Pr Vincent Calvez

Sorbonne University School of Medicine

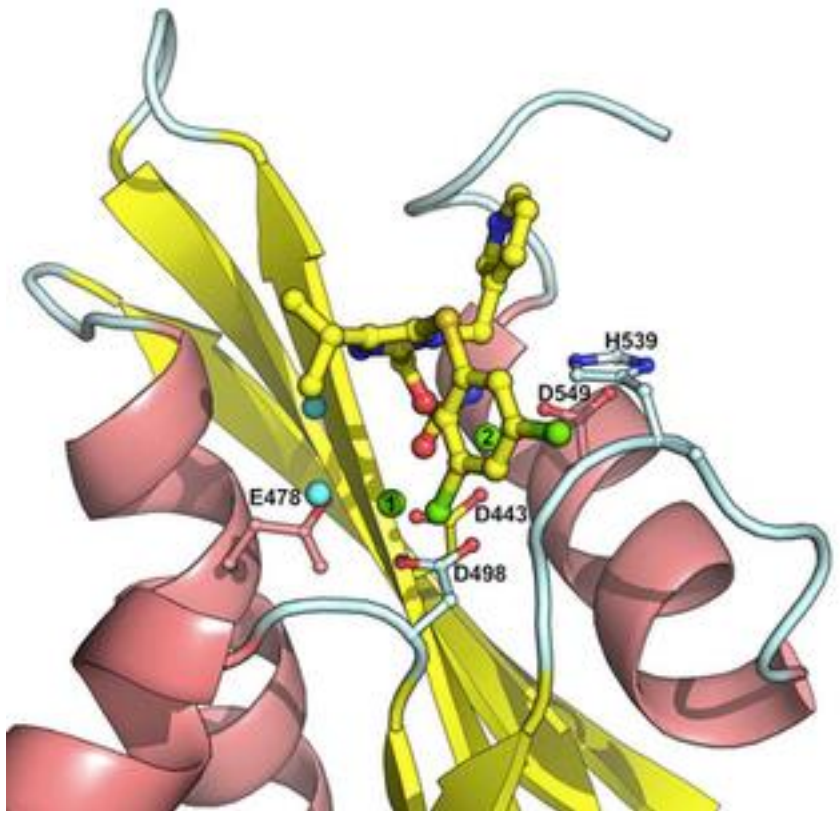
Sorbonne University - INSERM 1136 research Unit

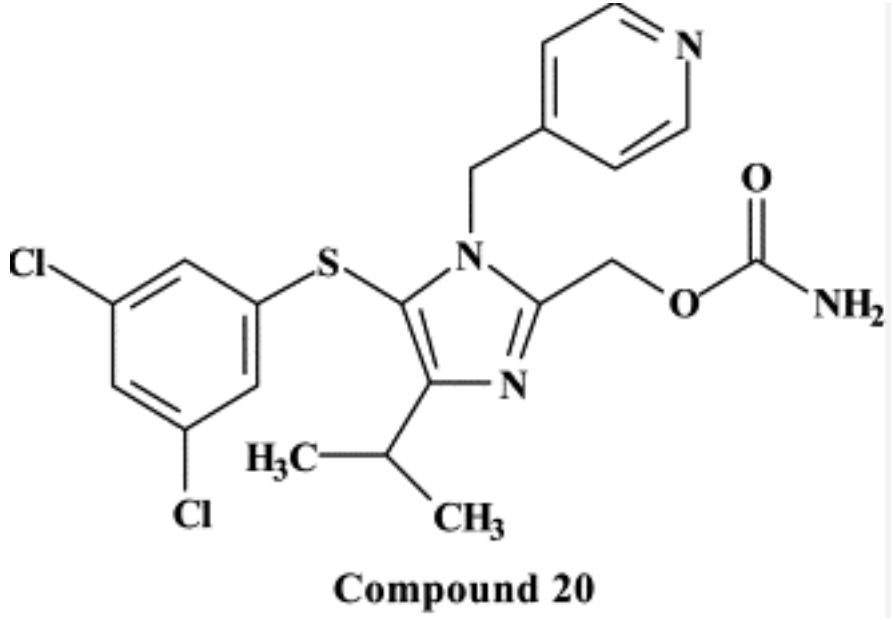
Department of Virology Pitié-Salpêtrière and Saint Antoine Hospitals, Paris, France

ANRS AC MIE (Clinical Virology and pharmacology network)

