Real-world observational study in Europe on the effectiveness and safety of two-drug regimens containing an integrase inhibitor and reverse transcriptase inhibitor (COMBINE-2): Week 96 stable switch population results

Cristina Mussini[1], Cassidy Henegar[2], Lambert Assoumou[3,4], Stephane De Wit[5], Margaret Johnson[6], Eugenia Quiros Roldan[7], Leigh Ragone[2], Bryn Jones[8], Jean van Wyk[8], Michael Aboud[2], Carl Fletcher[9], Annie Duffy[9], Anton Pozniak[4,10], Vani Vannappagari[2].

[1]University of Modena and Reggio Emilia, Modena, Italy; [2]ViiV Healthcare, Durham, US; [3]INSERM, Paris, France; [4]The European treatment network for HIV, hepatitis and global infectious diseases (NEAT ID), Belgium; [5]CHU Saint-Pierre, Brussels, Belgium; [6]Royal Free Hospital, London, UK; [7]University of Brescia, Italy; [8]ViiV Healthcare, Brentford, Middlesex, UK; [9]Research Organization (KC) Ltd, London, UK; [10]Chelsea and Westminster hospital, London, UK.

Introduction

- In clinical trials, suppressed switch from a three-drug regimen to a daily oral two-drug regimen (2-DR) containing an integrase inhibitor (INI) and a reverse transcriptase inhibitor (RTI) maintained viral suppression with low rates of failure 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 (VF):
  - 2 consecutive VLs ≥ 50 copies/mL
    or
  - 1 VL ≥ 50 copies/mL followed by regimen discontinuation
    or
  - 1 VL ≥ 50 copies/mL with no additional VL measures
- Sensitivity analysis: VL ≥200 copies/mL used for VF definitions

- Regimen discontinuation: modification or discontinuation of the baseline regimen
- Drug-related non-serious and serious adverse events (AEs and SAEs) were identified and classified by clinicians during routine clinical practice

Analysis

- Kaplan-Meier (KM) methods were used to estimate event (virologic, discontinuation) probabilities over follow up.

- 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

- A total of 735 individuals suppress-switched to an INI+RTI 2-DR
  - 534 (73%) dolutegravir (DTG)+ lamivudine(3TC)
  - 186 (25%) DTG+ rilpivirine (RPV)
  - 15(2%) other INI +RTI 2-DR

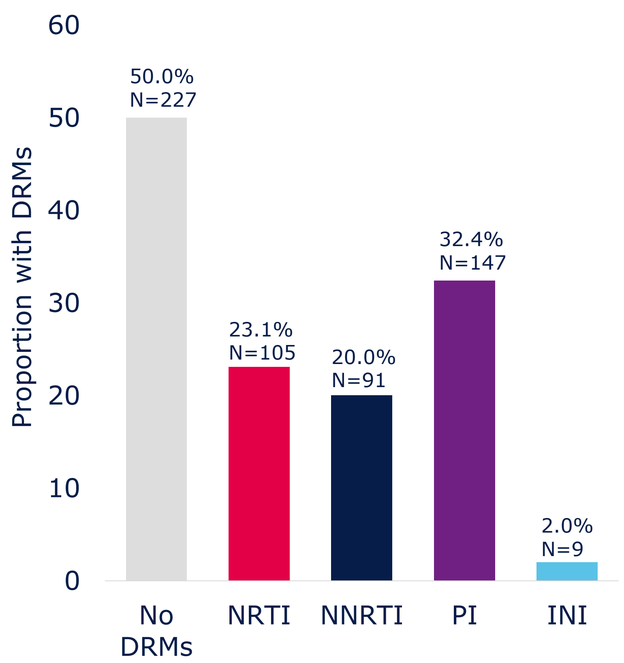
Table 1. Baseline Characteristics

	Suppressed switch N=735
Age, years, median (IQR)	54 (47-59)
Gender, n (%): Male	556 (75.7)
Ethnicity, n (%):	
White	492 (66.9)
Black	140 (19)
Other	8 (1.1)
Unknown	95 (12.9)
Duration of antiretroviral treatment (years): median (IQR)	10.2 (4.7-18.8)
CD4 count nadir (cells/mm^3): median (IQR)	250.5 (134-365)
CD4 count baseline count (cells/mm^3): median (IQR)	684 (534-920)
Comorbidities, n(%):	
Hypertension	177 (24.1)
Hyperlipidemia	190 (25.9)
Renal disorder	102 (13.9)
Liver disorder	60 (8.2)
Diabetes	46 (6.3)

- The 5 most common regimens individuals were being switched from were:
  - DTG+ABC+3TC- 134(18.2%)
  - DTG+TAF+FTC – 50 (6.8%)
  - DTG+TDF+FTC – 42 (5.7%)
  - EFV+TDF+FTC- 36 (4.9%)
  - EVG/c+TAF+FTC- 31 (4.2%)

- 454 (61.8%) individuals suppressed switching to a 2-DR had ≥ 1 documented resistance test at any point prior to baseline (38.2% had no resistance test results). Of those tested, 50.0% had documented resistance mutations in at least one class of ARVs. (Figure 1)

Figure 1. History of drug resistance mutations, by ART class



DRMs: Drug resistance mutations
Resistance to a class of ART drugs indicated by presence of ≥1 mutation conferring reduced susceptibility to any drug within that class; resistance testing data were abstract from medical records

- Among the 5 individuals who experienced a VF event on DTG+3TC, no one had a documented history of INSTI- or NRTI-associated resistance mutations.
- Among the 5 individuals who experienced VF on DTG+RPV, 2 had history of NNRTI-associated resistance mutations (neither had mutations associated with reduced susceptibility to RPV) and no one had a history of INSTI-associated mutations.

