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

Short running title: Dolutegravir regimens outcome by sex

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Synopsis

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: PLWH from ICONA were included if started dolutegravir in 2- or 3-Drug Regimen (DR) from ART-naïve or virologically-controlled ART-experienced. Primary end-point: time-to-treatment failure (virological/clinical failure or dolutegravir discontinuation). Secondary end-points: time-to-dolutegravir discontinuation due to toxicity and to neuropsychiatric adverse events (NPAEs); time-to-virological failure. Univariable and multivariable (Cox regression) analyses focused on differences in outcomes by sex.

Results: 2,304 PLWH (15% women) initiated dolutegravir-based therapy from ART-naïve and 1,916 (19.8% women) while experienced. After a median follow-up of 2.2 (IQR: 0.9-3.9) years in ART-naïve and 2.4 (IQR: 1.1-4.3) in experienced, the 4-year risk of treatment failure was 33% (95%CI 30.5-35.1) and 20% (95%CI 17.8-22.3). In the multivariable analyses, in ART-naïve – the risk of treatment failure was higher for women, but not different after excluding women discontinuing dolutegravir for pregnancy concerns. Moreover, we observed a higher risk of discontinuation for toxicity in women (ART-naives: 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-naïve and 8.3% (95% CI 6.9-9.9) in experienced. No evidence for a difference in time to NPAE or virological failure according to sex was observed.

Conclusions: In our large 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 stand transfer inhibitor (INSTI), has been approved for treatment of HIV-1 infection in both antiretroviral (ART)-naïve 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 (ABC/3TC) or tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) or tenofovir alafenamide/emtricitabine (TAF/FTC). Up to now, two-drug (2-DR) dolutegravir -based regimens are also recommended as starting therapy in ART-naïve or as switch strategies for virologically suppressed PLWH, in association with either lamivudine (3TC) or rilpivirine (RPV). [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 ~~to~~ in the most severe cases, anxiety, depression, identified as neuropsychiatric adverse events (NPAEs). [3-6] A higher risk of discontinuation of dolutegravir-based regimen for all reasons, both in ART-naïve and -experienced has also been observed in women compared to men.[7-10] This difference was confirmed also 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 from mothers who received dolutegravir during pregnancy was initially shown in the Tsepamo ~~-~~study from Botswana[13]~~.~~ These findings have led international guidelines to initially (approximately up to December 2021 in Europe) warns 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 aim to extend previous analyses and compare the risk of treatment failure to 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 triple. 3-DR, regimens).

Patients and methods

Criteria for inclusion in the study

PLWH enrolled in the ICONA cohort were included in the analyses if fulfilling the following criteria: i) they newly started a dolutegravir-including 2-DR or 3-DR regimen from ART-naïve or from ART-

experienced while on virologically controlled (HIV-RNA <50 copies/ml) ART regimens in January 1, 2014- March 31, 2022 and ii) had at least one clinical follow up visit. The data-base was frozen for analysis on July 31, 2022. We also insisted on participants initiating specific regimens: 3-DR regimens had to include exactly dolutegravir plus ABC+3TC or FTC+TAF or FTC+TDF; similarly for 2-DR they had to include exactly 3TC or rilpivirine (RPV), the latter only in experienced PLWH as by EMA registration.[17]

The ICONA cohort is a nation-wide cohort enrolling PLWH naïve from ART, prospectively followed in 53 Italian Infectious Diseases centers. 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 both in the context of 3-DR and 2-DR regimens.

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

We also analyzed as secondary endpoints: a) time to dolutegravir discontinuation due to toxicity (DT); b) time to discontinuation of dolutegravir due to NPAEs; c) time to VF (same definition 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 Clinical Record Forms (CRFs): failure (virological, immunological, clinical), simplification, patient decision, toxicity (gastrointestinal intolerance, NPAEs, renal, metabolic, dermatologic, allergies), other (pregnancy, planned pregnancy, inclusion in trial, unspecified, other). For the secondary endpoint a) we also used the alternative definition of DT which counted participants discontinuing for other reasons as events. This under the assumption that some stops due to toxicity could be classified by clinicians as ‘other’ or ‘patient’s decision’. Again, we also performed a sensitivity analysis after excluding stops due to pregnancy in women.

