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Virological efficacy of switch to DTG plus 3TC in a retrospective observational cohort of suppressed HIV-1 patients with or without past M184V: the LAMRES study

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ABSTRACT

Objectives: The aim of this study was to assess the efficacy of dolutegravir plus lamivudine (DTG+3TC) in a large set of virologically suppressed HIV-1 infected individuals with or without past M184V mutation. **Methods:** This observational study included individuals who switched to DTG+3TC with ≥ 1 genotype before switch. Survival analysis was used to evaluate the role of past M184V on virological rebound (VR) or blips after DTG+3TC switch.

Results: A total of 712 individuals followed in several clinical centres in France, Italy and Spain were analysed. Past M184V was present in 60 (8.4%) individuals. By 3 years after switch, the overall probability of VR and blips was 6.7% and 6.9%, respectively, without any statistical significance according to the presence/absence of past M184V. A significantly higher probability of VR was found in individuals harbouring M184V before DTG+3TC with a duration of virological suppression (Ts) ≤ 3.5 years compared to others (M184V+Ts ≤ 3.5 years: 22.7%; M184M+Ts ≤ 3.5 years: 9.0%; M184V+Ts > 3.5 years: 7.8%; M184M+Ts > 3.5 years: 4.9%; $P = 0.007$). This finding was not confirmed in multivariable models adjusting for behavioural and demographic variables. Genotypic resistance test after VR under DTG+3TC was available for 8/39 individuals; one poorly adherent individual developed M184V. No resistance to INIs was found. **Conclusion:** In this retrospective observational study, the probability of VR and blips in patients switching to DTG+3TC was very low after 3 years of treatment regardless M184V. The effect of a short duration of previous virological suppression in individuals with M184V remains troubling and needs ad hoc clinical trials to be confirmed.

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1. Introduction

Since its introduction in 1996, combined antiretroviral therapy (ART) has dramatically reduced HIV-associated morbidity and mortality and has transformed HIV infection into a manageable chronic

condition [1,2]. In view of the prolongation of life expectancy for people living with HIV (PLWH), the question of ART optimization, which is still a life-long treatment, becomes central. While most PLWH achieve virological success, their treatments often need to be optimized to limit adverse events and drug interactions and to improve adherence. The switch to dual-regimen strategies represents one of the approaches for treatment optimization [3,4]. In this context, the dual regimen containing dolutegravir (DTG) plus lamivudine (3TC) has shown excellent results in registrational studies for its usage as first-line treatment in HIV-1 infected ART-naïve individuals and as a treatment simplification strategy in virologically suppressed individuals [5–8]. In the randomized trials of the dual regimens in simplification, such as TANGO and SALSA, patients with prior virological failures and/or resistance mutations were excluded [8,9]. However, real-life data show that today, in simplification strategies, the dual-regimen therapies are prescribed even in patients with a history of virological failure or drug resistance [10–24]. Regarding drug resistance, it should be highlighted that circulating HIV-1 resistant variants can be archived in viral reservoirs, where they can persist for an unknown duration and re-emerge in case of therapeutic selective pressure [25]. In particular, previous selection of M184V may have an effect on virological response to dual regimen DTG+3TC. In vitro studies showed that M184V is associated with high-level resistance to lamivudine, but also with reduced viral replication capacity [26]. In clinical trials the presence of pre-existent resistance and in particular of the M184V mutation did not affect virological outcome [27–29]. However, data from real-life settings on a direct comparison of DTG+3TC efficacy in patients harbouring or not harbouring M184V are few, on a limited number of individuals and may be controversial [17,18,22,30,31]. In retrospective observational studies, the presence of M184V was associated with an increased risk of virological failure in individuals with a shorter duration of virological suppression before DTG+3TC switch [17,18,32].

Thus, there is a clinical urgent need to answer the key question whether DTG+3TC could be safely used even in patients with past M184V mutation in a large set of patients followed in different clinical settings.

According to the above considerations, the aim of the present study was to assess the efficacy of DTG+3TC in a large set of virologically suppressed HIV-1 infected individuals, followed in different European clinical centres, with or without a history of M184V detection in a previous resistance genotype.

2. Materials and methods

2.1. Study population

This is a European retrospective, noninterventional/observational study including several clinical and virological centres involved in HIV care from France, Italy and Spain. Individuals who switched to the dual therapy DTG+3TC for any reason were included in the analysis according to the following criteria: (i) age ≥ 18 years; (ii) to be virologically suppressed (plasma HIV-RNA ≤ 50 copies/mL) on any ART regimen at the moment of DTG+3TC switch; (iii) availability of at least one previous plasma HIV-1 RNA or HIV-DNA genotype resistance testing (GRT); (iv) availability of a virological follow-up after switching to DTG+3TC.

2.2. Sanger sequencing and drug resistance evaluation

Sanger sequencing for protease, reverse transcriptase (RT) and integrase was performed at each reference laboratory during the standard follow-up of patients. Resistance interpretation was made according to the Stanford algorithm (HIVdb version 8.9-1, <https://hivdb.stanford.edu/>).

For each individual, the cumulative resistance was evaluated by considering the resistance detected in all available GRTs before DTG+3TC switch. For the evaluation of the occurrence of M184V, any sequences produced having a mixture of wild-type and mutant amino acid residues was considered to have the mutant at the position 184. Similarly, in case of the presence of quasispecies I/V, both mutations were considered. The cumulative class-resistance was defined by the presence of at least one major resistance mutation among protease inhibitors (PI), nucleos(t)ide reverse transcriptase inhibitor (NRTI) excluding the M184V, non-NRTI (NNRTI) and integrase inhibitor.

2.3. HIV-RNA quantification

Plasma HIV-1 RNA was measured by using commercially available polymerase chain reaction (PCR) assays Abbott (Abbott Real Time HIV-1, Chicago, IL), Aptima (Aptima® HIV-1 Quant Dx assay, Hologic, Inc., San Diego, CA), and Roche (Ampliprep COBAS TaqMan v.2.0, Roche, Meylan, France; Roche Cobas CA/CTM v.2.0, Mannheim, Germany), which measure quantitative HIV-1 RNA of 40 copies/mL, 30 copies/mL and 20 copies/mL, respectively, and generate qualitative target detected (TD) or target not detected (TND) results for viremia value <40 , 30 or 20 copies/ml [33–35].

2.4. Objectives

The primary objective of the study was to evaluate the probability of experiencing virological rebound (VR) after DTG+3TC start according to the past presence/absence of M184V together with previous time of virological suppression.

For this analysis, time of virological suppression was considered as binary variable. The first quartile of time of virological suppression in individuals with past M184V was used as the cutoff, to minimize the difference in duration of virological suppression before DTG+3TC switch among individuals with past M184V and those without past M184V.

VR was defined as plasma HIV-RNA >50 copies/mL in two consecutive determinations or one ≥ 200 copies/mL in a single determination. Secondary objectives were: (i) to evaluate the role of past M184V on experiencing a blip according to the previous time of virological suppression after DTG+3TC switch; (ii) to determine other predictors of VR or viral blips; (iii) to evaluate the emergence of resistance in individuals who experienced VR under DTG+3TC.

Viral blip was defined as a single HIV-RNA in the range 51–199 copies/mL preceded and followed by ≤ 50 copies/mL measurements).

2.5. Statistical analysis

All analyses were executed using the SPSS v.26.0 software package for Windows (SPSS, Inc., Chicago, IL). For all the analyses, *P* values of less than 0.05 were considered significant.

A descriptive analysis was performed on the overall population and by stratifying the individuals in two groups according to the past presence/absence of M184V. Potential differences between the two groups were investigated by Mann-Whitney exact test for quantitative variables and χ^2 or Fisher exact test for qualitative variables, when appropriate.

