POSTER #510

Virologic Response To 2-Drug ART Regimens Among Treatment-Experienced HIV+ Patients

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BACKGROUND

- Toxicity concerns with nucleoside reverse transcriptase inhibitors (NRTIs), combined with the potency of new agents, have led to the re-emergence of the two-drug regimen (2-DR) concept; dolutegravir (DTG)/rilpivirine (RPV) has been approved in the US and clinical trials to assess various other 2-DR combinations are ongoing[1,2]
- Drug-sparing regimens have the potential to increase tolerability and adherence, as well as reduce complexity, long-term toxicity, drug-drug interactions, and cost of ART[3]

OBJECTIVE:

To describe 2-DR use among ART-experienced HIV+ patients in a large clinical cohort, and to compare virologic outcomes of 2-DRs and three-drug regimens (3-DRs) following switch

METHODS

- The study population was identified from the OPERA Observational Database; a collaboration of over 400 healthcare providers at 79 HIV out-patient clinics in 15 U.S. states following 79,803 people living with HIV
- Prospective electronic health record data is cleaned, categorized, and anonymized before being aggregated into a national database which complies with all HIPAA and HITECH requirements receiving approval by Advarra IRB
- Study population: ART-experienced patients initiating 2-DR or 3-DR regimens of at least 30 days in duration after their first active visit in OPERA, between 1/1/2010 and 6/30/2016
- Patients were observed from regimen start date (baseline) until regimen discontinuation (d/c), loss to follow-up, death, or study end (6/30/2017)
- Statistical comparisons of patient characteristics by regimen type (2-DR vs. 3-DR) were made using Pearson's chi-square or Fisher exact tests for categorical variables and Wilcoxon rank-sum test for continuous variables
- Kaplan-Meier methods were used to estimate time to suppression for patients switching while viremic and time to failure for patients stable at switch
- Cox models for each outcome were comparisons of 2-DR vs. 3-DR (referent) fit to estimate adjusted hazard ratios (aHR); covariates are listed in Figure 3 and Figure 4

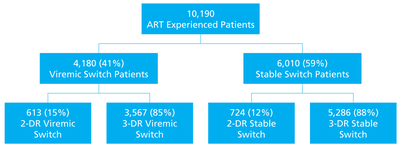
Table 1. Criteria for Stratification and Outcomes Definition

STRATIFICATION AT BASELINE		OUTCOMES	
Stratum	**Definition**	**Outcome**	**Definition**
Viremic Switch	VL ≥50 copies/mL	Virologic Suppression	1 VL <50 copies/mL
Stable Switch	VL <50 copies/mL	Virologic Failure	2 consecutive VLs ≥200 copies/mL or 1 VL ≥200 copies/mL + d/c after <50 copies/mL

RESULTS

- 10,190 ART-experienced patients were identified (Figure 1) who switched during the study period to a 2-DR (n=1,337, 13%) or 3-DR (n=8,853, 87%)

Figure 1. Treatment Experienced Patients by Regimen Type and Stratification



- The most common 2-DRs (55%) comprised a protease inhibitor and an integrase strand transfer inhibitor combination (Figure 2)
- The most common 3-DRs were evenly distributed across the three main classes of core ART agents with two nucleoside reverse transcriptase inhibitors (Figure 2)

