CROI
Conference on Retroviruses and Opportunistic Infections
Seattle, Washington
March 4-7, 2019

0493 - FACTORS ASSOCIATED WITH THERAPEUTIC FAILURE OF 2 DRUG REGIMENS (DAT'AIDS COHORT)

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BACKGROUND

- Switching an effective regimen to an alternative regimen can now be considered only if viral suppression is maintained without jeopardizing future treatment options
- There is growing evidence that some 2 drugs regimens (2-DR) are effective in maintaining virologic control and are becoming a key strategy in maintenance therapy to spare antiretroviral (ARV) classes, reduce toxicities and minimize drug-drug interactions.
- In the most recent guidelines (DHHS, EACS and French guidelines), some 2-DR can be offered in maintenance therapy
- Data in real life setting are scarce and most often limited to small sample size and short time follow-up.
- We investigated factors associated with therapeutic failure on the most frequently prescribed 2-DRs in the large French National Dat'AIDS cohort (NCT02898987).

OBJECTIVES

- The primary objective is to investigate the associated factors with virologic failure (VF) defined as 2 consecutive pVL > 50 copies/mL in subjects receiving a 2-DR in maintenance therapy
- The secondary objectives are to:
  - describe the patients' characteristics
  - evaluate the occurrence of adverse events (AE) leading to discontinuation

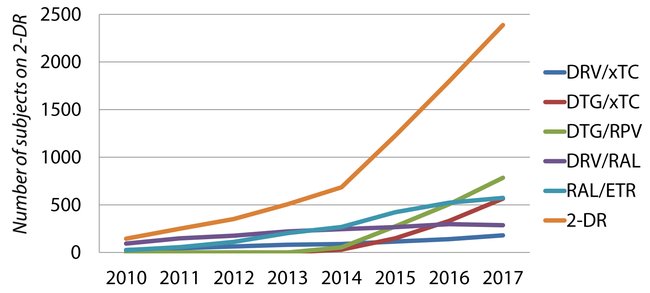
METHODS

- **Study setting and design**
  - The Dat'AIDS cohort is a collaboration of 22 major French HIV centres (NCT 02898987 clinicaltrials.gov).
  - Retrospective analysis in individuals participating in the Dat'AIDS cohort and receiving a 2-DR in maintenance therapy from January 2010 to December 2017
  - The analysis was restricted to the 5 most frequent 2-DR: dolutegravir + rilpivirine (DTG/RPV), raltegravir + etravirine (RAL/ETR), dolutegravir + 3TC or FTC (DTG/xTC), darunavir/ritonavir + RAL (DRVr/RAL) and darunavir/ritonavir + 3TC or FTC (DRVr/xTC).
  - The following Baseline patient characteristics were extracted : Age, gender, HCV and HBV co-infection, group of HIV transmission (MSM/heterosexual/other), ARV history, duration of undetectable viral load before 2-DR initiation, number of previous ARV regimen, history of virological failure, zenith plasma viral load (pVL), nadir CD4, CD4 at 2-DR initiation
  - Reasons for discontinuation were collected from the electronic medical record. We classified them in 4 groups : ARV-related adverse event (AE), virologic failure (VF), treatment simplification, and miscellanous reasons
- **Inclusion criteria**
  - HIV-1 infected subject
  - Age ≥ 18 year-old
  - Subject starting a 2-DR as a maintenance strategy (plasma HIV RNA (pVL) < 50c/mL at baseline between 01 Jan 2010 and 31 Dec 2017
- **Statistical analysis**
  - A Cox proportional hazards model adjusted on socio-demographic, immuno-virologic and ARV history-related variables was used for analyses. A multivariable model including all characteristics was performed. This model allows estimation of the risk ratio for discontinuation for VF for each 2-DR, adjusted for all other variables.
  - All analyses were performed using R software
  - Data were censored on 31 Dec 2017

RESULTS

- Among the 65 679 subjects included in the Dat'AIDS cohort, 5286 subjects started a 2-DR in maintenance therapy between Jan 2010 and Dec 2017.
- 171 different combinations of 2-DR were listed
- The 5 most frequent 2-DR that represent 3484 2-DR initiations were selected for analysis
  - DTG/RPV n=974, 28%
  - RAL/ETR n=869, 25%
  - DTG/xTC n=677, 19%
  - DRV/RAL n=604, 18%
  - DRV/xTC n=360, 10%
- Prescription of the 2-DR from 2010 to 2017 are presented in Figure 1