Kaplan-Meier curves were used to evaluate the probability of experiencing VR or blips after DTG+3TC switch on the overall population and according to the historical presence/absence of M184V, also considering the time of virological suppression before switch. In blip analyses, individuals who experienced VR were excluded. Cox regression analysis was performed to investigate the role of factors associated to virological response by considering the following variables: sex, age, risk transmission factors, nationality,

ethnicity, levels of adherence to treatment, B and C hepatitis coinfection status, HIV-1 subtype, baseline and nadir CD4 count, previous viral blips experience, viremia zenith, HIV-1 RNA target not detected at switch, previous time under ART, number and type of previous failures, drugs received in the previous treatment history, reasons for treatment switch, previous cumulative resistance per each drug class. Concerning cumulative NRTI resistance, beyond the presence of past M184V, the number of thymidine analogue mutations (TAMS) and of other NRTIs mutations accumulated before switch was also considered (see Tables 2 and 3). Only variables significantly associated to virological response at univariable analyses ($P < 0.05$) were retained in multivariable models. Multivariable models excluding demographic and behavioural parameters were built to avoid potential biases related to individuals' heterogeneity.

Analyses were performed on patients who did not discontinue DTG+3TC (on treatment approach). Patients' follow-up was censored before DTG+3TC discontinuation. Sensitivity analyses were also performed by considering different definitions of VR. In particular, the following definitions for virological failure were considered: (i) HIV-RNA >50 copies/mL in two consecutive determinations; (ii) HIV-RNA >50 copies/mL in two consecutive determinations or a single determination ≥ 1000 copies/mL; (iii) HIV-RNA levels ≥ 200 copies/mL in two consecutive determinations or one HIV RNA level ≥ 200 copies/mL followed by DTG+3TC discontinuation. Moreover, a sensitivity analysis on the primary outcome was performed by using an intention to treat approach (ITT): therapy changes were ignored and patient follow-up was censored at the date of their last available viremia measurement or at the time of the first therapy interruption.

In individuals who experienced VR and for whom a subsequent GRT was available, resistance at failure was evaluated with a descriptive analysis.

3. Results

3.1. Patients' characteristics

Overall, 712 virologically suppressed individuals composed mainly of men (77.0%) with a median (IQR) age of 51 (43–58) were analysed (Table 1). They had a long treatment history with a median (IQR) of 7 (3–15) years under cART; 52.5% were under virological suppression for at least 5 years. Almost all of them had previously received 3TC or FTC (99.3%), and 30.3% had previously received DTG. Excluding M184V, 24.9% the individuals had at least one major resistance mutation. Regarding NRTI resistance, 10.7% and 2.4% of the individuals had at least one thymidine analogue resistance associated mutation (TAM) and other-NRTI resistance mutations (K65R, K70E, L74V/I, Y115F, M184I), respectively.

The mutation M184V was previously detected in 60 (8.4%) individuals who were in virological suppression for a median (IQR) time of 6.9 (3.5–12.5) years. At the last GRT, M184V was detected in HIV-1 RNA in 49 out of 60 (81.6%) individuals, whereas in 11 individuals (18.3%) it was detected in HIV-1 DNA. By evaluating cumulative resistance, M184V was previously detected in 48 (80.0%) individuals only in HIV-RNA GRTs, 10 (16.7%) exclusively in HIV-DNA and 2 (3.3%) in both HIV-DNA and -RNA. An overview of all patients harbouring M184V is reported in Supplementary Table S1.

M184I was detected only in HIV-DNA in six individuals (0.8%), never as a mixture with V substitution.

Patients' characteristics according to the presence/absence of M184V are summarized in Table 1. In particular, M184V was mostly detected in individuals with CD4 cell count nadir ≤ 200 cell/mm³ and with a longer treatment history. Moreover, individuals with M184V with a short previous time of virological suppression were less likely to switch to DTG+3TC. Indeed, these individu-

als showed a longer median (IQR) previous virological suppression (6.9 [3.5–12.5] years) compared to those without M184V (5.1 [2.5–9.2] years, $P = 0.010$).

Concerning historical resistance, individuals with past M184V had a higher prevalence of cumulative PI, NRTI and NNRTI resistance. No M184V was detected among the three individuals who had previous INI resistance before switch (G118R, $n = 1$; E138K + G163R, $n = 1$; S147G, $n = 1$).

3.2. Virological outcome, overall and according to past M184V in relationship with virological suppression

At 1, 2 and 3 years after DTG+3TC switch, the overall probability of VR was 3.1%, 5.2% and 6.9%, respectively. By stratifying for the presence/absence of past M184V, no significant difference in the probability of VR was found (Fig. 1A).

Subsequently, individuals were further stratified into four groups according to both presence/absence of past M184V and time of virological suppression before DTG+3TC switch (as the first quartile in presence of past M184V: 3.5 years; see Materials and Methods section) as follows: (i) without past M184V with >3.5 years of previous virological suppression; (ii) without M184V with ≤ 3.5 years of previous virological suppression; (iii) with past M184V with >3.5 years of previous virological suppression; (iv) with M184V with ≤ 3.5 years of previous virological suppression.

The highest probability of VR was found in individuals with M184V in a context of ≤ 3.5 years of virological suppression before switch compared to the others (Fig. 1B). Cox regression analyses confirmed that past M184V influenced VR only in the context of a shorter (≤ 3.5 years) previous virological suppression. In particular, at multivariable analysis, adjusting for virological and therapeutic parameters, individuals harbouring M184V and with ≤ 3.5 years of virological suppression before DTG+3TC switch had a higher adjusted hazard [95% CI] of experiencing VR compared to those without M184V in the context of a longer (>3.5 years) virological suppression (3.8 [1.0–14.4], $P = 0.046$; Table 2). This observation was not confirmed when demographical and behavioural variables were included in the adjusted model (2.3 [0.6–9.0], $P = 0.248$; Table 2). With regard to other factors, to be heterosexual or a drug abuser, having a viremia zenith $>100\,000$ copies/mL, having a previous history of failures to INI-based regimens and harbouring past NNRTI resistance were positively associated with VR, whereas having viremia target not detected at DTG+3TC switch was negatively associated with VR.

By 1, 2 and 3 years of treatment, the overall probability of experiencing a viral blip was 2.2%, 4.4% and 6.9%. There was no statistical association of M184V with the probability of having blips (Fig. 1C), even when considering the time of previous virological suppression (Fig. 1D). By Cox multivariable analyses, a higher number of PI-based regimens previously experienced, the presence of non-TAM NRTIs major resistance mutations and the absence of M184V in a context of short previous virological suppression before DTG+3TC switch were positively associated with viral blips, whereas those individuals whose viremia target was not detected at switch had a lower adjusted hazard of experiencing viral blips under DTG+3TC (Table 3).

3.3. Sensitivity analyses

Among the additional definitions of VR considered for sensitivity analyses, only the first (HIV-RNA >50 copies/mL in two consecutive determinations) and the second (HIV-RNA >50 copies/mL in two consecutive determinations or a single determination ≥ 1000 copies/mL) were considered, while the third one (HIV-RNA levels ≥ 200 copies/mL in two consecutive determinations or one HIV RNA level ≥ 200 copies/mL after DTG+3TC discontinuation) was not

Table 1
Patients' characteristics according to M184V detected before 3TC+DTG switch.

