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Uptake and discontinuation of integrase inhibitors (INSTIs) in a large cohort setting

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on behalf of the RESPOND study group

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Presenter Disclosure Information

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Lauren Greenberg

disclosed no conflict of interest

Background

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- INSTIs are recommended as part of initial antiretroviral therapy (ART) regimens for adults living with HIV [1]
- Clinical trials and small observational studies have shown:
  - good virological efficacy
  - fewer adverse events
  - lower rates of discontinuation

  with INSTIs vs non-nucleoside reverse transcriptase inhibitors and boosted protease inhibitors [2-5]
- However, limited data exists on the choice of INSTIs and discontinuation of INSTIs in large, heterogeneous real-world settings

[1] EACS Guidelines version 9.1, October 2018; [2] Steigbigel RT, et al. N Engl J Med 2008;
[3] Sax PE, et al. Lancet 2012; [4] Raffi F, et al. Lancet 2013; [5] Peñafiel J, et al. J Antimicrob Chemother 2017

Aims

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1. Identify characteristics associated with initiating:
   - dolutegravir (DTG)
   - cobicistat boosted elvitegravir (EVG/c)
   - raltegravir (RAL)

2. Describe time to and reasons for discontinuation of initial INSTI regimens

3. Identify characteristics associated with discontinuing INSTIs

RESPOND

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- The International Cohort Consortium of Infectious Diseases (RESPOND):
  - collaboration of 17 observational cohort studies
  - across Europe and Australia
  - including >28,000 individuals living with HIV-1

- Enrolment into RESPOND began in 2017:
  - data was retrospectively collected back to 2012
  - data is prospectively collected annually from enrolment

Inclusion criteria

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- Started DTG, EVG/c or RAL for the first time after the latest of:
  - date enrolled into local cohort, or
  - 1/1/2012
- Age ≥ 16
- CD4 cell count and viral load (VL) measured prior to or within 6 months after starting an INSTI

Outcomes/statistical methods

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1. Uptake of DTG, EVG/c, or RAL

Outcomes/statistical methods

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1. Uptake of DTG, EVG/c, or RAL

Multinomial logistic regression was used to assess associations between baseline* characteristics and the likelihood of starting:

RAL vs DTG

EVG/c vs DTG

*baseline - date of INSTI start

Outcomes/statistical methods

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2. Discontinuation of first INSTI regimen during follow-up

Outcomes/statistical methods

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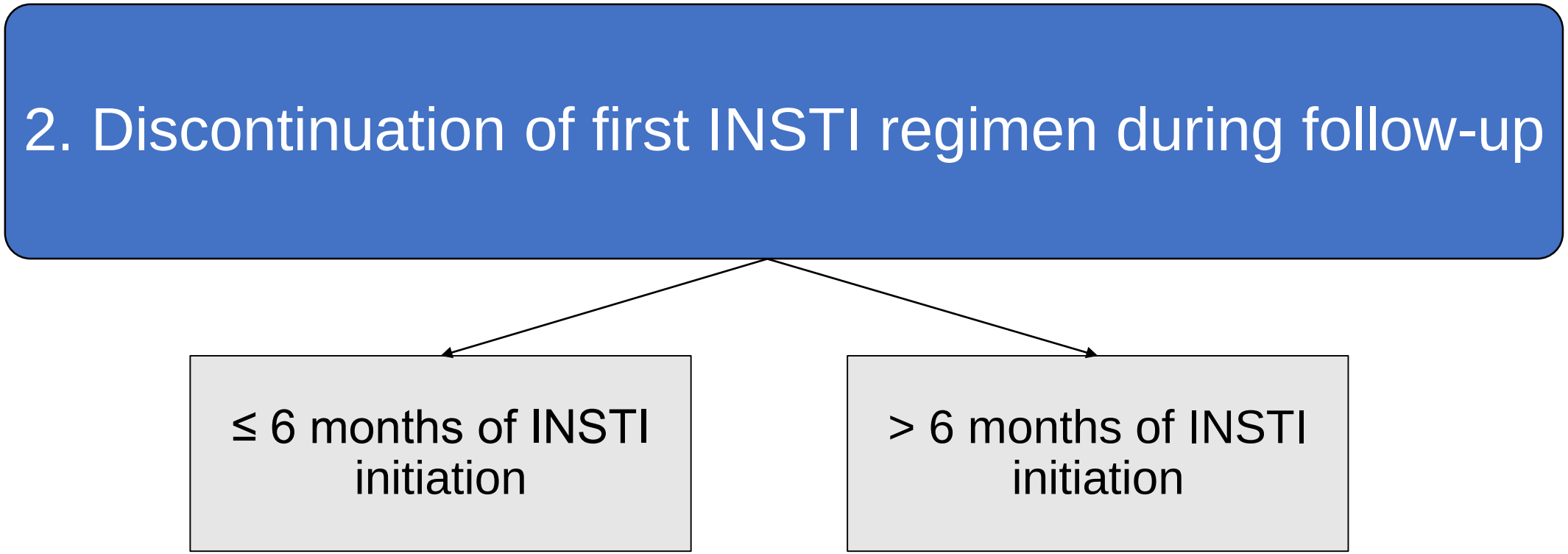

