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Effectiveness of dolutegravir-based vs boosted darunavir-based first-line 3-drug regimens in people with HIV with advanced disease: A trial emulation ☆

Roberta Gagliardini[1,*], Andrea Giacomelli[2], Cristina Mussini[3], Stephen R. Cole[4], Jessie K. Edwards[4], Carmela Pinnetti[1], Alessandro Raimondi[5], Spinello Antinori[2], Silvia Nozza[6], Valentina Mazzotta[1], Giulia Carla Marchetti[7], Sergio Lo Caputo[8], Alessandro Tavelli[9,10], Antonella d'Arminio Monforte[9], Andrea Antinori[1], Alessandro Cozzi-Lepri[11], On Behalf of Icona Foundation Study Group

[1] *National Institute for Infectious Diseases Lazzaro Spallanzani, IRCCS, Roma, Italy*
[2] *III Infectious Diseases Unit, ASST Fatebenefratelli-Sacco, DIBIC Luigi Sacco, University of Milan, Milan, Italy*
[3] *Department of Surgical, Medical, Dental and Morphological Sciences, Department of Infectious Diseases, University of Modena, Azienda Ospedaliero-Universitaria Policlinico of Modena, Modena, Italy*
[4] *Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, USA*
[5] *Department of Infectious Diseases, ASST Grande Ospedale Metropolitano Niguarda, School of Medicine and Surgery, Milan, Italy*
[6] *Infectious Diseases Unit, IRCCS San Raffaele Scientific Institute, Vita Salute San Raffaele University, Milan, Italy*
[7] *Clinic of Infectious Diseases, Department of Health Sciences, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy*
[8] *Department of Clinical and Surgical Sciences, Clinic of Infectious Diseases, University of Foggia, Foggia, Italy*
[9] *ICONA Foundation, Milan, Italy*
[10] *Department of Public Health, Experimental and Forensic Medicine, National PhD Program in One Health Approaches to Infectious Diseases and Life Science Research, University of Pavia, Pavia, Italy*
[11] *Centre for Clinical Research, Epidemiology, Modelling and Evaluation, Institute for Global Health, London, UK*

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ABSTRACT

Background: No randomized comparisons exist between dolutegravir (DTG) and boosted-darunavir (DRV/b) for people initiating treatment with advanced HIV.
Methods: Antiretroviral therapy (ART)-naïve people with HIV (PWH) with CD4 < 200 cells/mm^3 or AIDS who started a first-line three-drug regimen with DTG or DRV/b were included. The primary outcome was a composite endpoint of newly diagnosed AIDS, serious non-AIDS events (SNAE), death, virological failure (VF), or discontinuation of the anchor drug due to failure or toxicity. A marginal structural Cox regression model was used to estimate the effect of starting DTG vs DRV/b-based regimens.
Results: A total of 1323 advanced ART-naïve PWH were included, 895 starting DTG and 428 DRV/b. The unweighted risks of the composite endpoint by 48 months were 21.1% (95% CI: 18.1; 24.1%) for DTG vs 37.9% (95% CI: 32.7; 43.2%) for DRV/b ($P < 0.001$). First-line treatment with DTG showed a lower risk of experiencing the composite endpoint than DRV/b (wHR of DTG vs DRV/b 0.47, 95% CI: 0.35; 0.64, $P < 0.001$).
Conclusion: Under the stated assumptions, this analysis indicates that in ART-naïve PWH with advanced disease, ART initiation with DTG vs DRV/b-based regimens leads to a 50% reduction in the risk of AIDS/SNAE/death/VF/discontinuation. This observed difference is partly explained by discontinuation of the anchor drug.
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☆ Preliminary results were presented by Dr. Antinori A. et al. "Emulation of an RCT of Dolutegravir vs boosted-Darunavir in advanced ART-naïve" at Conference on Retrovirus and Opportunistic Infections (CROI), March 8-11, 2020, and at Glasgow HIV conference, November 2024.

* Corresponding author: Roberta Gagliardini, Clinical Department of Infectious Diseases and Research, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Via Portuense 292, 00149 Rome, Italy.
E-mail address: roberta.gagliardini@inmi.it (R. Gagliardini).

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Introduction

The efficacy of antiretroviral therapy (ART) has consistently improved over the years. This is mainly due to newer drugs with greater antiviral potency and enhanced tolerability, resulting in higher rates of viral suppression and improved ART adherence.

Second-generation integrase inhibitors (INSTIs) currently represent the most highly recommended option for first-line ART, according to the DHHS and EACS HIV Guidelines [1,2]. Three-drug regimens with boosted protease inhibitors (PI) (with darunavir, DRV, being the preferred PI) are recommended as initial regimens in specific clinical situations, according to the DHHS Guidelines and as alternative regimens in the EACS Guidelines [1,2].

Moreover, current guidelines recommend a rapid initiation of ART for all people with HIV (PWH), irrespective of their disease stage, with few exceptions [1,2].

Nevertheless, evidence to guide the choice of antiretroviral regimens for treating advanced HIV disease remains lacking. Indeed, PWH who present with advanced disease at HIV diagnosis (defined as CD4 cell count below 200 cells/mm^3 or with an AIDS-defining condition) are typically underrepresented or excluded from randomized controlled trials (RCTs) [3–6].

In the Flamingo study, dolutegravir (DTG)-based three-drug regimens were shown to be superior to darunavir-based three-drug regimens, but only 10% of enrolled PWH had CD4 $<$ 200 cells/mm^3 and 3% had AIDS at diagnosis, such that a post-hoc analysis in participants with advanced disease could not be performed [4].

