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Effectiveness and tolerability of dolutegravir/lamivudine for the treatment of HIV-1 infection in clinical practice

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Objectives: To assess the effectiveness and tolerability of dolutegravir (DTG)/lamivudine (3TC) among treatment-naive and virologically suppressed treatment-experienced individuals in the multicentre cohort of the Spanish HIV/AIDS Research Network (CoRIS) during the years 2018–2021.

Methods: We used multivariable regression models to compare viral suppression (VS) [HIV RNA viral load (VL) <50 copies/mL] and the change in CD4 cell counts at 24 and 48 (±12) weeks after initiation with dolutegravir/lamivudine or other first-line ART regimens.

Results: We included 2160 treatment-naive subjects, among whom 401 (18.6%) started with dolutegravir/lamivudine. The remaining subjects started bictegravir (BIC)/emtricitabine (FTC)/tenofovir alafenamide (TAF) ($n=949$, 43.9%), DTG+FTC/tenofovir disoproxil fumarate (TDF) ($n=282$, 13.1%), DTG/3TC/abacavir (ABC) ($n=255$, 11.8%), darunavir (DRV)/cobicistat(COBI)/FTC/TAF ($n=147$, 6.8%) and elvitegravir (EVG)/COBI/FTC/TAF ($n=126$, 5.8%). At 24 and 48 weeks after starting dolutegravir/lamivudine, 91.4% and 93.8% of the subjects, respectively, achieved VS. The probability of achieving VS with dolutegravir/lamivudine was not significantly different compared with any other regimen at 24 or 48 weeks, with the exception of a lower chance of achieving VS at 24 weeks for DRV/COBI/FTC/TAF (adjusted OR: 0.47; 95% CI: 0.30–0.74) compared with dolutegravir/lamivudine.
For the analysis of treatment-experienced virally suppressed subjects we included 1456 individuals who switched to dolutegravir/lamivudine, among whom 97.4% and 95.5% maintained VS at 24 and 48 weeks, respectively. During the first 48 weeks after dolutegravir/lamivudine initiation, 1.0% of treatment-naive and 1.5% of treatment-experienced subjects discontinued dolutegravir/lamivudine due to an adverse event.

Conclusions: In this large multicentre cohort, effectiveness and tolerability of dolutegravir/lamivudine were high among treatment-naive and treatment-experienced subjects.

Introduction

Although for many years the use of three antiretroviral drugs has been the standard treatment of HIV infection, two-drug regimens (dual therapy, DT) have been increasingly used with the aim of simplifying the treatment and minimizing toxicity. DT as a combination of dolutegravir (DTG) and lamivudine (3TC) has shown high efficacy and good safety and tolerability in clinical trials, both in treatment-naive[1,2] and treatment-experienced patients who are virologically suppressed.[3,4]

Clinical trials usually involve selected subjects that are not fully representative of the general population and take place in settings with frequent and standardized follow-up procedures that might not reflect day-to-day clinical practice.[5,6]. Therefore, it is important that the information from clinical trials of ART is complemented by real-life studies. Several cohort studies have evaluated the use of dolutegravir/lamivudine in clinical practice worldwide, confirming the results of the previous clinical trials.[7–10] However, these studies have several shortcomings, especially regarding treatment-naive patients. Most of them involve a limited number of subjects and/or a single centre: this limits the power of the study to compare its effectiveness with other ARTs and the analysis of certain subgroups of interest, such as those with low CD4 cell counts or high plasma viral loads (VLs). Most importantly, among treatment-naive patients, most of these cohorts are only descriptive, single-arm studies that do not compare the effectiveness of dolutegravir/lamivudine with other drug regimens. As an example, only two cohorts have studied dolutegravir/lamivudine as first-line therapy involving more than 100 subjects, and neither of them compared its effectiveness with other treatments.[7,10]

The aim of this study was to assess the effectiveness and tolerability of dolutegravir/lamivudine among treatment-naive and virologically suppressed treatment-experienced individuals in a large multicentre cohort in Spain. Specifically, among treatment-naive patients, we aimed to compare the effectiveness and tolerability of dolutegravir/lamivudine with the most frequently prescribed first-line three-drug regimens (3DRs), and to assess its effectiveness among specific subgroups such as those with low CD4 cell counts or high VLs.

Methods

Study design

The Cohort of the Spanish HIV/AIDS Research Network (CoRIS) is an open, multicentre, prospective cohort of HIV-positive adults, naive to ART at study entry, who were seen for the first time in a specialist HIV clinic from 1 January 2004 in any of the 47 centres from 14 of 17 Autonomous Regions in Spain, and followed up until 30 November 2021, the administrative censoring date for these analyses.

Briefly, CoRIS collects a minimum dataset as provided for in the cohort protocol, which includes baseline and follow-up sociodemographic, immunological and clinical data including data on antiretroviral medications with start and stop dates and reasons for drug discontinuation. Data are highly standardized and submitted to periodic quality control procedures. Individuals are followed up periodically in accordance with routine clinical practice.[11]

Study population

For analyses in treatment-naive individuals, we included those who started ART from August 2018 to November 2021. Individuals with no follow-up after ART initiation were excluded. Only regimens prescribed in >5% of individuals were considered.

