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Effectiveness of first-line lamivudine/dolutegravir antiretroviral therapy in persons with HIV: real-life data from the ICONA Foundation cohort

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Objectives: This analysis aimed to evaluate the rate of failure of first-line lamivudine/dolutegravir in a real-world setting and assess the effectiveness among people with HIV (PWH) at higher risk of suboptimal response.

Methods: The study included PWH from the ICONA cohort who started first-line lamivudine/dolutegravir between 2016 and 2024. The primary endpoint was time to treatment failure (TF), defined as virological failure (VF, two consecutive HIV-RNA of >50 copies/mL >6 months after treatment initiation) or discontinuation due to toxicity/lack virological control/non-adherence or death for any cause. Secondary endpoints were time to treatment discontinuation for any reason (TD) and pure VF. Main exposures of interest were baseline CD4 and HIV-RNA, age, sex at birth and nation of birth. Standard survival analysis and Cox regression models were used.

Results: Among 446 participants, after a median follow-up of 22 months, 4.3% ($n=19$) experienced TF, the 3 year cumulative probability was 5.8% (95% CI: 2.9%–8.7%). Baseline CD4 count was associated with a 3-fold higher risk of TF, which decreased after adjustments. Higher viral loads (>100 000 copies/mL), age >50 years and foreign-born status were also associated with an increased risk of TF. No differences in TF according to sex at birth were found. By 3 years the probabilities of TD and VF were 13.4% (95% CI: 9.1%–17.6%) and 2.3% (95% CI: 0.19%–4.4%), respectively.

Conclusions: In our real-world setting, the TF probability for first-line lamivudine/dolutegravir was below 6% at 3 years, lower than in randomized trials. Our data suggest that, as shown with other regimens, PWH starting lamivudine/dolutegravir with CD4 count of ≤200 cells/mm^3, HIV-RNA of >100 000 copies/mL, older age or foreign-born status may be at higher risk of TF, though larger studies are needed to qualify the magnitude of the effect.

Introduction

Current guidelines recommend starting ART immediately after an HIV diagnosis, with dolutegravir- or bictegravir-based regimens combined with one or two NRTIs as preferred first-line options.[1,2] Over time, the two-drug regimen (2DR) of dolutegravir combined with lamivudine has gained popularity, as recent clinical trials have shown that this 2DR is not inferior to traditional three-drug regimens (3DRs).[3–5] However, these trials often include carefully selected participants and may not fully represent the broader average person with HIV seen in clinical practice.[6,7] For example, most participants in GEMINI 1 and 2 trials were young and had no AIDS-related conditions, with 20% having HIV-RNA of >100 000 copies/mL and 8% having CD4 counts of <200 cells/mm^3 at ART start. In those with CD4 counts of <200 cells/mm^3, virological suppression at 144 weeks was lower in lamivudine/dolutegravir (67%) compared to 3DR (76%), but the difference was minimal.[5] The DOLCE trial confirmed that lamivudine/dolutegravir provides similar outcomes to a 3DR in severely immunosuppressed patients, with slightly greater differences in the group with HIV-RNA of >100 000 copies/mL.[8]

Real-world evidence (RWE) studies have shown viral suppression rates from 80% to 100% with lamivudine/dolutegravir in ART-naive individuals.[9–21] These studies, mostly short-term and with small sample sizes (the largest with 185 participants), found no significant difference in effectiveness between lamivudine/dolutegravir and integrase strand transfer inhibitor (INSTI)-based 3DR regimens. Follow-up was typically 48 weeks, with a few studies reporting data up to 96 weeks.[8,12–14,17,18]

Additionally, some studies included comparator groups, such as bictegravir/emtricitabine/tenofovir alafenamide or a dolutegravir-based 3DR; however, only a few of these evaluated the possible interaction between the type of treatment, pre-ART CD4 count and viral load on treatment outcomes. Overall, there is conflicting evidence that viral load at ART initiation might be an effect measure modifier for treatment response, although some more recent studies on ART-naive patients with high viral load (100 000–500 000 copies/mL) who started lamivudine/dolutegravir demonstrated high virological efficacy and good tolerability after 1 year.[22,23]

Some studies showed slightly lower short-term chance of achieving virological suppression in participants starting lamivudine/dolutegravir compared to a 3DR when their CD4 count was below 200 cells/mm^3, but no evidence for a difference was found. However, none of these studies formally tested this interaction (Table S1, available as Supplementary data at *JAC* Online).[10,11,15,16,19,20]

Additionally, the effectiveness of lamivudine/dolutegravir in foreign-born individuals, where adherence may be lower, and in older patients has been unexplored. While no racial differences in virological suppression were seen in the GEMINI trials, lower rates were observed in Black/African participants and women.[24–27] Real-world studies generally indicate that migrants have lower suppression rates. Further research in diverse populations is essential to assess long-term outcomes and treatment failure in vulnerable groups.

