

ACTUALITÉS et leurs CONSÉQUENCES PRATIQUES dans le VIH

ACP
VIH
20 ANS

Laho Business Center
5-9, rue Van Gogh
75012 Paris

28 | 2023
NOVEMBRE

Avec le soutien institutionnel de



Sous la caution scientifique de



ACTUALITES VIROLOGIQUES & RESISTANCES

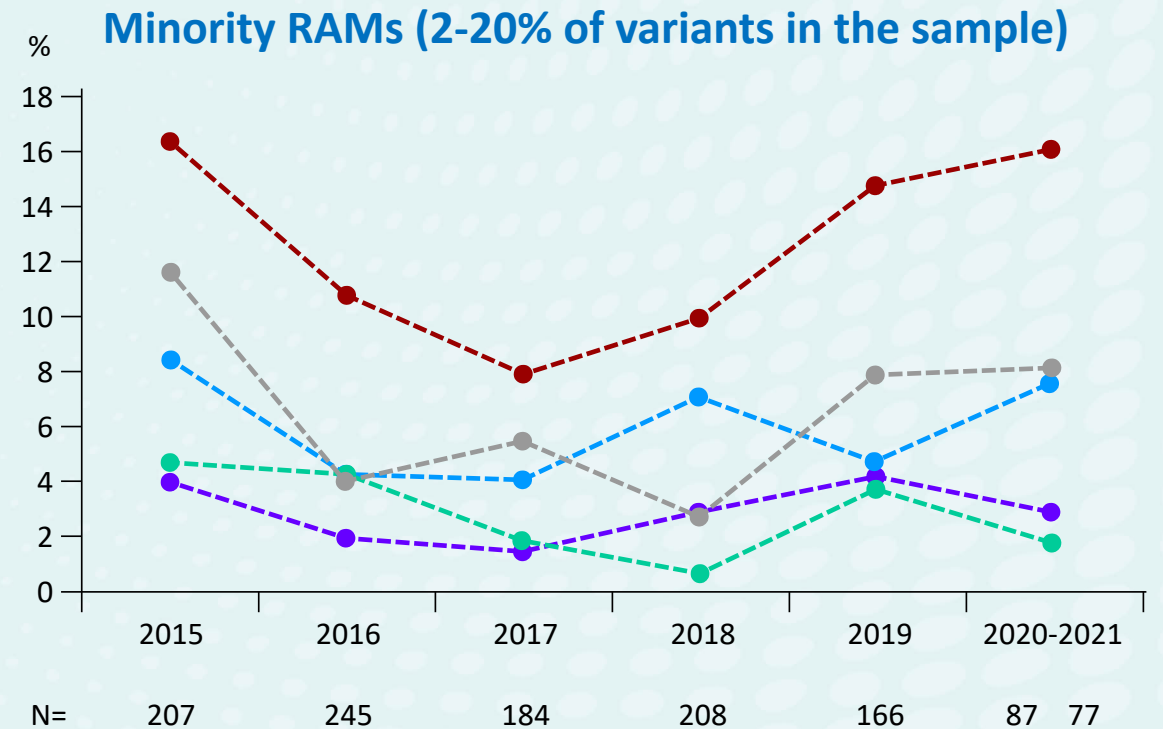
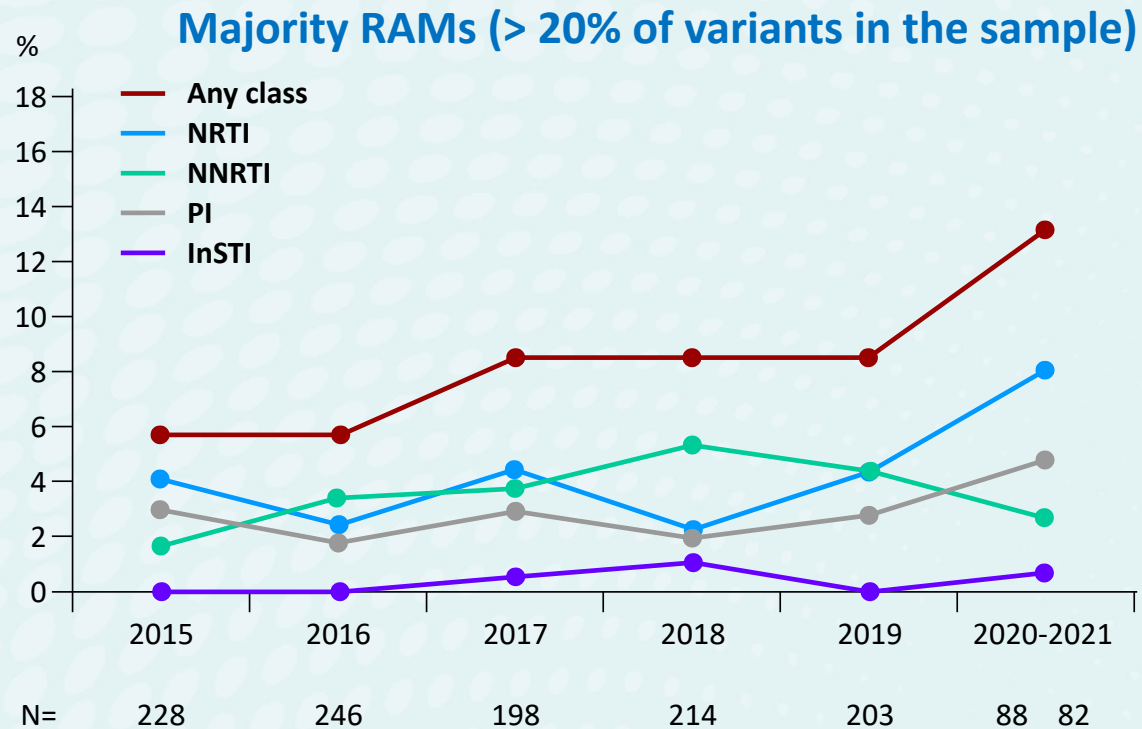
Pr Anne-Geneviève MARCELIN

Déclaration de liens d'intérêt

Anne-Geneviève Marcelin déclare avoir eu des liens d'intérêts (24 derniers mois) avec: **Gilead Sciences, GSK, Moderna, MSD, Pfizer, VIIV Healthcare**

Transmitted drug resistance in recently acquired infection = UK 2015-2021

- Recent (within 4 months) infection: Identified using the UK HSA Recent Infection Testing Algorithm (RITA)
- 1 211 recent HIV infection 2015-2021



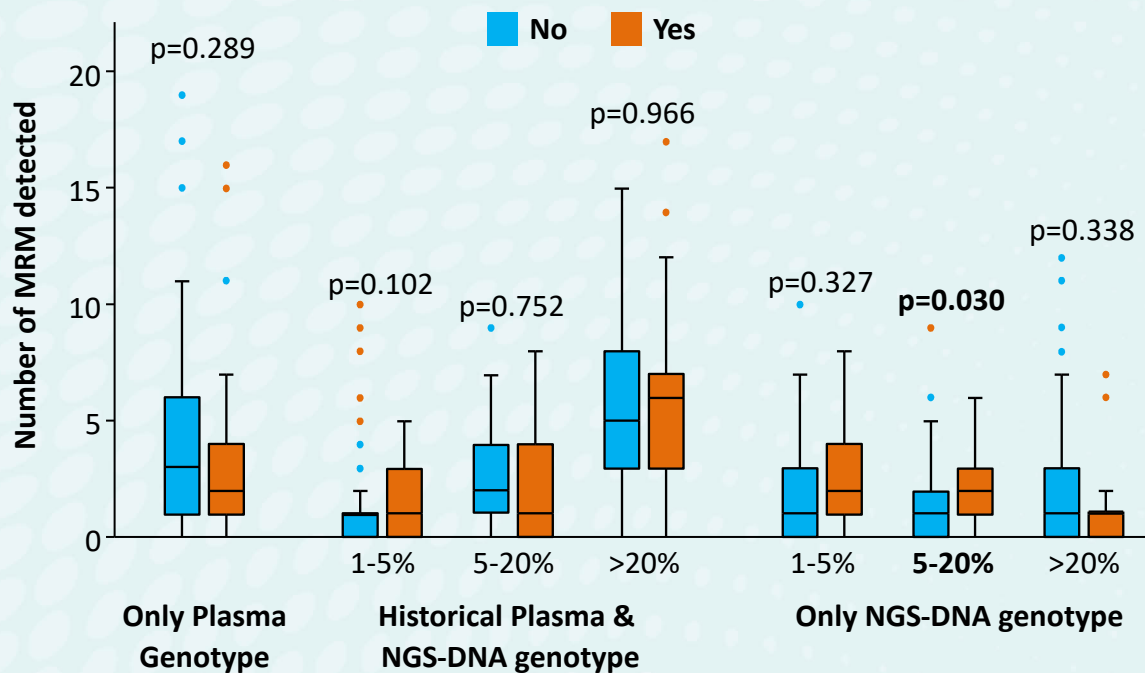
- M184V/I: 2.8% in 2020-2021 vs < 1% previous years

Subtypes: Through the years, subtype B declined from 55% to 37%; subtype A6 increased from 0% to 3.5%