For analyses in treatment-experienced individuals, we included those who were virologically suppressed switching to dolutegravir/lamivudine from January 2018 to November 2021. Specifically, individuals had to have an HIV RNA VL <50 copies/mL in the 6 months prior to switching to dolutegravir/lamivudine. Individuals with no follow-up after switching were excluded.

For all the analyses, we excluded individuals (i) aged <18 years and (ii) who received any of the regimens of interest in the context of a clinical trial.

Statistical analysis

Descriptive analyses were carried out using frequency tables for categorical variables, and median and IQR for continuous variables. Differences in sociodemographic and clinical characteristics were assessed with the non-parametric Mann–Whitney or Kruskal–Wallis test, as appropriate, for continuous variables, and the chi-squared test for independence for categorical variables.

To assess treatment effectiveness, for both antiretroviral-naive and treatment-experienced individuals, we calculated (i) the proportion of individuals who achieved or maintained, as appropriate, viral suppression (VS), defined as an HIV RNA VL <50 copies/mL; and (ii) the change in CD4 cell counts at 24 and 48 (±12) weeks after initiation or switch, respectively. Additionally, we calculated the proportion of virological failures (VFs), defined as two consecutive HIV RNA VL >50 copies/mL or one >1000 copies/mL after VS and prior to the assessment timepoint.

To assess treatment tolerability, we calculated the incidence and proportion of individuals who discontinued treatment due to adverse events (AEs) during the first 48 weeks after ART initiation or switching, as appropriate, as well as the substitution regimen. AEs were classified as neuropsychiatric (headache, dizziness, fatigue, insomnia, sleep disturbance, anxiety/depression, emotional instability), renal, gastrointestinal (nausea/vomiting, diarrhoea, abdominal pain), skin, liver, other and unknown.

To compare effectiveness and tolerability of dolutegravir/lamivudine with other first-line regimens in treatment-naive individuals, we used logistic regression models to estimate ORs of association between initial regimen and VS, linear regression to assess differences by initial regimen in mean changes in CD4 cell counts, and Poisson regression to estimate rate ratios (RRs) of association between initial treatment and the incidence of treatment discontinuations due to AEs. Multivariable models were adjusted for the following potential confounders: sex (male, female), age at ART initiation (<30, 30–49, ≥50 years), transmission category (MSM, heterosexual, other/unknown), educational level (no or compulsory education, secondary or university education, other/unknown), country of origin (Spain, foreign-born, unknown), CD4 cell count (<200, 200–500, >500 cells/mm^3, unknown) and VL (<100 000, ≥100 000 copies/mL, unknown) within the 6 months previous to ART initiation, hepatitis C virus antibodies (no, yes, unknown), hepatitis B virus surface antigen (no, yes, unknown) and AIDS at ART initiation (no, yes). To adjust for clustering of individuals within centres, robust methods were used to estimate standard errors. Wald tests were used to derive *P* values.

To assess the effectiveness of dolutegravir/lamivudine compared with other first-line antiretroviral regimens in different subgroups, we repeated the analyses of VS and change in CD4 cell counts in individuals who started ART with (i) CD4 <200 cells/μL, (ii) HIV RNA VL ≥100 000 copies/mL, (iii) HIV RNA VL ≥500 000 copies/mL, (iv) in those who started ART within 7 days from cohort enrolment, and (v) women.

For the analyses of VS and change in CD4 cell counts at 24 and 48 weeks after ART initiation or switch, only cases with available data within the assessment window were included; when more than one measurement was available within that window, we used the last available one. For the analyses of VF, only cases who achieved VS prior to the assessment timepoint and had at least one VL measurement after

achievement of VS and prior to the assessment timepoint were included. We performed both an ITT and on-treatment (OT) analyses. For ITT, outcomes were analysed by initial or switching regimen, as appropriate, and later changes in the regimen were ignored; therefore, once an individual started a regimen, he/she was assumed to remain on it. For OT, individuals who changed their initial or switching regimen before 24 or 48 weeks, as appropriate, were excluded from the analyses. In the subgroups analyses, only ITT analysis was performed.

All statistical analyses were performed using Stata software (version 16.0; Stata Corporation, College Station, TX, USA).

Ethics approval and informed consent

CoRIS cohort was approved by the Clinical Research Ethics Committee of the Gregorio Marañón General University Hospital. All individuals agree to participate in CoRIS by signing an informed consent form. This study was approved by the ethics committee of the Instituto de Salud Carlos III, Madrid, Spain (CEI PI 86_2020-v2).

Results

Treatment-naive individuals

During the study period, 2791 individuals aged ≥18 years initiated treatment. We excluded 84 (3.0%) with no follow-up after ART initiation, 276 (9.9%) starting ART in a clinical trial and 271 (9.8%) who initiated a treatment prescribed in <5% of individuals. Finally, 2160 individuals were included in the analyses, of whom 89.4% were male and 51.3% were foreign-born. Transmission route was homo/bisexual contact in 71.0% of the individuals and heterosexual contact in 22.9%. At treatment initiation, median age was 36 years (IQR: 28; 45), median CD4 cell count was 382 cells/mm^3 (IQR: 230; 551), 7.5% individuals had an AIDS-defining condition and 41.7% had an HIV RNA VL ≥100 000 copies/mL.

