Co-administration of ritonavir-boosted protease inhibitors and rate of tenofovir discontinuation in clinical practice

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ABSTRACT

Background: In clinical trials, toxicity leading to discontinuation of tenofovir (TDF) is a rare occurrence (3% by 2 years); however in clinical practice it seems to be higher. Previous studies suggested that TDF toxicity is higher when it is co-administered with ritonavir-boosted protease inhibitors (PI/r) instead of nonnucleoside reverse-transcriptase inhibitors (NNRTI). The aim of this study is to assess the rate of TDF discontinuations in clinical practice and to explore associated factors.

Methods: All previously antiretroviral-naive patients initiating a TDF-containing regimen were selected from the ICONA Foundation Study cohort, unless they were positive for hepatitis B surface antigen. The primary outcome was TDF discontinuation (>30 days) regardless of the reason, the secondary was TDF discontinuation due to toxicity. All analyses were repeated for the isolated stop of TDF (i.e., discontinuation or substitution of TDF, carrying on all other concurrent antiretrovirals). The main reason for discontinuation as reported by the treating physicians was used to classify stops. Kaplan-Meier (KM) analysis and Cox proportional hazards model were used. Patients were followed from the date of starting TDF until its discontinuation or their last recorded visit. In the secondary outcome analysis, follow-up was truncated at the date of stopping for a reason different from toxicity.

Results: 3,618 naïve patients were enrolled: 736 (20.2%) were female, the median age was 38 years, 54% of patients were on PI/r-based regimen and 46% on NNRTI; 80% of calculated estimated glomerular filtration rates (eGFR) were >90 ml/min. The probability of discontinuation of TDF regardless of the reason was of 10% (95% CI:8-11) at 2 years , 20% by 8 years. The causes of discontinuation were: non- adherence (51%), toxicity (20%), failure (5.3%), simplification (2.7%) and other/unknown causes (20%).The 5 year KM estimates in the PI/r vs NNRTI group were 31.8% vs. 11,7%, respectively (log-rank p=0.0001), for the outcome of stopping regardless of the reason, and 11,8% vs. 5,7% (p=0.0004) for discontinuation due to toxicity.In a multivariable Cox model, PI/r use and lower eGFR at baseline were associated with increased risk of discontinuing TDF regardless of the reason; PI/r use, to be older and lower eGFR at baseline was associated with increased risk of discontinuing TDF for toxicity and PI/r use was a factor associated with isolated stop of TDF. No differences in rates of TDF discontinuations between PIs were found.

Conclusion: In our cohort, the observed frequency of TDF discontinuations was low although higher than estimated in clinical trials (10% by 2 years). Co-administration of TDF with PI/r was associated with an increased rate of TDF discontinuations. This findings should guide further investigations of the mechanism that may have led to discontinuation of TDF in patients using PI/r.

INTRODUCTION

- In clinical trials, toxicity leading to discontinuation of tenofovir (TDF) is a rare occurrence (up to 3% by 2 years)
- In clinical practice, the frequency of TDF discontinuations due to toxicity or side effects seems to be higher
- Trial data suggested that the risk of TDF toxicity is higher when it is co-administered with PI/r vs. NNRTI

OBJECTIVES

The aim of our study is to describe the use of TDF in clinical practice, to assess the rate of its premature discontinuation and to explore factors associated with TDF discontinuation (including use of PI/r) in the setting of people starting their first ART regimen.

METHODS

Study population

Patients of Icona Foundation Study who started a first cART including TDF from ART-naïve

Exclusion : HBsAg+

Outcome

- Discontinuation of TDF (with other drugs or isolated)
- The main reason for discontinuation as reported by the treating physicians was used to classify TDF stops
- Stops followed by re-initiation of TDF-based regimens or 'changes in formulation' *within 1 month* not counted as events

Statistical analysis

Survival analysis using Kaplan-Meier (KM) and Cox proportional hazards model

Patients were followed from the date of starting TDF-based regimen until its discontinuation or their last recorded clinical visit

Competing risk analysis for the outcome of discontinuation due to toxicity

ITT approach (ignoring switches of PI/r, NNRTI, other NRTIs)