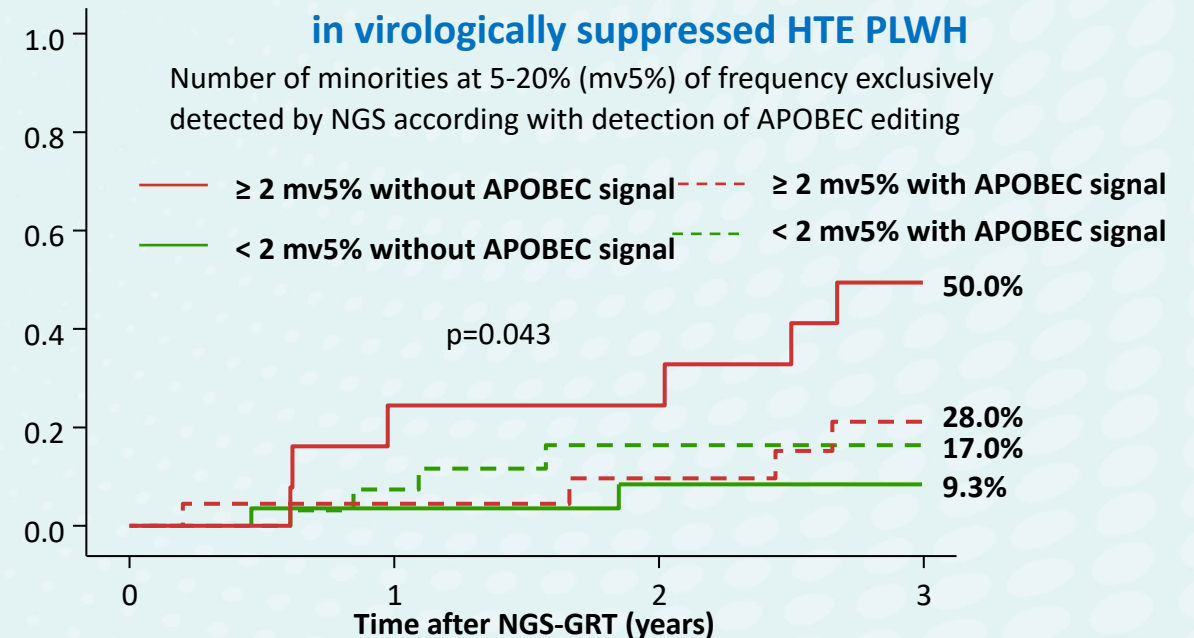
HIV DNA minority resistant variants and risk of rebound

- PRESTIGIO Registry, HTE PLWH with 4 drug class resistance and HIV RNA <50c/mL > 6 months
- NGS HIV-DNA performed on PBMC sample (cut-offs at $\geq 1\%$, $\geq 5\%$, $\geq 20\%$)
- Endpoint: probability of virological rebound (2 consecutive VL > 50 c/mL or 1 VL > 1000 c/mL) after NGS resistance assessment according to the detection of minority resistant variants and APOBEC editing signal

Virological rebound after NGS-GRT



Probability of experiencing VR after NGS-GRT in virologically suppressed HTE PLWH



- By 3 years after NGS-GRT, the probability of VR was 21.6% Having ≥ 2 mv5% exclusively detected by NGS without APOBEC signal was associated with VR

M184V mutation clearance in HIV DNA overtime

22 peoples living with HIV with past M184V and plasma HIV RNA <50 copies/mL for at least 5 years

18 males

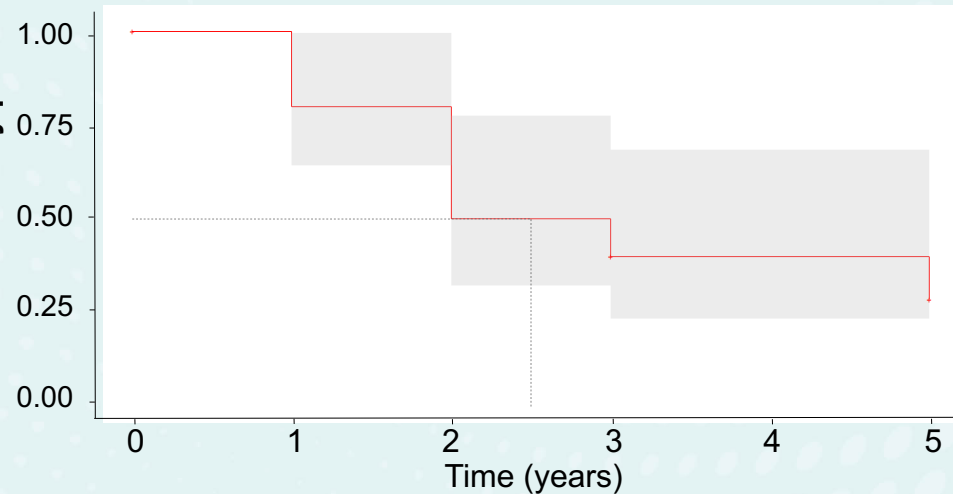
4 females

- Median age of 56 years [49-65]
- Virological suppression median of 7.7 years [7.0-10.0]
- CD4 cell count of 560/mm³ [465-807]
- CD4 Nadir median of 164/mm³ [77-259]
- Zenith HIV viral load median 4.99 log₁₀ copies/ml [4.20-5.56]
- All harboring M184V in HIV DNA using sanger sequencing at baseline

Longitudinal UDS on HIV-DNA samples during a 5 years follow-up

M184V undetectability probability

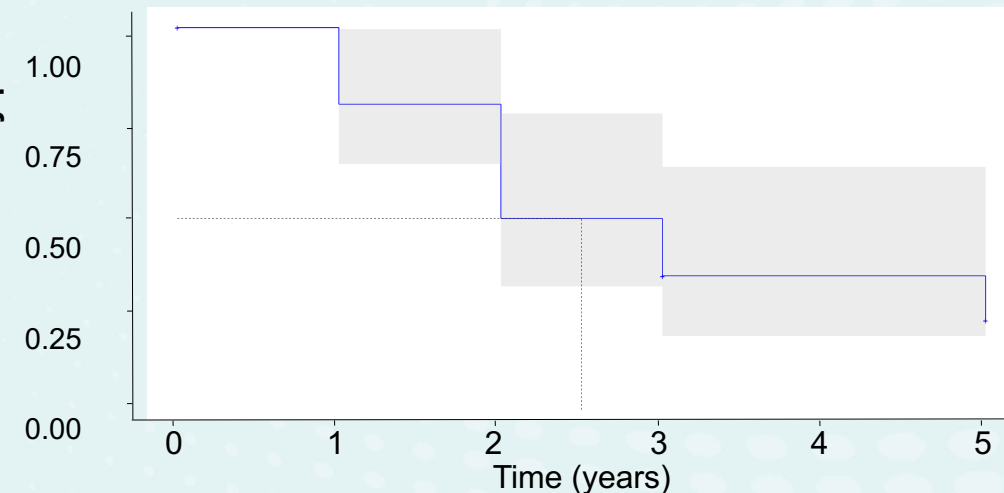
Survival curve threshold <2%



➤ At **2.5 years** after the first time-point the M184V lost was observed in 50% of patients

M184V undetectability probability

Survival curve threshold <5%

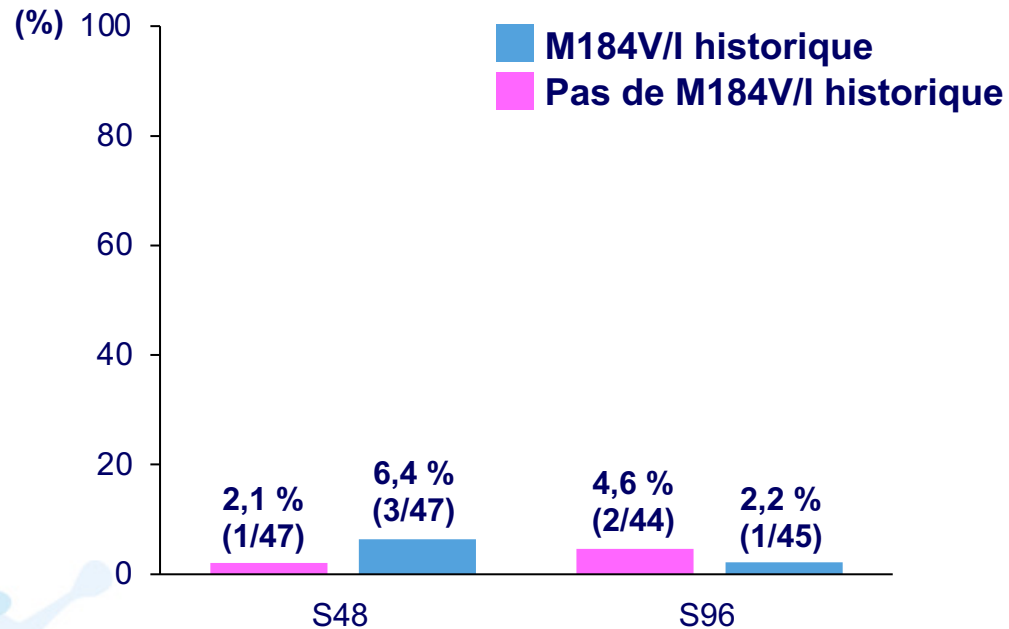


➤ At **2.5 years** after the first time-point the M184V lost was observed in 50% of patients