The most frequently prescribed initial regimen was bictegravir (BIC)/emtricitabine (FTC)/tenofovir alafenamide (TAF) (n=949, 43.9%), followed by dolutegravir/lamivudine (401, 18.6%), DTG+FTC/tenofovir disoproxil fumarate (TDF) (n=282, 13.1%), DTG/3TC/abacavir (ABC) (n=255, 11.8%), darunavir (DRV)/cobicistat (COBI)/FTC/TAF (n=147, 6.8%) and elvitegravir (EVG)/COBI/FTC/TAF (n=126, 5.8%). The preferred starting regimen changed over time: whereas DTG/3TC/ABC, DTG+FTC/TDF and EVG/COBI/FTC/TAF were the preferred options in 2018, BIC/FTC/TAF and dolutegravir/lamivudine were the most frequent options in 2021 (Figure 1). The proportion of subjects who started treatment with dolutegravir/lamivudine increased over time from 3.1% in 2018% to 26.8% in 2021 (Figure 1). A total of 1265 (56.8%) subjects started treatment during the first week after enrolment, of whom 226 (17.9%) started with dolutegravir/lamivudine.

There were differences in the sociodemographic and clinical characteristics of individuals according to their initial treatment (Figure 2). A higher proportion of MSM initiated treatment with dolutegravir/lamivudine. The proportion of migrants was higher among those initiating with EVG/COBI/FTC/TAF, and the proportion of individuals aged over 50 years was higher among those with DTG+FTC/TDF. The lowest proportion of individuals with CD4 counts <200 cells/mm^3 was found among those starting

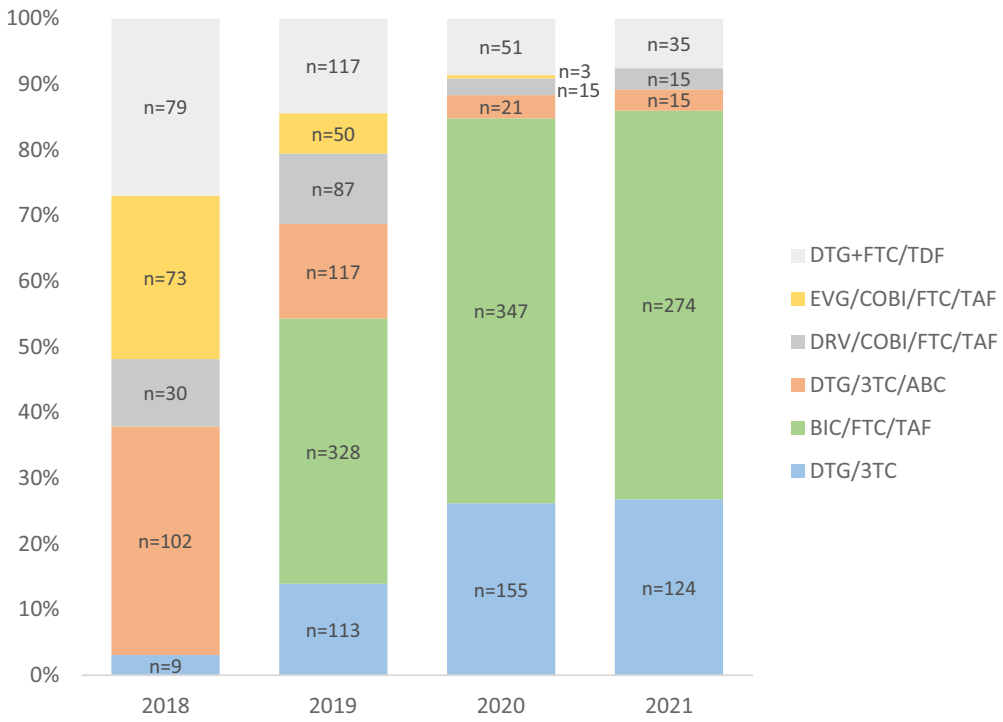

Figure 1. First-line antiretroviral regimens prescribed in antiretroviral-naive individuals from the CoRIS cohort, 2018–2021. DTG+FTC/TDF, dolutegravir+emtricitabine/tenofovir disoproxil fumarate; EVG/COBI/FTC/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; DRV/COBI/FTC/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DTG/3TC/ABC, dolutegravir/lamivudine/abacavir; BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; DTG/3TC, dolutegravir/lamivudine.