Outcomes/statistical methods

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2. Discontinuation of first INSTI regimen during follow-up

Cox proportional hazards models were used to assess factors associated with time to discontinuation within the first 6 months

Baseline characteristics

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Demographics

- Age
- Gender
- Ethnicity
- Smoking status
- Geographical region
- Cohort

HIV related

- Year of starting INSTI
- HIV risk category
- CD4 cell count nadir
- CD4 cell count at INSTI initiation
- ART experience and viral suppression status
- For discontinuation models, INSTI type was also included

Comorbidities

- Viral hepatitis B and C status (HBV/HCV)
- Hypertension
- Diabetes
- AIDS defining event (ADE)
- Non-AIDS defining malignancy (NADM)
- End stage liver disease
- Cardiovascular disease (CVD)
- Fracture
- Chronic kidney disease

Characteristics at INSTI start (**N=9702**)

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INSTI, n (%)		DTG 5051 (52.1)	RAL 2718 (28.0)	EVG/c 1933 (19.9)
		%		
Gender	Male	74.5	73.5	80.7
Ethnicity*	White	84.1	81.2	80.6
ART experience	Naïve	23.5	20.5	30.4
	Experienced, VL<400 cps/mL	69.9	66.2	62.8
HIV risk*	MSM	47.0	43.3	54.7
Geographical region of Europe	Western	59.9	38.5	55.6
	Southern	26.1	26.8	32.7
	Northern & Australia	10.0	27.0	7.9
	Eastern/Eastern Central	5.1	9.1	5.2
Any prior/current comorbidity		37.6	33.1	27.7
INSTI start date (median (IQR))		Jan16 (May15, Oct16)	Feb14 (Jan13, Apr15)	Dec15 (Oct14, Nov16)
Age, years (median (IQR))		48 (39, 55)	48 (41, 54)	45 (36, 53)
CD4 at INSTI start, cells/mm³ (median (IQR))		578 (369, 788)	507 (297, 714)	560 (386, 756)

*Denominator for percentages is all participants with non-missing data. Total unknown %: ethnicity 14.8, HIV risk 5.4

