Clinical Consequences of Raltegravir Failure in Spain

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Background

- ART with RAL plus OBT suppress triple-class drug-resistant HIV-1.
- RAL has a low genetic barrier to resistance.
- Single RAL-resistant mutants usually retain DTG susceptibility.
- RAL maintenance in the presence of viral replication ➔ accumulation of INSTI-associated mutations ➔ reduction on DTG activity.
- INSTI are increasingly being used for HIV treatment.
- INSTI resistance could be transmissible to newly infected subjects.
- VF to RAL-based salvage ART may be at higher risk of treatment exhaustion.
- We evaluated the prevalence and the incidence of VF to first-generation INSTI-based regimens in Spain as well as their clinical consequences.

Methods

- Retrospective observational multicenter study (10 HIV clinics in Spain, between January 2006 – June 2013)

- Subjects with consecutive VF to RAL or ELV-containing regimens were accepted for the resistance analysis, but only the first failing INSTI regimen was considered for analyses of clinical outcomes

- Definitions:
  - VF (2 consecutive VL ≥ 200 c/mL while receiving RAL or ELV),
  - low-level viremia (LLV, 2 consecutive VL between 50-200 c/mL),
  - loss of virological suppression (LVS, 2 consecutive VL > 50 c/mL)

Methods

- Assessments:
  - Incidence / prevalence of VF, LLV, LVS
  - INSTI associated mutations and susceptibility at VF;
  - The immune-virological evolution following VF
  - The rate of AIDS progression or death following VF.

- INSTI-resistance: Stanford HIVdb Rules (v6.3.1) modified:
  - Addition of scores: 148HRK plus 74I: 20 points
    148HRK plus 138T: 20 points
    74I: 5 points

- Clinical outcomes during the first 48 weeks after LVS: descriptive analyses, Kaplan-Meier curves and multivariate regression models.

Results

Number of treated HIV-infected patients, exposed to integrase inhibitors (INSTI) and with virological failure to INSTI during the study period (2006-2013)

Center*	Treated HIV-infected patients	Patients exposed to INSTI**	Patients with LVS while receiving INSTI	Patients with VF (HIV-1 RNA>200 copies/mL)	Patients with LLV (HIV-1 RNA >50 <200 copies/mL)
Total	15009	2799	209	138	71

- 18.6% of the total of treated population had RAL exposition.
- No patients with ELV exposition.
- Among the patients with RAL exposition, 7.5% had LVS.

Incidence and prevalence

- **Incidence of VF:** 2/100 failures/year (CI 95%: 1.65;2.32/100 failures/year)
- **Prevalence of VF:** P=138/2799= 4.93 % (CI 95%: 4.16;5.79)
- **Prevalence of LLV:** P=71/2799= 2.53 % (CI 95%: 1.99;3.19)

Resistance

Genotyping performed in patients with lost of virological suppression while receiving INSTI-based treatments.