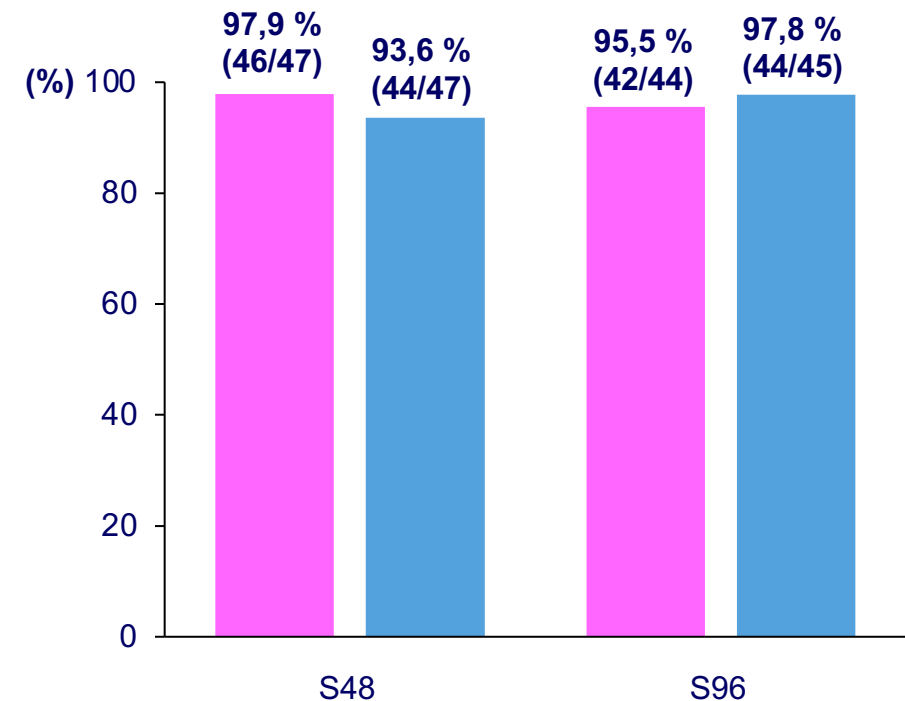
Switch pour DTG/3TC chez des patients avec antécédent de M184V/I

- SOLAR-3D : étude ouverte, prospective
- Adultes avec CV < 50 c/ml (durée médiane de suppression virologique : 11,8 ans), antécédent d'échec virologique
- Switch pour DTG/3TC (50 patients sans antécédent de M184V/I, 50 avec antécédent de M184V/I)

CV > 50 c/ml, FDA snapshot



CV < 50 c/ml, FDA snapshot

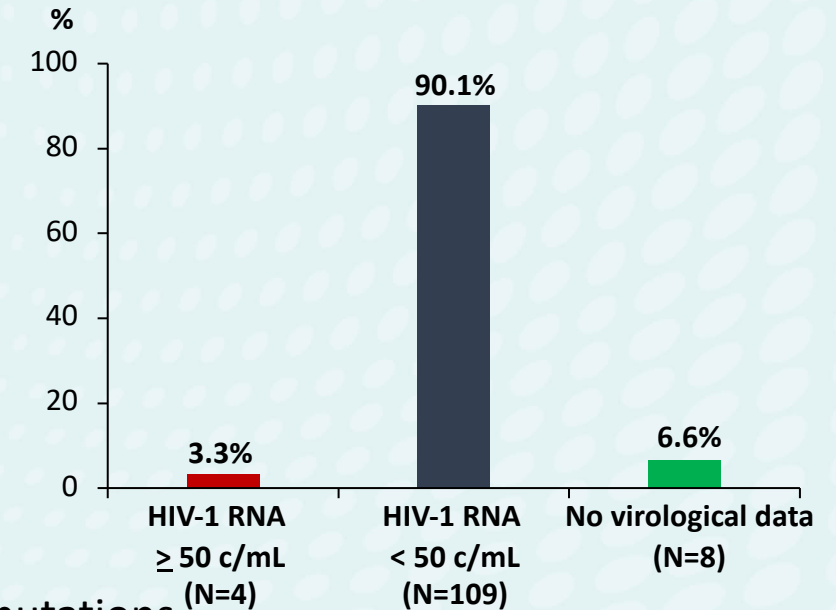


- **Importantes limites**
 - Etude non contrôlée
 - Faible nombre de sujets
 - Pas de distinction entre M184V et M184I (APOBEC ? Virus défectif ?)

DTG/3TC in virologically suppressed persons with expected or confirmed Resistance to 3TC: VOLVER trial

- VOLVER trial: open-label, multicentric, single arm study
- Inclusion criteria
 - Virologically suppressed PWH
 - Past 3TC resistance: confirmed by genotypic testing or suspected based on prior virological failure while receiving 3TC or FTC
 - No prior integrase resistance or virological failure under INSTI
 - CD4+ >200 cells/mm³
 - Sanger proviral DNA sequencing at screening without 3TC resistance mutations
- Primary endpoint: % HIV RNA \geq 50 c/mL at W48 (ITT-e, FDA snapshot)
- 121 patients enrolled

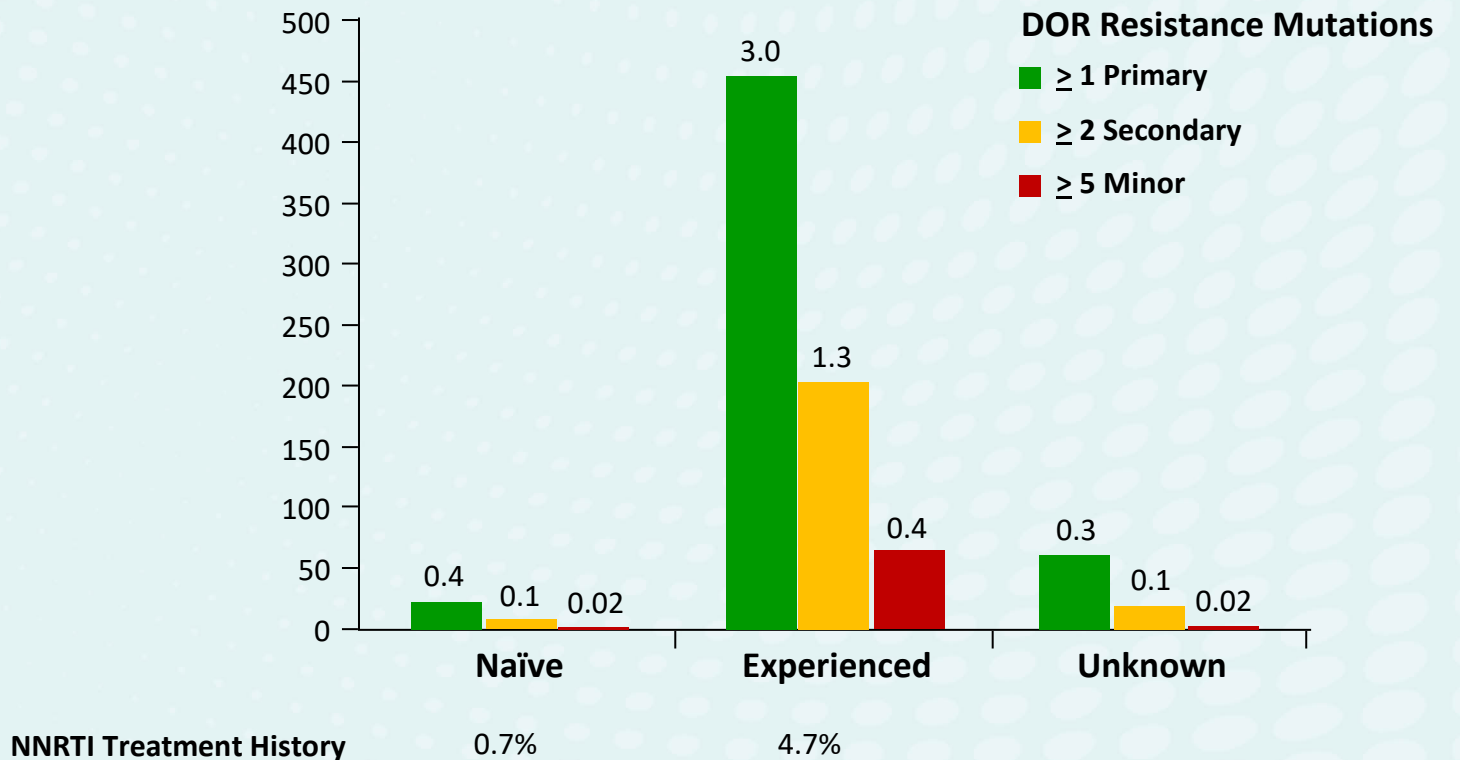
W48 outcomes



DOR-associated Resistance Mutations are uncommon

- British Columbia Centre for Excellence in HIV/AIDS, Vancouver
- 1996-2023: 38 808 genotypes from 10 279 PLWH
 - 14% NNRTI naïve, 40% NNRTI-experienced, 46% unknown (assumed to be NNRTI-naïve)
- 20.6% genotypes harbored NNRTI resistance
 - NNRTI naïve
 - 8.6% to EFV
 - 2.1% to ETR
 - 5.7% to RPV
 - NNRTI-experienced
 - 29.7% EFV
 - 14.0% ETR
 - 20.6% RPV

% of DOR RAM according to Number of Genotypes tested



DORAVIR: a French national survey of people with HIV-1 treated by an antiretroviral regimen including Doravirine

Cathia Soulié¹, Aliou Balde², Djeneba Fofana³, Charlotte Charpentier⁴, Pascale Bonnafous¹, Justine Sourice⁵, Anne De Monte⁶, Véronique Avettand-Fenoel⁷, Hélène Le Guillou-Guillemette⁸, Laurence Bocket⁹, Stéphanie Raymond¹⁰, Stéphanie Marque Juillet¹¹, Mary-Anne Traubaud¹², Brigitte Montes¹³, Anne Maillard¹⁴, Cedric Hartard¹⁵, Elodie Alessandri-Gradt¹⁶, Etienne Brochot¹⁷, Anne Signori-Schmuck¹⁸, Lambert Assoumou², Anne-Geneviève Marcelin¹

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 Cochin, 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 Service Biologie, unité de Microbiologie CH de Versailles, Versailles , France; 12 Laboratoire de Virologie, Institut des Agents Infectieux, Hospices civils de Lyon, Centre de Biologie Nord, Hôpital de la Croix Rousse, Lyon, France; 13 Laboratoire de Virologie, CHU Montpellier, Univ Montpellier, Montpellier, France ; 14 Laboratoire de Virologie, CHU de Rennes, Rennes, France; 15 CHRU Nancy, Laboratoire de Virologie, Nancy, France; 16 CHU de Rouen, Université de Rouen Normandie UNIRouen, Rouen, France; 17 CHU Amiens, Faculté de pharmacie Amiens, Amiens, France; 18 CHU Grenoble-Alpes, Laboratoire de Virologie, Grenoble, France.



