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Long-term efficacy of dolutegravir in treatment-experienced subjects failing therapy with HIV-1 integrase strand inhibitor-resistant virus

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Objectives: This study evaluated the virological efficacy of dolutegravir 50 mg twice daily in 190 HIV-1 failing antiretroviral-experienced patients with previous exposure to first-generation integrase strand transfer inhibitor (INSTI) over a 5 year follow-up using data from clinical practice.

Patients and methods: This analysis included HIV-1-infected patients who were ≥18 years of age, treatment experienced, had HIV-1 RNA >50 copies/mL, with INSTI-resistant virus, who started dolutegravir 50 mg twice daily plus optimized background therapy (OBT), recorded in the national prospective database PRESTIGIO (www.progettoprestigio.it). Follow-up accrued from the start of dolutegravir 50 mg twice daily + OBT until virological failure (VF) or dolutegravir discontinuation for any reason or the last treatment visit on dolutegravir 50 mg twice daily treatment. VF was defined by the lack of achievement of HIV-1 RNA <50 copies/mL by 6 months and thereafter, or the occurrence of two consecutive HIV-1 RNA ≥50 copies/mL after achievement of undetectable viral load.

Results: The estimated VF probabilities were 17% (95% CI = 12%–24%), 28% (95% CI = 21%–37%), 33% (95% CI = 25%–43%), 39% (95% CI = 29%–51%) and 52% (95% CI = 39%–67%) at 12, 24, 36, 48 and 60 months since baseline, respectively. A higher risk of VF was independently associated with baseline viral load >100000 copies/mL (adjusted HR = 4.73, 95% CI = 1.33–16.78, $P = 0.016$) and with ≥1 INSTI mutations plus Q148H/K/R/N and the G140S/A/C as compared with other subjects (adjusted HR = 4.18, 95% CI = 1.32–13.23, $P = 0.015$).

Conclusions: Our data showed a favourable long-term efficacy of dolutegravir 50 mg twice daily in association with OBT in treatment-experienced failing subjects, with INSTI-resistant virus, in the real world. A close monitoring of adherence is crucial for maintenance of virological response in this fragile subgroup of subjects.

Introduction

The availability of an effective rescue therapy for HIV-1-infected subjects with previous failure to an integrase strand transfer inhibitor (INSTI)-based regimen is an emerging clinical issue.

Resistance to INSTIs in antiretroviral-experienced patients has emerged in recent years,[1,2] with heterogeneous prevalence rates, ranging from 15.6% among treated subjects with an available INSTI resistance test in the USA between 2009 and 2012[3] to 3.4% in French treated subjects experiencing virological failure (VF) in 2014.[4]

Dolutegravir 50 mg twice daily with an optimized background therapy (OBT) has been proven to be effective as rescue therapy in treatment-experienced patients harbouring an INSTI-resistant virus,[5–7] with virological response rates ranging from 47%[7] to 75%[5] at week 24 and 40% at week 48;[7] no data are available for longer follow-up.

This study aimed to evaluate the long-term efficacy of dolutegravir 50 mg twice daily in combination with OBT, assessed by time to VF, among treatment-experienced HIV-1-infected failing subjects with INSTI-resistant virus using data from clinical practice.

Table 1. Patients' characteristics at the start of dolutegravir 50 mg twice daily plus OBT (BL)