»Best NNRTI ever developed to treat HIV »

F Raffi, Conference on Retroviruses and Opportunistic Infections, Boston, Feb 2005





Compound 20

EUROPEAN MEETING ON HIV & HEPATITIS 2024
TREATMENT STRATEGIES & ANTIVIRAL DRUG RESISTANCE
BARCELONA, SPAIN | 22 - 24 MAY 2024

HIV Reverse Transcriptase M184V mutation induces a better innate immunity recognition

Elisa Teyssou, Isabelle Malet, Sophie Sayon, Adelie Gothland, Romain Palich, Valerie Pourcher, Cathia Soulie, Anne Geneviève Marcelin, Vincent Calvez.

Sorbonne University School of Medicine
Sorbonne University -INSERM 1136 research Unit
Virology and Infectious and trocipal diseases departments
Pitié-Salpêtrière Hospital
Paris, France
ANRS AC 43 (Clinical Virology)

M184V

M184V the best way to stay faithful
IDRW Sitges 2002

M184V for ever
EACS

Introduction

- **Background: M184V resistance mutation**

➢ Leads to 3TC/FTC and abacavir resistance. (Boucher et al., 1993 ; Tisdale et al., 1997)

➢ Has a major effect on the reverse transcriptase (RT) processivity and fidelity. (Back et al., 1996)

➢ Improves adaptive immune recognition by changing some T cell epitopes leading to a better recognition. (Samir et al., 2000 ; Vollbrecht et al., 2012)

➢ Cohort studies and clinical trials have also shown a positive effect of this mutation on clinical progression.

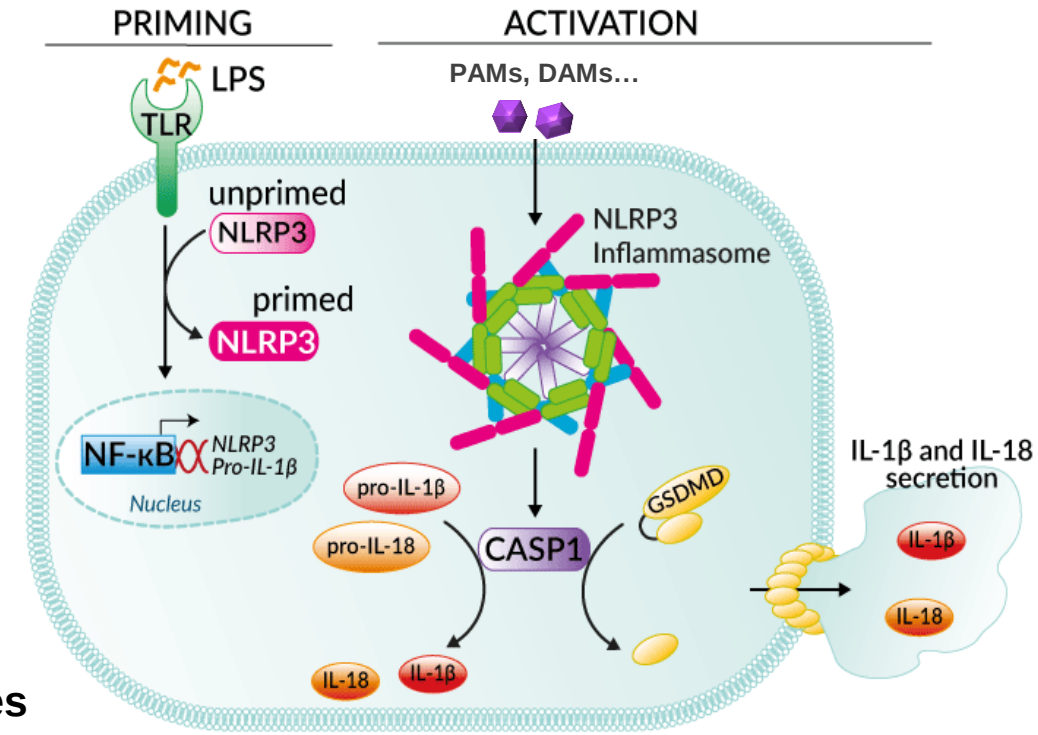
➢ **The objective of this study was to evaluate the effects of the M184V mutation on a part of the innate immunity**

