



# Nuovi paradigmi terapeutici: i dati della Coorte ICONA

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Disclosure of potential conflicts of interest, last 3years

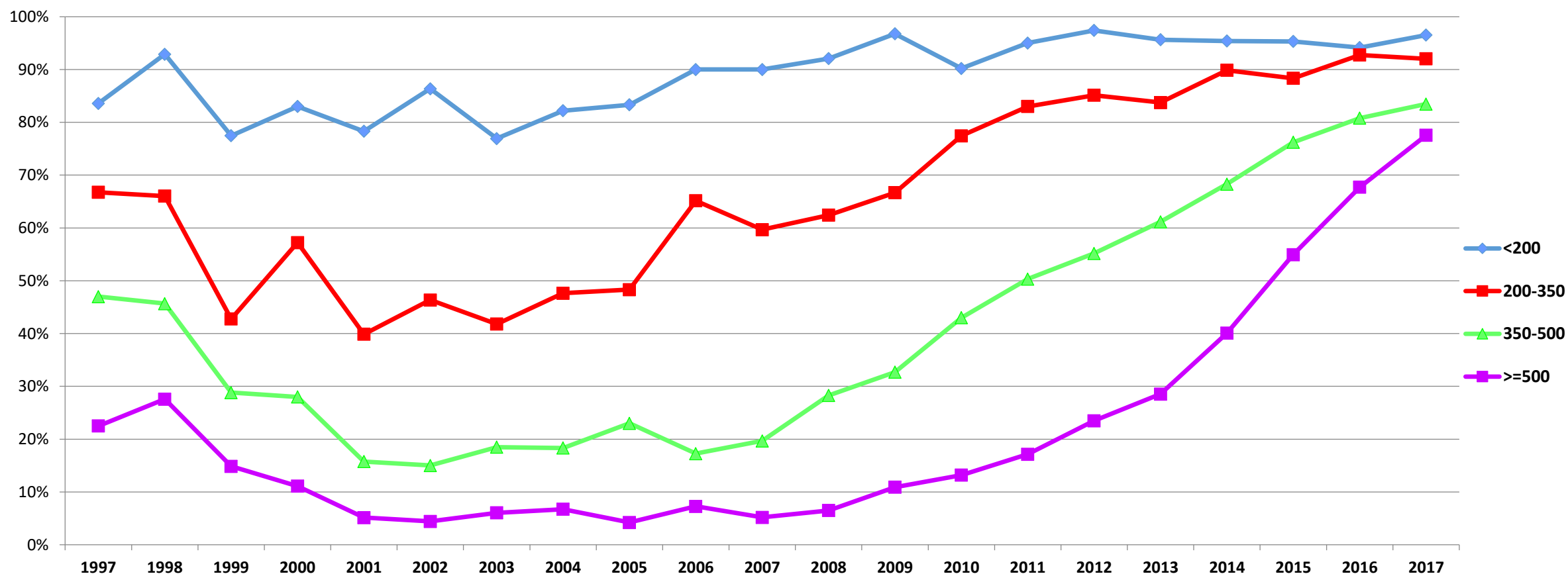
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- Advisor for AbbVie, BMS, Gilead, Janssen-Cilag, MSD and ViiV
- Speakers' honoraria from AbbVie, Angelini, BMS, Gilead, Janssen-Cilag, MSD and ViiV
- Support for travel meetings from AbbVie, BMS, Gilead, and ViiV
- Grant for research from Gilead, Janssen-Cilag, MSD and ViiV

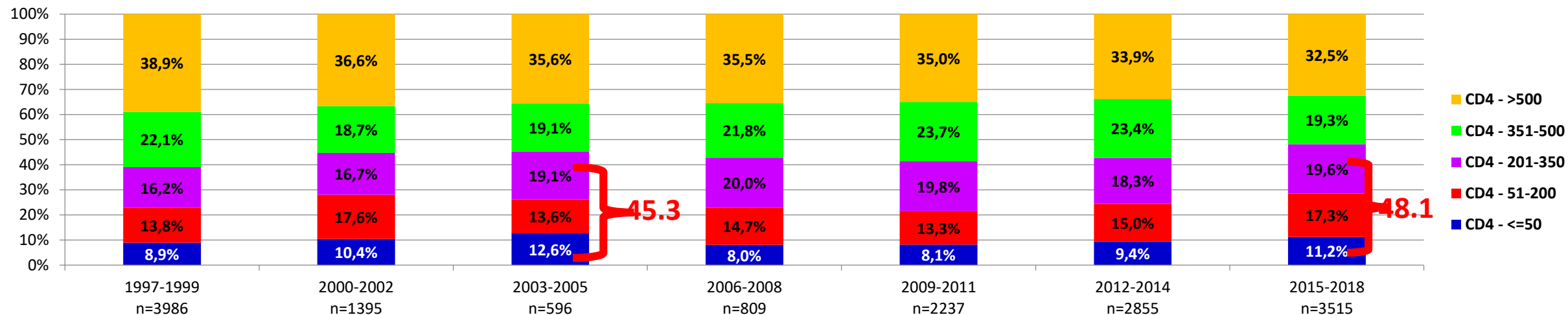
# La coorte Icona: regimi terapeutici a confronto

- ✓ Studio osservazionale
- ✓ Dati principalmente sui regimi di prima linea
- ✓ Variazioni temporali in accordo con le linee guida
- ✓ Data e cause di discontinuazione tabulate

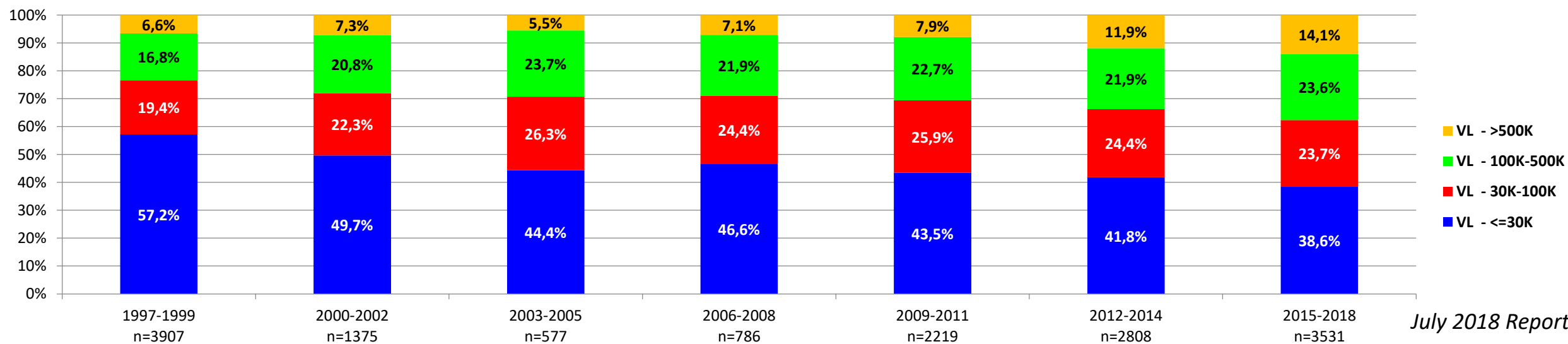
## Proportion of patients starting ART according to their CD4+ strata at the beginning of the year



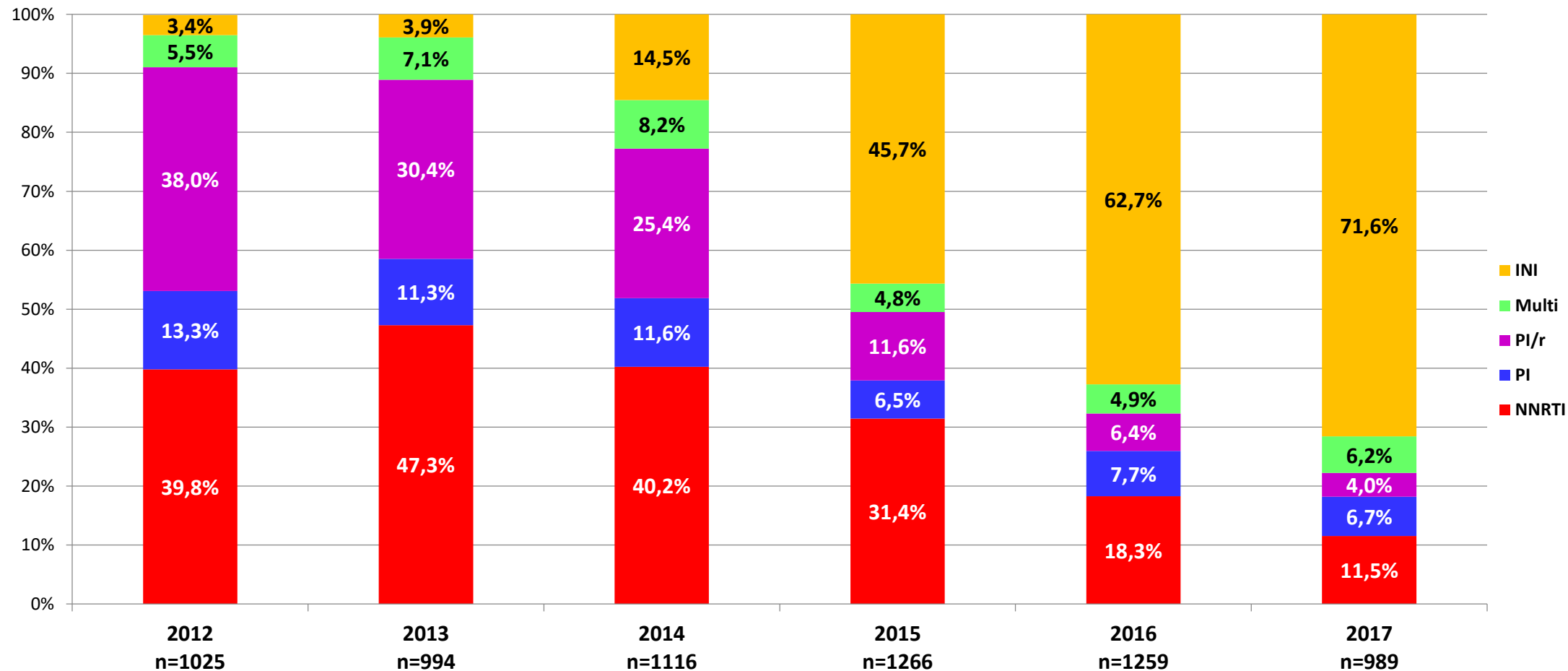
## CD4 cells/mm<sup>3</sup> count strata at enrolment according to calendar period