Table 2. Proportion of suppressed switch participants with virologic failure by 96 weeks

	Events (N)	% (95% CI)
Kaplan-Meier estimate of VF Week 96 (by any definition component)	**10**	**1.6 (0.9 – 3.0)**
By individual VF definition component:		
Two consecutive VL≥50 copies/mL	1	0.1 (0.0 – 1.0)
One VL≥50 copies/mL followed by 2-DR discontinuation	3	0.4 (0.1 – 1.4)
1 VL ≥50 copies/mL and no follow-up values thereafter	6	1.1 (0.5 – 2.3)

- Six VF events were identified by having a single VL ≥50 copies/mL at week 96, which was the end of study follow-up. Individuals may have resuppressed on their 2-DRs after follow up ended, but these outcomes were unobserved.
- A sensitivity analysis using a threshold of VL≥200 copies/mL to define VF (using all component definitions) identified 3 VF events (KM estimate: 0.5% [95% CI: 0.2-1.5%])

Table 3. Incidence rates of any viral load measurement ≥50 copies/mL by 96 weeks

	Weeks 0-24	Weeks 24-48	Weeks 48-72	Weeks 72-96	Overall 0-96 weeks
N of participants	735	712	668	574	**735**
Number of VL≥50 copies/mL	7	9	4	7	**27**
Person-years of follow-up	364	356	334	287	**1340**
Incidence rate per 100 p-y	1.9	2.5	1.2	2.4	**2.0**
95% confidence interval of IR	0.8-4.0	1.2-4.8	0.3-3.1	1.0-5.0	**1.3 – 2.9**

*Includes VF events from Table 2 plus viral blips

- There were 23 measurements of low-level viremia occurring over 1340 person-years of follow-up; incidence rate: 1.7 events per 100 person-years (95% CI: 1.1 – 2.6). 7 of 10 VF events were low-level viremia.
- There were 4 measurements of high-level viremia (VL ≥200 copies/ml), occurring over 1340 person-years of follow-up; incidence rate: 0.3 events per 100 person-years (95% CI: 0.1 – 0.8). 3 of 10 VF events were high-level viremia.

- No resistance tests to identify emergent resistance mutations following VF or viral blip events were documented in the medical records.

- There were 47 non-serious drug-related adverse events in 39/735 (5.3%) patients. The most common AE was weight gain, which occurred in 8 patients. Diarrhea (n=3), sleep disorders (n=3), pruritus (n=2), and rash (n=2) all occurred in a low number of patients. All other AEs occurred in single patients only.
- There were 2 drug-related SAEs which occurred in 2 patients: 1 instance of low mood and 1 instance of anxiety and depression.

Table 4. Kaplan-Meier estimates of baseline 2DR discontinuation

	Suppressed switch population Total N=735	
	N	% (95% CI)
Total discontinuation	**39**	**5.3 (3.8 – 7.2)**
Switch while virologically suppressed	2	0.3 (0 – 1.0)
Switch for failure*	4	0.5 (0.1 – 1.4)
Switch for tolerability	17	2.3 (1.3 – 3.7)
Switch for toxicity	5	0.7 (0.2 – 1.6)
Switch for other reasons	11	1.5 (0.7 – 2.7)

*Events included in table 2

Reason for discontinuation identified by provider in medical record

Conclusions

- In a real-world clinical setting, switching to an INI+RTI 2-DRs while suppressed was a highly effective treatment strategy for maintaining virologic suppression over 96 weeks of follow-up among ART-experienced adults with HIV-1.
  - Overall, 5/186 (2.7%) of individuals on DTG+RPV and 5/534 (0.9%) of individuals on DTG+3TC experienced virologic failure (any definition).

- INI+RTI 2-DRs were well-tolerated and durable, with low rates of adverse events and discontinuations over 96 weeks of follow up.

- There were high rates of maintenance of viral suppression despite lack of resistance data prior to initiation for 38% of participants and common history of resistance mutations (50% with documented history of resistance in ≥1 ARV class) among those with resistance test results.

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

•Acknowledgments: This research would not be possible without the generosity of people living with HIV and their caregivers in the NEAT-ID Network

•This research was sponsored by ViiV Healthcare.

Presented at IAS 2023, the 12th IAS Conference on HIV Science

IAS 2023 23 – 26 July

This content was acquired following an unsolicited medical information enquiry by a healthcare professional. Always consult the product information for your country, before prescribing a ViiV medicine. ViiV does not recommend the use of our medicines outside the terms of their licence. In some cases, the scientific Information requested and downloaded may relate to the use of our medicine(s) outside of their license.