Introduction

Inflammasomes

Major part of the innate immune system ➡ First line of defense against pathogens

- **Multiprotein complex composed of 3 major proteins :**
  - A cytoplasmic pattern recognition receptors (NLRP family)
  - An adaptor protein containing a caspase-recruitment domain (ASC)
  - A pro-caspase-1
- **Two-signal activation**
- **IL-1β and IL-18 major secreted cytokines**
- **Leads to pyroptosis = cell death**



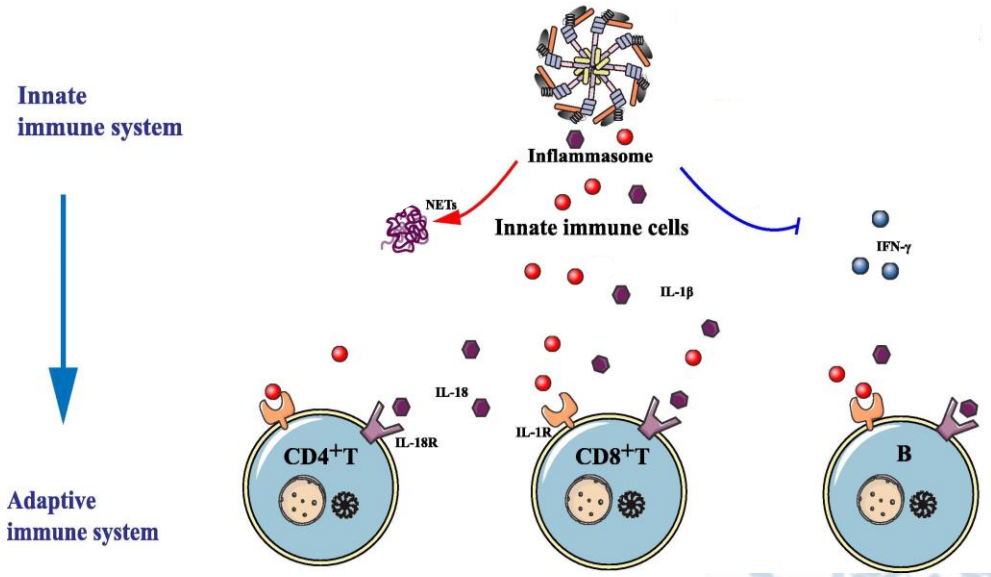
(From Invivogen)

Introduction

Inflammasomes

- **Cross-talk between innate and adaptive immune responses**

  - Inflammasome cytokines lead to immune cell infiltration and promote helper T-cell differentiation and B cells activation (Arbore et al., 2016)