Sex at birth was the exposure of interest and analyses were stratified according to whether participants had started a 2-DR vs 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 have been conducted separately in ART-naïve and ART-experienced virologically suppressed groups. Differences between men and women in baseline characteristics were assessed by means of chi-square test for categorical variables or Wilcoxon rank sum test for continuous factors. The numbers and the outcomes of pregnancies during the exposure of 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 intention-to-treat approach was used for the virological failure 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 NPS toxicity, the follow-up of PLWH discontinuing for reasons different from that of interest was truncated at the date of last clinical follow-up or the date of discontinuation of dolutegravir for the alternative reason whichever occurred first, assuming non-informative censoring.

The effect of sex on the time to each endpoint is shown by means of hazard ratio (HR) with 95% confidence intervals (CI) from fitting separate standard Cox regression models conditioned on covariates for each of the defined endpoints. Sex is un-confounded by definition but in order to increase the precision of the estimates we decided to fit also models adjusted for two strong predictors of outcome: age and nation of birth (Italian vs non-Italian native) (Supplemental Figure 1). In order to further assess the robustness of the results against potential unmeasured confounding bias, the e-value was calculated and compared to the magnitude of the relative hazard seen for the predictor showing the strongest association with the outcome (i.e. nationality).[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 (2DR vs 3DR). This is in light of the known difference in tolerability and genetic barriers between these regimens. The interaction between sex and type of regimen started has been 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 2DR vs. 3DR. All statistical analyses were performed using Stata (version 14.0). All p-values presented are 2-sided and a p-value <0.05 indicated conventional statistical significance.

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 4,220 PLWH were included in the analyses: 2,304 out of 8,237 (28%) ART-naïve and 1,916 out of 7,938 (24.1%) ART-experienced starting dolutegravir regimens. Women accounted for 15.5% (n=356*)* of PLWH initiating dolutegravir from ART-naïve 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 -1-A, and ART-experienced -1-B). Regardless of treatment history, women were older, more frequently non-Italian, more frequently Hepatitis C Virus (HCV) coinfected; in the ART-naïve group, advanced HIV infection appeared to be more prevalent in women than in men (nadir CD4 counts <200/cmm in 40.2% vs 30.5% of men; p<0.001).

Overall, the number of PLWH starting dolutegravir-containing 2-DR regimen as first-line ART was low, accounting for only of 10.4%; this was particularly true for women, with only 27 (7.6%) of them initiating 3TC/DTG (the only dual ART licensed for use in first-line).

The picture was different among experienced PLWH: more than half (52.3%) of PLWH starting dolutegravir 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 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 specified primary and secondary end-points in ART-naïve group according to sex are reported in Figure 1. The 4-year cumulative probability of TF was of 32.8% (95%CI 30.5-35.1); in women: 40.6% (95%CI 34.8-46.9); in men: 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 discontinuation due to toxicity was higher for women compared to men: by 4 year 7.7% (95%CI 6.5-9.2); in women: 11.6% (95%CI 8.0-16.6), in men:

7.1% (95%CI 5.8-8.7) (log-rank p=0.009, Figure1C), while no evidence for a difference was found according to sex in the cumulative probability of discontinuing dolutegravir for NPAEs: Kaplan Meier estimate at 4-years was 5.3% (95%CI 2.8-10.0) for women vs. 3.4% (95%CI 2.6-4.6) for men (log-rank p=0.266, Figure 1D). Finally, in the ITT analysis 133 virological failures occurred, the 4-year cumulative probability of virological failure was 6.5% (95%CI 4.1-10.3) for women and 7.3% (95%CI 6.4-8.8) for men, the data carried no evidence for a difference according to sex (log-rank p=0.827, Figure 1E). In the ART-naïve 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 discontinuation due to toxicity: AHR 1.58 (95%CI: 1.05-2.39) as compared to men. Results were similar after using the alternative definition of DT which included as cause of dolutegravir discontinuation also 'other reasons' and 'patients' decision', as stop due to toxicity (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 events (women AHR: 1.41, 95%CI: 0.74-2.66) and of virological failure (women AHR: 0.83, 95%CI: 0.5-1.37) according to sex (Table 2A). In the ART-naïve 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 2DR 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 discontinuation for any reason, 31 virological failure, 22 death and 10 new AIDS events). The cumulative probabilities of experiencing the various end-points according to sex (women versus men) are reported in Figure 2. Similar to the analysis conducted among the ART-naive, experienced women showed a higher probability of TF as compared to men in the univariable analysis: the 4-year cumulative probability were 20.0% (95%CI 17.8-22.3) overall; 23.4% (IQR: 18.9-28.9) in women; 19.1% (IQR: 16.7-21.8) in men (log-rank p=0.035, Figure 2A). However, in this group, even before controlling for other factors, 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 discontinuation due to toxicity was only marginally higher for women

