Factors associated with virological response and resistance profile in virologically suppressed HIV-1 infected patients switching to a dual therapy containing integrase inhibitors in clinical practice

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Background

- The introduction of integrase inhibitors (INIs) has strengthen combined antiretroviral therapy (cART) due to their remarkable efficacy observed in both clinical trials and clinical practice.
- The usage of INIs in treatment optimization strategies based on two drugs showed high rates of maintenance of virological suppression.
- However, data about the role of baseline resistance profiles and viro-immunological factors on virological response are still few in clinical setting.

Aim

We evaluated the virological response and the resistance profile (at baseline and at failure) in a large cohort of Italian virologically suppressed HIV-1 infected patients switching to a dual regimen containing INI.

Methods

Data from virologically suppressed patients in care for HIV-1 infection switching for the first time to a INI containing dual-regimen were examined. Patients were included according to the following criteria: i) viremia <50 copies/mL; ii) presence of at least one previous genotypic resistance test (GRT) for protease (PR) and reverse transcriptase (RT); iii) viremia zenith and CD4 cell count nadir available before switch; iv) viremia follow-up available after switch. Patients were followed-up under treatment and censored at the last viremia available before a treatment change or a full stop of therapy (on treatment approach).

Survival analyses were used to evaluate the probability and risk of virological failure defined as two consecutive viremia >200 copies/mL.

Previous resistance and its evolution at virological failure were also evaluated. Major resistance mutations (MRMs) and accessory resistance mutations (ARMs) were evaluated according to the Stanford resistance list 2018.

Cumulative genotypic susceptibility score for companion drugs (cGSS) was also evaluated (HIVdb algorithm ver.8.4). The score was calculated considering all the mutations cumulated among previous plasma GRTs available before switch. Patients were stratified according two groups: i) patients with a fully susceptible virus to the companion drug included in the dual treatment switch; ii) patients with an intermediate/fully resistant virus to the companion drug included in the dual treatment switch.

Baseline patients' characteristics: Overall, 248 cART-treated patients virologically suppressed from a median time of 1.9 (IQR: 0.6-4.5) years and starting an INI-based dual therapy in 2015 (IQR: 2011-2016) were analyzed.

Variables	Overall (N=248)	INI used in treatment switch strategy		P value[a]
		Dolutegravir (N=82)	Raltegravir (N=166)	
Calendar year of INI switch, median (IQR)	**2015 (2011-2016)**	**2016 (2016-2016)**	**2012 (2010-2015)**	**<0.001**
Male, n (%)	176 (71.0)	57 (69.5)	119 (71.7)	0.723
Age, years, median (IQR)	51 (46-56)	51 (48-56)	50 (46-56)	0.297
Risk factor, n (%)				
Homosexual	65 (26.2)	23 (28.0)	42 (25.3)	0.648
Heterosexual	97 (37.1)	37 (45.1)	60 (36.1)	0.213
Drug abuser	61 (24.6)	18 (22.0)	43 (25.9)	0.534
Other/unknown	25 (10.1)	4 (4.9)	21 (12.7)	0.056
Subtype, n (%)				
B	185 (74.6)	66 (80.5)	119 (71.7)	0.134
CRF02_AG	9 (3.6)	4 (4.9)	5 (3.0)	0.483
F	9 (3.6)	3 (3.7)	6 (3.6)	1.000
C	6 (2.4)	3 (3.7)	3 (1.8)	0.400
Other	**39 (15.7)**	**6 (7.3)**	**33 (19.9)**	**0.011**
Nadir CD4 cell count (cells/mm^3), median (IQR)	140 (49-266)	179 (79-272)	127 (43-262)	0.115
Baseline CD4 cell count (cells/mm^3), median (IQR)	**520 (365-770)**	**687 (479-886)**	**459 (295-691)**	**<0.001**
Viremia Zenith (Log$_{10}$ copies/mL)	5.2 (4.7-5.7)	5.2 (4.7-5.6)	5.2 (4.7-5.7)	0.530
Time of previous suppression, n (%)				
<6 months	**51 (20.6)**	**7 (8.5)**	**44 (26.5)**	**<0.001**
6 months-1 year	39 (15.7)	13 (15.9)	26 (15.7)	0.969
1-3 years	61 (24.6)	17 (20.7)	44 (26.5)	0.321
>3 years	**97 (39.1)**	**45 (54.9)**	**52 (31.3)**	**<0.001**

a. Chi Squared test, Fisher exact test or Mann-Whitney test as appropriate. P values <0.05 are indicated in boldface.
INI: integrase inhibitor. IQR: interquartile range.

