# M184V/I does not impact the efficacy of abacavir/lamivudine/dolutegravir use as switch therapy in virologically suppressed patients

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

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

**Abstract**

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

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

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

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

## Introduction

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

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

## Patients and methods

Study population

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

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

Ethics

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

Virological and pharmacological assays

Plasma HIV-1 RNA was measured using a commercially available PCR assay (Ampliprep COBAS TaqMan V2.0, Roche, Meylan, France). This assay provides quantitative results for HIV-RNA values ≥20 copies/mL. Qualitative results are also given as HIV-RNA detected (but <20 copies/mL) or when PCR target is not detected (VL considered <1 copy/mL). [5] Virological failure was defined as HIV-RNA >50 copies/mL in 2 consecutive determinations. The plasma concentrations of dolutegravir, abacavir and lamivudine were determined using a validated LC-MS/MS method (Waters Acquity UPLC-TQD, Milford, MA, USA). Dolutegravir trough levels were interpreted according to different effective cut-offs of

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

**Results**

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

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

During the 12 months of follow-up, all patients maintained a VL < 50 copies/mL except three patients who had a blip (53, 62 and 106 copies/mL) at month 3 followed by a subsequent viral load < 50 copies/mL. Overall, none of the patients harbored a virologic failure (Table 2). Among the 3 blips, at M1, one had no available plasma VL, one had a VL with HIV-RNA detected and the last one a VL with HIV-RNA undetected. The three plasma samples corresponding to the blips were sequenced to search for selection of any new resistance mutations in RT and integrase genes and no emergence of mutation was evidenced. Plasma measurements of abacavir, lamivudine and dolutegravir during blip episodes showed that they were all in therapeutic recommended values.

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

**Discussion**

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

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

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

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

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

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

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

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

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## References

1. Tisdale M, Kemp SD, Parry NR, *et al*. Rapid in vitro selection of human immunodeficiency virus type 1 resistant to 3'-thiacytidine inhibitors due to a mutation in the YMDD region of reverse transcriptase. *Proc Natl Acad Sci USA* 1993; **90**: 5653–6.

2. Tisdale M, Alnadaf T, Cousens D. Combination of mutations in human immunodeficiency virus type 1 reverse transcriptase required for resistance to the carbocyclic nucleoside 1592U89. *Antimicrob Agents Chemother* 1997; **41**: 1094–8.

3. Brun-Vézinet F, Descamps D, Ruffault A, *et al.* Clinically relevant interpretation of genotype for resistance to abacavir. *AIDS* 2003; **17**: 1795–802.

4. Harrigan PR, Stone C, Griffin P, *et al.* Resistance profile of the human immunodeficiency virus type 1 reverse transcriptase inhibitor abacavir (1592U89) after monotherapy and combination therapy. CNA2001 Investigative Group. *J Infect Dis* 2000; **181**: 912–20.

5. Perrier M, Charpentier C, Peytavin G, *et al.* Switch as maintenance to elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate: week 48 results in a clinical cohort. *J Antimicrob Chemother* 2017; **72**: 1745–51.

6. Jung BH, Rezk NL, Bridges AS, *et al*. Simultaneous determination of 17 antiretroviral drugs in human plasma for quantitative analysis with liquid chromatography-tandem mass spectrometry. *Biomed Chromatogr* 2007; **21**: 1095–104.

7. Gagliardini R, Ciccullo A, Borghetti A, *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.

8. De Miguel Buckley R, Rial-Crestelo D, Dominguez-Dominguez L, *et al.* Dolutegravir (DTG) and Lamivudine (3TC) for Maintenance of HIV Viral Suppression in Adults With and Without Historical Resistance to Lamivudine: 48-Week Results of a Pilot Clinical Trial (ART-PRO) - 17th European AIDS Conference, November 6-9, 2019, Basel, Switzerland – Oral presentation PS7/5.

9. Olearo F, Nguyen H, Bonnet F, *et al.* Impact of the M184V/I Mutation on the Efficacy of Abacavir/Lamivudine/Dolutegravir Therapy in HIV Treatment-Experienced Patients. *Open Forum Infect Dis* 2019; **6**: ofz330.

10. Andreatta K, Willkom M, Martin R, *et al.* Switching to bictegravir/emtricitabine/tenofovir alafenamide maintained HIV-1 RNA suppression in participants with archived antiretroviral resistance including M184V/I. *J Antimicrob Chemother* 2019; **74**: 3555–64.

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

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| **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

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

| | Before the switch to ABC/3TC/DTG | | | After the switch to ABC/3TC/DTG | |
|---|---|---|---|---|---|
| **ARV treatment** | **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 |

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