Ospedale San Paolo
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Sistema Socio Sanitario
Regione Lombardia
ASST Santi Paolo e Carlo

UNIVERSITÀ DEGLI STUDI DI MILANO

Terapia antiretrovirale triplice

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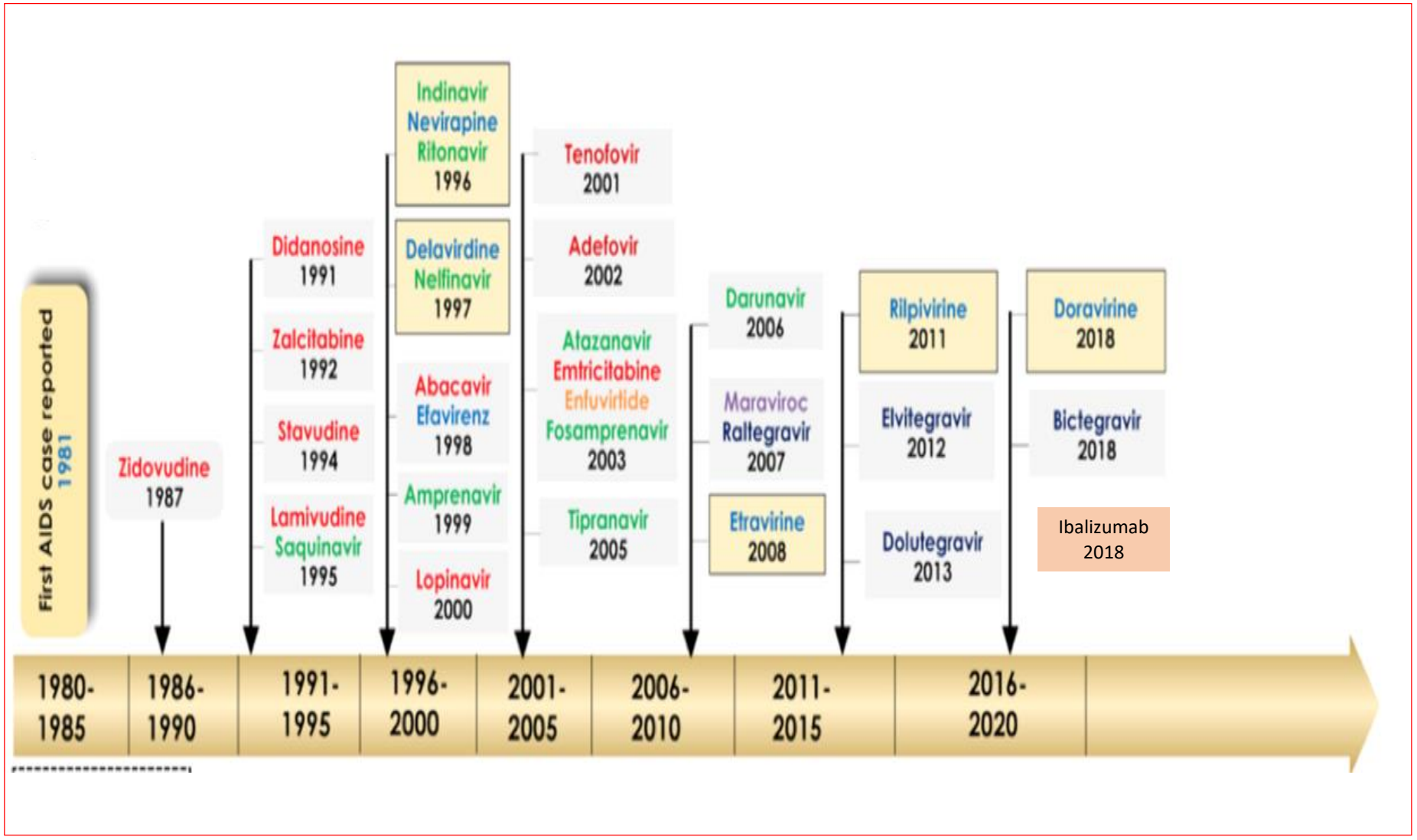
Disclosure of potential conflicts of interest, last 3years

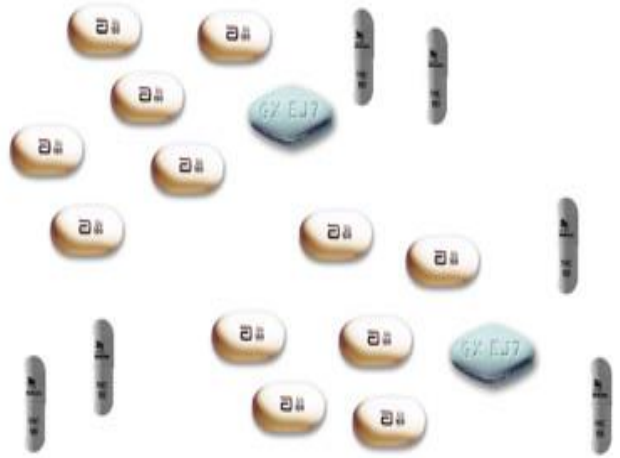
- Advisor for Gilead, Janssen-Cilag, MSD and ViiV
- Speakers' honoraria from Gilead, Janssen-Cilag, MSD and ViiV
- Support for travel meetings from Gilead, and ViiV
- Grant for research from Gilead, Janssen-Cilag, MSD and ViiV

HIV infection : the Journey of antiretroviral Drugs



Antiretroviral therapy for HIV infection

In the 1990s



Up to 20 pills daily, taken at different intervals throughout the day

Today

As little as 1 pill delivering 2 drugs

#35YearsOfAIDS

Initial ART regimens

EACS Guidelines, 2021

Regimen	Main requirements	Additional guidance (see footnotes)
Recommended regimens		
2 NRTIs + INSTI		
ABC/3TC + DTG ABC/3TC/DTG	HLA-B*57:01 negative HBsAg negative	I (ABC: HLA-B*57:01, cardiovascular risk) II (Weight increase (DTG))
TAF/FTC/BIC		II (Weight increase (BIC, TAF))
TAF/FTC or TDF/XTC + DTG		II (Weight increase (DTG, TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing)
TAF/FTC or TDF/XTC + RAL qd or bid		II (Weight increase (RAL, TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) IV (RAL: dosing)
1 NRTI + INSTI		
XTC + DTG or 3TC/DTG	HBsAg negative HIV-VL < 500,000 copies/mL Not recommended after PrEP failure	II (Weight increase (DTG)) V (3TC/DTG not after PrEP failure)
2 NRTIs + NNRTI		
TAF/FTC or TDF/XTC + DOR or TDF/3TC/DOR		II (Weight increase (TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VI (DOR: caveats, HIV-2)
Alternative regimens		
2 NRTIs + NNRTI		
TAF/FTC or TDF/XTC + EFV or TDF/FTC/EFV	At bedtime or 2 hours before dinner	II (Weight increase (TAF) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VII (EFV: neuro-psychiatric adverse events. HIV-2 or HIV-1 group 0)
TAF/FTC or TDF/XTC + RPV or TAF/FTC/RPV or TDF/FTC/RPV	CD4 count > 200 cells/μL HIV-VL < 100,000 copies/mL Not on gastric pH increasing agents With food	II (Weight increase (TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VIII (RPV: HIV-2)
2 NRTIs + PI/r or PI/c		
TAF/FTC or TDF/XTC + DRV/c or DRV/r or TAF/FTC/DRV/c	With food	II (Weight increase (TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) IX (DRV/r: cardiovascular risk) X (Boosted regimens and drug-drug interactions)

Initial ART regimens

DHHS Guidelines, 2022

For people who do not have a history of CAB-LA use as PrEP, the following regimens are recommended:

INSTI plus Two NRTIs

- BIC/TAF/FTC **(AI)**[a]
- DTG/ABC/3TC **(AI)—if HLA-B*5701 negative**
- DTG plus (TAF or TDF)[c] plus (FTC or 3TC) **(AI)**

INSTI plus One NRTI

- DTG/3TC **(AI),** except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available

For people with HIV and a history of CAB-LA use as PrEP, INSTI genotypic resistance testing should be performed before the start of ART. If treatment is begun prior to results of genotypic testing, the following regimen is recommended:

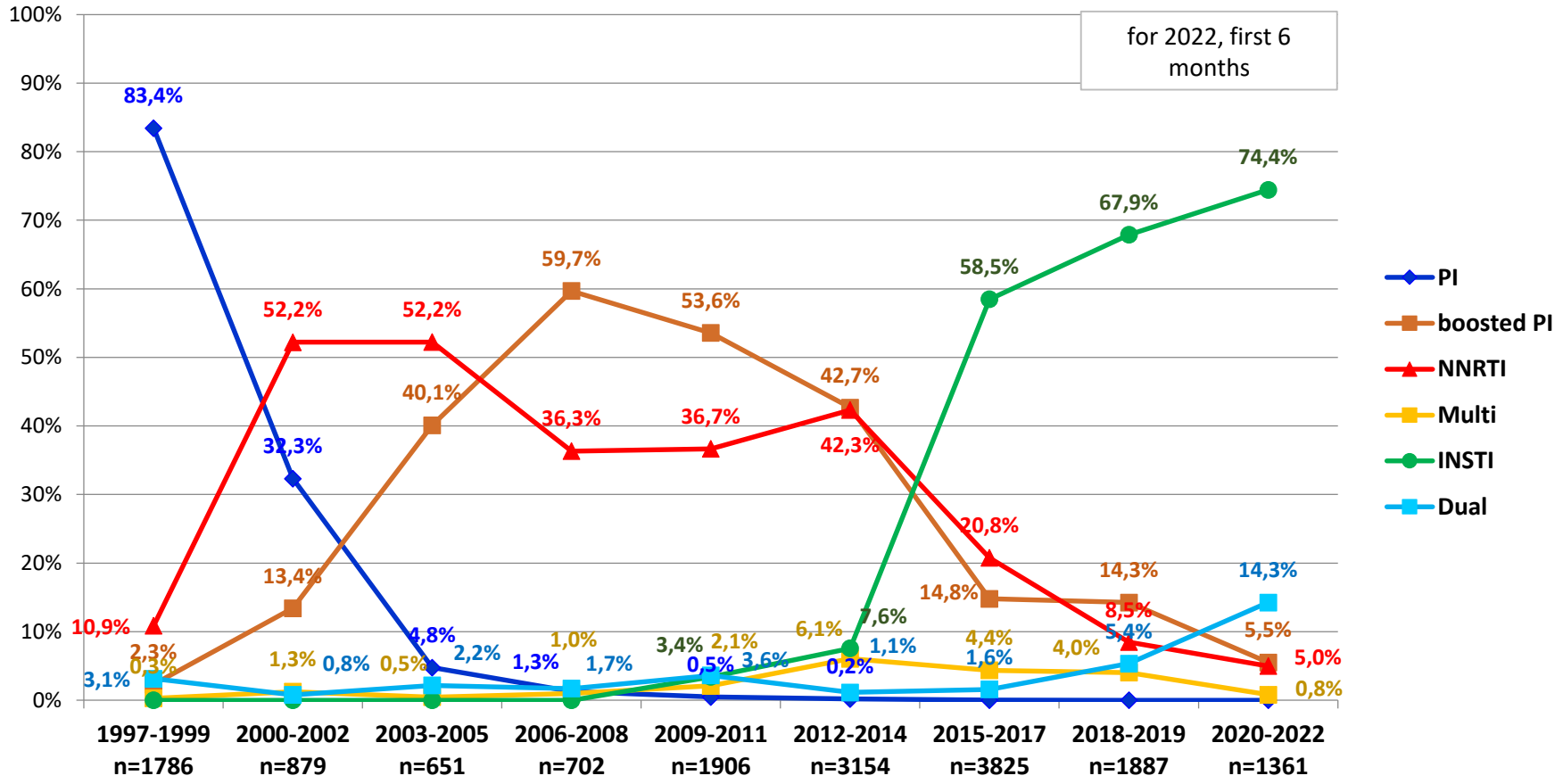
- DRV/c[b] or DRV/r with (TAF or TDF)[c] plus (FTC or 3TC)—pending the results of the genotype test **(AIII)**

