

# Long-term effectiveness and tolerability of dolutegravir/lamivudine in treatment-naïve people with HIV: an analysis of a multicentre cohort at 96 weeks

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**Objectives:** To evaluate the long-term effectiveness, persistence and tolerability of dolutegravir (DTG)/lamivudine (3TC), compared with the most frequently prescribed first-line treatment regimens, among antiretroviral-naïve people with HIV from CoRIS, a multicentre cohort in Spain, in 2018–23.

**Methods:** We used multivariable regression models to compare viral suppression (VS) (HIV RNA viral load <50 copies/mL), change in CD4 cell counts, persistence and treatment discontinuations due to adverse events (AEs), at 96 (±24) weeks after treatment initiation.

**Results:** Of 2359 participants, DTG/3TC was prescribed in 472 (20.0%), bicittegravir/tenofovir alafenamide (TAF)/emtricitabine (FTC) in 1134 (48.1%), DTG + tenofovir disoproxil fumarate/FTC in 300 (12.7%), DTG/abacavir/3TC in 273 (11.6%) and darunavir/cobicistat/TAF/FTC in 180 (7.6%). At 96 weeks from treatment initiation, 94.0% of participants initiating with DTG/3TC achieved VS, and the mean increase in CD4 cell counts was 295.5 cells/μL (95% CI: 269.9–321.1). During the first 96 weeks after DTG/3TC initiation, 9.8% and 1.3% discontinued their initial regimen, overall and due to AEs, respectively. In multivariable analyses, we did not find significant differences in VS or increase in CD4 cell counts among participants initiating with DTG/3TC compared with other regimens. Initiating ART with a regimen other than DTG/3TC was associated with a higher risk of treatment discontinuation, overall and due to AEs.

**Conclusions:** Among treatment-naïve people with HIV from this large multicentre cohort, DTG/3TC had similar effectiveness and better persistence and tolerability than those of the most frequently prescribed first-line regimens at 96 weeks.

## Introduction

Dolutegravir (DTG)/lamivudine (3TC) has shown high efficacy as a first-line antiretroviral treatment (ART) for people with HIV (PWH) in clinical trials<sup>1,2</sup> and is now recommended in the main clinical practice guidelines for treatment-naïve and virally suppressed PWH.<sup>3–5</sup> The use of DTG/3TC in clinical practice has allowed an increasing number of cohort studies that have confirmed its effectiveness in diverse real-world settings.<sup>6</sup> Evidence from cohort studies is important, as they usually include participants that are more representative of the general population than those from clinical trials, and they take place in settings that better relate to day-to-day clinical practice.<sup>7</sup>

As PWH need life-long ART, it is important to assess its long-term effectiveness and durability. Results from the GEMINI clinical trials have confirmed the efficacy, safety and high barrier to resistance of DTG/3TC at 96 and 144 weeks in treatment-naïve participants.<sup>8,9</sup> However, there is very little evidence on long-term effectiveness of DTG/3TC from cohort studies. Specifically, in treatment-naïve participants, only two cohorts have assessed its effectiveness at specific timepoints beyond 48 weeks: REDOLA, including 185 participants in Spain,<sup>10</sup> and URBAN, including 31 participants in Germany.<sup>11</sup> Both were descriptive studies, and neither of them compared the effectiveness of DTG/3TC with other first-line treatments.

We have previously published the treatment outcomes of treatment-naïve and virally suppressed participants at 48 weeks after initiation of DTG/3TC from CoRIS, a large multicentre cohort of PWH in Spain.<sup>12</sup> The aims of this study were to assess the effectiveness, tolerability and persistence of DTG/3TC at 96 weeks among treatment-naïve participants in the CoRIS cohort, compared with other first-line ARTs, and to assess its effectiveness and tolerability in specific subgroups that are underrepresented in clinical trials and might be at risk of suboptimal response to ART in the long term.