Moreover, there are two RCTs performed mainly in low-income settings that included about one-third of PWH with CD4 below 200 cells/mm^3, but they compared DTG with efavirenz and darunavir with lopinavir, respectively [7,8].

Thus, the superiority of second-generation INSTIs-based to boosted-PI regimens in the specific target population of people with advanced HIV disease has never been demonstrated in a direct randomized comparison. An independent RCT comparing bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) to darunavir/cobicistat/emtricitabine/tenofovir alafenamide (DRV/c/FTC/TAF) in people with advanced HIV disease is currently ongoing [9].

In observational data, the proportion of PWH who present with advanced HIV infection or with late presentation (defined as CD4 cell count below 350 cells/mm^3 or with an AIDS-defining condition) remains high across Europe [10].

For example, 64% of PHW diagnosed in 2009-2022 in Italy were late presenters, and 27% had AIDS at presentation to care [11]. Late or advanced HIV diagnosis is an important public health concern as it is associated with a higher risk of virological failure (VF), poor immunological recovery, disease progression, and death [11–13].

Furthermore, observational studies provided conflicting results. Some studies conducted in Europe comparing INSTI to PI regimens in naïve PWH with CD4 below 200 cells/mm^3 or AIDS failed to reveal differences in terms of treatment discontinuation or VF [14,15].

In contrast, other studies showed better outcomes with INSTI (mostly DTG) than PI regimens [16,17].

These results were corroborated in an RCT focusing on naïve PWH with CD4 below 100 cells/mm^3, although sample size was small [18].

DTG has been shown to be superior in terms of virological suppression and durability to older drugs, such as efavirenz, in symptomatic PWH with AIDS in a previous observational study [19]. Further, boosted darunavir and DTG have shown great antiviral potency and high genetic barrier and are suitable to be initiated before obtaining genotypic testing results.

However, all previous observational analyses, apart from the one by Mounzer et al. [20] evaluated the response to first-line ART strategies using traditional statistical techniques, which compared PWH as they were treated in the natural course. Here we aimed to perform an analysis that emulates a trial comparing DRV-based vs DTG-based regimens in the setting of ART-naïve PWH with advanced HIV disease.

Material and methods

Study population and definitions

This work includes PWH seen for care in Italy and enrolled in the ICONA Foundation Study cohort. ICONA Foundation Study is an Italian prospective observational cohort of PWH, including adult subjects infected with HIV-1 who are ART-naïve at the time of enrollment. All participating centers' Institutional Review Boards approved the ICONA Foundation Study. Each PWH signed a consent form to comply with the ethical standards of the committee on human experimentation and the Helsinki Declaration (last amendment October 2013).

The ongoing Laptop RCT [9], which compares BIC/FTC/TAF to DRV/c/FTC/TAF in people with advanced HIV disease, was the target trial that we wished to emulate, with some differences as specified in *Supplementary Information on target trial and definitions*.

We first identified the target population for this trial emulation. Specifically, we included all PWH enrolled in the ICONA cohort who were naïve to ART, at least 18 years of age, with advanced HIV disease (defined as a CD4 count $\leq$200 cells/mm^3 or with an AIDS-defining event at HIV diagnosis [21] at presentation and started a DTG or boosted-darunavir (with ritonavir or cobicistat) -based three-drug regimen over the period 2014-2023. We excluded: i) PWH diagnosed with cancers, tuberculosis, and other mycobacterial infection before ART initiation because the potential drug-drug interactions that could have prevented the prescription of the ART strategies; ii) PWH diagnosed with cryptococcosis before ART initiation, in whom generally ART initiation is deferred; iii) PWH who started DTG or DRV/b bis *in die* (*Supplementary Information on target trial and definitions*).

Baseline was defined as the date of ART initiation.

The dataset used for this analysis was last updated on July 31, 2024.

Study outcomes

The primary outcome of the study was a composite endpoint defined as the time to newly developing AIDS, serious non-AIDS events (SNAE, as defined in *Supplementary Information on target trial and definitions*), death, VF, or treatment discontinuation of the anchor drug (DRV/b or DTG) due to failure, intolerance or toxicity, whichever occurred first. Treatment discontinuations due to ART simplification and any modifications of the nucleoside reverse transcriptase inhibitor (NRTI) backbone did not count as events. VF was defined as a confirmed HIV-RNA $>$200 copies/mL after at least 6 months from the ART initiation. The choice of 200 copies/mL as threshold was derived from DHHS definitions of VF and virological rebound [1].

We also evaluated clinical secondary outcomes which were subsets of the primary outcome and defined as follows: i) time to newly development of AIDS or death, whichever occurred first; ii) time to newly development of SNAE or death, whichever occurred first; iii) treatment failure defined as the time to VF or treatment discontinuation of the anchor drug due to failure, intolerance or toxicity, whichever occurred first. We also evaluated another secondary outcome of time to CD4 count recovery $>$200 cells/mm^3. A cause-specific hazard analysis with censoring weights was performed for these secondary analyses.