Characteristic	Median (IQR) or frequency (%), ($n = 190$)
Age (years)	50.6 (45.4–54.0)
Male gender	138 (73%)
Italian nationality	174 (92%)
HCV coinfection	61 (32%)
Years since HIV-1 infection	21.0 (15.0–25.0)
Previous inclusion in the VIKING or EAP	59 (31%)
BL DTG calendar year	
≤2014	69 (36%)
2015	86 (45%)
2016	35 (18%)
BL HIV-1 RNA (log_{10} copies/mL)	3.69 (2.72–4.64)
>100000 copies/mL	36 (19%)
BL CD4 + (cells/mm^3)	299 (138–518)
≤200 cells/mm^3	68 (36%)
OBT	
OBT >3 drugs (including DTG)	49 (26%)
PI-sparing regimens	48 (25%)
NNRTI-sparing regimens	136 (72%)
NRTI-sparing regimens	106 (56%)
NRTI most frequently used	
TDF	52 (27%)
FTC	42 (22%)
3TC	30 (16%)
NNRTI most frequently used	
ETV	39 (21%)
RPV	12 (6%)
PI/r most frequently used	
DRV/r	117 (62%)
ATV/r	13 (7%)
LPV/r	9 (5%)
enfuvirtide use	11 (6%)
maraviroc use	41 (22%)
HIV-1 co-receptor tropism	
false positive rate (FPR; available in 107 subjects)	15.8 (2.3–48.8)
non-R5 (FPR <10%)	54/117 (46%)
R5 (FPR ≥10%)	63/117 (54%)
Genotypic drug-resistance test	
HIV-1 subtype strains (available in 95 subjects)	
B	87 (91.7%)
CRF02 AG	2 (2.1%)
D/B	2 (2.1%)
F	2 (2.1%)
C	1 (1.0%)
CRF28 BF	1 (1.0%)
≥1 PI resistance mutation	77/142 (54%)
≥1 NNRTI resistance mutation	80/142 (56%)
≥1 NRTI resistance mutation	96/142 (68%)
≥1 INSTI resistance mutation	117/142 (82%)
≥2 INSTI resistance mutations	77/142 (54%)
≥1 major primary INSTI resistance mutation	105/142 (74%)
Q148H/K/R/N	45 (32%)
N155H	44 (31%)
G140S/A/C	36 (25%)
Y143C/R/H	15 (11%)
E138K/A/T	13 (9.2%)
T66A/I/K	4 (2.8%)
E92Q	4 (2.8%)
S147G	4 (2.8%)
≥1 major accessory INSTI resistance mutation	45/142 (32%)
T97A	23 (16%)
total GSS	106/142 (75%)
0	4 (3.8%)
1	23 (22%)
≥2	79 (75%)
GSS_{OBT}	106/142 (75%)
0	17 (16%)
1	46 (43%)
≥2	43 (41%)

3TC, lamivudine; ATV, atazanavir; DRV, darunavir; DTG, dolutegravir 50 mg twice daily; EAP, expanded access program; ETV, etravirine; FTC, emtricitabine; LPV, lopinavir; OBT, optimized background therapy; PI, protease inhibitor; /r, combined with ritonavir; RPV, rilpivirine; TDF, tenofovir.

Patients and methods

HIV-1-infected patients who were ≥18 years of age, treatment experienced, had HIV-1 RNA >50 copies/mL, had INSTI-resistant virus [at baseline (BL) or previously documented], who started dolutegravir 50 mg twice daily plus OBT were included in this study. Patients' information is prospectively recorded in the national electronic database PRESTIGIO, implemented in November 2014, based on a request of the Italian Medicines Agency (AIFA, Agenzia Italiana del Farmaco) aimed at monitoring the appropriateness of dolutegravir 50 mg twice daily prescriptions (www.progettoprestigio.it). The database includes patients on treatment with dolutegravir 50 mg twice daily at the time of the drug marketing authorization in Italy or those who started this drug thereafter and records, at least annually, demographic (age, gender, ethnicity), clinical (HCV coinfection, date of first HIV-positive test, prescribed antiretroviral drugs, reasons for discontinuation, death) and virological [viral load (VL), drug-resistance tests] and immunological (CD4+ cell count) characteristics.

Ethics Committees of 40 Italian Infectious Diseases Clinical Centres were notified of the PRESTIGIO data collection, required by AIFA; owing to this mandatory request, informed consent was not covered.

Follow-up accrued from the date of dolutegravir 50 mg twice daily plus OBT start (BL) until the date of VF or dolutegravir discontinuation for any reason or participation to randomized clinical trials on experimental drugs or the last treatment visit on dolutegravir 50 mg twice daily treatment (last update 31 January 2017), whichever occurred first.