Patients and methods

We used the data of the Icona Foundation Study cohort, an observational multicentre study conducted in 61 centres across Italy and covering 16 Italian regions.[28]

Study population

People with HIV (PWH) enrolled in the Icona Foundation Study cohort were included in this analysis if they (i) started a dual regimen with lamivudine/dolutegravir, either as a single or multi-tablet regimen, from ART-naive people between 2016 and 2024, and (ii) had at least one clinical follow-up visit after ART initiation. PWH with known acute HIV infection were excluded from the analyses.

Exposure and endpoint definitions

The main exposure of interest was baseline CD4 cell count at initiation of lamivudine/dolutegravir (a categorical factor using the threshold of 200 cells/mm^3). Secondary exposures of interest were HIV-RNA at initiation of lamivudine/dolutegravir (a categorical factor using the threshold of 100 000 copies/mL), nation of birth (Italian-born versus foreign), sex assigned at birth (male versus female), age (18–50 versus >50 years old) and calendar year of ART initiation (as continuous factor).

The main endpoint was the time to treatment failure (TF), a composite endpoint of treatment discontinuation (TD) due to toxicity or lack of virological control or non-adherence, virological failure with >50 copies/mL (VF) or death from any cause. VF was defined at the time of the first of two consecutive HIV-RNA of >50 copies/mL, after at least 6 months from initiation of lamivudine/dolutegravir (baseline) and while the participants were still receiving the regimen (true viraemic breakthroughs). Secondary endpoints were the time to (i) pure TD regardless of the reason, and (ii) pure VF with >50 copies/mL threshold.

For the classification of the reason for discontinuation, we used the primary reason reported by the treating physicians, as coded in the ICONA Clinical Record Forms (CRFs): simplification, patient's decision, adherence issues, toxicity (gastrointestinal intolerance, neuropsychiatric adverse events, renal, metabolic, dermatological, allergies, other toxicities), other (pregnancy/planned pregnancy, inclusion in trial, drug–drug interaction, unspecified reasons and other reasons not listed) or failure (lack of virological control, lack of immunological recovery, clinical failure). Lack of virological control included clinical decisions, as reported by treating physician, to switch ART due to persistently detectable viraemia or perceived insufficient response and, unlike the VF endpoint, could occur also prior to the 6 months. Changes from multi- to single-tablet formulations of lamivudine/dolutegravir were not counted as events.

Statistical analysis

Baseline characteristics of participants were described overall and after stratification for CD4 count, viral load at initiation of lamivudine/dolutegravir, and nation of birth using median and IQR for continuous variables, and absolute and relative frequencies for categorical variables. Differences by groups were assessed by means of the chi-squared test (and Fisher's exact test when the expected cell count was <5) or Wilcoxon rank sum test, as appropriate.

We used standard Kaplan–Meier curves to estimate the cumulative probability of developing the outcomes by 1, 2 and 3 years from lamivudine/dolutegravir initiation; log-rank test was used to test the association between the exposures of interest and outcomes.

These same associations have been investigated in multivariable analysis and the effects of each of these factors estimated by means of adjusted HR (aHR) with 95% CI from fitting separate standard Cox regression models. For the analysis on TD for any reason as the endpoint, only events

due to TD and contributing to the TF endpoint were counted. A tailored set of confounding factors was identified for each of these models. The models with HIV-RNA and nation of birth as exposure were controlled for year of ART initiation, age and sex at birth. The model with CD4 count at ART as exposure was further controlled for geographical location of the Icona enrolling site (a three-way categorical variable: Northern, Central and Southern Italy) and HIV-RNA at starting ART. Statistical analyses were performed using SAS (version 9.4; Cary, NC, USA). All tests were two-sided, and we used the conventional threshold of 5% for the type I error in hypothesis testing.

Ethics

The ICONA Foundation study was approved by the local ethics committees of participating clinical sites. The latest amendment was approved centrally by the Lazio Area 4 Territorial Ethics Committee on 1 July 2024 (approval no. 83-2024). All patients provided written informed consent for study participation and data processing, in accordance with the ethical standards of the committee on human experimentation and the Declaration of Helsinki (last amended in October 2013).