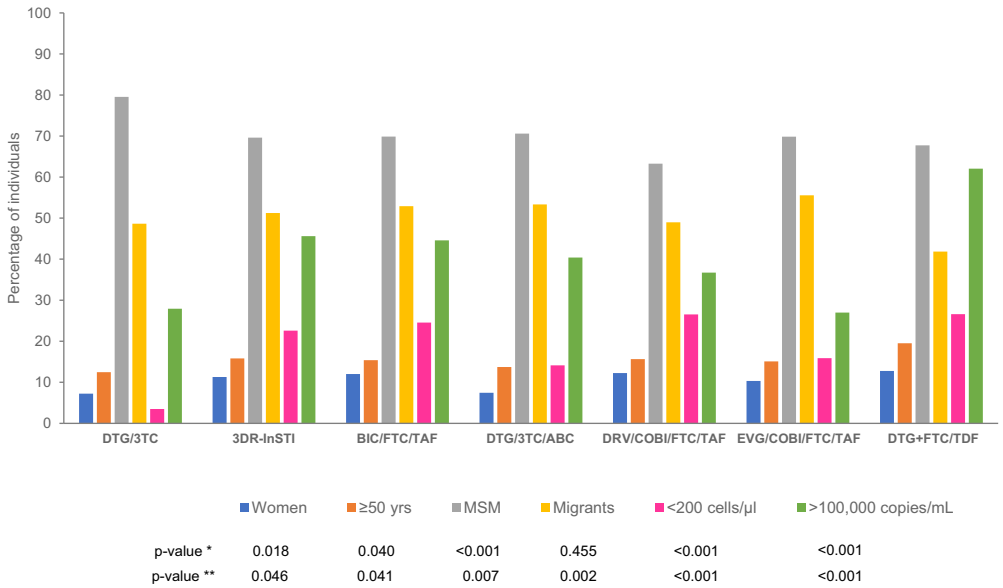

Figure 2. Sociodemographic and clinical characteristics of individuals at ART initiation according to first-line antiretroviral regimen, CoRIS cohort, 2018–2021. p-value ** 0.046 0.041 0.007 0.002 <0.001 <0.001 p-value * 0.018 0.040 <0.001 0.455 <0.001 <0.001 P values* for the comparison between DTG/3TC vs 3DR-InSTI (three-drug regimen including integrase inhibitor: BIC/FTC/TAF, DTG/3TC/ABC, EVG/COBI/FTC/TAF and DTG+FTC/TDF). P values** for the global comparison according to initial regimen. DTG/3TC, dolutegravir/lamivudine; 3DR-InSTI, three-drug regimen including integrase inhibitor (BIC/FTC/TAF, DTG/3TC/ABC, EVG/COBI/FTC/TAF and DTG+FTC/TDF); BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; DTG/3TC/ABC, dolutegravir/lamivudine/abacavir; DRV/COBI/FTC/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; EVG/COBI/FTC/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; DTG+FTC/TDF, dolutegravir+emtricitabine/tenofovir disoproxil fumarate.

with dolutegravir/lamivudine, and those starting with DTG+FTC/TDF showed a higher proportion of individuals with VL ≥100 000 copies/mL.

At 24 and 48 weeks from ART initiation, 91.4% and 93.8% of subjects initiating with dolutegravir/lamivudine achieved VS, and mean increase in CD4 cell counts was 205.7 cells/mm^3 (95% CI: 181.1–230.2) and 258.6 cells/mm^3 (224.0–293.2), respectively (Table 1). In multivariable analyses, we did not find significant differences in VS or CD4 cell count increase among individuals initiating with dolutegravir/lamivudine or other regimens, except for a lower chance of achieving VS at 24 weeks for DRV/COBI/FTC/TAF (adjusted OR: 0.47; 95% CI: 0.30–0.74) (Figure 3). Similar results were observed in the OT analyses (Table S1, available as Supplementary data at *JAC* Online).

Among the 401 subjects who started dolutegravir/lamivudine, 165 (41.1%) had baseline resistance tests available for NRTIs and 85 (21.2%) for integrase inhibitors. No subjects had resistance mutations for dolutegravir, and only one subject had baseline resistance mutations to lamivudine (M184V). This subject switched to DRV/COBI/FTC/TAF 1 week after the start of dolutegravir/lamivudine and achieved VS at 24 and 48 weeks.

Only two (1.4%) and three (1.5%) individuals who started dolutegravir/lamivudine experienced VF prior to 24 and 48 weeks, respectively. They are described in detail in Appendix S1. Due to the low number of VFs, we could not perform multivariable analysis to compare this outcome among all treatment regimens.

Table S2 summarizes results on the comparison of dolutegravir/lamivudine with other first-line antiretroviral regimens in VS and change in CD4 cell counts at 24 and 48 weeks from ART initiation in specific subgroups. The percentage of individuals starting dolutegravir/lamivudine who achieved VS at 24 weeks was 81.8% in those initiating with CD4 <200 cells/µL, 78.9% in those with HIV RNA VL ≥100 000 copies/mL and 55.6% in those initiating with a VL ≥500 000 copies/mL. These percentages increased to 83.3%, 89.5% and 83.3%, respectively, at 48 weeks from initiation of ART. In multivariable analyses, we did not find significant differences in the effectiveness of dolutegravir/lamivudine compared with other first-line antiretroviral regimens among individuals who started ART with an HIV RNA VL ≥100 000 copies/mL. Due to the small number of subjects who started dolutegravir/lamivudine with a CD4 cell count <200 cells/µL or with a VL ≥500 000 copies/mL, we were not able to provide adjusted estimates for comparisons in those subgroups. Among the individuals who started dolutegravir/lamivudine within 7 days of their enrolment in CoRIS, 89.4% and 92.2% achieved VS at 24 and 48 weeks, respectively, and no significant differences with other first-line antiretroviral regimens were found in multivariable analyses. Ninety percent of women who started ART with dolutegravir/lamivudine achieved VS at 24 weeks, this percentage increasing to 100.0% at 48 weeks. Due to the low number of women, we were not able to provide adjusted estimates for comparisons with other first-line ART regimens.