Initial ART regimens among the Italian ID centers

Data from the ICONA Foundation cohort

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

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



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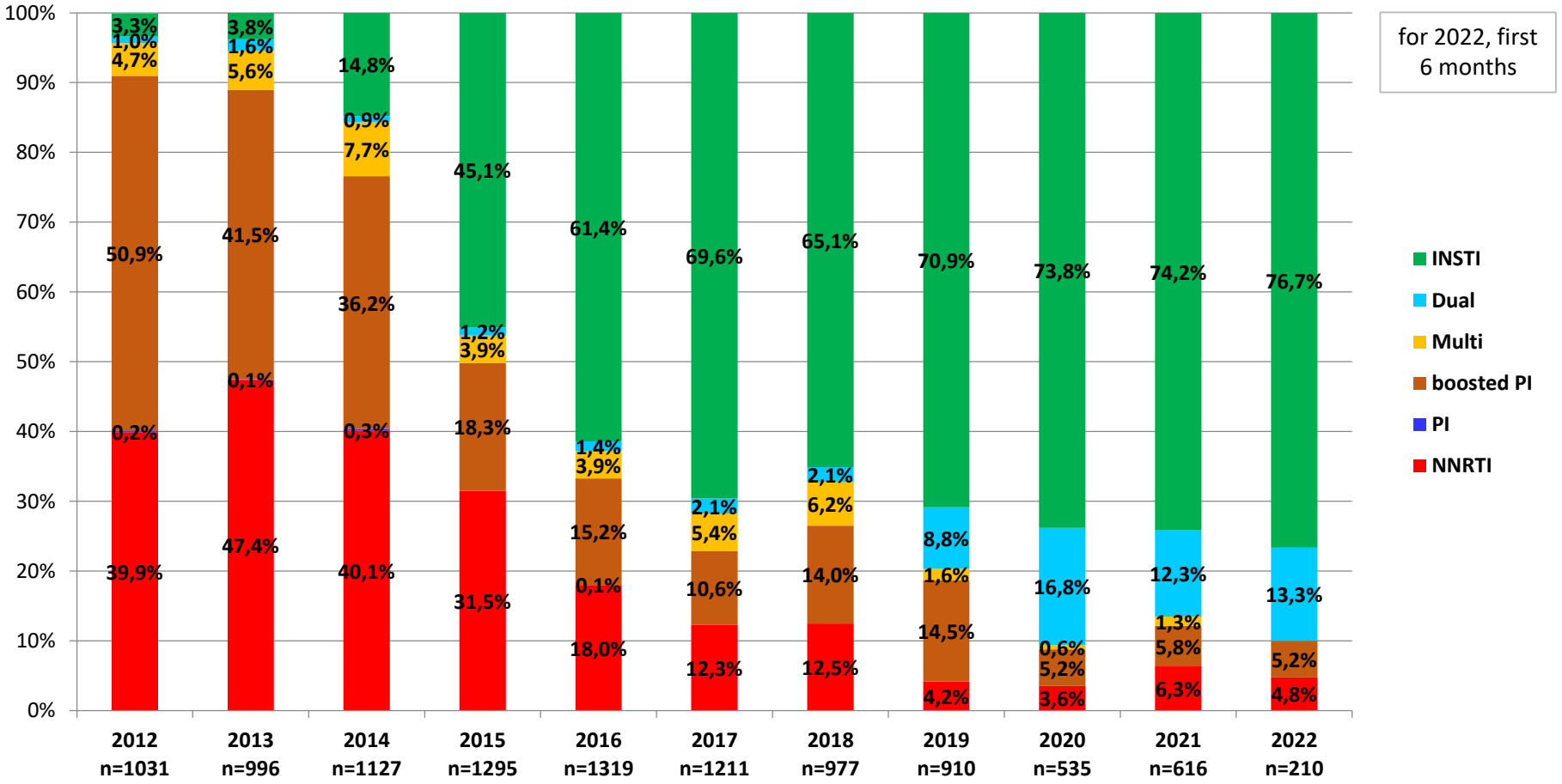
Proportion of usage of different ART classes as third drug in first line regimen according to calendar year of starting



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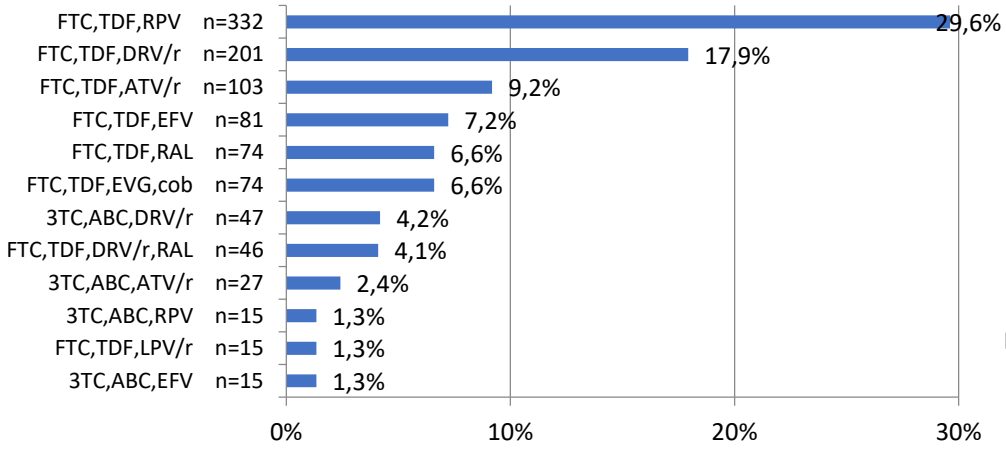
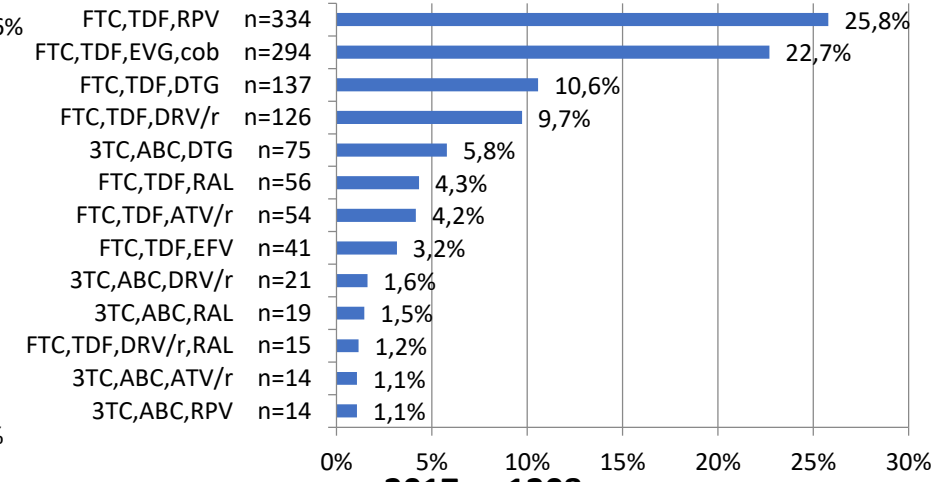
Distribution of most frequent first line regimens in patients starting ART from 2014 to 2017

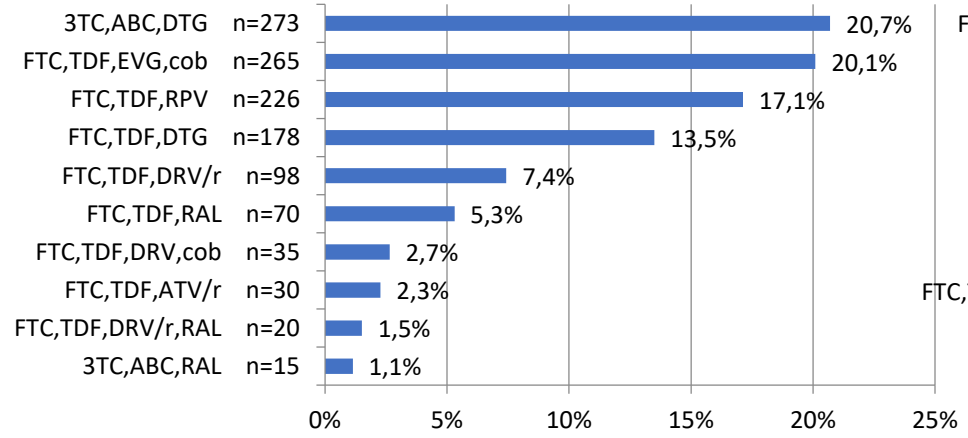
2014, n=1121



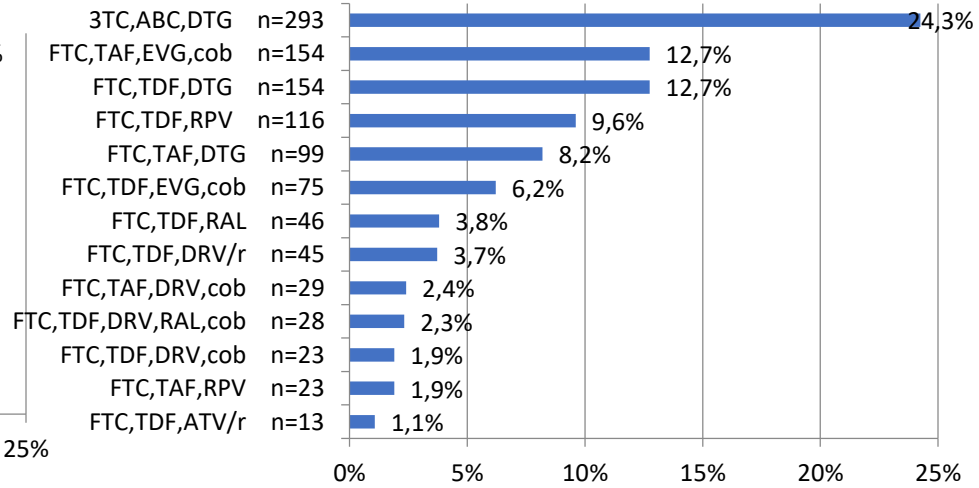
2015, n=1296



2016, n=1319



2017 n=1208



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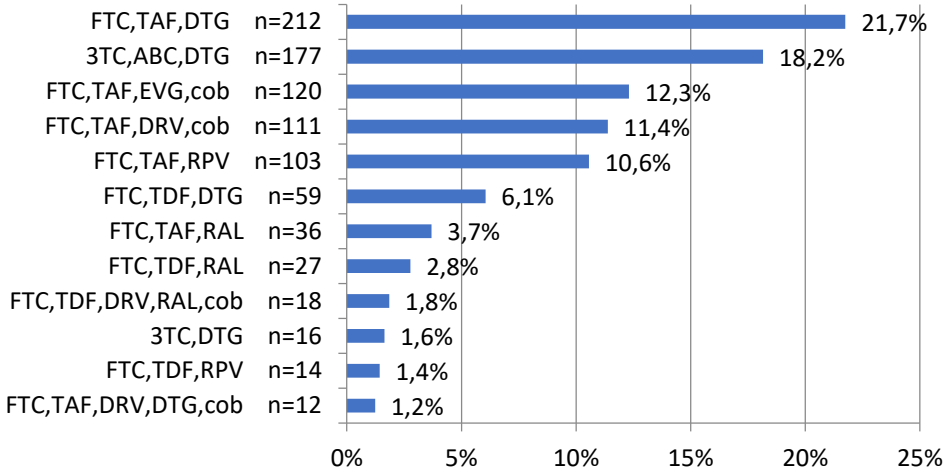
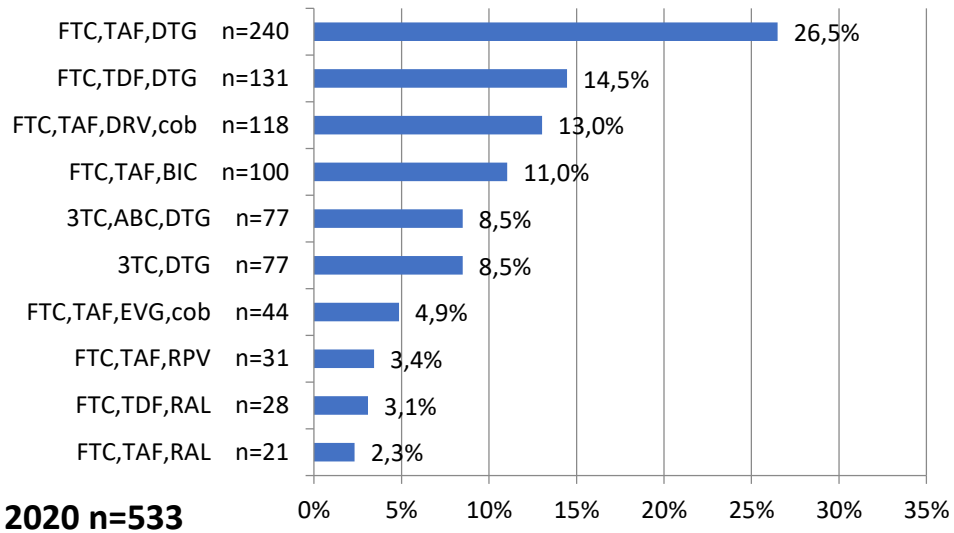
Distribution of most frequent first line regimens in patients starting ART from 2018 to 2020