Results

Characteristics of study population

A total of 446 PWH were included in this analysis: 80% (358/446) started lamivudine/dolutegravir with HIV-RNA ≤100 000 copies/mL and 20% (88/446) with HIV-RNA >100 000 copies/mL; no participants were HBsAg positive. The median age was 37 years (IQR 29–46), 15% were female, and 57% were reported as MSM. The median CD4 count was 478 cells/mm^3 (IQR 350–652), only 6% had a CD4 count of ≤200 cells/mm^3, less than 1% (3/446) had an AIDS diagnosis at the time of starting lamivudine/dolutegravir (one had TB with a CD4 count of 222 cells/mm^3; one had wasting syndrome and oesophageal candidiasis with a CD4 count of 2 cells/mm^3; one had *Pneumocystis jirovecii* pneumonia with a CD4 count of 12 cells/mm^3).

After stratifying the study population according to CD4 count at initiation of lamivudine/dolutegravir, we found that compared with participants with a CD4 count of >200 cells/mm^3, those in the CD4 ≤200 cells/mm^3 group were older (47 versus 36 years; $P<0.001$), more likely to be female (34.6% versus 13.8%; $P=0.004$), and had more frequently acquired HIV through heterosexual sexual contacts (56.0% versus 32.8%, $P=0.017$). Overall, 20% of our sample had an HIV-RNA of >100 000 copies/mL and this proportion was even higher in the CD4 count ≤200 cells/mm^3 group. All the characteristics of the study population stratified by CD4 count at ART start are shown in Table 1.

General characteristics of the study population stratified by the other exposures of interest (HIV-RNA, nationality, sex at birth and age groups) are reported in Tables S2–S5. As expected, compared with PWH with HIV-RNA of >100 000 copies/mL group, CD4 counts at the time of ART initiation were higher in those with baseline HIV-RNA of ≤100 000 copies/mL (Table S2).

Foreign-born PWH were more frequently female (21.7% versus 12.7%; $P=0.019$), younger (median age of 32 (IQR 28–41) versus 38 years old (IQR 30–48), $P<0.001$) and with higher proportion being unemployed at enrolment (26.8% versus 5.9%, $P<0.001$, Table S3).

More females mainly acquired HIV infection through unprotected heterosexual intercourse than men (94% versus 23.5%; $P<0.001$) and a higher proportion of females were diagnosed with HIV in more recent years (51% in 2021–22 versus 39.7%). Female participants were older than male participants with a median (IQR) age of 41 (31–47) versus 35 (29–46) years,($P=0.037$), more frequently had a pre-ART CD4 count of ≤200 cells/mm^3 (13.4% versus 4.2%; $P=0.003$) and a higher proportion were unemployed at enrolment (20% versus 9.5%; $P=0.004$, Table S4). In addition, there was a higher proportion of young PWH with a pre-ART CD4 count of ≤200 cells/mm^3 (13.6% versus 4.2%; $P=0.002$), with a lower median (IQR) count of 416 cells/mm^3 (263–578) versus 521 cells/mm^3 (364–665) in older participants ($P=0.003$) and interestingly, 28.8% of younger participants had a pre-ART HIV-RNA of >500 000 copies/mL compared with older participants (18.2%; $P=0.023$) (Table S5).

TF: TD for toxicity/lack of virological control/non-adherence, VF or death

Over a median follow-up of 22 (IQR: 6–38) months (18 months, IQR 9–33, for the ≤200 CD4 cells/mm^3 group and 22 months, IQR 6–38, for the >200 CD4 cells/mm^3 group, $P=0.684$), a total of 19 PWH (4.3%, 95% CI: 2.6%–6.6%) experienced TF: 5 VFs, 3 deaths and 11 discontinued lamivudine/dolutegravir for toxicity/lack of virological control/non-adherence. Two of these 11 discontinuations were classified as lack of virological control: one person with HIV did not achieve viral suppression after 4 months, while the second one had two viral blips (HIV-RNA between 50 and 200 copies/mL followed by viral suppression) while on lamivudine/dolutegravir; both were switched to a 3DR. The Kaplan–Meier estimates of the overall cumulative probabilities of TF at 1, 2 and 3 years were: 2.2% (95% CI: 0.7%–3.7%), 4.2% (95% CI: 1.9%–6.4%) and 5.8% (95% CI: 2.9%–8.7%), respectively (Figure 1a). Participants who started lamivudine/dolutegravir with a CD4 count of ≤200 copies/mL showed a higher cumulative risk of TF compared with those starting with a CD4 count of >200 cells/mm^3: 18.2% (95% CI: 1.9–34.5) versus 3.7% (95% CI: 1.4–6.0) by 2 years (log-rank $P=0.0017$; Figure 1b); we also found a higher probability of TF for higher baseline HIV-RNA strata (>100 000 versus ≤100 000 copies/mL: log rank $P=0.0139$; Figure 1c) and older PWH (>50 versus 18–50 years: log-rank $P=0.031$; Figure 1d). In contrast, we found no evidence on the risk of TF according to nation of birth (foreign versus Italian natives: log-rank $P=0.336$; Figure 1e) or sex at birth (female versus male: log-rank $P=0.5198$; Figure 1f). Crude risks of TF according to each exposure are given in Table S7.