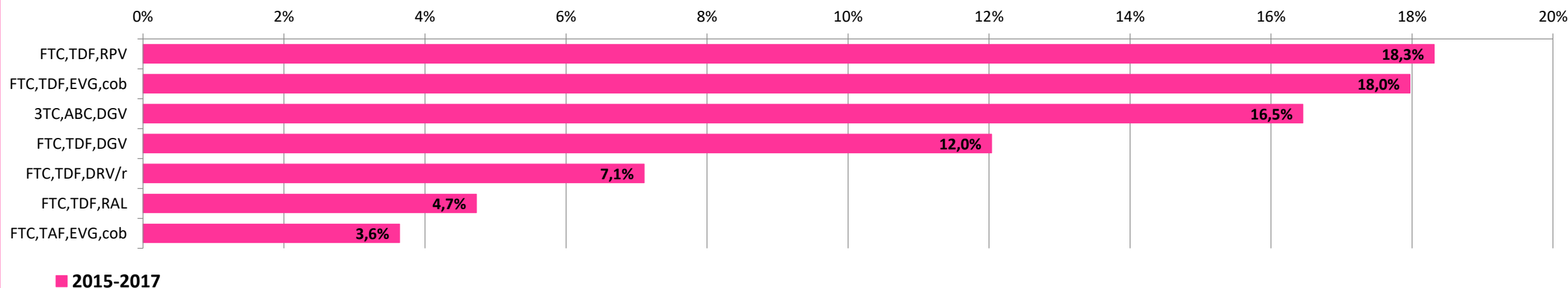
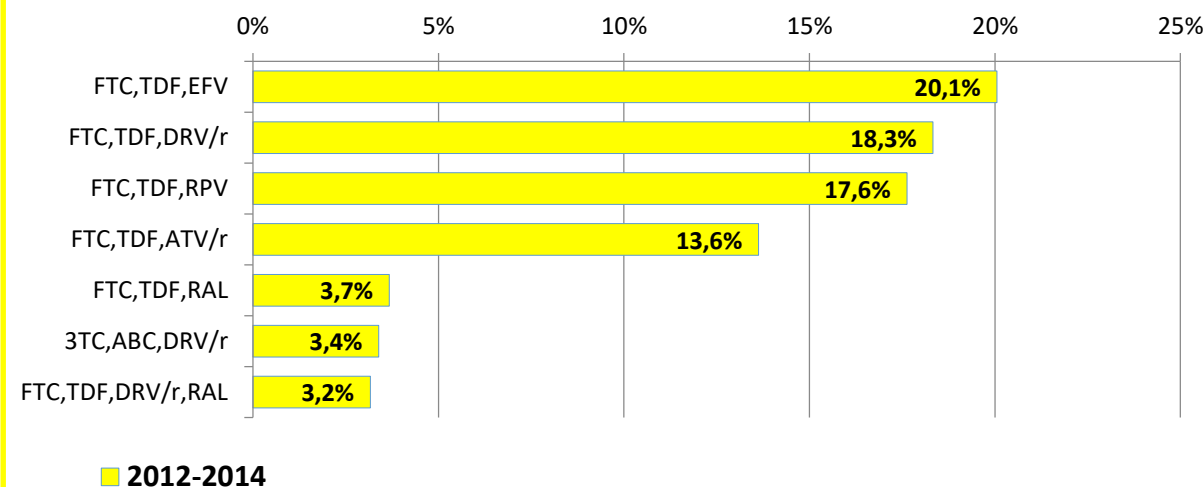
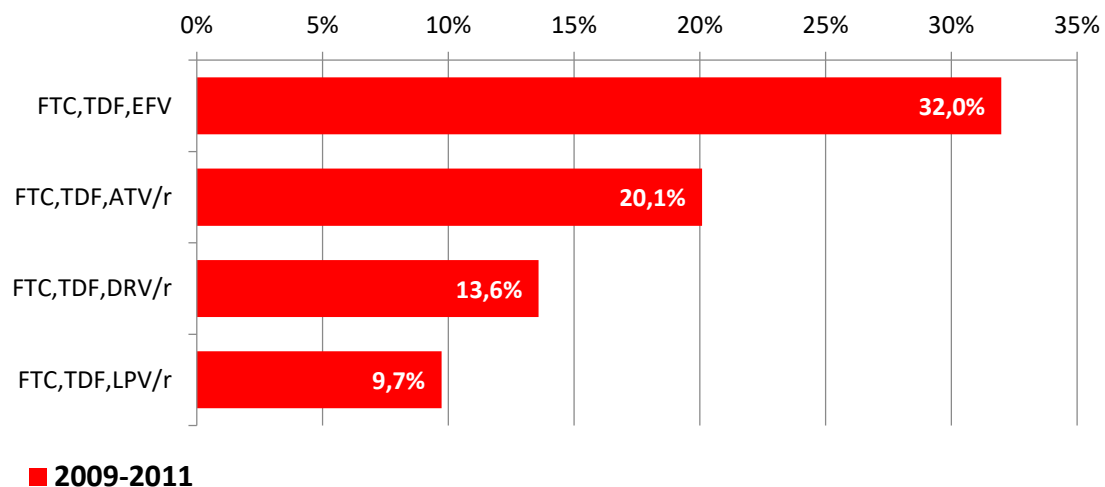
## HIV-RNA strata at enrolment according to calendar period



## Proportion of usage of different ART classes as third drug in first line regimen according to calendar year of starting (NRTIs not considered)