Baseline resistance: Previous resistance to INIs was very low (<3%), while >64% of patients showed previous resistance to PIs, NRTIs and/or NNRTIs, regardless the INI used at therapy switch.

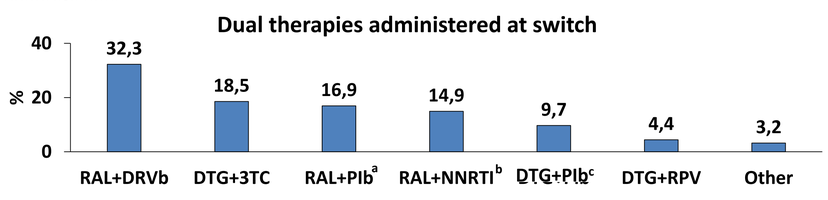
Variables	Overall (N=248)	INI used in treatment switch strategy		P value[a]
		Dolutegravir (N=82)	Raltegravir (N=166)	
INI resistance				
Accessory mutations[b], n (%)	12 (17.1)	6 (31.3)	6 (11.8)	0.074
Major mutations[b], n (%)	2 (2.9)	1 (5.3)	1 (2.0)	0.472
PR/RT resistance (≥1 MRM) , n (%)				
PI	68 (27.4)	19 (23.2)	49 (29.5)	0.292
NRTI	141 (56.9)	42 (51.2)	99 (59.6)	0.208
NNRTI	111 (44.8)	37 (45.1)	74 (44.6)	0.935
Class resistance, n (%)				
0	88 (35.5)	35 (42.7)	53 (31.9)	0.096
1	44 (17.7)	10 (12.2)	34 (20.5)	0.108
2	72 (29.0)	23 (28.0)	49 (29.5)	0.810
≥3	44 (17.7)	14 (17.1)	30 (18.1)	0.846
Fully susceptible cGSS, n (%)	198 (79.8)	62 (75.6)	136 (81.9)	0.243

a. Chi Squared test or Fisher exact test as appropriate. b. Calculated on 70 patients with an integrase GRT before switch. cGSS: Cumulative genotypic susceptibility score for companion drugs. GRT: genotypic resistance test. INI: integrase inhibitor. MRM: major resistance mutation. PR: protease; PI: protease inhibitor. NRTI: Nucleos(t)ide reverse transcriptase inhibitor. NNRTI: non-NRTI. RT: reverse transcriptase.

Overview of previous treatments and of drugs administered at INI switch.

Variables	Overall (N=248)	INI used in treatment switch strategy		P value[a]
		Dolutegravir (N=82)	Raltegravir (N=166)	
Time under cART, years, median (IQR)	**10 (3-18)**	**13 (5-20)**	**10 (3-15)**	**0.004**
No. of previous regimens	5 (2-9)	6 (3-10)	5 (2-9)	0.192
Previous INI exposure, n (%)	80 (32.3)	31 (37.8)	49 (29.5)	0.189
Type of last regimen received before switch to INI				
PIb + 2NRTI	**82 (33.1)**	**18 (22.0)**	**64 (38.6)**	**0.008**
NNRTI + 2NRTI	37 (14.9)	15 (18.3)	22 (13.3)	0.304
INI+ 2 NRTI	7 (2.8)	1 (1.2)	6 (3.6)	0.430
Dual-Monotherapy	**74 (29.8)**	**38 (46.3)**	**36 (21.7)**	**<0.001**
Other	48 (19.4)	10 (12.2)	38 (22.8)	0.054

a. Chi Squared test, Fisher exact test or Mann-Whitney test as appropriate. P values <0.05 are indicated in boldface. cART: combined antiretroviral therapy. INI: integrase inhibitor. PIb: cobicistat/ritonavir boosted protease inhibitor. NRTI: Nucleos(t)ide reverse transcriptase inhibitor. NNRTI: non-NRTI.