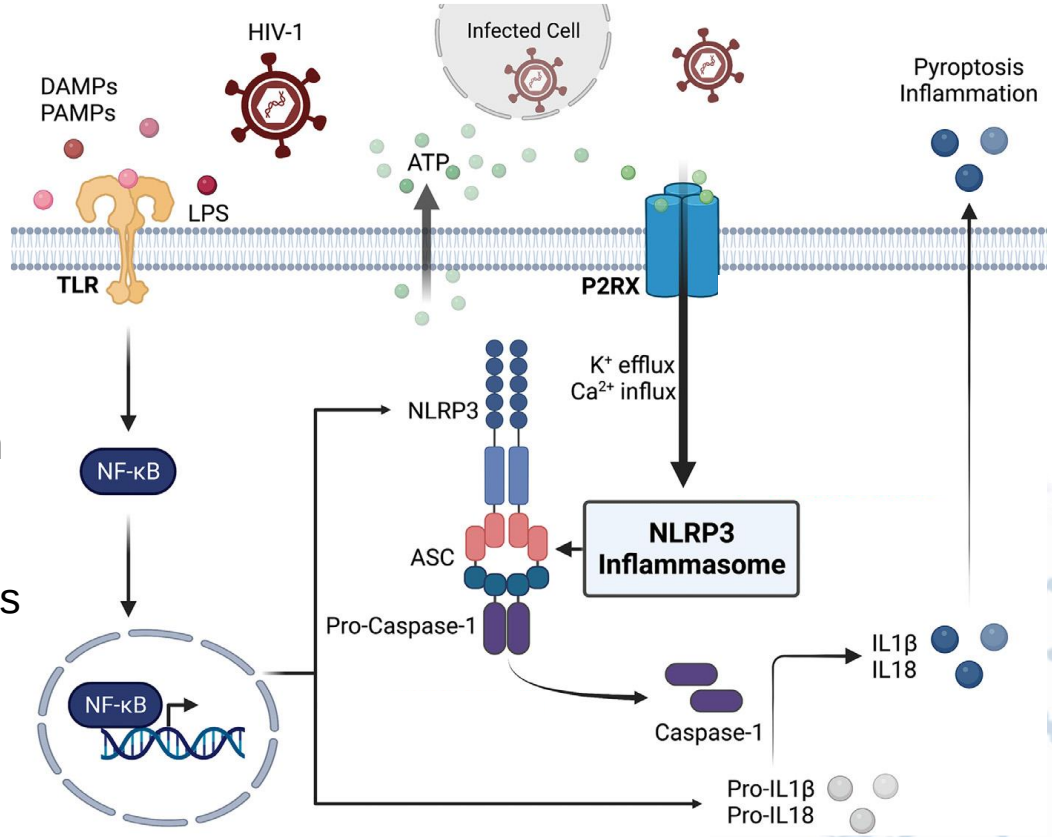


(From Zhang et al. 2023)

Introduction

Inflammasomes

- **HIV-1 infection leads to activation of NLRP3 which is the most studied inflammasome.**



(From Min et al., *Transl Res* 2023)

- IL-1β and IL-18 inhibit HIV-1 replication in PBMCs (Wang et al., 2016)
- Death of HIV-1 infected cells by pyroptosis

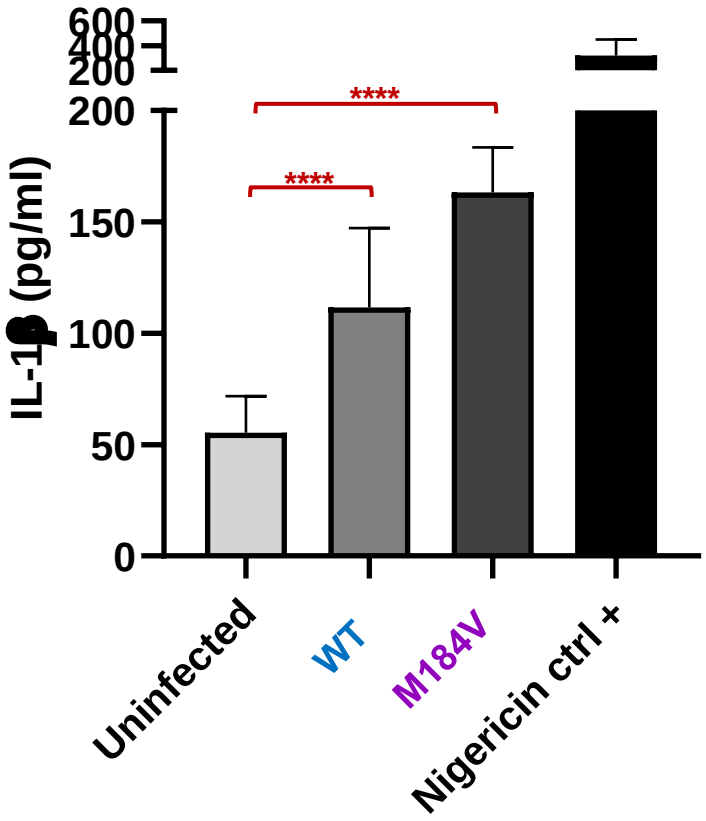
Objectives

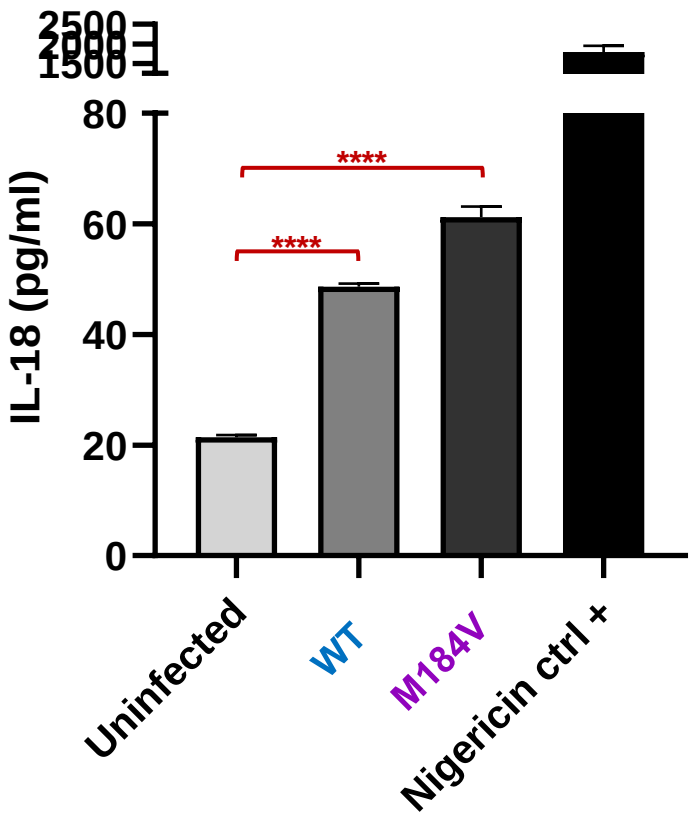
To assess the impact of M184V mutation on inflammasome activation