compared to men: by 4-year overall 8.3% (IQR: 6.9-9.9); in women: 11.1% (IQR: 7.9-15.5), in men: 7.5% (IQR: 6.0-9.3) (log-rank p=0.080, Figure 2C). Also in the ART-experienced virologically suppressed group, there was no evidence for a difference in the risk of dolutegravir discontinuation for NPAEs according to sex: 4-years 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 virological failure 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, 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, nationality, the risk of TF in women was not significantly higher than men (AHR 1.30, 95%CI: 1.01-1.69) also excluding pregnant women or those planning a pregnancy (women vs men AHR: 1.19, 95%CI: 0.95-1.16).

Of note, the excess of risk of discontinuation for toxicity 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 stopping for toxicity. In this analysis, an unmeasured confounder that was associated with both the outcome and the exposure each with a relative hazard of 2.45 could explain away the estimate for sex, but weaker confounding could not. Similarly, to move the confidence interval 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 prospective, the relative hazard associated with the measured factor showing the strongest association was lower than 2.45 (RH=2.09 for nationality).

Overall, 6.4% PLWH discontinued for toxicity. When stratifying the data in 3-DR and 2-DR, overall, we observed a consistently lower incidence of DT, from 10.2% in 3-DR to 3.1% in 2-DR. However, while in 3D recipients the incidence was similar by sex (10.8% in women vs 10.0% in men), in 3DR recipients the incidence appeared to be higher in women than in men (6.3% vs. 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 2-DR regimen although the overall incidence of discontinuation was low (1.*5%),* risk of discontinuation by NPAEs was higher in women versus 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 with a substantial difference in terms of the magnitude of the effect (AHR 1.54, 95%CI 0.81-2.93). To note, in the 2-DR setting, despite observing only a total of 8 virological failures (0.8%), women showed a higher although 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 of dolutegravir discontinuation in ART-naïve and ART-experienced PLWH

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

Both in the ART-naïve and in the ART-experienced setting, 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 of 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 of dolutegravir discontinuation (47.6%) among men. Of note, weight gain was the main reason for dolutegravir discontinuation only in 3 PLWH on first-line ART and in one ART experienced. Details on cause of discontinuations according to sex, in 2-DR and 3-DR settings are shown in Supplemental Tables S1A-S1B-S1C-S1D.

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 (one women underwent 3 pregnancies). Among these, in 15 cases dolutegravir was discontinued because of the pregnancy and in other 9 it was discontinued because of a planned pregnancy; all these were reported by the treating physician as 'other reasons' for discontinuing DTG. For the remaining 7 episodes (of which 3 from the same woman), dolutegravir was not discontinued. No cases of abnormalities were detected in the 7 newborns from dolutegravir taking pregnant women. Interestingly, before 2021, year of change on recommendation of dolutegravir use during pregnancy in the European HIV Guidelines 11.0[1] 22 dolutegravir discontinuation for pregnancy occurred over a total of 1,572 PYFU for an Incidence Rate of 1.39 x 100 PYFU (95%CI 0.92-2.12); from 2021 two dolutegravir discontinuation for pregnancy were recorded, for a Incidence Rate Ratio of 0.38 X 100 PYFU (95%CI 0.04-1.53).

Discussion

In our real-life setting of a cohort of more than 4,000 PLWH who started dolutegravir-containing double or triple regimens, over a median of 2 years exposure to the drug, we showed a higher risk of treatment failure in women which however was mainly explained by discontinuations due to pregnancy These results are consistent with clinicians following the guidelines and to doctors' and PLWH' ingrained concerns of possible dolutegravir side effects in pregnant women. Indeed, the large majority of our participants started dolutegravir before 2021, when European HIV treatment

guidelines did not recommend use of dolutegravir in pregnant women or in those planning pregnancy.[1]

The difference by sex was larger and unaccounted by pregnancy when we evaluated the alternative endpoint of discontinuing dolutegravir because of toxicity. In this analysis, even after controlling for known strong predictors of outcome, both in ART-naïve and experienced participants, women showed a 50% higher risk of dolutegravir discontinuation due to toxicity versus men. Although the relative difference in risk appears to be remarkable, it is important to note that the risk of discontinuation for toxicity even after 4 years from starting dolutegravir-based regimens was low, ranging between 7.7% in ART-naïve and 8.3% in ART-experienced.