RESULTS

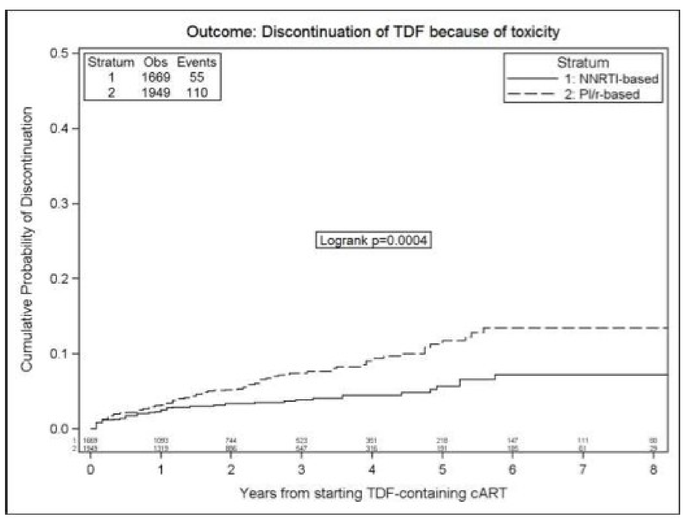
Drug class	PI/r N=1,669	NNRTI N=3,618	Total N=1,949	Characteristics
Female, %	22,6%	17,7%	20,3%	
Age at enrolment, median (IQR)	38 (32-45)	37 (31-43)	38 (32-44)	
MSM, %	37,1%	43,5%	40,1%	
Black ethnicity, %	7,7%	5,1%	6,5%	
Calendar year, median	2011	2011	2011	
AIDS, %	7,5%	4,1%	5,9%	
VL at cART (log), median	4.90	4.60	4.74	
CD4 count at cART, median	253	330	296	
eGFR (CKD-Epi) at cART, median	106.5	105.9	106.2	

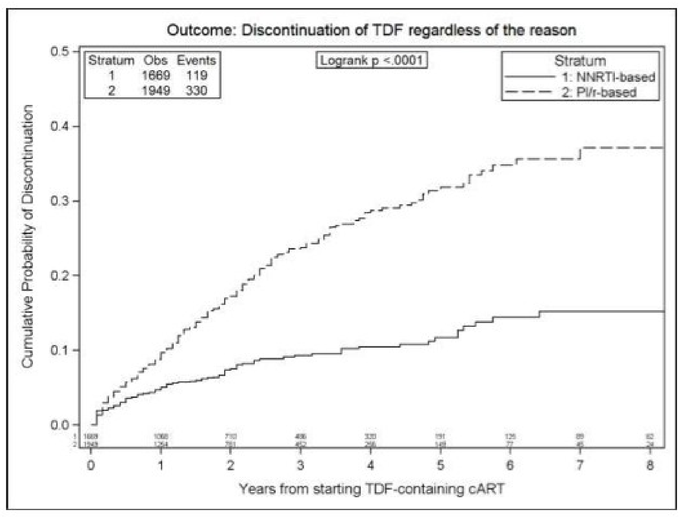
Three thousands six hundred and eighteen HIV-infected patients were enrolled: 1669 (46%) on NNRTI based regimen and 1949 (54%) on PI/r based regimen. Their median age was 38 years-old and 80% had baseline eGFR >90 ml/min. Patients on PI/r based regimen were more likely to be female, to have AIDS diagnosis and to have a lower CD4-T cell count.

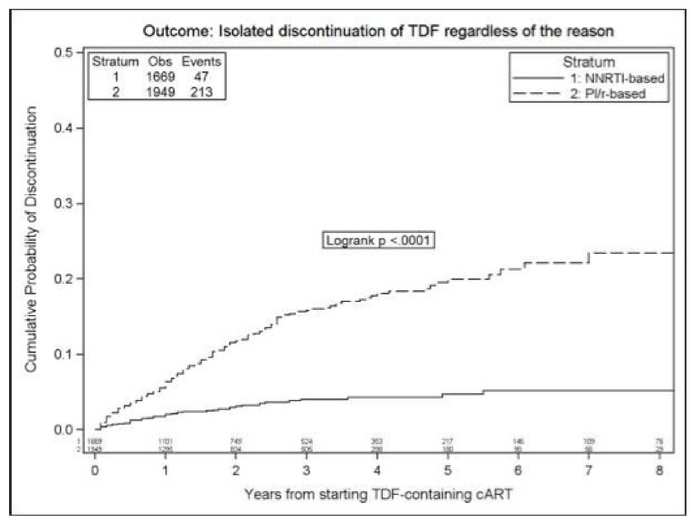
Among 1949 patients on PI/r based regimen, 783 (40.2%) were on atazanavir/r (ATZ/r), 676 (34.7%) were on darunavir/ritonavir (DRV/r) and 490 (25.1%) were on lopinavir/r (LPV/r). A detailed description of the characteristics of the patients is depicted in the Table.

The causes of discontinuation were: non- adherence (51%), toxicity (20%), failure (5.4%), simplification (2.7%) and other/unknown causes (21.1%).

