History of drug resistance mutations and virologic outcomes for 2-drug regimens: Data from COMBINE-2

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Background

- Dolutegravir (DTG) + lamivudine (3TC) and DTG + rilpivirine (RPV) are both complete two-drug regimens (2-DRs) indicated for treatment of HIV infection in adults to replace a current antiretroviral (ARV) regimen in those who are virologically suppressed (HIV-1 RNA <50 copies/mL) with no history of treatment failure and no known substitutions associated with resistance to the individual regimen components.
- In real-world clinical settings, however, resistance data may not be routinely available or reviewed prior to initiation of a DTG-based 2-DR initiation.
- The aim or this analysis is to assess the availability of resistance data prior to initiating DTG+3TC or DTG+RPV, the prevalence of historical HIV drug resistance mutations (DRMs), and their impact on regimen effectiveness in a real-world clinical setting.

Methods

Study Population and Design

- The COMBINE-2 Study is a prospective, observational study utilizing electronic medical record data from clinics in the European treatment network for HIV, hepatitis, and global infectious diseases (NEAT-ID) Network.
- Participating clinical sites are in the UK, Spain, France, Belgium, Italy, and Portugal.
- Inclusion Criteria:
  - HIV diagnosis, ≥18 years old
  - Treatment experienced and switching to a 2-DR of DTG+ 3TC or DTG+RPV on or after 01JAN2014
  - Last viral load (VL) prior to 2-DR initiation <50 copies/mL
- Follow-up occurred between 2-DR regimen start date (baseline) and the earliest of 96 weeks post-baseline, regimen discontinuation, loss to follow-up, or death.

Outcomes

- Outcomes were described for each 24-week period of follow up (24-, 48-, 72-, and 96-weeks post-baseline).
- Sustained suppression: VL <50 copies/mL
- Low-level viremia: ≥50 and <200 copies/mL
- Virologic failure: 2 consecutive VLs ≥ 200 copies/mL or 1 VL ≥ 200 copies/mL followed by regimen discontinuation

Results

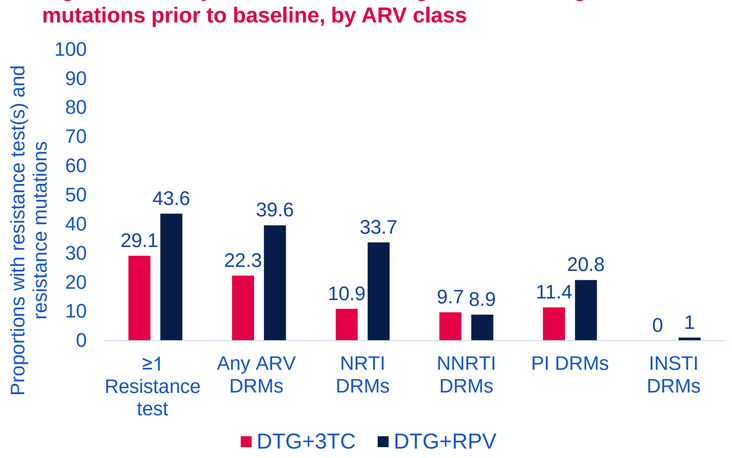
- In total, 175 adults suppressed switched to DTG+3TC and 101 adults suppressed switch to DTG+RPV.

Table 1. Baseline demographic and clinical characteristics of patients switching while suppressed to DTG+3TC or DTG+RPV 2-DRs

Baseline Characteristic	DTG+3TC n=175	DTG+RPV n=101
Age, years, median (IQR)	56 (49-60)	57 (51-60)
Sex, male, n(%)	129 (73.7)	66 (65.3)
Race, White, n(%)	134 (76.6)	76 (75.2)
Black, n(%)	27 (15.4)	15 (14.9)
Time on ART, years, median (IQR)	12 (4-19)	12 (5-21)
CD4 count (cells/mm^3), median (IQR)	701 (558-963)	656 (502-881)
Nadir CD4 count (cells/mm^3), median (IQR)	254 (130-376)	174 (107-281)

- Resistance testing performed at the time of baseline regimen initiation (±1 week) was uncommon: 0% (n=0) for DTG+3TC and 3.0% (n=3) for DTG+RPV.

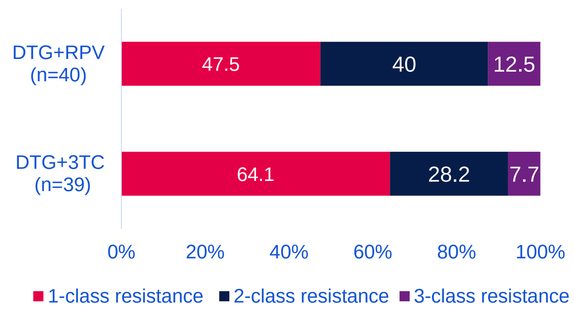
Figure 1. History of resistance testing and HIV-1 drug resistance mutations prior to baseline, by ARV class



NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; INSTI: integrase strand transfer inhibitor