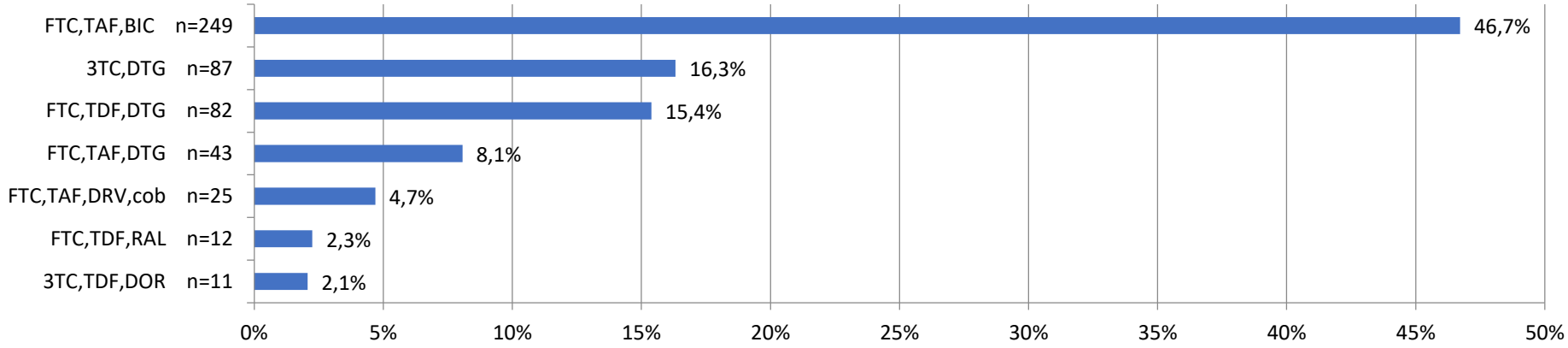
2018 n=975



2019 n=906



2020 n=533



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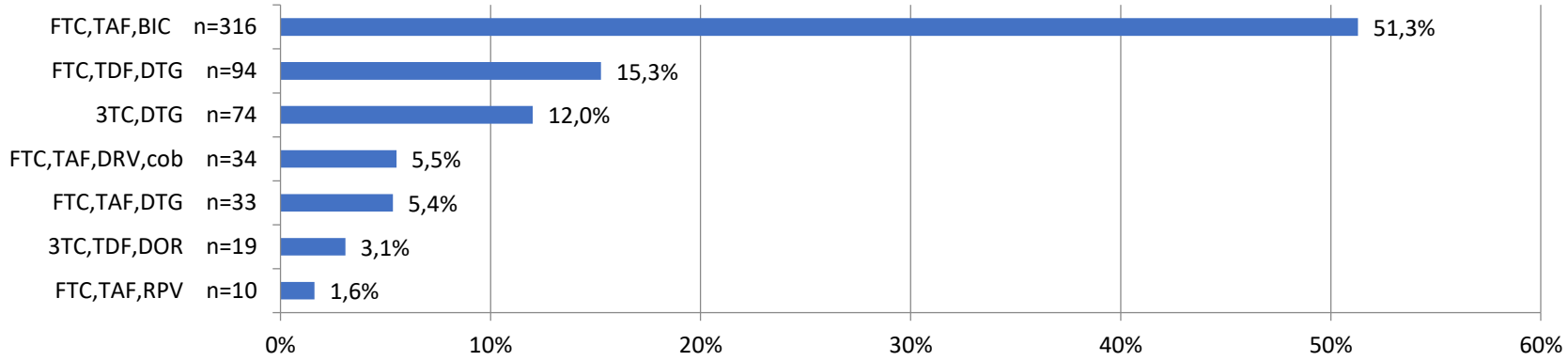
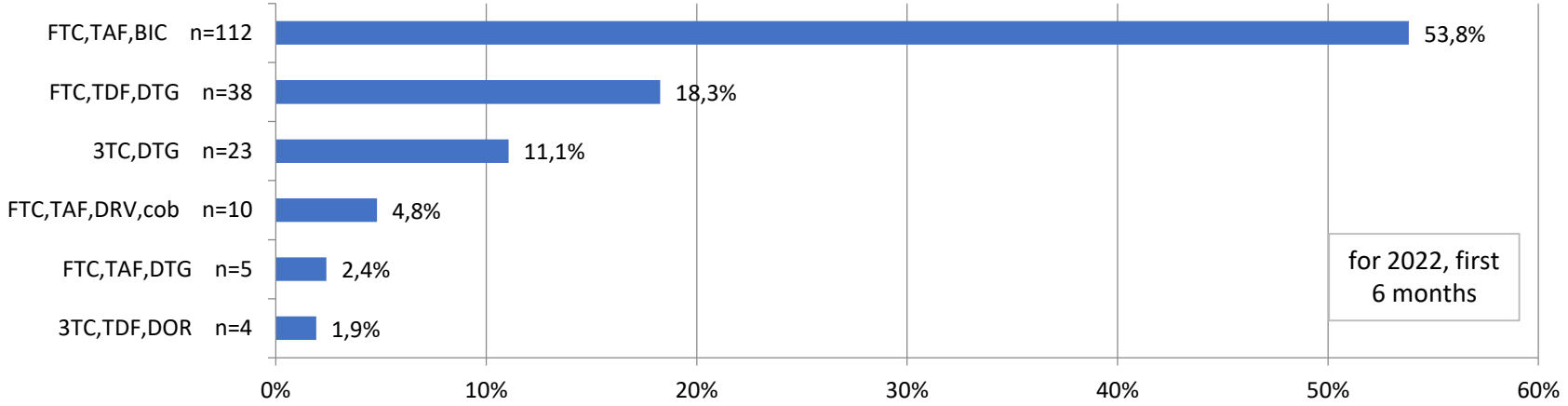
Distribution of most frequent first line regimens in patients starting ART from 2021 to 2022

2021 n=616



2022 n=208



Distribution of first line regimens in patients starting ART according to CD4 count in 2020-2022

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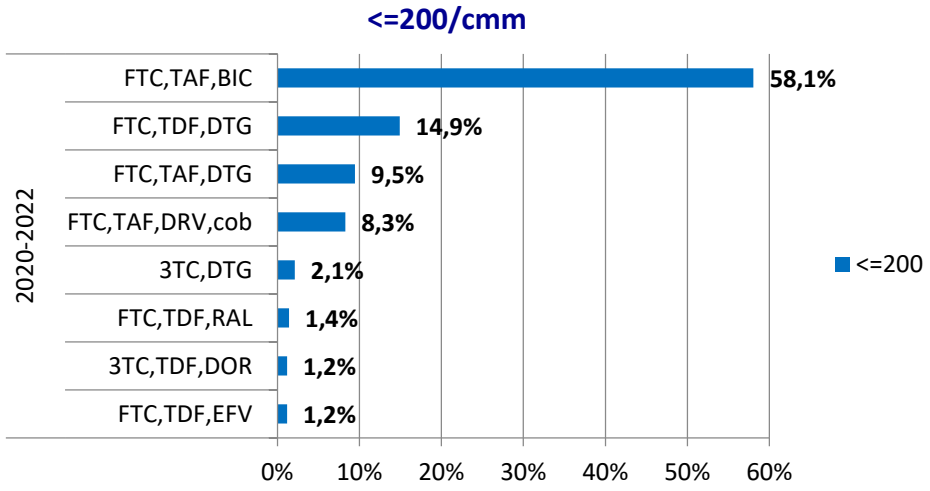
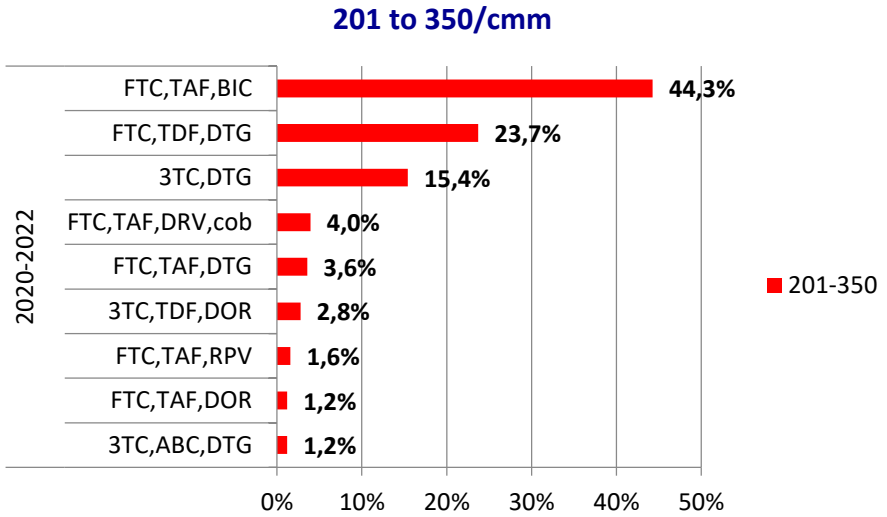
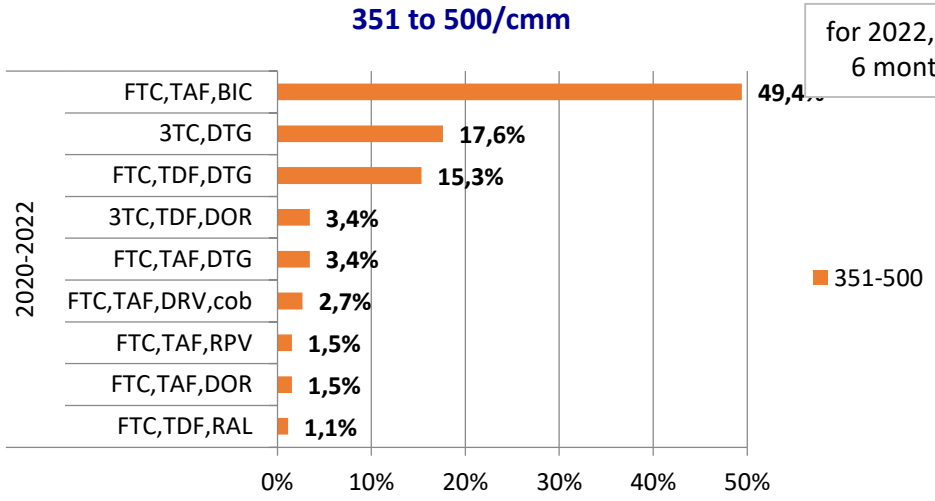
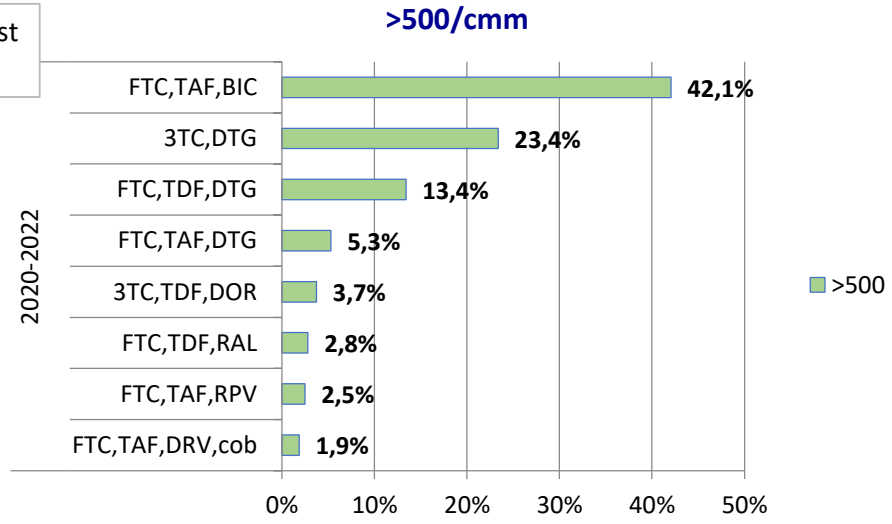






for 2022, first 6 months



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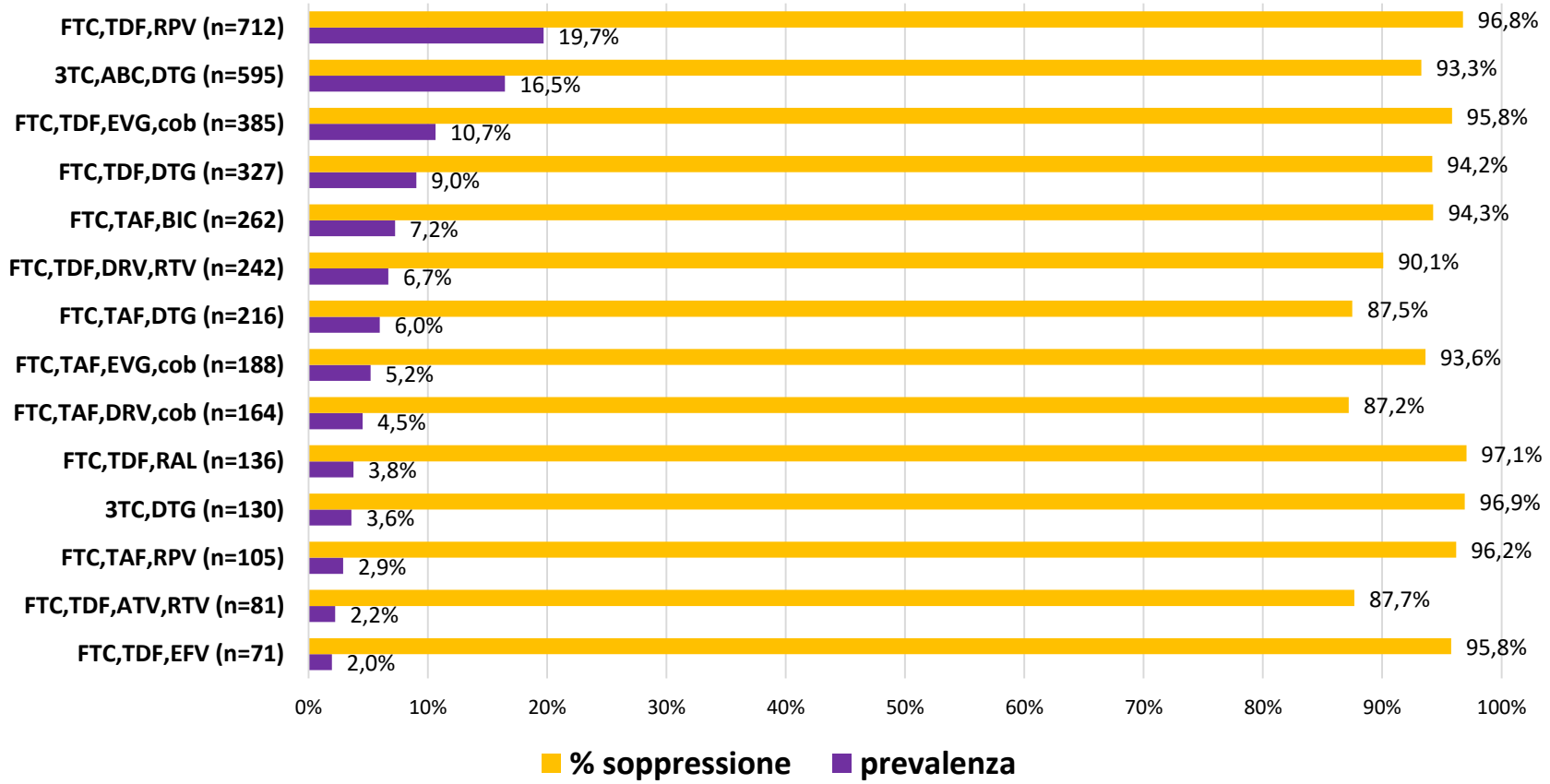
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Prevalence of VL suppressed patients starting a first line regimen from 2014 within 1 year of follow-up (n=3614, therapy prevalence >1%)