Figure 1 - *Evolution of patients on a 2-DR between 2010 and 2017*



- Treatment discontinuations occurred in 1178 cases due to AE (n=417, 12%), simplification (n=245, 7%), VF (n=122, 3.5%) and miscellaneous reasons (n=394, 11.3%).
- Frequency and reasons for treatment discontinuations are detailled in Table 2

n (%) or median (IQR)	DTG/RPV n=974	DTG/xTC n=677	DRV/RAL n=604	DRV/xTC n=360	RAL/ETR n=869	2-DR n=3484
2-DR discontinuation	**215 (22)**	**127(18.7)**	**326(53.9)**	**192(53.3)**	**318(36.5)**	**1178 (33.8)**
Time on 2-DR before discontinuation (mo.)	5 [2, 13]	4 [2, 10]	15 [6, 31]	10 [3, 25]	14 [4, 26]	10 [3, 23]
Virologic failure	**18 (1.8)**	**12 (1.7)**	**37 (6.1)**	**10 (2.7)**	**45 (5.1)**	**122 (3.5)**
Adverse event	**114 (11.7)**	**59 (8.7)**	**101 (16.7)**	**52 (14.4)**	**91 (10.4)**	**417 (12)**
CNS symptom	43 (4.4)	24 (3.5)	12 (2.0)	9 (2.5)	20 (2.3)	108 (3.1)
GI disturbance	11 (1.1)	10 (1.5)	20 (3;3)	17 (4.7)	12 (1.4)	70 (2.0)
Lipodytrophy	4 (0.4)	(0)	14 (2.3)	3 (0.8)	9 (1.0)	30 (0.9)
Dyslipidemia	(0)	(0)	12 (2.0)	10 (2.8)	1 (0.1)	23 (0.7)
Cutaneous symptom	5 (0.5)	3 (0.4)	4 (0.7)	(0)	9 (1.0)	21 (0.6)
Renal impairment	3 (0.3)	2 (0.3)	3 (0.5)	2 (0.6)	(0)	10 (0.3)
Other AE	48 (4.9)	20 (3.0)	36 (6.0)	11 (3.1)	40 (4.6)	155 (4.4)
Simplification	**8 (0.8)**	**13 (1.9)**	**101 (16.7)**	**51 (14.2)**	**72 (8.3)**	**245 (7.0)**
Miscellanous	**75 (7.7)**	**43 (6.4)**	**87 (14.4)**	**79 (21.9)**	**110 (12.7)**	**394 (11.3)**

Table 2 - *Rate and reasons for treatment discontinuations*

% or median (IQR)	DTG/RPV	DTG/xTC	DRV/xTC	DRV/RAL	RAL/ETR	2-DR
n	974	677	360	604	869	**3484**
Age (y.)	54.4 [48, 61]	53 [45, 61]	49.1 [42, 59]	52 [46, 59]	54.4 [49, 61]	**53.6 [46, 61]**
Male	68.2	69.4	59.7	68.4	71.0	**67.9**
CDC Stage C	28.3	18.9	27.2	39.6	32.3	**29.3**
MSM	37.4	40.6	28.6	32.9	39.9	**37**
Other	20.2	20.8	24.2	30.3	24.6	**76.4**
Heterosexual	42.4	38.6	47.2	36.8	35.4	**39.4**
Hepatitis C coinfection	19.5	17.4	23.6	23.0	19.6	**17.2**
Hepatitis B coinfection	3.5	3.5	7.8	4.1	2.5	**3.8**
CD4 at 2-DR initiation (/mm3)	678 [456, 917]	722 [518, 949]	576 [403, 794]	587 [393, 806]	653.5 [459, 884]	**646 [457, 857]**
Nadir CD4 (/mm3)	195 [95, 308]	281 [162, 407]	220 [101, 342]	144 [51, 257]	175 [70, 286]	**199 [87, 315]**
CD4 < 200/mm3	51.1	32.6	45.8	63.8	55.9	**50.1**
Zenith pVL(log c/mL)	5 [4.3, 5.5]	4.9 [4.2, 5.4]	4.9 [4.2, 5.4]	5.1 [4.4, 5.7]	5 [4.2, 5.5]	**5 [4,3, 5.5]**
pVL > 5 log c/mL	44.9	42.5	42.0	51.2	46.6	**48**
Duration of undetectable pVL (mo.)	89 [45, 128]	79 [43, 126]	59 [24, 106]	57 [21, 103]	80 [48, 115]	**76.3 [39, 119]**
Duration < 12 mo.	6.6	6.6	16.7	18.0	6.7	**9.1**
Previous ARV lines	7 [4, 11]	4 [3, 8]	5 [3, 9]	8 [5, 13]	9 [5, 13]	**7 [4, 11]**
First ARV line <1996	27.5	14.2	16.1	38.1	37.7	**28.1**
Previous VF	26	13.7	36.4	51.8	47.8	**39.7**
Duration of 2-DRs (mo.)	13 [5, 24]	23 [10, 37]	11 [4, 23]	24 [10, 48]	13 [4, 30]	**16 [6, 30]**