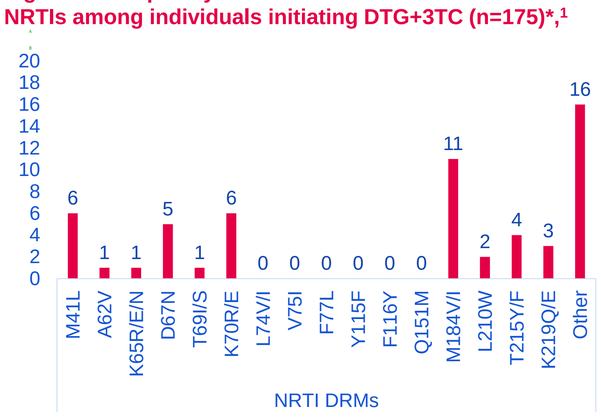
- 29.1% (n=51) of DTG+3TC users and 43.6% (n=44) of DTG+RPV users had at least one resistance test documented at any point prior to baseline.
- Median (IQR) months from most recent resistance test to baseline were 77 months (19-150) for DTG+3TC and 103 months (9-174) for DTG+ RPV.
- 22.3% of all DTG+3TC users (76.5% of those with test records) and 39.6% of all DTG+RPV users (90.9% of those with test records) had a history of any documented substitutions.

Figure 2. Proportions with resistance-associated mutations to drugs in one, two, and three ARV classes in persons with documented resistance prior to switch



- No one had documented 4-class resistance.

Figure 3. Frequency of mutations associated with resistance to NRTIs among individuals initiating DTG+3TC (n=175)*,[1]

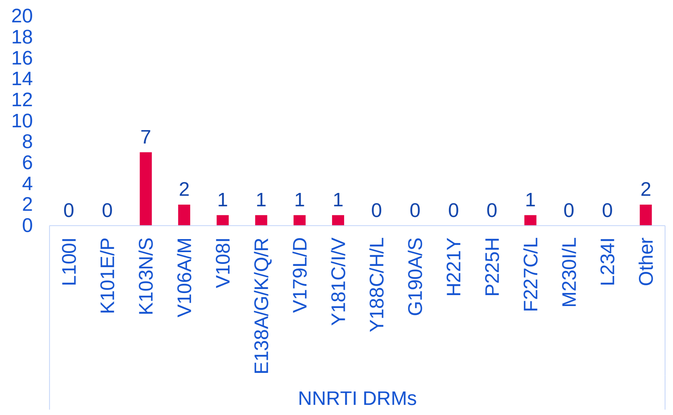


* Individuals may have multiple mutations within the same class
1. Mutations identified from 2019 IAS drug resistance mutations list

Virologic Outcomes:

- During the 96-week follow-up period, 6 individuals (3 on DTG+3TC and 3 on DTG+RPV) experienced a single VL ≥50 copies/mL; all detectable viral loads indicated low-level viremia.
- No single participant experienced more than 1 VL ≥50 copies/mL.
- No one experiencing low-level viremia had a history of DRMs associated with reduced susceptibility to either component of their 2-DRs.

Figure 4. Frequency of mutations associated with resistance to NNRTIs among individuals initiating DTG+RPV (n=101)*,[1]



* Individuals may have multiple mutations within the same class
1. Major mutations identified from 2019 IAS drug resistance mutations list

Table 2. Details of 6 participants with ≥1 viral load >50 copies/mL during 96 weeks of follow up

	Regimen	VL.24	VL.48	VL.72	VL.96	DRMs prior to baseline
1	DTG+3TC	48			**91**	none
2	DTG+3TC		**56**		19	PI: H69K L89M M36I
3	DTG+3TC		**63**		<50	none
4	DTG+RPV	**77**	20		20	NRTI: L210W M41L T215S
5	DTG+RPV		20		**95**	none
6	DTG+RPV	<50	<50	**53**	<50	none

Discussion

- Most individuals suppressed switching to DTG+3TC (70.9%) and DTG+RPV (56.4%) had an unknown history of resistance mutations (no test data) at baseline.
- Among those with prior resistance data, historical DRMs associated with reduced susceptibility to at least one ARV class were common.
- Documented history of INSTI DRMs were rare (n=1); no mutations associated with reduced susceptibility to DTG were identified.
- Among those taking DTG+3TC, 6.3% (n=11) and 0.6% (n=1) had a documented history of M184V/I and K65R/E/N mutations, respectively, the major mutations associated with resistance to 3TC. None of the individuals with these mutations experienced low-level viremia or virologic failure during follow-up.
- One individual taking DTG+RPV had a single major mutation (E138A) associated with reduced susceptiblity to RPV. This person did not experience low-level viremia or virologic failure.
- Six individuals experienced a single event of low-level viremia.
- Among all DTG+3TC and DTG+RPV users, there were no events of virologic failure over 96 weeks of follow up.

Conclusions

In the real-world setting of the COMBINE-2 Study, most PLWH initiated a DTG 2-DR with no documented history of resistance testing. Among those with resistance data, small proportions had history of DRMs associated with reduced susceptibility to their current 2-DR. Regardless of resistance history, DTG 2-DRs were highly effective, with no virologic failures over 96 weeks of follow up.

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Reference: 1. Wensing AM, Calvez V, Ceccherini-Silberstein F, et al. 2019 Update of the Drug Resistance Mutations in HIV-1. Top Antivir Med. 2019; 27(3).

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