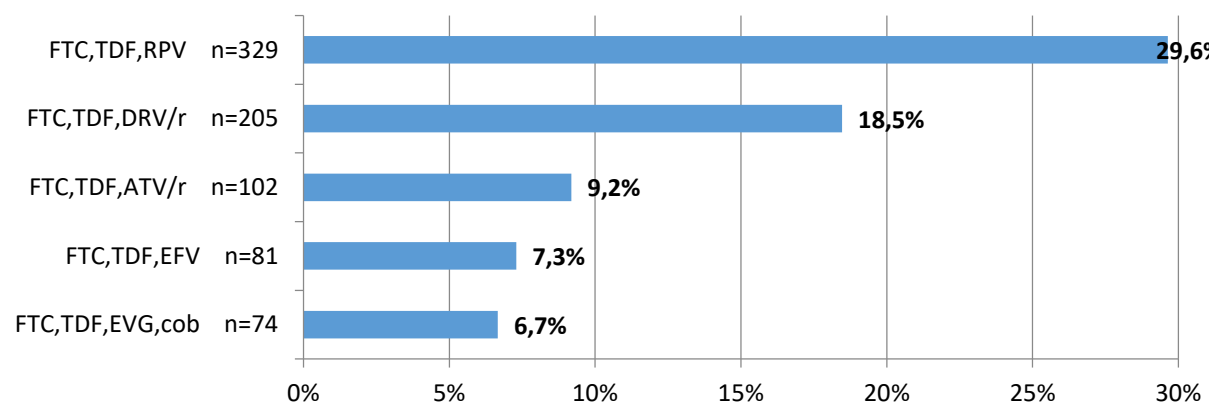


## Most frequent regimens used in first line according to calendar period of starting

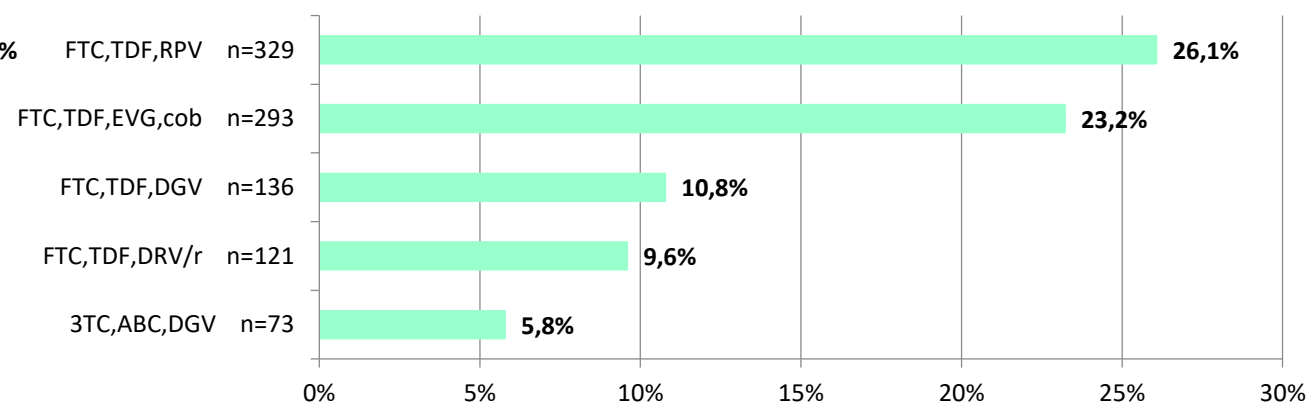


## Distribution of most frequent first line regimens in patients starting ART from 2014 to 2017

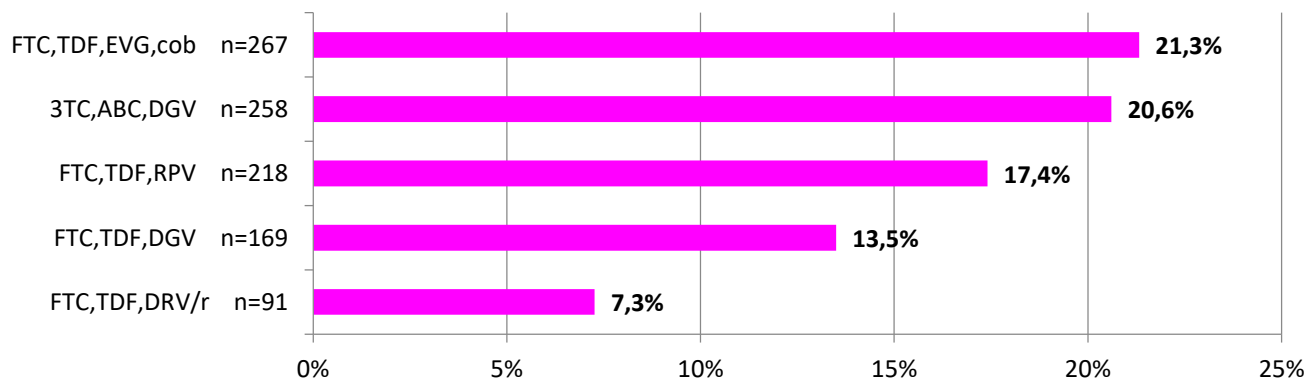
**2014**



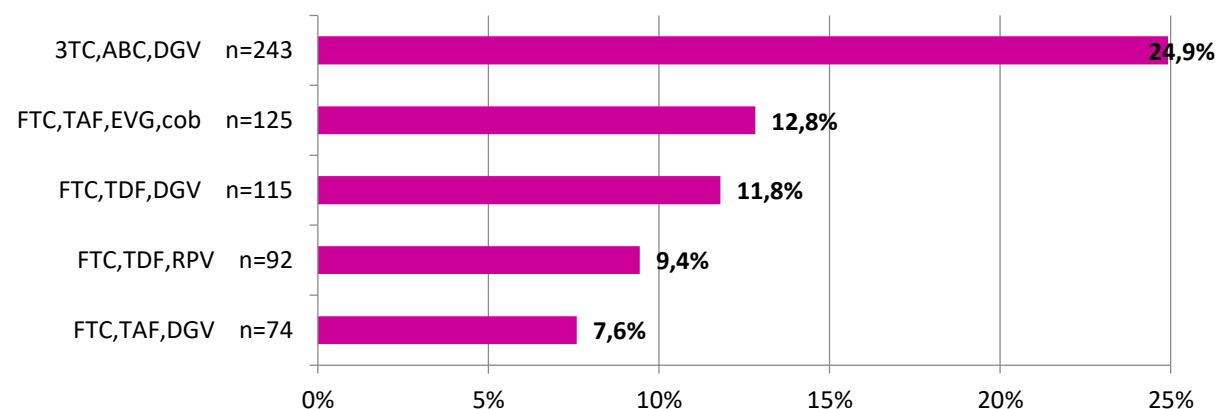
**2015**



**2016**



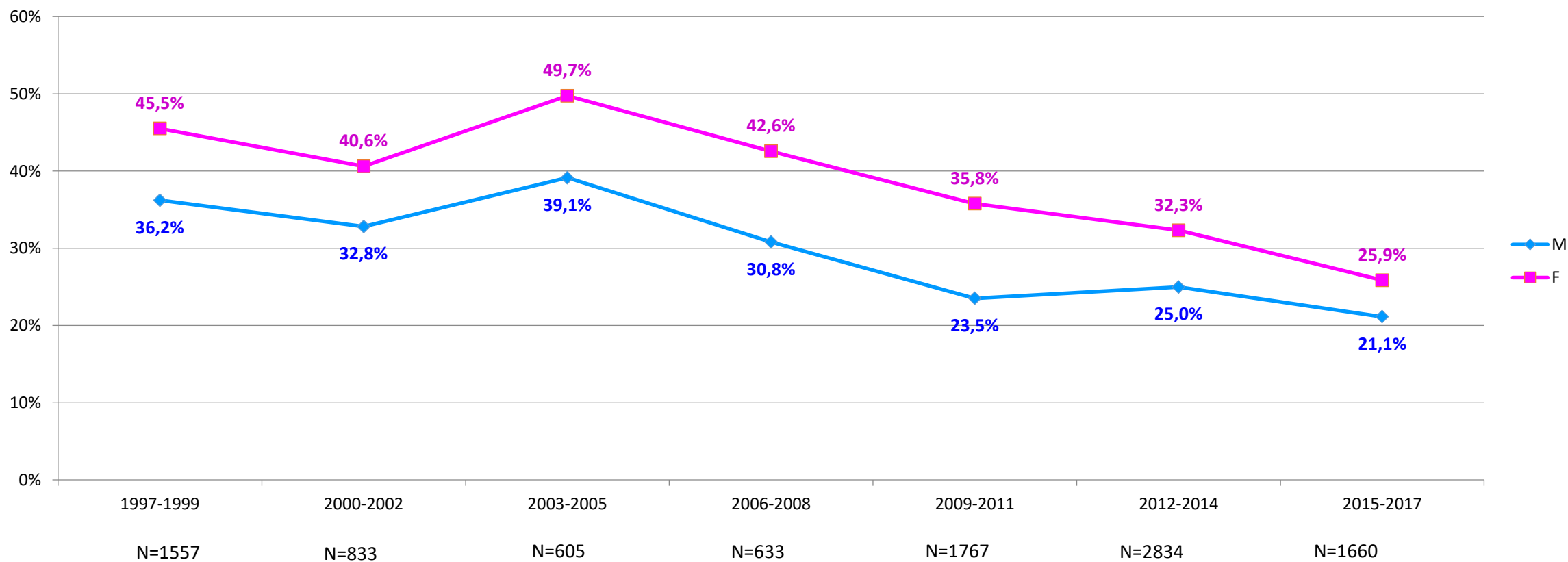
**2017**







## Proportion of patients stopping at least one drug of their first ART within 1 year according to gender and calendar period of starting



Late presenters

# Response to First-Line Ritonavir-Boosted Protease Inhibitors (PI/r)-Based Regimens in HIV Positive Patients Presenting to Care with Low CD4 Counts: Data from the Icona Foundation Cohort

Antonella d'Arminio Monforte<sup>1\*</sup>, Alessandro Cozzi-Lepri<sup>2</sup>, Franco Maggiolo<sup>3</sup>, Giuliano Rizzardini<sup>4</sup>, Paolo Emilio Manconi<sup>5</sup>, Nicola Gianotti<sup>6</sup>, Tiziana Quirino<sup>7</sup>, Carmela Pinnetti<sup>8</sup>, Stefano Rusconi<sup>9</sup>, Andrea De Luca<sup>10</sup>, Andrea Antinori<sup>8</sup>, Icona Foundation Study cohort<sup>11</sup>

[PLOS One](#). 2016 Jun 27;11(6):e0156360.

## Study Population

- Subjects with CD4  $\leq 350$  cells/mm<sup>3</sup> (low CD4-LC) or CD4 counts  $\leq 200$  cells/mm<sup>3</sup> (very low CD4-VLC) and/or AIDS
- Starting PI/r-based regimen after 01/01/2008 from ART-Naive

## Endpoints

1. Virological Failure [VF] (2 consecutive VL $>200$  cps/mL,  $>6$ months)
2. PI/r discontinuation for any cause [TD]
3. PI/r discontinuation for toxicity [TDT]
4. Treatment Failure [TF] (VF or TD).

## Stats

KM and Cox regression (time to outcomes)

## Results

1,362 LC patients [813 VLC (59.7%)]:

- 607 (44.6%) DRV/r
- 552 (40.5%) ATV/r
- 203 (14.9%) LPV/r

Median follow-up of 18 months (IQR:7–35)

Table 3. LC patients: RH of various endpoints from fitting a Cox regression analysis.

	Crude and adjusted relative hazards			
	Crude RH (95% CI)	p-value	Adjusted* RH (95% CI)	p-value
<b>VL&gt;200 copies/mL</b>				
<b>Group</b>				
LPV/r	1.00		1.00	
ATV/r	1.97 (1.11, 3.51)	0.021	1.92 (0.86, 4.28)	0.111
DRV/r	0.63 (0.32, 1.25)	0.185	1.13 (0.45, 2.85)	0.801
<b>Discontinuation</b>				
<b>Group</b>				
LPV/r	1.00		1.00	
ATV/r	0.51 (0.40, 0.64)	<.001	0.47 (0.37, 0.60)	<.001
DRV/r	0.47 (0.37, 0.59)	<.001	0.36 (0.28, 0.47)	<.001
<b>Discontinuation due to toxicity</b>				
<b>Group</b>				
LPV/r	1.00		1.00	
ATV/r	1.97 (1.11, 3.51)	0.021	1.71 (0.91, 3.23)	0.095
DRV/r	0.63 (0.32, 1.25)	0.185	0.51 (0.24, 1.09)	0.081
<b>VL&gt;200 copies/mL or discontinuation</b>				
<b>Group</b>				
LPV/r	1.00		1.00	
ATV/r	0.54 (0.42, 0.67)	<.001	0.49 (0.39, 0.63)	<.001
DRV/r	0.46 (0.36, 0.58)	<.001	0.38 (0.29, 0.50)	<.001

\*adjusted for age, gender, nation of birth, mode of HIV transmission,hepatitis co-infection status, AIDS diagnosis, nucleoside pair started,baseline CD4 count and viral load and year of starting cARTand stratified by clinical center

## LC patients (<350 CD4)

- 57 (4.2%) VF
  - 507 (37.2%) TD
  - 97 (7.1%) TDT
  - 485 (35.6%) TF
- 
- No differences in the risk of VF according to the PI/r
  - Risk of TD higher for LPV/r (vs. ATV/r and vs. DRV/r).
  - Risk of TF was higher for LPV/r (vs. ATV/r and vs. DRV/r)

Table 4. VLC patients: RH of various endpoints from fitting a Cox regression analysis.