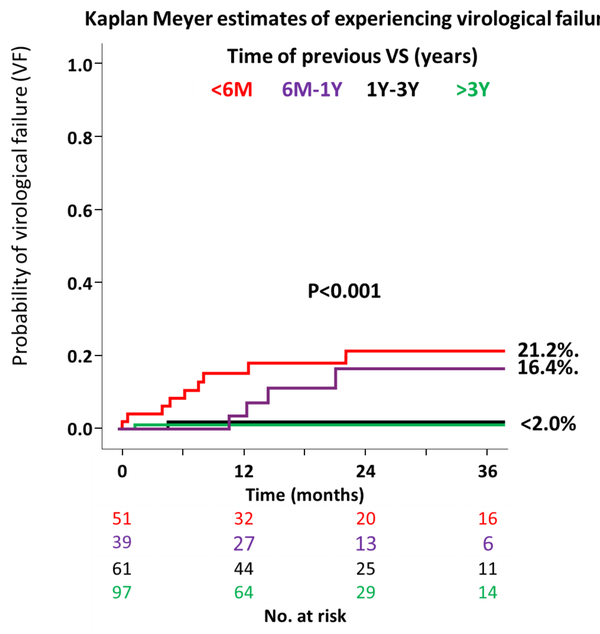


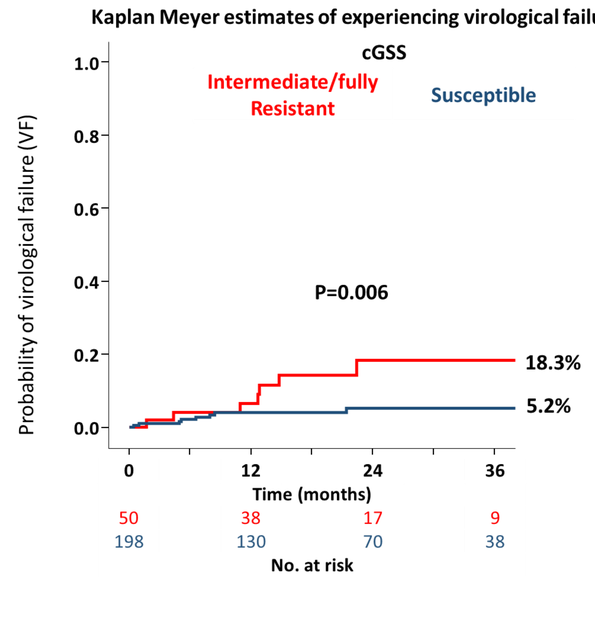
a. ATV, N=20; FPV, N=4; LPV,N=15; SQV, N=1; TPV, N=2. b. ETR, N=22; NPV, N=12; RPV, N=3. c. ATV, N=2; DRV, N=22. b. 3TC: lamivudine; DRVb: cobicistat/ritonavir boosted darunavir; DTG: dolutegravir; ETR: etravirine; FPV: fosamprenavir; LPV: lopinavir; RAL: raltegravir; RPV: rilpivirine; SQV:saquinavir; TPV: tipranavir.

Keplan Meyer estimates of virological failure: By 36 months after switch, the overall probability of virological failure was 8.3% (median [IQR] viremia at VF: 10,458 [1,829-51,596] copies/mL).

Longer was the duration of virological suppression (VS) before switch, lower was the probability of virological failure. Of note, no failures were observed among patients with >5 years of previous VS (N=53).

Patients showing intermediate/fully resistant cGSS had a higher probability of experiencing virological failure compared to those with a fully susceptible cGSS.





*Virological failure: two consecutive viremia >200 copies/mL. M:months; Y:years.

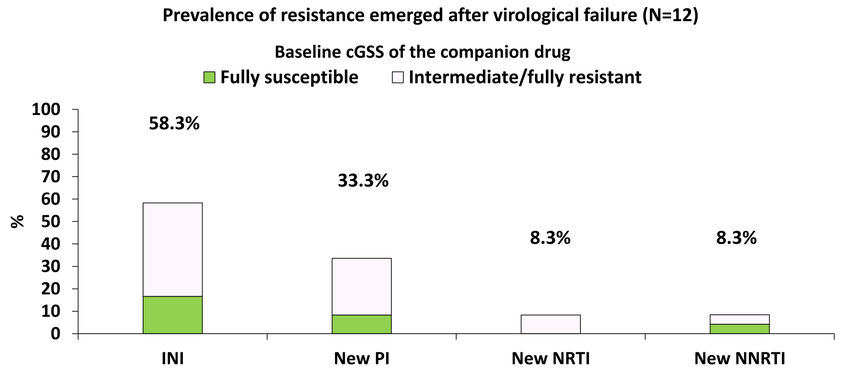
Multivariable Cox-regression: A previous suppression longer than one year, fully susceptible cGSS and previous INI-experience were negatively associated with virological failure.