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INSTI Uptake

Choice of INSTI

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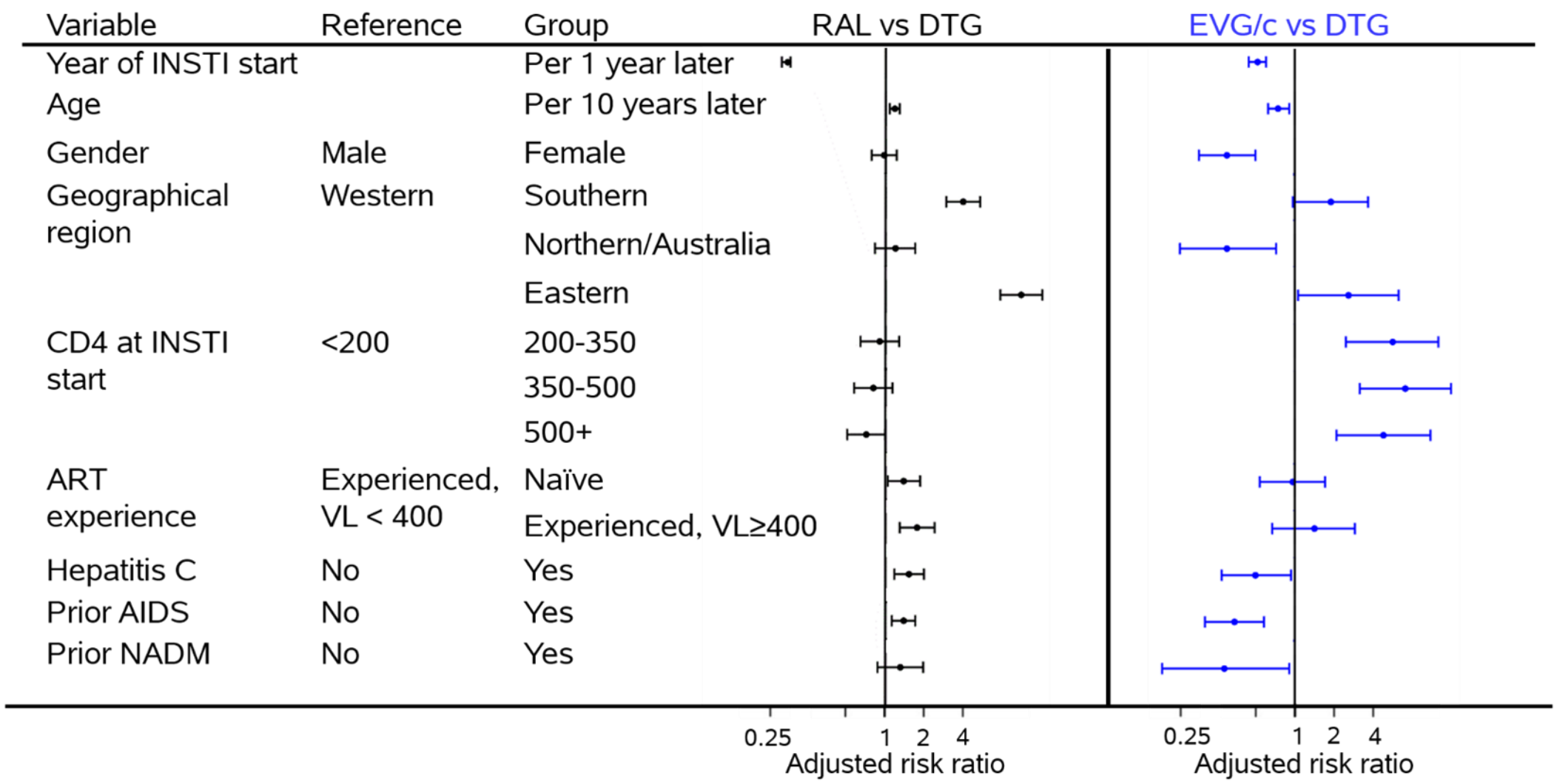

Results from a multinomial logistic regression model, additionally adjusted for ethnicity, HIV risk group, CD4 nadir, smoking status, hepatitis B, hypertension, diabetes, end stage liver disease, cardiovascular disease, fracture, chronic kidney disease and all other factors in the figure. Missing data was fitted using unknown categories (data not shown)

Discontinuation of INSTIs

Discontinuation

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	Overall (n=9702)	DTG (n=5051)	RAL (n=2718)	EVG/c (n=1933)
Median (IQR) follow-up, months	20.0 (9.9-32.4)	17.1 (8.5-26.2)	33.4 (16.7-48.3)	17.7 (7.6-31.7)