	Crude and adjusted relative hazards			
Outcomes	Crude RH (95% CI)	p-value	Adjusted* RH (95% CI)	p-value
<b>VL&gt;200 copies/mL</b>				
<b>Group</b>				
LPV/r	1.00		1.00	
ATV/r	1.62 (0.83, 3.18)	0.159	3.70 (1.16, 11.74)	0.027
DRV/r	0.45 (0.20, 1.01)	0.054	3.10 (0.89, 10.80)	0.076
<b>Discontinuation</b>				
<b>Group</b>				
LPV/r	1.00		1.00	
ATV/r	0.57 (0.43, 0.76)	<.001	0.50 (0.37, 0.69)	<.001
DRV/r	0.41 (0.31, 0.55)	<.001	0.31 (0.22, 0.43)	<.001
<b>Discontinuation due to toxicity</b>				
<b>Group</b>				
LPV/r	1.00		1.00	
ATV/r	1.62 (0.83, 3.18)	0.159	1.11 (0.51, 2.43)	0.795
DRV/r	0.45 (0.20, 1.01)	0.054	0.31 (0.12, 0.78)	0.013
<b>VL&gt;200 copies/mL or discontinuation</b>				
<b>Group</b>				
LPV/r	1.00		1.00	
ATV/r	0.64 (0.48, 0.86)	0.003	0.56 (0.41, 0.79)	<.001
DRV/r	0.42 (0.31, 0.57)	<.001	0.34 (0.24, 0.48)	<.001

\*adjusted for age, gender, nation of birth, mode of HIV transmission,hepatitis co-infection status, AIDS diagnosis, nucleoside pair started,baseline CD4 count and viral load and year of starting cARTand stratified by clinical center

## 813 VLC patients (<200CD4) [median FU of 15 months (6–33)]

- 28 (3.4%) VF
- 162 (19.9%)TD
- 28 (3.4%) TDT
- 167 (20.5%) TF
- Risk of VF was significantly higher for DRV/r and ATV/r vs. LPV/r.
- Both ATV/r and DRV/r showed a lower risk of TD vs. LPV/r.
- DRV/r showed a lower probability of TDT vs. LPV/r.
- Risk of TF was lower for both ATV/r and DRV/r vs LPV/r

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High Virological potency, no differences by PI/r (in LC), but lower risk of VF in VLC group for LPV/r.

Larger differences were observed when comparing longer-term endpoints such as TF or TD (higher risk for LPV/r) and TDT (lower risk for DRV/r in VLC group)

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- Both ATV/r and DRV/r showed a lower risk of TD vs. LPV/r.
- DRV/r showed a lower probability of TDT vs. LPV/r.
- Risk of TF was lower for both ATV/r and DRV/r vs LPV/r

# Durability of Different Initial Regimens in Patients Starting ART with CD4+ Counts <200 cells/ $\mu$ L and HIV-RNA >5 log<sub>10</sub> copies/mL.

Nicola Gianotti<sup>1</sup>, Patrizia Lorenzini<sup>2</sup>, Alessandro Cozzi-Lepri<sup>3</sup>, Andrea De Luca<sup>4</sup>, Giordano Madeddu<sup>5</sup>, Laura Sighinolfi<sup>6</sup>, Carmela Pinnett<sup>2</sup>, Carmen Santoro<sup>7</sup>, Paola Meraviglia<sup>8</sup>, Cristina Mussini<sup>9</sup>, Andrea Antinori<sup>2</sup>, Antonella d'Arminio<sup>10</sup>  
on behalf of the ICONA Foundation Study Group



CROI 2018  
Boston, March 4-7, 2018

## Study Population

- From ART-Naive: TDF/FTC or ABC/3TC + bPI or NNRTI or InSTI
- CD4<200 and HIV-RNA>100,000 copies/mL

## Endpoint

### Primary Endpoint

1. Treatment failure [TF], defined as: virological failure [VF] ( 2 consecutive VL>50 cps/mL, >6 months ) or discontinuation of class of the anchor drug

### Secondary endpoints

2. TF in the stratum VL>500,000 copies/mL
3. VF
4. CD4+ cell counts during follow-up.

## Stats

KM and Poisson regression (time to outcomes)

## Results

1127 patients

- 729 with a bPI  
(48% DRV/r, 29% ATV/r, 21% ATV/r, 2% FPV/r)
- 305 with an InSTI (48% DTG, 29% EVG, 23% RAL)
- 193 with a NNRTI (94% EFV, 3% RPV, 2% NVP, 1% ETV)



Figure 1. Cumulative probability of TF according to the anchor drug of the initial ART regimen.

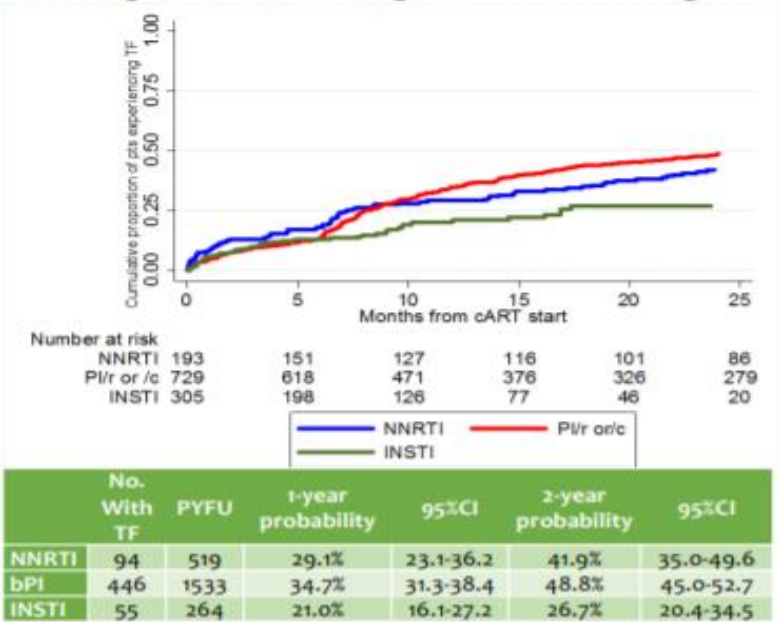


Figure 2. Cumulative probability of VF according to the anchor drug of the initial ART regimen.

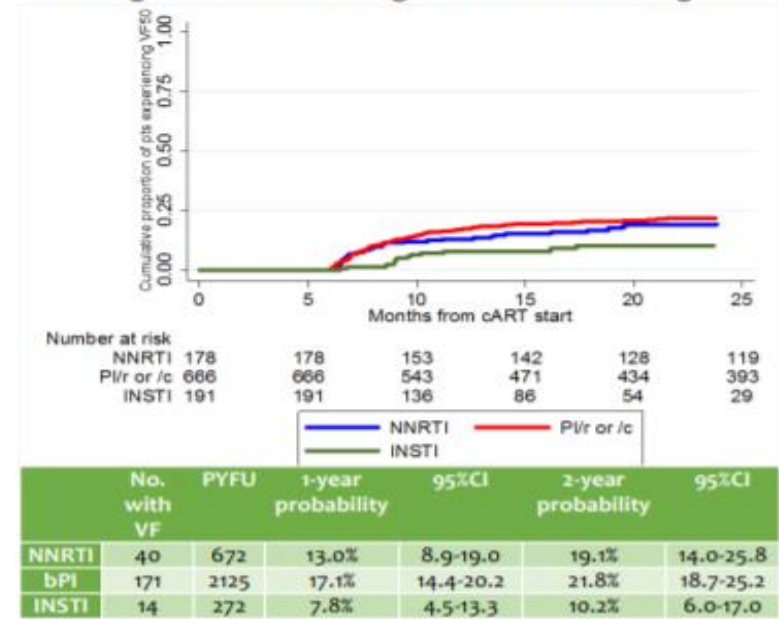


Table 3. Univariable and multivariable analysis of factors associated with TF

	Unadjusted IRR (95% CI)	p-value	Adjusted IRR (95% CI)	p-value
Anchor drug class (alternative 1)				
NNRTI	1.00		1.00	
bPI	1.61 (1.29-2.01)	<0.001	1.54 (1.22-1.93)	<0.001
INSTI	1.15 (0.83-1.61)	0.407	1.07 (0.76-1.50)	0.704
Anchor drug class (alternative 2)				
NNRTI	0.62 (0.50-0.78)	<0.001	0.65 (0.52-0.82)	<0.001
bPI	1.00		1.00	
INSTI	0.72 (0.54-0.95)	0.019	0.69 (0.52-0.92)	0.012

- InSTI and NNRTI more effective than bPIs
  - Better tolerability of InSTIs compared to NNRTIs and particularly to bPIs
- The association not confirmed with baseline HIV-RNA >500,000 cps/mL.

The only other factor independently associated with TF and VF was the VL before ART start.

