No impact of the M184I/V mutation on the efficacy of tenofovir or abacavir+lamivudine+doravirine in HIV treatment-experienced people

C Soulié[1], A Baldé[2], D Fofana[3], C Charpentier[4], P Bonnafous[1], J Sourice[5], A De Monte[6], V Avettand-Fenoel[7], H Le Guillou-Guillemette[8], L Bocket[9], S Raymond[10], M-A Trabaud[11], B Montes[12], A Maillard[13], C Hartard[14], E Alessandri-Gradt[15], E Brochot[16], A Signori-Schmuck[17], L Assoumou[2], **A-G Marcelin[1]**

1 Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP, Hôpitaux Universitaires Pitié Salpêtrière - Charles Foix, laboratoire de virologie, Paris, France; 2 Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France; 3 Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP, Hôpital Universitaire Saint Antoine, laboratoire de virologie, Paris, France; 4 Université Paris Cité, INSERM UMR 1137 IAME, AP-HP Nord Hôpital Bichat–Claude-Bernard, Laboratoire de Virologie, Paris, France; 5 Laboratoire de Virologie, CHU Nantes, Nantes, France; 6 Laboratoire de Virologie, CHU Nice, Nice, France; 7 Hôpital Necker, APHP GHU Centre - Université Paris Cité, Laboratoire de Virologie, Paris, France; 8 Laboratoire de Virologie, CHU Angers and HIFIH Laboratory EA 3859, LUNAM, Angers, France ; 9 Univ. Lille, CHU Lille, Laboratoire de Virologie, Lille, France; 10 INSERM UMR 1291, Laboratoire de Virologie, CHU Toulouse Purpan, Toulouse, France; 11 Laboratoire de Virologie, Institut des Agents Infectieux, Hospices civils de Lyon, Centre de Biologie Nord, Hôpital de la Croix Rousse, Lyon, France; 12 Laboratoire de Virologie, CHU Montpellier, Univ Montpellier, Montpellier, France ; 13 Laboratoire de Virologie, CHU de Rennes, Rennes, France; 14 CHRU Nancy, Laboratoire de Virologie, Nancy, France; 15 CHU de Rouen, Université de Rouen Normandie UNIRouen, Rouen, France; 16 CHU Amiens, Faculté de pharmacie Amiens, Amiens, France; 17 CHU Grenoble-Alpes, Laboratoire de Virologie, Grenoble, France.

BACKGROUND

State of the art

Doravirine (DOR) is the latest NNRTI to be approved for the treatment of people living with HIV-1 (PLWHIV) and has a different resistance profile from first-generation NNRTIs. The impact of the M184I/V mutation on the rate of virological failure (VF) in PLWHIV switching to a triple-drug regimen DOR+3TC +ABC or TDF has not been evaluated.

Objectives

Virological failure at week 24 of a triple therapy with DOR was evaluated in PLWHIV with and without a pre-existing M184I/V mutation in clinical practice.

MATERIAL AND METHODS

Patients

- A national French retrospective survey including PLWHIV-1,
- November 2020 to December 2022,
- ARV-experienced receiving an antiretroviral tritherapy including DOR in a context of switch.

Virology

- VF: 2 consecutives plasma viral load (VL) ≥ 50 copies/mL or 1 VL > 200 copies/mL,
- Reverse transcriptase (RT): sequenced at baseline = before the switch (DNA or RNA),
- Mutations associated with resistance and the genotypic susceptibility score (GSS) of the current regimen with DOR, according to the latest Stanford (https://hivdb.stanford.edu/) and ANRS (https://hivfrenchresistance.org/) algorithms.

Statistical analysis

The M184I/V was studied as a potential factor associated with VF or VB, adjusted for the following items:

- Gender,
- Nadir CD4 count, CD4 count at baseline,
- Viral subtype, log zenith plasma HIV-1 RNA, log plasma HIV-1 RNA at baseline,
- NNRTI resistance mutations at baseline and GSS (Stanford and ANRS algorithms).