The genotypic susceptibility score (GSS) was determined both for the BL dolutegravir 50 mg twice daily-based regimen (i.e. dolutegravir plus OBT; total GSS) and for OBT only (GSS_{OBT}) of each study participant by use of the Stanford University HIV Drug Resistance Database (version 8.3, last updated 2 March 2017):[8] for each drug, 'susceptible' or 'potential low-level or low-level resistance' was scored as 1 point and 'intermediate or high-level resistance' was scored as 0 points. The total GSS and the GSS_{OBT} were calculated as the sum of the scores for the individual drugs included in the BL regimen.

Table 2. Characteristics of 16 subjects who failed dolutegravir 50 mg twice daily-based regimen with available INSTI genotype both at BL and at VF

ID	DTG exposure (months)	BL HIV-1 tropism	BL HIV-RNA (copies/mL)	BL CD4+ (cells/mm^3)	BL INSTI RAM	BL GSS_{OBT}	HIV-RNA at VF (copies/mL)	CD4+ at VF (cells/mm^3)	INSTI RAM at VF
1	50	CXCR4	3700	34	G140S, Q148H, E138A, Y143H/R/C	0	220096	7	G140S, Q148H, Y143H, E138A, T97A
2	34	CXCR4	18290	191	G140S, Q148H, E138A	2	10473	301	G140S, Q148H, T97A
3	21	CXCR4	357	422	G140S, Q148H	0	7441	434	G140S, Q148H, E138K
4	43	CXCR4	147000	131	G140S, Q148H	1	195	145	G140S, Q148H, T97A, L74I
5	69	CXCR4	18621	530	G140S, Q148H, E138K	2	1668	641	G140S, Q148H, E138K, T97A
6	9	CXCR4	414403	38	G140S, Q148H	0	50435	152	G140S, Q148H
7	33	NA	519	345	G140S, T97A	0	14332	493	G140S, Q148H, E138K, T97A
8	57	CXCR4	2118674	19	G140S, Q148H	0	5711	11	G140S, Q148H, E138K, T97A
9	80	CCR5	134924	39	Y143C	0[a]	294300	21	G140S, Q148H, E138K, T97A
10	21	CXCR4	3997	323	Q148R, N155H, S147G, E138K, H51Y, T97A	NA	6756	488	none
11	41	CCR5	7771	174	Y143C, T97A, G163R	3	803884	69	Y143C, T97A, G163R
12	34	CXCR4	212	384	G140S, Q148H, L74ILM	0	613	494	G140S, Q148H, T66I, T97A
13	24	CXCR4	138674	43	Y143C, L74M	0	193	187	none
14	51	NA	818	763	N155H	1	269	1267	none
15	12	CXCR4	45257	139	Q148R	2	22328	128	none
16	36	CXCR4	576176	122	N155H	1	62	391	N155H

DTG, dolutegravir 50 mg twice daily; RAM, resistance-associated mutations; NA, not available.
HIV-1 CXCR4-tropic virus was defined by a geno2pheno false positive rate <10%; a CCR5-tropic virus was defined by a geno2pheno false positive rate ≥10%.
[a]This subject had previous failure to maraviroc despite the presence of CCR5-tropic virus.

HIV-1 CCR5-tropic virus was defined by a geno2pheno false positive rate ≥10%.

VF was defined by (i) the lack of achievement of undetectable VL (HIV-1 RNA <50 copies/mL) by 6 months and thereafter, or (ii) the occurrence of two consecutive HIV-1 RNA ≥50 copies/mL after achievement of undetectable VL.

Treatment failure (TF) was defined by the occurrence of VF or discontinuation of dolutegravir 50 mg twice daily during follow-up.

Results were described as median (IQR) or proportions. Kaplan–Meier analysis was used to estimate and compare the time to VF (primary outcome) and TF; time to VF was also estimated according to BL VL, BL CD4+, BL INSTI mutations, BL total GSS and GSS_{OBT} and curves were compared by use of the log-rank test.