Type of initial regimens was not independently associates with VF.  
CD4+ cells gain during follow-up was optimal with any regimen and comparable among types of regimen

**In very advanced HIV infection (ART with <200 CD4+ and >5 log10 HIV-RNA copies/mL), the durability of regimens based on NNRTIs or InSTIs was longer than that of bPI-based regimens.**


HIV-RNA<100.000



# First-line antiretroviral therapy with efavirenz plus tenofovir disoproxil fumarate/emtricitabine or rilpivirine plus tenofovir disoproxil fumarate/emtricitabine: a durability comparison

DOI: 10.1111/hiv.12628

*HIV Medicine* (2018), 19, 475–484

L Taramasso <sup>1</sup>, A Di Biagio,<sup>2</sup> F Maggiolo,<sup>3</sup> A Tavelli,<sup>4</sup> S Lo Caputo,<sup>5</sup> S Bonora,<sup>6</sup> M Zaccarelli,<sup>7</sup> P Caramello,<sup>8</sup> A Costantini,<sup>9</sup> C Viscoli,<sup>1</sup> A d'Arminio Monforte<sup>10</sup> and A Cozzi-Lepri<sup>11</sup> on behalf of the Italian Cohort Naïve Antiretrovirals (ICONA) Foundation Study Group\*

## Study Population

TDF/FTC + RPV or EFV, with baseline VL < 100k copies/ml from ART-Naïve

## Endpoints

1. Durability: Discontinuation of any component of 1st-line regimen
2. VF50: Virological Failure (2 consecutive VL>50 cps/mL threshold, > 6 months)
3. VF200: Virological Failure (2 consecutive VL>200 cps/mL threshold, > 6 months,)

## Stats

KM and Cox regression (time to outcomes)

## Results

1,490 cART-naïve patients were included:

- 786 TDF/FTC/RPV (99% as STR)
- 704 TDF/FTC/EFV (30% as STR\*)

*\*switch to STR not counted as discontinuation event*

## Virological Failure

- By 2 years, 99.7% of patients in RPV and 96.3% in EFV with VL ≤50 cps/mL (p<0.0001).
- Patients in EFV were more likely to experience VF>50 cps/mL (7.8% EFV vs 2.1% RPV; p= 0.01)
- Not confirmed using threshold 200 cps/mL (p= 0.427)

## Durability (Discontinuation)

- 343 discontinuation; 218 by 2 years
- More frequent discontinuation in EFV group (23.6%), than RPV group (10.1%) (p <0.0001)
- EFV more likely to discontinue for any cause (aRH=4.09), for toxicity (aRH=2.23), for intolerance (aRH=5.17) and for proactive switch (aRH=10.96)
- In a subanalysis using only STR regimen proactive switch, resulted no longer significantly different (p=0.946).
- After adjustment, neither the probability of VF50 (p= 0.161) nor the achievement of VL ≤50 cps/mL (p=0.374) resulted significantly different.

**Table 3** Crude and adjusted relative hazards (RHs) for discontinuation of efavirenz (EFV) vs. rilpivirine (RPV) from fitting a Cox regression model

Outcome	Crude RH (95% CI)	P-value	Adjusted* RH (95% CI)	P-value
Discontinuation for any reason				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	2.47 (1.87–3.26)	< 0.001	4.09 (2.89–5.80)	< 0.001
Discontinuation because of toxicity				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	1.57 (0.86–2.86)	0.139	2.23 (1.05–4.73)	0.037
Discontinuation because of intolerance				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	4.16 (2.42–7.16)	< 0.001	5.17 (2.66–10.07)	< 0.001
Discontinuation because of proactive switch				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	3.69 (1.25–10.87)	0.018	10.96 (3.17, 37.87)	< 0.001
Single VL > 50 copies/mL				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	1.57 (0.86–2.86)	0.139	1.19 (0.78–1.82)	0.409
Confirmed VL > 50 copies/mL				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	2.03 (1.14–3.62)	0.016	0.70 (0.31–1.54)	0.374
Confirmed VL > 50 copies/mL or discontinuation				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	2.48 (1.91–3.22)	< 0.001	3.21 (2.30–4.48)	< 0.001
Success VL ≤ 50 copies/mL				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	0.83 (0.74–0.92)	< 0.001	0.89 (0.75–1.05)	0.161

## Virological Failure

- By 2 years, 99.7% of patients in RPV and 96.3% in EFV with VL ≤50 cps/mL ( $p < 0.0001$ ).
- Patients in EFV were more likely to experience VF >50 cps/mL (7.8% EFV vs 2.0% RPV,  $p = 0.01$ )
- Not confirmed using threshold 200 cps/mL ( $p = 0.427$ )

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- In a subanalysis using only TR regimen proactive switch, resulted no longer significantly different ( $p = 0.546$ ).
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TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	3.69 (1.25–10.87)	0.018	10.96 (3.17, 37.87)	< 0.001
Single VL > 50 copies/mL				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	1.57 (0.86–2.86)	0.139	1.19 (0.78–1.82)	0.409
Confirmed VL > 50 copies/mL				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	2.03 (1.14–3.62)	0.016	0.70 (0.31–1.54)	0.374
Confirmed VL > 50 copies/mL or discontinuation				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	2.48 (1.91–3.22)	< 0.001	3.21 (2.30–4.48)	< 0.001
Success VL ≤ 50 copies/mL				
TDF/FTC/RPV	1.00		1.00	
TDF/FTC/EFV	0.83 (0.74–0.92)	< 0.001	0.89 (0.75–1.05)	0.161

# Durability of rilpivirine- and integrase inhibitor-based first-line regimens in HIV-infected patients starting antiretroviral therapy with a viral load <100,000 copies/mL: data from the ICONA Foundation Study



On Revision

Nicola Gianotti\*, Franco Maggiolo, Alessandro Cozzi-Lepri, Andrea Antinori, Silvia Nozza, Giuseppe Lapadula, Andrea De Luca, Cristina Mussini, Andrea Gori, Annalisa Saracino, Massimo Andreoni, Antonella d'Arminio Monforte on behalf of the ICONA Foundation Study Group.

## Study Population

- First cART > 01/01/2012
- 2NRTIs + RPV- or InSTI-
- HIV-RNA < 100,000 copies/mL.

## Primary endpoint:

Treatment Failure [TF]: Virological Failure (2 confirmed VL>50 copies/mL, > 6 months) or discontinuation of ≥1 drug in the regimen

## Secondary Endpoints:

- Discontinuation for any reason [TD]
- Discontinuation due to Toxicity [TDT]
- Virological Failure [VF]

## Stats

KM and Cox regression (time to outcomes)

## Results

- 1782 patients:
  - 914 RPV
  - 868 InSTI (38% EVG/c, 43% DTG, 19% RAL)
- On TDF/FTC:
  - 96% (RPV)
  - 71% (InSTI)
- As FDC:
  - 96% (RPV)
  - 53% (InSTI)
- Median FU
  - RPV 19 months (9-31)
  - InSTI 10 months (3-17)

Table 4. Factors associated with the risk of secondary endpoints from fitting a Cox regression model.

Outcome	Crude RH (95% CI)	p-value	Adjusted RH (95% CI)	p-value
<b><i>Discontinuation for any reason</i></b>				
RPV-based regimen	1.00		1.00	
INSTI-based regimen	4.24 (3.26, 5.51)	<0.001	2.72 (1.96, 3.77)	<b>&lt;0.001</b>
<b><i>Discontinuation due to toxicity</i></b>				
RPV-based regimen	1.00		1.00	
INSTI-based regimen	1.49 (0.79, 2.80)	0.217	1.73 (0.77, 3.89)	0.182
<b><i>Confirmed VL&gt;50 copies/mL</i></b>				
RPV-based regimen	1.00			
INSTI-based regimen	0.89 (0.41, 1.91)	0.766	0.68 (0.25, 1.86)	0.454

Table 4. Factors associated with the risk of secondary endpoints from fitting a Cox regression model.

Outcome	Crude RH (95% CI)	p-value	Adjusted RH (95% CI)	p-value
<b><i>Discontinuation for any reason</i></b>				
RPV-based regimen	1.00		1.00	
INSTI-based regimen	4.24 (3.26, 5.51)	<0.001	2.72 (1.96, 3.77)	<b>&lt;0.001</b>
<b><i>Discontinuation due to toxicity</i></b>				
RPV-based regimen	1.00		1.00	
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<b><i>Confirmed VL&gt;50 copies/mL</i></b>				
RPV-based regimen	1.00			
INSTI-based regimen	0.89 (0.41, 1.91)	0.766	0.68 (0.25, 1.86)	0.454

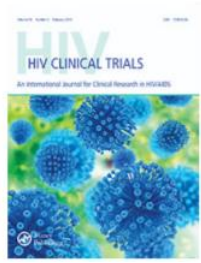
In patients starting ART with <100,000 HIV-RNA copies/mL, the risk of TF was lower in patients treated with a STR and in those with a RPV- rather than an INSTIs-based regimen:

STR → key factor for the durability of initial ART

The results of this study support maintaining the ranking of the STR of RPV/FTC/TAF (TDF) as “recommended” for starting ART in patients with <100,000 HIV-RNA copies/mL.

InSTI ERA





# Durability and tolerability of first-line regimens including two nucleoside reverse transcriptase inhibitors and raltegravir or ritonavir boosted-atazanavir or -darunavir: data from the ICONA Cohort

Antonella d'Arminio Monforte, Patrizia Lorenzini, Alessandro Cozzi-Lepri, Cristina Mussini, Antonella Castagna, Franco Baldelli, Massimo Puoti, Francesca Vichi, Adelaide Maddaloni, Sergio Lo Caputo, Nicola Gianotti, Andrea Antinori & on behalf of the Icona Foundation Study Group

## Mimic ACTG 5257 trial

### Study Population

RAL vs. DRV/r vs. ATV/r (+ TDF/FTC or ABC/3TC)  
from ART-naïve patients, after 01/01/2008

### Endpoints

1. Treatment failure [TF] = Virological Failure (2 consecutive VL>200 cps/mL, >6months) or discontinuation for any reason of the third drug.
2. Virological failure (50 copies/mL) [VF50]
3. Discontinuation of the 3<sup>rd</sup> drug due to intolerance/toxicity [TDT]

### Stats

KM and Cox regression (time to outcomes)

[HIV Clin Trials](#). 2018 Mar 1:1-9.