Figure 2. Most Common 2-DRs and 3-DRs

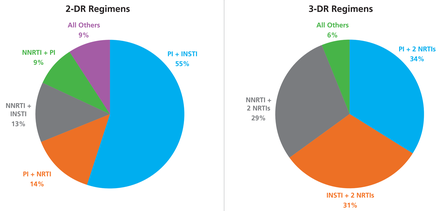


Table 2. Top 10 2-DRs and 3-DRs in Treatment Experienced Patients

	2-DR		3-DR	
	Regimen	**N (%)**	**Regimen**	**N (%)**
1.	darunavir/raltegravir	371 (27.7%)	efavirenz/emtricitabine/tenofovir	1,285 (14.5%)
2.	darunavir/dolutegravir	217 (16.2%)	darunavir/emtricitabine/tenofovir	1,022 (11.5%)
3.	etravirine/raltegravir	90 (6.7%)	abacavir/dolutegravir/lamivudine	877 (9.9%)
4.	darunavir/etravirine	89 (6.7%)	atazanavir/emtricitabine/tenofovir	731 (8.3%)
5.	atazanavir/raltegravir	75 (5.6%)	elvitegravir/emtricitabine/tenofovir	652 (7.4%)
6.	darunavir/tenofovir	52 (3.9%)	emtricitabine/raltegravir/tenofovir	613 (6.9%)
7.	atazanavir/tenofovir	48 (3.6%)	emtricitabine/rilpivirine/tenofovir	568 (6.4%)
8.	dolutegravir/rilpivirine	36 (2.7%)	emtricitabine/nevirapine/tenofovir	330 (3.7%)
9.	lopinavir/raltegravir	34 (2.5%)	abacavir/atazanavir/lamivudine	303 (3.4%)
10.	atazanavir/dolutegravir	18 (1.3%)	abacavir/darunavir/lamivudine	253 (2.9%)

Table 3. Baseline Demographics of Treatment-Experienced Patients Initiating 2-DRs and 3-DRs

	2-DR N= 1,337	3-DR N= 8,853	2-DR vs. 3-DR p-value
Age, median (IQR)	50.0 (44.0, 56.8)	46.4 (39.1, 52.7)	**<.0001**
Female Sex	296 (22.1%)	1441 (16.3%)	**<.0001**
African American Race	509 (38.1%)	2544 (28.7%)	**<.0001**
Hispanic Ethnicity	268 (20.0%)	2326 (26.3%)	**<.0001**
Risk of Infection: MSM	542 (40.5%)	4742 (53.6%)	**<.0001**
Region: South	813 (60.8%)	4031 (45.5%)	**<.0001**
Medicaid	369 (27.6%)	2106 (23.8%)	**0.0025**
Medicare	342 (25.6%)	1336 (15.1%)	**<.0001**
ADAP/Ryan White	297 (22.2%)	2610 (29.5%)	**<.0001**

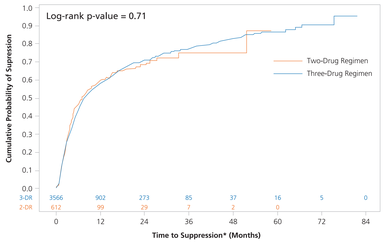
Table 4. Baseline Clinical Characteristics of Treatment-Experienced Patients Initiating 2-DRs and 3-DRs

	2-DR N= 1,337	3-DR N= 8,853	2-DR vs. 3-DR p-value
Experienced: 5+ prior lines of ART	558 (41.7%)	1773 (20.0%)	**<.0001**
Months since ART initiation, Median (IQR)	60.0 (20.1, 117.2)	45.8 (13.6, 98.1)	**<.0001**
Baseline Viral Load: Stable Switch <50 copies/mL	724 (54.2%)	5286 (59.7%)	**<.0001**
Baseline CD4 >500 cells/uL	528 (39.5%)	4367 (49.3%)	**<.0001**
AIDS defining event at or prior to regimen initiation	569 (42.6%)	2401 (27.1%)	**<.0001**
VACS Score†, Median (IQR)	27.0 (13.0, 43.0)	17.0 (6.0, 28.0)	**<.0001**
Cardiovascular Disease	282 (21.1%)	943 (10.7%)	**<.0001**
Invasive Cancers	175 (13.1%)	858 (9.7%)	**0.0001**
Endocrine Disorders	757 (56.6%)	4082 (46.1%)	**<.0001**
Liver Disease	353 (26.4%)	2034 (23.0%)	**0.0058**
Bone Disorders	71 (5.3%)	271 (3.1%)	**<.0001**
Peripheral Neuropathy	305 (22.8%)	1175 (13.3%)	**<.0001**
Renal Disease	437 (32.7%)	840 (9.5%)	**<.0001**
Hypertension	635 (47.5%)	2761 (31.2%)	**<.0001**

† VACS Mortality Index: Scored by summing pre-assigned points for age, CD4 count, HIV-1 RNA, hemoglobin, platelets, aspartate and alanine transaminase, creatinine, and viral hepatitis C infection. A higher score is associated with a higher risk of 5-year all-cause mortality.