The unadjusted Cox regression showed a nearly 5-fold higher risk of TF when comparing PWH with CD4 count of ≤200 cells/mm^3 versus those with CD4 > 200 cells/mm^3, but this was attenuated after adjusting for ART initiation year, age and sex at birth (an aHR of 3.73, 95% CI: 1.15–12.09), and attenuated even further after also controlling for geographical location and baseline HIV-RNA (aHR: 2.67, 95% CI: 0.75–9.49). In contrast, participants starting lamivudine/dolutegravir with an HIV-RNA of >100 000 copies/mL had three times higher the risk of TF compared with those with a viral load of ≤100 000 copies/mL, which remained significant after adjustment (aHR: 2.52, 95% CI: 1.01–6.33). aHR of TF among foreign-born individuals compared with Italian natives was 2.83 (95% CI: 0.98–8.18). Additionally, older participants (>50 years) had a significantly higher risk of TF

Table 1. Main characteristics of the study population according to baseline CD4 count

Characteristics	CD4 count ≤ 200 cells/mm^3 *N* = 25	CD4 count > 200 cells/mm^3 *N* = 421	*P* value[a]	Total *N* = 446
Sex at birth, *n* (%)			0.006	
Female	9 (36.0)	58 (13.8)		67 (15.0)
Age, years			<0.001	
Median (IQR)	47 (41–55)	36 (29–46)		37 (29–46)
Mode of HIV transmission, *n* (%)			0.013	
IDU	3 (12.0)	18 (4.3)		21 (4.7)
Homosexual contacts	8 (32.0)	247 (58.7)		255 (57.2)
Heterosexual contacts	14 (56.0)	138 (32.8)		152 (34.1)
Other/unknown	0 (0.0)	18 (4.3)		18 (4.0)
Nation of birth, *n* (%)			0.347	
Foreign-born	4 (16.0)	111 (26.4)		115 (25.8)
Geographical position of site, *n* (%)			0.047	
Northern Italy	18 (72.0)	197 (46.8)		215 (48.2)
Central Italy	4 (16.0)	156 (37.1)		160 (35.9)
Southern Italy	3 (12.0)	68 (16.2)		71 (15.9)
Education, *n* (%)			0.272	
Primary school	0 (0.0)	3 (0.7)		3 (0.7)
Secondary school	5 (20.0)	44 (10.5)		49 (11.0)
College	5 (20.0)	129 (30.6)		134 (30.0)
University	2 (8.0)	75 (17.8)		77 (17.3)
Other/unknown	13 (52.0)	170 (40.4)		183 (41.0)
Employment, *n* (%)			0.243	
Unemployed	3 (17.6)	34 (10.6)		37 (11.0)
Employed	6 (35.3)	170 (53.1)		176 (52.2)
Self-employed	6 (35.3)	69 (21.6)		75 (22.3)
Occasional	1 (5.9)	7 (2.2)		8 (2.4)
Student	0 (0.0)	22 (6.9)		22 (6.5)
Retired	1 (5.9)	6 (1.9)		7 (2.1)
Invalid	0 (0.0)	0 (0.0)		0 (0.0)
Housewife	0 (0.0)	2 (0.6)		2 (0.6)
Other/unknown	0 (0.0)	10 (3.1)		10 (3.0)
CD4 count, cells/mm^3			<0.001	
Median (IQR)	147 (60–177)	511 (372–668)		484 (352–660)
CD8 count, cells/mm^3			<0.001	
Median (IQR)	518 (358–764)	878 (674–1171)		869 (662–1127)
HIV-RNA, $\log_{10}$ copies/mL			0.002	
Median (IQR)	4.88 (4.23–5.45)	4.33 (3.80–4.85)		4.36 (3.83–4.87)
>100 000 copies/mL, *n* (%)	10 (40.0)	78 (18.5)	0.017	88 (19.7)
>500 000 copies/mL, *n* (%)	3 (12.0)	7 (1.7)	0.014	10 (2.2)
AIDS diagnosis, *n* (%)			0.009	
Yes	2 (8.0)	1 (0.2)		3 (0.7)
Time from HIV diagnosis to date of starting cART, months			0.135	
Median (IQR)	1 (0–2)	1 (0–2)		1 (0–2)
Calendar year of baseline			0.448	
Median (IQR)	2021 (2020–22)	2021 (2019–22)		2021 (2019–22)
2016–18	4 (16.0)	37 (8.8)		41 (9.2)
2019–21	13 (52.0)	227 (53.9)		240 (53.8)
2022–24	8 (32.0)	157 (37.3)		165 (37.0)
CVD diagnosis, *n* (%)			0.056	
Yes	1 (4.0)	0 (0.0)		1 (0.2)