European Meeting on HIV & Hepatitis 2023
Poster n°58

19th EUROPEAN
AIDS CONFERENCE
18-21 October 2023
Warsaw, Poland

eP.B1.029

Objectives

To study the factors associated with

- the virological failure (VF) to a doravirine (DOR)-containing regimen (2 VL > 50 cp/ml or 1 VL > 200 cp/ml)
- the emergence of reverse transcriptase (RT) mutations in case of VF.

Patients

- A national French survey including people living with HIV-1 (17 ANRS-MIE centers), n = 592
- November 2020 to December 2022,
- Naïve or experienced receiving an antiretroviral treatment including DOR.

RESULTS

Characteristics

Among the 592 people with HIV-1 treated by any DOR-containing regimen:

- 8.6% naïve (n=51),
- 91.4% previously experienced at baseline (n=459 VL <50 cp/ml and n=82 VL > 200 cp/ml),
- 337 (56.2%) were infected with HIV-1 B subtype,
- Median duration of current DOR regimen 12.7 months (IQR 7.1-18.9).

Characteristic	All (N=592)	Naïve (N=51)	Switch (N=459)	Failure (N=82)
	N	N	N	N
Male	592	51	459	82
Subtype B	592	51	459	82
Median duration of current Doravirine regimen, months (IQR)	592	51	459	82
Median zenith plasma HIV-1 RNA, copies/mL (IQR)	550	50	419	81
Median zenith plasma HIV-1 RNA, Log₁₀ copies/mL (IQR)	550	50	419	81
Median baseline plasma HIV-1 RNA, copies/mL (IQR)	585	51	452	82
Median baseline plasma HIV-1 RNA, Log₁₀ copies/mL (IQR)	585	51	452	82
Median nadir CD4 count cells/mm³ (IQR)	582	50	451	81
Median baseline CD4 count cells/mm³ (IQR)	577	51	448	78
CD4 count baseline <200 cells/mm³	577	51	448	78
Doravirine co-treatment	592	51	459	82
3TC+TDF	417 (70.4)	40 (78.4)	312 (68.0)	65 (79.3)
3TC+ABC	33 (5.6)	3 (5.9)	27 (5.9)	3 (3.7)
DTG	68 (11.5)	1 (2.0)	58 (12.6)	9 (11.0)
RAL	54 (9.1)	0 (0.0)	52 (11.3)	2 (2.4)
Other*	20 (3.4)	7 (13.7)	10 (2.2)	3 (3.6)
GSS before Doravirine	541	51	459	82
no full sensitive	275 (50.8)		223 (48.6)	52 (63.4)
full sensitive	266 (49.2)		236 (51.4)	30 (36.6)
GSS with Doravirine (Stanford)	592	51	459	82
no full sensitive	192 (32.4)	4 (7.8)	153 (33.3)	35 (42.7)
full sensitive	400 (67.6)	47 (92.2)	306 (66.7)	47 (57.3)
GSS with Doravirine (ANRS)	592	51	459	82
no full sensitive	144 (24.3)	1 (2.0)	118 (25.7)	26 (31.7)
full sensitive	448 (75.7)	50 (98.0)	342 (74.5)	56 (68.3)

Virological failure

• At M3, 69 patients were in VF (n=69/592, **11.7%**)
 Naïve 27.5% Switch 5.9% Failure 34.2%

• At M6, 88 patients were in VF (n=88/592, **14.9%**)
 Naïve 9.8% Switch 11.6% Failure 36.6%

Univariate and multivariate analysis for factors associated with VF

The factors associated with the VF:

- The HIV-1 subtype
- The context of Doravirine initiation
- The presence of V179D at baseline

Characteristic	Virological failure (VF)		Univariable analysis			Multivariable analysis		
	No n/N (%) or median (IQR)	Yes n/N (%) or median (IQR)	OR	95% CI	P value	OR	95% CI	P value
Gender					0.9813			
Male	343/403 (85.1)	60/403 (14.9)	1					
Female	161/189 (85.2)	28/189 (14.8)	0.994	0.611-1.617				
Viral subtype					<.0001			0.0026
B	300/337 (89.0)	37/337 (11.0)	1			1		
CRF02	84/117 (71.8)	33/117 (28.2)	3.185	1.879-5.401		2.817	1.550-5.119	
Non-B	120/138 (87.0)	18/138 (13.0)	1.216	0.666-2.220		1.258	0.669-2.365	
Nadir CD4 count (per 100 cells/mm³ increase)	230 (104-378)	190 (50-395)	0.999	0.998-1.000	0.2552			
CD4 count at baseline (per 100 cells/mm³ increase)	602 (414-816)	503 (318-766)	0.999	0.998-0.999	0.0386	1.000	0.999-1.000	0.7347
Log zenith plasma HIV-1 RNA (per 1 Log₁₀ copies/mL increase)	4.8 (4.0-5.5)	5.4 (4.5-5.9)	1.445	1.165-1.792	0.0008			
Log plasma HIV-1 RNA at baseline (per 1 Log₁₀ copies/mL increase)	1.6 (1.6-1.8)	2.0 (1.6-2.92)	1.425	1.186-1.712	0.0002	1.444	0.946-2.204	0.0885
GSS with Doravirine (Stanford)					0.5310			
no full sensitive	166/192 (86.5)	26/192 (13.5)	0.854	0.521-1.400				
full sensitive	338/400 (84.5)	62/400 (15.5)	1					
GSS with Doravirine (ANRS)					0.5176			
no full sensitive	125/144 (86.8)	25/144 (13.2)	0.835	0.483-1.442				
full sensitive	379/448 (84.6)	69/448 (15.4)	1					
Context of doravirine initiation					<.0001			0.0041
Naive	46/51 (90.2)	5/51 (9.8)	1			1		
Switch	406/459 (88.4)	53/459 (11.6)	1.201	0.457-3.156		4.094	0.780-21.493	
Failure	52/82 (63.4)	30/82 (36.6)	5.308	1.902-14.816		7.115	2.001-25.295	
NNRTI mutations at baseline								
A98G					0.0084			0.3730
no	448/526 (85.2)	78/526 (14.8)	1			1		
yes	8/14 (57.1)	6/14 (42.9)	4.308	1.455-12.755		1.784	0.499-6.379	
V179D					0.0377			0.0492
no	450/531 (84.8)	81/531 (15.2)	1			1		
yes	3/6 (50.0)	3/6 (50.0)	5.558	1.102-28.020		5.816	1.006-33.624	

Proportion of resistance-associated mutations (RAM)

Fourteen patients (n=14/88) presented HIV-1 with appearance of resistance associated mutations (n=29) in the RT at failure.

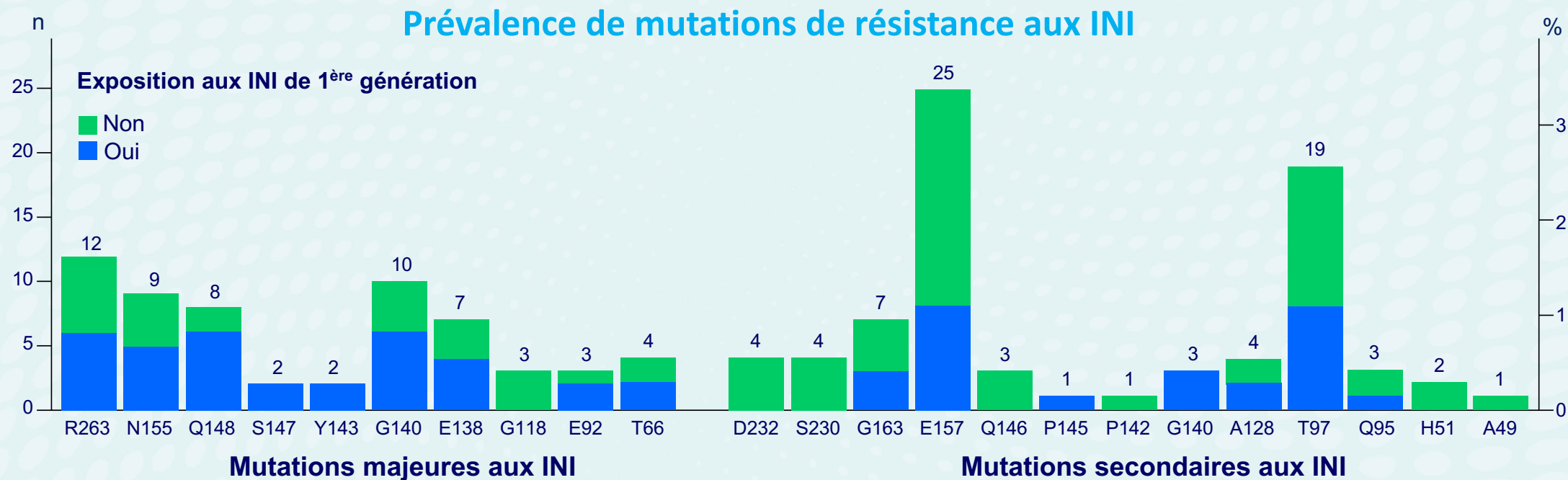
Patient	Doravirine co-treatment	Context of doravirine initiation	New mutations at VF	Stanford algorithm	ANRS Algorithm
1	RAL+DOR	Switch	E28K V90I K101E V106I T107A I135T T165I Y181C H221Y V276I	K101E V106I Y181C H221Y	K101E V106I Y181C H221Y
2	3TC+TDF+DOR	Switch	K20R E138A	E138A	E138A
3	3TC+TDF+DOR	Switch	L74I V108I H221Y	L74I V108I H221Y	L74I H221Y
4	3TC+TDF+DOR	Switch	K65R P225L F227C	K65R F227C	K65R F227C
5	3TC+TDF+DOR	Switch	V60I K103N S163T F214L D250E E291D V317A	K103N	K103N
6	3TC+TDF+DOR	Switch	E122K S162C V179D M184V	V179D M184V	V179D M184V
7	3TC+TDF+DOR	Switch	M41L I178L V179I T215Y	M41L T215Y	M41L V179I T215Y
8	3TC+TDF+DOR	Switch	T39A K103E T139K G190A T215N T215S T215Y A272P K277R K281R E297K	G190A T215N T215S T215Y	G190A T215N T215S T215Y
9	3TC+TDF+DOR	Switch	E28K E29K M41R K43R T58L D67N G93R G112E G112K G112R D121N E138K G141E G152R M184I D185N E194K G196R G231K G231R D256N G285R G316R G333R	D67N E138K M184I	D67N E138K M184I
10	3TC+TDF+DOR	Failure	S105T V106A V118I Q174S G190A F227L	V106A G190A F227L	V106A G190A
11	3TC+TDF+DOR	Failure	M184V	M184V	M184V
12	3TC+TDF+DOR	Failure	A158S S162A Q174E I178M T200A F227C	F227C	F227C
13	3TC+ABC+DOR	Failure	V21I K30R V118I P225H V292I I293V H315Y K347E	P225H	P225H
14	DRV+DOR	Failure	G99E M184V	M184V	M184V