- Among patients switching while viremic, virologic suppression during follow-up was comparable among patients on 2-DRs and 3-DRs (61% vs. 67%; aHR 1.00, 95% CI 0.88, 1.13) (Figure 3, Table 5).
- After viremic patients achieved suppression during follow up, 13% of 2-DR and 15% of 3-DR patients went on to experience a failure event.

Figure 3. Kaplan Meier estimation of time to virologic suppression among treatment-experienced patients switching while viremic, stratified by regimen type



** Suppression: † VL <50 copies/mL*

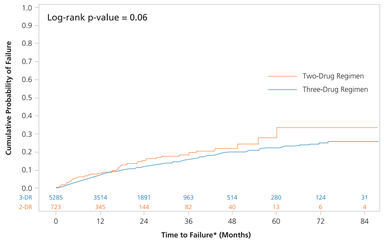
Table 5. Crude and adjusted hazard ratios comparing 2-DR vs. 3-DR on time to suppression, viremic at switch

	Suppression Events/ Viremic Patients w/ VLs (%)	Crude HR (95% CI)	Adjusted† HR (95% CI)
2-DR	318 / 518 (61.4%)	1.02 (0.91, 1.15)	1.00 (0.88, 1.13)
3-DR	2116 / 3141 (67.4%)	1.	1.

† Adjusted for age, race, sex, baseline viral load, ADAP/RW participation, substance abuse, time on ART, prior lines of ART, and comorbidities (diagnosis of peripheral neuropathy, cardiovascular disease, endocrine disorders, liver disease, or renal disease)

- Among stable switch patients, the difference in risk of virologic failure during follow-up was not statistically significant between 2-DR and 3-DR patients (10% vs. 11%; aHR 1.15, 95% CI 0.90, 1.48) (Figure 4, Table 6).

Figure 4. Kaplan Meier estimation of time to virologic failure among treatment-experienced patients switching while stable, stratified by regimen type



** Failure: 2 consecutive viral loads ≥200 copies/mL or one viral load ≥200 copies/mL followed by discontinuation*

Table 6. Crude and adjusted hazard ratios comparing 2-DR vs. 3-DR on time to failure, suppressed at switch

	Failure Events/ Suppressed Patients (%)	Crude HR (95% CI)	Adjusted† HR (95% CI)
2-DR	74 / 724 (10.2%)	1.26 (0.99, 1.61)	1.15 (0.90, 1.48)
3-DR	589 / 5286 (11.1%)	1.	1.

† Adjusted for age, race, sex, substance abuse, baseline CD4, time on ART, comorbidity (diagnosis of peripheral neuropathy, cardiovascular disease, endocrine disorders, liver disease, or renal disease), prior lines of ART, time on ART (modeled with quadratic splines)

DISCUSSION

- To our knowledge, this analysis is the first description of real world 2-DR utilization and outcomes within a large clinical cohort in the US
- Patients initiating 2-DRs presented older, with more comorbid conditions, lower CD4 counts, and more baseline AIDS defining events; suggesting that clinicians may be selecting 2-DRs for their more complex patients hoping that regimen simplification increases adherence and reduces toxicities and drug-drug interactions
- Careful consideration was given to the selection of covariates that may have influenced the prescription of a 2-DR over a 3-DR, as well as the outcomes; however, our results may still be biased from residual confounding due to unmeasured or unknown patient factors
- Even before the currently approved 2-DR, DTG/RPV, was included in the treatment guidelines, a sizeable population of patients were being treated with 2-DRs, suggesting that there is a need for additional drug-sparing regimens[2]
- Outcomes of this analysis suggest that 2-DRs may be virologically effective and tolerated, but further evaluation, including specific regimen comparisons, is needed

KEY FINDINGS:

Virologic outcomes were comparable between ART-experienced patients switching to two- and three-drug regimens, regardless of whether patients were virologically controlled at switch. These findings support the continued evaluation of 2-DRs in clinical trials and real-world settings. Long-term outcomes require further assessment.

REFERENCES

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