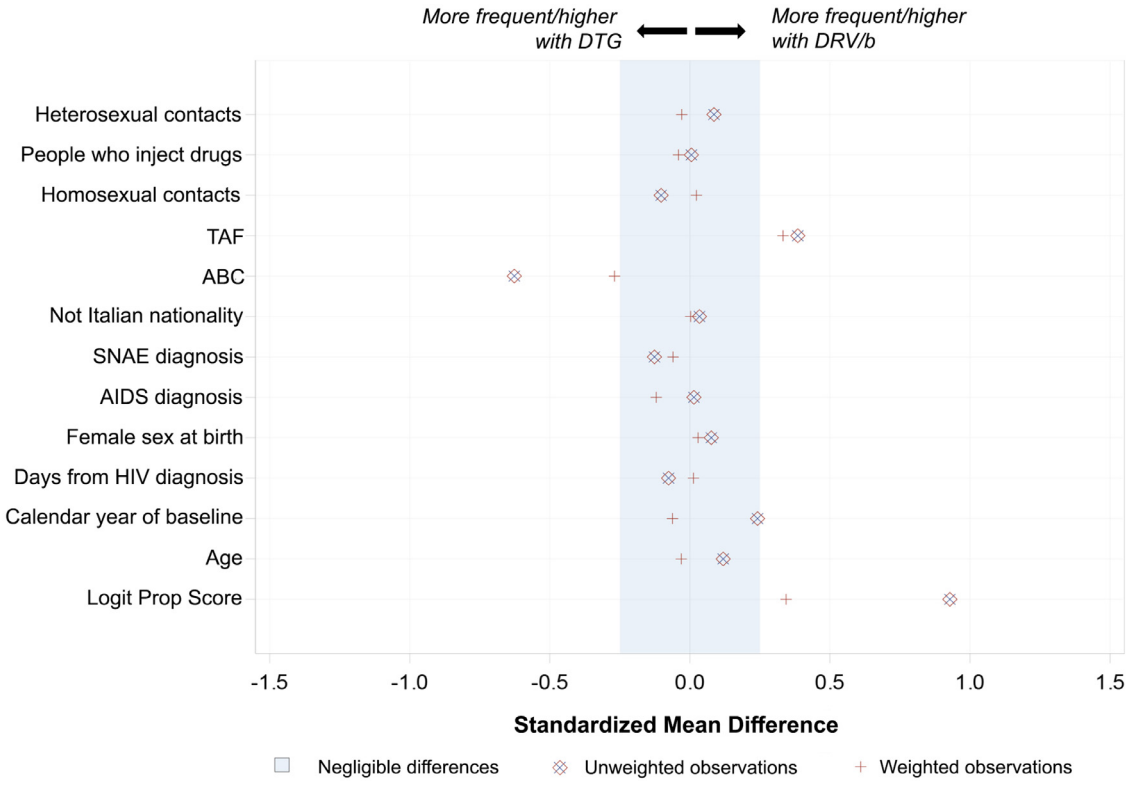

Figure 1. Standardized mean differences by treatment arm. ABC, abacavir; DRV/b, boosted darunavir; DTG, dolutegravir; SNAE, serious non-AIDS events; TAF, tenofovir alafenamide.

Statistical analysis

Our analysis aimed to emulate the setting of an RCT, where participants were randomly assigned to either initiate DTG-based or the DRV/b-based triple regimens in first-line ART through adjustment for time-fixed baseline confounders. Each participant was followed up from the date of ART initiation (baseline) until the earliest date of first occurrence of the composite outcome, date of last clinical visit (maximum date between that of HIV-RNA, clinical visit, or administrative censoring on July 31, 2024). Of note, in this setting, because of the recent calendar year of ART initiation (>2013) and the characteristics of the target population (advanced HIV disease), study entry for individuals and time zero for the survival analysis coincide. We estimated the observational equivalent of the intention-to-treat effect of initiating one or the other trial strategy, regardless of ART treatment changes over time. We controlled for baseline confounding and differential loss to follow-up by constructing inverse probabilities of treatment and censoring weights, respectively. Treatment weights were derived by means of a logistic regression model with a linear predictor which included the following factors: age, gender, mode of HIV transmission, nationality, calendar year of starting ART, AIDS/SNAE at baseline, time from HIV diagnosis, NRTI-pair, CD4 count and HIV-RNA as time-fixed factors measured at baseline. Another model applying the "disjunctive cause" criterion for selection of confounding [22] was also explored, including also hepatitis co-infection in the adjustment set. All continuous variables have been modeled with a single parameter (linear assumption, this applied also to age for example) except for time which was modeled using cubic splines. This same model with the addition of time-updated CD4 count and HIV-RNA (modeled as linear) and time (modeled using restricted cubic splines) was used to derive the censoring weights. The two sets of weights were then multiplied and applied to the Cox proportional hazard model (which was approximated by means of a pooled logistic regression model) for the composite outcome for initiating a DTG- vs DRV-based regimen [23].

We performed a number of visual checks for the model assumptions by means of boxplots of the stabilized weights, propensity score overlaps plots (Supplementary Figure 1), and standardized mean difference plots (Figure 1). Standardized mean differences for each identified potential confounding factor were calculated as the weighted mean (or proportion) difference between groups divided by the weighted pooled standard deviation. We also estimated the risk difference by means of double robust estimation with augmented inverse probability weighting. Furthermore, we also included unweighted and weighted Kaplan–Meier plots comparing the cumulative probability of developing the outcomes over time.

Because the frequency of use of the two strategies has varied over time (DTG more frequent in recent years), calendar year of ART initiation was a key potential confounder in this analysis and also a potential effect-measure modifier. Because of this, besides providing an overall estimate of the causal effect of the intervention we also presented the results after stratification for year of ART initiation fitting separate models for participants who started ART over 2014-2018 vs 2019-2023.

Finally, we performed two sensitivity analyses: i) after restricting the comparison to only regimens that included TAF/FTC or tenofovir disoproxil (TDF)/FTC as NRTI; ii) after restricting the comparison to only single tablet regimen (STR). We used the conventional level of 5% for the type I error and 2-sided tests. We also performed a basic sensitivity analysis for unmeasured confounding by calculating the e-value [24]. Further information on the investigations of the secondary outcomes is in *Supplementary Information on target trial and definitions.*

Baseline characteristics of participants according to ART regimen started as of the natural course in were compared by means of chi-square test for categorical variables or Wilcoxon rank-sum

(Mann–Whitney) test for continuous variables. Statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA).

