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MAJOR ARTICLE

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

Roberta Gagliardini,[1] Arturo Ciccullo,[2] Alberto Borghetti,[2] Franco Maggiolo,[3] Dario Bartolozzi,[4] Vanni Borghi,[5] Monica Pecorari,[6] Antonio Di Biagio,[7] Anna Paola Callegaro,[8] Bianca Bruzzone,[9] Francesco Saladini,[10] Stefania Paolucci,[11] Renato Maserati,[12] Maurizio Zazzi,[10] Simona Di Giambenedetto,[2] and Andrea De Luca[1,10]; on behalf of the ARCA Study Group

[1]Infectious Diseases Unit, AOU Senese, Siena, Italy; [2]Institute of Infectious Diseases, Catholic University of Sacred Heart, Rome, Italy; [3]Division of Infectious Diseases, ASST Papa Giovanni XXIII, Bergamo, Italy; [4]Clinic of Infectious and Tropical Diseases, Azienda Ospedaliera Universitaria Careggi, Firenze, Italy; [5]Clinica Malattie Infettive e Tropicali and [6]Microbiology and Virology Unit, Azienda Ospedaliero Universitaria di Modena, Modena, Italy; [7]Infectious Diseases, IRCCS AOU San Martino-IST, Genova, Italy; [8]Microbiology and Virology Unit, ASST Papa Giovanni XXIII, Bergamo, Italy; [9]Hygiene Unit, IRCCS AOU San Martino-IST, Genova, Italy; [10]Department of Medical Biotechnologies, University of Siena, Siena, Italy; [11]Virologia Molecolare, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [12]Infectious Diseases Clinic, S. Matteo Hospital, Pavia, Italy

Background. Dual therapy (DT) with boosted protease inhibitors (bPIs) plus lamivudine has been shown to be superior to bPI monotherapy in virologically suppressed patients despite previous selection of the lamivudine resistance M184V mutation. We compared the virological efficacy of lamivudine-based DT in patients with and without a history of M184V detection.

Methods. We retrospectively analyzed patients with HIV-RNA ≤50 copies/mL switching to DT with at least 1 previous resistance genotype in the ARCA database. Time to virological failure (VF; HIV-RNA ≥200 copies/mL or 2 consecutive HIV-RNA >50 copies/mL) and to treatment discontinuation (TD) was analyzed by survival analysis.

Results. Four hundred thirty-six patients switching to lamivudine plus bPIs (70%) or integrase inhibitors (30%) were included. Patients with M184V (n = 87) were older, had lower nadir CD4+ cell count, longer duration of antiretroviral therapy and of virologic suppression, and higher rate of hepatitis C virus infection compared with patients without M184V. The 3-year probability of remaining free from VF was 91.9% (95% confidence interval [CI], 86.6–97.2) without M184V and 87.8% (95% CI, 78.4–97.2) with M184V (P = .323). The time to TD did not differ between groups. Multivariate analysis adjusting for baseline variables differing between groups also did not detect M184V as being associated with VF or TD; however, the 3-year probability of remaining free of viral blips (isolated HIV-RNA 51–199 copies/mL) was 79.8% (95% CI, 67.8%–91.8%) with M184V vs 90.1% (95% CI, 84.0%–96.2%) without M184V (P = .016).

Conclusions. Previous selection of M184V did not increase the risk of VF or TD with lamivudine-based DT but was associated with a higher probability of viral blips.

Keywords. dual therapy; integrase inhibitors; lamivudine; M184V; NRTI mutations.

Combination antiretroviral therapy (ART) has radically changed the clinical course of HIV disease, reducing AIDS-related morbidity and mortality [1]. The disease has become chronic and requires life-long treatment, raising issues of treatment tolerability, toxicity, and adherence. Thus, several strategies of ART regimen simplification have been considered. Dual therapies (DTs) have been explored in a significant number of randomized clinical trials and are increasingly being used as maintenance therapy, particularly in some European countries. Lamivudine is the companion drug for many of the dual regimens investigated so far [2–7]. A meta-analysis of randomized trials showed a noninferior risk of virological failure with lamivudine plus boosted protease inhibitor (bPI) as compared with continuation of the 3-drug regimen [8]. Interestingly, the ANRS12286/MOBIDIP trial showed the superiority of DT with lamivudine plus bPI as compared with bPI monotherapy in a population of patients virologically suppressed on a second-line regimen of 2NRTI plus bPI, carrying the M184V mutation in many cases [9].

