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VIROLOGIC AND IMMUNOLOGIC OUTCOMES OF INTEGRASE INHIBITORS (INSTIs) IN RESPOND

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Background

- Outcomes of INSTI treatment for people living with HIV, have been evaluated in several randomized controlled trials [1-3]. However, experiences from large, demographically heterogeneous real-life settings are still limited.

Methods

- RESPOND is a newly formed collaboration of 17 observational HIV cohorts from Europe and Australia. Prospectively collected data have been obtained from 2012 to 2017. Currently, more than 27 000 individuals are under active follow up (FU).

- Logistic regression was used to analyse virologic and immunologic outcomes among RESPOND participants starting an **INSTI** (raltegravir, elvitegravir/cobicistat or dolutegravir) compared to a boosted (ritonavir or cobicistat) protease inhibitor (**bPI**; darunavir or atazanavir) or a non-nucleoside reverse transcriptase inhibitor (**NNRTI**; efavirenz or rilpivirine) containing regimen, for the first time between 1/1/12 to 1/10/17, with the potential for 6- or 12-months FU.

- Virologic outcomes were assessed at 12±3 months by a composite virologic outcome endpoint (cVO), with success defined as HIV viral load (VL) <400 cp/mL at FU and failure as ≥1 of either: VL ≥400 cp/mL, unknown VL in the time frame, any antiretroviral therapy (ART) regimen change, AIDS event or death. Favorable immunologic outcomes were defined as either a 25% increase in CD4 count from baseline, or a CD4 count ≥750 cells/μL at FU (excluding those with CD4 count ≥750 cells/μL at baseline).

- Sensitivity analysis were conducted using a VL cut-off of <50 cp/mL for cVO success, as an on-treatment analyses excluding those with unknown VL or any ART changes, and at 6±3 months.

Table 1: Baseline clinical characteristics

		INSTI		bPI		NNRTI	
		n	(%)	n	(%)	n	(%)
		7936	(52.8)	3625	(24.1)	3482	23.2
Gender	Male	6034	(76.0)	2558	(70.6)	2697	(77.5)
Ethnicity	White	5158	(65.0)	2508	(69.2)	2635	(75.7)
Mode of transmission	MSM	3627	(45.7)	1356	(37.4)	1688	(48.5)
HIV VL (cp/mL)	<400	5515	(69.5)	1899	(52.4)	1969	(56.5)
Prior ARV treatment	no (naïve)	2796	(35.2)	1330	(36.7)	1498	(43,0)
Hepatitis B	Positive	329	(4.1)	163	(4.5)	144	(4.1)
Hepatitis C	Positive	1758	(22.2)	841	(23.2	592	(17.0)
BMI (kg/m²)	≤18	194	(2.4)	102	(2.8)	51	(1.5)
	>30	483	(6.1)	202	(5.6)	199	(5.7)
Current Smoking		1997	(25.2)	899	(24.8)	824	(23.7)
Diabetes		536	(6.8)	162	(4.5)	148	(4.3)
Hypertension		1795	(22.6)	547	(15.1)	568	(16.3)
Cardiovascular disease		275	(3.5)	69	(1.9)	55	(1.6)
Chronic kidney disease		297	(3.7)	96	(2.6)	36	(1.0)
		Median	(IQR)	Median	(IQR)	Median	(IQR)
Age(yr)		48	(39 – 54)	44.05	(35 – 52)	52.0	(43 – 35)
Baseline date (mm/yy)	mm/yy	07/15	(08/14 - 05/16)	07/13	(07/12 - 09/12)	03/13	(03/14 - 06/15)
CD4 (cells/μL)		548	(352 – 760)	436	(248 – 660)	507	(347 – 719)

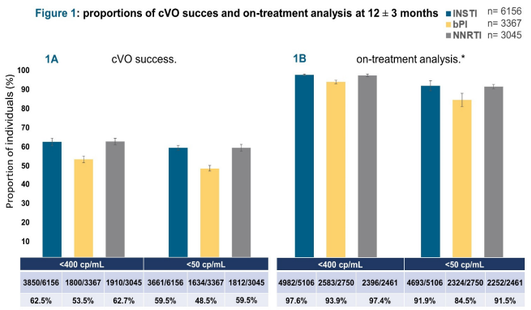
Percentage of unknown variables (all): Mode of transmission 9.3; Ethnicity 16.0; Hepatitis B 22.4; Hepatitis C 19.2; BMI 34.6; Smoking status 44.2; Hypertension 35.9; Diabetes 13.9; Cardiovascular disease 30.6; Chronic kidney disease 24.8
HCV positive: Ever positive if ever had a positive HCV antibody test, HCV RNA test, an HCV genotype assay or received HCV treatment prior to baseline
HBV positive: HBsAg positive

1. Molina JM, Clotet B, van Lunzen J, et al. *Lancet HIV* 2015; 2(4): e127-36.
2. Sax PE, DeJesus E, Mills A, et al. *Lancet* 2012; 379(9835): 2439-48.
3. Walmsley SL, Antela A, Clumeck N, et al. *N Engl J Med* 2013; 369(19): 1807-18.