A multivariate Cox regression model was used to determine the risk factors for VF; the model was fitted for time to VF and the effect estimate was reported as the adjusted HR (AHR) with the corresponding 95% CI. The multivariate model was built according to previous findings[5–7,9] and included main demographic (age, gender) and clinical variables (years of HIV infection, HCV coinfection) in addition to BL CD4+ cell count (≤200 versus >200 cells/mm^3), BL VL (≤100000 versus >100000 copies/mL), GSS_{OBT} (<2 or ≥2) and BL INSTI mutations (≥1 mutation plus the Q148H/K/R/N and the G140S/A/C versus other).

CD4+ changes from BL by timepoints (12, 24, 36, 48 and 60 months) were also calculated.

For all analyses, two-sided $P < 0.05$ was considered statistically significant. All analyses were performed using the SAS Software, release 9.4 (SAS Institute, Cary, NC, USA).

Results

A total of 190 HIV-1-infected patients were analysed. Of the total, 135 (73%) were males, 174 (92%) Italian, with a median (IQR) age of 51 (45–54) years, infected with HIV since 21 (15–25) years, 92% infected with subtype B strains, 61 (32%) HCV coinfected. At BL, HIV-1 RNA was 3.69 (2.72–4.64) $\log_{10}$ copies/mL and CD4+ cell count was 299 (138–518) cells/mm^3. Dolutegravir 50 mg twice daily was associated with ≥3 other antiretroviral drugs in 49 (26%) patients and darunavir/ritonavir [117 (62%)], etravirine [39 (21%)] and tenofovir [52 (27%)] were the most frequently combined drugs; maraviroc and enfuvirtide were used in 41 (22%) and 11 (6%) patients, respectively. At BL, 54% of patients harboured CCR5-tropic virus. A BL INSTI resistance test was available for 142 (75%) patients: 25 (18%), 40 (28%) and 77 (54%) had 0, 1 and ≥2 INSTI mutations, respectively; 105 (74%) had ≥1 primary INSTI mutation; the Q148H/K/R/N mutation was present in 45 (32%) patients, G140A/C/S in 36 (25%), N155H in 44 (31%) and E138A/K/T in 13 (9%) patients; and 16% of subjects had a GSS_{OBT} of 0. Other patients' characteristics are shown in Table 1.

During a median (IQR) follow-up of 17.9 (10.2–33.8) months [median number of VL determinations per patient: 5 (4–11)], 48 (25%) VF occurred. BL and follow-up genotypic drug resistance tests were available in 16 subjects with VF; patients' characteristics are detailed in Table 2.

Kaplan–Meier analysis showed that the estimated probabilities of VF were 17% (95% CI = 12%–24%), 28% (95% CI = 21%–37%), 33% (95% CI = 25%–43%), 39% (95% CI = 29%–51%) and 52% (95% CI = 39%–67%) at 12, 24, 36, 48 and 60 months since BL, respectively (Figure 1a). Time to VF was shorter in subjects with BL CD4+ ≤200 cells/mm^3 (log-rank test, $P = 0.035$; Figure 1c) or VL >100000 copies/mL (log-rank test, $P = 0.005$; Figure 1d).

Time to VF did not differ between patients with a total GSS or GSS_{OBT} <2 or ≥2 (log-rank test: $P = 0.435$ and $P = 0.699$,