## Materials and methods

### Study design

CoRIS is an open, multicentre and prospective cohort of adults with HIV who are naïve to ART at study entry. Participants in CoRIS were seen for the first time in specialist HIV clinics, recruited from 1 January 2004 in any of the 48 participating centres from 14 of 17 autonomous regions in Spain and followed up until 30 November 2023, 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.<sup>13</sup>

### Study population

For this study, we included ART-naïve individuals from the CoRIS cohort, aged  $\geq 18$  years, who started ART with DTG/3TC or other first-line regimens between 1 August 2018 and 30 November 2021 to ensure that all participants could be followed for at least 96 weeks. For all the analyses, we excluded individuals (i) who started ART in the context of a clinical trial or (ii) with no follow-up after ART initiation. Only regimens prescribed in  $>5\%$  of individuals were considered.

## Outcomes

The primary outcomes were as follows: (i) viral suppression (VS), defined as an HIV RNA viral load (VL)  $<50$  copies/mL at 96 ( $\pm 24$ ) weeks after initiation of ART, and (ii) virological failure (VF) after VS, defined as two consecutive HIV RNA VL levels  $>50$  copies/mL or one  $>1000$  copies/mL after VS and prior to 96 weeks after initiation.

The secondary outcomes included: (i) immunological response (IR), defined as the change in CD4 cell counts at 96 ( $\pm 24$ ) weeks after ART initiation, (ii) persistence, defined as time-to-treatment discontinuation (i.e. stopping or changing any component of the regimen) during the first 96 weeks after initiation of ART and reason for discontinuation and (iii) incidence of treatment discontinuations due to adverse events (AEs) over 96 weeks after initiation and description of the AE.

Reasons for treatment discontinuation were classified as treatment failure, AE, simplification, drug interaction, patient's wish/decision, pregnancy, enrolment in a clinical trial, cost reduction, toxicity prevention, other and unknown. In turn, AEs were classified as neuropsychiatric (headache, dizziness, fatigue, insomnia, sleep disturbance, anxiety/depression, emotional instability), renal, gastrointestinal (nauseas/vomiting, diarrhoea, abdominal pain), skin, liver, weight gain, other and unknown.

For the analyses of VS and IR at 96 weeks after ART initiation, 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 after VS, only cases with at least one measurement available after VS were included. We performed both ITT and on-treatment (OT) analyses. For ITT analysis, outcomes were analysed by initial regimen and later changes in the regimen were ignored; therefore, once a participant started a regimen, he/she was assumed to remain on it. For OT analysis, participants who changed their initial regimen before 96 weeks were excluded.

## 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 at ART initiation were assessed with the non-parametric Kruskal–Wallis test for continuous variables and the  $\chi^2$  test for independence for categorical variables.

We used logistic and linear regression, respectively, to assess differences by first-line regimen in the proportion of individuals who achieved VS and the mean change in CD4 cell count at 96 ( $\pm 24$ ) weeks after ART initiation. Additionally, among individuals who achieved VS any time within the first 96 weeks, we calculated the proportion who experienced VF prior to the assessment timepoint.

To describe persistence, we used the multiple decrement method to compute the cumulative incidence curve of treatment discontinuation, considering deaths before the discontinuation as competing events, and used proportional hazards models on the sub-distribution hazard to evaluate differences according to the initial regimen. The incidence rate of treatment discontinuations due to AE per 1000 persons-year was calculated, and Poisson's regression was used to assess differences by first-line regimen. For both analyses of persistence and incidence of treatment discontinuations due to AEs, follow-up started at ART initiation and ended at date of any treatment discontinuation or discontinuation due to AE, respectively, death, last study contact or after 96 weeks, whichever arose first.

In subgroup analyses, we specifically assessed VS and the incidence of treatment discontinuations due to AE in participants who started ART with (i) CD4  $<200$  cells/ $\mu\text{L}$ , (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, (v) in women and (vi) in those aged  $\geq 50$  years.