The M184V mutation is associated with high-level in vitro resistance to lamivudine but also with reduced viral replication capacity [10]. Previous selection of M184V may impact clinical decisions to implement lamivudine-containing DT, yet a direct comparison of efficacy in patients harboring or not harboring the M184V

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Correspondence: R. Gagliardini, MD, Infectious Diseases Unit, AOU Senese, Viale M Bracci 15—53100 Siena, Italy (roberta_gagliardini@yahoo.it).

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mutation has not been performed. This study aimed at comparing the virological efficacy of lamivudine-based maintenance DT in clinical practice patients with suppressed viral load, with (M184V+) or without (M184V-) a history of M184V detection.

METHODS

Patients Selection Criteria and Virological Characteristics

This is a retrospective observational study performed using the Antiviral Response Cohort Analysis (ARCA) database, which contains data on HIV resistance and antiretroviral therapy from >40 000 patients in Italy [11]. The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and later amendments. All patients signed an informed consent for use of their clinical and laboratory data in aggregated and anonymous form. Access to the database and data analyses were regulated by local institutional ethics committees and by Italian and European privacy legislation. The ARCA database was queried to retrieve the data of HIV-1-infected patients with (i) age ≥18 years, (ii) HIV-RNA ≤50 copies/mL on any ART regimen, (iii) subsequently switching to DT (lamivudine plus bPI or plus integrase inhibitor [INI]) for any reason, (iv) with at least 1 previous genotype, (v) with at least 1 virological and clinical follow-up after switching to DT. The occurrence of M184V was assessed using historical genotypic resistance tests (hGRTs); that is, any detection of this mutation in any previous resistance test was scored as positive. In a sensitivity analysis, only the most recent resistance genotype before baseline was considered. Patients treated with bPI monotherapy were selected with the same inclusion criteria (i–ii and iv–v) and were used as an additional control group.

A genotypic sensitivity score (GSS) was derived for each drug accompanying lamivudine (for the DT group) or for each monotherapy, based on the hGRT according to the AntiRetroScan 2.0 genotypic interpretation system, as detailed elsewhere [12]. Briefly, a GSS of 0 was assigned if the system interpreted "no activity," 0.25 if "minimal activity," 0.50 if "partial activity," 0.75 if "good activity," and 1 if "complete activity" [11]. For INI therapies without INI sequences available before BL, GSS was assigned as 1.

End Points and Statistical Analysis

The primary objective of the study was to compare time to virological failure and time to treatment discontinuation between the M184V- and M184V+ groups. Secondary objectives were to compare time to virological blips between the 2 groups and time to virological failure between the DT group (overall and with M184V+) and the bPI monotherapy group. Virological failure was defined as HIV-RNA >50 copies/mL in 2 consecutive determinations or ≥200 copies/mL in a single determination. Treatment discontinuation was defined as discontinuation of current DT for any reason or loss to follow-up. Viral blips were defined as a single HIV-RNA between 51 and 199 copies/mL preceded and followed by ≤50 copies/mL measurements.

Differences between groups were investigated by the Student *t* test and chi-square analysis. Standard survival analyses with Kaplan-Meier curves were used to analyze time to virological failure, time to treatment discontinuation, and time to viral blip. Patients were followed from baseline (ie, start of DT) to the study outcomes, last available follow-up, or February 28, 2017, whichever occurred first. For the time to viral blip analysis, patients with virological failure were excluded. Predictors were investigated by univariate Cox regression; variables showing a significant association at univariate analysis and those variables for which the 2 groups differed at baseline were evaluated in multivariable models. *P* values of less than .05 were considered significant.

We performed sensitivity analyses considering M184V only in the last available genotypic resistance tests and a different definition of virological failure (HIV-RNA >50 copies/mL in 2 consecutive determinations or a single determination ≥1000 copies/mL) and of virological blips (single HIV-RNA between 51 and 999 copies/mL not confirmed at the subsequent determination).

All analyses were executed using the SPSS v.22.0 software package.

RESULTS

Patients

A total of 436 patients starting lamivudine-based DT were selected, of which 349 (80%) did not have the M184V mutation and 87 (20%) did have the M184V mutation, according to the hGRT (patients' baseline characteristics in Table 1). DTs started at baseline were lamivudine plus bPI (70%; lopinavir/r [10%], atazanavir/r [24%], darunavir/r [36%]) and lamivudine plus INI (30%; dolutegravir [29%], raltegravir [1%]).