Results

Study population

We included a total of 1323 advanced ART-naïve PWH, of whom 895 (67.6%) started a DTG-based regimen and 428 (32.3%) a boosted DRV-based regimen.

In the natural course, DTG-based regimens were STR with abacavir/lamivudine (ABC/3TC) in 21.7% (194 out of 895). In the other cases, DTG was prescribed as a multiple tablet regimen with abacavir plus lamivudine in 5.5% (49 out of 895), with TAF/FTC in 32.7% (293 out of 895) and with TDF/FTC in 40.1% (359 out of 895) of cases. Boosted DRV-based regimens were given as STR (DRV/c/TAF/FTC) in 31.5% (135 out of 428), as multiple tablet regimen with TAF/FTC in 19.9% (85 out of 428), with TDF/FTC in 43.5% (186 out of 428) and with ABC/3TC in 5.1% (22 out of 428) of cases. Overall, 21% (275 of 1323) were females, median age was 45 years (interquartile range, IQR, 36-53), 32.7% (433 of 1323) were AIDS presenting, their median nadir CD4+ cells count was 70 cell/mm^3 (IQR 26-131) (Table 1). Before applying the weights, baseline characteristics appeared to be balanced between the two groups, with some differences in calendar year of baseline (more recent in DTG, $P < 0.001$) and in use of the NRTI backbone (TAF was prescribed in 32.7% of DTG-based regimens vs 51.4% of DRV/b-based regimens; ABC in 27.2% of DTG-based regimens vs 5.1% of DRV/b-based regimens, $P < 0.001$). All potential confounding factors showed a standardized difference below 10% after weighting (shown as the negligeable difference region in grey in Figure 1). Similar distributions of the main demographic and viro-immunological characteristics, regardless of calendar period of ART initiation (2014-2019 vs 2019-2023), were observed (Supplementary Tables 1 and 2).

Primary outcome: newly developed AIDS/SNAE, death, VF, or treatment discontinuation

A total of 181 events concurring to the composite primary endpoint were observed with DTG-based regimens: 52 (28.7% of the events) newly developed AIDS events, 46 (25.4%) deaths, 22 (12.2%) newly developed SNAEs, 20 (11.1%) confirmed VFs >200 copies/mL, 41 (22.7%) treatment discontinuations of the anchor drug due to toxicity or failure. Among the 41 treatment discontinuations of DTG, 9 (21.9% of treatment discontinuation events) occurred for neurological adverse events. Furthermore, a total of 142 events were observed with DRV/b-based regimens: 35 (24.7%) AIDS events, 16 (11.3%) deaths, 10 (7.0%) SNAEs, 16 (11.3%) VFs, 65 (45.8%) treatment discontinuations of the anchor drug (Supplementary Table 5a). Median follow-up for the primary outcome was 32 months (IQR 8-63).

The unweighted cumulative probabilities of developing the composite primary endpoint by 48 months were 21.1% (95% CI: 18.1; 24.1%) for DTG vs 37.9% (95% CI: 32.7; 43.2%) for DRV/b ($P < 0.001$, Figure 2a). This difference between the curves was confirmed after weighting, although absolute cumulative risk by 48 months was lower in both interventions: 18.4% (95% CI: 14.3; 22.7%) for DTG vs 35.0% (95% CI: 25.9; 44.2%) for DRV/b ($P = 0.0008$, Figure 2b).

Overall, ART initiation with DTG showed a lower risk of experiencing the primary composite endpoint in the unadjusted analysis (hazard ratio, HR, 0.51 vs DRV/b, 95% CI: 0.41; 0.64, $P < 0.001$). Results were similar in the weighted marginal Cox regression model: (weighted HR, wHR, of DTG vs DRV/b 0.47, 95% CI: 0.35; 0.64, $P < 0.001$, e-value=2.75, Supplementary Figure 3). Results were

