Long-term outcome of dolutegravir-containing regimens according to sex: data from the ICONA study

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Objectives: To compare the long-term risk of treatment failure of dolutegravir-based ART in men and women in a real-life setting.

Patients and methods: Persons living with HIV (PLWH) from the ICONA cohort were included if they had started dolutegravir in a two- or three-drug regimen as ART-naive or as virologically controlled ART-experienced. The primary endpoint was time to treatment failure (virological/clinical failure or dolutegravir discontinuation). Secondary endpoints were: time to dolutegravir discontinuation due to toxicity and to neuropsychiatric adverse events; and time to virological failure. Cox regression analyses focused on differences in outcomes by sex.

Results: A total of 2304 PLWH (15% women) initiated dolutegravir-based therapy from ART-naive, and 1916 (19.8% women) while experienced. After a median follow-up of 2.2 (IQR: 0.9–3.9) years in ART-naive and 2.4 (IQR: 1.1–4.3) years in experienced, the 4-year cumulative probability of treatment failure was 33% (95% CI 30.5–35.1) and 20% (95% CI 17.8–22.3), respectively. In the multivariable analyses, in ART-naive the risk of treatment failure was higher for women, but not different after excluding women discontinuing dolutegravir for pregnancy concerns. We also observed a higher risk of discontinuation for toxicity in women (ART-naives: Adjusted Hazard Ratio (AHR): 1.56%; 95% CI: 1.03–2.37; ART-experienced: AHR: 1.53%; 95% CI: 1.01–2.32), although the absolute 4-year probability was low: 7.7% (95% CI 6.5–9.2) in ART-naive and 8.3% (95% CI 6.9–9.9) in experienced.

Conclusions: In our cohort of PLWH treated with dolutegravir-based regimens and followed up for up to 4 years, we observed a low risk of treatment failure and no evidence for a difference by sex, after excluding discontinuation due to pregnancy concerns. However, we observed a higher risk of dolutegravir discontinuation for toxicity in women.

Introduction

Dolutegravir (DTG), a second-generation integrase strand transfer inhibitor (INSTI), has been approved for treatment of HIV-1 infection in both ART-naive and ART-experienced persons living with HIV (PLWH). Nowadays it is one of the most used ART drugs thanks to its great virological potency, combined with convenient dosing, lack of boosting, good tolerability and high barrier to resistance. It is currently recommended both as first-line and simplification strategy in combination with abacavir/lamivudine or tenofovir disoproxil fumarate/emtricitabine or tenofovir alafenamide/emtricitabine. Up to now, two-drug (2-DR)

dolutegravir-based regimens are also recommended as starting therapy in ART-naive, with lamivudine or as switch strategies for virologically suppressed PLWH, in association with either lamivudine or rilpivirine.[1,2]

Data from randomized clinical trials have shown an optimal safety profile of dolutegravir but real-life studies have revealed controversial concerns about dolutegravir tolerability, especially in the most severe cases with anxiety and depression, identified as neuropsychiatric adverse events (NPAEs).[3–6] A higher risk of discontinuation of dolutegravir-based regimens for all reasons, both in ART-naive and ART-experienced PLWH, has also been observed in women compared with men.[7–10] This difference was also confirmed in analyses restricted to discontinuation due to adverse events and, in particular, to NPAEs; however, all these studies had an average length of follow-up of 1 year.[11,12] In addition, an increased occurrence of neural defects in babies born of mothers who received dolutegravir during pregnancy was initially shown in the Tsepamo study from Botswana.[13] These findings led international guidelines to initially (approximately up to December 2021 in Europe) warn about the risk associated with dolutegravir use during pregnancy or in women planning pregnancy.[14] However, in the same Tsepamo study, the risk of defects in the newborns was reduced after longer follow-up and, further, it was not confirmed by randomized trials so that guidelines were more recently updated accordingly.[1,2,13,15,16]

Here, using the data of our large cohort of PLWH seen for care in Italy, we aimed to extend previous analyses and compare the risk of treatment failure with dolutegravir-based ART by sex over a time span of 4 years from the data of initiation and whether sex differences might vary according to the number of drugs used with dolutegravir (2-DR versus three-drug regimens, 3-DR).

Patients and methods

Criteria for inclusion in the study

PLWH enrolled in the ICONA cohort were included in the analyses if: (i) they started a dolutegravir-including 2-DR or 3-DR regimen from ART-naive or from ART-experienced while on virologically controlled (HIV-RNA <50 copies/mL) ART regimens during the period 1 January 2014 to 31 March 2022, and (ii) had at least one clinical follow-up visit. The database was frozen for analysis on 31 July 2022. We also insisted on participants initiating specific regimens: 3-DR regimens had to include dolutegravir plus abacavir/lamivudine or tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/emtricitabine; similarly, for 2-DR regimens they had to include lamivudine or rilpivirine, the latter only in experienced PLWH as by EMA registration.[17]

The ICONA cohort is a nationwide cohort enrolling PLWH naive from ART, prospectively followed in 53 Italian infectious diseases centres. Details of the ICONA cohort are described elsewhere.[18]

Study objectives

The primary objective of our analysis was to compare the risk of treatment failure (TF) of dolutegravir-based regimens between men and women, in the context of both 3-DR and 2-DR regimens.

The primary endpoint was time to TF, including virological failure (VF; i.e. HIV-RNA >50 copies/mL in two consecutive determinations, for ART-naive after 6 months from therapy start), and/or clinical failure (new AIDS-defining event or death) or dolutegravir discontinuation for any reasons. In a sensitivity analysis, reasons for dolutegravir discontinuation due to pregnancy concerns were not counted as events.

We also analysed as secondary endpoints: (i) time to dolutegravir discontinuation due to toxicity (DT); (ii) time to discontinuation of dolutegravir due to NPAEs; and (iii) time to VF (same definition as used for the VF component of the primary outcome).