Virological Failure and its Predictors

Main Results

In the DT group, during 693 person-years of follow-up (PYFU; median follow-up, 1.3 years; interquartile range [IQR], 0.7–2.5), 24 virological failures were detected: 7 during 139 PYFU in M184V+ patients (incidence, 5.1; 95% confidence interval [CI], 2.2%–9.9% per 100 PYFU) and 17 during 554 PYFU in M184V- patients (incidence, 3.1; 95% CI, 1.8%–4.8% per 100 PYFU). Virological failures were 4 on lamivudine plus atazanavir/r and 3 on lamivudine plus darunavir/r in the M184V+ group, 7 on lamivudine plus atazanavir/r, 5 on lamivudine plus darunavir/r, 3 on lamivudine plus lopinavir/r, and 2 on lamivudine plus dolutegravir in the M184V- group. GRT after virological failure was available only for 8 patients, all in lamivudine +bPI (Supplementary Table 1).

The estimated probability of remaining free from virological failure was comparable in the 2 groups: at 1 year 95.1% (95% CI, 89.6–100.6) in M184V+ and 96.2% (95% CI, 93.9–98.6) in M184V- patients; at 3 years 87.8% (95% CI, 78.4–97.2) in

Table 1. Baseline Characteristics of Patients Starting Lamivudine-Based Dual Therapies According to M184V Detection in the Historical Genotypic Resistance Test

	M184V- (n = 349)	M184V+ (n = 87)	*P*
Age, y[a]	46 (39–53)	52 (48–57)	**<.001**
Male sex	257 (72)	53 (61)	**.019**
Caucasians	308 (88)	84 (97)	.077
Risk factor			
Sexual	225 (64)	56 (64)	**.001**
IDU	40 (11)	21 (24)	
Other/unknown	84 (24)	10 (11)	
HCV infection	62 (18)	24 (28)	**<.001**
HBsAg+	12 (3)	2 (2)	**.001**
Previous AIDS events	40 (12)	16 (18)	.084
HIV-RNA at zenith, cp/mL[a]	104 750 (35 807–329 250)	107 910 (27 000–252 900)	.416
Years from HIV diagnosis[a]	7.8 (3.8–13.7)	19.2 (16.1–23.0)	**<.001**
Years from first ART initiation[a]	5.6 (2.8–10.0)	16.6 (12.8–18.9)	**<.001**
Duration of viral suppression, y[a]	3.8 (2.2–6.4)	6.6 (3.7–8.9)	**<.001**
Lines of ART[a]	4 (3–6)	8 (7–13)	**<.001**
Nadir CD4+, cells/μL[a]	224 (81–313)	147 (57–199)	**<.001**
Current CD4+, cells/μL[a]	620 (453–780)	632 (409–922)	.131
Type of DT			
Lamivudine + bPI	242 (69)	64 (74)	.441
Lamivudine + bDRV	122 (35)	33 (38)	
Lamivudine + bLPV	34 (10)	11 (13)	
Lamivudine + bATV	86 (24)	20 (23)	
Lamivudine + INI	107 (31)	23 (26)	
Lamivudine + DTG	105 (30)	21 (24)	
Lamivudine + RAL	2 (1)	2 (2)	
Pre-BL ART			
2NRTI + PI	176 (50)	44 (51)	.081
2NRTI + INI	26 (7)	7 (8)	
2NRTI + NNRTI	45 (13)	3 (3)	
DT	79 (23)	23 (26)	
Other	23 (7)	10 (12)	
Calendar year[a]	2014 (2013–2015)	2014 (2012–2015)	.121
GSS of the 2nd drug[b]	0.99 (0.07)	0.91 (0.20)	**<.001**
Major PI resistance mutations[c]	13 (4)	30 (34)	**<.001**

Abbreviation: ART, antiretroviral therapy; ATV, atazanavir; BL, baseline; bPI, boosted protease inhibitors; DRV, darunavir; DT, dual therapy; lamivudine, lamivudine; DTG, dolutegravir; GSS, genotypic sensitivity score; IDU, injective drug users; INI, integrase inhibitor; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; LPV, lopinavir; NNRTI, non-nucleoside reverse-transcriptase inhibitors; NRTI, nucleoside reverse-transcriptase inhibitors; RAL, raltegravir.

Values are expressed as n (%) except for [a]median (IQR) and [b]mean (SD). Significant *P* values (<.05) are in bold.