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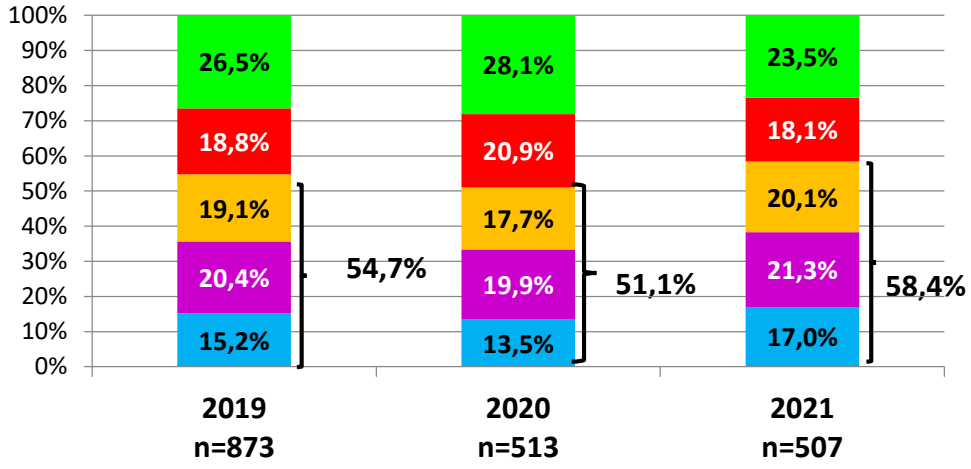
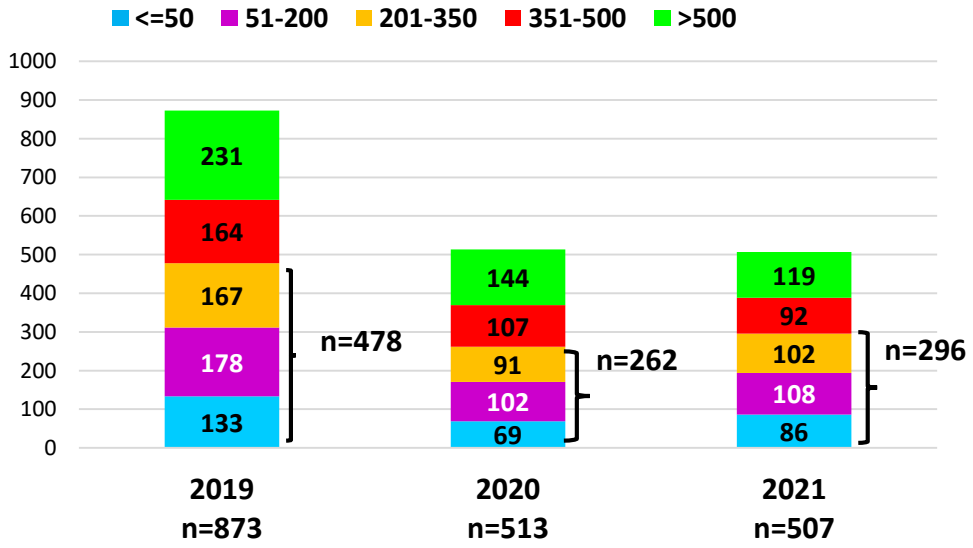
CD4 cells/mmc count strata according to calendar year of enrolment from 2019 to 2021





ISS-COA data 2019-2020

	2020	2019
Totale diagnosi	1.303	2.473
Genere		
Maschi	1.041	1.971
Femmine	262	502
Classe d'età		
< 25	99	177
25-39	542	1044
40-49	321	602
50-59	246	466
60 +	95	184
Area geografica		
Nord	552	1234
Centro	419	598
Sud e Isole	332	641
CD4		
< 350 o AIDS alla diagnosi[c]	*738	1348
≥ 350 alla diagnosi	485	951

*56,6% 54,5%

Dec 2021 Report

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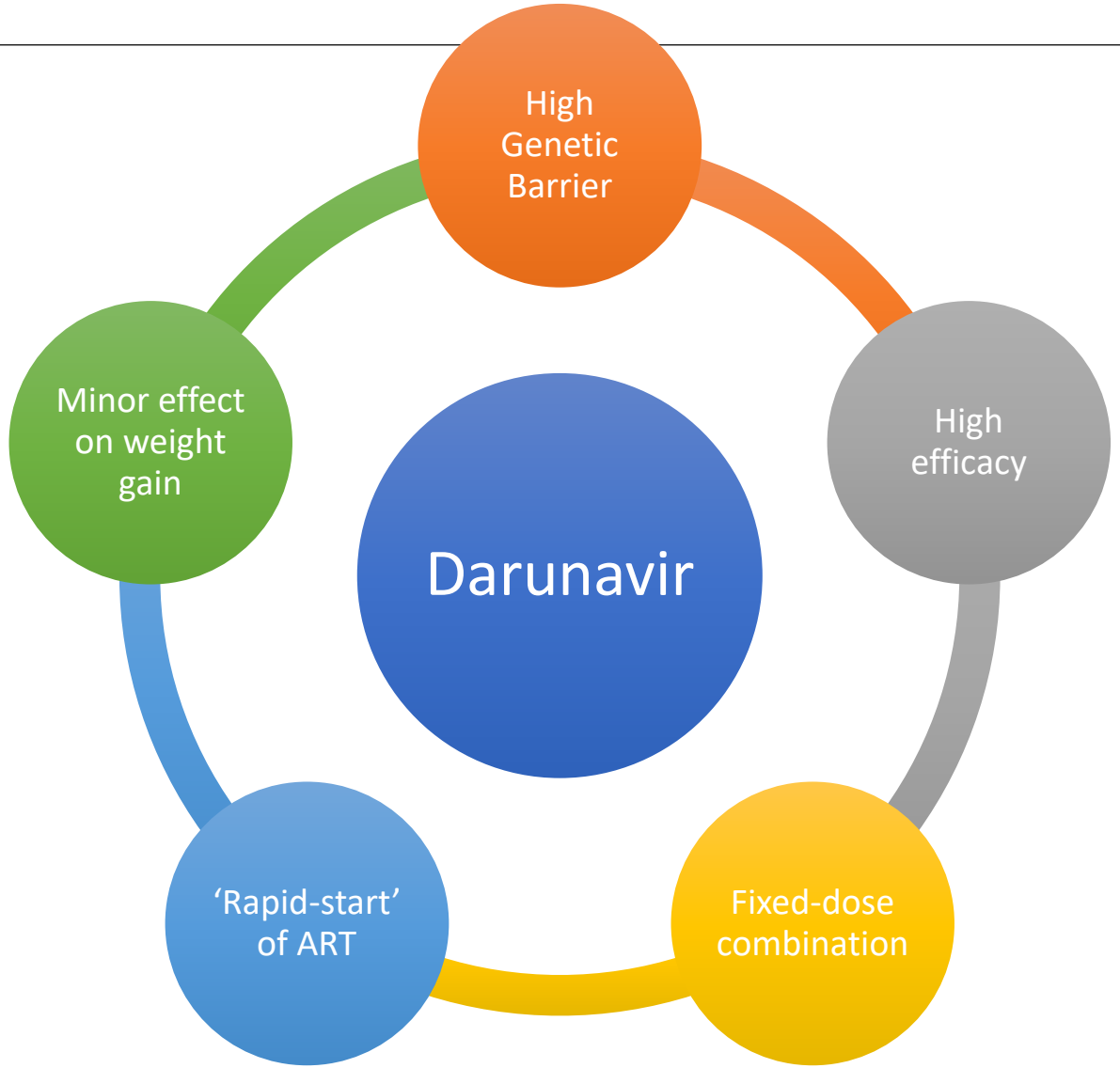
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Italian Cohort I. C. O. N. A. Naive Antiretrovirals

ICONA data

DRV/c, BICTEGRAVIR and DOLUTEGRAVIR

Background

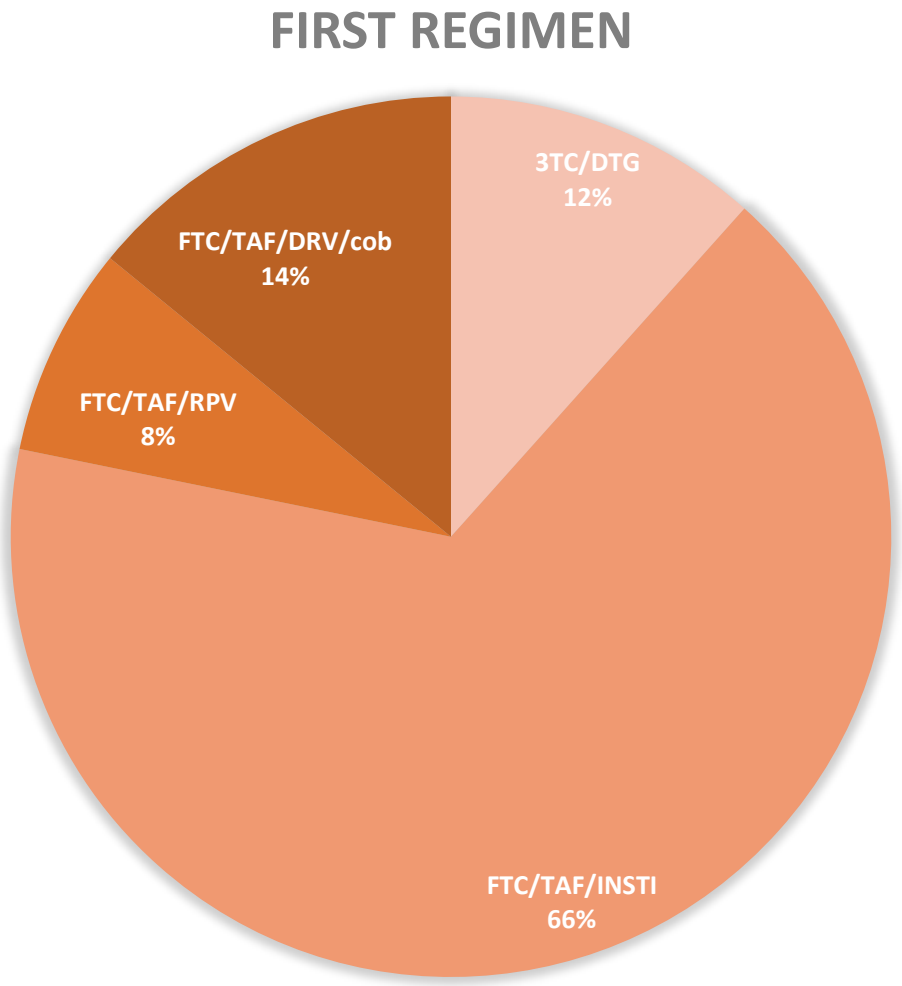


Provide insight into size & clinical characteristics of PLWH starting DRV/cob/TAF/FTC

Aims

Identify predictors of starting/ switching to DRV/cob/TAF/FTC

Results: ART-naive



Patients ' characteristics according to first ART regimen

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ITALIAN COHORT NAIVE ANTIRETROVIRALS

	2DR-INSTI		FTC/TAF-INSTI		FTC/TAF-NNRTI		FTC/TAF/DRV/COB		p-value	Total
	N=238	11.6%	N=1365	66.6%	N=158	7.7%	N=289	14.1%		N=2050
talian, n(%)	169	71.01%	1,009	73.92%	116	73.42%	209	72.32%	0.789	1,503
ender, Male, n(%)	210	88.24%	1,146	83.93%	116	73.42%	243	84.08%	0.001	1,715
ge, median (IQR)	38	29-48	41	32-51	37	30-47	41	33-48	0.002	40
IDS, Yes, n(%)	2	0.84%	163	11.9%	0	0.0%	58	20.1%	<0.001	223
D4, cells/mmc, median (IQR)	483	344-702	302	99-504	546	438-697	200	74-387	<0.001	337
200 cells/mmc, n(%)	11	4.62%	513	37.58%	1	0.63%	144	49.83%	<0.001	669
IV-RNA, log10 copie/mLn median (IQR)	4.46	3.80-4.91	5.04	4.41-5.62	4.13	3.62-4.56	5.19	4.63-5.64	<0.001	4.89
IV-RNA > 5 log copies/mL, n(%)	47	19.57%	675	49.45%	4	2.53%	160	55.36%	<0.001	866
ays from HIV diagnosis to ART start, edian(IQR)	30	18-74	21	11-44	52	28-223	22	12-50	<0.001	24
<=14 days from diagnosis (Rapid start), n(%)	34	14.29%	490	35.90%	15	9.49%	101	34.95%	<0.001	640

Dec 2021 Report

Methods: ICONA-BIC Study

Aim

- to evaluate effectiveness and tolerability of a triple regimen containing BIC/FTC/TAF in ART-naïve HIV positive adults who initiated BIC/FTC/TAF in a real-life setting, focusing on the subgroups of females, late-presenters, PLWH with advance disease and subjects >50 years old.