Multivariable models were adjusted for the following potential confounders: sex (male, female), age at ART initiation ( $<30$ ,  $30\text{--}49$ ,  $\geq 50$  years), transmission category (sex between men, sex between men and women, other/unknown), educational level (no education/compulsory education,

secondary/university education, other/unknown), country of origin (Spain, no Spain, unknown), CD4 cell count (<200, 200–500, >500 cells/μL, unknown) and VL (≤100,000, >100,000 copies/mL, unknown) within 6 months previous to ART initiation, HCV antibodies (no, yes, unknown), HBV surface antigen (no, yes, unknown) and previous AIDS diagnosis at ART initiation (no, yes). To adjust for clustering of participants within centres, robust methods were used to estimate standard errors. Wald’s tests were used to derive *P* values. All statistical analyses were performed using Stata software (version 18.0; 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 participants agreed 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

During the study period, 3121 PWH aged ≥18 years started ART. Of those, we excluded 326 (10.4%) who initiated ART in the context of a clinical trial, 18 (0.6%) with no follow-up after ART initiation and 418 (13.4%) who initiated a treatment prescribed in <5% of individuals. Finally, 2359 PWH were included; their socio-demographic and clinical characteristics at ART initiation are given in Table S1 (available as Supplementary data at JAC Online). DTG/3TC was prescribed in 472 (20.0%) PWH, bicitgravir (BIC)/tenofovir alafenamide (TAF)/emtricitabine (FTC) in 1134 (48.1%), DTG+FTC/tenofovir disoproxil fumarate (TDF) in 300 (12.7%), DTG/abacavir (ABC)/3TC in 273 (11.6%) and darunavir (DRV)/cobicistat (COBI)/TAF/FTC in 180 (7.6%). DTG/3TC was available as a single treatment regimen in Spain in January 2020, and therefore, in all centres, it was prescribed as two separate pills until January 2020 and as a single pill thereafter. The proportion of PWH who started DTG/3TC increased gradually from 4.4% in 2018 to 24.8% in 2021. PWH who initiated ART with DTG/3TC were more frequently younger men, had contracted HIV through sex between men and had secondary or university studies. Additionally, they often started ART with a higher CD4 cell count and a VL ≤100,000 copies/mL and without a previous AIDS diagnosis (Table S1). A total of 1336 (56.6%) PWH started treatment in the first week after cohort enrolment; among PWH starting DTG/3TC, 214/472 (45.3%) started treatment in the first week.

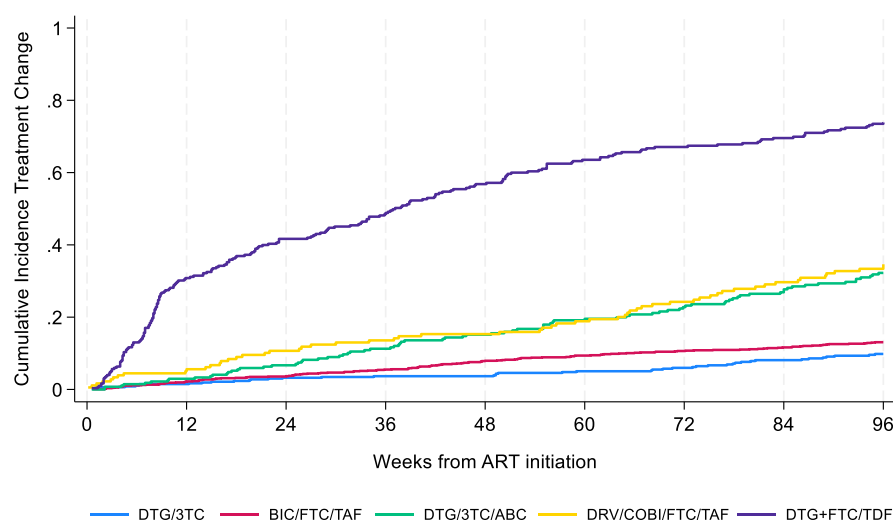
VS, IR and VF

Overall, in ITT analyses, VS and IR at 96 weeks after ART initiation were evaluated in 1798 (76.2%) and 1687 (71.5%) PWH, respectively. Reasons for exclusion in these analyses are detailed in Table S2. Briefly, we failed to find significant differences in the sociodemographic and clinical characteristics of participants included and excluded except for a slightly higher percentage of participants with CD4 cell count <200 cells/μL and VL >100,000 copies/mL among those included (data not shown). At 96 weeks from ART initiation, 94.0% of PWH initiating with DTG/3TC achieved VS, and the mean increase in CD4 cell counts was 295.5 cells/μL (95% CI: 269.9–321.1). In multivariable analyses, we did not find significant differences in VS and IR among participants initiating with DTG/3TC or other regimens (Table 1). Similar results were observed in the OT analyses (Table 1).

