).

A subset of 20% were further evaluated using 454 IN sequencing. For both analyses, we assessed major mutations based on the IAS-USA mutation table.

All integrase substitutions were classified according to their Stanford HIVdb score ≥ 10 for at least one INSTI. Minority variants (MV) were defined as substitutions present in 1-20% of viruses in the 454 analysis. Subtypes were determined from population sequencing data using the Rega Subtyping Tool vs 2 based on *pol*.

Results

For the population sequencing analysis, 278 samples were retrieved and successfully analysed **(Table 1)**. 67% of isolates were subtype B. No signature resistance mutations to INSTIs (N155H, Q148H/R/K Y143R/H/C) were detected. In 11 (4%) patients the following mutations on resistance associated positions were detected with HIV db score ≥10: L74M (n=2; 1%), T97A (n=2; 1%), E138A, A153F, E157Q (n=2; 1%), G163KT, R263K, V151I + G163EKR. In 31 (11%) patients mutations with HIVdb score <10 were found: L68I, L68V, L74I (n=13; 4.6%), L74V, T97S, A128T (n=2, 1%), E138D (n=2; 1%), E138G, G140W, V151I (n=6; 2%), 68V + L74V, 143DN + Q146E.

Subsequently 56 samples were analysed with 454 sequencing. Median overall coverage was 4294 reads/substitution **(Figure 1)**. Again, no signature mutations were detected. **(Figure 2, Table 2)** IN substitutions with HIVdb score≥10 were found in 7 (12.5%) subjects: E157Q in 5 (8.9%) subjects, 1 as MV; H51Y and G163R in 1 (1.7%) subject each, both as MVs; and G163K in 1 (1.7%) individual. IN mutations with HIV db score <10 were: V151I in 6 (10.7%), 3 as MVs; L74I in 3 (5.3%), 1 as MV; and A128T, N155D, H51Q and T97I in 1 (1.7%) subject each, all as MVs.

Table 1. Patient characteristics

Patient characteristics	n = 278		
Male Gender	231	83%	
Continent of origin			
Western Europe	180	65%	
Eastern Europe	48	17%	
Sub-saharan Africa	20	7%	
Latin America	16	6%	
CDC class A	230	83%	
CDC class B	21	8%	
CDC class C	22	8%	
CD4 cell count (median)	411		
Route of transmission			
MSM/bisexual	180	65%	
HSX	61	22%	
IDU use	5	2%	
Other/unknown/not reported	32	12%	
Viral Subtype			
Subtype B		67%	
Subtype C		5%	
Other prevalence <5%		28%	
Population sequencing results			
IAS USA Integrase mutations	5	2%	74M (2), 97A (2), 138A
Any INI related mutation	42	15%	
HIV DB score dolutegravir 5 - 9	4		
HIV DB score elvitegravir 5 - 9	8		
HIV DB score raltegravir 5 - 9	6		
HIV DB score dolutegravir ≥ 10	3		
HIV DB score elvitegravir ≥ 10	11		
HIV DB score raltegravir ≥ 10	10		
HIV DB score dolutegravir ≥ 20	0		
HIV DB score elvitegravir ≥ 20	1		
HIV DB score raltegravir ≥ 20	0		

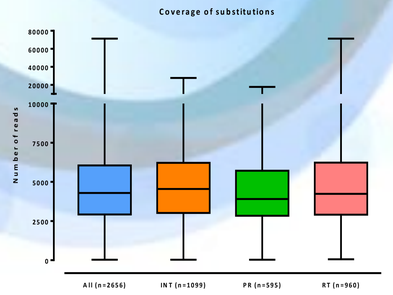

Figure 1: Coverage of substitutions. Median overall coverage was >4000 reads/substitution, being well balanced between genes.