### Results

2249 patients were included:

- 985 (44%) ATV/r
- 1023 (45%) DRV/r
- 241 (11%) RAL

Median follow-up of 3.6 years (IQR: 2.3–5.2) (ATV/r: 4.3; DRV/r: 3.4; RAL: 2.3)



**Table 2 All causes of discontinuation and details of causes of discontinuation due to toxicity according to the regimen given**

	ATV/r	DRV/r	RAL	Total
All causes of discontinuation	N = 627	N = 605	N = 125	N = 1357
Simplification	184 (29.4%)	276 (45.6%)	59 (47.2%)	519 (38.2%)
Toxicity	209 (33.3%)	124 (20.5%)	10 (8.0%)	343 (25.3%)
Other	70 (11.2%)	72 (11.9%)	11 (8.8%)	153 (11.3%)
Missing	38 (6.1%)	39 (6.5%)	9 (7.2%)	86 (6.3%)
Failure	50 (8.0%)	26 (4.3%)	7 (5.6%)	83 (6.1%)
Patient's decision	39 (6.2%)	23 (3.8%)	11 (8.8%)	73 (5.4%)
Clinical trial	14 (2.2%)	26 (4.3%)	11 (8.8%)	51 (3.8%)
Structured treatment interruption	18 (2.9%)	13 (2.2%)	6 (4.8%)	37 (2.7%)
Pregnancy	4 (0.6%)	4 (0.7%)	1 (0.8%)	9 (0.7%)
Death	1 (0.2%)	2 (0.3%)	0 (0.0%)	3 (0.2%)
<b>Causes of discontinuation due to toxicity</b>	<b>ATV/r</b> N = 209	<b>DRV/r</b> N = 124	<b>RAL</b> N = 10	<b>Total</b> N = 343
Gastrointestinal toxicity	31 (14.8%)	35 (28.2%)	2 (20.0%)	68 (19.8%)
Hyperbilirubinemia	58 (27.8%)	0 (0.0%)	0 (0.0%)	58 (16.9%)
Allergic reactions/rash	26 (12.4%)	24 (19.3%)	2 (20.0%)	52 (15.2%)
Lipid metabolism toxicity	15 (7.2%)	35 (28.2%)	0 (0.0%)	50 (14.6%)
Others	20 (9.6%)	15 (12.1%)	3 (30.0%)	38 (11.1%)
Hepatotoxicity <sup>a</sup>	28 (13.4%)	6 (4.8%)	0 (0.0%)	34 (9.9%)
Nephrotoxicity	23 (11.0%)	6 (4.8%)	2 (20.0%)	31 (9.0%)
Osteopenia/osteoporosis	4 (1.9%)	3 (2.4%)	1 (10.0%)	8 (2.3%)
Toxicity not specified	4 (1.9%)	0 (0.0%)	0 (0.0%)	4 (1.2%)

<sup>a</sup>Hepatotoxicity other than hyperbilirubinemia.

**Discontinuation**

627 (63.6%) ATV/r  
605 (59.1%) DRV/r  
125 (51.9%) RAL

Discontinuation due to toxicity was the main cause of interruption in patients on ATV/r ( 33.3%)

Simplification was the main cause of discontinuation both for patients on DRV/r (45.6%), and RAL (47.2%)

**CD4 count response**

After adjustment for baseline characteristics:

ATV/r showed higher mean CD4 recovery at 2 years (+27.2) as compared to DRV/r;  
RAL also showed a higher mean CD4 recovery at 2 years compared to DRV/r, although marginally statistically different (+37.6)

**Table 3 Hazard ratio from fitting three separate Cox regression models**

	# Event	PYFU	Crude HR (95%CI)	p-Value	Adjusted <sup>a</sup> HR (95%CI)	p-Value
TF (HIV-RNA>200 copies/mL or discontinuation)						
DRV/r	623 (43 VF200, 580 D)	2504	1.00		1.00	
ATV/r	679 (65 VF200, 614 D)	2497	1.08 (0.96–1.22)	0.200	1.26 (1.11–1.43)	0.001
RAL	131 (3 VF200, 128 D)	430	1.17 (0.96–1.42)	0.129	1.02 (0.83–1.26)	0.833
VF50 (HIV-RNA>50 copies/mL)						
DRV/r	149	2325	1.00		1.00	
ATV/r	154	2426	0.85 (0.66–1.09)	0.212	0.88 (0.67–1.15)	0.345
RAL	11	440	0.38 (0.20–0.71)	0.003	0.46 (0.24–0.87)	0.018
Discontinuation due to toxicity						
DRV/r	124	2351	1.00		1.00	
ATV/r	209	2403	1.79 (1.42–2.27)	<0.001	2.09 (1.63–2.67)	<0.001
RAL	10	422	0.42 (0.22–0.81)	0.010	0.37 (0.19–0.72)	0.003

Notes: (TF = treatment failure, VF = virological failure, VF200 = HIV-RNA > 200 copies/mL, D = discontinuation, PYFU = person-years follow-up, HR = hazard ratio).

<sup>a</sup>Each model adjusted for age, gender, nation of birth, mode of HIV transmission, hepatitis co-infection status, AIDS diagnosis, nucleoside pair started, baseline CD4 count and viral load and year of starting cART.

- **TF**  
ATV/r higher risk of TF vs. DRV/r and vs. RAL
- **VF50**  
RAL lower risk of VF50 vs. DRV/r and vs. ATV/r
- **TDT**  
RAL lower risk of TDT vs. DRV/r and vs. ATV/r  
ATV/r higher risk of TDT vs. DRV/r and vs. RAL

**Confirmed higher risk of TF and lower tolerability of ATV/r-based regimens compared to DRV/r or RAL**

# Durability of first line regimens including integrase strand inhibitors (INSTI): data from a real-life setting

JAC

*Under Review*

Antonella D'ARMINIO MONFORTE<sup>1</sup>, Alessandro COZZI-LEPRI<sup>2</sup>, Antonio DI BIAGIO<sup>3</sup>, Giulia MARCHETTI<sup>1</sup>, Sergio LO CAPUTO<sup>4</sup>, Stefano RUSCONI<sup>5</sup>, Nicola GIANOTTI<sup>6</sup>, Valentina MAZZOTTA<sup>7</sup>, Giovanni MAZZARELLO<sup>3</sup>, Andrea COSTANTINI<sup>8</sup>, Antonella CASTAGNA<sup>6</sup>, Andrea ANTINORI<sup>7</sup> in behalf of the Icona Foundation Study Group

## Study population

Patients starting 2NRTIs+INSTI from ART naïve, after Jan 2011 (RAL, EVG/c, DTG)

## Primary end-point

Treatment failure (TF): Occurrence of virological failure (VF: first of two consecutive HIV-RNA plasma levels  $\geq 200$  copies/ml after 24 weeks) or INSTI discontinuation for any reasons.

## Secondary endpoints

- Pure VF (ITT analysis)
- INSTI discontinuation for toxicity/intolerance (TDT)
- CD4 count change after 6 and 12 months

## Stats

Survival analysis by KM and Cox regression  
ANCOVA regression model

## Results

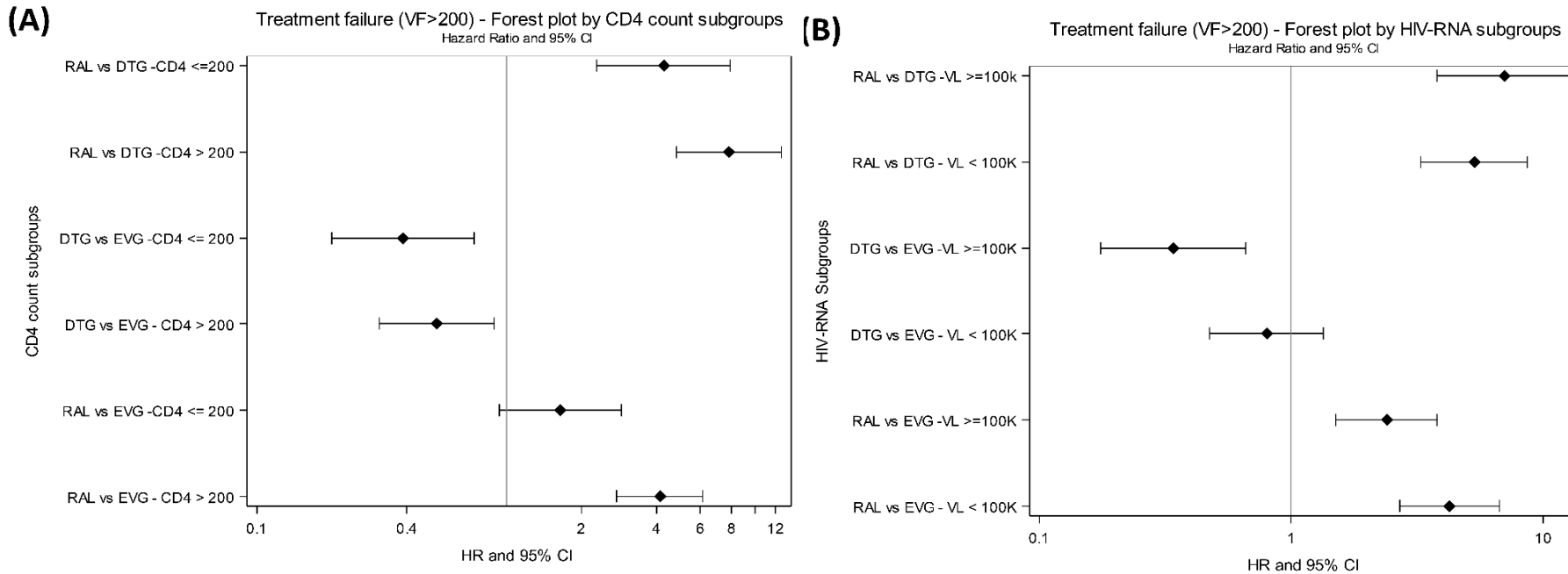
- 2,016 patients:
  - 310 (15.4%) RAL
  - 994 (49.3%) DTG
  - 712 (35.3%) EVG/c
- Median follow-up of 11 months (RAL 15, DTG 9, EVG/c 11 average months)