Table 1. VS, IR and VF at 96 weeks from ART initiation according to first-line antiretroviral regimen, CoRIS cohort, 2018–23

|                  | VS                |                                   | IR                                       |                                                                           | VF                |  |
|------------------|-------------------|-----------------------------------|------------------------------------------|---------------------------------------------------------------------------|-------------------|--|
|                  | N/N with data (%) | Adjusted OR (95% CI) <sup>a</sup> | Mean increase in CD4 cell count (95% CI) | Adjusted mean difference in CD4 cell count increase (95% CI) <sup>a</sup> | N/N with data (%) |  |
|                  |                   |                                   |                                          |                                                                           |                   |  |
| ITT analyses     |                   |                                   |                                          |                                                                           |                   |  |
| DTG/3TC          | 328/349 (94.0)    | Ref.                              | 295.5 (269.9; 321.1)                     | Ref.                                                                      | 6/386 (1.6)       |  |
| BIC/FTC/TAF      | 791/881 (89.8)    | 0.87 (0.48; 1.57)                 | 315.6 (299.1; 332.1)                     | 10.82 (−22.93; 44.56)                                                     | 63/972 (6.5)      |  |
| DTG/3TC/ABC      | 192/207 (92.8)    | 1.22 (0.52; 2.82)                 | 309.3 (276.8; 341.7)                     | 13.67 (−30.09; 57.43)                                                     | 17/235 (7.2)      |  |
| DRV/COBI/FTC/TAF | 123/135 (91.1)    | 1.12 (0.50; 2.52)                 | 294.5 (248.7; 340.2)                     | −2.57 (−69.88; 64.73)                                                     | 8/141 (5.7)       |  |
| DTG+FTC/TDF      | 199/226 (88.1)    | 0.93 (0.45; 1.92)                 | 362.6 (326.0; 399.1)                     | 43.09 (7.35; 78.82)                                                       | 13/241 (5.4)      |  |
| OT analyses      |                   |                                   |                                          |                                                                           |                   |  |
| DTG/3TC          | 302/318 (95.0)    | Ref.                              | 300.6 (274.5; 326.6)                     | Ref.                                                                      | 4/354 (1.1)       |  |
| BIC/FTC/TAF      | 703/771 (91.2)    | 0.76 (0.36; 1.60)                 | 318.0 (300.2; 335.7)                     | 13.34 (−24.87; 51.55)                                                     | 42/852 (4.9)      |  |
| DTG/3TC/ABC      | 137/145 (94.5)    | 1.28 (0.43; 3.79)                 | 314.6 (274.9; 354.3)                     | 14.29 (−37.67; 66.24)                                                     | 13/163 (8.0)      |  |
| DRV/COBI/FTC/TAF | 87/91 (95.6)      | 1.67 (0.45; 6.13)                 | 281.9 (222.0; 341.9)                     | −9.87 (−85.45; 65.70)                                                     | 3/91 (3.3)        |  |
| DTG+FTC/TDF      | 55/59 (93.2)      | 1.54 (0.43; 5.51)                 | 309.8 (240.2; 379.4)                     | −14.16 (−66.46; 38.13)                                                    | 3/64 (4.7)        |  |

<sup>a</sup>Adjusted for sex, age at ART initiation, transmission category, educational level, country of origin, CD4 cell count and VL within 6 months previous to ART initiation, presence of HCV antibodies, presence of HBV surface antigen and previous AIDS diagnosis at ART initiation.



|                         | 96-Week Cumulative Incidence | Adjusted sHR (95% CI)* |
|-------------------------|------------------------------|------------------------|
| <b>DTG/3TC</b>          | 9.8                          | Ref.                   |
| <b>BIC/FTC/TAF</b>      | 13.1                         | 1.44 (1.06; 1.95)      |
| <b>DTG/3TC/ABC</b>      | 32.2                         | 3.81 (2.45; 5.94)      |
| <b>DRV/COBI/FTC/TAF</b> | 34.6                         | 4.22 (2.82; 6.32)      |
| <b>DTG+FTC/TDF</b>      | 73.8                         | 15.82 (10.21; 24.53)   |

