Cabotegravir-rilpivirine long-acting injectable regimen: an analysis of the causes of interruption and impact of genotypic drug resistance in a multicentric cohort

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Background:
The use of combination regimens is paramount in the treatment of HIV infection. Virologically suppressed patients, may benefit to change their treatment in a two-drug regimen (2DR). Long acting (L-A) injectable 2DR may be a good option in selected patients (preference for a nondaily dosing, toxicity to oral therapy, prevention of long-term toxicity, adherence issues, dysphagia). The aim of this cohort study is to define the medical reasons (viral failure vs others) and the changes in GRT in interruption of cabotegravir-rilpivirine (CAB-RPV) regimen in an italian cohort of PWH who were subjected to a L-A injectable regimen according to prescriptive indications.

Methods:
We analyzed the data supplied by 10 infectious diseases units, where CAB-RPV regimen is available and administered, to make a descriptive analysis of the causes of interruption and the impact of genotyping drug resistance, when available.

Results:
The features of our population are described in Table1.
The total of patients receiving CAB-RPV was 758 ; 66 interrupted the treatment. The average age of the patients of this cohort was 53 years and average BMI was 25,26 kg/m2 (BMI max 44.28 kg/m2). Before starting the injectables, 32 patients took a triple oral therapy (regimen mostly used: TAF/FTC/RPV), while 33 assumed a 2DR regimen (regimens mostly used: DTG/3TC-DTG/RPV); as a whole, 42 took an INSTI-based regimen. Only one PWH received a mono therapy. 16 had an oral lead in. As far as the genotypic resistance pattern, 46 patients had a GRT before starting CAB-RPV; 5 patient had documented resistance to NNRTI (138A, which is an important risk factor of viral failure of RPV,K103S, Y181C, V179D, K103R, V106M, K103N), while none had INSTI resistance. We collected 14 documented viral failures. All of them carried out a GRT post VF; the results are shown in Table 2.

Table 2

	NRTI mutations (basal GRT)	NRTI mutations (after VF GRT)	NNRTI mutations (basal GRT)	NNRTI mutations (after VF GRT)	PI mutations (basal GRT)	PI mutations (after VF GRT)	INSTI mutations (basal GRT)	INSTI mutations (after VF GRT)
PATIENT 1	0	0	0	0	0	0	0	0
PATIENT 2	NA	**M41L;D67N;L210V;T215Y**	0	0	0	0	0	0
PATIENT 3	0	0	0	0	10I	0	0	0
PATIENT 4	0	0	0	0	0	0	0	0
PATIENT 5	0	**151M;70R;65R**	138A	**181I;190A**	10F	**73S;90M**	0	**140S;148H**
PATIENT 6	0	0	0	**138K;179I**	0	**10V**	0	**148R**
PATIENT 7	0	**D67N;K70R;M184V**	0	**K103N;V108I;P225H**	0	**K70R**	0	**G140S;Q148K**
PATIENT 8	T69A;S68G	S68G	0	0	0	0	0	**E138EK;G140S;G163R**
PATIENT 9	0	**V21V/I;V35V/I;V60/VI;K122E;D123E**	0	**V245E/K;A272P;K281R**	0	**A71T;V77I**	0	0
PATIENT 10	NA	**M41L;D67N;L210V;T215Y**	NA	0	NA	0	NA	0
PATIENT 11	0	GRT in progress	0	GRT in progress	M36I; L63P;L89M	GRT in progress	0	GRT in progress
PATIENT 12	0	0	0	**S68GV,E138A,Y188H**	0	0	0	**E138EK, Q148R**
PATIENT 13	0	0	0	**E138K**	0	0	0	**N155NH, H51Y**
PATIENT 14	39A;41L;67N;210W;211K;215Y;218E;219Q;M41L;D67N;K70R;Q151L;T215Y;K219Q;M41L;L74V:M184V;K219Q	M41L;D67N;K70R;L74V;M184V;T215Y; K219Q	101P;103N;K101P;K103S;Y181C	**V106VI; N348I**	13V;30N;35D;36V 63P;71V;77I;88DR;D30N;L33F;I50L;A71V;V82A;N88D;D30N	N88D	0	**G140S;Q148H; D232DN**

