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INSTI In-class Switching on Continued Viral Suppression in the OPERA Cohort

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BACKGROUND

The US DHHS HIV treatment guidelines include within-class switches to simpler and less frequent regimens as valid reasons to consider regimen changes in the setting of viral suppression. [1] With its low risk of cross-resistance and once daily dosing, clinicians may consider substituting dolutegravir (DTG) for raltegravir (RAL), both integrase strand transfer inhibitors (INSTIs), in an effort to improve adherence and durability. Few clinical trials have evaluated INSTI intra-class switching [2], and there are currently no real-world assessments of switch from RAL to DTG in stably suppressed patients.

OBJECTIVE:

To determine if patients stably suppressed on RAL and switched to DTG differed in risk of virologic failure (>200 copies/mL) from patients who continued on RAL.

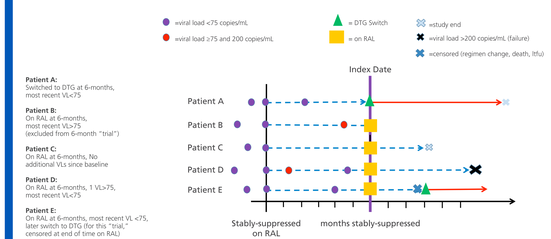
METHODS

Study Population/ Design

The study population was selected from the Observational Pharmaco-Epidemiology Research and Analysis (OPERA) cohort, which includes prospectively-captured, routine clinical data from patients at 79 outpatient clinics in the U.S. This analysis was updated with data through January 28, 2016.

Individuals who initiated RAL at least 90 days after their first prospectively-collected visit in the OPERA cohort and as a part of their first INSTI-containing regimen were identified. Patients became eligible for inclusion in the analysis once they achieved stable-suppression, defined as 2 consecutive viral loads <75 copies/mL, measured at least 90 days but not more than 365 days apart, and did not have a subsequent viral load >200 copies/mL (Figure 1).

Figure 1. Identification of Patients who Switch to DTG and those who Remain on RAL (No Switch) at Equivalent Times after Stable Virologic Suppression on RAL



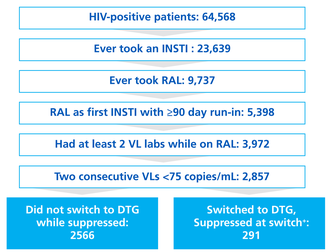
In an effort to mimic a clinical trial of patients who switched to DTG compared to patients who remained on RAL (no switch), we constructed monthly nested sequential subcohorts of patients who had achieved virological stability and followed them until they experienced virologic failure (VL >200 copies/mL) or were censored (stopped taking RAL or DTG, death, were lost to follow up, or data collection ended). This study compared incident switchers to incident non-switchers rather than "ever switched" vs. "never switched." At the time of a suppressed switch to DTG, patients starting DTG were compared to patients suppressed after an equal number of months on RAL who did not switch. Because patients initiated DTG after variable months on RAL, we conducted a sequential series of monthly "trials" from the time stable-suppression was first achieved on RAL. Monthly trials for each patient were included in the analysis if their most recent viral load was <75 copies/mL.

Statistical Analysis

Virologic failure after DTG-switch was compared to failure during RAL-continuation by estimating hazard ratios (HR). Propensity scores were calculated and applied to the Cox proportional hazards models with standardized mortality ratio (SMR) weights to control for measured confounders. Multiple observations per patient were accounted for by using a robust variance estimator.

RESULTS

Figure 2. OPERA Patients Eligible for Analysis as of January 28, 2016



+: switched from a regimen containing RAL to a regimen containing DTG with a gap between regimens of <30 days; Suppressed defined as most recent viral load <75 copies/mL

Of the 5,398 patients initiating RAL as their first INSTI while active in the OPERA cohort, 3,972 (74%) had a record of at least 2 viral load labs while on RAL that met our timing criteria. A total of 2,857 (53% of RAL patients) had 2 consecutive labs indicating suppressed viral load taken between 90 and 365 days apart. The majority of these patients (2,566, 90%) continued on RAL throughout their follow up. The remainder (291 patients, 10%) switched to DTG after achieving stable suppression (Figure 2).

Patients stably suppressed on RAL who didn't switch were similar to those who did switch to DTG in demographic characteristics (Table 1). Clinically, both groups were equally experienced to ART prior to starting RAL and had similar time to stable suppression. However, those who did not switch to DTG were more likely to have experienced an AIDS defining event prior to baseline and have lower CD4 counts at the time they initiated RAL.

Table 1. Characteristics of Patients who Achieved Stable Suppression on RAL; Overall and Stratified by Switch

	All RAL Stable Suppressed Patients n=2857	RAL No Switch to DTG n=2566	RAL Switch to DTG n=291	p-value
Male Sex	2393 (83.8)	2150 (83.8)	243 (83.5)	0.90
Age (Median years (IQR))	47.6 (41.6, 54.1)	47.6 (41.6, 54.1)	48.2 (41.8, 54.1)	0.76
Region of treatment				**0.01**
Northeast	49 (1.7)	46 (1.8)	3 (1.0)	
Mid-Atlantic	57 (2.0)	52 (2.0)	5 (1.7)	
South	1436 (50.4)	1316 (51.4)	120 (41.5)	
Midwest	3 (0.1)	3 (0.1)	0 (0.0)	
Southwest	8 (0.3)	8 (0.3)	0 (0.0)	
West	1296 (45.5)	1135 (44.3)	161 (55.7)	
African American Race	729 (25.5)	657 (25.6)	72 (24.7)	0.75
Hispanic Ethnicity	705 (24.7)	626 (24.4)	79 (27.2)	0.30
AIDS-defining event at or before baseline	869 (30.4)	801 (31.2)	68 (23.4)	**0.01**
CD4 count (Median cells/mm3 (IQR))	441 (277,643)	434 (276,639)	515 (290, 682)	**0.02**
ART experienced at RAL initiation	2815 (98.5)	2529 (98.6)	286 (98.3)	0.71
Time to stably-suppressed on RAL (median months (IQR))	7.2 (5.4, 10.9)	7.2 (5.4, 10.7)	7.3 (5.4, 11.6)	0.79
Time on RAL (from stably-suppressed to end of follow-up) (median months (IQR))	16.3 (7.1, 31.1)	15.8 (7.1, 29.8)	24.3 (7.5, 46.5)	**<0.001**