For the classification of discontinuations, we used the primary reason reported by the treating physicians, as coded in the ICONA case report forms: failure (virological, immunological, clinical), simplification, patient decision, toxicity (gastrointestinal intolerance, NPAEs, renal, metabolic, dermatological, allergies) and other (pregnancy, planned pregnancy, inclusion in trial, unspecified, other). As secondary endpoints we also used the alternative definition of DT, which counted discontinuing for other reasons as events. This assumed that some stops due to toxicity could be classified by clinicians as 'other' or 'patient's decision'. Again, a sensitivity analysis after excluding stops due to pregnancy in women was performed.

Sex at birth was the exposure of interest and analyses were stratified according to whether participants had started a 2-DR versus a 3-DR regimen. None of the variables included in the models had missing data so that results from different adjustments are directly comparable.

Statistical analyses

All the analyses were conducted separately in ART-naive and ART-experienced virologically suppressed groups. Differences between men and women in baseline characteristics were assessed by means of chi-squared test for categorical variables or Wilcoxon rank-sum test for continuous variables. The numbers and outcomes of pregnancies during exposure to dolutegravir have been evaluated, and the incidence rate of dolutegravir discontinuation due to pregnancy concerns has been calculated as number of discontinuations divided by person-years follow-up (PYFU) before and after 2021 (change of the European guidelines on dolutegravir use in pregnant women).[1]

In the survival analysis, follow-up accrued from the date of dolutegravir start until its discontinuation or the last available clinical visit. An ITT approach was used for the VF analysis, including only PLWH with two HIV-RNA determinations after dolutegravir start. We used a standard Kaplan–Meier and Cox regression model to compare the risk of dolutegravir discontinuation by sex for all and neuropsychiatric (NPS) toxicity, the follow-up of PLWH discontinuing for reasons different from that of interest was truncated at the date of discontinuation of dolutegravir for the alternative reason, assuming non-informative censoring.

The effect of sex on the time to each endpoint is shown by means of HR with 95% CI from fitting separate standard Cox regression models conditioned on covariates for each of the defined endpoints. Sex is unconfounded by definition but in order to increase the precision of the estimates we decided also to fit models adjusted for two strong predictors of outcome: age and nation of birth (Italian versus non-Italian native) (Direct Acyclic Graph in Figure S1; available as Supplementary data at *JAC* Online). In order to further assess the robustness of the results against potential unmeasured confounding bias, the e-value was calculated and compared with the magnitude of the relative hazard seen for the predictor showing the strongest association with the outcome (i.e. nationality); The higher the e-value, the stronger the confounder associations have to be to explain away the effect of the exposure-outcome found.[19]

As a separate aim, we were interested in knowing whether the risk of outcomes by sex might vary depending on the type of regimen started (2-DR versus 3-DR). The interaction between sex and type of regimen started was formally tested by including a product term in the model (and using a Wald test for the extra parameter), and in case of statistically significant interaction we reported the HR for sex after stratifying by 2-DR versus 3-DR regimen. Statistical analyses were performed using Stata (v.14.0). All *P* values presented are two-sided, with *P* < 0.05 indicating statistical significance.

Table 1. Characteristics of PLWH initiating a DTG-containing regimen according to sex

(A) From ART-naive

	Females		Males		Total		
	$N=356$	(15.5%)	$N=1948$	(84.5%)	$N=2304$	(100%)	P value
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
Mode of HIV transmission, n (%)							<0.001
Heterosexual	310	(87.1)	510	(26.2)	820	(35.6)	
IVDU	21	(5.9)	98	(5.0)	119	(5.2)	
MSM/WSW	2	(0.6)	1226	(62.9)	1228	(53.3)	
Other/unknown	23	(6.5)	114	(5.9)	137	(6.0)	
Year HIV diagnosis, median (IQR)	2017	(2016–2019)	2017	(2016–2019)	2017	(2016–2019)	0.021
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[a], n (%)	52	(14.6)	228	(11.7)	280	(12.2)	0.123
CD4 nadir, 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[b], mL/min/1.73 m^2, median (IQR)	106.4	(94.2–118.7)	108.0	(95.1–118.0)	107.9	(94.9–118.0)	0.814
BMI, kg/m^2, median (IQR)	21.6	(19.5–24.90)	23.2	(21.5–25.36)	23.1	(21.2–25.3)	<0.001
Diabetes diagnosis, n (%)	12	(3.4)	50	(2.6)	62	(2.7)	0.389
CVD diagnosis, n (%)	1	(0.3)	15	(0.8)	16	(0.6)	0.307
NADM diagnosis, n (%)	12	(3.4)	24	(1.2)	36	(1.6)	0.003
CKD diagnosis, n (%)	15	(4.2)	41	(2.1)	56	(2.4)	0.018
ESRD diagnosis, n (%)	3	(0.84)	5	(0.26)	8	(0.35)	0.084
ESLD diagnosis, n (%)	1	(0.3)	2	(0.1)	3	(0.1)	0.391
Antilipidaemics, n (%)	9	(2.5)	24	(1.2)	33	(1.4)	0.058
Antihypertensive[c], n (%)	17	(4.8)	68	(3.5)	85	(3.7)	0.237
Framinghham score[d], median (IQR)	2.6	(1.4–5.2)	4.4	(2.0–10.6)	4.1	(1.9–9.6)	0.007
Year cART start, median (IQR)	2017	(2016–2019)	2018	(2016–2019)	2018	(2016–2019)	0.089
DTG-containing cART regimen, n (%)							0.019
3TC/ABC/DTG	152	(42.7)	695	(35.7)	847	(36.8)	
3TC+DTG	27	(7.6)	212	(10.9)	239	(10.4)	
TDF-TAF/FTC+DTG	177	(49.7)	1041	(53.4)	1218	(52.9)	
DTG-containing cART regimen, n (%)							0.061
2-drug regimen (2-DR)	27	(7.6)	212	(10.9)	239	(10.4)	
3-drug regimen (3-DR)	329	(92.4)	1739	(89.2)	2.65	(89.6)	

(B) From ART-experienced

	Females		Males		Total		
	$N=379$	(19.8%)	$N=1537$	(80.2%)	$N=1916$	(100%)	P value
Italian, n (%)	291	(76.8)	1394	(90.7)	1685	(87.9)	<0.001
Ethnicity, Caucasian, n (%)	316	(83.9)	1434	(93.3)	1750	(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