Discontinuation

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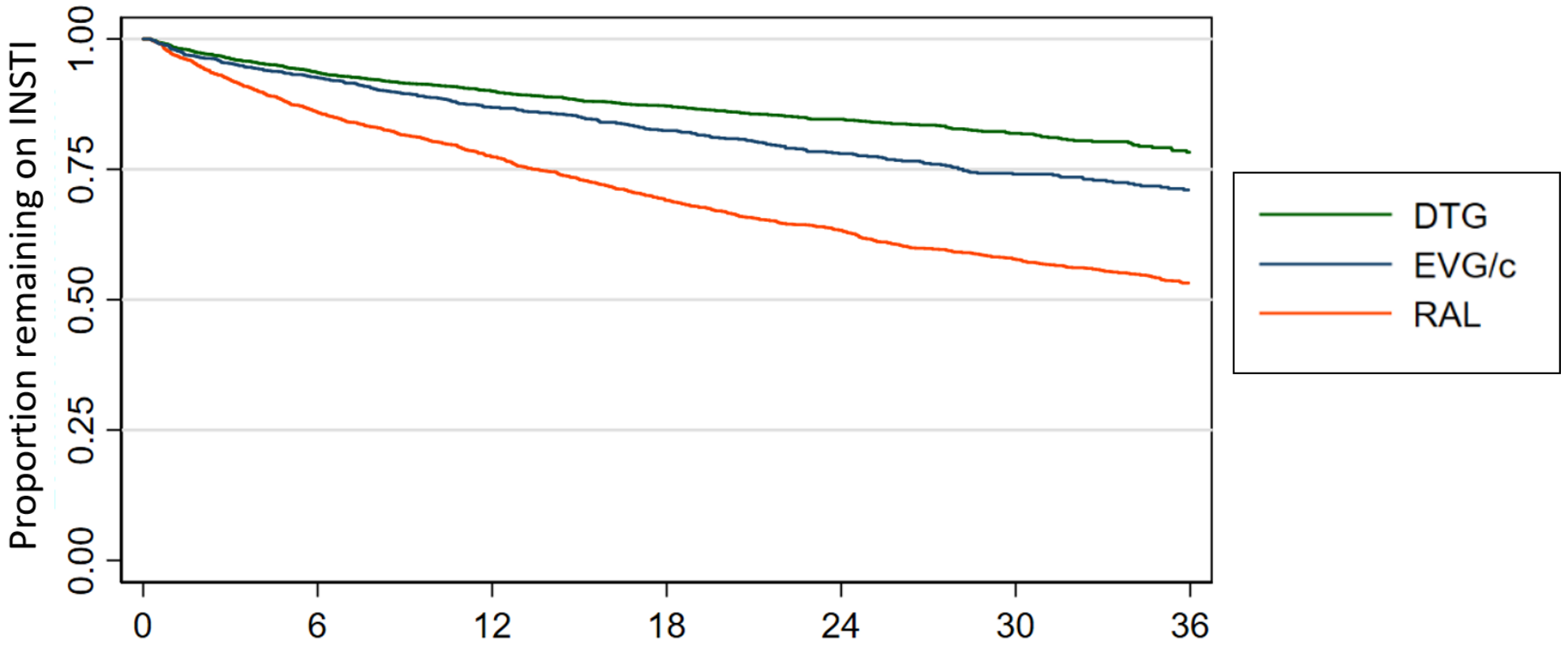
	Overall (n=9702)	DTG (n=5051)	RAL (n=2718)	EVG/c (n=1933)
Median (IQR) follow-up, months	20.0 (9.9-32.4)	17.1 (8.5-26.2)	33.4 (16.7-48.3)	17.7 (7.6-31.7)
Number (%) who discontinued during follow-up	2105 (21.7%)	619 (12.3%)	1145 (42.1%)	341 (17.6%)

Discontinuation



Number at risk

DTG	5051	3880	3011	2122	1325	669	255
RAL	2718	2143	1760	1393	1110	886	682
EVG/c	1933	1422	1059	790	582	416	274

Discontinuation

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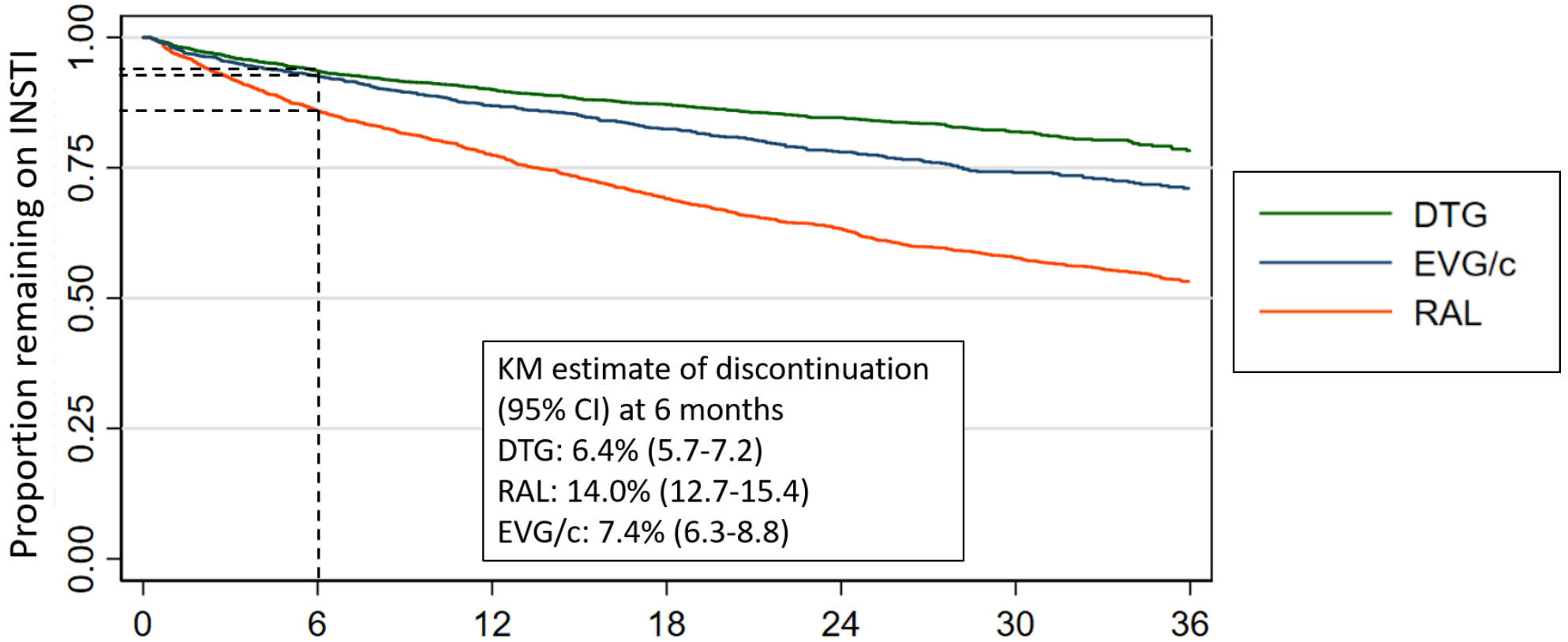