Variables at 3TC/DTG switch	Overall (N = 712)	M184V		P value
		No (N = 652)	Yes (N = 60)	
Male sex, n (%)	548 (77.0)	511 (78.4)	37 (60.7)	0.003
Age, years, median (IQR)	51 (43–58)	50 (42–58)	56 (51–61)	<0.001
Risk factor, n (%)				
Homosexual	332 (46.6)	323 (49.5)	9 (15.0)	<0.001
Heterosexual	233 (32.7)	201 (30.8)	32 (53.3)	
Drug abuser	82 (11.5)	65 (10.0)	17 (28.3)	
Sexual ^a	33 (4.6)	32 (4.9)	1 (1.7)	
Other/unknown ^b	32 (4.5)	31 (4.8)	1 (1.7)	
Nationality, n (%)				
Native (Italy, France, Spain)	537 (75.4)	494 (75.8)	43 (71.7)	0.480
Foreigner	175 (24.6)	158 (24.2)	17 (28.3)	
Ethnicity, n (%)				
Caucasian	485 (68.1)	449 (68.9)	36 (60.0)	0.255
Black	41 (5.8)	37 (5.7)	4 (6.7)	
Hispanic/Latino	27 (3.8)	26 (4.0)	1 (1.7)	
Other/unknown	159 (22.3)	140 (21.5)	19 (31.7)	
Adherence, n (%)				
High	212 (29.8)	201 (30.8)	11 (18.3)	0.022
Medium	35 (4.9)	28 (4.3)	7 (11.7)	
Low	6 (0.8)	5 (0.8)	1 (1.7)	
Unknown	459 (64.5)	418 (64.1)	41 (68.3)	
HCV infection, n (%) ^c	69 (9.7)	58 (8.9)	11 (18.3)	0.051
HBV infection, n (%) ^c	109 (15.3)	102 (15.6)	7 (11.7)	0.528
Subtype B, n (%)	512 (71.9)	468 (71.8)	44 (73.3)	0.798
Baseline CD4 cell count, cell/mm ³ , n (%)	695 (481–885)	682 (511–897)	695 (481–885)	0.960
Nadir CD4 cell count, cell/mm ³ , n (%)				
>200	433 (60.8)	411 (63.0)	22 (36.7)	<0.001
≤200	236 (33.1)	201 (30.8)	35 (58.3)	
Unknown	43 (6)	40 (6.1)	3 (5.0)	
At least one blip before switch, n (%)	213 (29.9)	184 (28.2)	29 (48.3)	
Viremia zenith (copies/mL), n (%)				
<100 000	304 (42.7)	272 (41.7)	32 (53.3)	0.386
100 000–500 000	217 (30.5)	202 (31.0)	15 (25.0)	
>500 000	148 (20.8)	138 (21.2)	10 (16.7)	
Unknown	43 (6)	40 (6.1)	3 (5.0)	
HIV-1 RNA target not detected at switch, n (%)				
No	219 (30.8)	204 (31.3)	15 (25.0)	0.594
Yes	435 (61.1)	395 (60.6)	40 (66.7)	
Unknown	58 (8.1)	53 (8.1)	5 (8.3)	
Time of previous virological suppression				
Years, median (IQR)	5.2 (2.6–9.4)	5.1 (2.5–9.2)	6.9 (3.5–12.5)	0.010
Years, n (%)				
<1	73 (10.3)	69 (10.6)	4 (6.7)	0.003
1–3	139 (19.5)	130 (19.9)	9 (15.0)	
3–5	126 (17.7)	117 (17.9)	9 (15.0)	
5–10	211 (29.6)	199 (30.5)	12 (20.0)	
>10	163 (22.9)	137 (21.0)	26 (43.3)	
Time under cART, years, median (IQR)	7 (3–15)	7 (3–12)	20 (18–22)	<0.001
Number of previous failures, median (IQR)	0 (0–1)	0 (0–1)	3 (2–4)	<0.001
Any INI failure, n (%)	20 (2.8)	16 (2.5)	4 (6.7)	0.079
Number of previous regimens experienced, median (IQR)	3 (2–5)	3 (2–5)	10 (6–13)	<0.001
Drug experience				
No. of NRTIs, median (IQR)	3 (2–4)	3 (2–4)	6 (5–7)	<0.001
3TC/FTC, n (%)	707 (99.3)	647 (99.2)	60 (100.0)	1.000
3TC, n (%)	410 (57.6)	352 (54.0)	58 (96.7)	<0.001
FTC, n (%)	611 (85.8)	565 (86.7)	46 (76.7)	0.034
No. of NNRTIs, median (IQR)	1 (0–1)	1 (0–1)	1 (1–2)	<0.001
No. of PIs, median (IQR)	2 (0–3)	2 (0–3)	4 (3–5)	<0.001
T20/MVC, n (%)	25 (3.5)	17 (2.6)	8 (13.3)	<0.001
No. of INIs, median (IQR)	1 (0–1)	1 (0–1)	1 (0–1)	0.598
RAL, n (%)	157 (22.1)	139 (21.3)	18 (30.0)	0.121
EVG, n (%)	104 (14.6)	102 (15.6)	2 (3.3)	0.010
DTG, n (%)	216 (30.3)	197 (30.2)	19 (31.7)	0.815
BIC, n (%)	3 (0.4)	3 (0.5)	0 (0)	1.000
Year of switch to DTG+3TC, median (IQR)	2018 (2017–2019)	2018 (2017–2019)	2017 (2016–2019)	0.095
Reasons for switch to DTG+3TC, n (%)				
Reduction of drugs or daily pills	404 (56.7)	377 (57.8)	27 (45.0)	0.009
Toxicity ^d	139 (19.5)	122 (18.7)	17 (28.3)	
Patient/clinician choice	34 (4.8)	30 (4.6)	4 (6.7)	
Other reasons of optimization ^e	27 (3.8)	23 (3.5)	4 (6.7)	
Drug-drug interaction	29 (4.1)	23 (3.5)	6 (10.0)	
Unknown	79 (11.1)	77 (11.8)	2 (3.3)	

(continued on next page)

Table 1 (continued)

Variables at 3TC/DTG switch	Overall (N = 712)	M184V		P value
		No (N = 652)	Yes (N = 60)	
Cumulative drug resistance, n (%)				
PI major	30 (4.2)	18 (2.8)	12 (20.0)	<0.001
Any NRTI major (excluding M184V) ^f	94 (13.2)	53 (8.1)	41 (68.3)	<0.001
Thymidine analogue mutations				
1	30 (4.2)	23 (3.5)	7 (11.7)	<0.001
2	22 (3.1)	10 (1.5)	12 (20.0)	
≥3	24 (3.4)	9 (1.4)	15 (25.0)	
Other NRTI resistance mutations	17 (2.4)	4 (0.6)	13 (21.7)	<0.001
NNRTI major	124 (17.4)	76 (11.7)	48 (80.0)	<0.001
INI major ^g	3 (1.2)	3 (1.3)	0 (0)	1.000
Median time of follow-up after switch, median IQR years	2.4 (1.6–3.5)	2.4 (1.7–3.5)	2.2 (1.0–3.6)	0.293

^a Transsexual or unknown sexual behaviours.

^b Transfusion (n = 4); perinatal infection (n = 1), unknown (n = 27).

^c Available for 708 patients.

^d Switch related to prevent or manage ART side effects related to nephrotoxicity (n = 23); osteoarticular toxicity (n = 15); gastro-intestinal toxicity (n = 6); hepatotoxicity (n = 8); neurotoxicity (n = 5); metabolic toxicity (n = 23); intolerance (n = 12); unspecified toxicity (n = 47).

^e Switch related to optimize treatment without decrease drugs or pill burden in turn to increase tolerability and/or genetic barrier.

^f Nineteen individuals had only M184V as major resistance mutation.

^g Integrase GRT before switch was available for 250 patients. Mutations detected were: G118R (n = 1), E138K (n = 1), S147G (n = 1).

Table 2

Factors associated with virological rebound in virologically suppressed patients switching to DTG+3TC treatment.

Variables ^a	Hazard ratio (HR) to experience virological rebound (N = 712)					
	Crude		Adjusted ^b		Adjusted ^c	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Demographic and behavioural parameters						
Male sex	0.3 (0.1–0.5)	<0.001			0.5 (0.2–1.1)	0.073
Risk factor						
Homosexual ^d	1				1	
Heterosexual	5.6 (2.3–13.8)	<0.001			4.2 (1.4–12.3)	0.009
Drug abuser	4.0 (1.3–12.6)	0.016			4.3 (1.2–15.6)	0.028
Sexual	1.7 (0.2–13.8)	0.637			1.6 (0.2–13.2)	0.685
Other/unknown	5.0 (1.3–20.1)	0.023			3.5 (0.7–16.8)	0.116
Nationality						
Native (Italy, France, Spain) ^c	1				1	
Foreigner	2.1 (1.1–4.1)	0.022			1.0 (0.4–2.7)	0.928
Ethnicity						
Caucasian ^d	1					
Black	3 (1.1–7.8)	0.029			1.0 (0.3–3.7)	0.979
Hispanic/Latino	2.8 (0.8–9.3)	0.094			4.2 (0.9–19.2)	0.066
Other/unknown	1.2 (0.5–2.6)	0.719			1.3 (0.5–3.7)	0.596
Viro-immunological parameters						
Viremia zenith (copies/mL)						
<100 000 ^d	1				1	
100 000–500 000	2.8 (1.1–7.0)	0.025	2.4 (1–6.1)	0.057	2.9 (1.1–7.3)	0.024
>500 000	5.1 (2.1–12.3)	0.000	4.9 (2–12)	0.001	4.3 (1.7–10.7)	0.002
Unknown	1.0 (0.1–8.2)	0.992	1.2 (0.1–10.1)	0.868	1 (0.1–8.2)	0.975
Target not detected at switch						
No ^d	1				1	
Yes	0.4 (0.2–0.8)	0.011	0.5 (0.3–1)	0.044	0.5 (0.2–1.0)	0.037
Unknown	0.4 (0.1–1.7)	0.200	0.5 (0.1–2.2)	0.347	0.5 (0.1–2.4)	0.369
Any INI failure	5.6 (2.2–14.3)	<0.001	3.5 (1.3–9.5)	0.015	2.6 (0.8–8)	0.100
Cumulative resistance						
NNRTI major	2.5 (1.3–4.9)	0.007	2.3 (1.1–4.8)	0.030	1.8 (0.8–3.8)	0.134
Past M184V and previous time under suppression (Ts)						
Never detected and Ts ≥3.5 years ^d	1		1		1	
Never detected and Ts <3.5 years	1.7 (0.9–3.3)	0.120	1.2 (0.6–2.5)	0.571	1.3 (0.6–2.7)	0.531
Detected and Ts <3.5 years	5.9 (1.7–20.2)	0.004	3.8 (1–14.4)	0.046	2.3 (0.6–9.0)	0.248
Detected and Ts ≥3.5 years	1.2 (0.3–5.1)	0.818	0.6 (0.1–3.0)	0.554	0.5 (0.1–2.4)	0.384