(From Min et al., *Transl Res* 2023)

Results

- Measure of inflammasome activation in infected cells

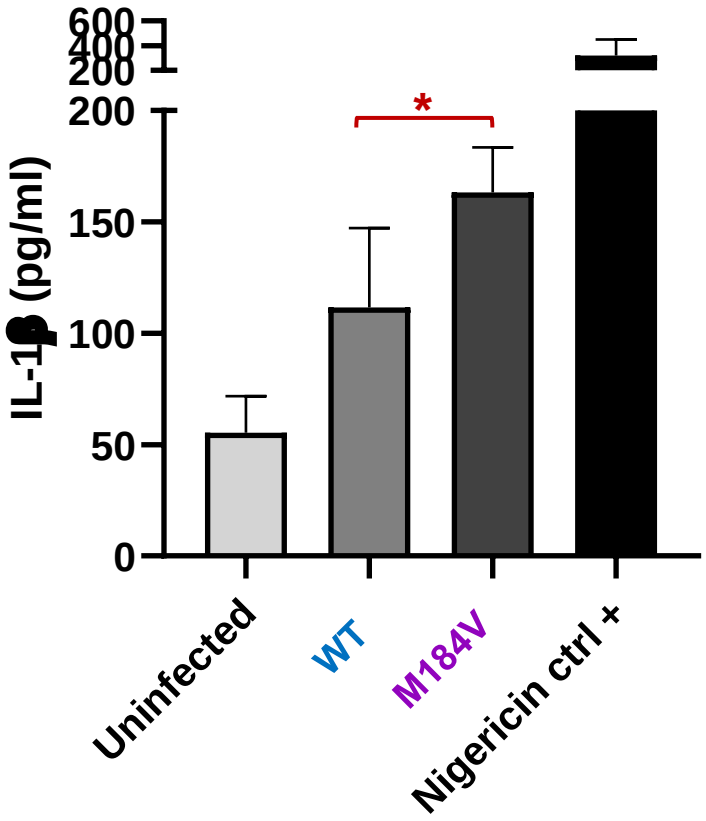


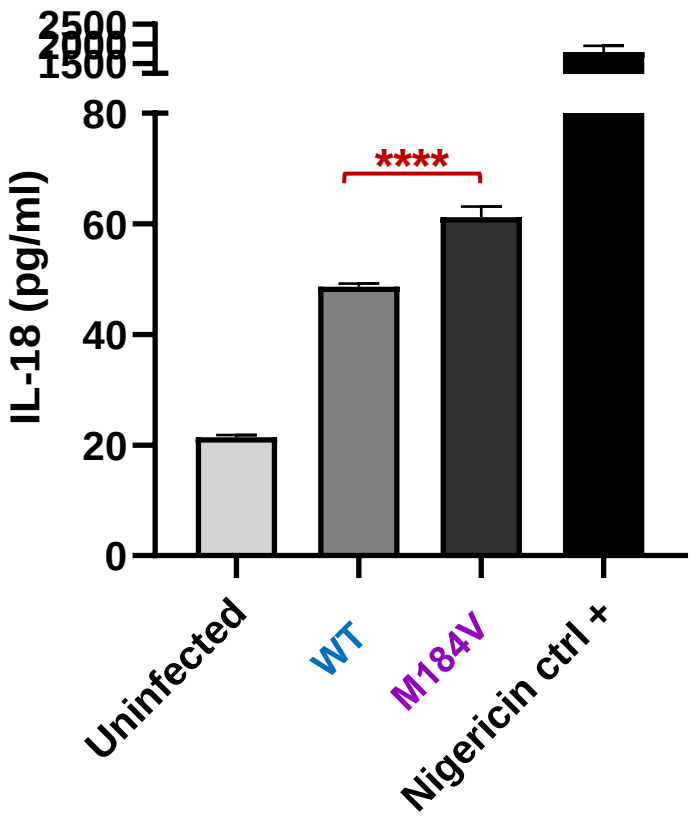


➢ **Increased of the IL-1β and IL-18 secretion by macrophages co-cultured with HIV-1 infected cells.**