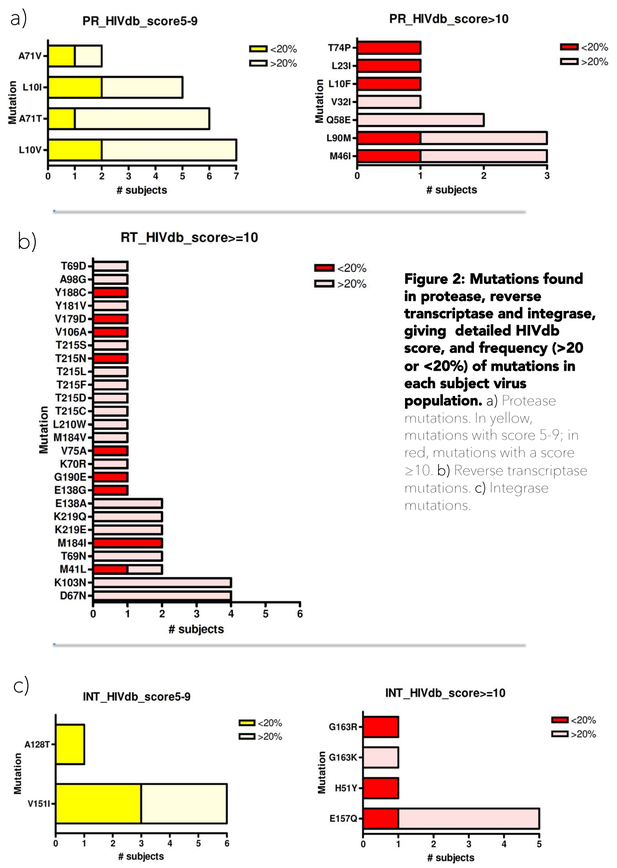

Figure 2: Mutations found in protease, reverse transcriptase and integrase, giving detailed HIVdb score, and frequency (>20 or <20%) of mutations in each subject virus population. a) Protease mutations. In yellow, mutations with score 5-9; in red, mutations with a score ≥10. b) Reverse transcriptase mutations. c) Integrase mutations.

Nº of appearances (N total = 56)	Frequence (%)	Mutations
56	100	G123S
49	88	N232D
47	84	D10E
35	63	V72I
32	57	V201I
30	54	A124T
24	43	E11D, T125A
23	41	L101I
20	36	D256E
15	27	T122I, V31I
13	23	S230N
14	25	M154I, S119P
13	23	M50I
11	20	A124N, K14R
10	18	I113V, S39C
9	16	S283G
8	14	R20K, T112V
7	13	D6E, I135V, V32I, T112I, V37I
6	11	A21T, A23V, D167E, D41N, E157K, K156N, L45Q, S17N, S24N, V151I, G70E, S119G
5	9	I208L, I220L, K136Q, K211R, S24G, T218S, Y227F, R157Q, L28I, T206S
4	7	A124S, D253E, D25E, I182V, K111T, K7E, L234I, P90S, V165I
3	5	A205S, D270E, D279G, D288N, D3N, E13D, G163E, G193E, I161T, I203M, I208M, I84M, K34R, L234V, L45V, L74I, N232E, R166K, S24D, T125V, T218I, V88I, E152K, G59E, K160Q, K215N, L101V, S119R, S119T, S17T, S255N
2	4	A21S, A23S, A265V, C56Y, D10K, D167G, D229E, D25N, D278N, D286N, D55N, D6S, E212A, E35Q, E48K, E96D, E96K, G134N, G163T, H171Q, H171Y, I84L, I84V, K103R, K111Q, K136R, K159R, K188E, K244R, K71R, L234F, L234H, M50T, M50V, N254H, N27S, Q274K, R199K, S17C, S255G, S283N, T112A, T112M, T122V, V259I, V32L, V77A, A80S, D6N, P30A, S39A
1	2	A124D, A124G, A128T, A196P, A33S, A33V, A8T, A91T, A98T, C280R, C43W, D10A, D10G, D116N, D202N, D207Y, D253H, D253Y, D256N, D278G, D288G, D3V, D41E, D41G, D41H, D41Y, D64A, D6T, D6V, E13K, E170K, E212H, E212I, E212Q, E212S, E212V, E35K, E69G, E85K, E96G, F100L, F100S, F181L, F185L, G118C, G134D, G163R, G163K, G189V, G193D, G4K, G52R, G70R, G82E, H51Q, H51Y, H67R, I113M, I141L, I141T, I141V, I161V, I204L, I217V, I220V, I251L, I251M, I268V, I5M, I60M, I60V, I89L, K111N, K111R, K127R, K136E, K136N, K14E, K160E, K160G, K160R, K173R, K188R, K211Q, K211T, K219N, K240R, K273E, K273R, K46R, K71I, K7Q, L28M, L28P, L2F, L45I, M22I, M22R, M275I, M275V, M50L, N155D, N222K, N254K, N27D, N27Y, P142S, Q216H, Q216R, Q44H, Q44R, Q95P, Q9P, R107G, R166G, R187K, R231K, R269G, R269K, R284G, S153A, S230G, S24T, S283D, S39M, S39N, T112R, T115A, T122S, T125M, T125P, T174A, T206A, T210I, T93S, T97I, V110I, V126L, V150A, V176I, V176L, V201M, V249I, V281M, V31L, V37A, V54L, V75I, Y15C, Y227H, Y271C, Y99C, D3E, G4E, N222H, S255R

Table 2: Substitutions in Integrase by 454 sequencing. In yellow, changes asssociated with an HIVdb score between 5 and 9; in red, those with a HIVdb score ≥10.

Conclusions

- No signature INSTI-resistant variants were circulating in Europe before the introduction of INSTIs, either as high- or low-frequency variants. However, polymorphisms contributing to INSTI resistance were not rare.
- 454 sequencing largely confirmed population sequencing findings, but led to the detection of some additional low frequency polymorphisms.
- As INSTI use becomes more widespread, continuous surveillance of primary INSTI resistance is warranted.
- These data provide a baseline for that purpose and will be key to model the kinetics of INSTI resistance transmission in Europe in the coming years.

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