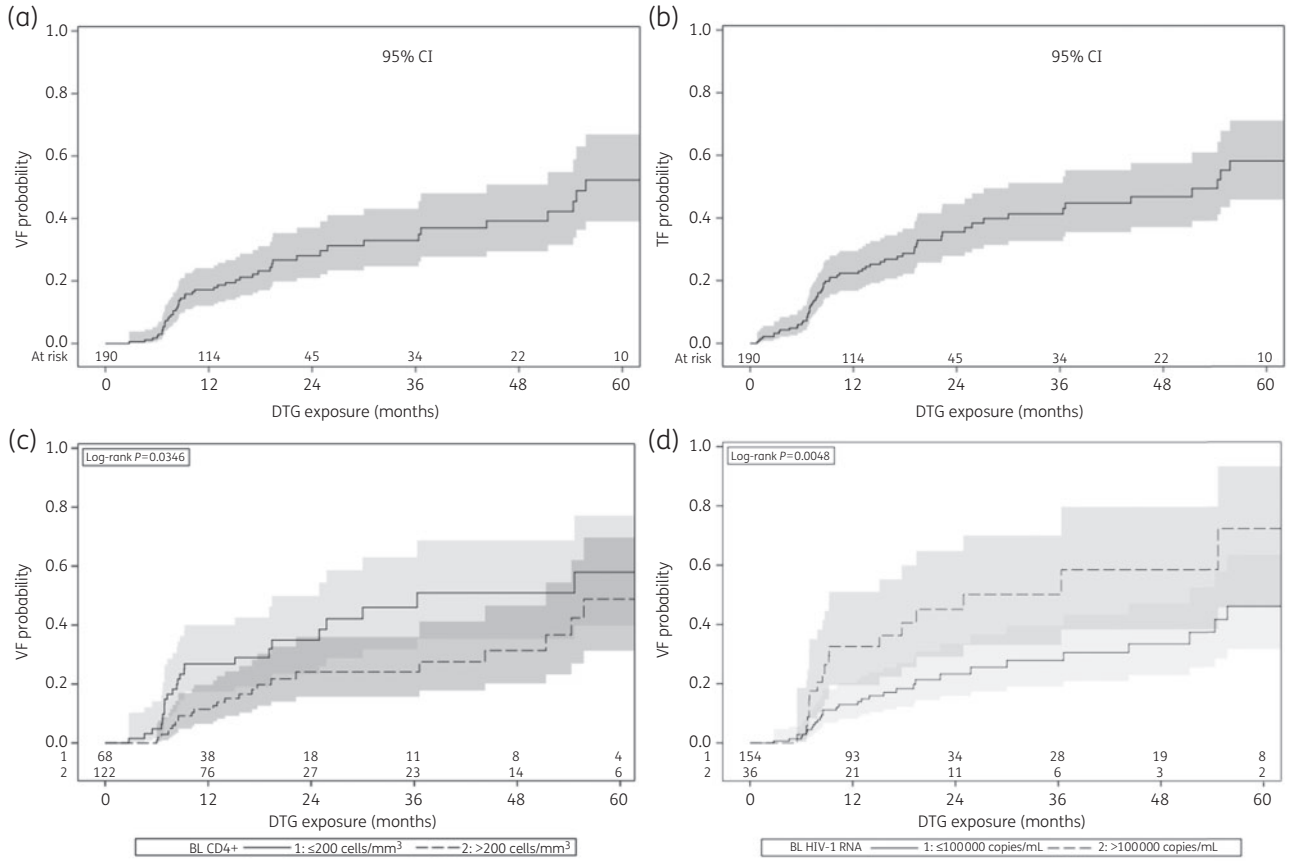

Figure 1. Estimated probabilities of VF and TF in the overall sample (a and b, respectively). Estimated probabilities of VF according to BL CD4 + (c) and BL VL (d). DTG, dolutegravir 50 mg twice daily.

respectively; Figure 2a and b). Patients with $GSS_{OBT} = 0$ tended to have higher VF probabilities than others (log-rank test, $P = 0.304$; Figure 2c); VF occurred in 7 of 17 (41%) patients with $GSS_{OBT} = 0$ as compared with 17% and 21% of those with $GSS_{OBT} = 1$ or ≥ 2, respectively. Time to VF was shorter also in subjects with ≥ 1 INSTI mutation in addition to the Q148H/K/R/N and the G140S/A/C mutations (log-rank test, $P = 0.020$; Figure 2d).

Dolutegravir 50 mg twice daily was discontinued in 28 (15%) subjects [10 VF, 9 regimen simplification, 3 patient's decision, 1 lost to follow-up, 1 drug-related adverse event (diarrhoea and rash), 4 deaths (1 acute myocardial infarction, 1 suicide, 2 sepsis)].