Results

- Comparison of inflammasome activation in HIV-1 WT and M184V infected cells

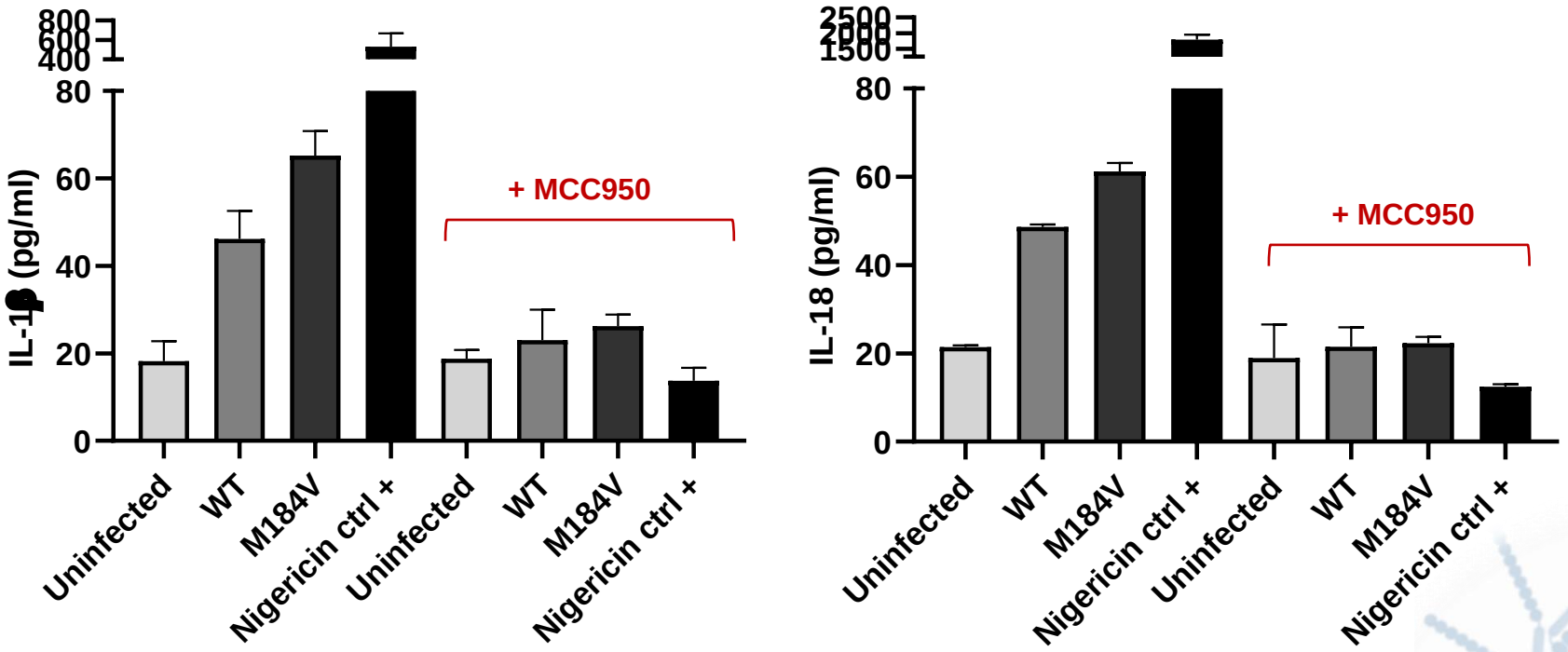




➢ **Stronger IL-1β and IL-18 secretion in cells co-cultured with M184V-infected cells compared to those with WT-infected cells.**