Univariate and multivariate analysis for factors associated to occurrence of RAM

The only factor associated with the occurrence of resistance-associated mutations (RAM) was the GSS regardless Stanford (OR 6.035, 95% CI 1.782-20.442) or ANRS (OR 3.519, 95% CI 1.043-11.874) algorithm.

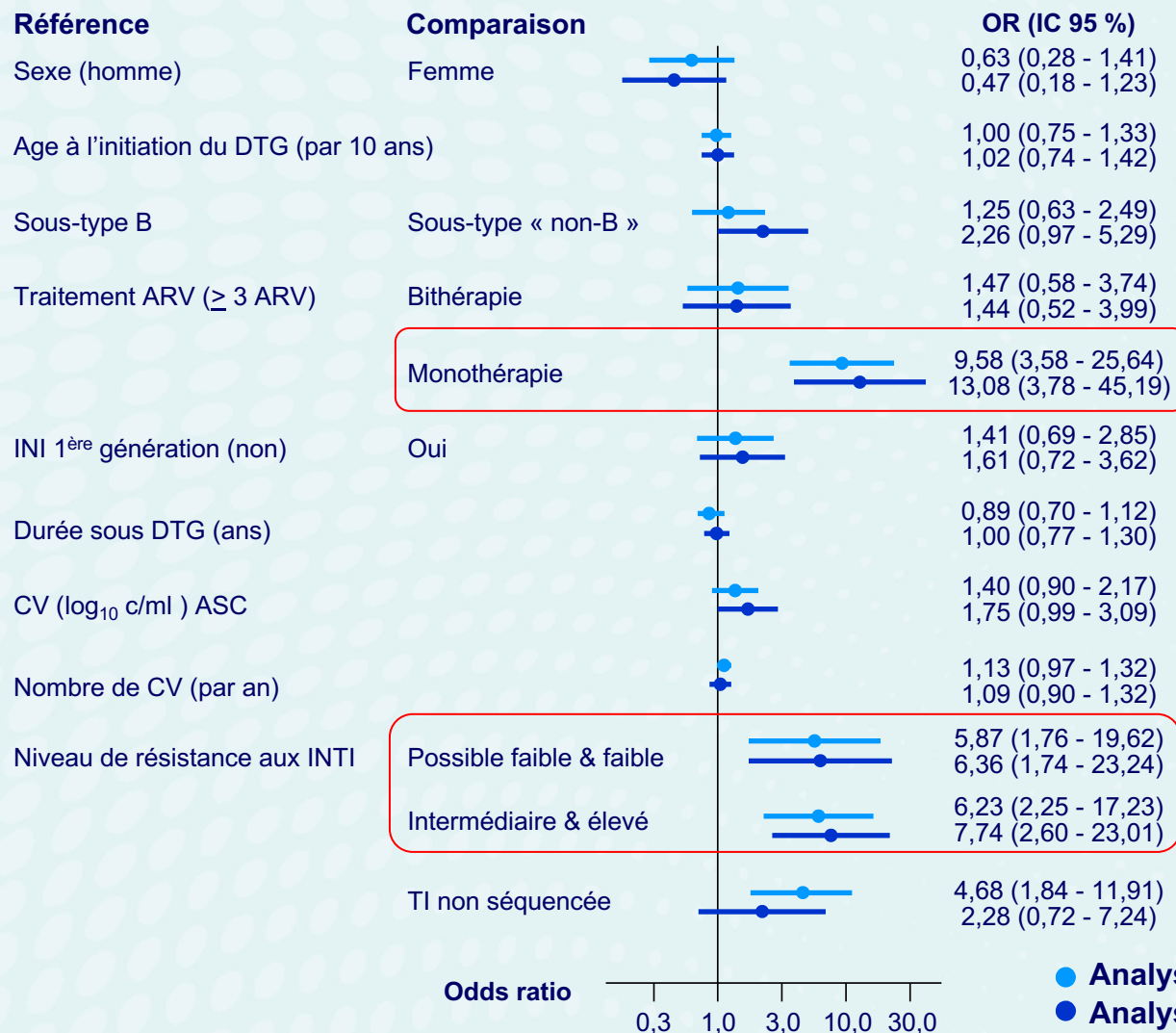
Analyse de la résistance à DTG dans plusieurs cohortes (1)

- Analyse de la résistance dans les échecs à un traitement à base de DTG dans 8 cohortes (Canada, Europe et Afrique du Sud)
- Liste de mutations aux INI : algorithme de Stanford
- 742 génotypes au moment de l'échec sous DTG
- Détection d'une mutation de résistance aux INI : 100/742 (13,5 %)



Analyse de la résistance à DTG dans plusieurs cohortes (2)

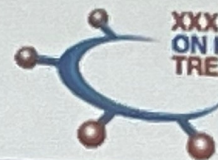
Facteurs prédictifs d'émergence de mutation de résistance à DTG



Conclusions

- Résistance à DTG en cas d'échec est rare (R263K = 1,6 %)
- Risque augmenté d'émergence de résistance à DTG en cas de monothérapie de DTG (à proscrire en raison du risque très élevé de résistance) et en cas de résistance aux INTI
- Surveillance nécessaire dans le contexte des pays du Sud (absence de génotypes de résistance et faible accès aux CV)

Mutational Pathways



XXX INTERNATIONAL WORKSHOP
ON HIV DRUG RESISTANCE AND
TREATMENT STRATEGIES

20-22 September 2023 • Cape Town, South Africa

R263K (n=40)

R263K (24)
R263K + M50I (6)
R263K + E157Q (5)
R263K + G163KR (1)
R263K + A49G + S230R (1)
R263K + A49G + M50I + E157Q (1)
R263K + A49G + E138T + S147G (1)
R263K + A49G + Q95K + E138K + S147G +
E157Q (1)

G118R (n=24)

G118R (6)
G118R + L74IM (2)
G118R + H51Y (1)
G118R + E92Q (1)
G118R + V151I (1)
G118R + D232N (1)
G118R + T66AI + E138K (3)
G118R + M50I + E138K (1)
G118R + T66I + L74I (1)
G118R + T97A + E138K (1)
G118R + M50I + T66I + E138K (1)
G118R + T66A + L74M + E138A (1)
G118R + T66A + L74M + V151I (1)
G118R + T66I + E138K + G149A (1)
G118R + M50I + T66I + L74I + E138K (1)
G118R + T66A + E138K + G149A + G163R (1)

Q148HKR (n=9)

Q148K (2)
Q148R (1)
Q148H + G140S (1)
Q148R + E138K + G140A (1)
Q148K + E138K + G140A (1)
Q148R + G140A + S147G (1)
Q148K + Q95K + E138K + G140A (1)
Q148H + T97A + E138T + G140S (1)

N155H (n=9)

N155H (3)
N155H + E92Q (1)
N155H + T97A (1)
N155H + S147G (1)
N155H + T97A + S147G (1)
N155H + E138K + G140S (1)
N155H + L74I + S147G + S230R (1)

G118R + R263K (n=4)

G118R + R263K (2)
G118R + R263K + E138K (1)
G118R + R263K + H51Y + E138K (1)

N155H + R263K (n=2)

N155H + R263K (1)
N155H + R263K + D232N (1)

Q148HR + N155H (n=2)

Q148R + N155H + S147G (1)
Q148H + N155H + E138K + G140S (1)

ETUDE ANRS S147G

- **Background :**

- La mutation S147G aux INSTI est rare.
- Impliquée dans la résistance à l' EVG et DTG dans l'algorithme de Stanford mais seulement EVG pour l' ANRS car trop peu de données pour le DTG.

- **Objectif :**

- Préciser le contexte de l'émergence de la S147G et le rôle du DTG.

- **Méthode :**

- Etudier tous les cas d'émergence d'une S147G dans le réseau ANRS-MIE avec étude de l'historique thérapeutique et virologique.

