Development of second generation integrase inhibitor resistance over the last six years in Germany

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Background

Selection of HIV-1 drug resistance mutations under second generation integrase inhibitors bictegravir- (BIC, approved 2018), dolutegravir- (DTG, 2014) and, to a lesser extent, cabotegravir- (CAB, 2021) containing treatment has been reported to occur rarely due to a higher genetic barrier against resistance. The focus of this retrospective cohort was to assess the prevalence of major integrase resistance mutations over the last six years.

Methods

EDTA plasma samples from patients with documented viremia and suspected resistance development were subject to next generation sequencing on an Iseq-100 sequencer platform. From 2017 to 2018, n=655 samples from different centres in Germany were tested for development of integrase inhibitor resistance. From 2019 to 2020 n=710 samples were tested accordingly and n=667 between 2021 and july 2022. Major integrase resistance mutations (according to Stanford Drug Resistance db and HIV GRADE algorithm) at position G118R, Q148H/K/R/N, N155H, S230R and R263K, leading to an intermediate grade of resistance against bictegravir, cabotegravir and/or dolutegravir, were documented anonymously and associated with historical and current treatment data, viral load, CD4 count and HIV-1 subtype.

Results

Integrase inhibitor resistance was rarely observed and remained on a constantly low level over the years with N155H being the most frequently detected major mutation in the range of 1.8% to 2.9% of resistance tests. About 50% of patients with available historic resistance data showed prior NRTI and/or NNRTI resistance (one patient with pre-existent integrase inhibitor resistance). Abnormalitites in HIV-1 subtype distribution were not observed. The development of G118R occurred in just two cases between 2021 and 2022. Substitutions at position Q148 increased from 0,9% to 1.1% and 2.1% over the years (Figure 1). Of seven specified pretreatments, three Q148 substitutions were most likely associated with a failing CAB-treatment, and two associated with EVG or RAL each (not shown), respectively. The prevalence of substitution R263K increased from 0.15% to 0.85% and 1.2%, respectively. Of seven specified pretreatments, six R263K substitutions were most likely associated with failing DTG-treatment, and one associated with CAB (Table 1).

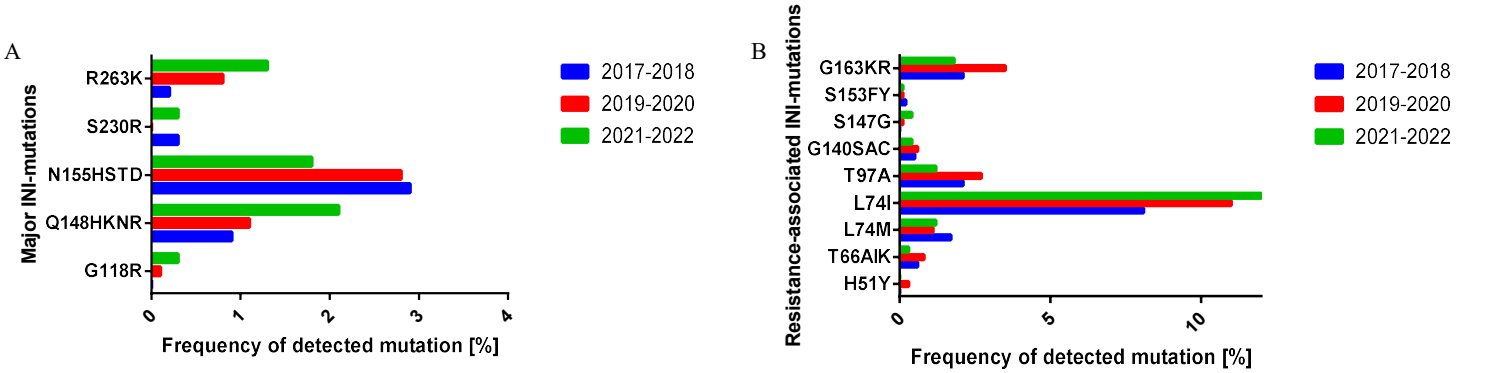

Figure 1: Frequency of detected INI-resistance mutations over the years. A) Slightly increasing prevalence of major INI resistance mutations (green bars) on a low level <3% max. B) Resistance-associated mutations fluctuating on equal levels over the years, L74I polymorphism over-represented in 2019-2021 and 2021-2022 as compared to 2017-2018.