[c]At least 1 major PI resistance mutation at the hystorical genotype according to Stanford hivdb [22].

M184V+ and 91.9% (95% CI, 86.6–97.2) in M184V- patients (*P* = .323) (Figure 1A).

Subanalyses

In a sensitivity analysis, where only a subset of 85 patients were classified in the M184V+ group based on the last available genotypic resistance test, almost identical virological outcomes were observed (Supplementary Figure 1A).

At a further sensitivity analysis using the more stringent definition of virological failure, as defined in the "Methods" and according to the hGRT, the probabilities of remaining free from virological failure in M184V+ and M184V- were similar (Supplementary Figure 1B).

To minimize the difference in duration of viral suppression before baseline between the groups, an analysis selecting patients with viral suppression of equal to or less than 6.6 years (the median duration of viral suppression in the M184V+ group) was performed (n = 308: 265 in the M184V- group and 43 in the M184V+ group). In this subset, the 1- and 3-year probabilities of remaining free from virological failure were, respectively, 94.4% (95% CI, 87.0–101.8) and 82.9% (95% CI, 67.2–98.6) in the M184V+ group and 97.3% (95% CI, 95.1–99.5) and 92.5% (95% CI, 86.8–98.2) in the M184V- group (*P* = .080). In an additional analysis selecting patients with equal to or less than 3 years of viral suppression, the respective 1- and 3-year probabilities of remaining free from virological failure were 100.0%