^a The following variables were tested for their potential role as predictor of virological rebound after DTG+3TC switch at univariable analyses: sex, age, risk transmission factors, nationality, ethnicity, levels of adherence to treatment, B and C hepatitis coinfection status, HIV-1 subtype, baseline and nadir CD4 count, previous viral blips experience, viremia zenith, HIV-1 RNA target not detected at switch, previous time under ART, number and type of previous failures, drugs received in the previous treatment history, reasons for treatment switch, previous cumulative resistance per each drug class, presence of past M184V, presence of past M184V according with previous time under suppression. Among them, in this table are reported only those that were significantly associated with virological rebound after DTG/3TC switch at univariable analysis.

^b Adjusted for variables significantly associated (P < 0.05) with virological response at univariable analysis excluding demographic or behavioural variables.

^c Adjusted for variables significantly associated at univariable analysis (P < 0.05).

^d Reference (dummy). 95% CI: 95% confidence interval; ND: not determined because no events observed.

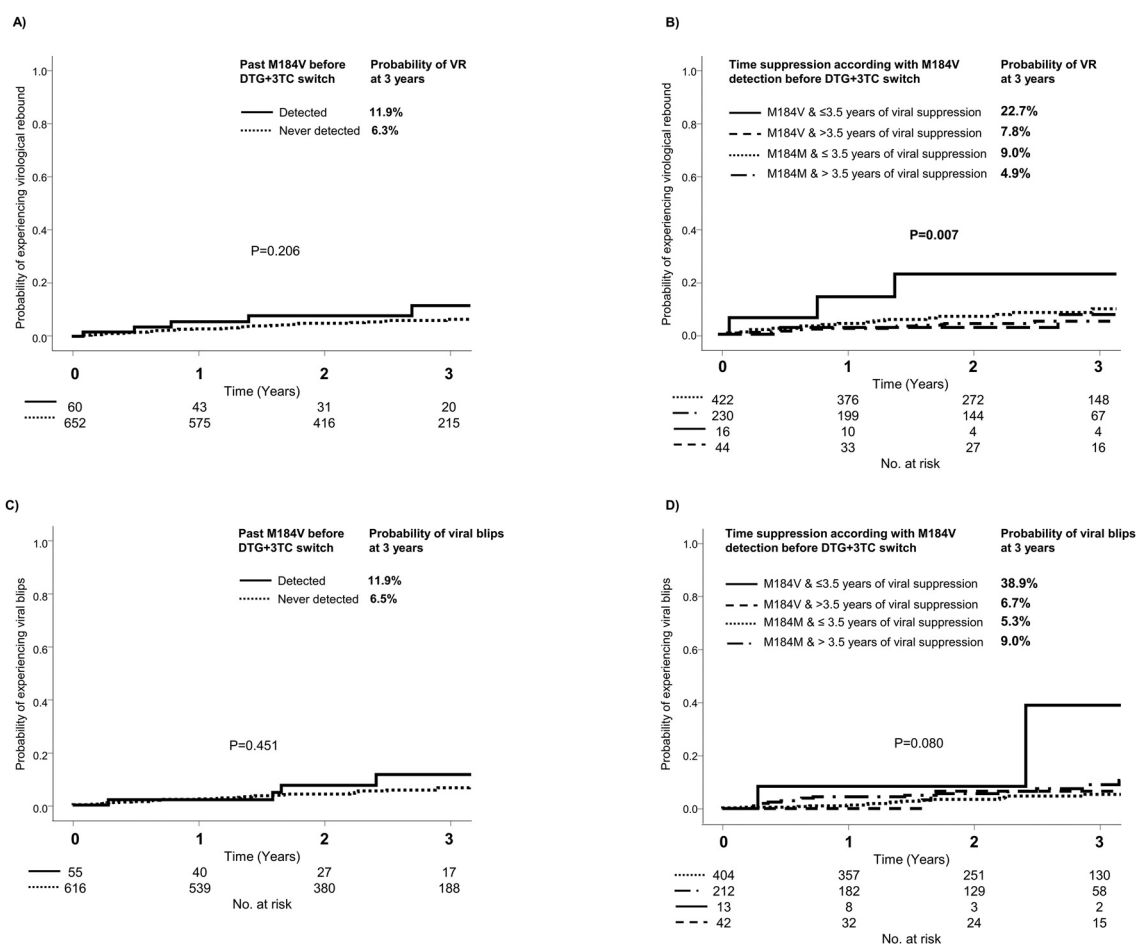


Fig. 1. Kaplan-Meier estimates of the probability of experiencing virological rebound or viral blips at 3 years under DTG+3TC treatment stratified according to the presence/absence of past M184V. (A) Virological rebound stratified according to presence/absence of past M184V. (B) Virological rebound stratified according to presence/absence of past M184V and previous time of virological suppression. (C) Virological blips stratified according to presence/absence of past M184V. (D) Virological blips stratified according to presence/absence of past M184V and previous time of virological suppression. P -values were calculated by using the Peto and Peto modification of the Gehan–Wilcoxon test and log-rank test, when appropriate. A P -value <0.05 was considered statistically significant. VR, virological rebound.

evaluated because few VR events ($n = 7$) were recorded at this setting.

Again, the presence of past M184V was not associated with the probability of VR after switch in all sensitivity analyses (Panels A–C, Supplementary Fig. S1).

The highest probability of VR was found in individuals with M184V in a context of ≤ 3.5 years of virological suppression before switch compared to the others, by using the second definition of VR (Supplementary Fig. S1, panel E) and in the ITT approach (Supplementary Fig. S1, panel F). Cox regression analyses, (both univariable and after adjusting for virological and therapeutical factors) confirmed these results, with a trend toward significance in multivariable analysis of the ITT approach (Supplementary Table S2).

3.4. Overview of virological rebound and resistance detected under DTG+3TC treatment after VR

In Table 4 an overview of the 39 individuals who experienced VR is reported. Eighteen of them (46.2%) re-suppressed without changing treatment, 16 (41.0%) changed treatment, 3 (7.7%) were lost at follow-up and 2 (5.1%) experienced episodes of low-level viremia under DTG+3TC. With regard to resistance, because of the low-level and often transient viremia detected, a GRT was performed only for eight (20.5%) individuals. M184V mutation was observed only in one individual (ID 451) who switched to DTG+3TC after a short period (one month)

of virological suppression. This patient previously experienced virological rebound (without any resistance evaluation) under elvitegravir/emtricitabine/tenofovir-alafenamide single-tablet regimen because of low compliance. After DTG+3TC VR, the patient switched to darunavir/cobicistat/tenofovir-alafenamide single-tablet regimen and later failed again; he was then lost at follow-up. No integrase resistance was observed in any of the six individuals tested for resistance at VR.