Table 1: Documented cases of treatment failure under ART with „second"-generation integrase-inhibitors and tested positive for major INI-resistance mutations. A) Documented Failure under BIC-containign treatment, B) documented failure under CAB-containing treatment and C) documented failure under DTG-containing treatment.

1a) Documented Integrase Resistance Development: **BIC**-containing treatment

ID No.	Current ART	Specified Pretreatment	Viral Load	CD4 count	Subtype	Pre-existent RAMs	R.Transkriptase-RAMs at failure	Protease RAMs at failure	Integrase RAMs at failure
#1	TAF/FTC/BIC	TAF/FTC/BIC	1000	n/a	C	None	V179I (35,12%), M184V (65%)	None	R263K (33%), H51Y (4%)
#2	TAF/FTC/BIC	TAF/FTC/BIC	225	n/a	B	None	None	None	R263K (7,2%)

1b) Documented Integrase Resistance Development: **CAB**-containing treatment

ID No.	Current ART	Specified Pretreatment	Viral Load	CD4 count	Subtype	Pre-existent RAMs	R.Transkriptase-RAMs at failure	Protease RAMs at failure	Integrase RAMs at failure
#3	CAB/RPV	Unspecified	11000	n/a	B	None	M230L (47,2%), H221Y (8,1%)	None	E138K (6%), Q148R (97,8%)
#4	CAB/RPV	ABC/3TC/DTG, TDF/FTC, DTG	3350	50	A1	V179I	V179I + E138K (99,8%)	None	Q148K (13,8%), S153FY(29,4%), R263K(7,5%)
#5	CAB/RPV, FOS	Salvage ART incl. Ibalizumab	5886	n/a	B	Unspecified	V179F, Y181C, K219N (99% each)	None	E138K (99,3%) + Q148K (99,2%)
#6	CAB/RPV	RPV, 3TC/ABC, RAL, NVP, FPV, TAF/FTC/DRV/c, DTG	57754	154	B	M184V, K101E, Y181C, V189I, G190S	E138D (93%), M230L (99%)	None	E138AK (97,3%) + Q148R (96,7%)

1c) Documented Integrase Resistance Development: **DTG**-containing treatment

ID No.	Current ART	Specified Pretreatment	Viral Load	CD4 count	Subtype	Pre-existent RAMs	R.Transkriptase-RAMs at failure	Protease RAMs at failure	Integrase RAMs at failure
#7	DTG/3TC	TDF/FTC, NVP, DRV/r, DTG	1468	852	B	K101R, V106I	K101R (99%), V106I (99%)	None	R263K (25,6%)
#8	DTG/3TC	DTG/3TC	89130	829	B	Unspecified	K103R (16,5%), M184V (59.7%)	None	R263K (6,5%)
#9	TDF/FTC+DTG	3TC/ABC/DTG	n/a	n/a	02_AG	V179I, M184V, R263K	V179I (94,4%), M184V (92,8%)	None	R263K (94%)
#10	TDF/FTC+DTG	TDF/FTC+DTG	1000	n/a	02_AG	Unspecified	M184I (98%)	None	G118R (8%)
#11	3TC/ABC/DTG	LPV/r, EFV, F/TDF	568	402	B	Unspecified	M184V (99%), L210F (99%)	None	T66I (99%), G118R (99%), E138K (99%)
#12	TAF/FTC/DRVc, DTG	3TC/ABC/DTG, RAL	325	369	D	V106I, V179A	V106I, V179A (99% each)	None	R263K (3%)
#13	TDF/FTC, DTG	TDF/FTC, DRV/r	2100	n/a	B	E138A, M184V	K70E, E138A, M184V (99% each)	None	R263K
#14	TDF/FTC/DRV/DTG	TDF/FTC+DRV/r+AZT	100	461	02_AG	M184V	K101E (53,7%) + M184V (98,7%)	None	R263K (98,4%)
#15	ABC/3TC/DTG	TDF/FTC, DTG	n/a	n/a	02_AG	Unspecified	V179I (68%), M184V (90%)	None	R263K (97,7%)

Conclusions

Integrase inhibitor resistance was rarely observed and remained on a constantly low level over the years. Pretreatment data suggests, that a major part of these patients already had anamnestic NRTI and/or NNRTI resistance before re-analysis. All documented cases were viremic. The increasing amount of patients receiving integrase inhibitor containing treatment may explain the slight increase of detected substitutions at position Q148 and R263 over time but should be be further documented.

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