Continued

Table 1. *Continued*

Characteristics	CD4 count ≤ 200 cells/mm^3 *N* = 25	CD4 count > 200 cells/mm^3 *N* = 421	*P* value[a]	Total *N* = 446
HBsAg, *n* (%)			0.418	
Negative	19 (76.0)	348 (82.7)		367 (82.3)
Positive	0 (0.0)	0 (0.0)		0 (0.0)
Not tested	6 (24.0)	73 (17.3)		79 (17.7)
HCVAb, *n* (%)			0.281	
Negative	17 (68.0)	334 (79.3)		351 (78.7)
Positive	1 (4.0)	14 (3.3)		15 (3.4)
Not tested	7 (28.0)	73 (17.3)		80 (17.9)
Diabetes, *n* (%)			0.251	
Yes	1 (4.0)	4 (1.0)		5 (1.1)
Smoking, *n* (%)			1.000	
No	8 (32.0)	142 (33.7)		150 (33.6)
Yes	9 (36.0)	149 (35.4)		158 (35.4)
Unknown	8 (32.0)	130 (30.9)		138 (30.9)
Use of statins, *n* (%)			0.294	
Yes	1 (4.0)	5 (1.2)		6 (1.3)
Use of blood pressure-lowering drugs, *n* (%)			0.037	
Yes	3 (12.0)	11 (2.6)		14 (3.1)
Blood glucose, mg/dL			0.369	
Median (IQR)	82 (75–89)	85 (78–92)		84 (78–92)
Total cholesterol, mg/dL			0.744	
Median (IQR)	162 (141–187)	166 (144–192)		166 (144–192)
HDL cholesterol, mg/dL			0.963	
Median (IQR)	44 (27–61)	43 (37–51)		44 (37–51)
eGFR, CKD-EPI formula, mL/min/1.73 m^2			<0.001	
Median (IQR)	84.35 (73.38–108.0)	108.6 (96.80–117.8)		108.0 (94.12–117.5)
Below 60, *n* (%)	3 (13.0)	5 (1.3)	0.007	8 (1.9)

IDU, injecting drug user; cART, combination ART; CVD, cardiovascular diseases (stroke, acute myocardial infarction and invasive cardiovascular procedures); eGFR CKD-EPI, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration formula; HBsAg, hepatitis B surface antigen; HCVAb, HCV antibody.

[a]Chi-squared/Fisher's exact test or Mann–Whitney test as appropriate.

(versus 18–50 years, HR: 3.62, 95% CI: 1.45–9.01), while no evidence for a difference according to sex at birth (HR female versus male: 1.50, 95% CI 0.43–5.17) (Table 2).

TD

Overall, 42 participants (9.4%) discontinued lamivudine/dolutegravir over the follow-up period. The majority of participants (*n* = 23; 54.7%) discontinued for simplification; of these, 20 (47.6%) discontinued for ART optimization towards a long-acting injectable cabotegravir and rilpivirine regimen, and 3 to a fewer-pill oral ART strategy (7.1%). In addition, seven participants (16.7%) discontinued for adherence/patient choice. Two PWH (4.9%) discontinued because of a lack of virological control and restarted abacavir/lamivudine/dolutegravir (ABC/3TC/DTG) and emtricitabine/tenofovir alafenamide/bictegravir (FTC/TAF/BIC), respectively; five (12.2%) discontinued because of toxicity [three switched to TAF/FTC/rilpivirine (RPV); one to TDF/3TC/doravirine (DOR) and the last one to DTG/darunavir (DRV)/cobicistat (c)]. One person with HIV interrupted for unknown reason. There were also five discontinuations (12.5%) for other reasons, detailed together with the others in Table S6.