During the first 48 weeks after dolutegravir/lamivudine initiation, 1.0% of subjects discontinued treatment due to AEs, mainly neuropsychiatric. In multivariable analyses, individuals initiating EVG/COBI/FTC/TAF (adjusted RR: 5.55; 95% CI: 1.64–18.80) and those initiating DTG+FTC/TDF (adjusted RR: 10.52; 95% CI: 3.92–28.1) showed higher rates of discontinuation due to AEs than those initiating dolutegravir/lamivudine (Table 2).

Table 1. Viral suppression, virological failure and change in CD4 cell count at 24 and 48 weeks from ART initiation according to first-line antiretroviral regimen, CoRIS cohort, 2018–2021

		DTG/3TC *n* = 401	3DR-InSTI *n* = 1759	BIC/FTC/TAF *n* = 949	DTG/3TC/ABC *n* = 255	DRV/COBI/FTC/TAF *n* = 147	EVG/COBI/FTC/TAF *n* = 126	DTG + FTC/TDF *n* = 282
Viral suppression								
Individuals included, *n* (%)	Week 24	266 (66.3)	1149 (71.3)	646 (68.1)	189 (74.1)	122 (83.0)	102 (81.0)	212 (75.2)
	Week 48	160 (39.9)	873 (54.2)	446 (47.0)	173 (67.8)	87 (59.2)	92 (73.0)	162 (57.4)
Viral suppression, *n* (%)	Week 24	243 (91.4)	962 (83.7)	537 (83.1)	158 (83.6)	91 (74.6)	92 (90.2)	175 (82.5)
	Week 48	150 (93.8)	781 (89.5)	395 (88.6)	157 (90.8)	75 (86.2)	87 (94.6)	142 (87.7)
Virological failure								
Individuals included, *n* (%)	Week 24	143 (35.7)		305 (32.1)	104 (40.8)	30 (20.4)	45 (35.7)	119 (42.2)
	Week 48	197 (49.1)		478 (50.4)	167 (65.5)	75 (51.0)	88 (69.8)	172 (61.0)
Virological failure, *n* (%)	Week 24	2 (1.4)		2 (0.7)	2 (1.9)	2 (6.7)	1 (2.2)	2 (1.7)
	Week 48	3 (1.5)		8 (1.7)	5 (3.0)	2 (2.7)	2 (2.3)	5 (2.9)
Change in CD4 cell count								
Mean (95% CI) CD4 count at ART initiation (cells/μL)		390.0 (376.5–403.5)	372.6 (355.5–389.7)	447.3 (413.2–481.4)	388.5 (338.8–438.2)	475.1 (411.8–538.4)	357.4 (328.2–386.7)	390.0 (376.5–403.5)
Individuals included, *n* (%)	Week 24	267 (66.6)	1019 (63.2)	563 (59.3)	175 (68.6)	110 (74.8)	91 (72.2)	190 (67.4)
	Week 48	156 (38.9)	789 (48.9)	391 (41.2)	160 (62.7)	80 (54.4)	82 (65.1)	156 (55.3)
Mean change (95% CI) in CD4 count	Week 24	205.7 (181.1; 230.2)	206.6 (193.9; 219.2)	201.4 (184.3; 218.4)	202.0 (173.7; 230.3)	187.5 (150.2; 224.7)	179.9 (131.5; 228.3)	238.9 (209.9; 267.9)
	Week 48	258.6 (224.0; 293.2)	258.3 (242.8; 273.8)	244.8 (223.3; 266.3)	264.7 (229.8; 299.7)	246.0 (198.8; 293.2)	269.7 (221.1; 318.3)	279.5 (242.7; 316.3)

DTG/3TC, dolutegravir/lamivudine; 3DR-InSTI, three-drug regimen including integrase inhibitor (BIC/FTC/TAF, DTG/3TC/ABC, EVG/COBI/FTC/TAF and DTG + FTC/TDF); BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; DTG/3TC/ABC, dolutegravir/lamivudine/abacavir; DRV/COBI/FTC/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; EVG/COBI/FTC/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; DTG + FTC/TDF, dolutegravir + emtricitabine/tenofovir disoproxil fumarate.