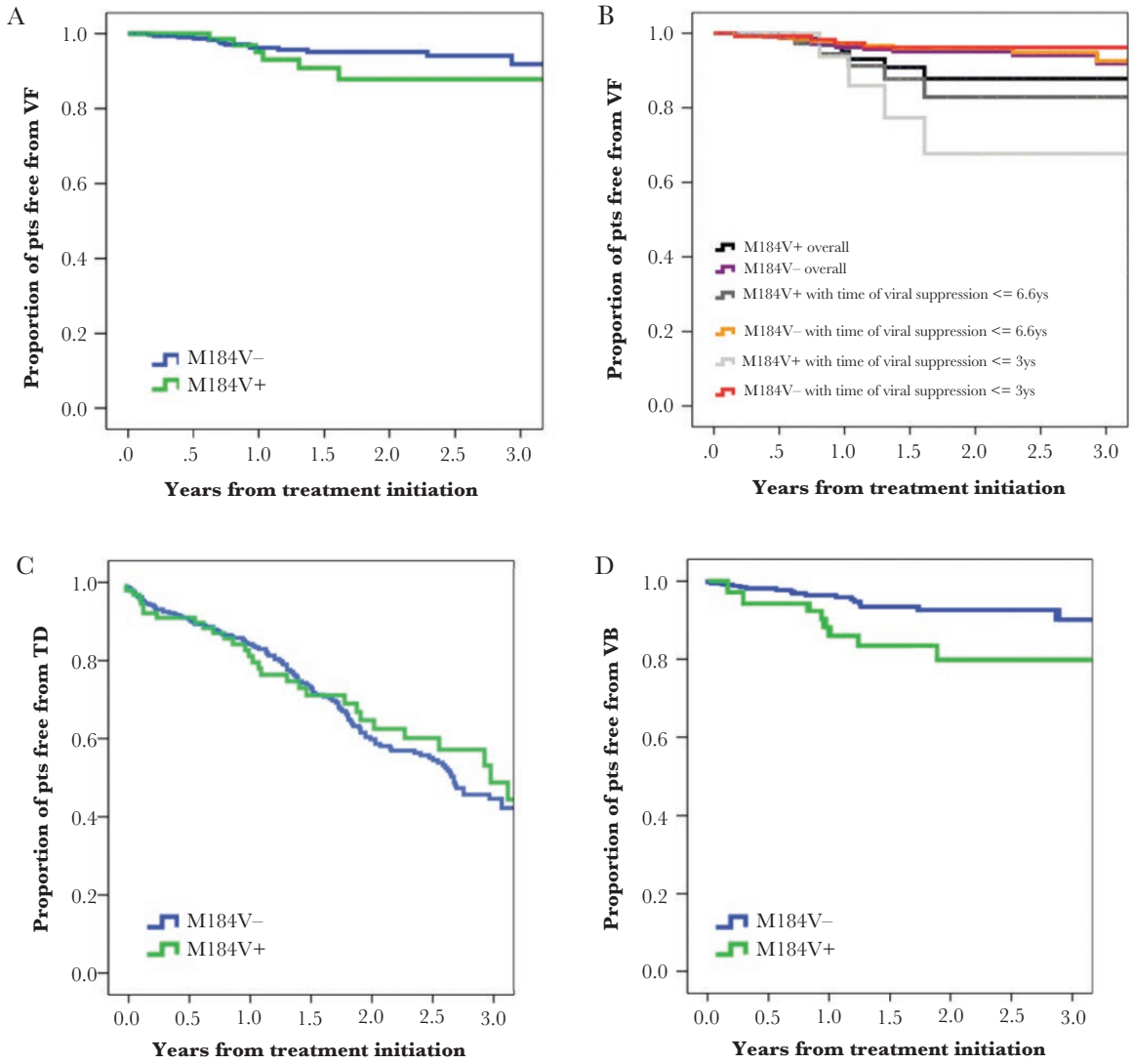

Figure 1. a: Estimated probability of being free from virological failure (VF) with dual therapy (M184V groups based on the hGRT). b: Estimated probability of being free from virological failure (VF) in the overall population of dual therapy and in patients with shorter time of viral suppression (M184V groups based on the hGRT). c: Estimated probability of being free from treatment discontinuation (TD) with dual therapy (M184V groups based on the hGRT). d: Estimated probability of being free from virological blips (VB) with dual therapy (M184V groups based on the hGRT).

and 67.7% in the M184V+ group and 97.3% an 96.2% in the M184V- group (P = .002) (Figure 1B). A sensitivity analysis considering only patients with more than 1 year of viral suppression showed similar results. No differences in virological failure were detected when DT with lamivudine + bPI was compared with lamivudine + INI (Supplementary Figure 1C).

When compared with the bPI monotherapy group (patients' baseline characteristics are in Supplementary Table 2), DT performed better; the 3-year estimated probabilities of remaining free from virological failure were 74.7% (95% CI, 65.9–92.3) with monotherapy and 91.1 % (95% CI, 86.4–95.8) with DT (P < .001). Even DT with previous detection of M184V performed better than bPI monotherapy: 87.8% (95% CI, 78.4–97.2) vs 74.7% (95% CI, 65.9–92.3), but without a statistically significant difference (P = .099). At Cox regression analysis, adjusting for hepatitis C virus (HCV) serostatus, duration of viral suppression, M184V status, and GSS of the regimen, being on a DT regimen (adjusted hazard ratio [aHR], 0.33; 95% CI, 0.14–0.81; P = .015) was independently associated with a lower risk of virological failure, whereas HBsAg positivity predicted a higher risk of virological failure (aHR, 2.96; 96% CI, 1.17–7.45; P = .022).

In the DT group, at univariate analysis, being HBsAg-positive, a longer history of ART, a higher HIV-RNA at zenith, and a lower GSS of the accompanying drug (bPI or INI) resulted in an association with greater risk of virological failure (Table 2). In a multivariate model adjusting for virological factors (duration of viral suppression, HIV-RNA at zenith, M184V, GSS of the accompanying drug), only higher HIV-RNA at zenith and lower GSS of the accompanying drug, but not M184V, were independently associated with virological failure, whereas another