ETUDE ANRS S147G

Résultats

- La S147G n'est pas un polymorphisme (pas de « naïfs »)
- Est surtout sélectionnée sous DTG :48% des cas (EVG:36%, RAL :10%)
- N'est pas liée à un sous type (B: 56%; CRF02 : 22%)
- Sous DTG, elle est associée à 3 autres mutations INSTI en médiane, parmi surtout 97A; 74I/M; 138K; 148R et 155H
- Intégration dans l'algo DTG de l'ANRS :

Modification Algorithme ANRS

<p>DTG* 50 mg QD</p>	<ul style="list-style-type: none"> ■ G118R [12,13] ■ F121Y [17] ■ E138A/K/T [15] ■ G140A/C/S [15] ■ N144D [42] ■ Q148H/K/R ■ V151L [9, 23] ■ S153F/Y [9, 23, 26, 34] ■ N155H [18] ■ S230R [29] ■ R263K [16] ■ T66K + L74M [9] ■ L74I + E92Q [30] 	<ul style="list-style-type: none"> ■ T66K [9] <div style="background-color: #FFD700; padding: 10px; text-align: center;"> <p>DTG QD POSSIBLE Res : At least 3 among : 74M ; 92Q ; 97A; 147G</p> </div>
<p>DTG* 50 mg BID</p>	<ul style="list-style-type: none"> ■ G118R [12,13] ■ F121Y [17] ■ N144D [42] ■ V151L [9,23] ■ S153F/Y [9, 23, 26, 34] ■ R263K [16] ■ T66K + L74M [9] ■ E92Q + N155H [9, 21, 22] ■ Q148H/K/R + at least 2 mutations among: L74I or T97A or E138A/K/T or G140A/C/S [15, 38, 39] ■ Q148H/K/R + N155H [9, 27,28] 	<ul style="list-style-type: none"> ■ T66K [9] ■ Q148H/K/R + 1 mutation among: L74I or E138A/K/T or G140A/C/S [15] <div style="background-color: #90EE90; padding: 10px; text-align: center;"> <p>DTG BID POSSIBLE Res : At least 4 among : 74I/M ; 97A ; 138K; 147G; 155H</p> </div>

Level of CVF and resistance with CAB + RPV LA

Summary for ATLAS, FLAIR, ATLAS-2M, CARISEL and SOLAR



N=308¹

94%
virologically
suppressed*

<1%

(3) participants had
CVF by Week 48



N=283²

80%
virologically
suppressed*

<2%

(4) participants had
CVF by Week 48



N=523³

94%
virologically
suppressed*

<2%

(9) participants had
CVF by Week 48



N=430⁴

87%
virologically
suppressed[†]

<1%

(2) participants had
CVF by Month 12[‡]



N=447⁵

90%
virologically
suppressed[†]

<1%

(3) participants had
CVF by Month 12^{||}

*N=308 (n=299 at Week 48, n=150 c/ml at Month 12). †One participant experienced CVF (two consecutive HIV-1 RNA measurements of >200 c/ml) and one met SVF criterion (one HIV-1 RNA measurements of >200 c/ml) twice but neither were confirmed upon retest and the participant withdrew following the second SVF. ‡Two participants in the population met the population-level criterion.

SVF, suspected virologic failure
Prescribing information for Vocabria (cabotegravir) and Rekambys (rilpivirine) is available via the QR code provided



PHASE 3 CLINICAL STUDIES WITH CAB: VF IN 1.3 % OF CASES (n = 13/1 039)

	Subtype	PBMC HIV DNA RT (D0)	PBMC HIV DNA INT (D0)	PBMC HIV DNA RT (VF)	PBMC HIV DNA INT (VF)
ATLAS #1	A/A1	E138E/A	L74I	E138A	L74I
ATLAS #2	CRF02_AG	V108I-E138K	None	V108I-E138K	None
ATLAS #3	A/A1	None	L74I	E138E/K	L74I-N155H
FLAIR #1	A1	None	L74I	E138E/A/K/T	L74I-Q148R
FLAIR #2	A1	None	L74I	K101E	L74I-G140R
FLAIR #3	A1	None	L74I	E138K	L74I-Q148R
ATLAS-2M #1	A1	None	None	K101E	Q148R
ATLAS-2M #2	C	Y188Y/F/H/L	G140G/R	Y188L	Q148Q/R-N155N/H
ATLAS-2M #3	B	None	None	None	None
ATLAS-2M #4	C	Y188L-P225H	None	Y188L-P225H	Not Amplified
ATLAS-2M #5	B	K103N-E138A-V108V/I	None	K103N-E138A	N155H
ATLAS-2M #6	B	None	None	None	N155N/H
ATLAS-2M #7	B	None	None	K101E-M230L	E138E/K-Q148R

Emergence of INSTI DRM in 9/12 evaluable cases (75 %)

CAB + RPV LA: MVA 2.0 (presented at Glasgow 2022)

CVF cases in ATLAS, FLAIR and ATLAS-2M

Participant data pooled from ATLAS (Week 96), FLAIR (Week 124) and ATLAS-2M (Week 152):¹

N = 1651 participants
23 CVF (1,4%)

Baseline factors analysis (BFA)
BFA using Poisson regression model for risk of CVF in participants receiving CAB + RPV LA (excludes factors not evaluable at BL)

Covariate	Expanded BFA adjusted IRR (95% CI) N=1,363
Archived RPV RAMs*	21.7 (5.80, 80.8), p<0.0001
HIV-1 subtype A6/A1	12.9 (4.42, 37.5), p<0.0001
BL BMI kg/m ² [†]	1.09 (1.00, 1.19), p=0.0447
Regimen (Q8W/Q4W)	Eliminated from model
Integrase L74I polymorphism [‡]	
Sex at birth	
Other NNRTI RAMs	
Archived CAB RAMs	
Other INI RAMs	

Archived RPV RAMs, HIV-1 subtype A6/A1 and BMI ≥30 kg/m² are predictive BL factors for the risk of CVF

*Assessed in ATLAS, FLAIR and ATLAS-2M. The IRR for BMI ≥30 kg/m² was 3.97, p=0.01; †Including mixtures except L74I/M. BFA, baseline factors analysis; BMI, body mass index; CVF, confirmed virologic failure; IRR, incidence rate ratio; Q4/8W, every 4/8 weeks. Prescribing information for Vocabria (cabotegravir) and Dakimys (rilpivirine) is available via the QR code provided.

Predictive value of risk factors identified in the BFA

Outcomes by presence of key risk factors

Pooled data from FLAIR through Week 124, ATLAS through Week 96, and ATLAS-2M through Week 152

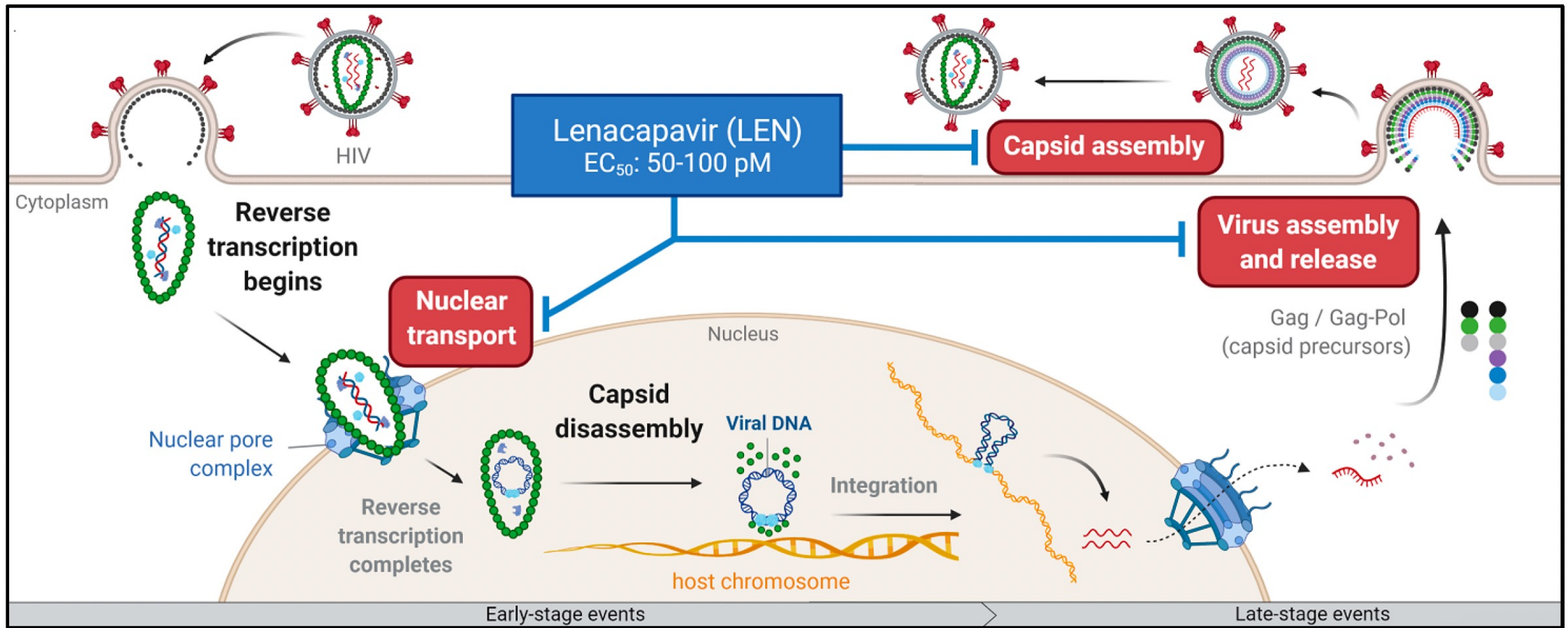
Factors*	CVF, n/N (%)	Virologic success, n/N (%)†
No BL factors	4/970 (0.4)‡	844/970 (87.0)
Any one BL factor	8/404 (2.0)§	343/404 (84.9)
Two or more BL factors	11/57 (19.3)	44/57 (77.2)
TOTAL [95% CI]	23/1,431 (1.6) [1.0, 2.4]	1,231/1,431 (86.0) [84.1, 87.8]