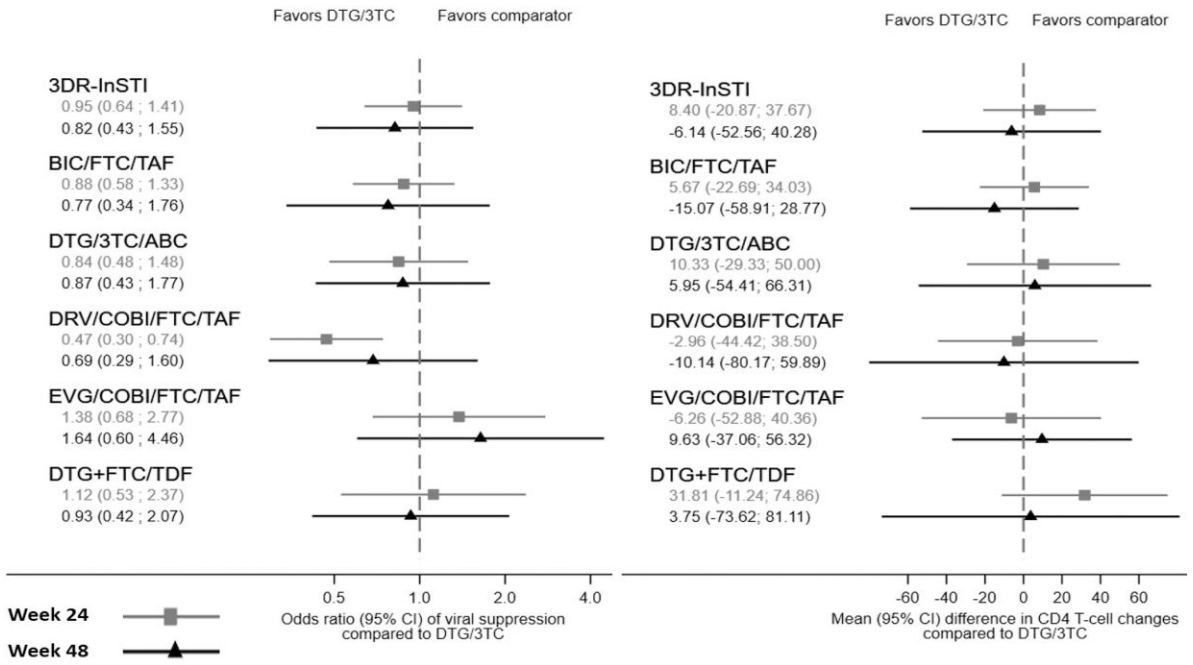

Figure 3. Adjusted comparison of viral suppression and change in CD4 cell counts at 24 and 48 weeks from ART initiation by first-line antiretroviral regimen, ITT analyses, CoRIS cohort, 2018–2021. Adjusted for sex, age at ART initiation, transmission category, educational level, country of origin, CD4 cell count and viral load within the 6 months previous to ART initiation, presence of hepatitis C virus antibodies, presence of hepatitis B virus surface antigen, and AIDS diagnosis at initiation of ART. Note: Subjects were not randomized to these treatments because they were prescribed in routine clinical practice. DTG/3TC, dolutegravir/lamivudine; 3DR-InSTI, three-drug regimen including integrase inhibitor (BIC/FTC/TAF, DTG/3TC/ABC, EVG/COBI/FTC/TAF and DTG+FTC/TDF); BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; DTG/3TC/ABC, dolutegravir/lamivudine/abacavir; DRV/COBI/FTC/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; EVG/COBI/FTC/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; DTG+FTC/TDF, dolutegravir+emtricitabine/tenofovir disoproxil fumarate.

Treatment-experienced individuals

A total of 1456 virally suppressed individuals switched to dolutegravir/lamivudine during the study period, of whom 87.1% were men, 69.6% were MSM and 43.8% were foreign-born. At treatment switching, median age was 43 years (IQR: 36; 52), median CD4 cell count was 746 cells/mm^3 (IQR: 548; 1022) and 12.3% of individuals had a history of an AIDS-defining condition. The proportion of individuals switching to dolutegravir/lamivudine increased from 12.4% in 2018% to 53.3% in 2021. Before the switch, subjects had been virologically suppressed for a median of 3.37 years (IQR: 1.40; 6.10), and they were receiving most frequently DTG/3TC/ABC (704 subjects, 48.5%) DTG+FTC/TDF (139, 9.6%) and DRV/COBI/FTC/TAF (109, 7.5%). Before switching to dolutegravir/lamivudine, 48 subjects (3.3%) had discontinued their treatment due to failure, of which 16 subjects (1.1%) had treatment failure with a regimen including lamivudine.

At 24 and 48 weeks after the switch, 97.4% (963/989) and 95.5% (682/714) of individuals maintained VS, the mean increase in CD4 cell counts was 18.7 cells/mm^3 (95% CI: 4.5–32.9) and 16.2 cells/mm^3 (95% CI: 0.1–32.3), and 8/1149 (0.7%) and 13/1264 (1.0%) individuals experienced VF, respectively. Among the 13 individuals who experienced VF prior to 48 weeks, 6 (46.2%) achieved VS again without treatment change, 4 (30.8%) achieved VS again after treatment change, and 3 (23.1%) did not achieve VS again before the censoring date.

Similar results were found in the OT analyses (data not shown). During the first 48 weeks after switching to dolutegravir/lamivudine, 1.5% of individuals discontinued treatment due to an AE, mainly neuropsychiatric (0.4%).