4. Discussion

The present study evaluated the virological response and the resistance profile in a large set of virologically suppressed patients followed in several clinical centres in France, Italy and Spain who were starting DTG+3TC treatment according to the presence/absence of M184V. We found a high rate of maintenance of virological suppression under DTG+3TC, thus confirming the excellent results already observed in clinical trials [6,8,36,37]. Specifically, we found that, after 3 years of treatment, the rate of VR was less than 10% and substantially further decreased by the fact that around 50% of those individuals who lost virological control resuppressed viremia without any treatment change.

This low rate of VR is also in line with that found in other observational studies that evaluated DTG+3TC in virologically suppressed patients [31,32,38]. Among eight individuals for whom a GRT was performed after VR, no resistance selection was found in

Table 3
Factors associated with viral blips in virologically suppressed patients switching to DTG+3TC treatment.

Variables	Hazard ratio (HR) to experience viral blips (N = 671)					
	Crude		Adjusted ^a		Adjusted ^c	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Demographic and behavioural parameters						
Adherence						
High ^d	1					
Medium	4.4 (1.3–14.6)	0.016			3.2 (0.9–11.6)	0.078
Low	0 (0–ND)	0.973			0 (0–ND)	0.978
Unknown	1.7 (0.8–3.7)	0.184			1.3 (0.6–2.9)	0.535
Viro-immunological parameters						
Target not detected at switch						
No ^d						
Yes	0.4 (0.2–0.7)	0.003	0.4 (0.2–0.8)	0.007	0.4 (0.2–0.8)	0.013
Unknown	0.5 (0.1–1.7)	0.252	0.5 (0.1–1.6)	0.212	0.5 (0.2–1.9)	0.322
Cumulative drug resistance						
Other NRTI RAMs						
	5.3 (1.9–14.9)	0.002	3.7 (0.9–14.5)	0.063	3.9 (1–15.4)	0.049
Past M184V and previous time under suppression (Ts)						
Never detected and Ts \geq 3.5 years ^d	1					
Never detected and Ts <3.5 years	2.0 (1.1–3.8)	0.029	2.2 (1.1–4.4)	0.019	2.2 (1.1–4.3)	0.026
Detected and Ts <3.5 years	4.7 (1.1–20.1)	0.039	2.4 (0.5–12.9)	0.303	1.5 (0.3–8.8)	0.629
Detected and Ts \geq 3.5 years	1.6 (0.5–5.5)	0.438	0.6 (0.1–2.5)	0.473	0.5 (0.1–2.2)	0.366
Treatment experience						
Drug experience						
No. of NRTIs	1.0 (0.8–1.2)	0.938				
3TC	1.6 (0.8–3.1)	0.147				
FTC	0.5 (0.2–1.0)	0.042	0.5 (0.3–1)	0.059	0.5 (0.3–1.1)	0.075
No. of NNRTIs	0.9 (0.6–1.3)	0.550				
No. of PIs	1.2 (1.0–1.4)	0.047	1.2 (1–1.5)	0.034	1.2 (1–1.5)	0.038
T20/MVC	1.0 (0.2–4.0)	0.958				
Any INIs	1.2 (0.6–2.1)	0.638				

^a The following variables were tested for their potential role as predictor of viral blips after DTG+3TC switch at univariable analyses: sex, age, risk transmission factors, nationality, ethnicity, levels of adherence to treatment, B and C hepatitis coinfection status, HIV-1 subtype, baseline and nadir CD4 count, previous viral blips experience, viremia zenith, HIV-1 RNA target not detected at switch, previous time under ART, number and type of previous failures, drugs received in the previous treatment history, reasons for treatment switch, previous cumulative resistance per each drug class, presence of past M184V, presence of past M184V according with previous time under suppression. Among them, in this table are reported only those that were significantly associated with virological rebound after DTG/3TC switch at univariable analysis.^b Adjusted for variables significantly associated ($P < 0.05$) with virological response at univariable analysis excluding demographic or behavioural variables.

^c Adjusted for variables significantly associated at univariable analysis ($P < 0.05$).

^d Reference (dummy). 95% C.I.: 95% confidence interval; ND: not determined because no events observed.

integrase, and only one individual showed M184V. This anecdotal case is related to a poorly compliant patient who failed a previous low genetic barrier regimen during which GRT was not performed. For this reason, it is not possible to assess whether the M184V occurred as a first time under DTG+3TC or by selection after the previous low genetic barrier regimen.

So far, the role of M184V mutation on DTG+3TC regimen is still to be completely elucidated, because, despite several clinical trials having evaluated this issue [6,8], few data from the clinical practice are available [31,32,38]. By analysing one of the largest populations with available complete previous treatment and resistance history from European real settings, the present observational study provides important information to elucidate the concerns about M184V. Likewise, in all the studies that evaluated the effect of M184V [17,31,32,38], our results confirm that DTG+3TC is effective regardless the presence of M184V.

However, the mere evaluation of the presence/absence of M184V might not be enough to confidently confirm the absence of any effect on DTG+3TC. Indeed, M184V might be present in the viral reservoir for a long time in people who have received 3TC/FTC in their therapeutic history [39]. Based on this consideration we can hypothesize that a longer time of virological suppression might be associated with a 'dilution' of quasispecies harbouring M184V in the viral reservoir.

In this context, clinicians might have some concerns in administering DTG+3TC to those individuals harbouring M184V but who also have a short time of previous suppression. Here, we consid-

ered the first quartile of the time under virological suppression in presence of M184V as the cutoff to identify these individuals of concern, and we found that individuals with M184V in a context of less than 3.5 years of previous suppression had an increased risk of experiencing VR under DTG+3TC. These results were not confirmed after adjusting for behavioural and demographic variables, probably because in clinical practice the heterogeneity of individuals and the clinical intervention might be biases. However, our results agree with other studies in which the presence of M184V seems to be more relevant if accompanied by a short period of virological suppression before switch [17,18,32].

Another important observation to point out is the fact that the detection of M184V in HIV-DNA might also be important. In our population, 20.0% of M184V was detected in HIV-DNA (16.7% exclusively in HIV-DNA; 3.3% in both HIV-DNA and -RNA). Reliability of resistance found in HIV-DNA is still debated because it might be present in defective viral genomes because of the activity of apolipoprotein B mRNA-editing enzyme, catalytic polypeptide (APOBEC) [40,41]. In particular, the presence of M184I mutation might be considered a marker of defective proviruses [27]. In this regard, there were no signals in our analyses of hypermutations nor mixture including M184I substitution observed in individuals harbouring M184V (data not shown). Among the five subjects who lost virological control and harboured pre-existent M184V, the mutation was previously detected in the HIV-DNA of three of them; two of them harboured M184V in both HIV-DNA and -RNA (Supplementary Table S1). Conversely, none of the in-

Table 4
Overview of patients who experienced VR under DTG+3TC.

