Highly Effective Two-drug Regimens of an Integrase Inhibitor and Reverse Transcriptase Inhibitor in Real-World Setting - Data from COMBINE-2 Study

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Poster PE2/48

Introduction

- In clinical trials, switching while virologically suppressed from a three-drug regimen to a two-drug regimen (2-DR) of an integrase inhibitor (INI) and a reverse transcriptase inhibitor (RTI) maintained viral suppression with low rates of failure, resistance, and adverse events. [1]
- The COMBINE-2 Study is a prospective, observational study assessing effectiveness and safety of INI+RTI 2-DRs among suppressed-switch patients in real-world clinical practice in Europe.

Methods

Study Population and Design

- Data source: electronic medical record data from clinics in the European treatment network for HIV, hepatitis, and global infectious diseases (NEAT-ID) Network
- Inclusion Criteria:
  - HIV diagnosis, ≥18 years old
  - Treatment experienced and switching to a 2-DR of an INI and an RTI (NRTI: Nucleoside Reverse Transcriptase Inhibitor or NNRTI: Non-nucleoside Reverse Transcriptase Inhibitor) on or after 01JAN2014
  - Last viral load (VL) prior to 2-DR initiation <50 copies/mL
- Follow-up occurred between 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
  - High-level viremia: ≥ 200 copies/mL
  - Virologic failure: 2 consecutive VLs ≥ 200 copies/mL or 1 VL ≥ 200 copies/mL followed by regimen discontinuation
  - Regimen discontinuation: modification or discontinuation of the baseline regimen
- Incidence rates (IR) per 100 person-years of follow up and 95% confidence intervals (CI) for virologic, discontinuation, and drug-related adverse event (AE) outcomes were estimated

Results

- 283 individuals switched while suppressed to an INI+RTI 2-DR
  - 175 (62%) dolutegravir (DTG)+ lamivudine(3TC)
  - 101 (36%) DTG+ rilpivirine (RPV)
  - 7(2%) other 2-DRs: 5 raltegravir + etravirine, 1 raltegravir + nevirapine, 1 DTG+ tenofovir disoproxil fumarate

Table 1. Baseline demographic and clinical characteristics of patients suppressed switching to an INI+RTI 2-DR

Baseline Characteristics	Switch Participants N=283
Age, years, median (IQR)	56 (50-60)
Sex, male, n (%)	200 (70.7)
Race, White, n(%)	214 (75.6)
Black, n(%)	45 (15.9)
Other, n(%)	24 (8.5)
Time on ART, years, median (IQR)	11.6 (4.6-19.2)
CD4 count (cells/mm^3), median (IQR)	677 (536-939)
Comorbidities – hypertension, n(%)	67 (23.7)
hyperlipidemia, n (%)	63 (22.3)
renal disorder, n(%)	32 (11.3)
liver disorder, n(%)	22 (7.8)
diabetes, n(%)	14 (4.9)

Figure 1. History of drug resistance mutations (DRMs)

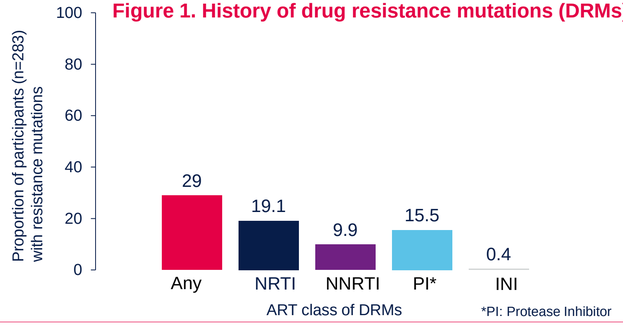


Table 2. Incidence rates of non-suppressed viremia during 96 weeks of follow up

	0-24 weeks	24-48 weeks	48-72 weeks	72-96 weeks	Overall (0-96 weeks)
Participants (N)	283	283	280	276	**283**
Viral Load ≥50 and <200 copies/mL	1	2	1	2	**6**
Incidence rate per 100 p-years (95% CI)	0.7 (0.0-3.9)	1.4 (0.2-5.1)	0.7 (0.0-4.0)	1.7 (0.2-6.0)	**1.1 (0.4-2.4)**
Viral Load ≥200 copies/mL	1	0	0	0	**1**
Incidence rate per 100 p-years (95% CI)	0.7 (0.0-3.9)	0.0 (0.0-2.6)	0.0 (0.0-2.6)	0.0 (0.0-3.0)	**0.2 (0.0-1.0)**

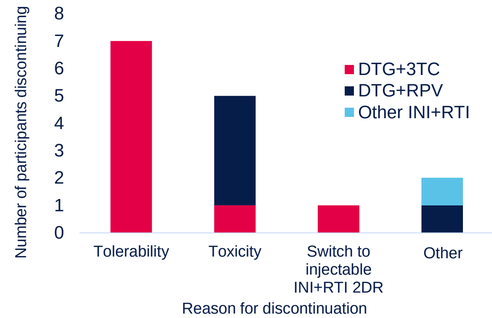
- A total of 7 detectable VLs ≥50 copies/mL were measured during the 96-week study period: 6 tests indicated low-level viremia and 1 test indicated high-level viremia (408 copies/mL)
- Only viral blips were experienced. No single participant experienced more than 1 VL ≥50 copies/mL
- There were no events of virologic failure

Table 3. Details of 7 participants with ≥1 viral load >50 copies/mL

	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
7	RAL+ETR	**409**	38		24	none

- Twenty-seven drug-related AEs were reported by 21 participants (IR: 5.0, 95% CI: 3.4-7.3)
  - 2 (7%) AEs were serious (1 weight gain and 1 anxiety/depression event)
  - Among all AEs (serious and non-serious), weight gain was the most commonly reported (n=8; IR: 5.0, 95% CI: 3.4-7.3); n=1 for all other reported drug-related AEs

Figure 2. Reason for discontinuation of INI+RTI 2-DR (n=15)



- A total of 15 participants discontinued a 2-DR within 96 weeks of initiation (IR: 5.3, 95% CI: 3.0-8.6)
- No discontinuations were due to virologic failure

Discussion

- The COMBINE-2 study included a representative proportion of women (29.3%) and Black (15.9%) participants
- At 96 weeks, 99.2% of remaining participants (n=276) were suppressed as of their last viral load
- In a real-world clinical setting, DRMs documented prior to initiating a 2-DR were common (29%)
  - Nearly all (98%) participants with prior DRMs maintained suppression throughout follow-up; 2% experienced a single blip

Conclusions

- Among suppressed PLWH in a real-world setting, INI+RTI 2-DRs were highly effective, with no events of virologic failure, and tolerable in maintaining virologic control over 96 weeks of follow-up.

References: 1. Cento V, Perno CF. *J Global Antimicrob Resistance* 2020; 20: 228-237

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