* Variables measured at baseline defined as at RAL initiation

Table 2. Crude, Adjusted, and Weighted Estimates from Cox Proportional Hazards Models

Person-"trials"	**60,135**
Unique patients	**2,857**
Unique patients switching to DTG	**291**
Unique failure events	
on DTG	**14**
on RAL	**628**
Crude HR (95% CI)	**0.47 (0.28, 0.81)**
Adjusted HR (95% CI)*	**0.61 (0.35, 1.04)**
PS Weighted HR (95% CI)±	**0.59 (0.34, 1.00)**

+ Model adjusted for baseline covariates including sex, age at RAL initiation, geographical region of treatment, race, ethnicity, treatment experience at RAL initiation, history of a diagnosis of an AIDS-defining event; also included were covariates measured separately for each observation in the stratified analysis, including time on RAL (time between first achieving stable-suppression on RAL and the start of the observational period), most recent CD4 count, recent clinic visit, and time since last viral load measurement.

± Propensity scores estimated using the same variables as the fully-adjusted models

Virologic failure, the outcome of interest, was defined as a single viral load measurement of >200 copies/mL. In the period between first achieving stable-suppression on RAL and the end of follow-up on RAL, 628 patients (22%) out of 2,857 patients had at least one viral load measurement >200 copies/mL while on RAL. Among the 291 patients who switched from RAL to DTG, 14 (5%) experienced virologic failure while on DTG. Using sequential stratification methods, 2,857 eligible patients contributed 60,135 observations to the multi-record dataset.

Figure 3. Probability of Virologic Failure after Switch/Index by INSTI Exposure

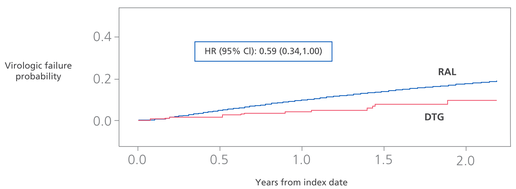


Table 3: Sensitivity Analyses: Weighted Estimates from Cox Proportional Hazards Models

	Weighted HR (95% CI)
Assessment of viral suppression definitions	
Suppressed defined as 2 consecutive VLs<75 copies/mL then 2 most recent VLs<75 copies/mL	0.50 (0.28, 0.92)
Suppressed defined as 2 consecutive VLs<75 copies/mL then 1 most recent VL<200 copies/mL	0.65 (0.40, 1.05)
Propensity Score Weight Stabilization & Trimming	
Removing observations in areas of non-overlap in the PS distribution	0.60 (0.35, 1.02)
& Trimming at the 99.5th percentile for untreated	0.60 (0.35, 1.02)
& Trimming at the 97.5th percentile for untreated	0.63 (0.37, 1.07)
& Trimming at the 95th percentile for untreated	0.67 (0.39, 1.14)
Assessment of Follow Up Time Definitions	
Follow-up time restricted to 2013 or later	0.62 (0.36, 1.06)
Follow-up time partitioned by clinic visit rather than 30 day intervals	0.61 (0.36, 1.04)
Follow-up time for each observation begins after 30 day window for exposure assessment	0.58 (0.35, 0.98)
Follow-up restricted to patients with VL >75 copies/mL at RAL initiation	1.01 (0.56,1.83)

DISCUSSION

In-class switching to achieve greater adherence through simpler, less frequent regimens is an acceptable treatment strategy. [1] This study sought to evaluate the risk of viral breakthrough upon switching from one INSTI (RAL) to another (DTG) in a population of stably suppressed patients. Using data from the OPERA longitudinal database, no statistically significant difference in the risk of virologic failure was observed in patients who maintained a RAL-containing regimen versus those who switched to a DTG-containing regimen. These results were unchanged in numerous sensitivity analyses.

The patients continuing on RAL were similar to those switching to DTG except they were more likely to have AIDS at baseline with a lower CD4 count and shorter total time on INSTIs. Patients switching from RAL to DTG had longer durations of RAL than those who remained on RAL. Patients with longer durations of viral suppression were observed to have less frequent viral load testing that may have had an impact on our ability to see failures. The median time from last viral load test to switch was only 15 days suggesting that most of the switching patients were confirmed suppressed proximate to the switch. Further, the majority of DTG exposure was on-going at data freeze suggesting that the full experience of these patients has yet to be observed in this cohort.

Finally, a limitation of this research could be that in-class switching from RAL to DTG was not commonly practiced. With only 352 patients attempting it out of 5,398 RAL users and even fewer patients attempting it under our strict criteria for viral suppression, there may have been characteristics about this patient population that were not captured through the medical records and therefore, could not be described or controlled for in our modeling.

KEY FINDING:

In an observational database of clinical care in the US, within-class switching from RAL to DTG was found to be equally successful at maintaining stable viral suppression as compared to continuing on RAL.

REFERENCES

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