ID	INIs experienced	INI failure before switch	Time of previous suppression (years)	Cumulative resistance at switch	Viremia at VR (copies/mL) ^a	Time VR (years)	GRT after VR	Time under DTG+3TC at GRT (years)	VR GRT compartment	Viremia at GRT (copies/mL)	Resistance after VR	Outcome after VR
642	DTG	No	17.9	NRTI: M184V, T215F;	348000	0.5	No	-	-	-	-	Re-suppression
107	DTG	No	1.9	PI: I50L, NRTI: M184V, T215F; NNRTI: K103N, Y181C	58→192	0.1	No	-	-	-	-	Re-suppression
376	RAL	Yes	1.2	NRTI: L210W, L74V, M184V, T215Y; NNRTI: K103N, L100I	1232	0.8	No	-	-	-	-	Change treatment
648	DTG	No	0.4	NRTI: M184V	224	1.4	No	-	-	-	-	Change treatment
234	None	No	10.4	NRTI: M184V; NNRTI: K101E, E138K, G190A	186→108	2.7	Yes	2.8	RNA	108	NRTI: M184V; NNRTI: E138A, G190A;	Change treatment
204	None	No	14.9	NRTI: M41L, D67N, L210W, T215Y; NNRTI: K101E, Y181C, G190A	56→783	4.1	Yes	4.5	DNA	41	NRTI: D67N, L210W	Re-suppression
169	RAL, EVG	No	4.1	None	85→136	0.1	Yes	0.1	DNA	136	None	Change treatment
451	EVG, DTG	Yes	0.1	None	509	0.3	Yes	0.3	RNA	3315	NRTI: <u>M184V</u>	Change treatment
231	None	No	5.7	NNRTI: E138A, K103N	75→65	0.6	Yes	0.8	DNA	65	NNRTI: E138A	Change treatment
64	RAL	No	5.3	None	1145	1.3	Yes	1.4	RNA	3415	None	Change treatment
109	DTG	Yes	0.6	NNRTI: E138A	218	2.3	Yes	2.4	RNA	98	NNRTI: E138A	Re-suppression
190	RAL	No	0.7	PI: L90M; NRTI: K219E; NNRTI: K103N	59073	3.0	Yes	3.0	DNA	59073	NRTI: K219E; NNRTI: K103N	Change treatment
24	None	No	1.7	NNRTI: E138A	119→392	0.9	No	-	-	-	-	Change treatment
164	None	No	6.2	NNRTI: E138A	771	1.8	No	-	-	-	-	Re-suppression
304	RAL	No	5.6	NNRTI: K103N	280	0.8	-	-	-	-	-	Re-suppression
166	DTG	Yes	0.1	NNRTI: V106I	50180	0.7	No	-	-	-	-	Lost to follow-up
371	None	No	11.4	NRTI: D67N, K70R, K129Q; NNRTI: G190A	58→53	1.4	No	-	-	-	-	Re-suppression
62	RAL	No	4.3	NRTI: L210W, T215Y	572	0.4	No	-	-	-	-	Re-suppression
710	None	No	14.9	NRTI: M184I	139→93	1.6	No	-	-	-	-	Change treatment
248	RAL	No	3.8	PI: L90M	417	2.5	No	-	-	-	-	Re-suppression
41	Unknown	Yes	2.6	None	110→110	0.3	No	-	-	-	-	Change treatment
97	EVG, DTG	No	4.3	None	412127	0.8	No	-	-	-	-	Re-suppression
201	None	No	0.7	None	15893	2.3	No	-	-	-	-	Re-suppression
325	None	No	2.6	None	68→89	0.4	No	-	-	-	-	Low level viremia ^b
342	None	No	5.5	None	260	0.3	-	-	-	-	-	Re-suppression
437	None	No	9.1	None	79→59	1.4	No	-	-	-	-	Change treatment
467	None	No	0.9	None	203	0.1	No	-	-	-	-	Re-suppression
470	EVG	No	1.5	None	44746	0.8	No	-	-	-	-	Re-suppression
476	DTG	No	0.7	None	797	0.2	No	-	-	-	-	Re-suppression
490	DTG	No	0.3	None	406	0.7	No	-	-	-	-	Re-suppression
536	RAL, DTG	No	14.5	None	90→52	1.8	No	-	-	-	-	Low level viremia ^b
590	None	No	3.3	None	181000	1.2	No	-	-	-	-	Re-suppression
635	RAL	No	2.3	None	4200000	1.3	No	-	-	-	-	Lost to follow-up
646	RAL, DTG	No	3.9	None	84→83	0.1	No	-	-	-	-	Change treatment
685	RAL	No	1.2	None	273→343	1.8	No	-	-	-	-	Change treatment
696	RAL	No	14.8	None	2110	0.5	No	-	-	-	-	Re-suppression
713	DTG	No	0.4	None	152→539	1.3	No	-	-	-	-	Change treatment
228	None	No	3.8	None	68→82	2.5	No	-	-	-	-	Change treatment
329	None	No	4.5	None	4932	0.6	No	-	-	-	-	Lost to follow-up

In bold are highlighted individuals with M184V present before DTG/3TC switch. New mutations detected after VR under DTG+3TC are underlined.

^a Viremia at VR was indicated as one value in case of single viremia >200 copies/mL or as two values separated by “→” symbol in case of two consecutive values >50 copies/mL.

^b Low-level viremia was defined as three consecutive plasma HIV-1 RNA values >50 and <200 copies/mL after DTG+3TC.

dividuals who maintained virological control harboured M184V in both HIV-DNA and -RNA.

These findings are in line with data from our previous study in which the presence of resistance in both HIV-DNA and -RNA was associated with an increased risk of losing virological control in virologically suppressed patients switching treatment [42]. Based on these considerations, we can speculate that M184V detected in HIV-DNA without APOBEC signals and/or detected in both HIV-DNA and -RNA might be a concern to carefully consider in patients who need to simplify their treatment with DTG+3TC.

Even though the main focus of this study is on the role of M184V, other factors such as a previous short time under virological suppression, a high viremia zenith and previous virological failures to INI-based regimens were significantly related with virological rebound. These results agree with those observed in several observational studies, on virologically suppressed patients, not only evaluating DTG+3TC [17,31,32,42,43].

In our study we also evaluated the effect of M184V on experiencing viral blips under DTG+3TC. In this regard, we found that the overall probability of experiencing viral blips was low (around 7%) without any effect of past M184V. This finding disagrees with that found in a previous study evaluating heterogenous 3TC-based dual therapies (including DTG+3TC in a subgroup) that showed a significant association of the mutation with viral blips under treatment [17]. These discordant observations were probably related to the fact that patients in our study received exclusively DTG+3TC, whereas in the other study a dual therapy containing less effective drugs (such as atazanavir plus lamivudine) was included. We found that factors positively associated to viral blips were to have experienced several PIs and the absence of M184V in a context of short previous suppression (<3.5 years). These findings might be related to the fact that a higher incidence of viral blips is observed in people taking PIs [44]. In fact, people who experienced several PIs might have less chances to have M184V because of the high PI genetic barrier. On the other hand, they might be more prone to have low-level viremia and viral instability [44] that explain the short previous suppression before DTG/3TC switch. Concerning the role of non-TAM NRTI MRMs on viral blips, we can hypothesize that it was mainly related to the presence of K65R mutation. In fact, in our data set the prevalence of K65R before switch was the only non-TAM NRTI MRM that showed significantly higher prevalence in individuals experiencing blips (3 out of 43, 7.0%) compared to those had undetectable viremia (3 of 628, 0.5%, $P = 0.004$, data not shown). Despite the few cases available, we can therefore suppose that K65R might be a marker of virological instability and consequently viral blips.

This study has some limitations. First of all, despite the large population analysed, we recorded few events of losing virological control because of the high efficacy of the DTG+3TC combination. Moreover, because of the observational nature of the cohort analysed, adherence data were not available for all individuals. It should be carefully taken into account that, in the context of treatment optimizations in real settings, we cannot exclude potential biases related to clinicians' decisions that might be more frequent according to the individualized management of patients. On this point, even though marginal, a certain number of individuals switched treatments despite previous resistance and or with short previous virological suppression.

In conclusion, our data from real settings confirm that DTG+3TC offers a virologically safe opportunity for ART regimen simplification in a vast majority of virologically suppressed individuals without particular concerns. However, the effect of a short duration of previous virological suppression in individuals with M184V on DTG+3TC response remains troubling and needs ad hoc clinical trials to be confirmed.

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Competing interests

Andrea Antinori is a paid consultant with honoraria from Gilead Sciences, GSK, Merck Sharp & Dohme, Janssen-Cilag, Roche, Theratechnologies, and ViiV Healthcare. Vincent Calvez has received funds for attending symposia, speaking and research grants from ViiV Healthcare, Gilead Sciences, Theratechnologies, and Merck Sharp & Dohme. Charlotte Charpentier has received funds for attending symposia, speaking, organizing educational activities and travel grants from Gilead Sciences, ViiV Healthcare, Merck Sharp & Dohme, Janssen-Cilag and Theratechnologies. Francesca Ceccherini-Silberstein has received funds for attending symposia, speaking, organizing educational activities, travel grants, advisory/consulting and/or research grants from Abbvie, Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme, Theratechnologies and ViiV Healthcare. Sidonie Lambert-Niclot has received funds for attending symposia, speaking, organizing educational activities and travel grants from Gilead Sciences, Merck Sharp & Dohme and ViiV Healthcare. Anne-Geneviève Marcelin has received funds for attending symposia, speaking and research grants from ViiV Healthcare, Gilead Sciences, Theratechnologies, and Merck Sharp & Dohme. Diane Descamps has received funds for attending symposia, speaking, organizing educational activities and travel grants from Gilead Sciences, ViiV Healthcare, Merck Sharp & Dohme and Janssen-Cilag. Roger Paredes has received research funding and consultancy fees from and has served on advisory boards for Gilead Sciences, Merck Sharp & Dohme, ViiV Healthcare, Theratechnologies Inc., and Eli Lilly and Company. Carlo Federico Perno has received funds for attending symposia, speaking, organizing educational activities and travel grants from Abbvie, Gilead Sciences, ViiV Healthcare, Merck Sharp & Dohme, Janssen-Cilag and Theratechnologies. Maria Mercedes Santoro has received funds for attending symposia, speaking and organizing educational activities from ViiV Healthcare, Janssen-Cilag and Theratechnologies. Ramón Santos has received research funding, consultancy fees and lecture sponsorships from and has served on advisory boards for Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme and ViiV Healthcare. All other authors declare that they have no competing interests.