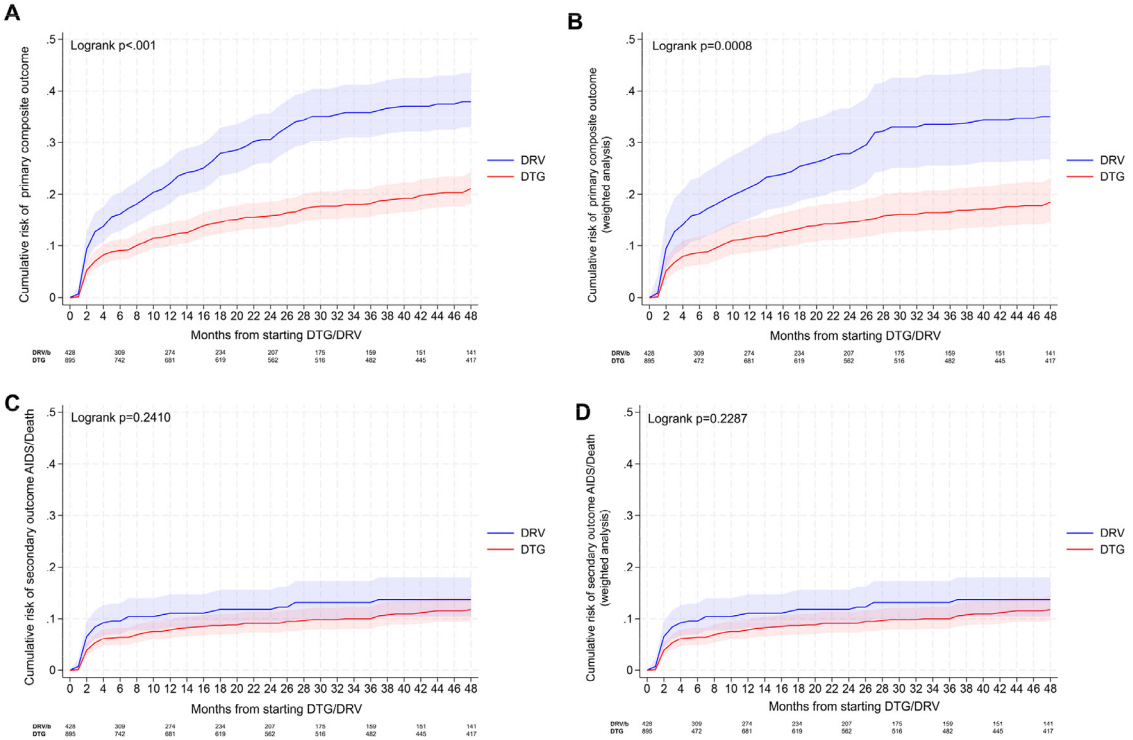

Figure 2. (a) Unweighted Kaplan–Meier curves by anchor drug (DTG vs DRV/b) for the composite endpoint of newly developed AIDS/SNAE, death, virological failure, or treatment discontinuation. (b) Weighted Kaplan–Meier curves by anchor drug (DTG vs DRV/b) for the composite endpoint of newly developed AIDS/SNAE, death, virological failure or treatment discontinuation. (c) Unweighted Kaplan–Meier curves by anchor drug (DTG vs DRV/b) for the endpoint of newly developed AIDS or death. (d) Weighted Kaplan–Meier curves by anchor drug (DTG vs DRV/b) for the endpoint of newly developed AIDS or death. DTG, dolutegravir; DRV/b, boosted darunavir.

Table 1
Main characteristics of the study population—overall and according to regimen started.

Characteristics	Regimen started			
	DRV/b $N = 428$	DTG $N = 895$	*P*-value	Total $N = 1323$
Gender, n(%)			0.191	
Female	99 (23.1%)	179 (20.0%)		278 (21.0%)
Mode of HIV transmission, n(%)			0.377	
PWID	22 (5.1%)	45 (5.0%)		67 (5.1%)
Homosexual contacts	142 (33.2%)	341 (38.1%)		483 (36.5%)
Heterosexual contacts	223 (52.1%)	428 (47.8%)		651 (49.2%)
Other/unknown	41 (9.6%)	81 (9.1%)		122 (9.2%)
Nationality, n(%)			0.562	
Not Italian	131 (30.6%)	260 (29.1%)		391 (29.6%)
AIDS diagnosis at BL, n(%)			0.810	
Yes	142 (33.2%)	291 (32.5%)		433 (32.7%)
SNAE diagnosis at BL, n(%)			0.036	
Yes	41 (9.6%)	122 (13.6%)		163 (12.3%)
HBsAg, n(%)			0.571	
Negative	371 (86.7%)	757 (84.6%)		1128 (8.53%)
Positive	3 (0.7%)	9 (1.0%)		12 (0.9%)
Not tested	54 (12.6%)	129 (14.4%)		183 (13.8%)
HCV-Ab, n(%)			0.059	
Negative	351 (82.0%)	683 (76.3%)		1034 (78.2%)
Positive	18 (4.2%)	55 (6.1%)		73 (5.5%)
Not tested	59 (13.8%)	157 (17.5%)		216 (16.3%)
Hepatitis co-infection, n(%)			0.076	
No	332 (77.6%)	644 (72.0%)		976 (73.8%)
Yes	21 (4.9%)	64 (7.2%)		85 (6.4%)
Not tested	75 (17.5%)	187 (20.9%)		262 (19.8%)
Calendar year of BL			<0.001	
Median (IQR)	2018 (2015, 2019)	2018 (2017, 2019)		2018 (2016, 2019)
2013-2018, n(%)	279 (65.2%)	543 (60.7%)	0.113	822 (62.1%)
2019-2023, n(%)	149 (34.8%)	352 (39.3%)		501 (37.9%)
Age, years			0.082	
Median (IQR)	44 (36, 51)	45 (36, 53)		45 (36, 53)
Mean (range)	44 (19, 76)	45 (19, 78)		45 (19, 78)
CD4 count nadir, cells/mm^3			0.278	
Median (IQR)	68 (23, 132)	71 (27, 130)		70 (26, 131)
Mean (range)	89 (0, 779)	95 (0, 1434)		93 (0, 1434)
CD4 count at BL, n(%)			0.804	
<200 cells/mm^3	412 (96.3%)	859 (96.0%)		1271 (96.1%)
Viral load at BL, log^{10} copies/mL			0.548	
Median (IQR)	5.33 (4.84, 5.79)	5.30 (4.71, 5.83)		5.30 (4.77, 5.81)
Time from HIV diagnosis to date of starting ART, days			0.839	
Median (IQR)	19 (10, 35)	19 (9, 37)		19 (10, 37)
TAF regimen at BL			<0.001	
n(%)	220 (51.4%)	293 (32.7%)		513 (38.8%)
ABC regimen at BL			<0.001	
n(%)	22 (5.1%)	243 (27.2%)		265 (20.0%)
TDF regimen at BL			0.248	
(%)	186 (43.5%)	359 (40.1%)		545 (41.2%)
NRTI pair started, n(%)			<.001	
ABC +3TC	22 (5.1%)	243 (27.2%)		265 (20.0%)
TDF+3TC	0 (0.0%)	1 (0.1%)		1 (0.1%)
TAF+3TC	0 (0.0%)	0 (0.0%)		0 (0.0%)
TAF+FTC	220 (51.4%)	293 (32.7%)		513 (38.8%)
TDF+FTC	186 (43.5%)	358 (40.0%)		544 (41.1%)
Follow-up time, months			<0.001	
Median (IQR)	21 (4, 60)	40 (11, 66)		32 (8, 63)