The 5 year KM estimates in the PI/r vs NNRTI group were 31.8% vs. 11.7%, respectively (log-rank p=0.0001), for the outcome of stopping regardless of the reason, and 11.8% vs. 5.7% (p=0.0004) for discontinuation due to toxicity.







In a multivariable Cox model, PI/r use and to have a lower eGFR at baseline were associated with increased risk of discontinuing TDF regardless of the reason; PI/r use, to be older and to have a lower eGFR at baseline was associated with increased risk of discontinuing TDF for toxicity and PI/r use was a factor associated with isolated stop of TDF. No differences in rates of TDF discontinuations between PIs were found.

Outcomes	Crude and adjusted relative hazards: Crude RH (95% CI)	p-value	Adjusted* RH (95% CI)	p-value
Discontinuation of TDF				
Drug class				
NNRTI	1.00		1.00	
PI/r	2.58 (2.08, 3.18)	<.001	2.38 (1.79, 3.17)	<.001
Baseline weight, Kg				
per 10 heavier	0.89 (0.82, 0.97)	0.006	0.90 (0.80, 1.01)	0.077
Baseline eGFR				
per 10 units higher	1.10 (1.04, 1.17)	<.001	1.09 (1.00, 1.18)	0.038
Discontinuation of TDF due to toxicity				
Drug class				
PI/r	1.00		1.00	
NNRTI	1.80 (1.30, 2.50)	<.001	1.68 (1.04, 2.71)	0.033
Age, years				
per 10 older	1.55 (1.33, 1.82)	<.001	1.36 (1.08, 1.72)	0.009
Calendar year				
per more recent	1.07 (0.99, 1.15)	0.080	1.10 (0.98, 1.25)	0.108
Baseline eGFR				
per 10 units higher	1.33 (1.23, 1.44)	<.001	1.27 (1.12, 1.43)	<.001
Isolated discontinuation of TDF				
Drug class				
PI/r	1.00		1.00	
NNRTI	4.16 (3.03, 5.72)	<.001	3.82 (2.54, 5.75)	<.001

*adjusted for age, gender, balck ethinicity, mode of HIV transmission,weight, hepatitis C co-infection status, AIDS diagnosis, baseline CD4 count and nadir,viral load at cART, year of starting cART, diabete, use of blood plressure lowering drugsat baseline, baseline eGFR and stratified by clinical center

A significantly higher proportion of patients co-treated with PI/r had discontinued TDF due to kidney toxicity compared to those treated with a NNRTI-based regimen. KM analysis shows a different probability of TDF discontinuation due to renal toxicity in NNRTI group and PI group (2.0% vs 6.1%). However, when discontinuation due to kidney toxicity was used as outcome measure of a separate Cox regression analysis, drug companion was not associated with the risk of TDF discontinuation. Also in this model, to have a lower baseline eGFR was an important independent predictor of TDF discontinuation (HR 1.41 ; 95%CI 1.17-1.69).

Outcomes	Crude and adjusted relative hazards: Unadjusted RH (95% CI)	p-value	Adjusted* RH (95% CI)	p-value
Discontinuation of TDF due to renal toxicity				
Drug class				
PI/r	1.00		1.00	
NNRTI	3.18 (1.79, 5.65)	<.001	1.53 (0.71, 3.27)	0.276
Age, years				
per 10 older	1.80 (1.43, 2.28)	<.001	1.42 (0.99, 2.02)	0.053
Calendar year				
per more recent	1.07 (0.95, 1.20)	0.283	1.10 (0.91, 1.32)	0.324
Baseline eGFR				
per 10 units higher	1.48 (1.32, 1.65)	<.001	1.42 (1.19, 1.70)	<.001

*adjusted for age, gender, balck ethinicity, mode of HIV transmission,weight, hepatitis C co-infection status, AIDS diagnosis, baseline CD4 count and nadir,viral load at cART, year of starting cART, diabete, use of blood plressure lowering drugsat baseline, baseline eGFR and stratified by clinical center

CONCLUSIONS

- Frequency of TDF discontinuations in clinical practice is 10% by 2ys, 20% by 8ys
- Co-administration with PI/r vs. NNRTI is associated with an increased rate of TDF discontinuations (regardless the reason, because of toxicity and isolated)
- Renal toxicity is more frequently reported in the PI/r group
- A lower eGFR is an independent predictor for TDF discontinuations (regardless the reason, because of toxicity and isolated)
- We also find no differences between PIs (LPV/r, ATV/r, DRV/r) in TDF discontinuations