Table 2. Predictors of Virological Failure With Lamivudine-Based Dual Therapies

	Univariate Analysis		Multivariable Analysis 1		Multivariable Analysis 2	
Variables	HR (95% CI)	*P* Value	aHR (95% CI)	*P* Value	aHR (95% CI)	*P* Value
M184V in hGRT	1.56 (0.64–3.76)	.327	1.23 (0.46–3.31)	.684	1.11 (0.38–3.23)	.847
Type of DT (PI vs INI)	0.42 (0.10–1.85)	.251				
Age (+10 y)	1.17 (0.83–1.65)	.381			1.11 (0.73–1.69)	.625
Gender (male vs female)	0.66 (0.29–1.50)	.320			0.61 (0.25–1.51)	.284
Ethnicity (Caucasian vs other)	0.60 (0.14–2.54)	.483				
Risk factor (ref. sexual)						
IDU	2.40 (0.85–6.75)	.098				
Other/unknown	1.51 (0.57–4.02)	.411				
HCV infection (ref. absent)						
Present	1.85 (0.78–4.37)	.163				
Unknown	0.16 (0.02–1.19)	.073				
HBsAg (ref. negative)						
Positive	8.85 (2.25–31.5)	**.001**			12.53 (2.15–72.96)	**.005**
Unknown	0.50 (0.15–1.71)	.269			1.67 (0.46–5.96)	.437
Previous AIDS-defining events	1.34 (0.46–3.93)	.594				
Time from first ART initiation (+1 y)	1.07 (1.01–1.13)	**.032**				
Duration of virological suppression before baseline (+1 y)	0.97 (0.86–1.16)	.965	0.95 (0.81–1.1)	.949	0.92 (0.79–1.08)	.306
Baseline CD4+ counts (+100 cells/μL)	0.99 (0.86–1.14)	.922				
Nadir CD4+ counts (+100 cells/μL)	0.86 (0.64–1.16)	.319				
Zenith HIV-RNA (+1 $\log_{10}$ copies/mL)	1.91 (1.06–3.42)	**.030**	1.91 (1.05–3.49)	**.035**	1.61 (0.89–2.91)	.116
GSS of the 2nd drug (+0.5)	0.36 (0.16–0.84)	**.018**	0.41 (0.16–1.03)	.058	0.41 (0.15–1.19)	.082

Abbreviations: aHR, adjusted hazard ratio; ART, combined antiretroviral therapy; DT, dual therapy; GSS, genotypic sensitivity score; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; hGRT, historical genotype resistance test; HR, hazard ratio; IDU, injective drug users; INI, integrase inhibitor, PI, protease inhibitors. Significant *P* values (<.05) are in bold.

model including HBsAg status, time of viral suppression, age, sex, HIV-RNA at zenith, M184V, and GSS of the accompanying drug showed an independent association between HBsAg positivity and virological failure and confirmed that lower GSS is probably linked to virological failure (Table 2). A sensitivity analysis excluding patients previously exposed to INI without INI sequences available before baseline (n = 398) showed similar results (not shown).

Treatment Discontinuation and its Predictors

During an overall 724 PYFU, 36 treatment discontinuations occurred in the M184V+ group during 153 PYFU, and 131 in the M184V- group during 571 PYFU (incidence, 23.5 and 22.9 per 100 PYFU, respectively; $P = .332$). Causes of treatment discontinuation were toxicity (55 in the M184V- group and 10 in the M184V+ group), virological failure (5 and 3, respectively), further simplification (23 and 6), and other (48 and 17). The estimated probabilities of remaining free from treatment discontinuation were also similar in the 2 groups: at 1 year 84.9% (95% CI, 80.8–89.0) in the M184V- and 83.3% (95% CI, 74.4–91.7) in the M814V+ group; at 3 years 44.6% (95% CI, 37.2–53.0) in the M184V- group and 48.8% (95% CI, 32.9–64.7) in the M184V+ group ($P = .847$) (Figure 1C). At a sensitivity analysis considering the last available genotypic resistance test, similar results were obtained (not shown). The only predictor of treatment discontinuation at univariate analysis was HBsAg positivity (HR, 2.42; 95% CI, 1.06–5.54; $P = .037$), which was confirmed in a multivariate model (aHR, 2.28; 95% CI, 0.99–5.27; $P = .053$) adjusting for duration of viral suppression, age, sex, and M184V status.

Viral Blips and Their Predictors

Main Analysis

Viral blips occurred in 10 of 80 (13%) M184V+ patients during 112 PYFU and 18 of 332 (5%) M184V- patients during 502 PYFU. The estimated probabilities of remaining free of viral blips were lower in patients with previous detection of M184V: at 1 year 85.9% (95% CI, 76.7–95.1) vs 96.4% (95% CI, 94.2–98.6) and at 3 years 79.8% (95% CI, 67.8–91.8) vs 90.1% (95% CI, 84.0–96.2) in the M184V- group ($P = .016$) (Figure 1D).

Subanalyses

At the sensitivity analysis considering the last available genotypic resistance test for M184V status classification, similar results were obtained (Supplementary Figure 1D).

In the subset of patients with viral suppression of ≤6.6 years, the difference in the 3-year probability of remaining free of blips was even larger (M184V+ group: 69.4%; 95% CI, 50.6–88.2; M184V- group: 91.1%; 95% CI, 84.8–97.4; $P < .001$).

At a further sensitivity analysis using a broader definition of viral blip (51–999 cp/mL; see the "Methods"), these occurred in

20 of 335 (6%) M184V- and 13 of 83 (16%) M184V+ patients (based on the hGRT classification). The 3-year estimated probabilities of remaining free from viral blips were similar to the ones in the main analysis (Supplementary Figure 1E).