Table 1. *Continued*

(B) From ART-experienced

	Females		Males		Total		
	N=379	(19.8%)	N=1537	(80.2%)	N=1916	(100%)	P value
Mode of HIV transmission, n (%)							<0.001
Heterosexual	306	(80.7)	436	(28.4)	742	(38.7)	
IVDU	50	(13.2)	151	(9.8)	201	(10.5)	
MSM/WSW	0	(0.0)	877	(57.1)	877	(45.77)	
Other/unknown	23	(6.1)	73	(4.8)	96	(5.0)	
Year HIV diagnosis, median (IQR)	2007	(1997–2012)	2011	(2006–2014)	2011	(2003–2014)	<0.001
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
Smoker, yes, n (%)	132	(34.8)	649	(42.2)	781	(40.8)	0.008
CDC C-stage[a], n (%)	59	(15.6)	207	(13.5)	266	(13.9)	0.290
Nadir CD4, cells/mmc, median (IQR)	255	(135–355)	291	(168–420)	281	(160–403)	<0.001
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
Total cholesterol, median (IQR)	202	(178–232)	190	(164–218)	193	(166–221)	<0.001
HDL cholesterol, median (IQR)	57	(48–68)	46	(38–55)	48	(40–58)	<0.001
Triglycerides, median (IQR)	106	(78–142)	122	(89–176)	119	(86–170)	<0.001
Serum glucose, median (IQR)	86	(78–93)	89	(81–98)	88	(81–97)	<0.001
eGFR[b], mL/min/1.73 m^2, median (IQR)	90.8	(75.7–104.7)	91.9	(77.0–104.4)	91.7	(76.7–104.4)	0.565
eGFR[b] >90 mL/min/1.73 m^2, n (%)	198	(52.2)	823	(53.6)	1021	(53.3)	0.702
BMI, kg/m^2, median (IQR)	22.7	(20.6–25.7)	24.2	(22.2–26.5)	23.9	(21.9–26.5)	<0.001
Diabetes diagnosis, n (%)	15	(4.0)	116	(7.6	131	(6.8)	0.013
CVD diagnosis, n (%)	2	(0.5)	34	(2.2)	36	(1.9)	0.031
NADM diagnosis, n (%)	19	(5.0)	72	(4.7)	91	(4.8)	0.788
CKD diagnosis, n (%)	83	(21.9)	243	(15.8)	326	(17.0)	0.005
ESRD diagnosis, n (%)	8	(2.1)	34	(2.2)	42	(2.2)	0.904
ESLD diagnosis, n (%)	1	(0.3)	7	(0.5)	8	(0.4)	0.604
Antilipidaemics[c], n (%)	48	(12.7)	223	(14.5)	271	(14.14)	0.556
Antihypertensive[c], n (%)	43	(11.4)	221	(13.7)	254	(13.3)	0.221
Framingham score[d], median (IQR)	4.4	(2.4–7.5)	10.3	(5.1–20.4)	8.6	(4.2–17.5)	<0.001
Year cART start, median (IQR)	2017	(2016–2019)	2018	(2016–2020)	2018	(2016–2020)	<0.001
ART class pre-DTG, n (%)							0.242
INSTI	78	(20.6)	344	(22.4)	422	(22.0)	
NNRTI	127	(33.5)	570	(37.1)	697	(36.4)	
PI	151	(39.8)	527	(34.3)	678	(35.4)	
Other	23	(6.1)	96	(6.3)	119	(6.2)	
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-drug regimen (2-DR)	175	(46.2)	827	(53.8)	1002	(52.3)	
3-drug regimen (3-DR)	204	(53.8)	710	(46.2)	914	(47.7)	

Ab, antibody; ABC, abacavir; cART, combined Antiretroviral Therapy; CDC, Centers for Disease Control; CKD, chronic kidney disease; cp, copies; CVD, cardiovascular disease; DTG, dolutegravir; eGFR, estimated glomerular filtration rate; ESLD, end-stage liver disease; ESRD, end-stage renal disease; FTC, emtricitabine; HBsAg, Hepatitis B surface antigen; INSTI, integrase strand inhibitor; IVDU, intravenous drug users; mmc, cubic millimiter; NADM, non-AIDS-defining malignancies; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; WSW, women who have sex with women; 3TC, lamivudine.

[a]According to 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults.

[b]Calculated according to CDK-EPI formula (Chronic Kidney Disease Epidemiology Collaboration).

[c]Intended as domiciliary therapy at the moment of DTG start.

[d]Calculated according to D'Agostino *et al.* General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008; **117**: 743–53.

Ethics

The ICONA Foundation study was approved by the Ethics Committee of each participating institution. All of the individuals enrolled provided a written informed consent at the time of the enrolment.

Results

Characteristics of study population

A total of 4220 PLWH were included in the analyses: of the 8237 ART-naive PLWH starting first ART in the Icona cohort in the same period 2304 (28%) started a dolutegravir-based regimen, while 1916 out of 7938 (24.1%) ART-experienced switching while virologically suppressed to dolutegravir regimens. Women accounted for 15.5% ($n=356$) of PLWH initiating dolutegravir from ART-naive and 19.8% ($n=379$) of the virologically controlled, ART-experienced PLWH switching to a dolutegravir-containing regimen. There were a number of differences among PLWH according to sex, as shown in Table 1 (ART-naïve: Table 1A; and ART-experienced: Table 1B). Regardless of treatment history, women were older, more frequently non-Italian and more frequently HCV coinfected; in the ART-naive group, advanced HIV infection appeared to be more prevalent in women than in men (nadir CD4 counts $<200/mm^3$ in 40.2% versus 30.5% of men; $P<0.001$).

Overall, the number of PLWH starting a dolutegravir-containing 2-DR regimen as first-line ART was low, accounting for only 10.4%; this was particularly true for women, with only 27 (7.6%) of them initiating lamivudine/dolutegravir.

The picture was different among experienced PLWH; more than half (52.3%) of PLWH while on virologically controlled regimens initiated a 2-DR dolutegravir regimen, although again somewhat less frequently in females: 46.2% of females ($n=175$) versus 53.8% of males ($n=710$) ($P=0.039$).

