Incidence and determinants of antiretroviral switching away from TDF-based backbone in the recent years in the Icona Foundation Cohort

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BACKGROUND

In the past years, NRTI backbone based on tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) has represented the standard of care in the antiretroviral setting.

Increasing concerns about TDF renal toxicity, as itself or in combination with other antiretrovirals, and the availability of effective and safe alternatives, as abacavir (ABC), tenofovir alafenamide (TAF) or NRTI-sparing less-drug regimens (LDRs), enhances chances of TDF substitution.

Rate and predictors of TDF discontinuation may have public health implications in the view of availability of TDF/FTC generic formulation.

AIM

To report data from real life on the incidence and factors associated with discontinuation of TDF in the INSTI antiretroviral era.

STUDY DESIGN AND METHODS

HIV-1 positive patients from the Icona Foundation Cohort, aged 18 years or over, initiating their first cART regimen with TDF-based backbone plus a 3rd drug from January 2009 onwards were included. Patients were included if they had been treated for >30 days with TDF, subject with HbsAg positivity were not included.

Primary endpoint of the analysis was TDF discontinuation for any reasons. The adjusted risk of TDF discontinuation was estimated by Cox regression according to main fixed covariates at baseline: gender, race, CDC C stage, mode of HIV transmission, HCVAb status, CD4 and CD8 count, HIVRNA, total and HDL cholesterol, total number of non-communicable comorbidities (NCC) (of whom CKD, hypertension, diabetes, previous cardiovascular or hepatic event) and third drug (the class or the single drug). eGFR during TDF exposure was estimated by CKD-EPI formula and was used in the models as time dependent covariate. Calendar year of cART initiation was divided into three periods: 2009-2011, 2012-2014, 2015-2017.

RESULTS I

5544 ART-naive patients were included in the analyses: 81% males, median age of 39 years (IQR 31-47), 10% were on a CDC stage C, median CD4 count 332 cells/mmc (178-474), median HIV RNA 4.74 (4.16-5.24) Log 10 cps/mL. 2296 (41.4%) started a NNRTI-based, 2015 (36.2%) a PI/b-based and 1233 (22.4%) a INSTI-based regimen. 2546 (46%) pts discontinued TDF after a median of 2.3 years (IQR 1.1-3.9).

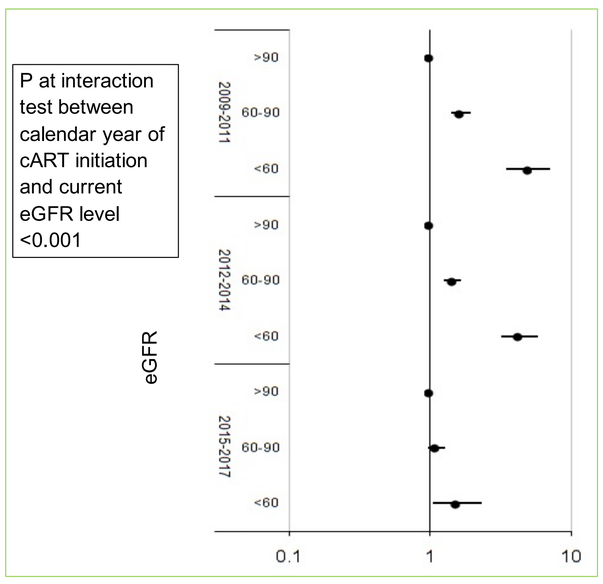
RESULTS II

The Incidence Rate (IR) of TDF discontinuation for any reason significantly increased from 10.3 (95%CI 9.5-11.1) per 100 PYFU in 2009-11, to 14.3 (13.4-15.2) in 2012-14 and to 34.9 (32.7-37.7) in 2015-17 (p<0.001). Two separate models [a) and b)] to estimate hazard risk by third drug class and by type of third drug were performed (Table 1). Using NNRTI as reference, an increased risk of TDF discontinuation was found both for PI/b (aHR 1.55; 95%CI 1.41-1.71) and INSTI (2.09; 1.85-2.35). DTG (2.78; 2.32-3.33), EVG/c (3.59; 2.94-4.39) and RAL (2.19; 1.79-2.69) also were associated with higher risk of discontinuation respect to EFV.