Proportion of Virological Failure and Blips

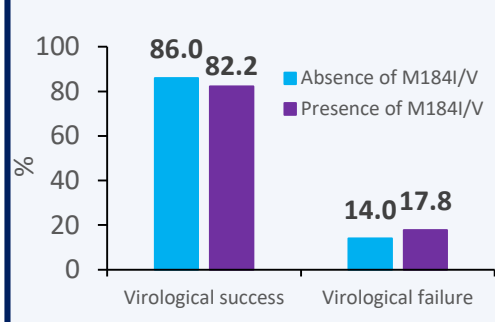

Figure 1: Proportions of virological success and virological failure at 6 months in patients with or without M184I/V mutation at baseline among switch participants

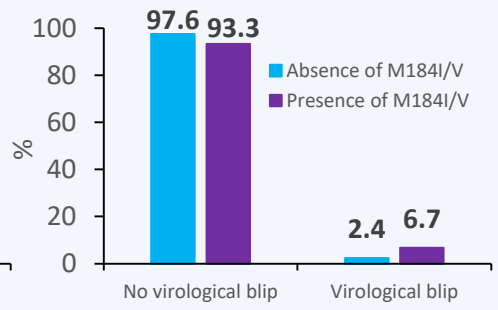

Figure 2: Proportions of virological blip or not at 6 months in patients with or without M184I/V mutation at baseline among switch participants

RESULTS

Characteristics

Among the 338 included PLWHIV:

- 45 had a genotypically documented M184I/V mutation before switching:
  - TDF+3TC: 29 M184V and 14 M184I
  - ABC+3TC: 2 M184V
  - DNA: 21 M184V and 11 M184I
  - RNA: 10 M184V and 3 M184I

Characteristic	M184I/V at baseline		
	No (n=293) n/N (%) or median (IQR)	Yes (n=45) n/N (%) or median (IQR)	P-value
Gender			0.3138
Male	191/293 (65.2)	33/45 (73.3)	
Female	102/293 (34.8)	12/45 (26.7)	
Viral subtype			0.5998
B	158/293 (53.9)	28/45 (62.2)	
CRF02	59/293 (20.2)	8/45 (17.8)	
Other Non-B	76/293 (25.9)	9/45 (20.0)	
Nadir CD4 count (cells/mm³)	257 (130-409)	157 (42-318)	**0.0246**
CD4 count at baseline (cells/mm³)	620 (467-846)	616 (421-910)	0.9044
Log zenith plasma HIV-1 RNA (Log_{10} copies/mL)	4.9 (3.9-5.5)	4.9 (4.3-5.7)	0.5038
Log plasma HIV-1 RNA at baseline (Log_{10} copies/mL)	1.6 (1.6-1.6)	1.6 (1.6-1.6)	0.9218
Doravirine co-treatment			0.5539
3TC+TDF	268/293 (91.5)	43/45 (95.6)	
3TC+ABC	25/293 (8.5)	2/45 (4.4)	
Nucleic acid sequence			0.1445
RNA	127/293 (43.3)	14/45 (31.1)	
DNA	166/293 (56.7)	31/45 (68.9)	
GSS with Doravirine (Stanford)	3.0 (3.0-3.0)	1.5 (1.0-2.0)	**<.0001**
0-1	2/293 (0.7)	13/45 (28.8)	**<.0001**
1.5-2.5	39/293 (13.3)	32/45 (71.2)	
3	252/293 (86.0)	0/45 (0.0)	
GSS with Doravirine (ANRS)	3.0 (3.0-3.0)	2.0 (1.5-2.0)	**<.0001**
0-1	2/293 (0.7)	7/45 (15.6)	**<.0001**
1.5-2.5	13/293 (4.4)	38/45 (84.4)	
3	278/293 (94.9)	0/45 (0.0)	
Number of NNRTI mutations at baseline	0 (0-1)	1 (0-2)	**<.0001**
0	204/293 (69.6)	13/45 (28.8)	**<.0001**
1	48/293 (16.3)	19/45 (42.4)	
≥2	41/293 (14.1)	13/45 (28.8)	

Table 1: Baseline characteristics of the study population (*n=338*). Values are expressed as number and percentages unless otherwise indicated.

