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POSTER

Antiretroviral therapy

P 12 Switching from 3TC/DTG and RPV/DTG to Triple Drug and Dual PI-Based therapies for toxicity/intolerance: data from the ICONA cohort

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ABSTRACT

Background: Two-drug regimens (2DR) [lamivudine (3TC)/dolutegravir(DTG) or rilpivirine(RPV/DTG)] are generally well tolerated but there is a proportion of people with HIV (PWH) who develops toxicity/intolerance to these regimens and are switched back to three-drug regimens (3DR) or dual PI-based therapies (2DR-PI/b). The frequency and factors associated with these switches have been poorly investigated.

Material and methods: We included all PWH enrolled in the Icona cohort who switched to 3TC/DTG or RPV/DTG with a plasma viral load (pVL) <50 copies/mL excluding people with a positive HBsAg. The primary aim was to estimate the cumulative incidence of switch from 3TC/DTG and RPV/DTG to 3DR or 2DR-PI/b due to toxicity and intolerance (including as events drug-drug interactions (DDI), pregnancies, other unknown reasons, and patients' decisions). An intention to treat approach has been used. PWH who switched to 2DR not PI-based were considered still at-risk. Secondary objectives were to describe the reasons behind discontinuations, and predictors of the discontinuation due to intolerance/toxicity were identified using a Fine-Gray Cox regression for competing events.

Results: We included 2,660 PWH for a total of 6,708 person-year-follow-up (PYFU). Of them, 2,078 (83%) started 3TC/DTG, and 427 (17%) RPV/DTG. The demographic and clinical characteristics are summarized in Table 1. Overall, 93 (3.5%) people discontinued the treatment due to toxicity/intolerance with a five-years cumulative incidence of 5.93% (95%CI 4.49-7.65%) (Figure 1). Specifically, 63 (67.7%) PWH discontinued their regimen due to toxicity, 6 (6.5%) PWH chose to discontinue, 8 (8.6%) due to pregnancy or for being planning it, 4 (4.3%) due to DDI, and 12 (12.9%) due to unknown reason, yet maintained an undetectable HIV-RNA level. Regimens started after 3TC/DTG or RPV/DTG discontinuation are detailed in Figure 2. In the multivariable analysis (Table 2), assigned female-sex at birth (AFAB) [aSHR 2,05 (95%CI 1.30-3.25)], and previous toxicities [aSHR 1.93 (95%CI 1.24-3.01)] were associated with an increased risk of discontinuation. Conversely, individuals previously exposed to DTG had a lower risk [aSHR 0.52 (95%CI 0.33-0.82]. After excluding discontinuation related to pregnancy, AFAB was still associated with a 50% higher risk of interruption, although no longer significant Results were consistent after excluding 12 people whose reasons for discontinuation were unknown.

Conclusion: In our study the discontinuation of 2DR regimens due to toxicities and intolerance followed by a switch to a 3DR was rarely observed. AFAB, naivety to DTG, and prior toxicities were key predictors of DTG discontinuation. After these stops, clinicians have chosen to avoid the use of DTG, and in most cases INSTI, and consequently abandon altogether not-boosted dual therapy as an option. These findings highlight the importance of treatment tailoring and previous-regimen assessment when starting a 2DR regimen.

Table 1. Demographic and clinical characteristics of 2660 people who started a treatment with 3TC/DTG or RPV/DTG

	No discontinuation	Discontinuation for toxicity/intolerance	Discontinuation for other reasons	*p-value*
Number of PWH	2,505 (94.2)	93 (3.5)	62 (2.3)	
AFAB, n(%)	441 (17.6)	28 (30.1)	11 (17.7)	0.009
Age (years), median (IQR)	47.0 (38.0 56.0)	44.0 (36.0 54.0)	50.0 (40.0 57.0)	0.123
Time on ART (years), median (IQR)	5.6 (3.1 9.2)	5.1 (3.0 8.6)	3.9 (1.9 10.3)	0.547
Italian, n(%)	2,179 (86.9)	80 (86.0)	58 (93.5)	0.296
Caucasian, n(%)	2,282 (91.1)	82 (88.2)	59 (95.2)	0.306
Risk factor for acquiring HIV, n(%) Heterosexual IDU MSM Other/Unknown	 886 (35.4) 174 (6.9) 1,296 (51.7) 149 (5.9)	 43 (46.2) 6 (6.5) 40 (43.0) 4 (4.3)	 20 (32.3) 4 (6.5) 36 (58.1) 2 (3.2)	0.399
History of AIDS, n(%)	291 (11.6)	13 (14.0)	13 (21.0)	0.066
Zenith HIV-RNA (log10 copies/mL) median (IQR)	4.7 (4.2 5.3)	4.7 (4.2 5.3)	4.7 (4.2 5.5)	0.527
Nadir CD4 (cells/mL), median (IQR)	349.0 (208.0 499.0)	330.0 (160.0 528.0)	339.5 (187.0 504.0)	0.965
CD4 cell count at 2DR start, median (IQR)	728.5 (551.0 951.5)	726.0 (575.0-969.0)	653.0 (482.0 977.0)	0.541
Anti HBcAg positive, n(%)	495 (24.7)	14 (18.9)	13 (30.2)	0.361
Anti HCV positive, n(%)	212 (8.9)	11 (12.5)	6 (10.2)	0.487
Number of previous regimens, median (IQR)	2.0 (1.0 3.0)	2.0 (1.0 4.0)	2.0 (1.0 4.0)	0.016
Previous INSTI exposure, n(%)	1,703 (68.0)	54 (58.1)	43 (69.4)	0.128
Previous DTG exposure, n(%)	1,122 (44.8)	25 (26.9)	27 (43.5)	0.003
Previous dual regimens, n(%)	290 (11.6)	18 (19.4)	8 (12.9)	0.073
Previous treatment, n(%) 2DR 2NRTI_INSTI 2NRTI_NNRTI 2NRTI_PI Other	 222 (8.9) 1,505 (60.1) 505 (20.2) 156 (6.2) 117 (4.7)	 15 (16.1) 45 (48.4) 21 (22.6) 7 (7.5) 5 (5.4)	 7 (11.3) 33 (53.2) 11 (17.7) 3 (4.8) 8 (12.9)	0.027
Previous drug toxicity, n(%)	995 (39.7)	55 (59.1)	37 (59.7)	<0.001
Previous virological failure, n(%)	174 (6.9)	8 (8.6)	9 (14.5)	0.064
Treatment, n(%) 3TC/DTG RPV/DTG	 2,078 (83.0) 427 (17.0)	 73 (78.5) 20 (21.5)	 50 (80.6) 12 (19.4)	0.486
Years of HIV-RNA <50 copies/mL before switch, median (IQR)	5.0 (2.6 8.0)	4.1 (2.3 7.0)	3.2 (1.1 7.6)	0.013