The Kaplan–Meier analysis estimated that the TF probabilities were 22% (95% CI = 17%–29%), 36% (95% CI = 28%–45%), 41% (95% CI = 33%–51%), 47% (95% CI = 37%–58%) and 58% (95% CI = 46%–71%) at 12, 24, 36, 48 and 60 months since BL, respectively (Figure 1b).

The median change in CD4+ cell count since BL was +65 (−6, +181), +130 (+12, +249), +203 (+107, +295), +269 (+119, +399) and +279 (+118, +427) cells/mm^3 at 12, 24, 36, 48 and 60 months, respectively.

After adjusting for age, gender, years of HIV infection, HCV coinfection, BL CD4+ cell count and GSS_{OBT}, a higher risk of VF was found for patients with BL VL >100000 copies/mL (AHR = 4.73, 95% CI = 1.33–16.78, $P = 0.016$) and with ≥ 1 INSTI mutation plus Q148H/K/R/N and the G140S/A/C as compared with other subjects (AHR = 4.18, 95% CI = 1.32–13.23, $P = 0.015$).

Discussion

Overall, we found that 75% of the patients achieved undetectable VL and that 48% of subjects had a durable virological suppression up to 5 years after starting dolutegravir 50 mg twice daily. Our results confirm the high long-term efficacy of dolutegravir 50 mg twice daily when added to an OBT in treatment-experienced subjects with INSTI-resistant virus and, in some cases, with very limited treatment options. The high response rates observed in this study likely reflect the real practice in which dolutegravir 50 mg twice daily was started in subjects previously treated with antiretroviral regimens including first-generation INSTI drugs and those with a higher CD4+ cell count, lower VL, lower number of INSTI resistance mutations at BL and more remaining therapeutic options than those enrolled in the VIKING studies.[5–7] As expected, also in our study, subjects with $GSS_{OBT} = 0$ tended to have the lower proportions of virological response.

Virological efficacy was affected by BL VL and the type and number of INSTI mutations, consistent with what has been reported in other previous studies.[6,10]

The main limitations of this study include the lack of collection of adherence data, known to be one of the stronger factors