Study Design

- Observational cohort study, enrolling subjects from the Icona Cohort who started BIC/FTC/TAF from ART-Naïve from June 2016 to December 2021, with no limitations in CD4 and HIV RNA at start and with at least 1 follow-up visit.

Real-word Effectiveness of BIC/FTC/TAF in naive PLWH

Observational study on ART-naïve PLWH who started BIC/FTC/TAF from Apr 2018 to Dec 2021. Primary endpoint: time to treatment failure (TF) defined as VF (2 HIV-RNA > 200 copies/ml or 1 HIV-RNA>1000 copies/ml) or discontinuation of BIC/FTC/TAF for any reason (TD).

- 416 patients started BIC/FTC/TAF from ART-naïve: 124 patients ≥50 years (29.8%), 73 female (17.5%), 241 late presenters (58%) and 165 with advanced HIV disease (40%).

	ART-naive (N=416)	
Italian, n(%)	239	70.43
Ethnicity, Caucasian, n(%)	329	79.1
Gender, Female, n(%)	73	17.5
Year HIV diagnosis, median (IQR)	2020	2019-2020
Year cART start, median (IQR)	2020	2020-2021
Age, years, median (IQR)	42	32-52
>50 years, n(%)	124	29.81
Mode of HIV Transmission, n(%)		
Heterosexual	172	41.35
IVDU	19	4.57
MSM	188	45.19
Other/Unknown	37	8.89
HCVAb positive status, n(%)	20	4.81
HBsAg positive status, n(%)	11	2.64
Smoker,Yes, n(%)	143	34.38
AIDS, n(%)	59	14.18
CD4, cells/mmc, median (IQR)	280	87-495
CD4<200 cells/mmc, n(%)	165	39.66
CD4<350 cells/mmc, n(%)	241	57.9
HIV-RNA, log10 copies/mL, median (IQR)	5.02	4.39-5.60
5 log10 copies/mL, median (IQR)	211	50.72
eGFR, CKD-EPI formula, ml/min/1.73m2, median (IQR)	106.4	92.2-117.5
BMI, Kg/m2, median (IQR)	23	20.6-24.7

Exposure of interest

Age<50 years	292 (70.2%)
Age>=50 years	124 (29.8%)
Female	73 (17.5%)
Male	343 (82.4%)
Late presenters (<350 CD4 or AIDS)	241 (57.9%)
Non late presenters	174 (41.8%)
Advance disease (<200CD4 or AIDS)	165 (39.7%)
Non advance disease	247 (59.4%)

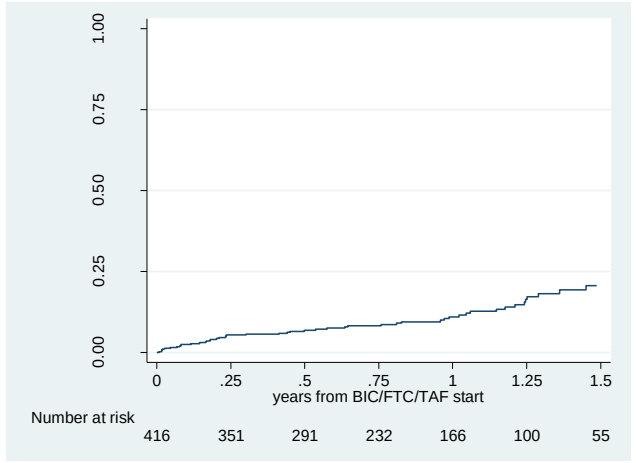
Tavelli A, et al. ICAR 2022 OP15

Real-word Effectiveness of BIC/FTC/TAF in naive PLWH

- **Treatment failure** [defined as treatment discontinuation (TD) for any reason or VF (2 consecutive HIV-RNA >200 copies/mL or 1 HIV-RNA >1000 copies/mL after 6 months from ART-initiation)].
  - Median FU: 0.89 years (IQR 0.44-1.24)
  - 51 TF (12.2%) → 7 VF + 44 TD

1-yr cumulative probability of TF by KM: 11.0% (95%CI: 7.9-15.1)

Kaplan-Meier curves for TF

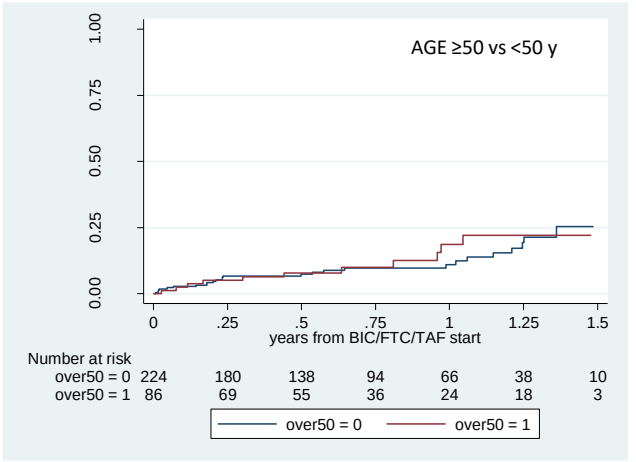


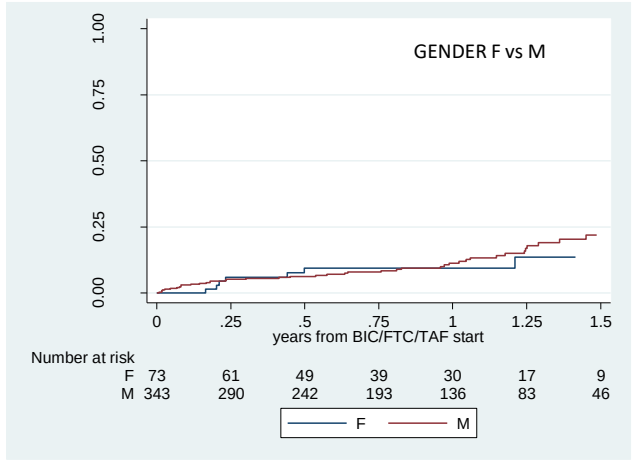
HR and AHR of TF from fitting different Cox regression models

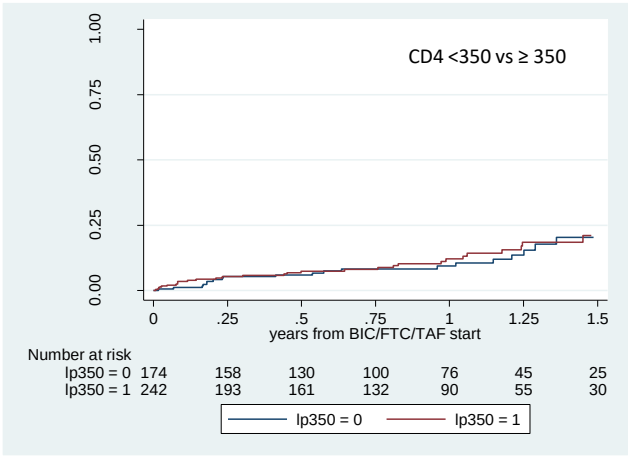
	TF					
	HR	**95%CI**	**p**	**AHR**	**95%CI**	**p**
Age, >=50 years (vs <50years)[1]	1.28	0.72-2.26	0.398	1.36	0.74-2.48	0.323
Gender, Male (vs. female)[2]	1.28	0.58-2.85	0.537	1.37	0.61-3.05	0.443
Late presenters (vs. non late-presenters)3	1.21	0.68-2.12	0.514	1.23	0.68-2.21	0.496
Advance HIV disease (vs. non advance)4	1.37	0.78-2.39	0.265	1.46	0.81-2.63	0.208

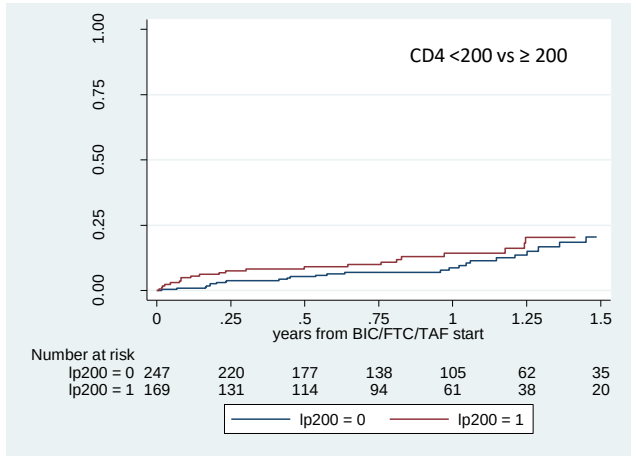
[1]AHR adjusted for nationality and mode of HIV transmission; [2]AHR adjusted for nationality; [3]adjusted for gender, mode of HIV transmission, HIV-RNA and nationality; [4]AHR adjusted for gender, mode of HIV transmission, HIV-RNA and nationality

None of the exposure groups analyzed have been found to be associated with a higher risk of TF





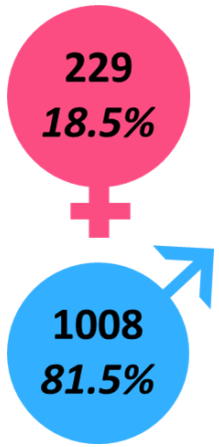




Real-word Effectiveness of BIC/FTC/TAF in experienced PLWH

- **Study Design:** Observational study on ART-experienced PLWH of the Icona cohort who switched to BIC/FTC/TAF while virologically suppressed, from Apr2018 to Dec2021, with at lest 1 follow-up after.
- **Primary endpoint:** Time to treatment failure (TF) defined as virological failure (2 HIV-RNA > 200 copies/ml or 1 HIV-RNA>1000 copies/ml) or discontinuation of BIC/FTC/TAF for any reason (TD).
- **Secondary endpoints:**
  1) TF excluding pregnancy as event (TFEP)
  2) TD regardless of the reason
  3) TD excluding pregnancy (TDEP)
  4) Virological failure (VF)

- **Exposure of interest:**



	Women		Men		p	Total	
	N=229	(18.50%)	N=1008	(81.50%)		N=1237	(100%)
Italian, n(%)	163	71.2	880	87.3	<0.001	1043	84.3
Ethnicity, Caucasian, n(%)	184	80.3	918	91.1	<0.001	1102	89.1
Year of BIC start, median (IQR)	2020	2019-2020	2019	2019-2020	0.852	2019	2019-2020
Year HIV diagnosis, median (IQR)	2012	2002-2016	2014	2009-2016	<0.001	2013	2008-2016
Year cART start, median (IQR)	2013	2009-2016	2015	2011-2017	<0.001	2015	2011-2017
Age, years, median (IQR)	48	39-56	47	39-55	0.526	47	39-55
Mode of HIV Transmission, n(%)					<0.001		
Heterosexual	194	84.7	262	25.99		456	36.86
IVDU	25	10.9	75	7.44		100	8.08
MSM	0	0	622	61.7		622	50.28
Other/Unknown	10	4.4	49	4.9		59	4.77
HCVAb pos, n(%)	25	10.9	104	10.3	0.756	129	10.43
HBsAg pos, n(%)	9	3.9	40	3.9	0.776	49	3.96
CDC C-stage, n(%)	50	21.8	153	15.2	0.014	203	16.41
CD4, cells/mmc, median (IQR)	733	507-946	697	505-925	0.356	702	505-928
HIV-RNA,copies/mL, median (IQR)	1	1-20	8	1-29	0.163	2	1-24
eGFR, CKD-EPI, median (IQR)	89	77.4-102.4	89.8	77.1-101.8	0.515	89.5	77.2-101.8
BMI, Kg/m2, median (IQR)	24	20.8-27.3	24.2	22.4-26.8	0.121	24.2	22.2-26.9
Diabetes, n(%)	9	3.9	60	5.9	0.229	69	5.58
CVD, n(%)	1	0.44	19	1.88	0.117	20	1.62
CKD, n(%)	37	16.2	131	13	0.207	168	13.58
FU on BIC, years, median (IQR)	1.3	0.9-1.7	1.4	1.0-1.7	0.461	1.37	0.97-1.67
Previous ART-regimen					0.77		
INSTI-based	193	84.3	868	86.1		1061	85.77
NNRTI-based	13	5.7	82	8.1		95	7.68
PI-based	18	7.9	44	4.4		62	5.01
Other	5	2.2	14	1.4		19	1.54

Real-word Effectiveness of BIC/FTC/TAF in experienced PLWH

- Over a Median FU of 1.36 years (0.97-1.67)

TREATMENT FAILURE

112 TF (9.1%)→ 14 VF + 98 TD

- 30/229 Women (13.1%)
- 82/1008 Men (8.1%)

p<0.001

Excluding 6 discontinuations for pregnancy

TREATMENT FAILURE EXCLUDING PREGANCY

106 TFEP (8.6%)→ 14 VF + 92 TD

- 24/229 Women (10.5%)
- 82/1008 Men (8.1%)

P=0.252

KM 1-yr probability TF:

	1-yr prob. of TF	95%CI	Log-rank p
Overall	4.6%	3.5-6.1	
Female	7.5%	4.7-12.0	0.098
Male	4.0%	2.9-5.5	

KM 1-yr probability TFEP:

	1-yr prob. of TFEP	95%CI	Log-rank p
Overall	4.2%	3.2-5.6	
Female	5.1%	2.8-9.0	**0.1619**
Male	4.0%	2.9-5.5	

HR and Adjusted HR of TF in women vs men

	Treatment Failure					
	HR	95%CI	p	AHR*	95%CI	p
Female (vs Male)	1.72	1.13-2.62	0.011	2.01	1.17-3.44	0.011

**Adjusted for nationality and mode transmission*

HR and Adjusted HR of TFEP in women vs men

	Treatment Failure exluding pregnancy					
	HR	95%CI	p	AHR*	95%CI	p
Female (vs Male)	1.38	0.87-2.18	0.164	1.63	0.93-2.90	**0.089**

**Adjusted for nationality and mode transmission*

ICONA BIC Study
Conclusions

Naïve:

- **First line therapy with BIC/FTC/TAF demonstrated high effectiveness in a real world setting. This was also confirmed in populations at risk of lower response to therapy, such as severely immuno-supressed individuals, female and older individuals**.