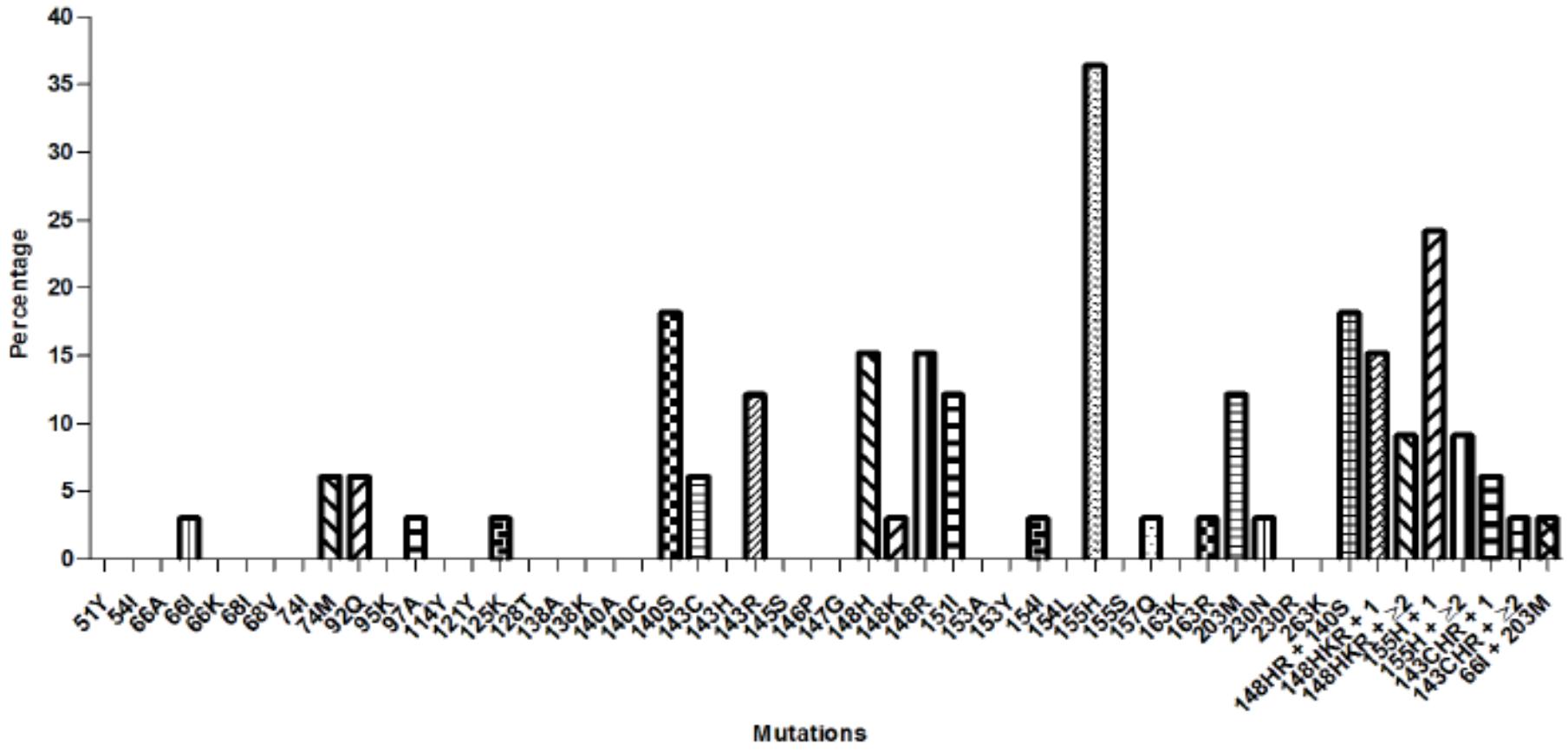
INSTI genotyping	VF	LLV	Total
Not performed/not available	90 (65.2)	64 (90.1)	154 (73.7)
Performed	48 (34.8)	7 (9.9)	55 (26.3)
Amplified	31 (22.5)	2 (2.8)	33 (15.8)
Not amplified	17 (12.3)	5 (7)	22 (10.5)
Total	138	71	209

INSTI, integrase inhibitors; VF, virological failure; LLV, low-level viremia. Results are shown as n (%)

- Only ¼ of patients with LVS had INSTI genotyping tests performed at failure.

- Out of 33 patients with available genotyping, 26/33 (78.8%) had INSTI mutations

Figure 1. Prevalence of integrase related mutations and their combinations in patients with loss of virological suppression under INSTI-based regimens (n=33)



- Most frequent mutations: 155H (36.4%), 140S (18.2%), 148H (15.2%) and 143R, 151I, 203M (12,1%).
- 148R mutation was observed in 9.1% of genotypes.
- 57.6% of genotypes had combinations of INSTI-related mutations (155H+1 mutation and 148HKR+1 mutation ➔ most frequent).