**Table 4. Relative hazards of reaching the end-points by univariate and multivariate Cox analyses**

Outcomes	Unadjusted and adjusted relative hazards			
	Unadjusted RH (95% CI)	p-value	Adjusted* RH (95% CI)	p-value
<b><i>Treatment failure</i></b>				
<i>Regimen</i>				
RAL-based	4.71 (3.43, 6.46)	<.001	5.74 (3.95, 8.34)	<.001
DTG-based	1.00		1.00	
EVG/c-based	1.53 (1.09, 2.16)	.015	1.79 (1.19, 2.68)	.005
<b><i>Confirmed VL&gt;200 copies/mL</i></b>				
<i>Regimen</i>				
RAL-based	4.55 (0.86, 24.04)	.074	6.32 (1.01, 39.55)	.049
DTG-based	1.00		1.00	
EVG/c-based	3.39 (0.68, 16.82)	.135	3.80 (0.61, 23.60)	.152
<b><i>Discontinuation for toxicity</i></b>				
<i>Regimen</i>				
RAL-based	1.33 (0.66, 2.68)	.419	1.55 (0.69, 3.50)	.286
DTG-based	1.00		1.00	
EVG/c-based	1.43 (0.87, 2.34)	.154	1.94 (1.00, 3.76)	.051

\*adjusted for age, gender, nation of birth, mode of HIV transmission, hepatitis co-infection status, AIDS diagnosis, baseline CD4 count and viral load and year of starting cART

**Figure 2. Subgroup analysis for CD4 count(A) and HIV-RNA(B)- forest plot for TF**



**Table 3. Mean CD4 counts/mmc according to the INSTI component**

	RAL-based	DTG-based	EVG-based	FDR* adjusted
Time point	Mean CD4 count* (95% CI)			p-value
<b>Month 6</b>	591.5 (565.2, 617.8)	632.7 (617.1, 648.4)	597.6 (580.3, 614.9)	<.001
<b>Month 12</b>	648.1 (615.6, 680.6)	682.6 (660.2, 705.0)	645.3 (621.6, 669.0)	<.001
<b>Month 24</b>	703.6 (665.0, 742.2)	722.4 (687.3, 757.5)	678.7 (646.8, 710.7)	<.001

\*adjusted for pre-ART CD4 count

**We demonstrated high potency and tolerability of all studied InSTI-based regimens. There was strong evidence for superiority of DTG vs. RAL for TF and VF and for TF only vs. EVG/c which needs to be confirmed in randomised comparisons.**

# Effectiveness of dolutegravir-based regimens as either first-line or switch antiretroviral therapy: data from the Icona cohort.



Annalisa Mondì<sup>1§</sup>, Alessandro Cozzi-Lepri<sup>2</sup>, Alessandro Tavelli<sup>3</sup>, Stefano Rusconi<sup>4</sup>, Francesca Vichi<sup>5</sup>, Francesca Ceccherini-Silberstein<sup>6</sup>, Andrea Calcagno<sup>7</sup>, Andrea De Luca<sup>8</sup>, Franco Maggiolo<sup>9</sup>, Giulia Marchetti<sup>10</sup>, Andrea Antinori<sup>1</sup>, Antonella d'Arminio Monforte<sup>10</sup> on behalf of Icona Foundation Study Group. |

JIAS in press

## Study Population

- ART-naïve and virologically-suppressed treatment-experienced (TE) patients
- Starting - for the first time- a DTG-based regimen
- From Jan 2015 to Dec2017 were included.

## Endpoints:

1. DTG discontinuation for any reason [DTG-TD]
2. DTG discontinuation due to toxicity/tolerability [DTG-TDT]
3. Virological failure [VF]: 2 consecutive VL>50 cps/mL (> 6 months after DTG-start for naïve).

## Stats

KM and Cox regression (time to outcomes)

## Results

1679 patients included:

- 932 ART-naïve(55%)
- 747 TE (45%)

- ART-naïve patients:
  - 95% started a standard triple therapy (52% ABC-based)
- TE group:
  - 70% of patients started a standard triple ART, mainly (81%ABC-based) a
  - 27% started DTG as part of a dual therapy

Table 2: Reasons for DTG discontinuation regardless of the reason and due to toxicity according to treatment group

REASONS FOR DTG DISCONTINUATION [n (% population)]	ART-NAIVE	TE
TOXICITY	39 (4.2%)	27 (3.6%)
LACK OF EFFICACY	8 (0.9%)	3 (0.4%)
SIMPLIFICATION	6 (0.6%)	5 (0.6%)
ADHERENCE ISSUES	3 (0.3%)	3 (0.4%)
OTHER/UNKNOWN	15 (1.6%)	12 (1.6%)
AEs LEADING TO DTG DISCONTINUATION [n (% population)]		
NEUROPSYCHIATRIC	20 (2.1%)	13 (1.7%)
GASTROINTESTINAL	3 (0.3%)	6 (0.8%)
ALLERGIC REACTIONS	9 (1.0%)	-
HEPATIC	3 (0.3%)	1 (0.1%)
OSTEOARTICULAR	-	3 (0.4%)
RENAL	1 (0.1%)	2 (0.3%)
OTHER/UNKNOWN	3 (0.3%)	2 (0.3%)
NEUROPSCHYTIC AEs LEADING TO DTG DISCONTINUATION [n] †		
Insomnia	7	4
Depression	4	1
Anxiety and mood disorders	4	1
Paraesthesia	2	1
Dizziness	1	2
Headache	2	3
Suicidal ideation	2	0
Other neurological AEs‡	5	1
Other psychiatric AEs§	2	0
Not specified	1	0

† more than one symptoms for each patient is possible.

‡ ART-naïve: anosmia, photophobia, visual disturbances, cognitive-motor slowing; TE:

§ ART naïve patients: paranoid behavior, hallucinations

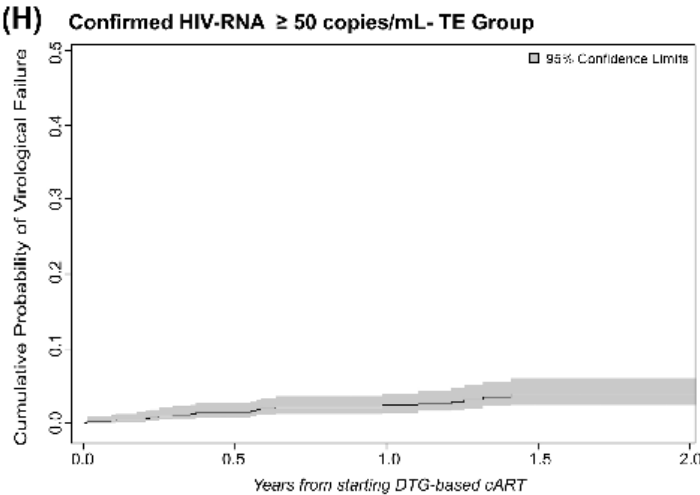
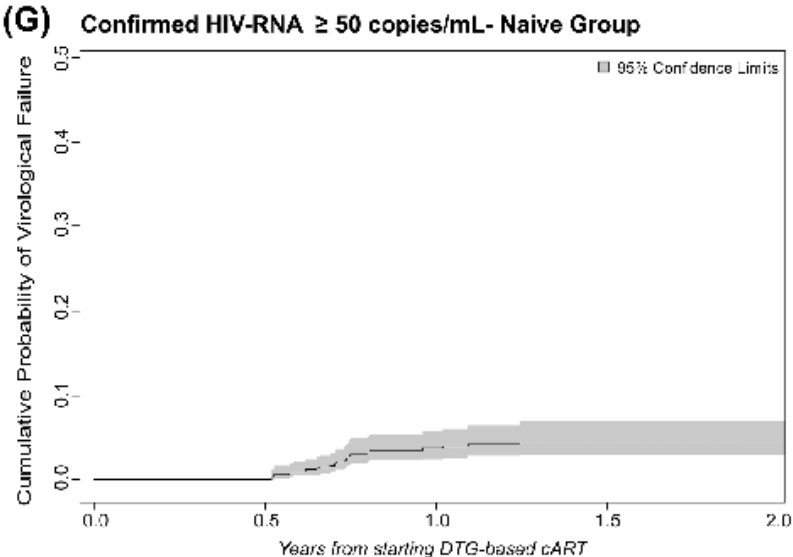
Cause of Discontinuation

In both ART-naïve and treatment-experienced, discontinuations of DTG were mainly driven by toxicity with an estimated risk of 4.0% and 2.5% by one year and 5.6% and 4.0% by two years, respectively.

Neuropsychiatric events were the main reason for stopping DTG in both ART-naïve (2.1%) and treatment-experienced (1.7%) patients.