Interestingly, a similar difference by sex has been reported for old ART regimens in the previous analyses of the ICONA cohort.[18] In a previous analysis we found no evidence for a difference in dolutegravir discontinuation by sex but the median follow-up was of only 11 months, and the sample size was smaller.[20] Mechanisms underlying this finding remain unclear but might relate to drugs 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 women starting dolutegravir were older and more frequently non-Italian than men, regardless of their treatment history. Further, in the ART-naïve group, women had been diagnosed later, as documented by lower CD4 counts at nadir. These data are expected and 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 men sex with men (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, an approximately equal and remarkable proportion of our population (~50%) switched to 2-DR from triple ART regimens regardless of sex, indicating that simplification to 2 drugs regimen is becoming increasingly popular.

Our data also show that treatment failure was mostly caused by dolutegravir discontinuation rather than virological or clinical failure. Of interest however, there were a total of 54 deaths occurring mainly in previously ART-naive PLWH.

We were also interested in evaluating the response to dolutegravir-based ART regimens by sex, according to the type of regimen started (2-DR vs 3-DR), especially for the toxicity outcomes. This was only possible in the setting of ART-experienced, due to low number of PLWH initiating 2-DR regimen from naïve. Overall, we found some evidence for a statistical interaction between sex and

type of regimen started but only for the analyses with endpoint discontinuation by toxicity or by NPAEs toxicity. The overall risk of stopping a 2-DR regimen due to toxicities was low, but, contrary to what seen for the 3DR regimens, we observed that this appeared to be higher in women than in men.

The same difference was observed in case of dolutegravir discontinuations due to NPAEs, a finding that has been also previously shown by others, although with conflicting data.[11,12] In addition, the low incidence of discontinuation in men receiving 2DR regimens has also been previously reported.[6,12] Some Authors have suggested that this finding might depend on higher dolutegravir concentration in CNS in women, resulting in lower tolerability of the drug for women vs. men.[12]

Our study has several limitations: first, it is observational, thus, although sex is given at birth 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 discontinuation due to toxicity end-point 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 in our cohort which was considerably longer than those of all previous studies so that we could give precise estimates of the risk of our endpoints up to 4 years after starting the dolutegravir-based regimen.

In conclusion, to our knowledge, this is the first study analyzing differences of response to dolutegravir-containing regimens by biological sex in a large and heterogenous population of PLWH, approximately 20% of whom being women, and followed-up for a median of 2 years.

One key finding is the fact that our analysis seems to confute the concerns regarding a higher risk of treatment failure in women as this excess of 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 cumulated evidence and treatment guidelines.[14] Further, we also conclude that in our setting of ART-experienced PLWH virological failure was an infrequent event in 2-DR regimens, thus confirming the virological potency of these combinations already observed in clinical trials.[6] Nevertheless, women appeared to carry a higher risk of stopping dolutegravir for toxicity. Reassuringly, despite the marked difference in terms of relative risks, the absolute risk of stopping dolutegravir for toxicity even after 4 years of follow-up remains low and below 9% of the treated with this drug.

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ADM served as consultant or participated in advisory boards sponsored by Gilead Sciences, ViiV Healthcare, Janssen-Cilag, GSK, Merck, Sharp & Dohme and received research grants for his institution from Gilead Sciences. AT, MS and ACL have nothing to declare. AM received speakers' honoraria from Gilead Sciences and ViiV Healthcare and participated in advisory boards sponsored by ViiV Healthcare.SR reports honoraria for presentations and scientific advice for Merck, Sharp & Dohme, Theratechnologies, GSK, Janssen Cilag, ViiV Healthcare, and Gilead Sciences and research grants for his institution from Janssen Cilag, ViiV Healthcare, and Gilead Sciences. SA repported consultancy fee Gilead; Pfizer Congress participation. MP received honoraria for presentations and advisory boards from AbbVie, Bristol Myers Squibb, Boehringen-Ingelheim, Janssen Cilag, Merck Sharp & Dohme, Gilead Sciences, Roche, and received research grants from Merck Sharp & Dohme and Gilead Sciences. BMC reports honoraria for presentations and scientific advice from Gilead Sciences, Bristol Myers Squibb, AbbVie, ViiV Healthcare, Mylan and Merck Sharp & Dohme and research grants for his institution from Gilead Sciences, ViiV and MSD. LT served as consultant or participated in advisory boards sponsored by Gilead Sciences, ViiV Healthcare, Janssen-Cilag. AS received speakers' honoraria or participated in advisory boards sponsored by Gilead Sciences, ViiV Healthcare, Merck Sharp & Dohme and Janssen Ciilag. AA reports honoraria for presentations and scientific advice from Astra-Zeneca, Gilead Sciences, Glaxo Smith Kline, Janssen Cilag, Merck Sharp & Dohme, Roche, Thera Technologies, and ViiV healthcare.