- Prevalence of ≥ 2 BL factors in Phase III study participants was low (4.0%, n=57/1,431)
- CVF occurred in 0.5% (n=1/216) of participants with BMI ≥ 30 kg/m² as their only BL factor

<1% of participants experienced CVF when no risk factors were present or when BMI ≥ 30 kg/m² was the only risk factor

*Archived RPV RAMs, HIV-1 subtype A6/A1, and BMI ≥ 30 kg/m²; †Based on the FDA Snapshot algorithm of HIV-1 RNA <50 c/mL at Week 48 for ATLAS, Week 124 for FLAIR, and Week 152 for ATLAS-2M ‡PPV 0.4%; NPV 95.9%; sensitivity 17.4%; specificity 31.4%; §Driven primarily by RPV RAMs and HIV-1 subtype A6/A1, not BMI. CVF occurred in 3.2% (n=1/31) of those with RPV RAMs only, 3.8% (n=6/157) of those with HIV-1 subtype A6/A1 only, and 0.5% (n=1/216) of those with BMI ≥ 30 kg/m²
NPV, negative predictive value; PPV, positive predictive value

LEN : Capsid inhibitor targets multiple stages of HIV replication cycle



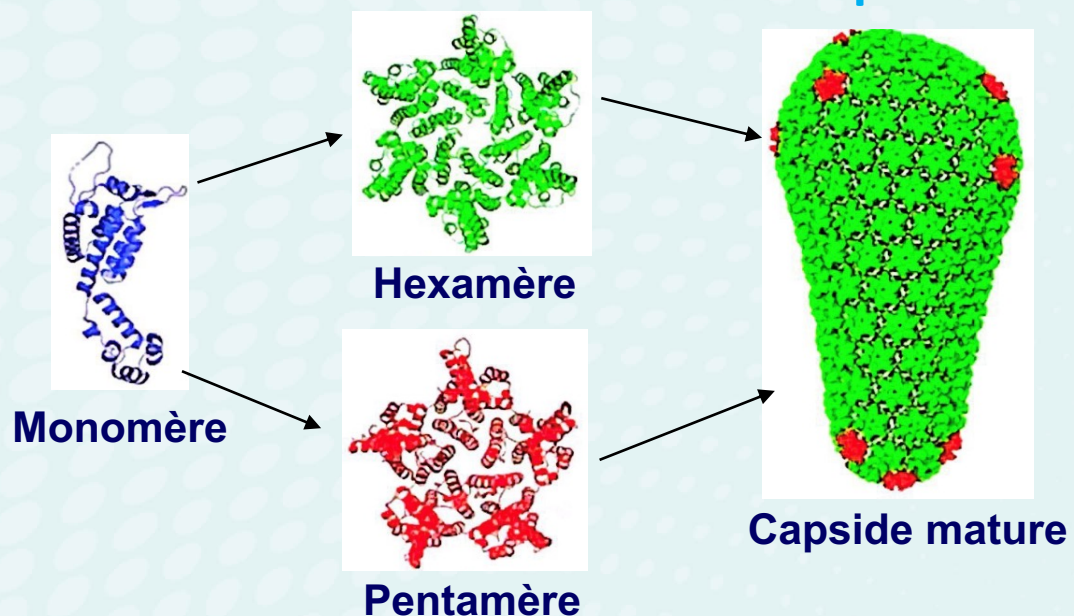
Link JO et al. Nature 2020 ; Bester et al. Science 2020

Picomolar mean EC50 values in primary human CD4 T cells (32pmol/l) and macrophages (56 pmol/l)

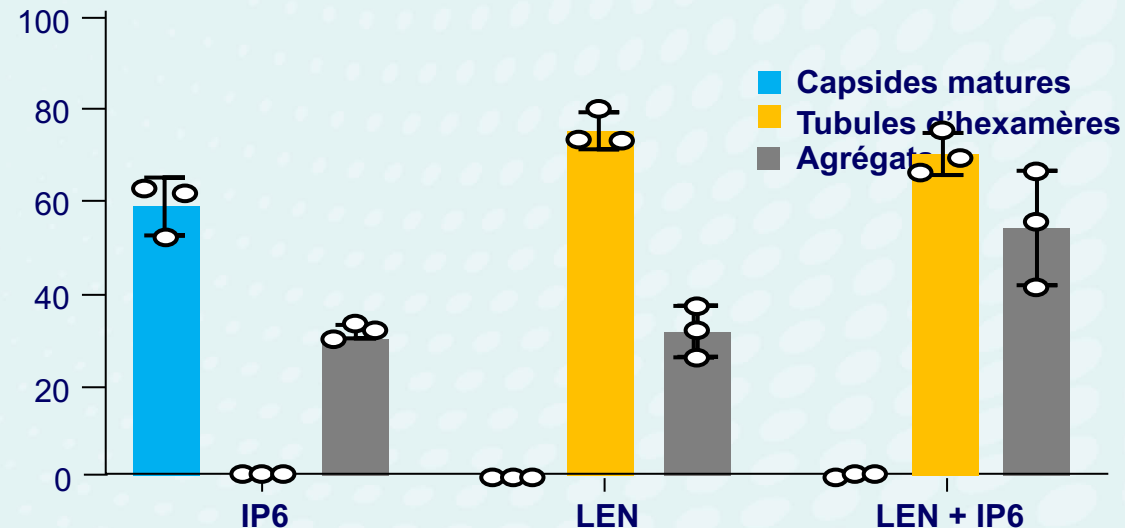
LEN : inhibition de la formation des pentamères de capside (1)

- Objectif : caractériser le mécanisme d'inhibition de la capside par LEN et l'impact de la présence de la mutation de résistance M66I

Schéma de formation de la capside



Nombre de particules de capside (/55 μm^2)



- En présence de LEN : inhibition de la formation des pentamères mais pas des hexamères

- L'ajout de l'inositol-6 phosphate (IP6) en présence de LEN ne permet pas de restaurer la formation de capsides matures

LEN : inhibition de la formation des pentamères de capside (2)

Nombre de particules de capside (/10 μm^2)

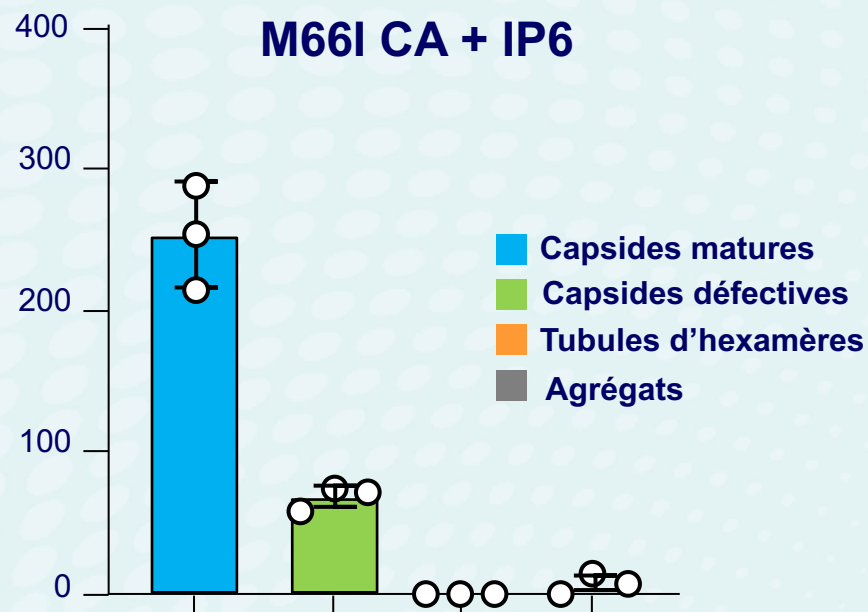
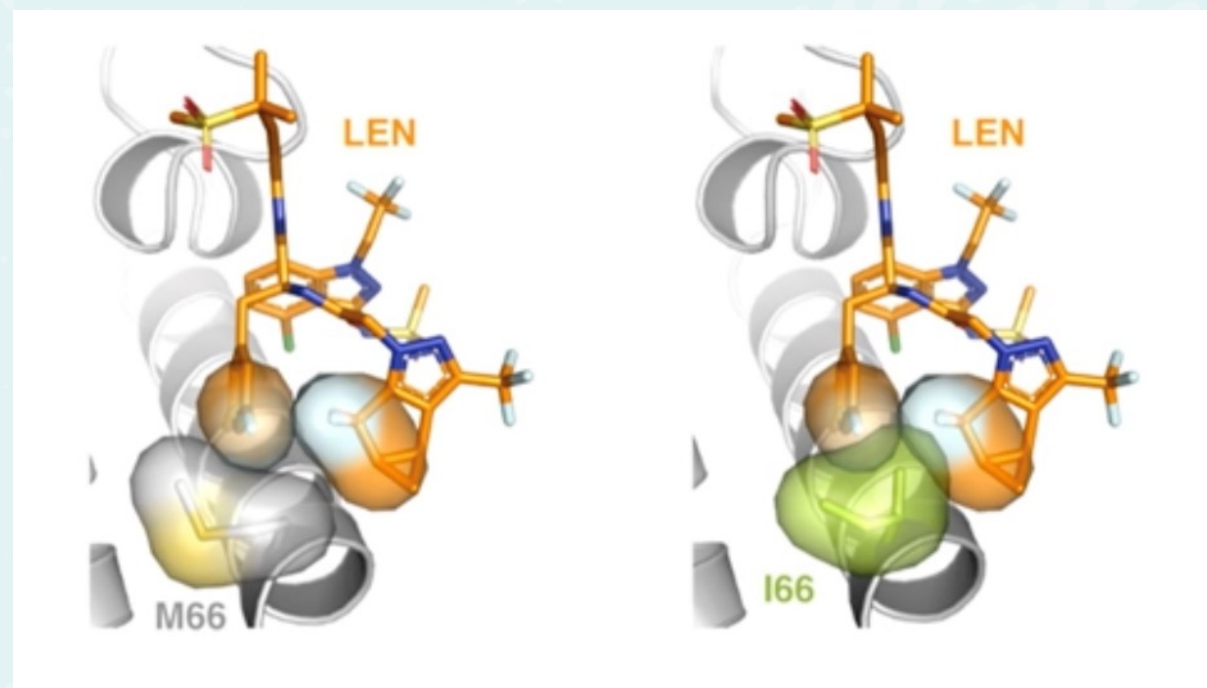