Risk of developing the outcomes by sex in ART-naive

Over a median follow-up of 2.1 (IQR: 0.8–3.8) years (1.6 years, IQR: 0.6–3.7 for women; 2.1 years, IQR: 0.8–3.9 for men) a total of 638 (27.7%) PLWH experienced TF (456 dolutegravir discontinuation for any reason, 114 VF, 36 new AIDS events and 32 deaths). The Kaplan–Meier curves showing the cumulative probabilities of reaching the primary and secondary endpoints in the ART-naive group according to sex are reported in Figure 1. The 4-year cumulative probability of TF was 32.8% (95% CI: 30.5–35.1); in women it was 40.6% (95% CI: 34.8–46.9), and in men it was 31.4% (95% CI: 29.0–34.0) (log-rank $P<0.001$; Figure 1a). In this univariable analysis, the probability of TF was higher for women, even after excluding from the analysis the 17 events of women stopping dolutegravir while they were pregnant or planning to become pregnant when receiving the drug (log-rank $P=0.041$; Figure 1b). The probability of dolutegravir DT was higher for women than men: by 4-year the overall cumulative probability was 7.7% (95% CI: 6.5–9.2); in women it was 11.6% (95% CI: 8.0–16.6), and in men 7.1% (95% CI: 5.8–8.7) (log-rank $P=0.009$; Figure 1c). No difference was found according to sex in the cumulative probability of discontinuing dolutegravir for NPAEs: the Kaplan–Meier estimate at 4 years was 5.3% (95% CI: 2.8–10.0) for women versus 3.4% (95% CI: 2.6–4.6) for men (log-rank $P=0.266$, Figure 1d). Finally, in the ITT analysis 133

VFs occurred; the 4-year cumulative probability of VF was 6.5% (95% CI: 4.1–10.3) for women and 7.3% (95% CI: 6.4–8.8) for men, with no evidence for a difference according to sex (log-rank $P=0.827$; Figure 1e). In the ART-naive group, and after controlling for age and nationality, the risk of TF was confirmed to be significantly higher for women (AHR: 1.26; 95% CI: 1.03–1.55). However, using this same adjusted model but in the sensitivity analysis not counting stops due to pregnancy as events ($n=17$), the difference was largely attenuated and no longer significant (AHR: 1.08; 95% CI: 0.87–1.34).

In contrast, women showed a statistically significant adjusted higher risk of dolutegravir DT (AHR: 1.58; 95% CI: 1.05–2.39) compared with men. Results were similar after using the alternative definition of DT, which also included as causes of dolutegravir discontinuation 'other reasons' and 'patient's decision' (women AHR: 2.07; 95% CI: 1.55–2.77), even after excluding pregnancies as events (women AHR: 1.55; 95% CI: 1.13–2.14). In contrast, there were no statistically significant differences in the risks of NPAEs (women AHR: 1.41; 95% CI: 0.74–2.66) and of VF (women AHR: 0.83; 95% CI: 0.5–1.37) according to sex (Table 2A). In the ART-naive group, there was no evidence for an interaction between sex and number of drugs initiated for the different endpoints (Table 2A). Of note this test is likely to be underpowered due to the low number of women starting a 2-DR regimen.

### Risk of developing the outcome by sex in ART-experienced

Over a median follow-up of 2.3 (IQR: 1.0–4.2) years (2.6 years, IQR: 1.0–4.5, for women; 2.2 years, IQR: 1.1–4.2, for men) a total of 312 (16.3%) PLWH experienced TF (249 dolutegravir discontinuations for any reason, 31 VF, 22 deaths and 10 new AIDS events). The cumulative probabilities of experiencing the various endpoints according to sex (women versus men) are reported in Figure 2. Similar to the ART-naives, experienced women showed a higher probability of TF compared with men in univariable: the 4-year cumulative probability was 20.0% (95% CI: 17.8–22.3) overall; 23.4% (IQR: 18.9–28.9) in women, and 19.1% (IQR: 16.7–21.8) in men (log-rank $P=0.035$; Figure 2a). However, in this group the difference was no longer detected after excluding events of women who were getting pregnant or planning to during ART ($n=7$) (log-rank $P=0.169$; Figure 2b). The probability of dolutegravir DT was only marginally higher for women compared with men: overall 4-year cumulative probability was 8.3% (IQR: 6.9–9.9); in women it was 11.1% (IQR: 7.9–15.5), and in men 7.5% (IQR: 6.0–9.3) (log-rank $P=0.080$; Figure 2c). Also in the ART-experienced group, there was no evidence for a difference in the risk of dolutegravir discontinuation for NPAEs according to sex: 4-year cumulative probability was 5.2% (95% CI: 3.1–8.6) for women and 3.6% (95% CI: 2.6–5.0) for men (log-rank $P=0.243$; Figure 1d). A total of 47 VFs were observed, with no difference in the risk of VF by sex: 4-year cumulative probability 3.9% (95% CI: 2.1–7.1) for women, and 2.8% (95% CI: 1.9–4.0) for men (log-rank $P=0.1378$; Figure 2e).

