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1 **M184V/I does not impact the efficacy of abacavir/lamivudine/dolutegravir use as switch**
2 **in virologically suppressed patients**

3

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19

20 **Short running title:** No impact of M184V/I on the efficacy of
21 abacavir/lamivudine/dolutegravir

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26

27 **Abstract**

28

29 **Objectives:** M184V/I nucleoside reverse transcriptase inhibitor (NRTI) resistance mutations
30 can be selected by either lamivudine/emtricitabine or abacavir. There are controversies about
31 the use of abacavir/lamivudine/dolutegravir combination in HIV-1 treated patients with a
32 fully suppressed HIV viral load and harboring M184V/I. We assessed the efficacy of
33 abacavir/lamivudine/dolutegravir combination when used in HIV pretreated patients with an
34 undetectable viral load (VL) and previously harboring on their genotypic resistance test a
35 M184V/I as unique NRTI resistance and without any resistance to integrase inhibitors.

36 **Patients and methods:** 154 patients with a fully suppressed HIV-1 plasma viral load (< 50
37 copies/mL) treated by tenofovir/emtricitabine/boosted protease inhibitor or
38 abacavir/lamivudine/boosted protease inhibitor and switched to an
39 abacavir/lamivudine/dolutegravir regimen with M184V/I as unique NRTI resistance mutation
40 in their therapeutic history were retrospectively analyzed up to 12 months after the switch to
41 abacavir/lamivudine/dolutegravir. Assessment of residual viraemia was performed at months
42 1, 3, 6 and 12. Plasma VL with undetected HIV-1 RNA corresponded to an absence of
43 residual viraemia.

44 **Results:** During the 12 months of follow-up, 3 patients had a blip of VL (53, 62 and 106
45 copies/mL) at month 3 followed by a subsequent VL < 50 copies/mL. No patient harbored a
46 virologic failure during the follow-up. Moreover, there was no evolution of residual viraemia
47 during the follow up.

48 **Conclusions:** M184V/I as a unique NRTI resistance mutation, regardless of possible selection
49 by regimen containing lamivudine/emtricitabine or abacavir, does not affect the virological
50 response of well controlled patients who switched to abacavir/lamivudine/dolutegravir for at
51 least 12 months.

52 **Introduction**

53 Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) remain the ‘backbone’ of
54 antiretroviral therapy. Abacavir was developed alone or in combination with lamivudine,
55 zidovudine and lamivudine + dolutegravir to treat HIV. Lamivudine was developed to be used
56 alone or in combination with zidovudine, abacavir, and abacavir + dolutegravir. 3'-
57 thiacytidine inhibitors (lamivudine and emtricitabine) as well as abacavir select rapidly a
58 mutation *in vitro* in the YMDD region of reverse transcriptase (RT) of HIV-1 (M184I then
59 M184V) leading to high level of resistance for lamivudine and emtricitabine and intermediate
60 level of resistance for abacavir. These *in vitro* M184V/I driven phenotypic resistance
61 mutations to lamivudine, emtricitabine or abacavir were confirmed in clinical trials.^{1,2,3,4}

62 As M184V/I RT mutation can impact the efficacy of both lamivudine and abacavir, there are
63 controversies about the use of abacavir/lamivudine/dolutegravir combination in HIV-1 treated
64 patients with a fully suppressed viral load and harboring M184V/I as unique NRTI resistance
65 without resistance to integrase inhibitors. The aim of this study was to assess the efficacy of
66 abacavir/lamivudine/dolutegravir (ABC/3TC/DTG) combination when used in pretreated
67 patients with an undetectable viral load and previously harboring on their genotypic resistance
68 testing M184V/I as unique NRTI resistance and without any resistance to integrase inhibitors.

69

70

71 **Patients and methods**

72 Study population

73 HIV-1-infected patients were selected from two French university hospitals (Pitié-Salpêtrière
74 and Bichat-Claude Bernard Hospitals). Inclusion criteria were as follows: being suppressed on
75 a triple antiretroviral treatment (ART) regimen with tenofovir/emtricitabine/boosted protease
76 inhibitor or abacavir/lamivudine/boosted protease inhibitor for at least 12 months, having an

77 historical genotypic resistance test (RNA or DNA) harboring a M184V/I mutation as a unique
78 NRTI mutation, switched to ABC/3TC/DTG between 2015-2018, with at least 12 months of
79 follow-up. One hundred fifty four patients fully suppressed for at least 12 months with an
80 HIV-1 plasma viral load (VL < 50 copies/mL) treated by 2 NRTIs + 1 boosted protease
81 inhibitor (PI) (tenofovir/emtricitabine/boosted darunavir (n=68),
82 tenofovir/emtricitabine/boosted atazanavir (n=56), abacavir/lamivudine/boosted darunavir
83 (n=10), abacavir/lamivudine/boosted atazanavir (n=20) and switched to an ABC/3TC/DTG
84 regimen were retrospectively analyzed at M1, M3, M6 and M12 after the switch to
85 ABC/3TC/DTG.