Impact of M184I/V mutation on Virological Failure and Blips after adjustment for potential confounders

Characteristic	Virological failure (VF)		Univariable analysis			Multivariable analysis		
	No n/N (%) or median (IQR) N=289	Yes n/N (%) or median (IQR) N=49	OR	95% CI	P value	OR	95% CI	*P value*
M184I/V mutation at baseline					0.5029			0.2121
no	252/293 (86.0)	41/293 (14.0)	1			1		
yes	37/45 (82.2)	8/45 (16.3)	1.329	0.578-3.055		2.066	0.664-6.425	
Gender					0.8634			
Male	191/224 (85.3)	33/224 (14.7)	1					
Female	98/114 (86.0)	16/114 (14.0)	0.945	0.496-1.801				
Viral subtype					0.1289			0.1120
B	163/186 (87.6)	23/186 (12.4)	1			1		
CRF02	52/67 (77.6)	15/67 (22.4)	2.044	0.994-4.206		1.629	0.977-2.716	
Other Non-B	74/85 (87.1)	11/85 (12.9)	1.053	0.488-2.274		0.887	0.527-1.492	
Nadir CD4 count (per 100 cells/mm³ increase)	258 (130-409)	202 (60-325)	0.892	0.760-1.047	0.1625	0.988	0.815-1.197	0.9010
CD4 count at baseline (per 100 cells/mm³ increase)	620 (467-849)	596 (465-878)	0.985	0.895-1.083	0.7472			
Log zenith plasma HIV-1 RNA (per 1 Log_{10} copies/mL increase)	4.8 (3.8-5.4)	5.5 (4.7-5.9)	**1.582**	**1.184-2.114**	**0.0019**	**1.654**	**1.188-2.304**	**0.0029**
Log plasma HIV-1 RNA at baseline (per 1 Log_{10} copies/mL increase)	1.6 (1.6-1.6)	1.6 (1.6-1.9)						
Doravirine co-treatment					0.2873			
3TC+TDF	264/311 (84.9)	47/311 (15.1)	1					
3TC+ABC	25/27 (92.6)	2/27 (7.4)	0.449	0.103-1.961				
Nucleic acid					0.2662			0.4795
RNA	117/141 (83.0)	24/141 (17.0)	1			1		
DNA	172/197 (87.3)	25/197 (12.7)	0.709	0.386-1.301		0.885	0.631-1.241	
GSS with Doravirine (Stanford)	3.0 (2.5-3.0)	3.0 (2.5-3.0)	1.014	0.606-1.697	0.9573	2.296	0.420-12.543	0.3401
0-1	13/14 (92.9)	1/14 (7.1)	0.573	0.144-2.282	0.6093			
1.5-2.5	59/71 (82.9)	12/71 (17.1)	1.479	0.665-3.291				
3	217/252 (85.9)	36/252 (14.1)	1					
GSS with Doravirine (ANRS)	3.0 (3.0-3.0)	3.0 (3.0-3.0)	1.071	0.557-2.059	0.8379			
0-1*	9/9 (100)	0/9 (0.0)			0.8606			
1.5-2.5	42/51 (82.7)	9/51 (17.3)	1.037	0.695-1.547				
3	238/278 (85.7)	40/278 (14.3)	1					
Number of NNRTI mutations at baseline	0 (0-1)	0 (0-1)	1.014	0.747-1.376	0.9306			
0	187/217 (86.3)	30/217 (13.7)	1		0.7122	1		0.7915
1	56/67 (83.9)	11/67 (16.1)	1.077	0.626-1.852		1.032	0.532-2.006	
≥2	46/54 (85.2)	8/54 (14.8)	1.047	0.587-1.870		1.106	0.368-3.322	

Table 2: Impact of the M184I/V mutation on the incidence of virological failure (VF) at 6 months after initiation of Doravirine among switch participants (GSS Stanford with 10 imputed datasets)