In the multivariable analysis, after controlling for age and nationality, the risk of TF in women was not significantly higher than in men (AHR: 1.30; 95% CI: 1.01–1.69); and also when excluding pregnant women or those planning a pregnancy (women versus men AHR: 1.19; 95% CI: 0.95–1.16).
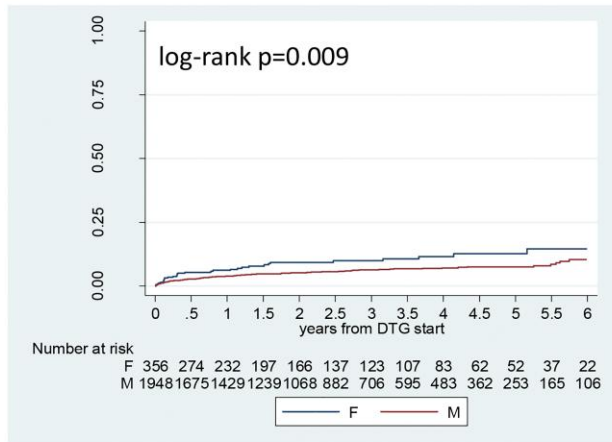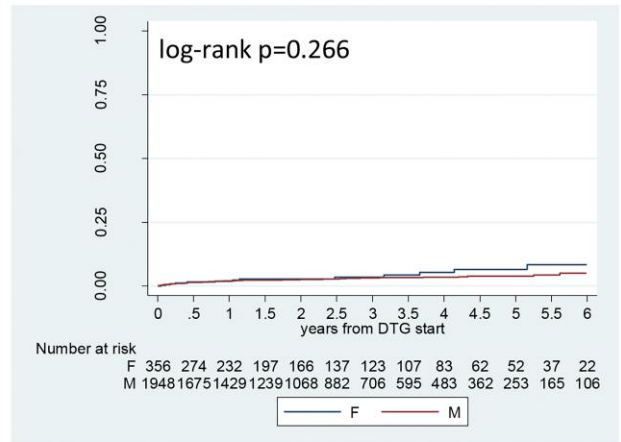
(a) Treatment Failure
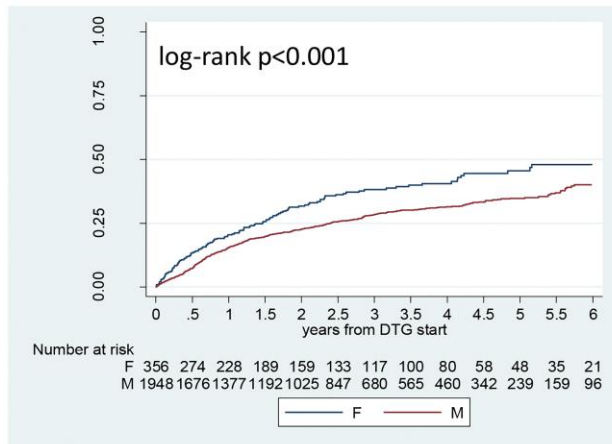
(b) Treatment Failure excluding pregnancies
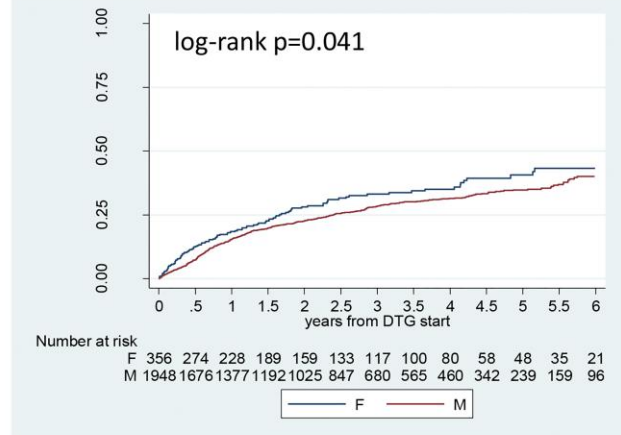
(c) DTG discontinuation for toxicity

(d) DTG discontinuation for NPAEs toxicity
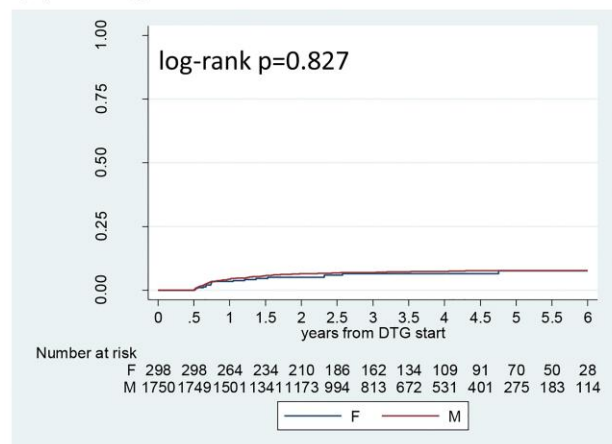

(e) Virological Failure

Figure 1. Kaplan–Meier probability of reaching the endpoints in female and male PLWH initiating dolutegravir-containing regimens from ART-naives.

Of note, the excess risk of DT in women was confirmed also in the ART-experienced group (AHR: 1.54; 95% CI: 1.03–2.31), and results were also similar when we used the alternative definition of DT. We have also evaluated the robustness of this association to potential uncontrolled confounders, and the e-value calculated was 2.45, so only a potential unmeasured confounder associated with both the outcome and the exposure each with a relative hazard of 2.45 could explain away the estimate found

Table 2. Univariable and multivariable analyses of role of sex in different outcomes of PLWH (A) initiating DTG-containing regimens from ART-naïve, and (B) switching to DTG-based regimen while virologically suppressed

(A) ART-naive

	n events/n study participants	HR	95% CI		P	AHR[a]	95% CI		P	P value 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				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				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				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	

(B) ART-experienced virologically suppressed

	n events/n study participants	HR	95% CI		P	AHR[a]	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	

Continued

Table 2. *Continued*

(B) ART-experienced virologically suppressed

	n events/*n* study participants	HR	95% CI		*P*	AHR[a]	95% CI		*P*	*P* value for interaction sex × type regimen
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	8.083	

DTG, dolutegravir; NPS, neuropsychiatric; 2-DR, two-drug regimen; 3-DR, three-drug regimen.
[a]Adjusted for age and nation of birth (Italy versus non-Italy).

for sex for DT, but weaker confounding could not. Similarly, to move the CI to include the null for sex, an unmeasured confounder that was associated with the outcome and the exposure each by a relative hazard of 1.21 could do so, but weaker confounding could not. To put this in perspective, the relative hazard associated with the measured factor showing the strongest association was lower than 2.45 (HR = 2.09 for nationality).

Overall, 6.4% PLWH discontinued for toxicity. When stratifying the data in 3-DR and 2-DR regimens, overall we observed a consistently lower incidence of DT, from 10.2% in 3-DR to 3.1% in a 2-DR regimen. However, whereas in 3-DR recipients the incidence was similar by sex (10.8% in women versus 10.0% in men), in 2-DR regimen recipients the incidence appeared to be higher in women than in men (6.3% versus 2.8%, interaction *P* value = 0.054).