86

87 Ethics

88 The research was conducted in accordance with the Declaration of Helsinki and national and
89 institutional standards. All the patients gave their written informed consent to have their
90 medical chart recorded in the electronic medical record system Nadis® (www.dataids.org;
91 CNIL number: 770134, 30 October 2001).

92

93 Virological and pharmacological assays

94 Plasma HIV-1 RNA was measured using a commercially available PCR assay (Ampliprep
95 COBAS TaqMan V2.0, Roche, Meylan, France). This assay provides quantitative results for
96 HIV-RNA values ≥ 20 copies/mL. Qualitative results are also given as HIV-RNA detected
97 (but <20 copies/mL) or when PCR target is not detected (VL considered <1 copy/mL).⁵

98 Virological failure was defined as HIV-RNA >50 copies/mL in 2 consecutive determinations.

99 The plasma concentrations of dolutegravir, abacavir and lamivudine were determined using a
100 validated LC-MS/MS method (Waters Acquity UPLC-TQD, Milford, MA, USA).

101 Dolutegravir trough levels were interpreted according to different effective cut-offs of

102 1000 ng/mL at 24 h, based on the pharmacokinetic/pharmacodynamic relationship from the
103 SAILING trial.⁶

104 **Results**

105 Baseline characteristics of the 154 virologically suppressed patients switched to
106 ABC/3TC/DTG are shown in Table 1. Most patients were male (71.4%), the median age was
107 44 years (IQR 36–50) and 70% were infected with a subtype B. Median time with VL <50
108 copies/mL before the switch to ABC/3TC/DTG was 36 months (IQR 14–44) and 12 patients had
109 received at least 3 different therapeutic regimens before the switch to ABC/3TC/DTG.

110

111 Out of the 154 patients: 16 were infected by a virus harboring M184V, 126 acquired
112 previously a M184V/I after a treatment failure to 2 NRTIs + NNRTI or 2 NRTIs + 1 PI
113 regimen. M184I was detected exclusively in DNA genotype and this represents only 6/154
114 patients. Patients were selected for having only M184V/I in their historical genotypes, so no
115 other mutations associated with resistance to NRTI were detected. A historical integrase
116 sequence was available for 40 patients (26%) with no evidence of resistance mutations.

117

118 During the 12 months of follow-up, all patients maintained a VL < 50 copies/mL except three
119 patients who had a blip (53, 62 and 106 copies/mL) at month 3 followed by a subsequent viral
120 load < 50 copies/mL. Overall, none of the patients harbored a virologic failure (Table 2).

121 Among the 3 blips, at M1, one had no available plasma VL, one had a VL with HIV-RNA
122 detected and the last one a VL with HIV-RNA undetected. The three plasma samples
123 corresponding to the blips were sequenced to search for selection of any new resistance
124 mutations in RT and integrase genes and no emergence of mutation was evidenced. Plasma
125 measurements of abacavir, lamivudine and dolutegravir during blip episodes showed that they
126 were all in therapeutic recommended values.

127

128 All plasma samples with VL < 50 copies/mL were assessed for the presence of PCR target or
129 not and no statistical evolution of the percentage of patients harboring a plasma VL below 1
130 copy/mL was evidenced. The percentage of patients with VL < 1 copy/mL was 70%
131 (108/154), 66% (67/101), 69% (85/124), 67% (73/110) and 73% (71/97), respectively.

132

133

134 **Discussion**

135 This study assessed the efficacy, including the impact on residual viraemia, of a switch to
136 ABC/3TC/DTG in virologically suppressed patients (VL <50 copies/mL) with an history of
137 M184V/I from a clinical setting with a follow-up of 1 year. Among these 154 patients, with
138 previous lamivudine or emtricitabine resistance, who received ABC/3TC/DTG, all maintained
139 virological suppression at month 12 with no evolution of residual viremia during the follow
140 up.

141

142 To our knowledge, this is the largest study evaluating the impact of M184V/I as a unique
143 NRTI resistance mutation on the virological response after a switch to ABC/3TC/DTG. In
144 addition, virological follow-up using the assessment of residual viraemia in patients switching
145 to ABC/3TC/DTG has not been previously reported. In our study we showed that 70% of
146 patients had no residual viraemia at baseline before switching and that this proportion
147 remained stable during the follow-up: 67% at month 6 and 73% at month 12.

