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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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Introduction/Summary

- Two-drug regimens (2DR) [lamivudine (3TC)/dolutegravir(DTG) or rilpivirine(RPV/DTG)] are generally well tolerated.
- 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.

Study Design

- 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).
- Secondary objectives were to describe the reasons behind discontinuations, and predictors of the discontinuation

Methods

- An intention to treat approach has been used. PWH who switched to 2DR not PI-based were considered still at-risk.
- Predictors of the discontinuation due to intolerance/toxicity were identified using a Fine-Gray Cox regression for competing events.

Results

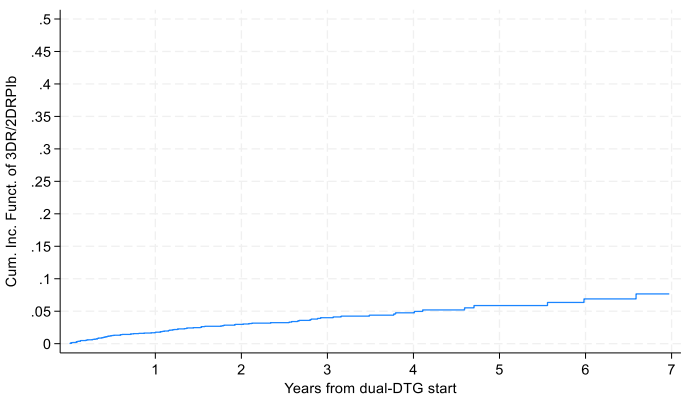
- We included 2,660 PWH for a total of 6,708 person-year-follow-up (PYFU). Of them, 2,078 (83%) started 3TC/DTG, and 427 (17%) RPV/DTG. The demographic and clinical characteristics are summarized in Table 1.
- 93 (3.5%) people discontinued the treatment due to toxicity/intolerance with a five-years cumulative incidence of 5.93% (95%CI 4.49-7.65%) (Figure 1).
- 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.

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

	No discontinuation	Discontinuation for toxicity or 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(%)	2,178 (86.9)	80 (86.0)	58 (93.5)	0.296
Risk factor for acquiring HIV, n(%)				
Heterosexual	886 (35.4)	43 (46.2)	20 (32.3)	0.399
IDU	174 (6.9)	6 (6.5)	4 (6.5)	
MSM	1,296 (51.7)	40 (43.0)	36 (58.1)	
Other/Unknown	149 (5.9)	4 (4.3)	2 (3.2)	
History of AIDS, n(%)	291 (11.6)	13 (14.0)	13 (21.0)	0.066
Zenit 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
Zenit HIV-RNA > 100'000 copies/mL	901 (36.9)	33 (36.3)	24 (40.0)	0.880
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
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, n(%)	1,703 (68.0)	54 (58.1)	43 (69.4)	0.128
Previous DTG, 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	222 (8.9)	15 (16.1)	7 (11.3)	0.027
2NRTI_INSTI	1,505 (60.1)	45 (48.4)	33 (53.2)	
2NRTI_NNRTI	505 (20.2)	21 (22.6)	11 (17.7)	
2NRTI_PI	156 (6.2)	7 (7.5)	3 (4.8)	
Other	117 (4.7)	5 (5.4)	8 (12.9)	
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	2,078 (83.0)	73 (78.5)	50 (80.6)	0.486
RPV/DTG	427 (17.0)	20 (21.5)	12 (19.4)	
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: Men 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.

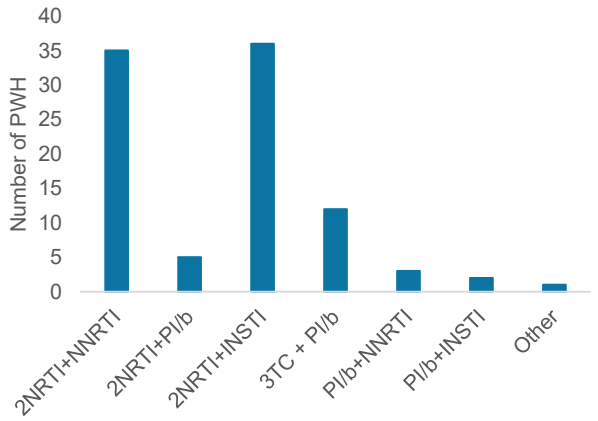
Figure 1. Cumulative incidence of 3TC/DTG or RPV/DTG discontinuation due to toxicity or intolerance. Interruptions due to virological failure, participation in clinical trials, and simplification to reduce the number of tablets were considered as competing events.



Results of 2

- The most common toxicity affected the nervous system in 25 people, gastrointestinal issues in 9, and dyslipidemia in 8.
- Regimens started after 3TC/DTG or RPV/DTG discontinuation are detailed in Figure 2.
- In the multivariable analysis 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.

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



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, "no previous history of DTG use, and prior toxicities were key predictors of DTG discontinuation. After these stops, clinicians have chosen to avoid the use of DTG, 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.

Study Group

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