Column proportions are used.
3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; BL, baseline; DRV/b boosted darunavir; DTG, dolutegravir; FTC, emtricitabine; IQR, interquartile range; NRTI, nucleoside reverse transcriptase inhibitor; PWID, people who inject drugs; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

also similar after stratification for calendar period (2014-2018 and 2019-2023), with a wHR in the most recent time window of 0.37 (95% CI: 0.24; 0.59, $P < 0.001$). Very similar results were obtained in the alternative weighted Cox regression model that included also hepatitis co-infections in the adjustment (Supplementary Table 3).

The weighted risk difference for DTG vs DRV/b for the primary cumulative endpoint from fitting a doubly robust marginal model was −10.3% (95% CI: −16.6; −4.1) ($P = 0.001$) (Supplementary Table 4). In terms of number needed to treat, this amounts to have to initiate ART in 10 PWH with advanced disease with DTG instead of DRV/b to prevent one case of clinical or treatment failure.

In the sensitivity analysis including only TAF/FTC or TDF/FTC as NRTI, a lower risk for the cumulative endpoint when comparing DTG- with DRV/b-based regimens was demonstrated (wHR of DTG

vs DRV/b 0.47; 95% CI: 0.34; 0.64, $P < 0.001$). Finally, in the other sensitivity analysis including only STR, similar results were obtained (wHR of DTG vs DRV/b 0.40; 95% CI: 0.24; 0.65, $P < 0.001$).

Secondary outcomes: clinical progression events and immunological recovery

A total of 52 newly developed AIDS events and 46 deaths were observed with DTG-based regimens, while 35 newly developed AIDS events and 16 deaths were observed with DRV/b-based regimens, over a median follow-up of 46 months (IQR 12-70). Breakdown of the events, overall and stratified by regimen, for the secondary outcomes are shown in Supplementary Tables 5b-e.

The unweighted cumulative probabilities of developing new AIDS or death by 48 months were 11.7% (95% CI: 9.4; 14.1%) for DTG vs 13.7% (95% CI: 10.0; 17.4%) for DRV/b ($P = 0.2410$, Figure 2c). These estimates were very similar after applying the weights: 10.0% (95% CI: 6.8; 13.1%) for DTG vs 13.5% (95% CI: 7.6; 19.4%) for DRV/b ($P = 0.2287$, Figure 2d).

The difference in risk of new AIDS or death by treatment strategy was still in favor of DTG but less compelling both in the unadjusted analysis (HR 0.74, 95% CI: 0.52, 1.06, $P = 0.1$) and in the weighted analysis (wHR 0.66, 95% CI: 0.41, 1.05, $P = 0.08$). Similar results were obtained when considering only the most recent period (2019-2023): wHR for DTG of 0.50 (95% CI: 0.23; 1.08, vs DRV/b, $P = 0.08$).

A total of 22 newly developed SNAE and 46 deaths were observed with DTG-based regimens, while 10 newly developed SNAE and 16 deaths were observed with DRV/b-based regimens, over a median follow-up of 49 months (IQR 16-71).

No evidence for a difference by treatment initiation strategy was found for the second clinical progression outcome restricted to SNAE/death: the unweighted cumulative risk for this outcome by 48 months was 8.6% (95% CI: 6.5; 10.8%) for DTG vs 7.7% (95% CI: 4.5; 10.9%) for DRV/b ($P = 0.72$) and similar after weighting, with 7.1% (95% CI: 4.1; 10.0%) for DTG vs 6.2% (95% CI: 1.4; 10.9%) for DRV/b ($P = 0.96$) (Supplementary Figure 2) and a wHR of 0.99 (95% CI:0.54-1.82, $P = 0.97$), from fitting the pooled Cox regression model. Finally, 726 and 324 individuals had CD4+ cells recovery with DTG and DRV/b, respectively, over a median follow-up of 4 months (IQR 1-12).

No evidence for a difference for the DTG- vs DRV/b-based strategy in CD4+ cells recovery was detected in the unadjusted analysis (HR 1.07, 95% CI: 0.94, 1.22, $P = 0.322$) and in the weighted analysis (wHR 1.06, 95% CI: 0.90, 1.25, $P = 0.488$) (unweighted and weighted Kaplan–Meier curves in Supplementary Figure 2).

Secondary outcome: treatment failure

We finally compared the strategies for the last secondary outcome of treatment failure (only VF and discontinuations were counted as events). A total of 61 and 81 treatment failures were observed with DTG and DRV/b, respectively, over a median follow-up of 39 months (IQR 12-67).

Overall, the risk of treatment failure was lower for the DTG- vs DRV/b-based strategy in the unadjusted analysis (HR 0.29, 95% CI: 0.21, 0.41, $P < 0.001$) and in the weighted analysis (wHR 0.29, 95% CI: 0.19, 0.44, $P < 0.001$) (unweighted and weighted Kaplan–Meier curves in Supplementary Figure 2). This result was confirmed even in the most recent calendar period, with a wHR for DTG vs DRV/b of 0.24 (95% CI 0.13, 0.46, $P < 0.001$).

Discussion

Our analysis aimed to emulate a clinical trial with treatment-related and clinical outcomes in the setting of PWH presenting with advanced HIV infection in recent years, almost all with CD4 below 200 cells/mm^3 and one-third of them with an AIDS event at presentation for care.