No evidence for difference by sex was seen for the risk of discontinuation due to NPAEs, but in the subset of those receiving a 2-DR regimen although the overall incidence of discontinuation was low (1.5%), the risk of discontinuation due to NPAEs was higher in women than men (AHR: 3.61; 95% CI: 1.24–10.48; interaction *P* value = 0.049). Also, in the ART-experienced group the time to VF did not significantly differ by sex, although there was a substantial difference in terms of the magnitude of the effect (AHR: 1.54; 95% CI: 0.81–2.93). Of note, in the 2-DR regimen setting, despite observing only a total of eight VFs (0.8%), women showed a higher although marginally not statistically different risk of VF than men (AHR: 3.63; 95% CI: 0.84–15.5; interaction *P* value = 0.103) (Table 2).

Reasons for dolutegravir discontinuation in ART-naive and ART-experienced PLWH

A total of 502 (21.8%) of ART-naive PLWH on first-line dolutegravir-containing regimens and 260 (13.6%) ART-experienced, virologically controlled PLWH discontinued dolutegravir. Detailed frequencies of the reasons for dolutegravir discontinuation according to sex, in ART-naive and ART-experienced, are shown in Table 3.

Both in the ART-naive and in the ART-experienced, the most frequent reason for discontinuing dolutegravir among women was toxicity, accounting for 30.5% and 25.4% of discontinuations, followed by 'other reasons' (including pregnancy), which accounted for 28.6% and 28.3% of discontinuations. In men the most frequent reason for dolutegravir discontinuation among previously ART-naive was simplification (42.3%), followed by toxicity (28.0%). In the ART-experienced group, toxicity was the main reason for dolutegravir discontinuation (47.6%) among men.

Of note, weight gain was the primary reason for dolutegravir discontinuation only in three PLWH on first-line ART and in one ART-experienced. Details of causes of discontinuations according to sex, in 2-DR and 3-DR regimen settings, are shown in Supplementary Table S1(A–D).

Pregnancy and planned pregnancy in the cohort

Overall, there were 31 episodes of pregnancy (*n* = 22) or planned pregnancy (*n* = 9) reported by 29 female participants (1 woman underwent 3 pregnancies). Among these, in 15 cases dolutegravir was discontinued because of the pregnancy and in the other 9 it was discontinued because of a planned pregnancy. For the remaining seven episodes (of which three were from the same woman), dolutegravir was not discontinued. No cases of abnormalities were detected in the seven newborns.

Interestingly, before 2021, the year when the recommendation for dolutegravir use during pregnancy was changed in the European HIV Guidelines 11.0,[1] 22 dolutegravir discontinuations for pregnancy occurred over a total of 1572 PYFU, for an incidence rate of 1.39 × 100 PYFU (95% CI: 0.92–2.12); from 2021 two dolutegravir discontinuations for pregnancy were recorded, for an incidence rate ratio of 0.38 × 100 PYFU (95% CI: 0.04–1.53).
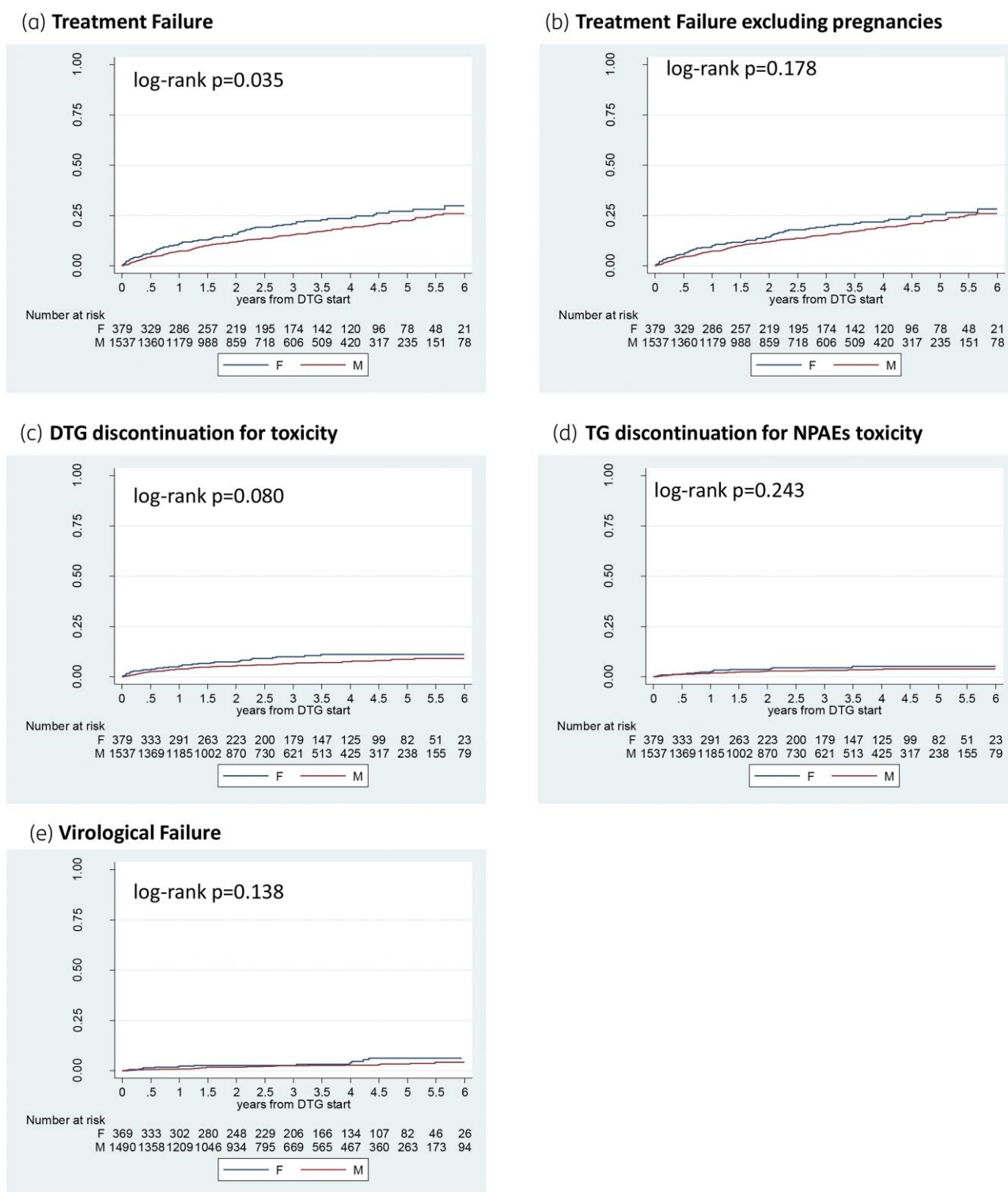
Figure 2. Kaplan–Meier probability of reaching the endpoints in female and male PLWH initiating dolutegravir-containing regimens from ART-experienced while virologically suppressed.