By multivariable Cox regression, a lower current eGFR was associated to higher risk of discontinuing TDF in all time periods. HR for eGFR<60 became considerably lower in last 3-year period (Table 2). There was a significant interaction between calendar year of cART initiation and current eGFR level (p<0.001) (Figure 1).

Non-communicable comorbidities (NCC) were associated in first and second periods, but not in third one. P at interaction test was significant (p<0.001) (Table 2).

Figure 1 – Adjusted hazard ratios of tenofovir disoproxil fumarate (TDF) discontinuation according to calendar year of TDF initiation and current e-GFR estimated by CKD-Epi formula.



Regimen started after TDF discontinuation are shown in Table 3.

Table 1 – Crude and adjusted hazard ratio (HR) of TDF discontinuation for any causes by 3rd drug class and by single 3rd drug

a)	HR	95%CI		p-value	aHR*	95%CI		p-value
NNRTI	1							
PI/b	1.36	1.25	1.50	<0.001	1.55	1.41	1.71	<0.001
INSTI	4.11	3.70	4.57	<0.001	2.09	1.85	2.35	<0.001

b)	HR	95%CI		p-value	aHR*	95%CI		p-value
EFV	1							
RPV	3.02	2.61	3.48	<0.001	1.56	1.33	1.83	<0.001
DRV/r or /c	2.48	2.17	2.83	<0.001	1.92	1.67	2.20	<0.001
ATV/r or /c	1.96	1.71	2.25	<0.001	1.92	1.67	2.20	<0.001
DTG	8.52	7.28	9.96	<0.001	2.78	2.32	3.33	<0.001
EVG	11.18	9.37	13.34	<0.001	3.59	2.94	4.39	<0.001
RAL	3.36	2.76	4.08	<0.001	2.19	1.79	2.69	<0.001
other	1.50	1.25	1.80	<0.001	1.59	1.31	1.92	<0.001

*adjusted for gender, ethnicity, mode of HIV transmission, HCV coinfection, CD4 and CD8 count, HIVRNA, total and HDL cholesterol, number of NCC, calendar year of cART initiation and current eGFR

Table 2 – Factors independently associated with TDF discontinuation according to three time periods (2009-11; 2012-14; 2015-17) of cART initiation. Significant results are reported in bold.

	2009-2011		2012-2014		2015-2017	
	aHR*	95%CI	aHR*	95%CI	aHR*	95%CI
Current e-GFR ml/min/1,73 m² (by CKD-EPI)						
- **>90 (ref.)**	1.00		1.00		1.00	
- **60-90**	**1.65**	**1.41-1.96**	**1.45**	**1.26-1.67**	1.11	0.96-1.28
- **<60**	**4.96**	**3.45-7.14**	**4.29**	**3.18-5.77**	**1.56**	**1.05-2.31**
NCC						
- **0 (ref.)**	1.00		1.00		1.00	
- **1**	**1.65**	**1.20-2.26**	1.23	0.94-1.60	1.01	0.75-1.35
- **2+**	**2.21**	**1.03-4.75**	**1.77**	**1.04-3.04**	1.12	0.63-2.02
ARV third drug class						
- **NNRTI (ref.)**	1.0		1.0		1.0	
- **PI/b**	**1.92**	**1.62-2.28**	**1.37**	**1.19-1.57**	**1.45**	**1.15-1.84**
- **INSTI§**	1.17	0.73-1.89	**2.12**	**1.70-2.64**	**2.43**	**2.04-2.89**

*adjusted for gender, ethnicity, mode of HIV transmission, HCV coinfection, CD4 and CD8 count, HIVRNA, total and HDL cholesterol

§ A sensitivity analysis, performed after excluding EVG/c, confirmed these results.

Table 3 - Regimen started after TDF discontinuation

Regimen started after TDF	Over 2224 pts who started a new regimen after TDF
TAF/FTC	1008 (45.3%)
ABC/3TC	601 (27.0%)
Other backbone	120 (5.4%)
NRTI-sparing LDRs	445 (20.0%)

CONCLUSIONS

In our cohort, a significant increase of TDF discontinuation was found after 2015. Associated drugs (PI/b and INSTI) and eGFR decline mainly predicted drug change, with a lower risk of switching away from TDF at declining eGFR levels in the last period. The remarkable risk of TDF switching in people receiving INSTI, increasingly in the last three years, may suggest physicians attitudes towards co-formulated regimens more than TDF safety concerns in clinical decision.

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