The cumulative probability of experiencing lamivudine/dolutegravir discontinuation regardless of the reason was 4.6% (95% CI: 2.5–6.8) at 1 year, 10.1% (95% CI: 6.6–13.6) at 2 years and 13.4% (95% CI: 9.1–17.6) at 3 years. In this unadjusted Kaplan–Meier analysis there was no evidence for an association between CD4 count and discontinuation of lamivudine/dolutegravir (*P* = 0.54). Similarly, there was no evidence for an association according to baseline HIV-RNA, nation of birth, sex at birth or age.

VF

We delve deeper into the five participants who experienced pure VF: by 3 years, the risk of pure VF by Kaplan–Meier was 2.3% (95% CI: 0.19%–4.4%). Figure S1 shows the spaghetti plot of the trajectories of the HIV-RNA ($\log_{10}$ scale) of these five individuals. It can be noted that four (66.7%) of these five VFs were virological

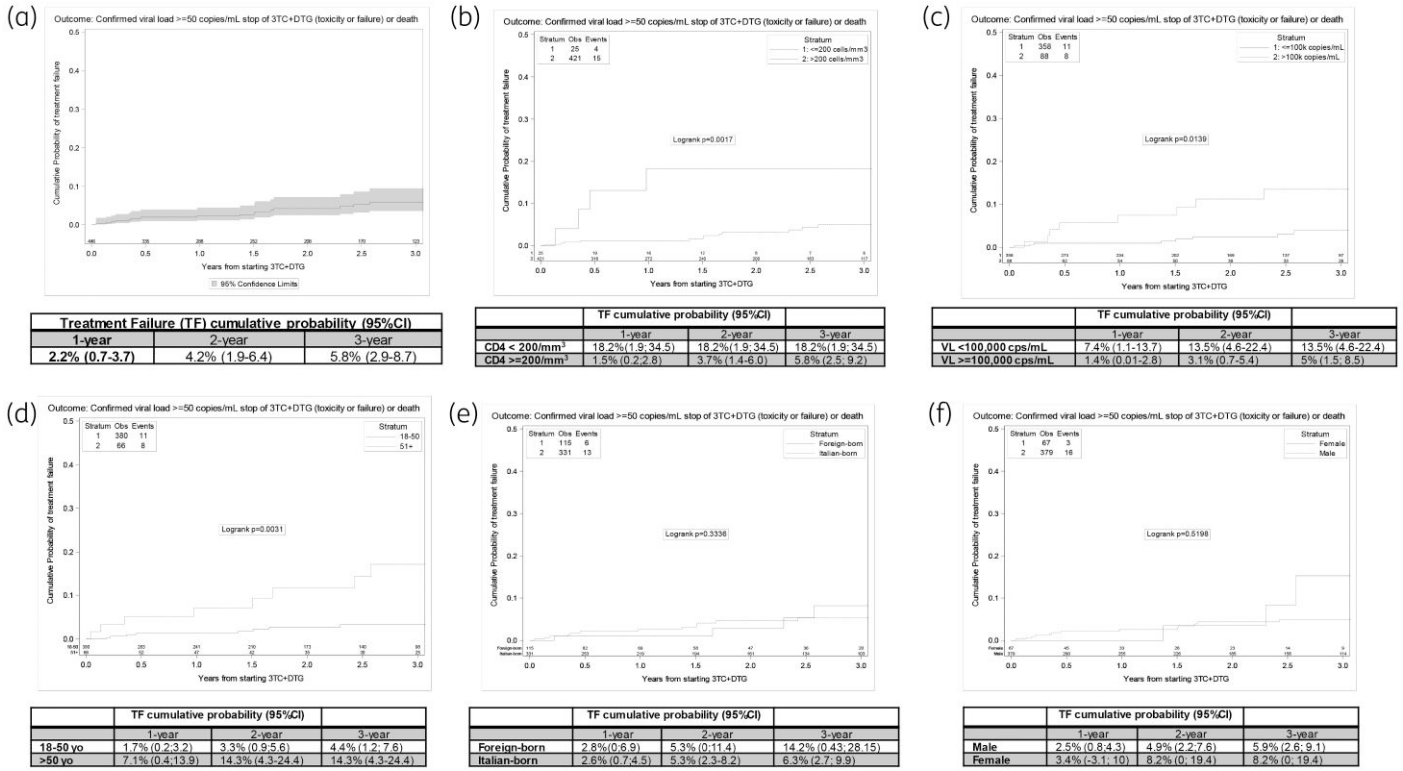

Figure 1. Kaplan–Meier curves and estimated probabilities of TF at 1, 2 and 3 years among PWH initiating lamivudine/dolutegravir as first-line ART; overall (a), according to CD4 strata (b), HIV-RNA strata (c), age strata (d), nation of birth (e) and sex at birth (f).