Under the assumptions of our trial emulation (e.g., exchangeability of those treated with each regimen conditional on measured characteristics), ART initiation with DTG plus two NRTIs showed approximately a 50% reduction in risk of newly developing AIDS/SNAE, death, VF, or treatment discontinuation due to toxicity/failure than starting ART with DRV/b plus two NRTIs. Our results were similar after restricting to recent calendar periods of ART initiation (2019-2023), to initiations with tenofovir-based backbones and with STR. We also found a difference in the risk of developing AIDS/death and in the risk of VF/discontinuation but not for the outcome of SNAE/death or for the immunological recovery one.

These results suggest that, although the difference in risk for the primary endpoint appeared to be mainly explained by anchor drug discontinuation and VF, there is a residual effect that is likely due to a difference in risk of clinical progression to AIDS/death, albeit not directly supported by the results of the analysis of CD4 count recovery. We would have expected that some of the total effect of treatment on the risk of developing AIDS would go throughout immunological recovery. In contrast, our data show little evidence for a difference in CD4 count response by strategy, thus they seem to suggest either a direct effect of treatment or other indirect pathways.

When interpreting the results, it should be noted that changes in the anchor drug due to simplification were not counted as events and modifications of the NRTIs have been ignored. Also, VF was infrequent in our sample and therefore most treatment failures in our analysis were driven by discontinuations due to safety issues (toxicity/intolerance) related to DTG or DRV/b.

Our data carry little evidence for a difference in the risk of developing SNAE by ART strategy, but consequences of ART for the risk of SNAE, such as cardiovascular disease and cancers, and their potential linkage to the amount of residual inflammation caused by specific antiretrovirals should be better explored with even longer studies.

There are currently no published results for the comparison between DTG and DRV/b in RCT in the advanced HIV setting. Our study confirms a benefit of initiating DTG- instead DRV/b-based therapy, as shown by an RCTs including participants with any CD4 cell count [4] and by another small RCT [4,18].

Other reports, although from observational studies conducted in Europe, documented a higher risk of treatment discontinuations with PI/b than with INSTI in the setting of advanced HIV [16,17,20], even though some of them reported only comparisons between drug classes, not individual drugs [16,17]. Conversely, two other studies found no evidence for a difference in terms of risk of overall treatment discontinuation regardless of the reason [14,15].

One study suggested a higher risk of treatment discontinuation due to central nervous system (CNS) toxicity with DTG and, as expected, a higher risk of treatment discontinuation for simplification with DRV/b [14].

Of note is that all these studies except one by Rava et al. [16] applied a generic definition of treatment discontinuation, so the results are not directly comparable to ours. We argue that changes of DTG or DRV/b due to simplification in clinical practice are typically triggered by convenience and do not jeopardize future therapeutic options. Because we were interested in the actual durability of the regimens, we intentionally used an endpoint that did not count discontinuations due to participants' choice as events. Despite this approach, DRV was found to be less effective than DTG in our study. Discontinuation due to intolerance or toxicity was the main factor contributing to the difference observed among the two strategies.

Some of these studies also documented better virological outcomes with INSTI- than with PI/b-based regimens [17,20], while others failed to detect a difference [14,15].

It has to be noted that in one of these studies, the comparison of interest was darunavir vs bictegravir, not DTG [20].

None of these studies use the exact definition of the composite outcome adopted by us, which was similar to the one applied in the protocol of the LAPTOP trial [9]. Still, some of them reported a lower risk of mortality in late presenters and advanced PWH starting an INSTI- vs PI/b-based regimen [17,25]. None of them compared the risk of developing SNAE events by these drug strategies. Importantly, all these analyses, apart from those of Mounzer et al. [20], used standard statistical methods comparing risks conditioned on covariates, so they are essentially answering a different question. In addition, our study findings could have broad applicability, even in low- and middle-income countries, where late and advanced HIV presentation is more prevalent [26,27], and could contribute to tailored strategies for resource-limited settings. In particular, our data support the WHO recommendation of considering DTG as the preferred first-line regimen for all population groups [28] and generic DTG is available as low-cost single or fixed-dose combination in low-income, lower-middle-income, and sub-Saharan Africa countries.

Our analysis has several strengths: the large sample size, the use of a statistical framework for analysis, which the European Medicines Agency considers the best way to formalize the design and analysis of nonrandomized studies with causal objectives, using observational data [29], a comprehensive endpoint that included both treatment and clinical outcomes, and a length of follow-up which is likely to be longer than that of ongoing and future RCTs.

Our analysis also has some limitations. First, the differences in risks revealed can be interpreted as causal under the usual assumptions for conducting causal inference analyses: causal consistency, exchangeability (no unmeasured confounding), positivity (overlap or common support of propensity scores), a correctly specified model for the treatment and censoring weights and, especially, no measurement error. We have also performed a sensitivity analysis for the assumption of unmeasured confounding by calculating the e-value [24], that confirms that our finding is robust (Supplementary Figure 3). Indeed, unmeasured confounders would require an RR of 2.75 or greater association with treatment assignment and outcome to explain away the effect. Moreover, exchangeability is a particularly strong assumption for this analysis as it is possible that individuals' perceived adherence to therapy and other unreported symptoms, which are predictors of response to ART, might have also determined the initial therapy choice. Also, DRV/b was compared to DTG and not to currently more popularly used second-generation INSTIs such as bictegravir. Indeed, in recent years in Italy, the majority of PWH are initiated with a BIC-based regimen, making real-world data comparison of BIC vs DRV (or even DTG) almost impossible to attempt. The study by Mounzer et al. [20] does not control for calendar year of starting ART and we suspect lack of positivity for this key confounding factor.