**Figure 1.** Cumulative incidence curve of treatment discontinuation during the first 96 weeks after ART initiation according to first-line antiretroviral regimen, CoRIS cohort, 2018–23. sHR, sub-distribution hazard ratio. \*Adjusted for sex, age at ART initiation, transmission category, educational level, country of origin, CD4 cell count and VL within 6 months previous to ART initiation, presence of HCV antibodies, presence of HBV surface antigen and previous AIDS diagnosis at ART initiation.

Of the PWH who started DTG/3TC and achieved VS anytime within the following 96 weeks, 6 (1.6%) subsequently experienced VF. They are described in detail in Tables S3A and S3B. Two of them had stopped taking their treatment and were not receiving any ART at the time of failure. Of the remaining four PWH on treatment at VF, three were still receiving DTG/3TC and one was receiving DTG/ABC/3TC. After VF, the two PWH who were not receiving treatment reinitiated DTG/3TC and the four PWH who were on treatment did not change their antiretroviral regimen (three of them continued with DTG/3TC and one continued with DTG/ABC/3TC). Among those PWH with VF who had resistance testing available, no *de novo* resistance mutations were documented.

### Persistence and tolerability

During the first 96 weeks of ART initiation, 9.8% of PWH who started DTG/3TC discontinued their initial regimen. The percentage of discontinuations varied between 13.1% and 73.8% among the other regimens analysed. In multivariable analysis, initiating ART with a regimen other than DTG/3TC was associated with a higher risk of treatment discontinuation (Figure 1). Simplification was the most frequent reason for treatment discontinuation in all regimens except DTG/3TC. A detailed description of reasons

for treatment discontinuation and substitution regimens is given in Table 2.

Treatment discontinuations due to AEs are given in Table 3. The percentage of discontinuations of DTG/3TC due to AEs was 1.3%; the rate of treatment discontinuations was lower for DTG/3TC than for all the other regimens, even after adjusting for other risk factors (Table 3). The most common AE leading to discontinuation was neuropsychiatric toxicity for all regimens except DRV/COBI/FTC/TAF and DTG+FTC/TDF (Table 3).

### Effectiveness and tolerability in specific subgroups

Table S4 summarizes the results of VS and treatment discontinuations due to AEs at 96 weeks after ART initiation according to first-line regimens in specific subgroups. For the subgroup who started treatment within 7 days of enrolment, the median time from HIV diagnosis to cohort enrolment was 2 (IQR: 0–5) days. In multivariable analyses, no significant differences in VS were found between DTG/3TC and other first-line ART regimens among PWH initiating treatment with >100 000 copies/mL, and those who started within 7 days of enrolment or aged ≥50 years. Due to the low number of participants initiating DTG/3TC, we could not perform multivariable analyses in the rest of the

**Table 2.** Reasons for treatment discontinuation during the first 96 weeks after ART initiation and substitution regimen, according to first-line regimen, CoRIS cohort, 2018–23