At multivariable Cox regression analysis, HCV infection and presence of M184V at hGRT were independently associated with a higher risk of viral blips (Table 3). In a different model also adjusting for baseline variables that were different between the 2 M184V groups (age, duration of viral suppression, CD4 at nadir, GSS of the accompanying drug), HCV infection (aHR, 2.96; 95% CI, 1.21–7.24; $P = .017$) and M184V at hGRT (aHR, 2.55; 95% CI, 0.98–6.62; $P = .052$) were confirmed as independently associated with viral blips.

DISCUSSION

Several randomized studies have shown noninferiority of lamivudine with bPI in virologically suppressed individuals, with respect to triple therapy [2–5]. DT with lamivudine and dolutegravir was also effective in a single-arm prospective study [6]. However, these studies excluded patients with previous resistance to the study drugs. Here we show that a previous selection of the M184V mutation has no major impact on the virological efficacy of lamivudine-based DT as a maintenance regimen. This finding was consistent throughout several sensitivity analyses using different classifications of M184V detection and virological failure. Multivariable analysis adjusting for factors differing between the M184V-positive and -negative groups at DT initiation confirmed the lack of association of this substitution with virological failure. DTs were also more effective than bPI monotherapies, independently from M184V. Moreover, we found no impact of previous M184V detection of the durability of lamivudine-based DT.

This is the first study directly comparing the efficacy of lamivudine-based DT in patients with or without previous detection of the M184V substitution. The ANRS12286/Mobidip trial demonstrated superior virological efficacy of lamivudine plus bPI over bPI monotherapy in patients on an undetectable viral load on bPI-based second-line therapy. In that study, all patients had a previous virological failure on a NNRTI-based firstline therapy, and their viruses harbored multiple mutations (97% had M184V, 59% at least 1 and 27% at least 3 thymidine analogue mutations) [9]. Our study confirms the efficacy of lamivudine-based DT in patients previously selecting the M184V mutation, despite relevant differences between the 2 studies in term of design, resource setting, population characteristics, and virological failure definition. In line with Mobidip, we also show lower rates of virologic failure with DT than with bPI monotherapy, even in patients harboring M184V, even though only the comparison between DT overall vs monotherapy reached statistical significance, not the one between DT with previous selection of the M184V vs monotherapy, probably due to the limited sample size. It has to be highlighted that the chosen comparator was PI monotherapy, not triple therapy, to test whether the lamivudine-based DT in patients carrying M184V could be considered "functional" monotherapy.

Table 3. Predictors of Viral Blips With Lamivudine-Based Dual Therapies

	Univariate Analysis		Multivariable Analysis	
Variables	HR (95% CI)	*P* Value	aHR (95% CI)	*P* Value
M184V in hGRT	2.51 (1.15–5.44)	**.020**	2.45 (1.09–5.53)	**.030**
Type of DT (PI vs INI)	0.56 (0.19–1.63)	.284		
Age (+10 y)				
Gender (male vs female)	1.79 (0.68–4.70)	.241		
Ethnicity (Caucasian vs other)	1.38 (0.18–10.20)	.751		
Risk factor (ref. sexual)				
IDU	1.57 (0.53–4.68)	.420		
Other/unknown	1.20 (0.54–3.14)	.558		
HCV infection (ref. absent)				
Present	2.89 (1.21–6.87)	**.017**	2.71 (1.14–6.48)	**.025**
Unknown	1.28 (0.50–3.25)	.607	1.57 (0.60–4.09)	.361
HBsAg (ref. negative)				
Positive	0.00 (0.00–0.01)	.975		
Unknown	1.17 (0.50–2.75)	.725		
Previous AIDS-defining events	1.08 (0.38–3.13)	.883		
Time from first ART initiation (+1 y)	1.04 (0.98–1.10)	.188		
Time of virological suppression (+1 y)	1.02 (0.90–1.16)	.753		
Baseline CD4+ (+100 cells/μL)	1.07 (0.95–1.21)	.233		
Nadir CD4+ (+100 cells/μL)	0.95 (0.73–1.22)	.671		
Log zenith HIV-RNA	1.10 (0.66–1.82)	.721		
GSS of the 2nd drug (+0.5)	0.29 (0.08–1.56)	.113		

Abbreviations: aHR, adjusted hazard ratio; ART, combined antiretroviral therapy; DT, dual therapy; GSS, genotypic sensitivity score; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; hGRT, historical genotype resistance test; HR, hazard ratio; IDU, injective drug users; INI, integrase inhibitor, PI, protease inhibitors. Significant *P* values (<.05) are in bold.