Finally, the very small number of CNS events, for which an increased risk was seen in real-world data of PWH using DTG [30–32], prevented us from comparing outcomes tailored to specific adverse events leading to anchor drug discontinuations. Because the initiation of ART (time zero for the analysis) coincided with enrollment in the cohort, we did not have to use tools to control for immortal-time bias.

Conclusions

Our findings suggest that an RCT conducted in a comparable target population of PWH with advanced disease is expected to show an approximately 50% reduction in the risk of treatment and clinical failure when a DTG- vs DRV/b-based therapies are initiated in first-line treatment. In the absence of results of randomized comparisons, our results represent the best available evidence to inform therapy decisions for first-line ART in the advanced HIV disease setting. In addition, our results are important to guide the design of future randomized studies and for feeding meta-analyses of observational data which may lead to change in recommendations. In case of eventual discrepancies with the results of RCTs (when they will become available), access by the same team of statisticians to both randomized and real-world data would be the ideal way to address these discrepancies [33].

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Author contributions

R. Gagliardini: Conceptualization, data curation, investigation, writing original draft, writing review and editing.

A. Giacomelli and A. d'Arminio Monforte: Investigation, writing review and editing.

C. Mussini, C. Pinnetti, A. Raimondi, S. Antinori, S. Nozza, V. Mazzotta, GC. Marchetti, and S. Lo Caputo: Investigation.

S.R. Cole and J.K. Edwards: Methodology, writing review and editing.

A. Tavelli: Data curation, investigation, writing review and editing.

A. Antinori: Conceptualization, investigation, writing review and editing.

A. Cozzi-Lepri: Conceptualization, data curation, formal analysis, methodology, writing review and editing.

Data availability statement

The datasets generated during the current study are not publicly available. Appropriate agreement of data sharing can be arranged after a reasonable request to the corresponding author.

Declarations of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: RG received consultation fees from Gilead, Viiv, and MSD. AG received consultation fees from Mylan, Gilead, ViiV, Janssen, MSD; Payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Mylan, Gilead, ViiV, Janssen, MSD, and Support for attending meetings and/or travel from Gilead, ViiV. SA AG received consultation fees from Pfizer, MSD, ViiV, Gilead. SLC received consultation fees from Gilead, Viiv, Janssen and MSD.SN received consultation fees from Gilead Sciences; ViiV Healthcare; Merck Sharp & Dohme; Jannsen Cilag. CP received consultation fees from Gilead and Janssen. VM received consultation fees from Gilead and Viiv. AA received grants/research supports from Gilead, ViiV; honoraria or consultation fees from Gilead, ViiV, Merck, Roche, Astrazeneca, Pfizer, GSK; participated in company-sponsored speaker's bureau

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Biological Bank INMI and San Paolo: M Augello, S Carrara, S Graziano, G Prota, S Truffa, D Vincenti, R Rovito, M Sgarlata.

Participating Physicians and Centers: Italy A Giacometti, A Costantini, V Barocci (Ancona); A Saracino, C Santoro, E Milano (Bari); L Comi, C Suardi (Bergamo); P Viale, L Badia, S Cretella (Bologna); EM Erne, A Pieri (Bolzano); E Quiros Roldan, E Focà (Brescia); B Menzaghi, C Abeli (Busto Arsizio); L Chessa, F Pes (Cagliari); P Maggi, L Alessio (Caserta); G Nunnari, BM Celesia (Catania); J Vecchiet, K Falasca (Chieti); A Pan, S Dal Zoppo (Cremona); D Segala (Ferrara); F Bartalesi, C Costa (Firenze); S Lo Caputo, S Ferrara (Foggia); M Bassetti, E Pontali, S Blanchi, N Bobbio (Genova); C. Del Borgo, R. Marocco, G. Mancarella (Latina); S Piconi, C Molteni (Lecco); S Rusconi, G Canavesi (Legnano); G Pellicanò (Messina); G Marchetti, S Antinori, G Rizzardini, M Puoti, A Castagna, A Bandera, V Bono, MV Cossu, A Giacomelli, R Lolatto, MC Moioli, L Pezzati, S Diotallevi, C Tincati (Milano); C Mussini, M Menozzi (Modena); P Bonfanti, G Lapadula (Monza); V Sangiovanni, I Gentile, V Esposito, N Coppola, FM Fusco, G Di Filippo, V Rizzo, N Sangiovanni, S Martini (Napoli); AM Cattelan, D Leoni (Padova); A Cascio, M Trizzino (Palermo); D Francisci, E Schiaroli (Perugia); G Parruti, F Sozio (Pescara); D Messeri, SI Bonelli (Pistoia); C Lazzaretti, R Corsini (Reggio Emilia); A Antinori, R Cauda, C Mastroianni, L Sarmati, A Latini, A Cingolani, I Mastrorosa, S Lamonica, M Capozzi, M Camici, I Mezzaroma, M Rivano Capparuccia, G Iaiani, C Stingone, L Gianserra, J Paulicelli, MM Plazzi, G d'Ettore, M Fusto, M Lichtner (Roma); I Coledan (Rovigo); G Madeddu, A De Vito (Sassari); M Fabbiani, F Montagnani (Siena); A Franco, R Fontana Del Vecchio (Siracusa); D Francisci, C Di Giuli (Terni); GC Orofino, G Calleri, G Di Perri, S Bonora, G Accardo (Torino); C Tascini, A Londero (Udine); G Battagin, S Nicolè (Vicenza); G Starnini, S Dell'Isola (Viterbo).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.107883.

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