Table 2. HR and aHR of TF from fitting a Cox regression model

	Unadjusted		Adjusted		Adjusted	
Factor	HR (95% CI)	*P* value	HR[a] (95% CI)	*P* value	HR[b] (95% CI)	*P* value
CD4 count, cells/mm^3						
≤200 versus >200	4.93 (1.63–14.90)	0.005	3.73 (1.15–12.09)	0.028	2.67 (0.75–9.49)	0.130
HIV-RNA, copies/mL						
>100 000 versus ≤100 000	2.97 (1.19–7.38)	0.019	2.52 (1.01–6.33)	0.049		
Nation of birth						
Foreign versus Italy	1.61 (0.61–4.25)	0.338	2.83 (0.98–8.18)	0.055		
Age, years						
50+ versus 18–50	3.62 (1.45–9.01)	0.006				
Calendar year of ART initiation						
per 1-year increase	0.87 (0.65–1.16)	0.330				
Sex at birth						
Female versus male	1.50 (0.43–5.17)	0.523				

[a]Adjusted for year of ART initiation, age and sex at birth.
[b]Adjusted for year of ART initiation, age, sex at birth, geographical location of attending site and HIV-RNA.

rebounds occurring after an initial suppression. Three of the five VFs (60.0%) were suspected to be non-adherent participants, as they subsequently switched to the single-tablet combination of lamivudine/dolutegravir for adherence issues (descriptive details are given in Table S8).

Discussion

In this real-world data analysis, we examined the risk of failure of lamivudine/dolutegravir when used as first-line therapy in a large population of ART-naive PWH, routinely seen for care in Italy.

Although previous studies suggested that both low CD4 count and high viral load are potential risk factors for TF, results are conflicting and there is no convincing evidence that risk is exacerbated in PWH starting first-line treatment with lamivudine/dolutegravir.[9,10,14,15,18,19] Because data on PWH starting lamivudine/dolutegravir with HIV-RNA of >500 000 copies/mL are sparse, the European AIDS Clinical Society guidelines recommend the use of lamivudine/dolutegravir in first-line therapy only to individuals with an HIV-RNA of <500 000 copies/mL.[1]

In our study population, 20% had a viral load of >100 000 copies/mL and <6% of the participants initiated lamivudine/dolutegravir with a CD4 count of ≤200 cells/mm^3; these proportions are consistent with those seen in the GEMINI trials (20% and 9%) and in another similar large cohort in Spain (26% and 3.6%).[20]

In our sample, we estimated a cumulative risk of TF of 5.8% by 3 years from therapy initiation.

We observed an increased risk of TF in PWH who started lamivudine/dolutegravir with HIV-RNA >100 000 copies/mL and to a smaller extent also in those with pre-ART CD4 count ≤200 cells/mm^3, although with large uncertainty around the relative risk estimates. The association with HIV-RNA at ART initiation is well established and seems to occur despite good adherence to ART.[29–31] These findings are also in line with those of a recent meta-analysis showing that both a CD4 count of ≤200 cells/mm^3 and an HIV viral load of >100 000 copies/mL reduce the effectiveness of ART across all preferred regimens, even in the era of modern ART with widespread use of INSTIs.[32] However, it is difficult to speculate from the present analysis whether the risk that we estimated with lamivudine/dolutegravir is higher than those seen with other regimens.