|                                              | DTG/3TC<br>n = 472      | BIC/FTC/TAF<br>n = 1134 | DTG/3TC/ABC<br>n = 273 | DRV/COBI/FTC/TAF<br>n = 180 | DTG + FTC/TDF<br>n = 300 |
|----------------------------------------------|-------------------------|-------------------------|------------------------|-----------------------------|--------------------------|
| No. of treatment discontinuations            | 43                      | 140                     | 82                     | 60                          | 216                      |
| Reason for treatment discontinuation [N (%)] |                         |                         |                        |                             |                          |
| Treatment failure                            |                         |                         |                        |                             |                          |
| AE                                           | 5 (1.1)                 | 13 (1.1)                | 2 (0.7)                | 3 (1.7)                     | 3 (1.0)                  |
| Simplification                               | 6 (1.3)                 | 31 (2.7)                | 16 (5.9)               | 10 (5.6)                    | 36 (12.0)                |
| Drug interaction                             | 4 (0.8)                 | 27 (2.4)                | 48 (17.6)              | 16 (8.9)                    | 136 (45.3)               |
| Patient's wish/decision                      | 1 (0.2)                 | 7 (0.6)                 | 1 (0.4)                | 9 (5.0)                     | 3 (1.0)                  |
| Pregnancy                                    | 9 (1.9)                 | 9 (0.8)                 | 3 (1.1)                | 2 (1.1)                     | 2 (0.7)                  |
| Enrolment in a clinical trial                | 1 (0.2)                 | 11 (1.0)                | 0                      | 3 (1.7)                     | 1 (0.3)                  |
| Cost reduction                               | 4 (0.8)                 | 8 (0.7)                 | 1 (0.4)                | 3 (1.7)                     | 1 (0.3)                  |
| Toxicity prevention                          | 0 (0.0)                 | 1 (0.1)                 | 0                      | 0                           | 1 (0.3)                  |
| Other                                        | 2 (0.4)                 | 11 (1.0)                | 2 (0.7)                | 2 (1.1)                     | 15 (5.0)                 |
| Unknown                                      | 8 (1.7)                 | 18 (1.6)                | 7 (2.6)                | 8 (4.4)                     | 15 (5.0)                 |
| Most frequent substitution regimens (%)      |                         |                         |                        |                             |                          |
|                                              | 3 (0.6)                 | 4 (0.4)                 | 2 (0.7)                | 4 (2.2)                     | 3 (1.0)                  |
|                                              | BIC/FTC/TAF (27.9)      | DTG/3TC (24.3)          | DTG/3TC (64.6)         | BIC/FTC/TAF (38.3)          | DTG/3TC (45.8)           |
|                                              | DRV/COBI/FTC/TAF (16.3) | DRV/COBI/FTC/TAF (17.1) | BIC/FTC/TAF (13.4)     | DTG/3TC (16.7)              | DTG/3TC/ABC (27.8)       |
|                                              | CAB + RPV (11.6)        | DTG/3TC/ABC (7.1)       | DRV/COBI/FTC/TAF (6.1) | DTG/RPV (8.3)               | BIC/FTC/TAF (11.6)       |

subgroups analysed. The percentage of discontinuations of DTG/3TC due to AEs was <4% in all the subgroups analysed.

Discussion

In this large multicentre cohort, we have shown high effectiveness and tolerability of DTG/3TC at 96 weeks among treatment-naïve PWH. Moreover, we have shown that its effectiveness did not differ significantly to that of the most frequently prescribed three-drug regimens and has higher persistence and lower rate of discontinuations due to AEs than these regimens. To our knowledge, this is the first cohort study comparing long-term effectiveness and tolerability of DTG/3TC to other ARTs among treatment-naïve PWH. These results are consistent with a previous analysis at 48 weeks of this same cohort.<sup>12</sup>

During the study period, the proportion of PWH who started ART with DTG/3TC increased gradually from 4.4% in 2018 to 24.8% in 2021. This trend reflects the changes in the national clinical guidelines for ART: regarding the recommendations for initial ART, DTG/3TC was not included as an option in 2018, it was considered alternative in 2019 and it was included as a preferred treatment since 2020.<sup>14–16</sup>

The assessment of long-term treatment effectiveness is especially important in real-life clinical practice, as the participants are usually not selected, have less strict follow-up procedures and might be more difficult to treat than those enrolled in clinical trials. However, there is very little evidence on DTG/3TC from long-term cohort studies, since the vast majority of them have assessed the outcomes at 48 weeks or less.<sup>6</sup> Only two cohorts have analysed its long-term effectiveness in treatment-naïve PWH. The REDOLA study enrolled 185 participants who started DTG/3TC in Spain, showing VS in 83.8% and 95.7% of the participants in the ITT and PP analysis, respectively, at 96 weeks.<sup>10</sup> The URBAN cohort showed 77.8% effectiveness among 27 treatment-naïve participants 3 years after starting DTG/3TC in Germany.<sup>11</sup> Additionally, the TANDEM cohort enrolled 126 treatment-naïve participants starting DTG/3TC in the USA who were followed for a median of 1.3 years (IQR: 0.8–1.8): this study reported that 83.3% of them remained virologically suppressed during follow-up but did not provide effectiveness data at specific timepoints.<sup>17</sup> These were only descriptive studies, and neither of them compared DTG/3TC with other first-line treatments.