Ethics approval

The study was conducted on data routinely collected for clinical purposes. The research was conducted in accordance with the principles of the Declaration of Helsinki. All data used in the study were previously anonymized, according to the requirements set by the EU Regulation 2016/679 and by the Data Protection Code of each country involved in the study. Written informed consent for medical procedures/interventions performed for routine treatment purposes was collected from each individual. All information, including virological and clinical data, was recorded in an anonymized database.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jgar.2022.07.022](https://doi.org/10.1016/j.jgar.2022.07.022).

References

- [1] Samji H, Cescon A, Hogg RS, Modur SP, Althoff KN, Buchacz K, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS One* 2013;8:e81355. doi:10.1371/journal.pone.0081355.
- [2] Lohse N, Obel N. Update of survival for persons with HIV infection in Denmark. *Ann Intern Med* 2016;165:749–50. doi:10.7326/L16-0091.
- [3] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services (last update 20 January 2022). <https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf>.
- [4] European AIDS Clinical Society. Guidelines: version 11.0 2021. https://www.eacsociety.org/media/final2021eacsguidelinesv11.0_oct2021.pdf.
- [5] Cahn P, Rolón MJ, Figueroa MI, Gun A, Patterson P, Sued O. Dolutegravir-lamivudine as initial therapy in HIV-1 infected, ARV-naïve patients, 48-week results of the PADDLE (Pilot Antiretroviral Design with Dolutegravir Lamivudine) study. *J Int AIDS Soc* 2017;20:1–7. doi:10.7448/IAS.20.01.21678.
- [6] Taiwo BO, Marconi VC, Berzins B, Moser CB, Nyaku AN, Fichtenbaum CJ, et al. Dolutegravir plus lamivudine maintains human immunodeficiency virus-1 suppression through week 48 in a pilot randomized trial. *Clin Infect Dis* 2018;66:1794–7. doi:10.1093/cid/cix1131.
- [7] Cahn P, Madero JS, Arribas JR, Antinori A, Ortiz R, Clarke AE, et al. Durable efficacy of dolutegravir plus lamivudine in antiretroviral treatment-naïve adults with HIV-1 infection: 96-week results from the GEMINI-1 and GEMINI-2 randomized clinical trials. *J Acquir Immune Defic Syndr* 2020;83:310–18. doi:10.1097/QAI.0000000000002275.
- [8] Van Wyk J, Ajana F, Bishopp F, De Wit S, Osiyemi O, Portilla Sogorb J, et al. Efficacy and safety of switching to dolutegravir/lamivudine fixed-dose 2-drug regimen vs continuing a tenofovir alafenamide-based 3-or 4-drug regimen for maintenance of virologic suppression in adults living with human immunodeficiency virus type 1: phase. *Clin Infect Dis* 2020;71:1920–9. doi:10.1093/cid/ciz1243.
- [9] Llibre JM, Brites C, Cheng C-Y, Osiyemi O, Galera C, Hocqueloux L, et al. Efficacy and safety of switching to the 2-drug regimen dolutegravir/lamivudine versus continuing a 3- or 4-drug regimen for maintaining virologic suppression in adults living with HIV-1: week 48 results from the phase 3, non-inferiority SALSA randomized trial. *Clin Infect Dis* 2022. doi:10.1093/CID/C1AC130.
- [10] Maggiolo F, Gulminetti R, Pagnucco L, Digaetano M, Benatti S, Valenti D, et al. Lamivudine/dolutegravir dual therapy in HIV-infected, virologically suppressed patients. *BMC Infect Dis* 2017;17:215. doi:10.1186/s12879-017-2311-2.
- [11] Borghetti A, Baldin G, Lombardi F, Ciccullo A, Capetti A, Rusconi S, et al. Efficacy and tolerability of lamivudine plus dolutegravir as a switch strategy in a multicentre cohort of patients with suppressed HIV-1 replication. *HIV Med* 2018;19:452–4. doi:10.1111/hiv.12611.
- [12] Baldin G, Ciccullo A, Rusconi S, Madeddu G, Sterrantino G, Freedman A, et al. Single tablet regimen with abacavir/lamivudine/dolutegravir compared with two-drug regimen with lamivudine and dolutegravir as different strategies of simplification from a multicenter HIV cohort study. *Le Infez Med* 2019;27:410–14.
- [13] Allavena C, Deschanvres C, Peytavin G, Rey D, Valantin MA, Bani-Sadr F, et al. Factors associated with therapeutic failure of 2 drug regimens (DAT/AIDS Cohort) Conference on Retroviruses and Opportunistic Infections (CROI) 2019 Seattle, WA; 2019. 4–7 March[Abstract 493].
- [14] Battagin G, Parisi S, Giordani M, et al. Dual HIV treatment in experienced HIV patients HIV Glasgow Conference 2020; 2020. Virtual. 5–8 October[Abstract P045].
- [15] Gagliardini R, Lorenzini P, Cozzi Lepri A, et al. Effect of past virological failure on dolutegravir + lamivudine as maintenance regimen Conference on Retroviruses and Opportunistic Infections (CROI) Boston, MA; 2020. 8–11 March[Abstract 0486].
- [16] Postel N, Schneeweiss S, Wyen C, et al. Real-world data from the prospective URBAN cohort study on the use of dolutegravir (DTG) + lamivudine (3TC) in ART naïve and pre-treated people living with HIV in Germany HIV Glasgow Conference 2020; 2020. Virtual. 5–8 October[Poster 044].
- [17] Gagliardini R, Ciccullo A, Borghetti A, Maggiolo F, Bartolozzi D, Borghi V, et al. Impact of the M184V resistance mutation on virological efficacy and durability of lamivudine-based dual antiretroviral regimens as maintenance therapy in individuals with suppressed HIV-1 RNA: a cohort study. *Open Forum Infect Dis* 2018;5:ofy113. doi:10.1093/ofid/ofy113.
- [18] Baldin G, Ciccullo A, Borghetti A, Di Giambenedetto S. Virological efficacy of dual therapy with lamivudine and dolutegravir in HIV-1-infected virologically suppressed patients: Long-term data from clinical practice. *J Antimicrob Chemother* 2019;74:1461–3. doi:10.1093/jac/dkz009.
- [19] Borghetti A, Lombardi F, Gagliardini R, Baldin G, Ciccullo A, Moschese D, et al. Efficacy and tolerability of lamivudine plus dolutegravir compared with lamivudine plus boosted PIs in HIV-1 positive individuals with virologic suppression: A retrospective study from the clinical practice 11 Medical and Health Sciences 1103 Clinical Sci. *BMC Infect Dis* 2019;19:1–9. doi:10.1186/s12879-018-3666-8.
- [20] Ciccullo A, Baldin G, Capetti A, Rusconi S, Sterrantino G, d'Ettoire G, et al. A comparison between two dolutegravir-based two-drug regimens as switch strategies in a multicentre cohort of HIV-1-infected patients. *Antivir Ther* 2019;24:63–7. doi:10.3851/IMP3270.
- [21] Canetti D, Galli L, Gianotti N, Celotti A, Calza L, Gagliardini R, et al. Simplification to high genetic barrier 2-drug regimens in people living with HIV harboring 4-class resistance enrolled in the PRESTIGIO Registry. *J Acquir Immune Defic Syndr* 2020;84:e24–8. doi:10.1097/QAI.0000000000002378.
- [22] Galizzi N, Poli A, Galli L, Muccini C, Mastrangelo A, Dell'Acqua R, et al. Retrospective study on the outcome of two-drug regimens based on dolutegravir plus one reverse transcriptase inhibitor in virologically-suppressed HIV-infected patients. *Int J Antimicrob Agents* 2020;55. doi:10.1016/j.ijantimicag.2020.105893.
- [23] Armenia D, Bouba Y, Gagliardini R, Fabeni L, Borghi V, Berno G, et al. Virological response and resistance profile in highly treatment-experienced HIV-1-infected patients switching to dolutegravir plus boosted darunavir in clinical practice. *HIV Med* 2021;22:519–25. doi:10.1111/hiv.13062.
- [24] Fabbiani M, Rossetti B, Ciccullo A, Oreni L, Lagi F, Celani L, et al. Efficacy and durability of two- vs. three-drug integrase inhibitor-based regimens in virologically suppressed HIV-infected patients: data from real-life ODOACRE cohort. *HIV Med* 2021;22:843–53. doi:10.1111/hiv.13146.
- [25] Noë A, Plum J, Verhofstede C. The latent HIV-1 reservoir in patients undergoing HAART: an archive of pre-HAART drug resistance. *J Antimicrob Chemother* 2005;55:410–12. doi:10.1093/jac/dki038.
- [26] Miller V, Stark T, Loeliger AE, Lange JMA. The impact of the M184V substitution in HIV-1 reverse transcriptase on treatment response. *HIV Med* 2002;3:135–45. doi:10.1046/j.1468-1293.2002.00101.x.
- [27] Charpentier C, Montes B, Perrier M, Meftah N, Reynes J. HIV-1 DNA ultra-deep sequencing analysis at initiation of the dual therapy dolutegravir/lamivudine in the maintenance DOLULAM pilot study. *J Antimicrob Chemother* 2017;72:2831–6. doi:10.1093/jac/dkx233.
- [28] Rial-Crestelo D, De Miguel R, Montejano R, Dominguez-Dominguez L, Aranguren-Rivas P, Esteban-Cantos A, et al. Long-term efficacy of dolutegravir plus lamivudine for maintenance of HIV viral suppression in adults with and without historical resistance to lamivudine: Week 96 results of ART-PRO pilot study. *J Antimicrob Chemother* 2021;76:738–42. doi:10.1093/jac/dkaa479.
- [29] G. Blick, E., Cerreta, G., Mancini AC. SOLAR 3D: a prospective comparative study switching from 3- or 4-drug ART to DTG/3TC for maintenance of viral suppression in the setting of current and historical M184V/I and prior virologic failures: 48 week primary endpoint results. In: EACS 2021 Oct 27–30, 2021.
- [30] Hocqueloux L, Allavena C, Secher S, Makinson A, Rey D, Huleux T, et al. Archived mutation M184V does not increase virologic failure during maintenance therapy with dolutegravir + lamivudine in the French DAT/AIDS cohort. EACS, 27–30 October 2021.
- [31] Patel R, Evitt L, Mariolis I, Di Giambenedetto S, d'Arminio Monforte A, Casado J, et al. HIV treatment with the two-drug regimen dolutegravir plus lamivudine in real-world clinical practice: a systematic literature review. *Infect Dis Ther* 2021. doi:10.1007/s40121-021-00522-7.
- [32] Ciccullo A, Borghi V, Giacomelli A, Cossu M V, Sterrantino G, Latini A, et al. Five years with dolutegravir plus lamivudine as a switch strategy: much more than a positive finding. *J Acquir Immune Defic Syndr* 2021. doi:10.1097/QAI.0000000000002787.
- [33] Paba P, Fabeni L, Ciccozzi M, Perno CF, Ciotti M. Performance evaluation of the COBAS/TaqMan HIV-1 v2.0 in HIV-1 positive patients with low viral load: a comparative study. *J Virol Methods* 2011;173:399–402. doi:10.1016/j.jviromet.2011.03.014.
- [34] Sire J-M, Vray M, Merzouk M, Plantier J-C, Pavie J, Maylin S, et al. Comparative RNA quantification of HIV-1 group M and non-M with the Roche Cobas AmpliPrep/Cobas TaqMan HIV-1 v2.0 and Abbott Real-Time HIV-1 PCR assays. *J Acquir Immune Defic Syndr* 2011;56:239–43. doi:10.1097/QAI.0b013e3182099891.
- [35] Longo S, Bon I, Musumeci G, Bertoldi A, D'Urbano V, Calza L, et al. Comparison of the Aptima HIV-1 Quant Dx assay with the COBAS AmpliPrep/COBAS TaqMan HIV-1 v2.0 Test for HIV-1 viral load quantification in plasma samples from HIV-1-infected patients. *Heal Sci Reports* 2018;1. doi:10.1002/hsr2.31.