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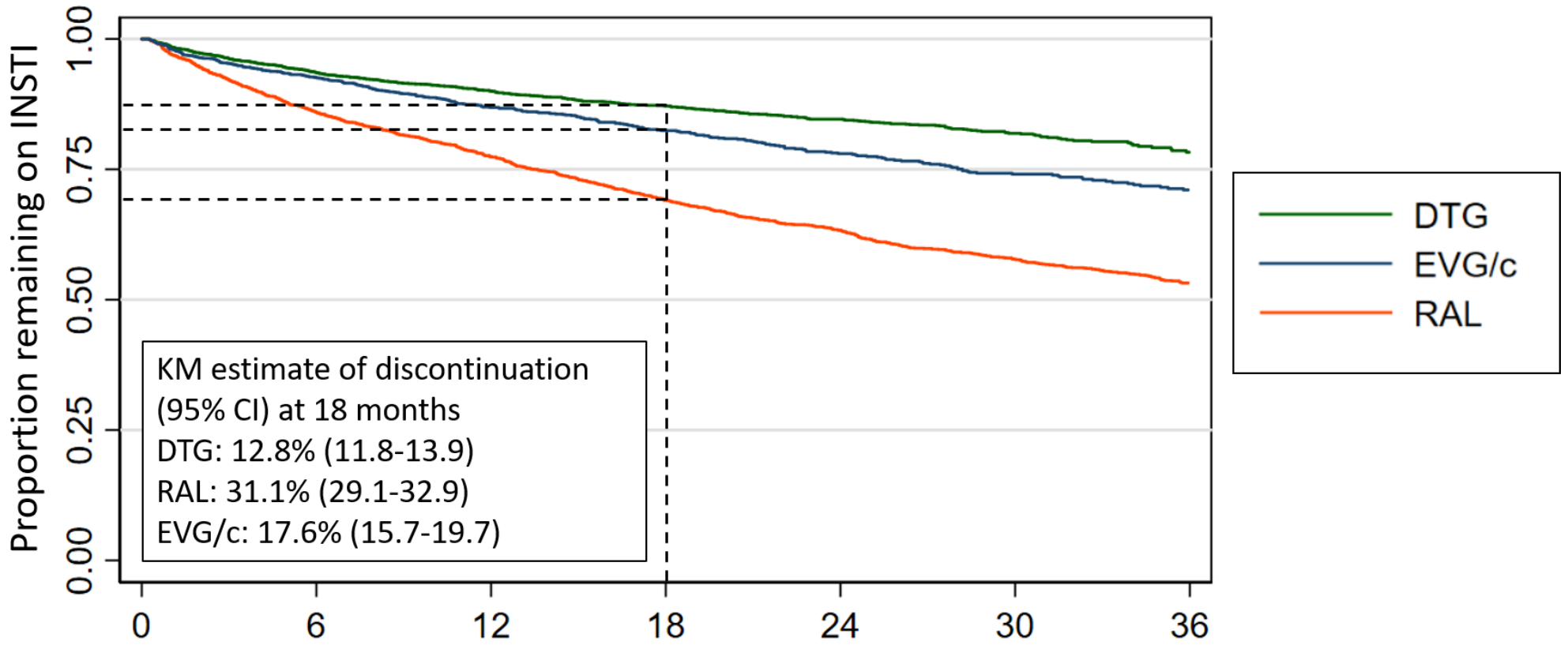

