Trends in modification and discontinuation of initial antiretroviral treatment (ART) in Turkish HIV-TR Cohort, 2011-2017.

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Objective

Rates and reasons for ART modification or discontinuation have been investigated in a number of studies. Studies comparing the durability of older regimens with contemporary regimens in observational cohorts are few. The aim of this study was to determine the frequency, reasons and the predictors for modification and discontinuation of initial ART before and after the availability of better tolerated and less complex novel regimens.

Materials & Methods

A total of 3019 antiretroviral-naive adult patients (> 18 years of age) registered in the HIV-TR cohort who started ART between Jan 2011 and Feb 2017 were studied. Epidemiologic, clinical and laboratory data of all were recorded retrospectively by a web-based data collection system. Patients who were lost to follow up during the first year after initiating treatment were not eligible for the study.

Regimen modification was defined as a change in at least one antiretroviral drug in the regimen not including dose changes. Discontinuation is defined as discontinuation of all drugs in the regimen for at least 14 days. Since discontinuations in this study were noted only for a minority of patients, the term 'regimen modification' covers both modification and discontinuation. ART regimens were grouped in a non-nucleoside reverse transcriptase inhibitor (NNRTI), boosted protease inhibitor (PI), or integrase inhibitor (InSTI) based regimen or an integrase inhibitor combined with a boosted protease inhibitor (InSTI/PI). NNRTI/InSTI and NNRTI/PI-based regimens were categorized as InSTI-based and PI-based, respectively, according to the most potent component.

Only the first modification for each patient within 1 year was included in the analyses. Reasons were classified as listed in the coded form in the web based database. Time to first treatment modification or death, whichever occurred earlier, was analyzed using Kaplan-Meier curves and log-rank tests. Follow-up time of patients who did not discontinue any drug after the first year of observation was censored at 12 months. Factors associated with regimen modification were examined using Cox proportional hazards models.

Results

The initial regimen was modified in 379 out of 3019 patients (12.6%) within the first year. Baseline characteristics of patients were shown in Table 1. The main reason for modification was intolerance/toxicity (41.7%), followed by treatment simplification (9%), death (7.4%), patient's willingness (6.9%), poor compliance (6.6%), to prevent future toxicities (5.5%), virological failure (5%), and clinician's preference (5%). The reasons for modification by study period were shown in Table 2.

Table 1. Baseline characteristics of patients at treatment initiation

Characteristic	Total=3019	Modified=379	Continued=2668	p
	n (%)	n (%)	n (%)	
Gender				.151
Male	2605 (100)	318 (12.2)	2287 (87.8)	
Female	414 (100)	61 (14.7)	353 (85.3)	
Age (years)				**<.001**
<30	885 (100)	**81 (9.2)**	**804 (90.8)**	
30-45	1383 (100)	**175 (12.7)**	**1208 (87.3)**	
>45	751 (100)	**123 (16.4)**	**628 (83.6)**	
Mode of transmission				.397
MSM/Bisexual	1038 (100)	120 (11.6)	918 (88.4)	
Heterosexual	1683 (100)	214 (12.7)	1469 (87.3)	
IVDU	6 (100)	1 (16.7)	5 (83.3)	
Other	62 (100)	12 (19.4)	50 (80.6)	
Unknown	230 (100)	32 (13.9)	198 (86.1)	
Pretreatment CD4 cell count (mm^3)				**<.001**
<200	723 (100)	**124 (17.2)**	**599 (82.8)**	
≥200	2103 (100)	**234 (11.1)**	**1869 (88.9)**	
Pretreatment viral load (copies/mm^3)				.104
<100,000	1218 (100)	137 (11.2)	1081 (88.8)	
≥100,000	1546 (100)	206 (13.3)	1340 (86.7)	
AIDS diagnosis				**.006**
Yes	793 (100)	**135 (17.0)**	**658 (83.0)**	
No	2048 (100)	**224 (10.9)**	**1824 (89.1)**	
ART regimen type				**<.001**
InSTI	1135 (100)	**72 (6.3)**	**1063 (93.7)**	
InSTI/PI	6 (100)	**1 (16.7)**	**5 (83.3)**	
NNRTI	798 (100)	**114 (14.3)**	**684 (85.7)**	
PI	1080 (100)	**192 (17.8)**	**888 (82.2)**	
Type of initial ART				
EFV/TDF/FTC	750 (100)	**106 (14.1)**	**644 (85.9)**	
LPV/r/TDF/FTC	743 (100)	**130 (17.5)**	**613 (82.5)**	
EVG/c/TAF/FTC	680 (100)	**40 (5.9)**	**640 (94.1)**	
DTG/TDF/FTC	351 (100)	**17 (4.8)**	**334 (95.2)**	
DRV/r/TDF/FTC	276 (100)	**35 (12.7)**	**241 (87.3)**	
RAL/TDF/FTC	65 (100)	**12 (18.5)**	**53 (81.5)**	
LPV/r /ZDV/3TC	53 (100)	**24 (45.3)**	**29 (54.7)**	
EFV/ZDV/3TC	39 (100)	**7 (17.9)**	**32 (82.1)**	
Other	62 (100)	**8 (12.9)**	**54 (87.1)**	
Year of initial ART				**.035**
2011-2012	603 (100)	**83 (13.8)**	**520 (86.2)**	
2013-2014	892 (100)	**128 (14.3)**	**764 (85.7)**	
2015-2017 (Feb)	1524 (100)	**168 (11.0)**	**1356 (89.0)**	