148

149 Interestingly, M184V/I as a unique NRTI resistance mutation, regardless of possible selection
150 by regimens containing lamivudine or emtricitabine or abacavir, did not affect the response of
151 these virologically suppressed patients who switched to ABC/3TC/DTG even when switching

152 from a TDF containing regimen. This was true both at the 50 copies/mL and 1 copy/mL cut-
153 off. Previous studies have addressed the effect of the M184V/I mutation on the efficacy of a
154 dolutegravir-containing regimen (dual or triple) in this context of switch and they all
155 described low virological failure rates, irrespective of the presence of the M184V/I mutation.
156 In the retrospective study by Gagliardini *et al.*, in patients with a shorter duration of viral
157 suppression before simplification to dolutegravir dual regimen, the group with previous
158 detection of M184V showed higher hazards of virological failure, and the gap of efficacy
159 between the groups increased when reducing the duration of suppression, particularly below 3
160 years.⁷ However, in a recent prospective pilot study (n = 41), lamivudine/dolutegravir was
161 effective in maintaining virologic control in integrase inhibitor naïve patients with historical
162 lamivudine resistance when baseline proviral DNA Sanger genotype did not detect the
163 persistence of lamivudine resistance-associated mutations.⁸ This has to be confirmed by
164 larger prospective studies that could assess the factors associated with virological success of
165 lamivudine/dolutegravir dual regimen. There was another study that showed no impact of
166 M184V/I on the risk of virological failure in virologically suppressed patients switching to
167 ABC/3TC/DTG, but in this study they did not analyze clearly the impact of M184V/I as
168 unique NRTI resistance mutation, because at least 2 thymidine analogue mutations were
169 documented in 42.3% of patients with M184V/I.⁹

170

171 The findings of our study can be explained probably by the characteristics (potency and high
172 genetic barrier to resistance) of dolutegravir that is able to control HIV replication even in a
173 context where the total genotypic sensitivity score is less than 3. Indeed, in presence of
174 M184V/I dolutegravir is considered sensitive (1), lamivudine resistant (0) and abacavir
175 possibly resistant (0.5), thus associated with a genotypic sensitivity score of 1.5. Similarly,
176 high rates of tenofovir alafenamide/emtricitabine/bictegravir treatment efficacy have been

177 observed among patients with pre-existing resistance substitutions, such as M184V/I,
178 indicating that baseline genotype did not affect tenofovir
179 alafenamide/emtricitabine/bictegravir outcomes in suppressed participants switching
180 regimens.¹⁰ Together, these results indicate that three-drug regimens with second generation
181 integrase inhibitors, ABC/3TC/DTG and tenofovir alafenamide/emtricitabine/bictegravir, are
182 a treatment option for suppressed patients, including those with evidence of archived
183 resistance, such as M184V/I.

184

185 Our study has several limitations. First, the observational nature of the study could have
186 affected the results due to missing or incomplete data (such as HIV DNA). Second, the
187 limited follow-up should be taken into consideration when interpreting the clinical relevance
188 of our findings. Furthermore, we cannot exclude residual confounding given the absence of
189 data on treatment adherence.

190

191 In conclusion, our findings obtained in a clinical cohort confirmed data reported in clinical
192 trials, showing high rate of patients maintaining pVL <50 copies/mL up to 12 months, with a
193 stable proportion of patients (around 70%) without detectable residual viremia during the first
194 year following the switch to ABC/3TC/DTG even in presence of an history of M184V/I as
195 single NRTI mutation.

196

197

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201

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205

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210

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244

245

246 **Table 1.** Baseline characteristics of the patients

247

Characteristic	n = 154
Male, n (%)	110 (71.4)
Age (years), median (IQR)	44 (36–50)
Time since HIV diagnosis (years), median (IQR)	15 (12–23)
Duration of ART (years) before switch, median (IQR)	11 (9–13)
Number of previous ART lines before switch, median (IQR)	2 (1–3)
History of INSTI-containing regimen, n (%)	0 (0)
Duration of plasma HIV-1 RNA < 50 copies/mL before switch (months), median (IQR)	36 (14–44)
Duration between the last genotype with M184V/I and time of switch (months), median (IQR)	52 (20–62)

248 ART, antiretroviral treatment; INSTI, integrase inhibitors

249 **Table 2.** Characteristics of the patients before and after the switch to
 250 abacavir/lamivudine/dolutegravir
 251

ARV treatment	Before the switch to ABC/3TC/DTG			After the switch to ABC/3TC/DTG	
	Type of 184 mutation (n)	Median pretherapeutic VL (cp/mL)	Median pretherapeutic CD4 cell count (mm ³)	Blips	Virologic failure
TDF/FTC+r/DRV (n=68)	M184V (66) M184I (2)	68000	286	1 (62 cp/mL at M3)	None
TDF/FTC+r/ATV (n=56)	M184V (54) M184I (2)	27000	368	2 (106 and 53 cp/mL at M3)	None
ABC/3TC+r/DRV (n=10)	M184V (9) M184I (1)	43000	371	None	None
ABC/3TC+ r/ATV (n=20)	M184V (19) M184I (1)	50000	411	None	None

252 ABC, abacavir ; ARV, antiretroviral ; ATV, atazanavir ; DRV, darunavir ; DTG, dolutegravir ; FTC, emtricitabine ; TDF, tenofovir ; 3TC,
 253 lamivudine ; VL, viral load

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256