Note: newly emerged mutations are in bold

The other 52 patients interrupted L-A therapy for other reasons (local pain, adverse events, toxicity, patient's choice, drugs interactions). The mean time of duration of L-A regimen was 5.23 months: 5.83 (+/- 4.38 SD) months for patients with VF and 5.07 (+/- 4.79 SD) for patients who interrupted for other reasons, without statistical significance.
Lastly, we collected blood viremia at failure; mean viremia is 2,085 cp/ml (max 7,975 cp/mL, min 27 min/mL), as shown in Figure 1.
The duration of LA therapy in these 14 PWH is shown in Figure 2.

Table 1 – Study population

Age	
Mean (years)	53
Max	75
Min	27
Zenith HIV RNA	
Mean	648,803
Max	1,541,062
Min	20
Nadir CD4	
Mean	362
Max	1,270
Min	5
Suboptimal therapy	
Mean (months)	12
Max	173
Min	16
Oral lead in	
Total	16
BMI	
Mean	25.2
Max	44.2
Min	18.6
Risk factors	
MSM	34
Eterosex	22
TD	5
NA	3
Bisex	1
MSM + ex TD	1
Viral subtype	
NA	32
B	27
B/RTIe D/IP	1
G	1
C	1
F	1
CRF15_01B	1
A1	1
A	1

Note. NA: not available

Figure 1

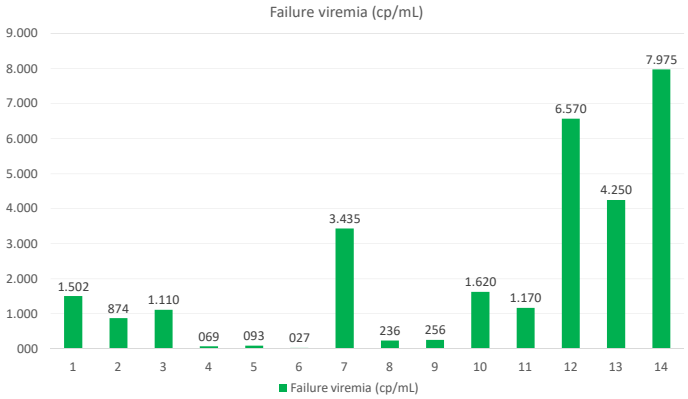
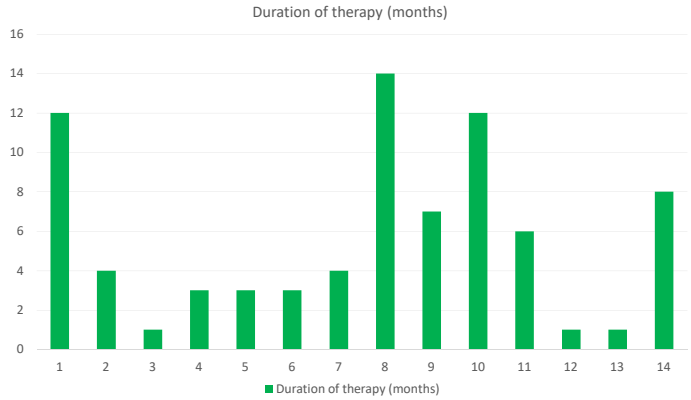


Figure 2



Conclusions:
One.eight % of our cohort experienced a VF; this result is coherent with the main studies evaluating alow failure rate of CAB-RPV.CAB-RPV L-A regimen was well-tolerated in our cohort. Respect of eligibility criteria and awareness of risk factors for VF plus strict monitoring of viro-immunological parameters are fundamental in reducing the risk of VF and the possible onset of new NNRTI/INSTI resistance mutations.

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