Abbreviations: EFV:Efavirenz, TDF:tenofovir disoproxil fumarate, FTC:emtricitabine, LPV:Lopinavir, r:ritonavir, EVG/c:Elvitegravir/cobicistat, TAF:tenofovir alafenamide, DTG:Dolutegravir, DRV:Darunavir, RAL:Raltegravir, ZDV:Zidovudine, 3TC:Lamivudine, InSTI:integrase strand transfer inhibitor, NNRTI:non-nucleoside reverse transcriptase inhibitors, PI protease inhibitors

Table 2. Reasons for ART modification by study period

Reasons for modification	Year of initial ART			
	2011-2012 n (%)	2013-2014 n (%)	2015-2017 n (%)	Total n (%)
Intolerance/toxicity	35 (42.2)	56 (43.8)	67 (39.9)	158 (41.7)
Treatment simplification	4 (4.8)	8 (6.3)	22 (13.1)	34 (9.0)
Virological failure	9 (10.8)	8 (6.3)	2 (1.2)	19 (5.0)
To prevent future toxicities	2 (2.4)	4 (3.1)	15 (8.9)	21 (5.5)
Clinician's preference/patient's wish	8 (9.6)	14 (10.9)	23 (13.7)	45 (11.9)
Death	6 (7.2)	12 (9.4)	10 (6.0)	28 (7.4)
Other	19 (22.9)	26 (20.3)	29 (17.3)	74 (19.5)
Total	83 (100)	128 (100)	168 (100)	379 (100)

Median time to treatment modification was shorter in patients treated with NNRTI- compared with InSTI- and protease PI-based regimens (3.9, 4.9 and 5.6 months, respectively); p=0.049, (Figure 1). Prescribing patterns between 2011 and Feb 2017 were shown in Figure 2. (Single tablet regimens (STRs) containing efavirenz or rilpivirine and one major PI (atazanavir) were not available in the country during the study period.)

Figure 1: Months to first regimen discontinuation by ART regimen type

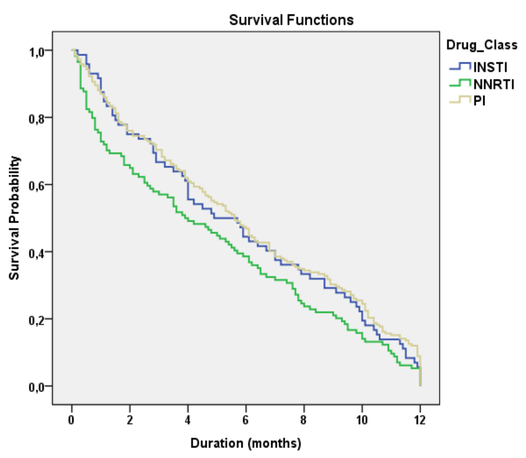
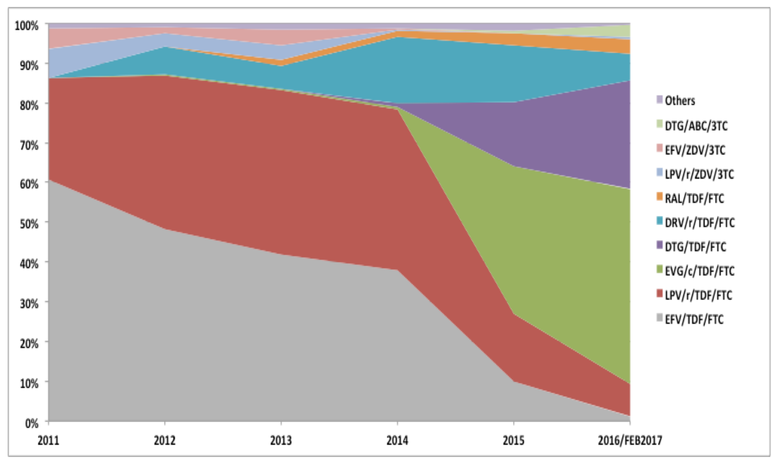


Figure 2: Prescribing patterns for initial ART in HIV-TR cohort between 2011 and Feb 2017.



In a multivariable Cox model, only predictor of modification was baseline AIDS diagnosis, (aHR=1.4, 95 % CI 1.1–1.8); p= 0.01 (Table 3).