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514 **Table 1. Characteristics of PLWH initiating a DTG-containing regimens according to sex**

a– from ART-naïve

	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
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[†], 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[‡], 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
BMI, Kg/m^2, median (IQR)	21.6	19.5-24.9	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
Antilipidemic[s], n(%)	9	2.5	24	1.2	33	1.4	0.058
Antihypertensive[§], n(%)	17	4.8	68	3.5	85	3.7	0.237
Framinghham Score[¶], median (IQR)	2.6	1.4-5.2	4.4	2-10.6	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 drugs regimen (2DR)	27	7.6	212	10.9	239	10.4	
3 drugs regimen (3DR)	329	92.4	1739	89.2	2.65	89.6	

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b– from 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
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[†], 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[‡], ml/min/1.73m^2, median (IQR)	90.8	75.7-104.7	91.9	77.0-104.4	91.7	76.7-104.4	0.565
eGFR[‡] > 90 ml/min/1.73m^2, n (%)	198	52.2	823	53.6	1,021	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
Antilipidemics[§], n(%)	48	12.7	223	14.5	271	14.14	0.556
Antihypertensive[§], n(%)	43	11.4	221	13.7	254	13.3	0.221
Framingham Score[¶], 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 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

ART = antiretroviral therapy; IQR = interquartile range; IVDU = intravenous drug users; MSM/WSW = men who have sex with men/women who have sex with women; LDL = low-density lipoprotein; HDL = high-density lipoprotein; eGFR = estimated glomerular filtration rate; BMI = body mass index; CVD = cardiovascular disease; NADM = non AIDS-defining malignances; CKD = chronic kidney disease; ESRD = end-stage renal disease; ESLD = end-stage liver disease; DTG = dolutegravir; INSTI = integrase-strand inhibitor; NNRTI = non-nucleotidic reverse trascriptase inhibitor; PI = protease inhibitor; 3TC = lamivudine; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate; TAF = tenofovir alafenamide fumarate; FTC = emtricitabine; ABC = abacavir.

†: according to 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among adolescents and Adults;
‡: calculated according to CDK-EPI formula;
§: intended as domiciliary therapy at the moment of DTG start;
¶: calculated according to Ralph B D'Agostino et al., General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008 February 12, 117 (6): 743-53

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

(A) ART-NAIVE

	N events/N study participants (%)	HR	95%CI		p	AHR§	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								.
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	

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)

(B) ART-EXPERIENCED VIROLOGICALLY SUPPRESSED

	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	
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)

525 **Table 3. Reasons of DTG discontinuation according to sex**
526

A - ART naïve type III p-value <0.001	**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 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 type III p-value = 0.003	**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**	

† = percentages calculated on the total of the study group;
‡ = percentages calculated on the total of dolutegravir discontinuation;
n.e.= number of events; NPS=Neuro-psychiatric; CV=cardiovascular; RCT=Randomized Clinical Trial

Figure 1. Kaplan Meier probability of reaching the end points in females and males PLWH initiating DTG-containing regimens from ART naives

Figure 2- Kaplan Meier probability of reaching the end points in females and males PLWH initiating DTG-containing regimens from ART experienced while virologically suppressed

Additional file

Supplementary table 1- Reasons of DTG discontinuation according to sex. Description of naïve and experienced study participants taking 3-DR or 2-DR**.**

Supplementary Figure 1 – Direcy Acyclic Graph (DAG) showing the key assumptions regarding the underlying causal link between measured factors**.**