Observational studies with small sample size and short follow-up also support the view that past M184V has no impact on the efficacy of lamivudine plus dolutegravir. In a prospective study of 27 patients, 8 carried the M184V mutation in their hGRT, and none of them experienced virological failure in the first year of DT [7], whereas in a cohort of 36 patients switching to this dual regimen, 3 had a prior detection of M184V, and none of these experienced virological failure [13].

One possible explanation for the absence of a major negative impact of the prior M184V mutation on the efficacy of lamivudine-based DT could be its association with decreased viral fitness and with lower replication capacity, lowering the probability of virus rebound [10, 14, 15]. Moreover, recent in vitro studies indicated a protective role of M184V against the selection of dolutegravir resistance mutations, further explaining the lack of impact of this mutation on the efficacy of lamivudine plus dolutegravir [16]. Interestingly, in our cohort, 21 patients on lamivudine plus dolutegravir carried M184V, and none failed after a median follow-up of 10 months, whereas dolutegravir maintenance monotherapy studies have shown measurable failure rates during follow-up of similar duration [17, 18].

Although the main results did not show a significant role for M184V, some sensitivity analyses suggested an effect on treatment efficacy. In particular, in patients with a shorter duration of viral suppression before simplification to DT, the group with previous detection of M184V showed higher hazards of virological failure, and the gap of efficacy between the groups increased when reducing the duration of suppression, particularly below 3 years. This trend is compatible with a progressive decline of the impact of M184V with increasing time since the mutation was last detected. Although the concept of a time-dependent effect likely applies to any resistance mutation (ie, the longer the time the mutation has been not detected, the lower its impact on virological outcome), the declining effect could be faster for those variants with impaired replication, such as M184V. The size of the viral reservoir progressively decreases during the initial 3–4 years of suppressive ART and tends to plateau thereafter [19]. Longer duration of viral suppression could disproportionally reduce the size of the reservoir of replication-impaired viruses because of reduced probability to reseed the reservoir in the context of residual replication under suppressive therapy [20, 21]. Measuring the dynamics of M184V HIV-DNA relative to total HIV-DNA levels over time under suppressive therapy would be required to test this hypothesis. Although the mechanism underlying the time-dependent effect of M184V remains to be clarified, simplification to lamivudine-based DT appears safer in patients carrying M184V who have been fully virologically suppressed for a longer period.

The higher rate of viral blips in patients with past M184V confirms that previous selection of M184V has some negative effect on maintaining complete viral suppression. However, this negative effect was probably mitigated by the activity of the drug accompanying lamivudine. In line with this hypothesis, the GSS of the accompanying drug played a key role in predicting virological failure, together with the higher HIV-RNA zenith. These findings suggest that maintenance DT should be carefully selected based on prior virological history.

Finally, we found an expected negative impact of hepatitis B virus (HBV) co-infection on virological efficacy and durability, as HBsAg is a relative contraindication to lamivudine-containing DT, given lamivudine-limited anti-HBV activity and low genetic barrier to HBV resistance. Even if switching HBsAg+ patients to a regimen without tenofovir is not recommended, it could be partially explained by clinical practice mistakes or by the use of other HBV-active medications (eg, entecavir in patients with contraindications to tenofovir), but these data unfortunately were not available in the database.

This study presents some limitations. Due to its retrospective nature, significant confounders may have gone undetected. The achieved statistical power to detect differences between M184V groups for the main virological failure end point was low. Data about adherence were lacking, measures of medication adherence and exposure were not available, and several baseline characteristics differed between groups.

Nonetheless, when we adjusted the analyses for these characteristics in several multivariable models, still no impact of M184V on virological failure was found.

In conclusion, DT with lamivudine plus bPI or dolutegravir could represent a safe and cheap strategy of ART simplification, both in resource-limited and high-income countries. Even in consideration of the efforts to reach universal access to ART, the possibility to prescribe maintenance regimens with lower toxicity and decreased cost could represent a significant advantage. Based on our findings, a previous selection of M184V should not represent a major obstacle to the efficacy of these regimens, provided that viral suppression has been consolidated and the activity of the drug accompanying lamivudine is fully preserved.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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