Discussion

This is, to our knowledge, the study that provides the highest number of treatment-naive and -experienced patients treated with dolutegravir/lamivudine in clinical practice reported to date. In this large multicentre cohort, we found high VS rates in both treatment-naive and in virologically suppressed, treatment-experienced patients at 24 and 48 weeks after dolutegravir/lamivudine initiation. Overall, the treatment had good tolerability in both groups of patients. The effectiveness of dolutegravir/lamivudine as first-line treatment was similar to that of the 3DRs analyzed.

Our cohort of treatment-naive subjects included mainly young MSM, and half of them were migrants, reflecting the epidemiology of HIV in Spain and other Western countries.[12] Among the subjects who started dolutegravir/lamivudine, 3.5% had CD4 counts <200 cells/mm^3 and 28% had high VL >100 000 copies/mL; as a comparison, the proportions of these subgroups in GEMINI trials were 9% and 20%, respectively.[1] The lower proportion of subjects with low CD4 counts and high VLs among those

Table 2. Treatment changes due to adverse events during the first 48 weeks after ART initiation, the reason for the change and substitution regimen, according to first-line antiretroviral regimen in the CoRIS cohort, 2018–2021

	DTG/3TC	3DR-InSTI	BIC/FTC/TAF	DTG/3TC/ABC	DRV/COBI/FTC/TAF	EVG/COBI/FTC/TAF	DTG+FTC/TDF
Treatment changes due to AE, *n* (%)	4 (1.0)	65 (4.0)	20 (2.1)	10 (3.9)	5 (3.4)	7 (5.6)	28 (9.9)
Gastrointestinal	1 (0.2)	9 (0.6)	3 (0.3)	3 (1.2)	2 (1.4)	2 (1.6)	1 (0.4)
Liver	0 (0.0)	2 (0.1)	1 (0.1)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Neuropsychiatric	3 (0.7)	11 (0.7)	3 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	7 (2.5)
Renal	0 (0.0)	17 (1.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	16 (5.7)
Skin	0 (0.0)	7 (0.4)	3 (0.3)	0 (0.0)	3 (2.0)	1 (0.8)	3 (1.1)
Other	0 (0.0)	17 (1.1)	7 (0.7)	5 (2.0)	0 (0.0)	4 (3.2)	1 (0.4)
Unknown	0 (0.0)	2 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Interruption rate due to AE	1.5 (0.6; 4.0)	6.1 (4.8; 7.8)	3.1 (2.0; 4.8)	5.0 (2.7; 9.3)	4.4 (1.8; 10.6)	9.0 (4.3; 18.8)	19.5 (13.5; 28.3)
Adjusted RR (95% CI)[a]	1	3.67 (1.27; 10.71)	1.74 (0.62; 4.86)	3.11 (0.87; 11.13)	2.69 (0.79; 9.18)	5.55 (1.64; 18.80)	10.52 (3.92; 28.19)
Most frequent substitution regimen, *n* (%)	RPV+FTC/TAF (50.0)	DTG/3TC/ABC (18.5)	DTG/3TC (20.0)	EVG/COBI/FTC/TAF (30.0)	BIC/FTC/TAF (60.0)	BIC/FTC/TAF (28.6)	DTG/3TC/ABC (25.0)

AE, adverse event; DTG/3TC, dolutegravir/lamivudine; 3DR-InSTI, three-drug regimen including integrase inhibitor (BIC/FTC/TAF, DTG/3TC/ABC, EVG/COBI/FTC/TAF and DTG+FTC/TDF); BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; DTG/3TC/ABC, dolutegravir/lamivudine/abacavir; DRV/COBI/FTC/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; EVG/COBI/FTC/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; DTG+FTC/TDF, dolutegravir+emtricitabine/tenofovir disoproxil fumarate.

[a]Adjusted for sex, age at ART initiation, transmission category, educational level, country of origin, CD4 cell count and viral load within the 6 months previous to ART initiation, presence of hepatitis C virus antibodies, presence of hepatitis B virus surface antigen, and AIDS diagnosis at initiation of ART.

starting dolutegravir/lamivudine is probably due to the fact that Spanish HIV treatment guidelines recommended starting treatment with dolutegravir/lamivudine only for patients with VL <500 000 copies/mL and CD4 count ≥200 mm^3 throughout the study period.[13]

Since January 2019 Spanish HIV treatment guidelines have recommended dolutegravir/lamivudine for treatment-naive subjects,[13] and its prescription increased after that year: in 2020 and 2021, one in four patients started ART with dolutegravir/lamivudine. The effectiveness of dolutegravir/lamivudine as first-line treatment was high at 24 and 48 weeks both in the ITT and the OT analyses; these findings are in line with those found in the GEMINI trials and in other cohort studies.[1,9] Most importantly, dolutegravir/lamivudine effectiveness did not differ significantly from that of the triple first-line treatments analyzed including an integrase inhibitor: this is the first reasonably sized cohort study that shows comparative effectiveness of dolutegravir/lamivudine and other ARTs among treatment-naive patients. We only found a lower probability of VS among subjects starting treatment with DRV/COBI/FTC/TAF compared with dolutegravir/lamivudine at week 24 (but not at week 48): we cannot exclude that this difference could be in part due to residual confounding because physicians might be more likely to prescribe darunavir-based regimens to individuals with perceived risk of low treatment compliance. CD4 count recovery did not show differences among any of the first-line treatments.