Virological Failure

1-year probability of VF was 1.2% for Naïve Group and 2.2% for TE Group



**Table 3: Predictors of DTG discontinuation for any reason and for toxicity by multivariable Cox regression models according to treatment group (3A, ART-naïve group and 3B, TE group)**

(A) ART-NAÏVE GROUP					(B) TE GROUP				
VARIABLES	DTG DISCONTINUATION FOR ANY REASON		DTG DISCONTINUATION FOR TOXICITY		VARIABLES	DTG DISCONTINUATION FOR ANY REASON		DTG DISCONTINUATION FOR TOXICITY	
	ADJUSTED* RH (95% CI)	P-VALUE	ADJUSTED* RH (95% CI)	P-VALUE		ADJUSTED** RH (95% CI)	P-VALUE	ADJUSTED** RH (95% CI)	P-VALUE
<b>Gender</b>					<b>Gender</b>				
Female	1.46 (0.67-3.19)	0.340	1.48 (0.45-4.84)	0.515	Female	1.11 (0.52-2.33)	0.799	1.78 (0.66-4.78)	0.255
<b>Age, years</b>					<b>Age, years</b>				
per 10 older	1.15 (0.94-1.40)	0.181	1.26 (0.88-1.79)	0.208	per 10 older	1.07 (0.81-1.41)	0.639	0.97 (0.66-1.42)	0.869
<b>AIDS diagnosis</b>					<b>AIDS diagnosis</b>				
Yes vs. No	3.38 (1.62-7.05)	<b>0.001</b>	2.82 (0.96-8.28)	0.060	Yes vs. No	1.32 (0.64-2.72)	0.450	1.35 (0.50-3.68)	0.552
<b>Calendar year of baseline</b>					<b>Calendar year of baseline</b>				
per more recent year	1.26 (0.81-1.95)	0.313	1.37 (0.74-2.52)	0.318	per more recent year	1.06 (0.60-1.88)	0.839	0.89 (0.43-1.87)	0.767
<b>Baseline CD4 count, cells/mm3</b>					<b>DTG-regimen#</b>				
per 100 higher	0.98 (0.86-1.11)	0.730	0.96 (0.81-1.13)	0.601	- Dual	1.00		1.00	
<b>Viral load, log10 copies/mL</b>					- Triple with ABC	2.50 (1.06-5.93)	<b>0.037</b>	5.26 (1.17- 23.56)	<b>0.030</b>
per log higher	1.27 (0.87-1.84)	0.216	1.13 (0.69-1.87)	0.623	- Triple with tenofovir	3.56 (1.33-9.53)	<b>0.012</b>	6.60 (1.29- 33.85)	<b>0.024</b>
<b>NRTI backbone</b>					<b>Duration of virological suppression</b>				
- Tenofovir/FTC	1.00		1.00		per 6 months longer	0.94 (0.88-0.99)	<b>0.028</b>	0.94 (0.83- 1.07)	0.352
- 3TC/ABC	1.39 (0.79-2.46)	0.253	3.30 (1.34-8.11)	<b>0.009</b>					

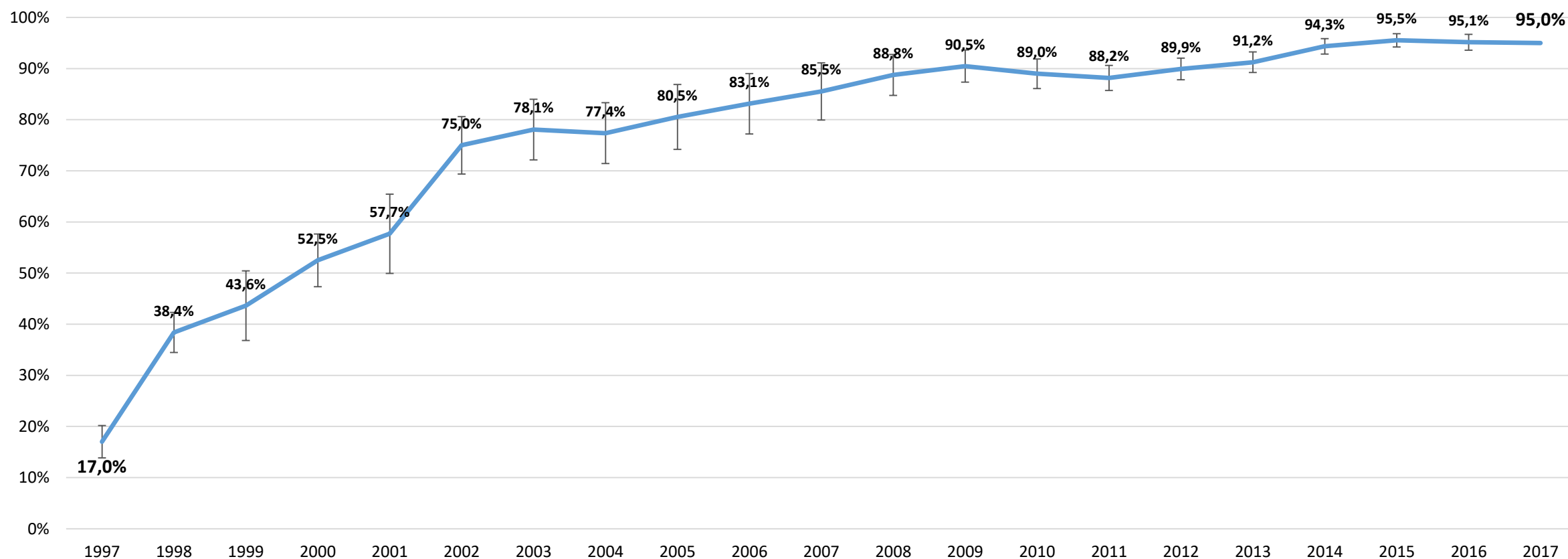
Having started DTG in combination with ABC compared to TDF or TAF was associated to a significantly higher risk of interrupting DTG for adverse events in previously untreated patients by multivariable analysis

TE patients starting DTG as part of a dual regimen compared to triple therapy, regardless of the backbone, had a lower risk of discontinuation for any cause and for toxicity

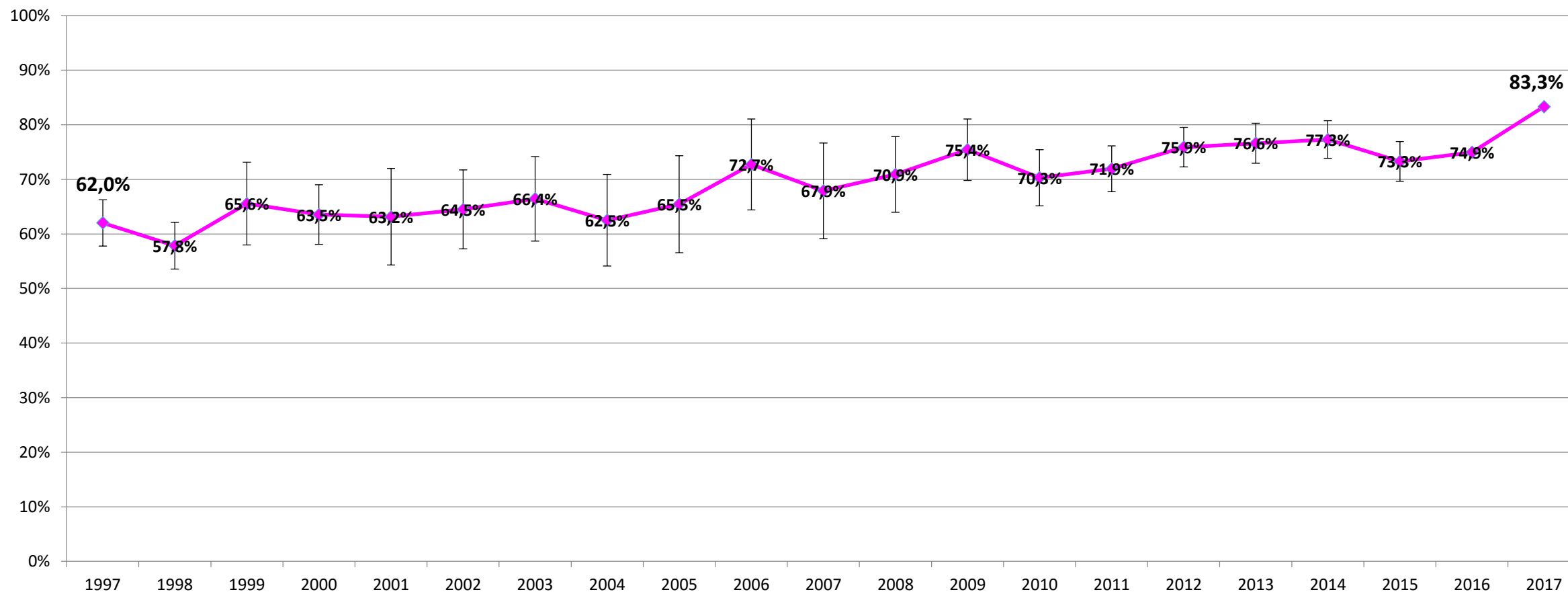
**DTG showed an optimal efficacy and tolerability, with a low rate of discontinuations, both in ART-naïve and ART-experienced.**  
**Although adverse events, especially neuropsychiatric symptoms, represented the main reason to stop DTG, their frequency was relatively low.**



## Proportion of patients with a VL≤80 copies/mL at 12 months from starting their first ART regimen by calendar year of initiation



## Proportion of patients with an increase of CD4 cells count $\geq 120$ cells/cmm at 12 months from starting their first ART regimen by calendar year of initiation



90%?

Diagnosed?

90%?

On treatment?

90%?

Virally suppressed?

90%?

Good health-  
related quality  
of life?