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Session: 263. HIV: ART Resistance and Adherence
Saturday, October 5, 2019: 12:15 PM

Background. DRV has demonstrated high efficacy and barrier to resistance development across diverse populations, from TN to heavily TE patients. We evaluated resistance data from 10 clinical studies of different DRV 800 mg QD–based antiretroviral regimens and formulations.

Methods. The analysis included patients from 10 phase 2/3 studies (48–192 weeks in duration) of ritonavir- and cobicistat-boosted DRV 800 mg QD–based regimens in TN and virologically failing or suppressed TE patients with HIV-1 (table). Three were phase 3 studies of the DRV/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10 mg single-tablet regimen (STR). Post-baseline resistance was evaluated in patients experiencing protocol-defined virologic failure (PDVF); definitions and criteria for resistance testing varied slightly among studies. Resistance-associated mutations (RAMs) were based on respective International Antiviral Society–USA mutation lists over time.

Results. Of the 3,635 patients evaluated, 250 met PDVF criteria and 205 had post-baseline genotypes/phenotypes. Overall, 4 (0.1%) patients developed (or had identified [switch studies]) ≥1 DRV and/or primary protease inhibitor (PI) RAM (table), and only 1 (< 0.1%, ODIN) patient lost DRV phenotypic susceptibility; this TE patient had prior VF with lopinavir. Among those who used a nucleos(t)ide reverse transcriptase inhibitor (NRTI) backbone (mostly emtricitabine [FTC] + tenofovir [TFV]), 12 (0.4%) patients had ≥1 NRTI RAM, including 10 with M184I/V associated with FTC resistance. No TFV RAMs were observed. Among patients receiving D/C/F/TAF (n = 1,949), none had post-baseline DRV, primary PI, or TFV RAMs; only 2 (0.1%) patients developed an FTC RAM.

Conclusion. Across a large, diverse population using DRV 800 mg QD–based regimens and formulations, resistance development remains rare; 0.1% of patients had ≥1 DRV and/or primary PI RAM post-baseline. Among 3 trials of the D/C/F/TAF STR, no patients developed a DRV or primary PI RAM. After > 10 years of investigating DRV 800 mg QD–based regimens in clinical trials, loss of phenotypic susceptibility to DRV has never been observed in TN or TE virologically suppressed patients and was only once observed in a TE patient with prior VF on multiple antiretrovirals, including a PI.

Table. Post-Baseline Resistance-Associated Mutations Across Studies*

Study (duration)	Population	Treatment (N)	PDVF (n); post-BL resistance data (n')†	Patients with ≥1 (emergent) RAM, n (%)	
				DRV‡ and/or Primary PI	NRTI
ARTEMIS (192 weeks)	TN	DRV+rtv+F/TDF (343)	55; 43	1 (*V11I*)	3 (M184I/V) 1 (M184V+ K70E)
GS-US-299-0102 (48 weeks)	TN	DRV/cobi/F/TAF (103)	4; 4	0	0
		DRV+cobi+F/TDF (50)	1; 1	0	0
GS-US-216-0130 (48 weeks)	TN and TE	DRV+cobi+2 NRTIs (313)	15; 15	1 (**I84I/V**)	2 (M184V)
ODIN (48 weeks)	TE	DRV+rtv+ ≥2 NRTIs (294)	65; 60	1 (V32I+ M46I+ **L76V+ I84V**)§	1 (M184V) 1 (V75I+ M184V) 1 (T215F) 1 (T215Y)
INROADS (48 weeks)	TN and TE (with transmitted resistance)	DRV+rtv+ETR (54)	7; 2	0	–
MONET (144 weeks)	Virologically suppressed	DRV monotherapy+rtv (127)	21; 31	1 (*L33F*)	–
		DRV+rtv+2 NRTIs (129)	13; 23	0	0
PROTEA (96 weeks)	Virologically suppressed	DRV monotherapy+rtv (137)	1; 2	0	–
		DRV+rtv+2 NRTIs (136)	2; 1	0	0
EMERALD (96 weeks)	Virologically suppressed	D/C/F/TAF (763)	24; 4	0	0
		Switch to D/C/F/TAF¶ (352)	8; 2	0	0
AMBER (96 weeks)	TN	D/C/F/TAF (362)	15; 9	0	1 (M184I/V)#
		DRV/cobi+F/TDF switch to D/C/F/TAF (363)	19; 8	0	1 (M184V)**
DIAMOND (48 weeks)	TN (newly-diagnosed)	D/C/F/TAF (109)	0; 0	0	0
Total (3,635)			250; 205	4 (0.1)	12 (0.4)††
Total Phase 3 D/C/F/TAF STR studies‡‡ (1,949)			66; 23	0	2 (0.1)