Characteristic	Virological blip (VB)		Univariable analysis			Multivariable analysis		
	No n/N (%) or median (IQR) N=328	Yes n/N (%) or median (IQR) N=10	OR	95% CI	P value	OR	95% CI	*P value*
M184I/V mutation at baseline					0.1312			0.3965
no	286/293 (97.6)	7/293 (2.4)	1			1		
yes	42/45 (93.3)	3/45 (6.7)	2.918	0.726-11.726		1.973	0.411-9.468	
Gender					0.8004			
Male	217/224 (96.9)	7/224 (3.1)	1					
Female	111/114 (97.4)	3/114 (2.6)	0.838	0.213-3.303				
Viral subtype					0.2521			0.3220
B	181/186 (97.3)	5/186 (2.7)	1			1		
CRF02	63/67 (94.0)	4/67 (6.0)	2.298	0.598-8.828		2.018	0.676-6.021	
Other Non-B	84/85 (98.8)	1/85 (1.2)	0.431	0.050-3.746		0.445	0.101-1.966	
Nadir CD4 count (per 100 cells/mm³ increase)	254 (127-399)	180 (69-414)	0.918	0.663-1.271	0.6074	1.039	0.707-1.526	0.8474
CD4 count at baseline (per 100 cells/mm³ increase)	620 (471-849)	389 (361-880)	0.873	0.692-1.102	0.2526			
Log zenith plasma HIV-1 RNA (per 1 Log_{10} copies/mL increase)	4.9 (4.0-5.5)	5.0 (2.7-5.5)	0.979	0.606-1.581	0.9307	1.085	0.583-2.019	0.7962
Log plasma HIV-1 RNA at baseline (per 1 Log_{10} copies/mL increase)	1.6 (1.6-1.6)	1.6 (1.6-1.6)						
Doravirine co-treatment					0.8119			
3TC+TDF	302/311 (97.1)	9/311 (2.9)	1					
3TC+ABC	26/27 (96.3)	1/27 (3.7)	1.291	0.157-10.587				
Nucleic acid					0.9111			0.9069
RNA	137/141 (97.2)	4/141 (2.8)	1			1		
DNA	191/197 (97.0)	6/197 (3.0)	1.076	0.298-3.885		1.045	0.501-2.179	
GSS with Doravirine (Stanford)	3.0 (2.5-3.0)	2.8 (1.0-3.0)	0.476	0.218-1.041	0.0628	1.471	0.184-11.765	0.7161
0-1	12/15 (80.0)	3/15 (20.0)	**4.888**	**1.769-13.505**	**0.0038**			
1.5-2.5	69/71 (97.2)	2/71 (2.8)	0.541	0.185-1.581				
3	247/252 (98.0)	5/252 (2.0)	1					
GSS with Doravirine (ANRS)	3.0 (3.0-3.0)	3.0 (2.0-3.0)	0.585	0.224-1.526	0.2729			
0-1	8/9 (88.9)	1/9 (11.1)	2.393	0.533-10.735	0.3922			
1.5-2.5	49/51 (96.1)	2/51 (3.9)	0.813	0.244-2.711				
3	271/278 (97.5)	7/278 (2.5)	1					
Number of NNRTI mutations at baseline	0 (0-1)	1 (0-2)	1.474	0.923-2.354	0.1048			
0	213/217 (98.2)	4/217 (1.8)	1		0.2899	1		0.8683
1	64/67 (95.5)	3/67 (4.5)	1.306	0.506-3.370		1.363	0.342-5.435	
≥2	51/54 (94.4)	3/51 (5.6)	1.510	0.571-4.000		0.600	0.068-5.270	

Table 3: Impact of the M184I/V mutation on the incidence of virological blip (VB) at 6 months after initiation of Doravirine among switch participants (GSS Stanford with 10 imputed datasets)

CONCLUSIONS

- In antiretroviral-experienced PLWHIV switching to DOR+3TC + ABC or TDF in clinical practice, we found no evidence of an impact of the previously acquired M184I/V mutation on treatment response.
- A higher zenith of HIV RNA VL was the only factor associated with the VF as it has been previously shown in the analysis of the entire cohort of PLWHIV receiving a regimen including DOR or in different contexts of ARV regimen switching. [1-4]
- Limitation: only a small proportion of the PLWHIV were treated by DOR+3TC+ABC, so the results for this combination should be taken cautiously.
- These results should be confirmed in prospective clinical trials.

1. Soulie C, *J Antimicrob Chemother* 2024; **79**: 1974–84. 2. Gantner P, *PLoS One* 2016; **11**: e0164240. 3. Bocket L. *J Antimicrob Chemother* 2016; **71**: 2651–3. 4. Wirden M. *J Antimicrob Chemother* 2015; **70**: 2347–53.

Contact: cathia.soulie-ext@aphp.fr

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