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Reasons for discontinuation (n=2105)

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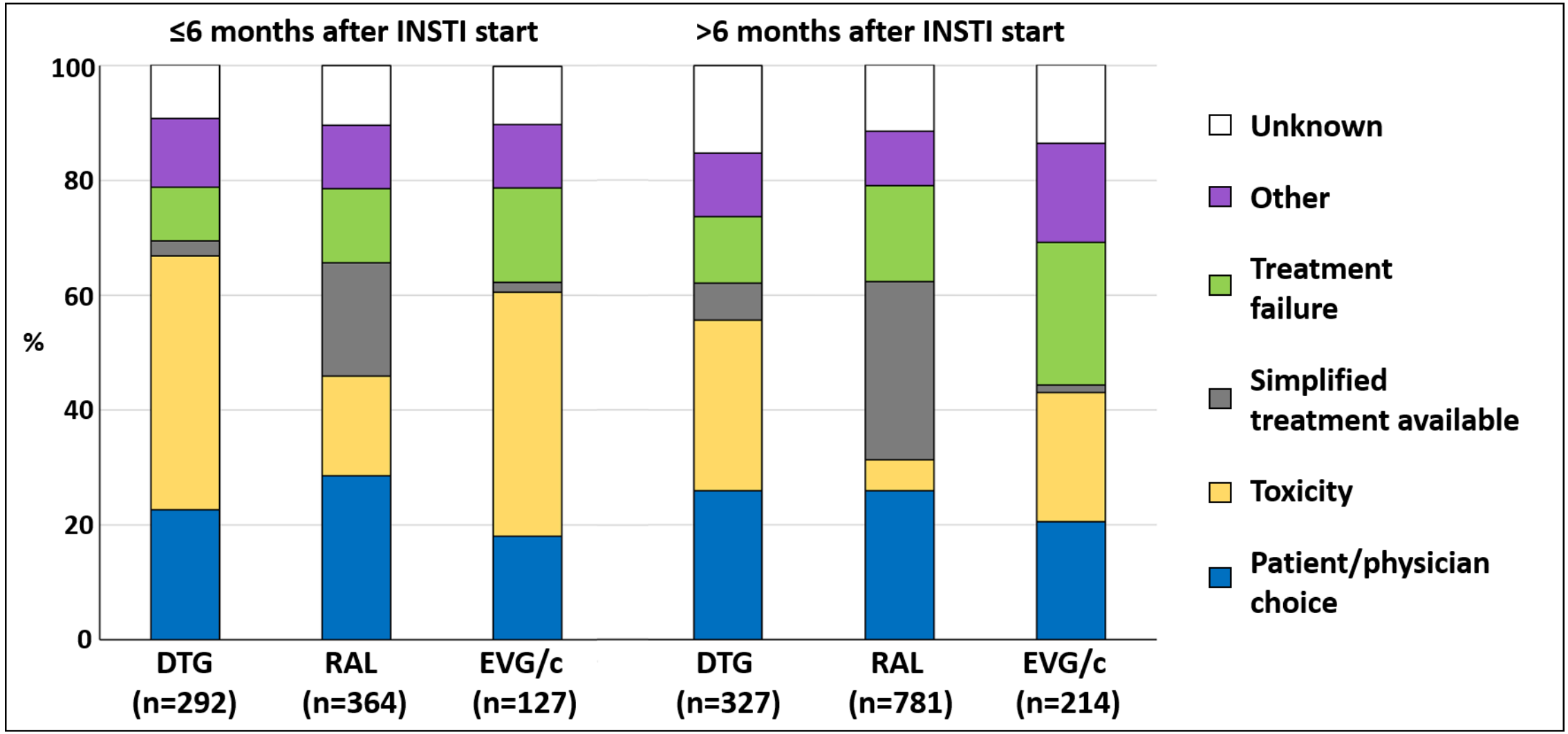
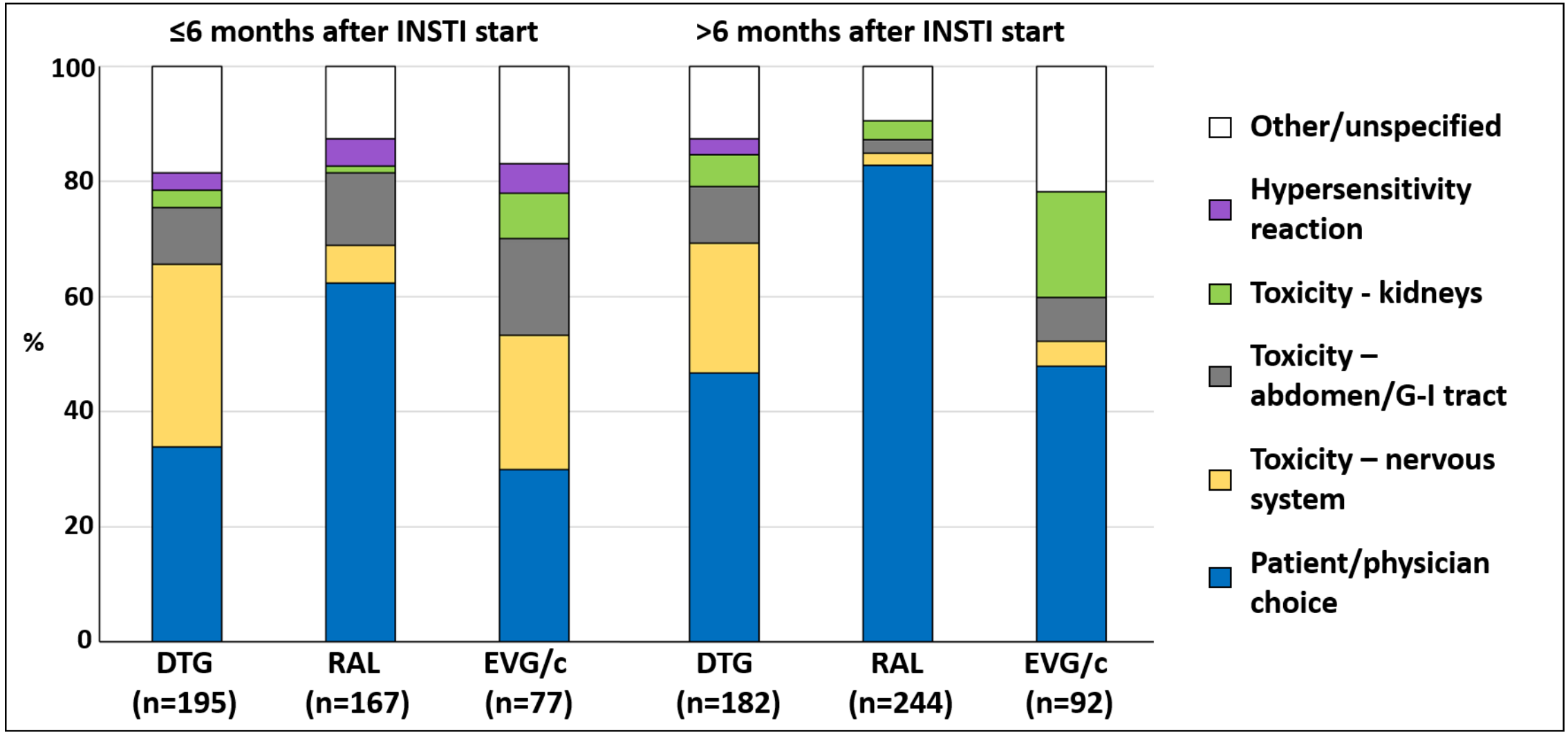