Our study provides the largest number of treatment-naïve PWH starting DTG/3TC from a single cohort providing long-term outcomes. Also, since our cohort includes PWH starting different ARTs, we have been able to compare the effectiveness of DTG/3TC with other first-line three-drug regimens: this analysis is rarely reported in other cohorts. As the treatments were not randomized, these results are prone to confounding. Our estimates were adjusted for several potential confounders; however, as in all observational studies, we cannot exclude residual confounding. DTG/3TC was prescribed less frequently than other regimens to women, elderly persons or PWH with low education, low CD4 counts or high VLs. Our estimates were adjusted for these variables, among others, in the multivariable analysis.

Our findings are consistent with the 96-week analysis of the GEMINI studies, which showed non-inferiority of DTG + 3TC compared with DTG + TDF/FTC among treatment-naïve PWH and high tolerability of DTG + 3TC.<sup>8</sup> In these trials, there was a low

**Table 3.** Treatment discontinuation due to AEs during the first 96 weeks after ART initiation, type of AE and substitution regimen, according to first-line antiretroviral regimen, CoRIS cohort, 2018–23

|                                               | DTG/3TC<br>n = 472      | BIC/FTC/TAF<br>n = 1134 | DTG/3TC/ABC<br>n = 273  | DRV/COBI/FTC/TAF<br>n = 180 | DTG + FTC/TDF<br>n = 300 |
|-----------------------------------------------|-------------------------|-------------------------|-------------------------|-----------------------------|--------------------------|
| Treatment discontinuations due to AEs [N (%)] |                         |                         |                         |                             |                          |
| Incidence rate (95% CI) × 100 py              | 6 (1.3)                 | 31 (2.7)                | 16 (5.9)                | 10 (5.6)                    | 36 (12.0)                |
| Adjusted RR (95% CI) <sup>a</sup>             | 0.8 (0.3; 1.7)          | 1.7 (1.2; 2.5)          | 4.1 (2.5; 6.7)          | 3.8 (2.1; 7.1)              | 14.1 (10.2; 19.5)        |
| Type of AE [n (%)]                            | Ref.                    | 2.06 (1.02; 4.18)       | 5.55 (2.09; 14.75)      | 5.39 (2.38; 12.24)          | 17.07 (8.76; 33.30)      |
| Gastrointestinal                              | 1 (0.2)                 | 5 (0.4)                 | 3 (1.1)                 | 4 (2.2)                     | 2 (0.7)                  |
| Liver                                         | 0                       | 1 (0.1)                 | 1 (0.4)                 | 0                           | 0                        |
| Neuropsychiatric                              | 5 (1.1)                 | 11 (1.0)                | 5 (1.8)                 | 0                           | 7 (2.3)                  |
| Renal                                         | 0                       | 2 (0.2)                 | 0                       | 0                           | 21 (7.0)                 |
| Skin                                          | 0                       | 6 (0.5)                 | 1 (0.4)                 | 5 (2.8%)                    | 4 (1.3)                  |
| Weight Gain                                   | 0                       | 2 (0.2)                 | 1 (0.4)                 | 0                           | 0                        |
| Other                                         | 0                       | 3 (0.3)                 | 5 (1.8)                 | 1 (0.6%)                    | 2 (0.7)                  |
| Unknown                                       | 0                       | 1 (0.1)                 | 0                       | 0                           | 0                        |
| Most frequent substitution regimens (%)       | RPV + FTC/TAF (33.3)    | DRV/COBI/FTC/TAF (25.8) | DTG/3TC (25.0)          | BIC/FTC/TAF (40.0)          | DTG/3TC/ABC (27.8)       |
|                                               | BIC/FTC/TAF (16.7)      | DTG/3TC (22.6)          | RAL + 3TC/ABC (18.7)    | DTG/3TC (20.0)              | BIC/FTC/TAF (19.4)       |
|                                               | DRV/COBI/FTC/TAF (16.7) | DTG/3TC/ABC (9.7)       | EVG/COBI/FTC/TAF (18.7) | DTG/3TC/ABC (10.0)          | DTG/3TC (19.4)           |

RR, rate ratio; py, persons-year; RAL + 3TC/ABC, raltegravir + lamivudine/abacavir; EVG/COBI/FTC/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.

