In the past years, NRTI backbone based on tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) has represented the core of the standard care in antiretroviral setting. Increasing concerns about TDF renal toxicity, as itself or in combination with other antiretrovirals, and the availability of effective and safer 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 the INSTI antiretroviral agent.

STUDY DESIGN AND METHODS

HIV-1 positive patients from the Iacona Foundation Cohort, aged 18 years or over, initiated 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 ltbAg positivity were not included.

Primary endpoint of interest was analysis of TDF discontinuation for any reasons. The adjusted risk of TDF discontinuation was estimated by Cox regression analysis according to main fixed covariates at baseline: gender, race, CDC stage, mode of HIV transmission, HCV/STT status, CD4 and CD6 count, HIV RNA, total and HDL cholesterol, total number of non-communicable comorbidities (NCC) (of which 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. CART discontinuation was defined into three periods: 2009-2011, 2012-2014, 2015-2017.

RESULTS

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 (<0.001).

Two separate Cox regression analyses assessing hazard risk by type of third drug were performed (Table 1). Using NNRTI as reference, an increased risk of TDF discontinuation was found both for P/br (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 multivariant 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).

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

CONCLUSIONS

In our cohort, a significant increase of TDF discontinuation was found after 2015. Associated drugs (Pib 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.

ICONA Foundation is supported by unrestricted grants from BMS, Gilead Sciences, Janssen, MSD and VIV Healthcare