Discussion

In our real-life setting of a cohort of more than 4000 PLWH who started dolutegravir-containing double or triple regimens, over a median of 2 years of exposure to the drug, we showed a difference in the risk of TF by sex, although the higher risk of TF in women was mainly explained by discontinuations due to

Table 3. Reasons for DTG discontinuation according to sex

(A) ART-naive

	Females (n=356)			Males (n=1948)			Total (n=2304)			
	n.e.	%[a]	%[b]	n.e.	%[a]	%[b]	n.e.	%[a]	%[b]	P value
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
Neurological	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	—
Dermatological	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 toxicity	1	0.3	1.0	5	0.3	1.3	6	0.3	1.2	—
Unknown	0	0.0	0.0	2	0.1	0.5	2	0.1	0.4	—
Other	30	8.4	28.6	76	3.9	19.1	106	4.6	21.1	<0.001
RCT	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	—

(B) ART-experienced

	Females (n=379)			Males (n=1537)			Total (n=1916)			
	n.e.	%[a]	%[b]	n.e.	%[a]	%[b]	n.e.	%[a]	%[b]	P value
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
Neurological	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	—
Dermatological	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	—

Continued

Table 3. *Continued*

(B) ART-experienced

	Females (*n*=379)			Males (*n*=1537)			Total (*n*=1916)			
	n.e.	%[a]	%[b]	n.e.	%[a]	%[b]	n.e.	%[a]	%[b]	*P* value
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	

CV, cardiovascular; DTG, dolutegravir; n.e., number of events; NPS, neuropsychiatric; RCT, randomized controlled trial.

[a] Percentages calculated on the total of the study group.

[b] Percentages calculated on the total of dolutegravir discontinuation.

pregnancy. These results are consistent with clinicians following the guidelines and to the ingrained concerns of doctors and PLWH of possible dolutegravir side effects in pregnant women before 2021.[1]

The difference by sex was larger and not explained by pregnancy when we evaluated the alternative endpoint of DT. In this analysis, women showed a 50% higher risk of DT than men. Although the relative difference in risk appears to be remarkable, it is important to note that the probability risk of DT, even after 4 years from starting dolutegravir-based regimens, was low, and below 9%.

Interestingly, a similar difference by sex has been reported for old ART regimens in a previous paper of the ICONA cohort.[18] More recently, we found no evidence for a difference in dolutegravir discontinuation by sex, but with a shorter follow-up and a smaller sample size.[20] Mechanisms underlying this finding have not been specifically examined and remain unclear but might relate to drug metabolism driven by estrogens, lack of weight-adjusted doses, higher level of adherence in women or even differences in CD4 count recovery over follow-up.[21]

Regarding the characteristics of the PLWH included, we showed that the women starting dolutegravir were older and more frequently non-Italian than the men, regardless of their treatment history. Further, in the ART-naive group, women had been diagnosed later, as documented by lower CD4 counts at nadir. These data are consistent with the observation that ART-naive women have a higher viral load set-point and low CD4 count for a given viral load.[22] The results are also consistent with the evolution of HIV epidemics in Italy, with recent infections being predominantly in MSM and in women who acquire HIV by heterosexual contacts from stable partners and are unaware of being infected, thus leading to late HIV diagnoses.[23]

Of note, in our virologically controlled setting of PLWH switching to dolutegravir-based regimens, a remarkable proportion (~50%) switched to 2-DR regimen from triple ART regimens regardless of sex, indicating that simplification to a 2-DR regimen is becoming increasingly popular.

We were also interested in evaluating the response to dolutegravir-based ART regimens by sex, according to the type of regimen started (2-DR versus 3-DR), especially for the toxicity outcomes. Overall, we found some evidence for a statistical interaction between sex and type of regimen started but only in the endpoints driven by general and NPAEs specific for the analyses with endpoint DT or by NPAE toxicity in ART-experienced group. The overall risk of stopping a 2-DR regimen due to toxicities was low, but higher in women than in men.

The same difference was observed in case of dolutegravir discontinuations due to NPAEs, a finding previously shown by others, although with conflicting data.[11,12] Some authors have suggested that this finding might depend on different higher dolutegravir concentrations in the CNS in women, reflecting differences in pharmacokinetics (PK) among women and men resulting in lower tolerability of the drug in women than men.[12]

Our study has several limitations. First, it is observational, thus we cannot completely exclude the possibility of unmeasured confounding being present. However, we calculated the e-value, which indicated that our results are fairly robust against sources of potential unmeasured confounding. Further, the DT endpoint is potentially subjective as it is based on patients' and clinicians' reporting. Nevertheless, results were similar when we used an alternative definition of toxicity including as events also discontinuations that were reported by the treating physicians as 'other'.

One strength of our analysis is the length of follow-up, which was considerably longer than those of all previous studies, so that we could give estimates of the risk of endpoints up to 4 years.

To our knowledge, this is the first study analysing differences of response to dolutegravir-containing regimens by biological sex in a large population of PLWH, approximately 20% of whom were women, and followed-up for a median of 2 years. On the basis of our results, we conclude that dolutegravir-containing regimens are as potent and safe in women as in men, both when used as first-line and as switch therapy.