Results

- Baseline characteristics of the 15043 included persons are shown in **Table 1**. For those where 12 months FU could be assessed, 6156 were treated with an INSTI (2117 (34.4%) ART-naïve), 3367 with a bPI (1261 (37.5%) naïve) and 3045 with a NNRTI (1355 (44.5%) naïve) containing regimen. Baseline characteristics were similar for persons with 6- or 12-months FU.

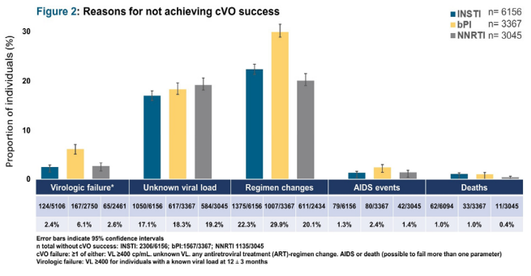
Figure 1: proportions of cVO succes and on-treatment analysis at 12 ± 3 months



- A total of 7560 (60.2%) persons experienced cVO success. The proportions obtaining success were similar for INSTIs and NNRTIs, and slightly lower for bPIs (**Fig. 1A**). The on-treatment analysis also showed that a greater proportion on INSTIs or NNRTIs had a VL <400 cp/mL at 12±3 months compared to persons treated with bPIs (**Fig. 1B**).

- The most common reasons for cVO failure in all three treatment groups were: Any changes in regimen and unknown VL. A greater proportion of virological failures and regimen changes were seen in persons on bPIs compared to persons on INSTIs and NNRTIs (**Fig. 2**).

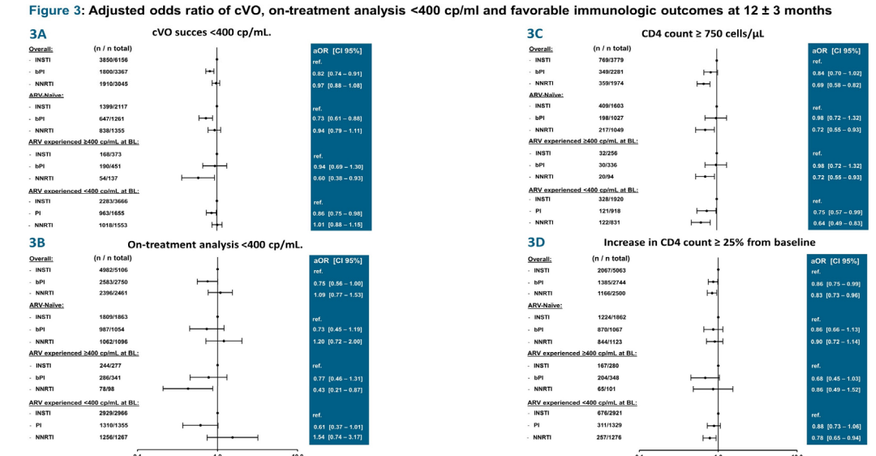
Figure 2: Reasons for not achieving cVO success



- The adjusted odds ratio (aOR) of cVO success at FU was similar for persons on INSTIs and NNRTIs (**Fig. 3A**), but lower for persons on bPIs. No significant differences were seen between the treatment groups in the on-treatment analysis (**Fig. 3B**). For favorable immunologic outcomes the aORs were similar for INSTIs and bPIs but lower for persons on NNRTIs (**Fig. 3C and 3D**). All sensitivity analyses were consistent with the main analyses.

- There was some evidence suggesting that associations between treatment group and outcomes differed according to baseline treatment status (p<0.0001 all interactions); INSTIs and NNRTIs performed similar and better compared to bPI for ART naïves and ART experienced with VL <400 cp/mL. By contrast, INSTIs and bPIs performed better compared to NNRTIs for ART experienced with VL ≥400 cp/mL.

Figure 3: Adjusted odds ratio of cVO, on-treatment analysis <400 cp/ml and favorable immunologic outcomes at 12 ± 3 months



Models adjusted for: Age, ethnicity, mode of transmission, baseline calendar year, smoking status, hypertension, diabetes, prior AIDS event, cardiovascular disease, chronic kidney disease, end stage liver disease, prior fractures, HBV and HCV status, viral load, CD4 count (nadir and baseline) treatment regimen and number of drugs in regimen.

Limitations

- Confounding by indication cannot be excluded due to the observational nature of the study.

Conclusions

- In this large cohort collaboration, odds of cVO success were slightly higher for INSTI-compared to bPI containing regimens, but similar to NNRTI containing regimens, when using a composite endpoint.

- We found no significant differences in the odds of obtaining a VL <400 cp/mL between INSTI, bPI or NNRTI containing regimens in the on-treatment analysis. The odds of favorable immunologic outcomes were similar between the INSTI- and bPI containing regimens, but slightly lower for NNRTI containing regimens.

- There were some indications that the outcomes differed according to treatment status at baseline, however INSTIs consistently did as well as bPIs and NNRTIs.

- Overall, these data suggest that INSTI containing regimens perform as well as bPI and NNRTI containing regimens in a real life setting.

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