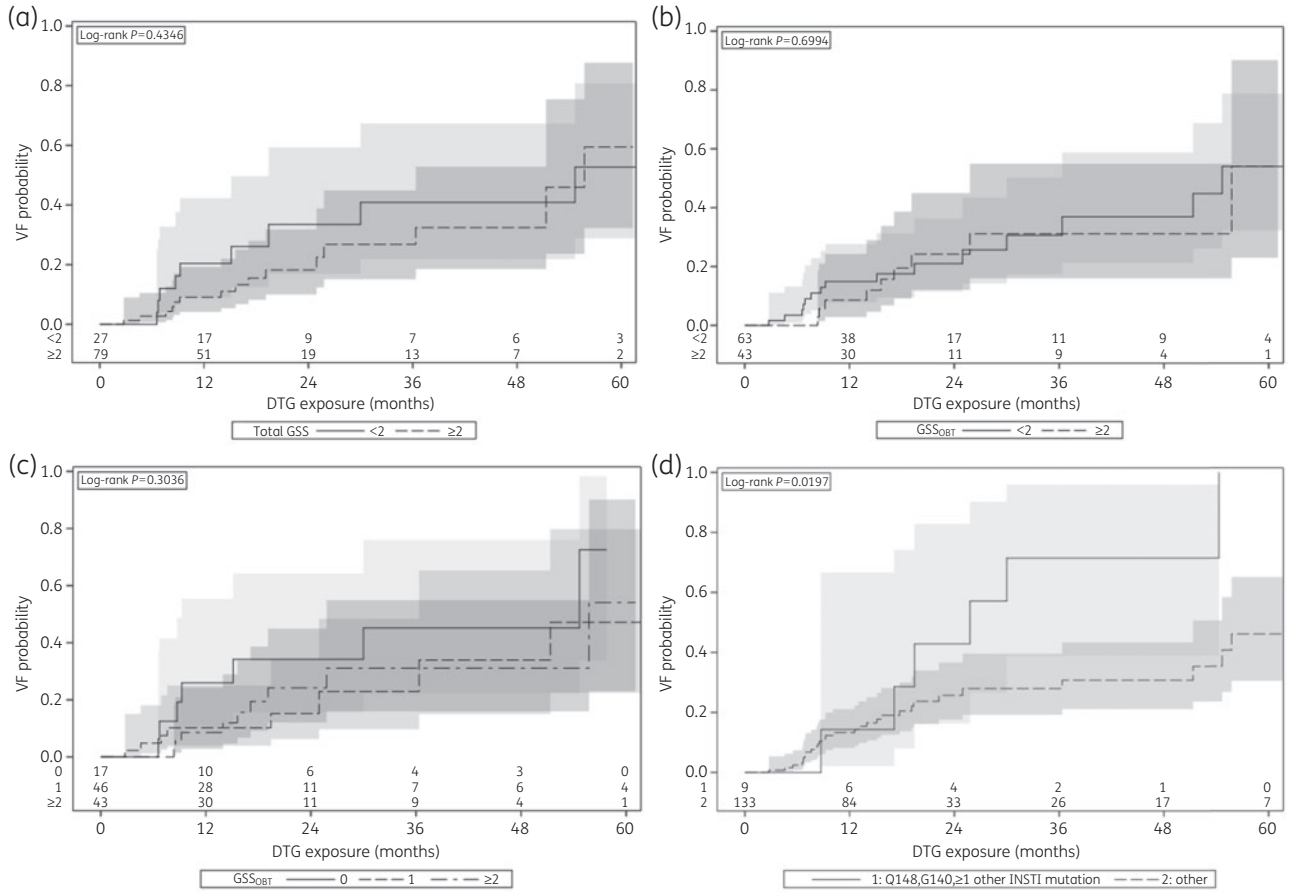

Figure 2. Estimated probabilities of VF according to: the total GSS (a) or the GSS_{OBT} (b) classified as <2 and ≥2; the GSS_{OBT} (c) classified as 0, 1 and ≥2; BL INSTI resistance mutations (Q148, G140 and ≥1 INSTI mutation versus other; d). DTG, dolutegravir 50 mg twice daily.

associated with either VF or emergence of INSTI resistance;[11] the lack of adherence may partially explain both the high BL VL and the absence of INSTI resistance at failure observed in some cases. In addition, our results may not apply to subjects with different ethnicity and HIV-1 subtype.

In subjects with an extensive degree of INSTI resistance at BL a limited further genotype evolution has been observed at VF, although this observation is preliminary, owing to the very limited sample size of subjects with available data. A potential explanation is that most of these subjects had the Q148/G140 INSTI mutations, which are known to cause up to a 10–20-fold reduced susceptibility to dolutegravir particularly when a third INSTI resistance mutation is also present.[1] A clearer interpretation of INSTI resistance evolution in subjects with VF could be also achieved by measuring cumulative rather than circulating resistance.

It is interesting to note that initiation of dolutegravir 50 mg twice daily and VF occurred in patients with highly heterogeneous CD4 values; moreover, dolutegravir 50 mg twice daily was maintained in 79% of subjects with VF, likely due to a lack of therapeutic alternatives. These findings outline the need for new drugs and new strategies[12–14] for the immediate and long-term management of subjects with different risks of disease progression.

In conclusion, our data showed a favourable long-term efficacy of dolutegravir 50 mg twice daily in association with OBT in treatment-experienced failing subjects, with INSTI-resistant virus, in the real world. Close monitoring of adherence is crucial for maintenance of the virological response in this fragile subgroup of subjects.

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Transparency declarations

None to declare.

Author contributions

A. C., A. L., A. R. and L. G. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept: A. C. and A. L. Data collection, administrative or material support: M. F., L. C., G. S., G. C., M. Z., E. F. and A. R. Statistical analysis: L. G. Drafting of the manuscript: A. C. and L. G. Data interpretation and critical revision of the manuscript: all authors.

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