Experienced:

- **In this large real-world study of ART-experienced PLWH, switching to BIC/FTC/TAF showed high effectiveness with a very low rate of VF.**
- The higher risk of TF and TD reported in females compared to males has been exclusively due to discontinuation for pregnancy events; after excluding them the success of BIC/FTC/TAF resulted similar in both populations.
- First case reports of BIC/FTC/TAF use in pregnancy are promising but more comprehensive studies need to be completed in this important clinical condition.

Characteristics of PLWH initiating a DTG-containing regimens according to sex- naives

	Females		Males.		Total		P – value
	N = 356	15.5%	N = 1948	84.5%	N = 2304	100%	
Italian, n(%)	191	53.7	1567	80.4	1758	76.3	< 0.001
Ethnicity, Caucasian, n(%)	239	67.1	1670	85.7	1909	82.9	< 0.001
Age, years, median (IQR)	43	33-51	39	30-49	40	31-49	< 0.001
Age, >50 years, n(%)	105	29.5	464	23.8	569	24.7	0.022
HCV-Ab positive status, n(%)	29	8.2	107	5.5	136	5.9	0.027
HBsAg positive status, n(%)	6	1.7	48	2.5	55	2.3	0.499
Smoker, Yes, n(%)	99	27.8	796	40.9	895	38.9	< 0.001
CDC C-stage[†], n(%)	52	14.6	228	11.7	280	12.2	0.123
CD4, cells/mmc, median (IQR)	227.5	83-481	352	1447-556.5	341	138.5-541	< 0.001
CD4<200 cells/mmc, n(%)	143	40.2	595	30.5	738	32.0	< 0.001
CD4<350 cells/mmc, n(%)	217	61.0	963	49.4	1180	51.2	< 0.001
HIV-RNA, $\log_{10}$ cp./mL, median (IQR)	4.66	4.01-5.37	4.89	4.26-5.47	4.86	4.22-5.46	0.002
HIV-RNA > 5 $\log_{10}$ cp./mL, n (%)	135	37.9	877	45.0	1012	43.9	0.0130
Total Cholesterol, mg/dL, median (IQR)	166	145-194	154	131-179	156	134-181	< 0.001
HDL cholesterol, mg/dL, median (IQR)	48	38-56	39	32-46	40	32-48	< 0.001
Triglycerides, mg/dL, median (IQR)	95	67-141	101	73-138	99	71-139	0.196
Serum Glucose, mg/dL, median (IQR)	84	77-92	86	79-94	85	79-93	0.006
eGFR[‡], ml/min/1.73m^2, median (IQR)	106.4	94.2-118-7	108.0	95.1-118.0	107.9	94.9-118.0	0.814
DTG-containing cART regimen, n(%)							
2 drugs regimen (2DR)	27	7.6	212	10.9	239	10.4	
3 drugs regimen (3DR)	329	92.4	1739	89.2	2068	89.6	

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Reasons of DTG discontinuation according to sex: naives

A - ART naïve: type III p-value = 0.003										
	Females (n=356)			Males (n=1948)			Total (n=2304)			p - value
	n.e.	%†	%‡	n.e.	%†	%‡	n.e.	%†	%‡	
Failure	7	2.0	6.7	33	1.7	8.3	40	1.7	8.0	0.718
Patient's decision	8	2.3	7.6	9	0.5	2.3	17	0.7	3.4	< 0.001
Simplification	28	7.9	26.8	168	8.6	42.3	196	8.5	39.0	0.637
Toxicity	32	9.0	30.5	112	5.8	28.0	144	6.3	28.5	0.020
Toxicity (no NPS)	19	5.3	18.1	57	2.9	14.4	76	3.3	15.1	0.019
NPS toxicity	13	3.7	12.4	54	2.8	13.6	67	2.9	13.4	0.364
Neurologic	2	0.6	1.9	15	0.8	3.8	17	0.7	3.4	-
Psychiatric	9	2.5	8.6	39	2.0	9.8	48	2.1	9.6	-
Unknown	2	0.6	1.9	0	0.0	0.0	2	0.1	0.4	-
Allergic	8	2.2	7.6	13	0.7	3.3	21	0.9	4.2	-
Renal	1	0.3	1.0	8	0.4	2.0	9	0.4	1.8	-
Hepatobiliary and pancreatic	1	0.3	1.0	6	0.3	1.5	7	0.3	1.4	-
Gastrointestinal	5	1.4	4.8	7	0.4	4.8	12	0.5	2.4	-
Dermatologic	1	0.3	1.0	2	0.1	0.5	3	0.1	0.6	-
Metabolic/CV	2	0.6	1.9	14	0.7	3.5	16	0.7	3.2	-
Weight gain	1	0.3	1.0	2	0.1	0.5	3	0.1	0.6	-
Other	30	8.4	28.6	76	3.9	19.1	106	4.6	21.1	< 0.001
Randomized clinical trial	3	0.8	2.9	21	1.1	5.3	24	1.0	4.8	-
Pregnancy	17	4.8	16.2	0	0.0	0.0	17	0.7	3.4	-
Other	4	0.2	3.8	16	0.8	4.0	20	0.9	4.0	-
Unspecified	6	0.3	5.7	39	1.7	9.8	45	2.0	9.0	-
TOTAL	105	29.5	100.0	397	20.4	100.0	502	21.8	100.0	-

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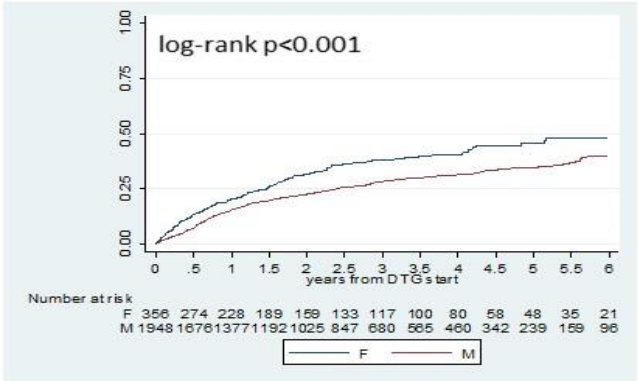
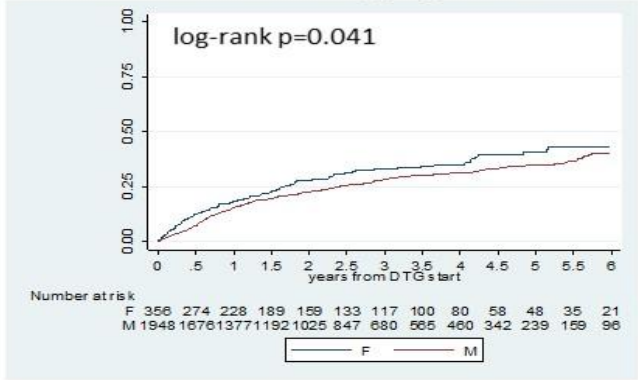
. Kaplan Meier probability of reaching the end points in females and males PLWH initiating DTG-containing regimens from ART naives

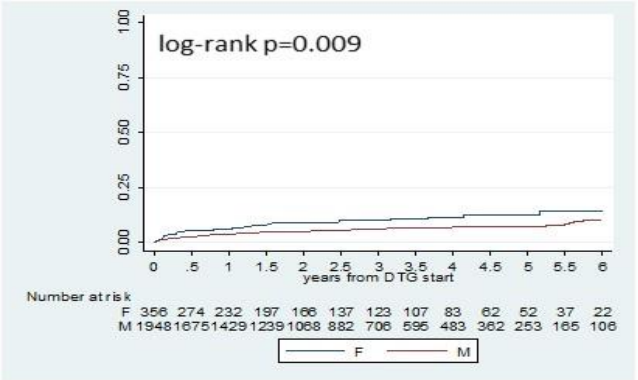
A-Treatment Failure



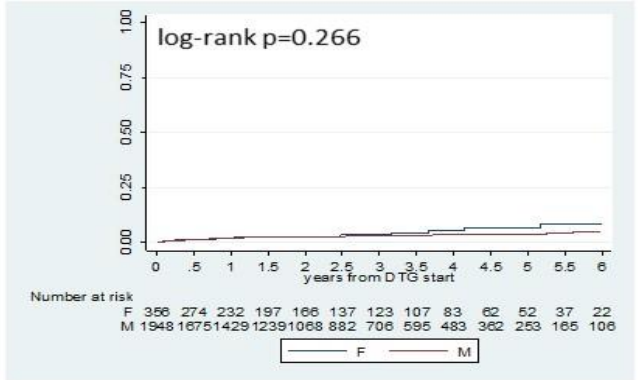
B-Treatment Failure excluding pregnancies



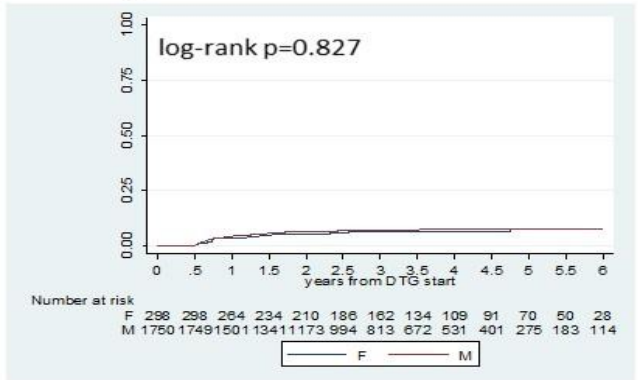
C-DTG discontinuation for toxicity



D-DTG discontinuation for NPAEs toxicity



E- Virological Failure



Uni- and multivariable analyses on role of sex in different outcomes of PLWH initiating DTG containing regimens from naives

	N events/N study participants (%)	HR	95%CI		p	AHR§	95%CI		p	p for interaction sex*type regimen
TREATMENT FAILURE										
Men	514/1948(26.4%)	1.00				1.00				0.398
Women	124/356 (34.8%)	1.44	1.18	1.75	<0.001	1.26	1.03	1.55	0.027	
TREATMENT FAILURE EXCLUDING PREGNANCIES										
Men	514/1948(26.4%)	1.00				1.00				0.286
Women	107/356 (30.0%)	1.24	1.01	1.53	0.041	1.08	0.87	1.34	0.478	
DTG DISCONTINUATION FOR TOXICITY										
Men	112/1948 (5.7%)	1.00				1.00				0.812
Women	32/356 (9.0%)	1.67	1.13	2.48	0.01	1.58	1.05	2.39	0.029	
DTG DISCONTINUATION FOR NPS TOXICITY										
Men	54/1948 (2.8%)	1.00								.
Women	13/356 (3.6%)	1.41	0.77	2.57	0.269	1.41	0.74	2.66	0.296	
DTG DISCONTINUATION FOR TOXICITY/OTHER REASONS/PATIENTS' DECISION										
Men	196/1948 (10.6%)	1.00								0.670
Women	70/356 (19.7%)	2.11	1.61	2.77	<0.001	2.07	1.55	2.77	<0.001	
DTG DISCONTINUATION FOR TOXICITY/OTHER REASONS/PATIENTS' DECISION EXCLUDING PREGNANCIES										
Men	196/1948 (10.6%)	1.00								0.452
Women	53/356 (14.9%)	1.59	1.18	2.16	0.003	1.55	1.13	2.14	0.006	
VIROLOGICAL FAILURE										
Men	114/1750 (6.5%)	1.00				1.00				0.230
Women	19/298 (6.4%)	0.95	0.58	1.54	0.827	0.83	0.5	1.37	0.472	

Characteristics of PLWH initiating a DTG-containing regimens according to sex- ART experienced

	Females	Males		TOTAL		P - value
	n = 379	19.8%	n = 1,537	80.2%	n = 1,916	100%	
Italian, n(%)	291	76.8	1394	90.7	1685	87.9	< 0.001
Ethnicity, Caucasian, n(%)	316	83.9	1,434	93.3	1,750	91.3	< 0.001
Age, years, median (IQR)	50	42-56	48	39-56	49	40-56	0.031
Age, >50 years, n(%)	196	51.7	708	46.1	904	47.2	0.048
HCV-Ab positive status, n(%)	68	17.9	186	12.1	254	13.3	0.009
HBsAg positive status, n(%)	8	2.1	39	2.5	47	2.5	0.203
CDC C-stage[†], n(%)	59	15.6	207	13.5	266	13.9	0.290
CD4, cells/mmc, median (IQR)	716	530-969	707	524-914	708	528-920	0.413
CD4<200 cells/mmc, n(%)	3	0.8	35	2.3	38	2.0	0.063
CD4<350 cells/mmc, n(%)	37	9.8	132	8.6	169	8.9	0.470
HIV-RNA, cp./mL, median (IQR)	1	1-20	1	1-21	1	1-21	0.584
Framingham Score[¶], median (IR)	4.4	2.4-7.5	10.3	5.1-20.4	8.6	4.2-17.5	< 0.001
DTG-containing cART regimen, n(%)							0.039
3TC + DTG	138	36.4	629	40.9	767	40.0	
RPV+DTG	37	9.8	198	12.9	235	12.3	
TDF-TAF/FTC + DTG	43	11.4	132	8.6	175	9.1	
3TC/ABC/DTG	161	42.5	578	37.6	739	38.6	
Type of cART regimen, n(%)							0.008
2 drugs regimen (2DR)	175	46.2	827	53.8	1,002	52.3	
3 drugs regimen (2DR)	204	53.8	710	46.2	914	47.7	