Schéma de l'impact de la mutation M66I sur la liaison LEN-capside



La mutation de résistance M66I entraîne

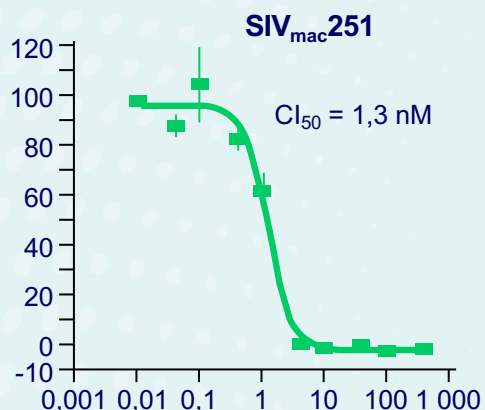
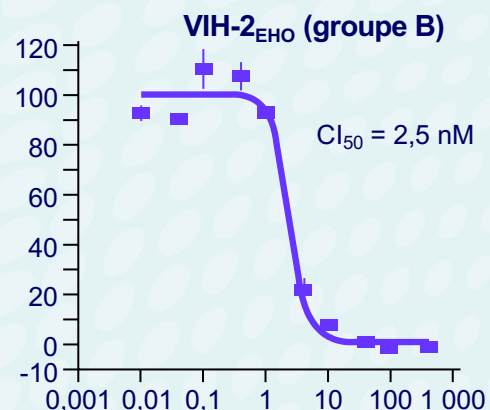
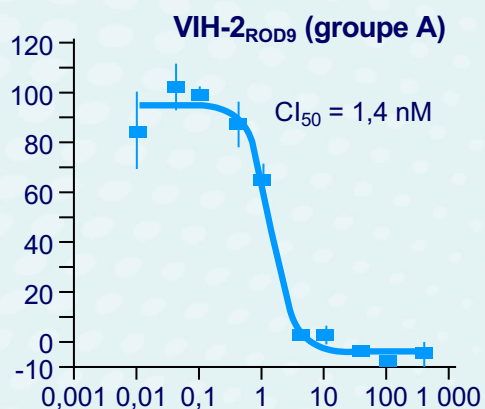
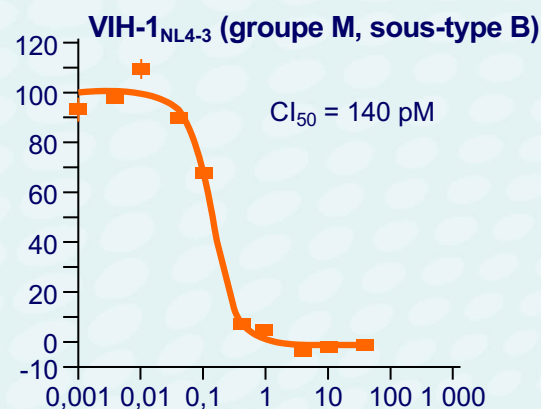
- un encombrement stérique empêchant la liaison de LEN
- une augmentation de la vitesse d'assemblage de la capside

Détermination de la sensibilité phénotypique du VIH-2 à LEN

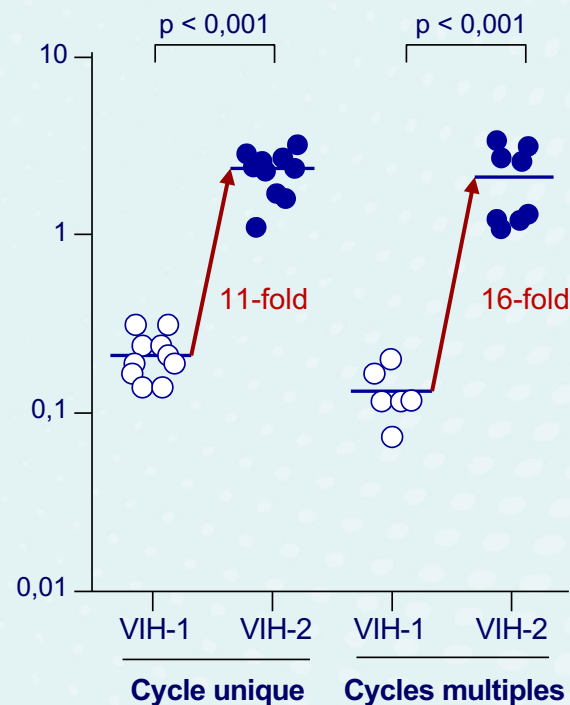
- Réalisation de tests phénotypiques en cycle unique et en cycles multiples d'infection
- 8 VIH-2 groupe A, 3 VIH-2 groupe B, SIVmac251 et 6 virus avec mutations INTI +/- INI

Courbes concentration-réponse VIH-2 à LEN (nM)

(cycle unique)



CI_{50} LEN (nM)



- Pas d'impact de la présence de mutations dans la TI ou IN sur la CI_{50} de LEN
- Efficacité in vitro de LEN sur VIH-2 réduite d'environ 10 à 15 fois par rapport à VIH-1
- Nécessité d'un suivi virologique régulier si un patient VIH-2 reçoit un traitement de sauvetage avec LEN

Essai CALIBRATE : phase 2 de LEN en 1^{ère} ligne

Résultats à S80 (3)

Analyse de la résistance

	Groupe 1 LEN oral/sc + FTC/TAF puis LEN sc + TAF (n = 52)	Groupe 2 LEN oral/sc + FTC/TAF puis LEN sc + BIC (n = 53)	Groupe 3 LEN oral qd + FTC/TAF (n = 52)	Groupe 4 BIC/FTC/TAF (n = 25)
Participants avec critère d'évaluation de la résistance*	2	1	3	1
Émergence de résistance à LEN	1 (Q67H + K70R)	1 (Q67H + K70R)	1 (Q67H + K70R)	0

* Tests génotypiques et phénotypiques réalisés si : (i) CV confirmée ≥ 50 c/ml et réduction CV $< 1 \log_{10}$ c/ml à S10, (ii) rebond ≥ 50 c/ml après obtention d'une CV < 50 c/ml, (iii) augmentation CV $> 1 \log_{10}$ c/ml par rapport au nadir de CV

- Emergence de résistance à LEN chez 3 des 157 participants sous LEN (2 %)
 - Mutations Q67H + K70R (FC LEN = 20) dans la capsid et M184M/I à **S10** chez 1 participant du groupe 2 (M184I et M184V détectées à S2 et S4)
Le profil d'émergence des mutations suggère une observance incomplète à FTC/TAF
 - Mutation Q67H (FC LEN = 7) à **S54** puis émergence de K70R chez 1 participant du groupe 3
Une inobservance vis à vis de TAF/FTC était documentée par décompte des comprimés et concentrations plasmatiques
 - Mutations Q67H + K70R à **S80** pour 1 participant du groupe 1

CAPELLA study: LEN resistance emergence at W104

- CAPELLA: 72 HTE with limited treatment options
- Virologic suppression with LEN + OBR in 82% of participants at W104

Emergent LEN Resistance, N (%)

	CAPELLA (N=72)
Participants meeting criteria for resistance testing (confirmed HIV RNA \geq 50 c/mL)	27 (38%)
Emergent LEN resistance	14 (19%)
• M661	6
• Q67H/K/N	8
• K70H/N/R/S	7
• N74D/H/S	3
• A105S/T	4
• T107A/C/N	3

- All 14 participants with emergent LEN resistance were at high risk for resistance (0 active drugs in OBR, N=4 ; inadequate adherence to OBR, N=10)
- 5/10 non adherent resuppressed without any treatment change
- 2/4 with no active drugs in OBR resuppressed with LEN + change in OBR

Resistance Analysis of Long-Acting Lenacapavir in Heavily Treatment-Experienced People with HIV after 104 Weeks of Treatment

Nicolas Margot, Vamshi Jogiraju, Laurie VanderVeen, Vidula Naik, Hadas Dvory-Sobol, Martin S. Rhee, and Christian Callebaut

Patient Clones and Site-Directed Mutants

#	Genotype			RC (%) ^a	LEN FC ^a	LEN FC MT-2 ^b
A.	M66I			0.6	>869.0	<i>Non-infectious</i>
B.	M66I	A105T		1.2	>869.0	<i>Non-infectious</i>
C.	M66I			1.5	>869.0	<i>Non-infectious</i>
D.	M66I	Q67H	K70R	3.1	>869.0	<i>Non-infectious</i>
E.	M66I			12.0	>869.0	<i>Non-infectious</i>
F.	M66I	T107S		24.0	>869.0	<i>Non-infectious</i>
G.	M66I	K70S		AF	AF	<i>Non-infectious</i>
H.	A105T			AF	AF	<i>Non-infectious</i>
I.	K70R			9.7	1.2	<i>Non-infectious</i>
J.	K70H			9.8	154.2	<i>Non-infectious</i>
K.	K70H			37	84.8	345
L.	K70S			AF	AF	<i>Non-infectious</i>
M.	N74D			49.0	17.0	42.4
N.	Q67H			58.0	4.8	7.7
O.	Q67H	K70R	T107S	109.0	46.3	45.3

Merci