Additionally, being a foreigner or migrant appears to be a risk factor for TF. Migrants often face unique challenges in HIV care, including issues with healthcare access, stress and unstable living situations, all of which can negatively affect adherence or lead to TD.[26] Specific groups, such as women and older migrants, may face even greater difficulties, making it harder for them to achieve virological suppression.[24,25]

Moreover, participants over 50 years old showed a higher cumulative probability of TF at 2 years. In this group, TF may be linked to a combination of ageing-related factors, comorbidities and a reduced immune response and higher susceptibility to side effects that could lead to more treatment discontinuations.[27] A similar trend was observed in another analysis within the same ICONA cohort, which included different regimens like a 3DR with TAF/FTC/BIC.[33]

Our estimate of the risk of TD for any reason (9%), which was mainly for simplification strategies or patient preference, falls within the range of the rates observed in other RWE studies that evaluated the same outcome,[9–11,13–15,17–20] and is also consistent with what was found in a meta-analysis (5.0% at Week 48 and 13.0 at Week 96).[34] Toxicity might represent a concern for second-generation integrase inhibitors such as dolutegravir, which have been associated with the risk of metabolic changes and toxicity of the CNS.[35–39] In our data, only five participants discontinued lamivudine/dolutegravir because of toxicity/intolerance (1.1%), a risk which appears lower than reported in most other studies, and only one was due to CNS toxicity.[9–13,15,17,20]

The tolerability of lamivudine/dolutegravir appeared to be excellent in our sample, with fewer than 2% of patients needing to change their treatment due to adverse events, fully comparable to what has already been reported in a recent systematic review indicating that changes of lamivudine/dolutegravir due to adverse effects ranged from 1.7% to 7.9% across seven cohorts.[29] Finally, we observed a risk of VF of 2.3% by 3 years, which is also consistent with the rate reported in the pooled analysis of the GEMINI 1 and 2 randomized controlled trials (RCTs),[5] as well as other studies.[9,12,13,15,17,18,20,29,40] Additionally, most of these events were virological rebounds after initial suppression or sustained viral blips, which were resolved without the need to change treatment, but after switching to the single-tablet regimen (STR) of lamivudine/dolutegravir when available.

Our analysis has some limitations. First, we detected a very low prevalence of key exposure factors such as low CD4 count and high viral load. Indeed, small sample size and low statistical power are possible explanations for our inconclusive results regarding the association between baseline CD4 count and risk of TF. The small proportion of participants with a baseline viral load of >500 000 copies/mL prevented us from evaluating a possible dose–response relationship between the viral load setpoint level and risk of TF. In addition, as in all analyses of real-world data, we cannot rule out residual and unmeasured confounding. The association with high viral load is intriguing and might be mediated by factors such as access to care and adherence to the regimen, which are unmeasured in our cohort. Like in other similar studies, there was low statistical power to evaluate long-term pure VF endpoints. An additional limitation concerns the variability in the criteria used to define VF (e.g. using the threshold of 200 instead of 50 copies/mL). This heterogeneity may limit the direct comparison of virological outcomes across studies.

Nevertheless, our study also has some strengths. First, real-world datasets like ours are the ideal setting to investigate risk factors for failure of 2DR regimens as they include vulnerable individuals who are typically excluded from RCTs and they also have longer follow-up. As such, our data are useful in describing the long-term response to lamivudine/dolutegravir when used as first-line treatment overall and in subgroups of vulnerable PWH. Although similar prospective studies have been performed before, to our knowledge ours is the one with the largest sample size and the longest follow-up, which allowed us to produce reliable estimates of the rate of failure up to 3 years from therapy initiation.

In conclusion, lamivudine/dolutegravir appears to be a safe and effective first-line regimen with good tolerability. However, as for other ART regimens, the main concern remains for PWH with advanced disease, particularly those with baseline viral load of >100 000 copies/mL and vulnerable populations with potential restricted access to care and therapy monitoring, who may face a higher risk of treatment failure in the long term. Further studies are needed to evaluate whether the risks estimated with lamivudine/dolutegravir are even higher than those seen with alternative first-line recommended regimens. Nevertheless, our findings underline the fact that clinicians should exercise special caution when starting ART in these vulnerable subgroups to prevent suboptimal adherence or discontinuations that could result in treatment failure.

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Author contributions

Conception: A.A., A.D.M., S.L.C.; study design: A.A., A.D.M., A.C.L., A.T.; accessing and verifying data: A.C.L., A.T.; statistical analysis: A.C.L.; acquisition of data: A.T., V.M., E.S., G.O.; draft of the manuscript: A.V., A.C.L, A.T., A.D.M.; patient enrolment: V.M., E.S., G.O., C.M., S.N., A.C.; review of the article and critical revision for important intellectual content: all authors; reading and final approval of the submitted version: all authors.

Data availability

The datasets generated during the current study are not publicly available because they contain sensitive data that must be treated under data protection laws and regulations. An appropriate data-sharing agreement can be arranged after a reasonable request to the corresponding author.

Supplementary data

Figure S1 and Tables S1–S8 are available as Supplementary data at *JAC* Online.

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