Multivariable Cox regression analyses to estimate risk of virological failure according to demographic, viro-immunological and therapeutic factors

Variables	Adjusted relative hazard[a]	95% C.I		P Value
		Lower	Upper	
Age (per 5 years higher)	0.863	0.628	1.187	0.365
Male vs. female	1.969	0.460	8.427	0.361
B vs. non-B subtype	0.602	0.150	2.413	0.474
Risk factor				
Homosexual	1			
Heterosexual	2.195	0.288	16.748	0.448
Drug abuser	0.471	0.067	3.296	0.448
Other/unknown	0.650	0.096	4.422	0.660
Time of previous virological suppression				
<6 months	1			
6 months-1 year	0.350	0.081	1.516	0.160
1-3 years	0.027	0.002	0.334	**0.005**
>3 years	0.018	0.001	0.245	**0.002**
Viremia Zenith >500,000 copies/mL	1.980	0.359	10.924	0.433
Nadir CD4 cell count <50 cells/mm^3	2.561	0.723	9.072	0.145
Previous INI exposure	0.169	0.030	0.941	**0.042**
INI used at switch (Raltegravir vs. Dolutegravir)	0.180	0.017	1.945	0.158
Switch after first line treatment	0.945	0.144	6.201	0.953
Calendar year of treatment switch	0.700	0.483	1.014	0.059
Fully susceptible cGSS	0.071	0.013	0.397	**0.003**
Two vs. ≥3 drugs at therapy before switch	1.741	0.310	9.762	0.529

a. adjusted for: age, gender, subtype, risk factor, time of previous virological suppression, viremia Zenith, Nadir CD4 count, previous INI exposure, INI used at switch, switch from first line treatment, calendar year of treatment switch, cGSS, previous INI resistance, 2 vs. ≥3 drugs at therapy before switch. C.I: Confidence interval; cGSS: Genotypic susceptibility score for companion drugs; INI: integrase inhibitor; virological failure: two consecutive viremia >200 copies/mL.

Resistance after virological failure: Among patients experiencing virological failure, 12 were tested for resistance in a median (IQR) time of 11 (5-17) months after switch. INI resistance was detected in 7 (58.3%) patients (six under raltegravir, one under dolutegravir); 4 (33.3%) patients (all receiving raltegravir) accumulated further major resistance mutations to companion drugs (PI: 33.3%; NRTI: 8.3%, NNRTI: 8.3%). The majority of patients who accumulated new resistance had an intermediate/fully resistance cGSS at baseline.



Overview of patients harboring resistance after virological failure to a dual therapy based on integrase inhibitors.

ID	Previous ARVs experienced		Time under VS before switch (months)	Baseline cGSS	Drugs received at switch	Viremia at GRT (copies/mL)	Time under INI-based dual therapy (months)	Resistance mutations detected after VF				
	No of ARV classes	INI						INI MRMs	INI Accessory	PI MRM	NRTI MRM	NNRTI MRM
357[a]	6	RAL	7	F/I	DTG, DRV/r	297,560	11.3	**Y143YCHR**	**T97TA**	None	None	None
326	5	None	37	F/I	RAL, ATV/r	1,786	7.1	**G140S, Q148H**	None	L90M	M184V	None
1321	5	RAL	<1	F/I	RAL, SQV/r	3,356	19.5	**Y143YCHR**	T97A	V32I, L33F, M46I, I47V, **I50V**, I54L	K70R, K219Q	None
3507	5	RAL	1	F/I	RAL, LPV/r	7,590	34.2	**N155H**	None	M46L,**I54V**, V82A	M41L, **D67G,** L210W, T215Y, K219E	None
7583	5	RAL	24	F/I	RAL, NVP	4,627	2.1	**N155H**	None	**M46L, I84V**	M184V, T215Y	K103N, Y188L
10930	6	None	44	S	RAL, ATV/r	2,709	11.6	None	**G163R**	None	None	None
11067	4	None	16	S	RAL, FPV/r	1,045	10.9	**Y143S**	None	**L76V**	None	None

Among 12 patients with an available GRT after virological failure, 7 showed resistance. In bold are indicated mutations selected after virological failure.
[a] The patient was previously heavily treated and developed the mutation N155H after raltegravir failure. /r: ritonavir-boosted; ATV: atazanavir; cGSS: cumulative genotypic susceptibility score for companion drugs; DRV: darunavir; DTG: dolutegravir; F/I: fully/intermediate resistant cGSS; GRT: genotypic resistance test; INI: integrase inhibitor; LPV: lopinavir; MRM: major resistance mutation; NRTI: nucleos(t)ide reverse transcriptase-inhibitor; NNRTI: non-NRTI; PI: protease inhibitor; RAL: raltegravir; S: susceptible cGSS; SQV: saquinavir; VF: virological failure; VS: virological suppression.

Conclusions

- ✓ In pluri-treated virologically suppressed patients, switching to a dual therapy including dolutegravir or raltegravir ensures a high rate of virological control.
- ✓ Being in stable virological suppression for at least 1 year, and having INI associated with a fully active companion drug, are factors linked to a greater rate of success.

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