<sup>a</sup>Adjusted for sex, age at ART initiation, transmission category, educational level, country of origin, CD4 cell count and VL within 6 months previous to ART initiation, presence of HCV antibodies, presence of HBV surface antigen and previous AIDS diagnosis at ART initiation.

proportion of VFs with no treatment-emergent resistance. We also found a low proportion of VFs in our participants who started DTG/3TC. Among those with available resistance tests, no resistance mutations developed at VF.

We found DTG/3TC to be highly effective in all the subgroups analysed. Among PWH with VL >100 000 copies/mL and those who started rapid treatment (within a week of their first visit), its effectiveness was comparable to other first-line regimens, even after adjusting for other risk factors. The low number of participants receiving DTG/3TC in the other subgroups (women and those with low CD4 counts or VL >500 000 copies/mL) does not allow us to draw firm conclusions. Spanish guidelines recommended not prescribing DTG/3TC as initial treatment to PWH with VLs >500 000 copies/mL during 2019 or <200 CD4 cells/ $\mu$ L throughout the study period.<sup>14,15</sup> Also, due to the findings of the Tsepamo study,<sup>18,19</sup> during 2019 and 2020 they also recommended not prescribing this regimen to women of childbearing age who were not using contraception.<sup>14,15</sup>

A high proportion of PWH were treated within the first week after cohort enrolment. Since PWH are enrolled in CoRIS at their first visit to the specialized clinical centre after HIV diagnosis, we can assume that they started treatment on a 'test-and-treat' basis and resistance test results were not available. Also, these participants were enrolled in the cohort very shortly after HIV diagnosis. The high effectiveness of DTG/3TC in this subgroup confirms the results of the STAT clinical trial.<sup>2</sup> Other cohorts have shown high effectiveness of a 'test-and-treat' strategy with DTG/3TC in clinical practice<sup>20–22</sup>; however, neither the STAT trial nor these cohorts compared DTG/3TC with other treatment regimens.

We found DTG/3TC to have significantly higher persistence than all the other treatment regimens after adjusting for baseline clinical and demographic variables. Most of the other regimens' main reason for discontinuation was simplification; however, these other regimens also had a higher risk of discontinuation due to AEs than DTG/3TC in the multivariable analysis. The accumulated incidence of treatment discontinuations increased gradually for all regimens except DTG+TDF/FTC, for which discontinuation rates were highest during the first 12 weeks of treatment: this two-pill regimen was probably prescribed awaiting resistance and HLA B5701 test results, and changed shortly after they were available.

There are several limitations of our study. Firstly, because it is an observational study, it could be prone to biases such as confounding by indication. In fact, PWH who started DTG/3TC had less risk factors for treatment failure than those receiving other regimens. However, our results were adjusted for these risk factors. Secondly, we could not compare our outcomes in some of the subgroups due to a low number of participants. The main strengths of our study are a national multicentre cohort that is representative of the newly diagnosed PWH in Spain<sup>23</sup> and has strict quality control criteria; the reasonable high number of treatment-naïve PWH, which provides the highest number treated with DTG/3TC from a single cohort published to date; and the comparative analysis with other first-line regimens.

## Conclusions

We have analysed the long-term effectiveness, persistence and tolerability of DTG/3TC among treatment-naïve PWH in a large multicentre cohort. We found DTG/3TC to have comparable

effectiveness to other widely used three-drug first-line regimens, in all the cohort and specifically among PWH with VL >100 000 copies/mL and those who started rapid treatment. Compared with all the first-line treatments analysed, DTG/3TC was the most durable and better tolerated regimen. These findings are consistent with the results of clinical trials and support the use of DTG/3TC as a first-line treatment for HIV infection.

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

**Supplementary data**

Tables S1–S4 are available as [Supplementary data](#) at JAC Online.

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