One key finding is the fact that our analysis seems to confute the concerns regarding a higher risk of TF in women because this excess risk appears to be associated mainly with discontinuations of dolutegravir when used in pregnancy; this event is less frequent in most recent calendar years due to new cumulative evidence and treatment guidelines.[14] Further, we also conclude that in ART-experienced PLWH VF was an infrequent event in 2-DR regimens, thus confirming data already observed in clinical trials.[6]

Nevertheless, women appeared to carry a higher risk of DT. Reassuringly, the absolute risk of DT, even after 4 years of follow-up, remains low and below 9% of those treated with this drug.

Supplementary data
Figure S1 and Table S1 are available as Supplementary data at *JAC* Online.

References
1 European AIDS Clinical Society. EACS Guidelines version 11.0; October 2021. https://www.eacsociety.org/media/final2021eacsguidelinesv11.0_oct2021.pdf

2 Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf

3 Walmsley SL, Antela A, Clumeck N *et al.* Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med* 2013; **369**: 1807–18. https://doi.org/10.1056/NEJMoa1215541

4 Molina JM, Clotet B, van Lunzen J *et al.* Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study. *Lancet HIV* 2015; **2**: 127–36. https://doi.org/10.1016/S2352-3018(15)00027-2

5 van Wyk J, Orkin C, Rubio R *et al.* Durable suppression and low rate of virologic failure 3 years after switch to dolutegravir + rilpivirine 2-drug regimen: 148-week results from the SWORD-1 and SWORD-2 randomized clinical trials. *J Acquir Immune Defic Syndr* 2020; **85**: 325–30. https://doi.org/10.1097/QAI.0000000000002449

6 Osiyemi O, de Wit S, Ajana F *et al.* Efficacy and safety of switching to dolutegravir/lamivudine (DTG/3TC) versus continuing a tenofovir alafenamide-based 3- or 4-drug regimen for maintenance of virologic

suppression in adults living with HIV-1: results through week 144 from the phase 3, non-inferiority TANGO randomized trial. *Clin Infect Dis* 2022; **75**: 975–86.

7 Taramasso L, de Vito A, Ricci ED *et al.* Durability of dolutegravir-based regimens: a 5-year prospective observational study. *AIDS Patient Care STDs* 2021; **35**: 342–53. https://doi.org/10.1089/apc.2021.0089

8 Greenberg L, Ryom L, Wandeler G *et al.* Uptake and discontinuation of integrase inhibitors (INSTIs) in a large cohort setting. *J Acquir Immune Defic Syndr* 2020; **83**: 240–50. https://doi.org/10.1097/QAI.0000000000002250

9 Elzi L, Erb S, Furrer H *et al.* Adverse events of raltegravir and dolutegravir. *AIDS* 2017; **31**: 1853–8. https://doi.org/10.1097/QAD.0000000000001590

10 Borghetti A, Baldin G, Capetti A *et al.* Efficacy and tolerability of dolutegravir and two nucleos(t)ide reverse transcriptase inhibitors in HIV-1-positive, virologically suppressed patients. *AIDS* 2017; **31**: 457–9. https://doi.org/10.1097/QAD.0000000000001357

11 Llibre JM, Montoliu A, Miró JM *et al.* Discontinuation of dolutegravir, elvitegravir/cobicistat and raltegravir because of toxicity in a prospective cohort. *HIV Med* 2019; **20**: 237–47. https://doi.org/10.1111/hiv.12710

12 Hoffmann C, Welz T, Sabranski M *et al.* Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. *HIV Med* 2017; **18**: 56–63. https://doi.org/10.1111/hiv.12468

13 Zash R, Holmes L, Diseko M *et al.* Neural-tube defects and antiretroviral treatment regimens in Botswana. *N Engl J Med* 2019; **381**: 827–40. https://doi.org/10.1056/NEJMoa1905230

14 European AIDS Clinical Society. EACS Guidelines version 9.1; October 2018. https://www.eacsociety.org/media/guidelines_8_0-english_web.pdf

15 Lockman S, Brummel SS, Ziemba L *et al.* Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet* 2021; **397**: 1276–92.

16 Abrams E, Myers L. Lessons from dolutegravir and neural tube defects. *Lancet HIV* 2021; **8**: e3–4. https://doi.org/10.1016/S2352-3018(20)30280-0

17 Committee for Medicinal Products for Human Use (CHMP). Juluca. International non-proprietary name: dolutegravir/rilpivirine. Procedure No. EMEA/H/C/004427/0000 2018. https://www.ema.europa.eu/en/medicines/human/EPAR/juluca#authorisation-details-section

18 D'Arminio Monforte A, Cozzi-Lepri A, Rezza G *et al.* Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naïve patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naïve Patients. *AIDS* 2000; **14**: 499–507.

19 VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med* 2017; **167**: 268–74. https://doi.org/10.7326/M16-2607

20 Mondi A, Cozzi-Lepri A, Tavelli A *et al.* Effectiveness of dolutegravir-based regimens as either first-line or switch antiretroviral therapy: data from the Icona cohort. *J Int AIDS Soc* 2019; **22**: e25227. https://doi.org/10.1002/jia2.25227

21 Murri R, Cozzi Lepri A, Phillips AN *et al.* Access to antiretroviral treatment, incidence of sustained therapy interruptions, and risk of clinical events according to sex: evidence from the I.Co.N.A. Study. *J Acquir Immune Defic Syndr* 2003; **34**: 184–90. https://doi.org/10.1097/00126334-200310010-00008

22 Rezza G, Cozzi Lepri A, d'Arminio Monforte A, *et al.* Plasma viral load concentrations in women and men from different exposure categories and with known duration of HIV infection. I.CO.N.A. Study Group. *J Acquir Immune Defic Syndr* 2000; **25**: 56–62.

23 Notiziario Istituto Superiore di Sanità, Vol. 33, No 11; 2020. https://www.iss.it/documents/20126/0/COA+2020+%284%29.pdf/60413180-3338-4696-827f-49205f22f277?t=1608303402218