BL, baseline; rtv, ritonavir; cobi, cobicistat; TDF, tenofovir disoproxil fumarate; ETR, etravirine.
*ARTEMIS (ClinicalTrials.gov Identifier: NCT00258557), GS-US-299-0102 (NCT01565850), GS-US-216-0130 (NCT01440569), ODIN (NCT00524368), INROADS (NCT01199939), MONET (NCT00458302), PROTEA (NCT01448707), EMERALD (NCT02269917; AMBER (NCT02431247), and DIAMOND (NCT03227861).
†Resistance testing was performed on samples from patients experiencing PDVF, except in MONET and PROTEA, for which any sample that exceeded an HIV-1 RNA level of 50 copies/mL was tested.
‡Primary DRV RAMs are bolded; secondary DRV RAMs are italicized.
§For this patient, post-baseline RAMs were not detected pretreatment by deep sequencing; however, the patient did already have 2 lopinavir RAMs (L63P and V77I) and 4 NRTI RAMs (M41L, M184V, L210W, and T215Y).
¶From switch to D/C/F/TAF (Week 52) through Week 96.
#For this patient, M184V was detected pretreatment by deep sequencing as a minority variant (9.4%).
**For this patient, M184V was not detected pretreatment by deep sequencing.
††The percentage reported in parentheses is based on a denominator of 3,317 (the total number of patients who used an NRTI).
‡‡EMERALD, AMBER, and DIAMOND.

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2510. Systematic Literature Review of Multiclass Resistance in Heavily Treatment Experienced Persons with HIV

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Session: 263. HIV: ART Resistance and Adherence
Saturday, October 5, 2019: 12:15 PM

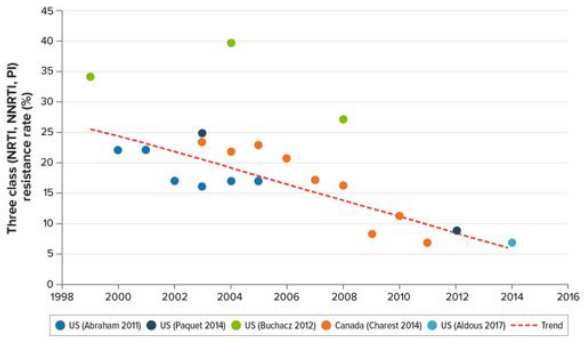
Background. Because of progress in antiretroviral therapy (ART), fewer people with HIV experience virologic failure with multiclass resistance. We sought to estimate the prevalence of multiclass resistance since the introduction of INSTI-based regimens using a systematic literature review.

Methods. A systematic literature search using PubMed, Embase, and the Cochrane Library was conducted of articles published since 2008, the year when INSTI-based regimens for treatment-experienced people with HIV became widely used. Bibliographies of existing literature reviews, websites of European and International organizations reporting data on HIV and AIDS, and abstracts presented from 2016–2018 at conferences were searched to identify additional relevant studies. Using predefined criteria, two reviewers independently reviewed studies reporting multiclass (three-class or greater) resistance in persons with HIV infection who are treatment experienced and were either perinatally infected or infected as adults. Studies from Western Europe, Australia, Canada and the United States (US) using any type of resistance definitions and resistance tests were included.

Results. A total of 441 unique articles were identified, 343 were excluded during level 1 screening and 98 articles were included for full-text review. A total of 34 articles (11 US studies, 3 from Canada, 1 from Australia, and 19 from Western European countries.) met the inclusion criteria and were included in data extraction analysis. Over the past decade, a modest decrease in the prevalence of three-class (NNRTI, NRTI, PI) resistance was observed in studies from the United States and Canada, ranging from 8.3% in 2009 to 6.7% in 2014 (Figure 1). Western European countries and Australia showed similar trends. The prevalence of 4-class resistance (including INSTIs) with virologic failure in the current treatment era is low, less than 2% (Figure 2).

Conclusion. The prevalence of multiclass resistance has decreased over the past decade, with three-class resistance continuing to decline and four-class resistance rare. Although the population with treatment failure and no viable options for a suppressive regimen is currently small, this group of people with HIV are in urgent need of novel treatment options.

Figure 1. Trends of Resistance Rates to Three-Class Drug (NRTI + PI + NNRTI) in the US and Canada



NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; US = United States.

Figure 2. Resistance Rates to Four-Class Drug (NRTI + PI + NNRTI + INSTI)

Study	2009	2010	2011	2012	2013	2014	2015	2016	Resistance
France (Assoumou 2017)						0.3			All in class (major INSTI mutations)
US (Hurt 2014)		2.3							Major INSTI resistance mutations
US (Aldous 2017)						0.4			Stanford algorithm (cumulative genotype)[a]
US (Menza 2017)					0.3				Major INSTI resistance mutations
US (Brown 2017)						~1			Major INSTI resistance mutations[b]
US (Davy 2017)							1		One in class (major mutations)[c]
US (Wang 2016)				1.6					Stanford (1 major mutation/class)

INSTI = integrase strand transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; US = United States.

[a] 2014 Stanford HIVDB genotypic resistance interpretation algorithm (including intermediate and high-level resistance mutations) was used to estimate the prevalence of resistance.
[b] No mutations were observed in patients treated with dolutegravir.
[c] Resistance to three or more classes

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2511. Characterization of Patient Pill Preferences from a Prospective Placebo vs. Placebo Ease of Swallowability Study