- [36] Joly V, Burdet C, Landman R, Vigan M, Charpentier C, Katlama C, et al. Dolutegravir and lamivudine maintenance therapy in HIV-1 virologically suppressed patients: results of the ANRS 167 trial (LAMIDOL). *J Antimicrob Chemother* 2019;74:739–45. doi:[10.1093/jac/dky467](https://doi.org/10.1093/jac/dky467).
- [37] Gagliardini R, Baccini M, Modica S, Montagnani F, Zanelli G, Borghetti A, et al. Impact of resistance mutations on efficacy of dolutegravir plus rilpivirine or plus lamivudine as maintenance regimens: a cohort study. *J Glob Antimicrob Resist* 2022. doi:[10.1016/j.jgar.2022.01.018](https://doi.org/10.1016/j.jgar.2022.01.018).
- [38] Borghetti A, Giacomelli A, Borghi V, et al. Nucleoside reverse-transcriptase inhibitor resistance mutations predict virological failure in human immunodeficiency virus-positive patients during lamivudine plus dolutegravir maintenance therapy in clinical practice. *Open Forum Infect Dis* 2021;8:ofab103. doi:[10.1093/ofid/ofab103](https://doi.org/10.1093/ofid/ofab103).
- [39] Palich R, Teyssou E, Sayon S, Abdi B, Soulie C, Cuzin L, et al. Kinetics of archived M184V mutation in treatment-experienced virally suppressed HIV-infected patients. *J Infect Dis* 2021. doi:[10.1093/infdis/jiab413](https://doi.org/10.1093/infdis/jiab413).
- [40] Kieffer TL, Kwon P, Nettles RE, Han Y, Ray SC, Siliciano RF. G→A hypermutation in protease and reverse transcriptase regions of human immunodeficiency virus type 1 residing in resting CD4+ T cells in vivo. *J Virol* 2005;79:1975–80. doi:[10.1128/JVI.79.3.1975-1980.2005](https://doi.org/10.1128/JVI.79.3.1975-1980.2005).
- [41] Noguera-Julian M, Cozzi-Lepri A, Di Giallonardo F, Schuurman R, Däumer M, Aitken S, et al. Contribution of APOBEC3G/F activity to the development of low-abundance drug-resistant human immunodeficiency virus type 1 variants. *Clin Microbiol Infect* 2016;22:191–200. doi:[10.1016/j.cmi.2015.10.004](https://doi.org/10.1016/j.cmi.2015.10.004).
- [42] Armenia D, Zaccarelli M, Borghi V, Gennari W, Di Carlo D, Giannetti A, et al. Resistance detected in PBMCs predicts virological rebound in HIV-1 suppressed patients switching treatment. *J Clin Virol* 2018. doi:[10.1016/j.jcv.2018.04.001](https://doi.org/10.1016/j.jcv.2018.04.001).
- [43] Armenia D, Di Carlo D, Calcagno A, Vendemiati G, Forbici F, Bertoli A, et al. Pre-existent NRTI and NNRTI resistance impacts on maintenance of virological suppression in HIV-1-infected patients who switch to a tenofovir/emtricitabine/rilpivirine single-tablet regimen. *J Antimicrob Chemother* 2016;72:855–65. doi:[10.1093/jac/dkw512](https://doi.org/10.1093/jac/dkw512).
- [44] Dijkstra S, Hofstra LM, Mudrikova T, Wensing AMJ, Oomen PGA, Hoepelman AIM, et al. Lower incidence of HIV-1 blips observed during integrase inhibitor-based combination antiretroviral therapy. *J Acquir Immune Defic Syndr* 2022;89:575–82. doi:[10.1097/QAI.0000000000002898](https://doi.org/10.1097/QAI.0000000000002898).