Although dolutegravir/lamivudine was prescribed less frequently to individuals with CD4 counts <200 mm^3 or VLs ≥100 000 copies/mL, women or elderly persons, the results of the comparative analysis did not change after adjusting for these and other potential confounding factors. Also, in the subgroup analysis, dolutegravir/lamivudine had high effectiveness among subjects with VLs ≥100 000 copies/mL, and it did not show significant differences with the 3DRs analyzed after adjusting for other factors. Effectiveness was also high among subjects with CD4 counts <200 mm^3 and those with VLs ≥500 000 copies/mL, but we could not assess the comparative effectiveness in these subgroups due to the low number of persons who received dolutegravir/lamivudine. Due to the low number of patients who received this regimen with CD4 counts <200 mm^3 and with VLs ≥500 000 copies/mL, we cannot draw firm conclusions about its effectiveness compared with other first-line treatments.

The STAT clinical trial demonstrated the efficacy of initiating dolutegravir/lamivudine less than 14 days after HIV diagnosis and without availability of baseline laboratory test results.[2] Our results suggest that this test-and-treat approach is also effective in clinical practice. More than half of the subjects who started ART with dolutegravir/lamivudine did so within 1 week after their first specialist consultation: among these 226 subjects, treatment effectiveness was high and similar to that of 3DRs. In Spain, both HIV-specific laboratory tests (such as CD4 count, VL and resistance testing) and HIV treatment prescription can only be provided in specialized clinics. Two other cohorts have assessed this rapid treatment approach. At 48 weeks after starting first-line ART, Hidalgo-Tenorio *et al.* found an effectiveness of 86% among 88 patients who started dolutegravir/lamivudine in the first week after their first specialist consultation,[8] and Cabello *et al.* found an effectiveness of 85% among 135 patients, 72% of whom did not have the results of resistance testing available

at the start of treatment;[7] neither cohort compared dolutegravir/lamivudine treatment effectiveness with 3DRs.

Similar to treatment-naive subjects, the virally suppressed individuals who switched to dolutegravir/lamivudine were also mainly MSM and with a high proportion of migrants. Almost one-third of them were over 50 years old, and they generally had a good immunological status. Among these subjects, effectiveness was also high because more than 95% of them remained virally suppressed at 24 and 48 weeks after the switch.

Tolerability of dolutegravir/lamivudine was excellent in both treatment-naive and treatment-experienced subjects, with less than 2% of the patients having to change their treatment due to adverse events. This proportion is consistent with the good tolerability found in clinical trials[1,2,4] and is in the low range of those reported by other real-world studies: a recent systematic review described a proportion of treatment changes due to adverse effects ranging from 1.7% to 7.9% among seven cohorts.[9] Among treatment-naive subjects, dolutegravir/lamivudine had the lowest proportion of subjects who changed their treatment due to adverse events and, after adjusting for other risk factors, the risk of this change was significantly lower for dolutegravir/lamivudine compared with either EVG/COBI/FTC/TAF or DTG + FTC/TDF.

Our study has several strengths. It is a large multicentre cohort with strict quality control procedures, and is representative of the newly diagnosed HIV-infected general population in Spain.[12] It also provides a high number of treatment-naive and treatment-experienced subjects, which allows the comparison of effectiveness among different first-line regimens. The limitations include those inherent to observational studies, such as residual confounding. The selection of the treatments was not randomized and, as we have shown, neither was it homogeneous according to different clinical and demographic characteristics; therefore, we cannot exclude selection bias. Also, due to the retrospective design, there are missing data for all outcomes and the proportion of VFs might have been underestimated. The study timeframe included the start of the COVID-19 pandemic in Spain, which probably increased the amount of missing data during that period. Finally, the frequency of VL testing is the one used in routine clinical practice and therefore it is not standardized for all patients in the cohort: this could bias our results if different treatment regimens had different frequency of VL testing.

Regarding generalizability, our cohort includes subjects treated in the public healthcare system, where ART, specialist consultations and laboratory tests are provided free of charge for all patients; the results might not be fully applied to other settings such as private healthcare systems or low-income countries.

In conclusion, in this Spanish multicentre cohort, dolutegravir/lamivudine showed high effectiveness and tolerability at 24 and 48 weeks. This is the first analysis of dolutegravir/lamivudine compared with 3DRs among treatment-naive individuals in a large cohort in clinical practice, showing that its effectiveness is comparable to 3DRs including those with VL ≥100 000 copies/mL and those starting treatment in the first week of specialist consultation. Effectiveness and tolerability were also high among virally suppressed subjects who switched to dolutegravir/lamivudine. These findings confirm the results of clinical trials in a real-world setting.

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Author contributions

All authors were involved in the setting up of the cohort and contributed to its design. All authors were involved in data collection. I.J. and I.S.-G. asked the research question and designed the study. B.A. analysed the data. B.A., I.S.-G. and I.J. wrote the first draft of the paper. All authors were involved in the interpretation of the data and commented on interim drafts. All authors have read and approved the final draft.

Supplementary data

Tables S1 and S2 and Appendix S1 are available as Supplementary data at *JAC* Online.

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