Toxicity includes abnormal fat redistribution, concern of cardiovascular disease, hypersensitivity reaction, abdomen/gastrointestinal tract, nervous system, kidney, or endocrine system toxicities, unspecified side effects

Reasons for discontinuation due to toxicity (n=957)



Factors associated with INSTI discontinuation within 6 months

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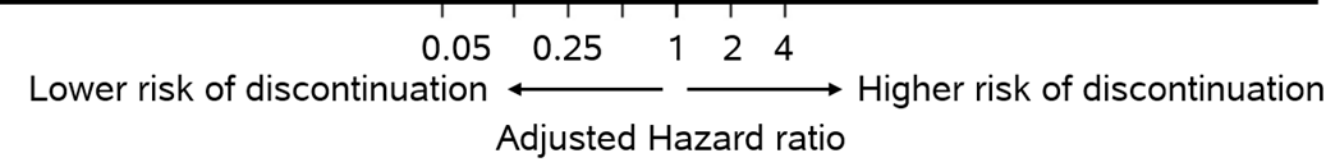
Variable	Reference	Group	aHR (95% CI)
INSTI type	DTG	RAL	3.03 (2.47, 3.71)
		EVG	1.37 (1.10, 1.70)
Year of INSTI start		Per 1 year later	1.11 (1.04, 1.18)
Gender	Male	Female	1.28 (1.06, 1.56)
ART experience	Experienced, VL < 400	Naïve	1.10 (0.87, 1.39)
		Experienced, VL≥400	1.36 (1.07, 1.73)
Hepatitis C	No	Yes	1.32 (1.06, 1.66)
Prior NADM	No	Yes	1.55 (1.13, 2.12)
Geographical region	Western	Southern	0.58 (0.43, 0.78)
		Northern/Australia	0.90 (0.64, 1.25)
		Eastern	0.31 (0.20, 0.50)



Plot includes variables with p<0.05 from a Cox proportional hazards model, additionally adjusted for age, ethnicity, HIV risk group, CD4 nadir, CD4 at INSTI start, smoking status, hepatitis B, hypertension, diabetes, prior AIDS, end stage liver disease, cardiovascular disease, fracture, chronic kidney disease. Missing data for hepatitis C and prior NADM were fitted using unknown categories (data not shown)

Limitations

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- Individuals in RESPOND were not randomly selected as we pre-specified the minimum number on INSTIs to be included
- Not possible to rule out residual confounding
- Completeness of data varies between cohorts
- Only one reason for discontinuation per antiretroviral was collected, without further detail

Conclusion (I)

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- This is one of the first large, multi-national studies investigating the choice of INSTIs and discontinuation of INSTIs in real life settings

- Uptake of DTG vs EVG/c or RAL has increased:
  - over calendar time
  - more in Western Europe compared to other European regions

Conclusion (II)

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- INSTI discontinuation was mainly due to toxicity in the first 6 months and patient/physician choice thereafter, but was low overall
- Discontinuation was significantly higher for RAL, mainly due to treatment simplification
- Discontinuation was lowest on DTG
- However discontinuation due to nervous system toxicities was highest on DTG
- Our findings highlight the need for further research to better understand adverse effects on INSTIs

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Cohort principal investigators:.

De Wit (St. Pierre, Brussels), R. Zangerle (AHICOS), M. Law (AHOD), F. Wit (ATHENA) G. Wandeler (EuroSIDA), C. Stephan (Frankfurt), N. Chkhartishvili (IDACIRC), C. Pradier (Nice HIV cohort), A. d'Arminio Monforte (ICoNA), C. Mussini (Modena), J. Casabona & J.M. Miro (PISCIS), H. Günthard (SHCS), A. Sönnerborg (Swedish InfCare), C. Smith (Royal Free HIV cohort), A. Castagna (St. Rafael, Milano), J.C. Wasmuth (Bonn, HIV Cohort) and J.J. Vehreschild (Cologne, HIV cohort).

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RESPOND Scientific Steering committee: J. Lundgren (co-chair), H. Günthard (Co-Chair), C. Mussini, R. Zangerle, A. Sönnerborg, V. Vannappagari, J.C. Wasmuth, M. Law, F. Wit, R. Haubrich, H. Bucher, C. Pradier, H. Garges, C. Necsoi, G. Wandeler, C. Smith, J.J. Vehreschild, F. Rogatto, C. Stephan, N. Chkhartishvili, A. d'Arminio Monforte, A. Bruguera and A. Castagna.

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Scientific interest group moderators:

L. Ryom, A. Mocroft (Outcomes with antiretroviral treatment), L. Peters, J. Rockstroh (Hepatitis), D. Raben and J. Kowalska (Public Health), O. Kirk, A. Philips, V. Cambiano and Jens Lundgren (PrEP)

Members of the scientific interest group:

Hepatis, Public Health, Outcomes with antiretroviral treatment, PrEP, Resistance. Details at: https://www.chip.dk/Studies/RESPOND/Scientific-Interest-Groups

Statisticians:

A. Mocroft and L. Greenberg

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