Susceptibility to different INSTI after failing to RAL, n=33

Stanford HIVdb susceptibility*	RAL	ELV	DTG
Susceptible	11 (33.3%)	15 (45.5%)	22 (66.7%)
Intermediate§	5 (15.2%)	3 (9.1%)	11 (33.3%)
Resistant	17 (51.5%)	15 (45.5%)	-
Total	33	33	33

- High resistance to RAL in 51.5% of cases, and to ELV in 45.5% of cases.
- 66.7% of cases remained susceptible to DTG
- No cases of high resistance to DTG

Clinical outcomes

Characteristics of patients failing to INSTI-based regimens (n=192)

	Patients with LVS (n=192)	Patients with VF (n=125)	Patients with LLV (n=67)
Age (years)[b]	46 (42-51)	46 (42-52)	47 (42-50)
Gender			
Male	142 (74)	87 (69.6)	55 (82.1)
Female	50 (26)	38 (30.4)	12 (17.9)
Co-infection HCV/HVB	79 (41.1)	54 (43.2)	25 (37.3)
IDU	61 (31.8)	40 (32)	21 (31.3)
CDC stage			
A	33 (17.2)	19 (15.2)	14 (20.9)
B	27 (14.1)	12 (9.6)	15 (22.4)
C	67 (34.9)	45 (36)	22 (32.8)
Unknown	65 (33.9)	49 (39.2)	16 (23.9)
Time on treatment with INSTI (years)[b]	1.16 (0.66-1.93)	1.175 (0.644-1.916)	1.145 (0.685-2.08)
Nadir CD4+ T (cells/mm^3)[b]	80 (27.75-170)	72 (24-176)	100 (40.5-171)
Zenit HIV-1 RNA (log)	5.49 (4.99-5.88)	5.56 (5.04-5.92)	5.31 (4.94-5.82)
Time since HIV diagnose (years)	14.9 (10.5-18.9)	14.8 (10.6-19.2)	14.9 (9.9-18.3)
Adherence			
<90%	69 (30.7)	60 (39.7)	9 (12.2%)
>90%	116 (51.6)	59 (39.1)	56 (75.7)
Not available	40 (17.8)	32 (21.2)	9 (12.2)

Reasons for starting with INI based regimens in patients with lost of virological suppression (n=192)

	Patients with LVS (n=192)	Patients with VF (n=125)	Patients with LLV (n=67)
Virological failure	106 (55.2)	69 (55.2)	37 (55.2)
Simplification	67 (34.9)	43 (34.4)	24 (35.9)
Toxicity	9 (4.7)	5 (4)	4 (6)
Immunological failure / discordance	49 (25.5)	33 (26.4)	16 (23.9)
Naïve to ARV treatment	4 (2.1)	2 (1.6)	2 (3)
Previous treatment interruption	5 (2.6)	3 (2.4)	2 (3)
Pharmacological interactions	8 (4.2)	4 (3.2)	4 (6)
Others	4 (2.1)	3 (2.4)	1 (1.5)

Salvage regimens:

- The most frequent salvage drugs were: DRV/r (67.2%), 3TC/FTC (55.7%), RAL (53.1%), TDF (49.0%), ETR (38.5%) and MVC (23.4%).

- RAL was stopped in 90 (46.9%) cases.

AIDS/death progression following VF:

- 125/192 (65%) of patients experienced VF

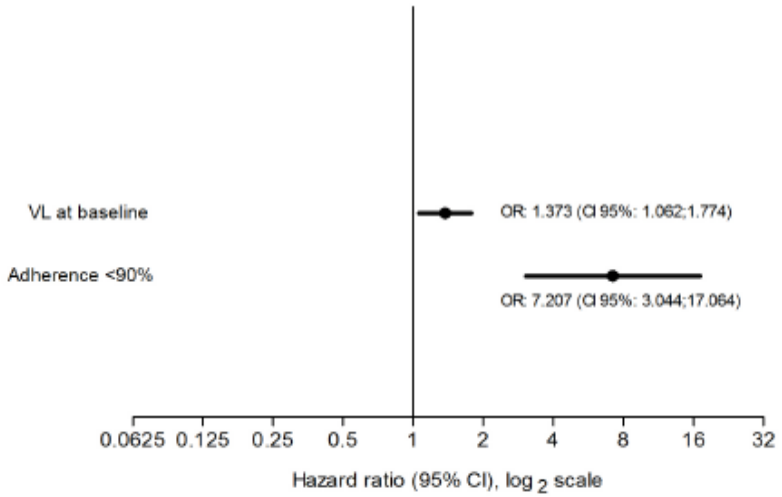
- CD4+ cells increased from 291 (133.75-512.25) cells/mm^3 at baseline to 362.5 (177.5-565.75) cells/mm^3 at week 48 ($p<0.001$)

- There were 10 (5.2%) new events of AIDS and 10 (5.2%) deaths during the 48 weeks of follow-up .

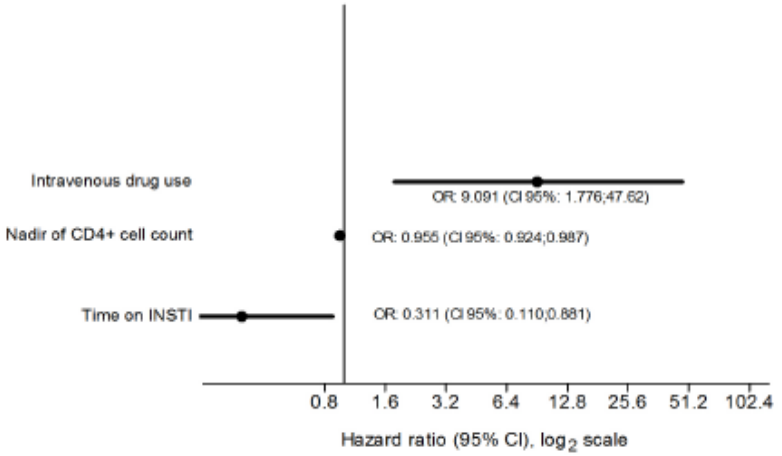
- The mean time to AIDS progression or death was 45.9 (CI 95%: 44.6;47.2) weeks.

Factors associated to VF (HIV RNA >200 c/mL) and AIDS progression or death in patients with salvage regimens after failure to INSTI based treatments

Factors associated to virological failure (VL >200 c/mL)



Factors associated to AIDS progression / death



All analyses are intention-to-treat. Full multivariable model included: age, gender, IDU as mode of HIV transmission, hepatitis B/C viruses coinfection, CDC stage before baseline, CD4+ cell count at baseline, increase in CD4+ cell count, CD4+ cell count nadir, VL at baseline, zenith of VL, decrease in VL, time since HIV diagnosis, time on treatment with INSTI, adherence, viral tropism, and reasons for INSTI based treatment initiation (VF vs switching strategy). Only factors with significant association are shown.

Conclusions

- Prevalence of VF in patients treated with INSTI in Spain was low.
- Proportion of failing patients without integrase genotyping tests was very high. It is very important to take the necessary measures to extend the testing of genotypes in integrase-failing patients.
- Integrase associated mutations or their combinations that could impact on DTG efficacy were infrequent. DTG remains fully active in most of integrase failing patients.
- The rate of VF following an integrase failure was high. 5% of patients with VF to INSTI-based regimens experienced AIDS progression or death during the 1st year after failure, mainly in heavily pretreated patients.
- Factors associated to VF >200 c/mL were baseline VL and low treatment adherence.
- Factors associated to AIDS progression or death:
  - Higher nadir of CD4+ and higher time on treatment with INSTI➔ lower risk
  - IDU➔ higher risk

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