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Reasons of DTG discontinuation according to sex: ART experienced

	Females (n=379)			Males (n=1537)			Total (n=1916)			p - value
	n.e.	%†	%‡	n.e.	%†	%‡	n.e.	%†	%‡	
Failure	**1**	**0.3**	**1.4**	**13**	**0.9**	**6.9**	**14**	**0.7**	**5.4**	**0.233**
Patient's decision	**2**	**0.5**	**2.8**	**4**	**0.3**	**2.1**	**5**	**0.3**	**2.3**	**0.404**
Simplification	**15**	**4.0**	**21.1**	**47**	**3.1**	**25.4**	**62**	**3.2**	**24.2**	**0.375**
Toxicity	**33**	**8.7**	**46.5**	**91**	**5.9**	**47.6**	**124**	**6.5**	**47.3**	**0.048**
Toxicity (no NPS)	18	4.8	25.4	48	3.1	25.4	66	3.4	25.4	0.120
NPS toxicity	15	4.0	21.1	42	2.7	22.2	57	3.0	21.9	0.209
Neurologic	2	0.5	5.6	9	0.6	4.8	13	0.7	5.0	-
Psychiatric	10	2.6	14.1	33	2.1	17.5	43	2.2	16.5	-
Unknown	0	0.0	1.4	1	0.1	0.0	1	0.1	0.4	-
Allergic	3	0.8	4.2	5	0.3	2.7	8	0.4	3.1	-
Renal	1	0.3	1.4	12	0.8	6.4	13	0.7	5.0	-
Hepatobiliary and pancreatic	0	0.0	0.0	5	0.3	2.7	5	0.3	1.9	-
Gastrointestinal	8	2.1	11.3	3	0.2	1.6	11	0.6	4.2	-
Dermatologic	1	0.3	1.4	0	0.0	0.0	1	0.1	0.4	-
Metabolic/CV	5	1.3	7.0	15	1.0	7.9	20	1.0	7.7	-
Weight gain	0	0.0	0.0	1	0.1	0.5	1	0.1	0.4	-
Other toxicity	0	0.0	0.0	6	0.4	3.2	6	0.3	2.3	-
Unknown	0	0.0	0.0	2	0.1	1.1	2	0.1	0.8	-
Other	**20**	**5.3**	**28.2**	**35**	**2.3**	**18.0**	**55**	**2.9**	**20.8**	**0.001**
RCT	0	0.0	0.0	4	0.3	2.1	4	0.2	1.5	-
Pregnancy	7	1.8	9.9	0	0.0	0.0	7	0.4	2.7	-
Other	4	1.1	5.6	9	0.6	4.8	13	0.7	5.0	-
Unspecified	9	2.4	12.7	21	1.4	11.1	30	1.6	11.5	-
TOTAL	**71**	**18.7**	**100.0**	**189**	**12.3**	**100.0**	**260**	**13.6**	**100.0**	

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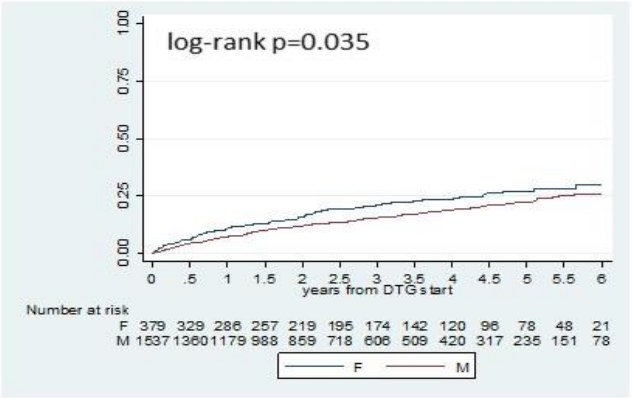
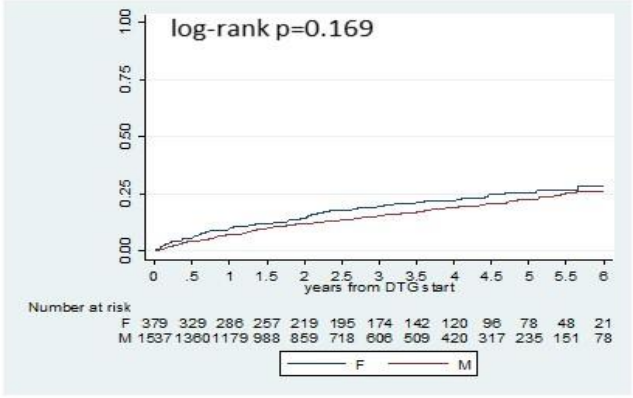
. Kaplan Meier probability of reaching the end points in females and males PLWH initiating DTG-containing regimens: ART experienced

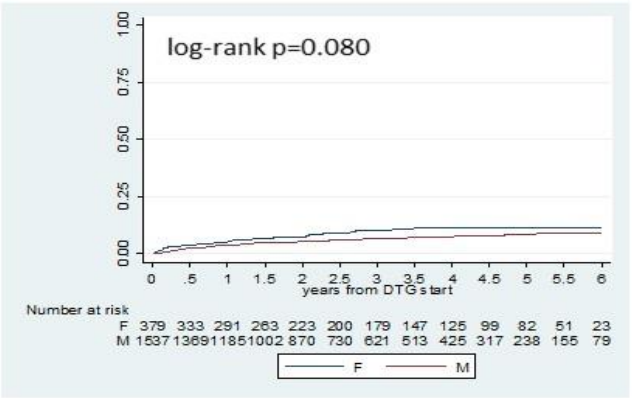
A-Treatment Failure



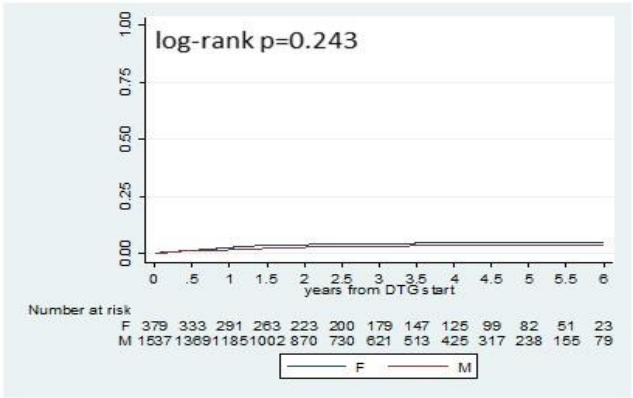
B-Treatment Failure excluding pregnancies



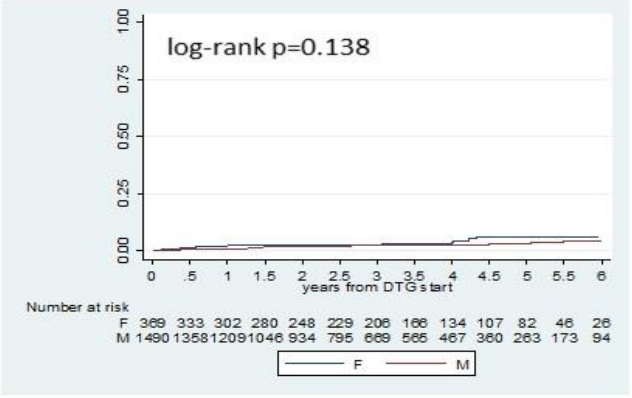
C-DTG discontinuation for toxicity



D-DTG discontinuation for NPAEs toxicity



E- Virological Failure



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Uni- and multivariable analyses on role of sex in different outcomes of PLWH initiating DTG containing regimens:
ART experienced

	N events/N study participants	HR	95%CI		p	AHR§	95%CI		p	p-value for interaction sex*type regimen
TREATMENT FAILURE										
Men	233/1537(15.1%)	1.00				1.00				0.782
Women	79/379 (20.8%)	1.31	1.02	1.69	0.035	1.3	1.01	1.69	0.043	
TREATMENT FAILURE EXCLUDING PREGNANCIES										
Men	233/1537(15.1%)	1.00				1.00				0.831
Women	72/379	1.19	0.92	1.56	0.18	1.19	0.95	1.16	0.301	
DTG DISCONTINUATION FOR TOXICITY										
Men	91/1537 (5.9%)	1.00				1.00				0.054
Women	33/379 (8.7%)	1.42	1.08	2.37	0.082	1.54	1.03	2.31	0.035	
DTG DISCONTINUATION FOR TOXICITY (Only 3-DR)										
Men	71/710 (10.0%)	1.00				1.00				
Women	22/204 (10.8%)	1.1	0.68	1.77	0.702	1.18	0.73	1.91	0.492	
DTG DISCONTINUATION FOR TOXICITY (Only 2-DR)										
Men	20/827 (2.4%)	1.00				1.00				
Women	11/175 (6.3%)	2.39	1.14	5.02	0.021	2.43	1.14	5.2	0.022	
DTG DISCONTINUATION FOR NPS TOXICITY										
Men	42/1537 (2.7%)	1.00				1.00				0.049
Women	15/379 (3.9%)	1.41	0.79	2.55	0.246	1.62	0.89	2.94	0.114	
DTG DISCONTINUATION FOR NPS TOXICITY (Only 3-DR)										
Men	33/710 (4.6%)	1.00				1.00				
Women	9/204 (4.4%)	0.96	0.46	2.01	0.952	1.05	0.5	2.2	0.902	
DTG DISCONTINUATION FOR NPS TOXICITY (Only 2-DR)										
Men	9/827 (1.1%)	1.00				1.00				
Women	6/175 (3.4%)	2.99	1.06	8.41	0.038	3.61	1.24	10.48	0.018	

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Uni- and multivariable analyses on role of sex in different outcomes of PLWH initiating DTG containing regimens:
ART experienced

DTG DISCONTINUATION FOR TOXICITY/OTHER REASONS/PATIENTS' DECISION										
Men	129/1537 (8.4%)	1.00								0.544
Women	55/379 (14.5%)	1.66	1.21	2.28	0.002	1.69	1.23	2.34	0.001	
DTG DISCONTINUATION FOR TOXICITY/OTHER REASONS/PATIENTS' DECISION EXCLUDING PREGNANCIES										
Men	129/1537 (8.4%)	1.00								0.652
Women	48/379 (12.7%)	1.45	1.04	2.02	0.027	1.49	1.06	2.09	0.020	
VIROLOGICAL FAILURE										
Men	33/1490 (2.2%)	1.00				1.00				0.103
Women	14/369 (3.8%)	1.6	0.85	2.99	0.141	1.54	0.81	2.93	0.184	
VIROLOGICAL FAILURE (Only 3-DR)										
Men	29/700 (4.1%)	1.00				1.00				
Women	10/201 (5.0%)	1.22	0.59	2.5	0.587	1.17	0.56	2.43	0.672	
VIROLOGICAL FAILURE (Only 2-DR)										
Men	4/790 (0.5%)	1.00				1.00				
Women	4/168 (2.4%)	4.00	0.99	16.11	0.051	3.63	0.84	15.48	0.083	

PLWH = people living with HIV; HR = Hazard Ratio; CI = confidence interval; 2-DR = two-drug regimen; 3-DR = three-drug regimen; NPS = neuropsychiatric; type of regimen = 2-DR or 3-DR
§Adjusted for age and nation of birth (Italy vs non Italy)

Conclusions on DTG containing regimens

- DTG-containing regimens are as potent and safe in women as compared to men, both when used as first-line and as switch therapy after achieving virological control.
- The excess of risk of treatment failure in women appears to be associated mainly with discontinuations of DTG when used in pregnancy; this event is less frequent in most recent calendar years due to new evidences and guidelines.
- In our setting of ART-experienced PLWH virological failure was a infrequent event in 2-DR regimens, thus confirming the potency of these combinations already observed in clinical trials.
- On the other hand, women appeared to carry a higher risk of stopping DTG for toxicity. Reassuringly, despite the marked difference in terms of relative risks, the absolute risk of stopping DTG even after 4 years of follow-up remains low and below 9% of the treated.

Dolutegravir and NPS events: comparison with EFV

STUDY AIM:

The aims of the study were:

- to **estimate and compare the risk of neuropsychiatric toxicity** among **DTG-based, EFV-based regimens** as well as **other currently recommended first-line antiretroviral regimens**

- **to assess the predictive factors of treatment discontinuation due to NPAEs**

in a large Italian cohort.

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METHODS

STUDY DESIGN AND POPULATION:

- **Prospective, observational, multicentric study** analysing data from Icona Foundation Study Cohort.

- All consecutive **HIV-infected ART-naïve patients**, aged 18 years or more, enrolled in ICONA cohort, **who started a first-line recommended (as main or alternative) ART according to EACS guidelines 2018**, from **January 2006 to December 2018**, were included in the analysis.

✓ **DTG group**: patients starting a **DTG-based ART**

✓ **EFV group:** patients starting an **EFV-based ART**

✓ **Other group**: patients starting a **non EFV non-DTG ART**

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METHODS II:

OUTCOME DEFINITIONS:

- **Treatment Discontinuation for NPAEs:**

  Discontinuation of the third drug, ignoring changes in the backbone, **due to NPAEs**, as reported by the treating physician.