Table 1 – *Patients' characteristics (n=3484)*

		Hazard Ratio [CI 95%]	p	Adjusted HR [CI 95%]	p	Adjusted HR [CI 95%]
Age > 50 y.		0.98 (0.68-1.41)	0.905	0.93 (0.63-1.36)	0.703	
Male		0.86 (0.58-1.28)	0.452	0.71 (0.44-1.15)	0.162	
CDC Stage C		1.09 (0.74-1.59)	0.664	0.97 (0.65-1.45)	0.891	
Transmission	Other	0.85 (0.51-1.39)	0.513	0.91 (0.52-1.57)	0.722	
(ref MSM)	Heterosex.	1.21 (0.81-1.8)	0.346	1.5 (0.94-2.41)	0.091	
HBV or HCV coinfection		1.06 (0.69-1.63)	0.796	1.15 (0.72-1.85)	0.556	
Nadir CD4 < 200/mm³		1.33 (0.92-1.9)	0.125	0.96 (0.63-1.46)	0.853	
Zenith pVL > 5 log c/mL		2.08 (1.44-3.01)	< 0.001	**1.86 (1.27-2.74)**	**0.002**	
Undetectable pVL < 12 mo.		2.30 (1.48-3.58)	< 0.001	**2.29 (1.45-3.63)**	**< 0.001**	
Previous ARV lines < 7		0.61 (0.42-0.87)	0.007	0.75 (0.46-1.22)	0.248	
2-DR	DTG/RPV (ref)	-	-	-	-	
	DRV/RAL	1.81 (1.02-3.23)	0.044	1.6 (0.87-2.92)	0.129	
	DTG/xTC	1.03 (0.5-2.14)	0.94	1.35 (0.64-2.85)	0.435	
	DRV/xTC	1.16 (0.53-2.53)	0.709	1.2 (0.54-2.65)	0.658	
	RAL/ETR	1.74 (1-3.03)	0.05	**1.85 (1.05-3.27)**	**0.033**	
First ARV line < 1996		1.33 (0.92-1.92)	0.125	0.95 (0.59-1.54)	0.835	
Previous VF		1.06 (0.69-1.63)	0.796	**1.63 (1.09-2.46)**	**0.018**	

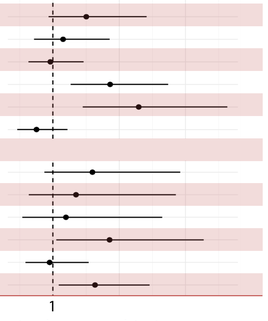


Table 3 - *Associated factors with virologic failure, Cox proportional hazards model adjusted on socio-demographic, immuno-virologic and ARV history-related variables*

DISCUSSION / CONCLUSION

- This study is the first one that compare the five most prescribed 2-DRs in maintenance strategy in real life setting.
- In this large French cohort:
  - 3484 subjects starting a 2DRs in maintenance therapy between 2010 and 2017 were included
  - 2-DRs were prescribed mostly to an aging and highly experienced population
  - 2-DRs show a high efficacy in virologically controlled subjects with a low rate of virologic failure (3.4 %).
- Factors associated with virologic failure are :
  - zenith pVL > 5 log10 c/mL (HRa 1.85 [1.27-2.74]
  - duration of undetectable pVL less than 12 months (HRa 2.29 [1.45-3.63])
  - history of virologic failure (HRa 1.63 [1.09-2.46])
  - treatment with raltegravir + etravirine (HRa 1.85 [1.05-3.27]).
- Despite a non significative result due to a possible lack of power, treatment with darunavir/r + raltegravir could be associated with more virologic failure
- These results confort the place of 2DRs in maintenance strategies

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