Table 3. Association of various characteristics with the initial ART modification in the naive patients starting therapy between Jan 2011 and Feb 2017

Characteristic	Univariate analysis		Multivariable analysis	
	Crude Hazard Ratio (95% CI)	P-value	Adjusted Hazard Ratio (95% CI)	P-value
Age(years)				
<30	1.0		1.0	
30-45	0.9 (0.7-1.2)	.72	0.8 (0.6-1.1)	.38
>45	1.0 (0.8-1.4)	.63	0.9 (0.7-1.3)	.87
Gender				
Male	1.0		1.0	
Female	0.9 (0.7-1.2)	.75	0.8 (0.6-1.2)	.42
Mode of transmission				
MSM/Bisexual	1.0		1.0	
Heterosexual	1.1 (0.8-1.3)	.61	0.9 (0.7-1.2)	.64
IVDU	1.6 (0.2-12.0)	.60	-	-
Other	0.8 (0.4-1.5)	.47	0.7 (0.3-1.5)	.42
Unknown	1.3 (0.9-2.0)	.11	1.2 (0.8-1.9)	.31
Pretreatment viral load (copies/mm^3)				
<100,000	1.0		1.0	
≥100,000	0.8 (0.7-1.1)	.24	0.8 (0.6-1.0)	.07
AIDS diagnosis				
Category C or CD4<200	**1.3 (1.0-1.6)**	**.01**	**1.4 (1.1-1.8)**	**.008**
Year of initial ART				
2011-2012	1.0		1.0	
2013-2014	0.8 (0.6-1.1)	.18	0.8 (0.5-1.1)	.18
2015-2017(Feb)	0.7 (0.6-1.0)	.07	0.8 (0.6-1.2)	.35
ART regimen type				
InSTI	1.0		1.0	
InSTI/PI	0.9 (0.1-6.9)	.97	-	-
NNRTI	1.2 (0.9-1.6)	.20	0.8 (0.3-2.2)	.79
PI	0.9 (0.7-1.2)	.55	0.9 (0.5-1.7)	.84
Type of initial ART (> 30 patients)				
EVG/c/TAF/FTC	1.0		1.0	
EFV/TDF/FTC	1.3 (0.9-1.9)	.13	1.3 (0.5-3.2)	.49
LPV/r/TDF/FTC	0.9 (0.6-1.4)	.98	1.0 (0.6-1.7)	.96
DTG/TDF/FTC	1.3 (0.7-2.3)	.30	1.3 (0.7-2.3)	.39
DRV/r/TDF/FTC	0.8 (0.5-1.3)	.56	0.8 (0.4-1.5)	.54
RAL/TDF/FTC	1.1 (0.5-2.0)	.88	1.1 (0.5-2.3)	.77
LPV/r /ZDV/3TC	1.2 (0.7-2.0)	.41	4.2 (0.4-37.3)	.27
EFV/ZDV/3TC	1.1 (0.5-2.6)	.67	1,4 (0.4-3.3)	.48

Modification rate was higher among PI- (17.8%) and NNRTI- (14.3%) compared to InSTI-based regimens (6.3%), (p<0.001). The rate of treatment modification for intolerance/toxicity was lower with INSTI-based regimens (2%) than with NNRTI-based (6.6%) and PI-based regimens (7.5%) (p<0.001). However, patients receiving InSTI-based regimens had less severe disease, indicated by fewer baseline AIDS diagnoses and lower HIV RNA levels than those on PI-based and NNRTI-based regimens. Similarly, those on InSTI-based STRs had fewer baseline AIDS diagnoses, but similar HIV RNA levels compared to those on non-STR INSTI-based regimens.

The rate of modification for intolerance/toxicity decreased over time (6.3% for 2013-2014 vs. 4.4% for 2015-2017; while modification for treatment simplification displayed an increasing trend (0.7%, 0.9% and 1.4% during 2011-2, 2013-4 and 2015-17, respectively). Patients who achieved HIV RNA <50 and < 200 copies/ml within 12 months of ART initiation were 85 and 91% in the ART modified group vs. 87 and 93.9% in the continued group (p>0.05).

Conclusions

Drug intolerance/toxicity was the major reason for treatment modification during the first year of ART. While incidence of modification because of intolerance/toxicity declined over time simplification strategies became more frequent in recent years. InSTI-based regimens were less likely to be modified than PI and NNRTI-based ART. There was a relatively low rate of modification and discontinuation of ART regimens within the first 12 months as compared with other countries.[1-4]

References: 1- Vo TT, Ledergerber B, Keiser O, et al. Durability and outcome of initial antiretroviral treatments received during 2000--2005 by patients in the Swiss HIV Cohort Study. J Infect Dis 2008;197:1685-94. **2**- Di Biagio A, Cozzi-Lepri A, Prinapori R, et al. Discontinuation of Initial Antiretroviral Therapy in Clinical Practice: Moving Toward Individualized Therapy. J Acquir Immune Defic Syndr 2016;71:263-71. **3**- Sun J, Liu L, Shen J, Qi T, Wang Z, Song W, Zhang R, Lu H. Reasons and Risk Factors for the Initial Regimen Modification in Chinese Treatment-Naïve Patients with HIV Infection: A Retrospective Cohort Analysis. PLoS One. 2015;10:e0133242. **4**- Sheth AN, Ofotokun I, Buchacz K, et al. Antiretroviral Regimen Durability and Success in Treatment-Naive and Treatment-Experienced Patients by Year of Treatment Initiation, United States, 1996-2011. J Acquir Immune Defic Syndr. 2016;71:47-56.

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