- **Neuropsychiatric toxicity:**

  Composite endpoint defined as

  - ✓ **treatment discontinuation due to NPAEs** (as defined above) or
  - ✓ **an event classified as neuropsychiatric** by the treating physician (including psicosis, depression, anxiety, cognitive disorder or other) or
  - ✓ **the new start of a psychoactive drug** (including antidepressant, benzodiazepine, antiepileptic, neuroleptic or other).

RESULTS: BASELINE CHARACTERISTICS

Characteristic	TOTAL POPULATION (N=7,854) DTG group (n=1,322, 16.8%)	EFV group (n=1,542, 19.6%)	OTHER group (4,990, 63.5%)	p-value
Female gender, n (%)	223 (16.9)	230 (14.9)	1016 (20.4)	**<0.001**
Age, years, median (IQR)	40 (31-49)	39 (32-46)	39 (31-47)	0.051
Non-Italian born, n (%)	556 (42.1)	289 (18.7)	1351 (27.1)	**<0.001**
Risk Factor for HIV, n (%)				**<0.001**
- Homosexual contacts	703 (53.7)	701 (45.9)	2293 (46.4)	
- Heterosexual contacts	442 (33.4)	599 (38.8)	1948 (39.0)	
- IDU	62 (4.7)	121 (7.9)	381 (7.7)	
- Other/Unknown	102 (7.8)	107 (7.0)	322 (6.5)	
AIDS diagnosis, n (%)	163 (12.3)	136 (8.8)	486 (9.7)	**0.005**
HCV Antibodies Positive, n (%)	69 (5.2)	151 (9.8)	416 (8.3)	**<0.001**
CD4 count nadir, cells/mm^3, median (IQR)	333 (129-526)	307 (213-399)	337 (191-480)	**<0.001**
Baseline calendar year, median (IQR)	2016 (2016-2017)	2011 (2009-2012)	2014 (2012-2016)	**<0.001**
Time from HIV diagnosis to ART, months, median (IQR)	1 (1-3)	11 (2-39)	3 (1-24)	**<0.001**
Baseline CD4 cells count, cell/mm3, median (IQR)	349 (139-562)	324 (226-420)	351 (199-503)	**<0.001**
Baseline HIV-RNA, log10 copies/mL, median (IQR)	4.62 (4.10-5.24)	4.75 (4.23-5.14)	4.57 (4.00-5.04)	**<0.001**

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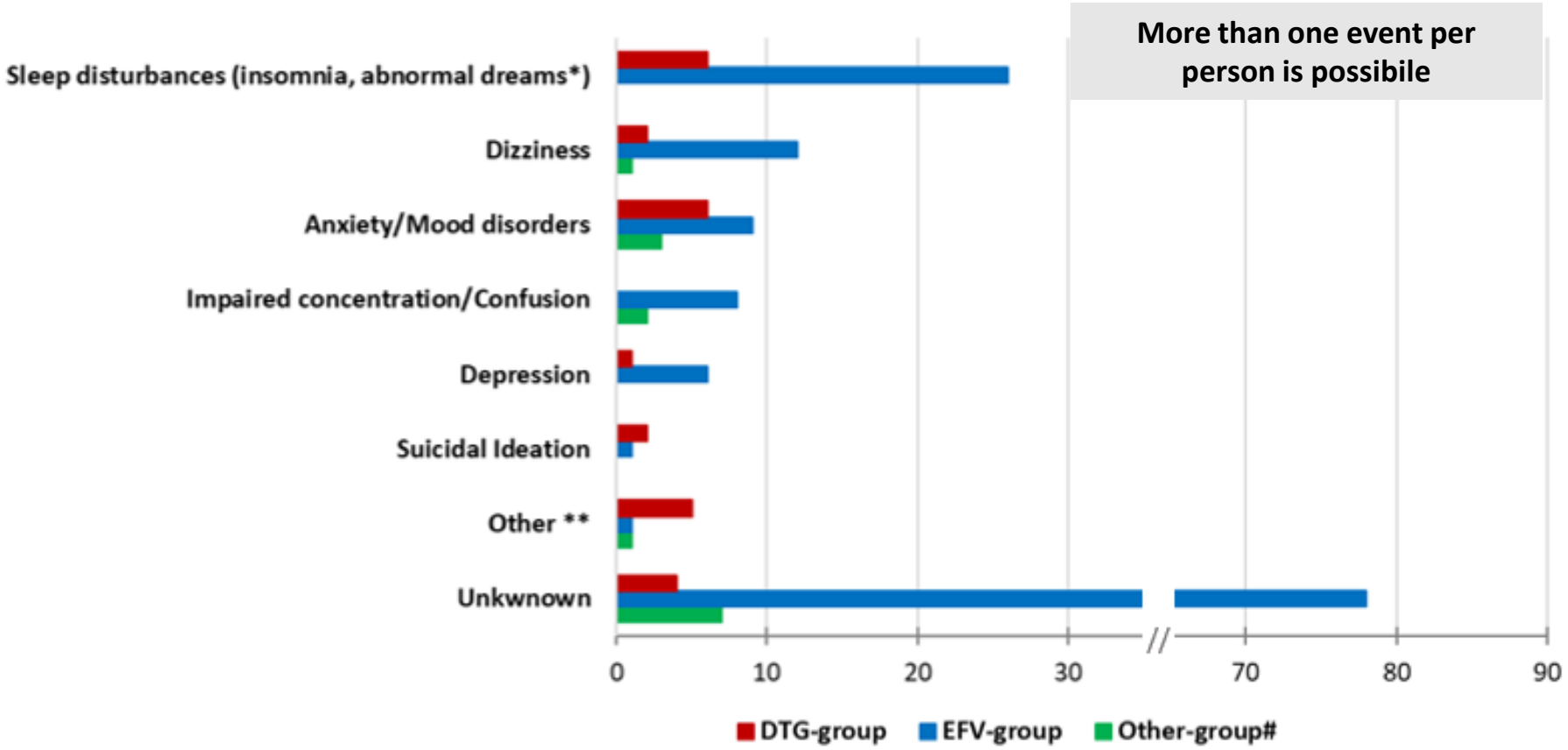
RESULTS: NPAEs LEADING TO TREATMENT DISCONTINUATION ACCORDING TO TREATMENT GROUP



Other-group included the following ART: TDF/FTC/RPV (6); ATV/r-based ART (3): TAF/FTC/EVG/C (2); RAL-based ART (2).
* Abnormal dreams reported only in EFV-group
** Other NPAEs includes: paresthesia, anosmia, paranoid ideation, allucinations and headeache (DTG group); allucinations (EFV-group) and hands shacking (other-group)

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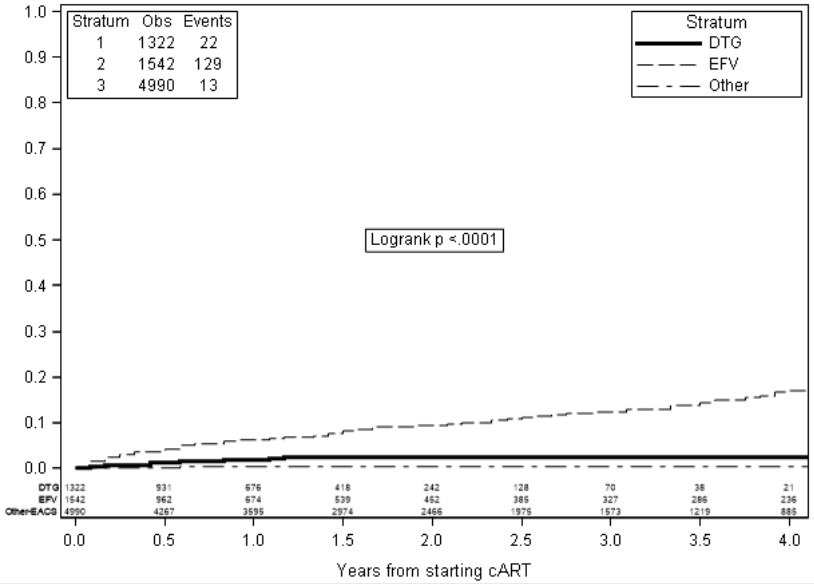
RESULTS: PROBABILITY OF NEUROPSYCHIATRIC TOXICITY

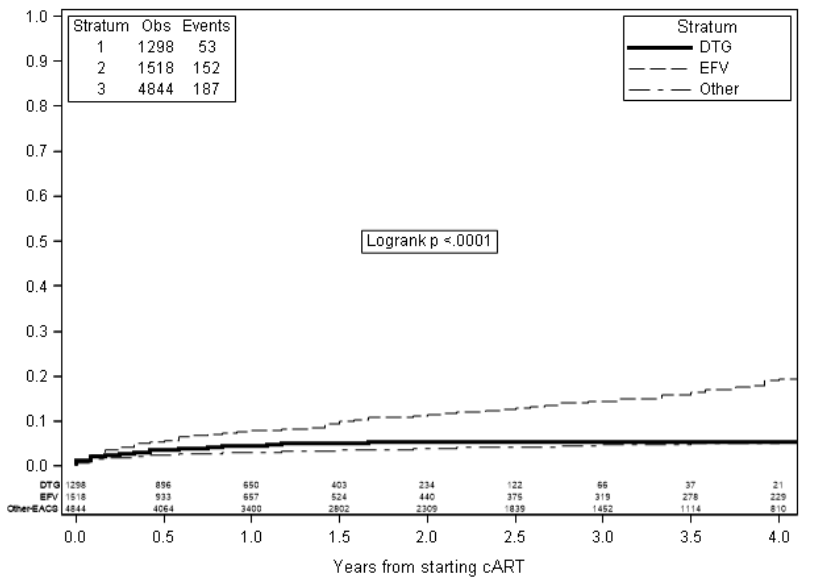
Median follow-up time: 16 months (IQR 6-33)

TREATMENT DISCONTINUATION FOR NPAEs



Estimated probability of TD due to NPAEs (95% CI)	DTG-group	EFV-group	Other group
1-year	1.6% (0.9-2.4)	5.3 % (4.0-6.6)	0.3 % (0.1-0.4)
2-year	2.4 % (1.4-3.4)	6.9 % (5.4-8.5)	0.3 % (0.1-0.4)
3-year	2.4 % (1.4-3.4)	10.7 % (8.5-12.9)	0.3 % (0.1-0.4)

NEUROPSYCHIATRIC TOXICITY



Estimated probability of NPAEs (95% CI)	DTG-group	EFV-group	Other group
1-year	3.9% (2.8-5.1)	6.9 % (5.4-8.3)	2.7 % (2.2-3.2)
2-year	5.2% (3.7-6.6)	8.5 % (6.8-10.2)	3.2 % (2.7-3.7)
3-year	5.2% (3.7-6.6)	12.4 % (10.1-14.8)	4.1 % (3.5-4.7)

RESULTS: PREDICTORS OF TREATMENT DISCONTINUATION DUE TO NPAEs

	Overall Period (2006-2018)				Sensitivity Analysis 2011-2018			
	HR (95% CI)	p	aRH* (95% CI)	p	HR (95% CI)	p	aRH* (95% CI)	p
Gender								
Female versus Male					0.55 (0.31-0.99)	**0.045**	1.00 (0.36-2.78)	0.994
Calendar year of starting ART								
per more recent	0.86 (0.81-0.91)	**<.001**	1.06 (0.96-1.18)	0.254	0.82 (0.74-0.91)	**<.001**	1.12 (0.92-1.36)	0.279
Nationality								
Foreign vs Italian	0.56 (0.36-0.86)	**0.008**	0.51 (0.24-1.09)	0.081	0.56 (0.34-0.91)	**0.020**	0.39 (0.16-0.99)	**0.046**
Anchor drug								
DTG	1.00		1.00		1.00		1.00	
EFV	4.37 (2.75-6.93)	**<.001**	6.84 (2.91-16.04)	**<.001**	5.05 (3.14-8.12)	**<.001**	6.01 (2.21-16.38)	**<.001**
Other EACS	0.10 (0.05-0.20)	**<.001**	0.10 (0.03- 0.31)	**<.001**	0.09 (0.04-0.19)	**<.001**	0.08 (0.03-0.28)	**<.001**
STR								
Yes versus no	1.56 (1.15-2.12)	**0.005**	1.15 (0.73-1.81)	0.545	1.66 (1.16-2.37)	**0.006**	1.51 (0.88-2.59)	0.137

* After adjusting for: gender, age, mode of HIV transmission, AIDS diagnosis (yes vs no), BMI, CD4 count nadir, NRTI backbone, highest level of education and employement

CONCLUSIONS:

- In this large observational study, **the use of DTG-based first line regimens was associated to a 2.5% risk of stopping DTG due to NPAEs by two years.** Despite not negligible, this estimated risk was one of the lowest reported for DTG in observational settings.

- **The risk of neuropsychiatric toxicity in patients on DTG-based first-line regimens** is significantly **lower than that experienced by subjects taking EFV-based regimens but higher than seen for people starting other recommended ART.**

- **The neuropsychiatric toxicity profile of DTG and EFV seems to be only partially comparable.** However, these findings should be interpreted cautiously due to the lack of characterization of most EFV-related NPAEs, and the lack of assessment of neurocognitive impairment and mood disorders.

Triple antiretroviral therapy: what future

- New regimens with less drugs
- Long acting regimens

- ….. But Triple cART has a long history of success and will be part of therapy during a long period of individual HIV therapy course

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