PWH: People With HIV; AFAB: Assigned Female at Birth; IQR: Interquartile Range; ART: Antiretroviral Treatment; IDU: Injective Drug User; MSM: Man Who Have Sex With Men; INSTI: Integrase Strand Transfer Inhibitors; DTG: Dolutegravir; 2DR: Two-Drugs Regimen; NRTI: Nucleoside Reverse Transcriptase Inhibitor; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; PI/b: Protease Inhibitors/boosted; 3TC: Lamivudine; RPV: Rilpivirine.

Figure 1. Cumulative incidence of 3TC/DTG or RPV/DTG discontinuation due to toxicity or intolerance. Interruptions due to virological failure, participation in clinical trials, and simplification to reduce the number of tablets were considered as competing events.

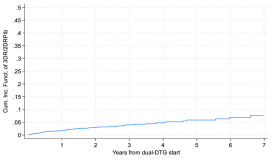

Figure 2. **Regimens initiated after the 93 discontinuations due to toxicity/intolerance**

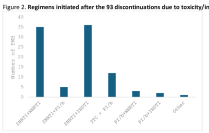

Table 2. Fine-Gray Cox Regression analysis to assess the relationship between demographics, clinical characteristics and discontinuation due to toxicity/intollerance

	Unadjusted				Adjusted models				
	SHR	**95%CI**		***p***	**aSHR**	**95%CI**		***p***	
AFAB	1,91	1,22	2,99	0,001	2,05	1,30	3,25	0,002	Adjusted for age
Caucasian	0,67	0,36	1,26	0,219	0,84	0,45	1,57	0,581	Adjusted for age and sex
Italian	0,84	0,47	1,50	0,551	1,05	0,58	1,90	0,872	Adjusted for age and sex
Risk factor for acquiring HIV									Adjusted for age and sex
Heterosexual	Ref.				Ref.				
IDU	0,73	0,31	1,70	0,464	0,83	0,35	1,95	0,664	
MSM	0,65	0,42	0,99	0,046	0,73	0,42	1,26	0,255	
Other/Unknown	0,60	0,22	1,67	0,328	0,67	0,24	1,88	0,451	
Year of start ≥ 2019	0,64	0,40	1,03	0,067	0,66	0,41	1,06	0,089	Adjusted for age and sex
STR (vs MTR)	0,87	0,55	1,38	0,554	1,23	0,68	2,23	0,49	Adjusted for age, sex and year ART
Previous virological failure	1,23	0,59	2,54	0,578	1,27	0,58	2,74	0,551	Adjusted for age, sex, years on ART, Zenith HIV-RNA
Years of VS pre switch 2DR, per 1 more									
0-2	Ref.				Ref.				
2-5	1,09	0,63	1,91	0,755	1,12	0,64	1,96	0,682	
5>	0,91	0,53	1,56	0,725	1,00	0,58	1,71	0,997	
Previous regimen									Adjusted for age and sex
2NRTI + INSTI	Ref.				Ref.				
2DR	1,48	0,79	2,80	0,22	1,56	0,82	2,96	0,177	
2NRTI + NNRTI	1,20	0,71	2,02	0,50	1,22	0,72	2,05	0,459	
2NRTI + PI/b	1,32	0,60	2,90	0,49	1,24	0,56	2,75	0,595	
OTHER	1,14	0,44	2,92	0,79	1,20	0,47	3,07	0,708	
Previous DTG exposure	0,53	0,33	0,84	0,01	0,52	0,33	0,82	0,005	Adjusted for age and sex
History of AIDS	1,25	0,70	2,24	0,458	1,37	0,76	2,47	0,301	Adjusted for age and sex
Previous ART toxicities	1,77	1,16	2,70	0,008	1,93	1,24	3,01	0,004	Adjusted for age and sex

SHR: Sub-distribution Hazard Ratio; CI: Confidence Interval; AFAB: Assigned Female at Birth; IDU: Injective Drug User; MSM: Man Who Have Sex With Men; STR: Single Tablet Regimen; MTR: Multiple Tablet Regimen; VS: Virological Suppression; 2DR: Two Drug Regimen; NRTI: Nucleoside Reverse Transcriptase Inhibitor; INSTI: Integrase Strand Transfer Inhibitors; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; PI/b: Protease Inhibitors/boosted; DTG: Dolutegravir; ART: antiretroviral treatment