Results

- **Effects of NLRP3 inhibitor on IL-1β and IL-18 secretion**



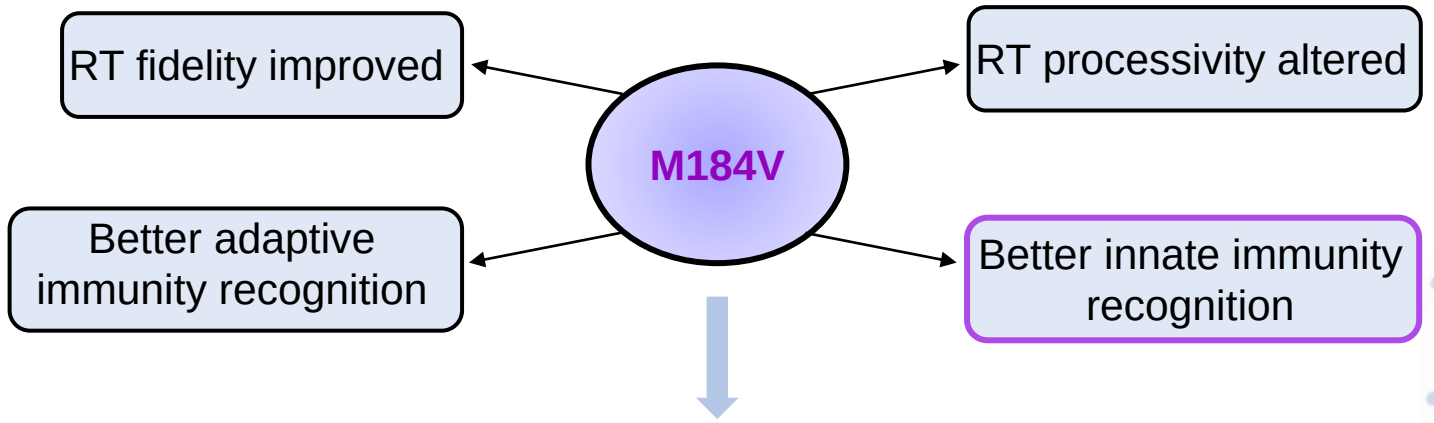
➢ **IL-1β and IL-18 secretion in cells co-cultured with HIV-1 infected cells were abolished by specific NLRP3 inhibitor (MCC950)**

Conclusions

- **NLRP3 Inflammasome activation is greater in macrophages co-cultured with M184V infected cells than in those with WT virus.**

This phenomenon, in addition to the known effects on RT and adaptive immunity, may be related to the attenuated behavior of M184V mutant viruses:

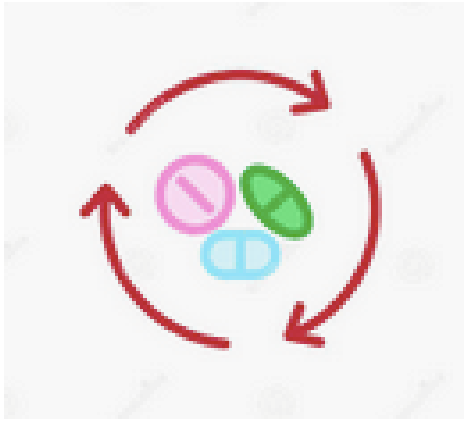
- Enhanced recognition by the innate immunity
- More pyroptosis of the HIV-1 infected cells

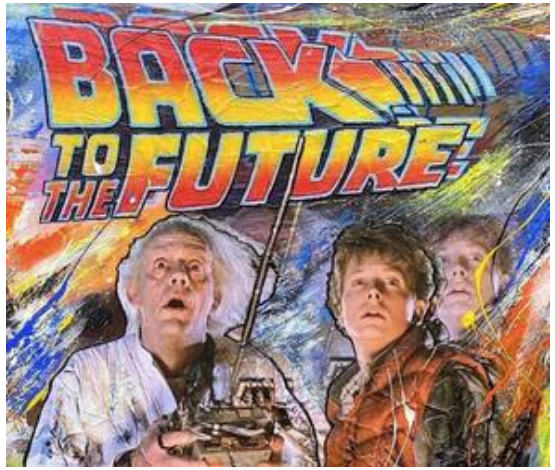


Positive impact on clinical progression

Antiretroviral resistance clearance

Time for recycling drugs ?





EUROPEAN MEETING ON HIV & HEPATITIS 2023
TREATMENT STRATEGIES & ANTIVIRAL DRUG RESISTANCE
ROME, ITALY | 7 - 9 JUNE 2023

Factors associated with M184V mutation clearance in the HIV reservoir over time

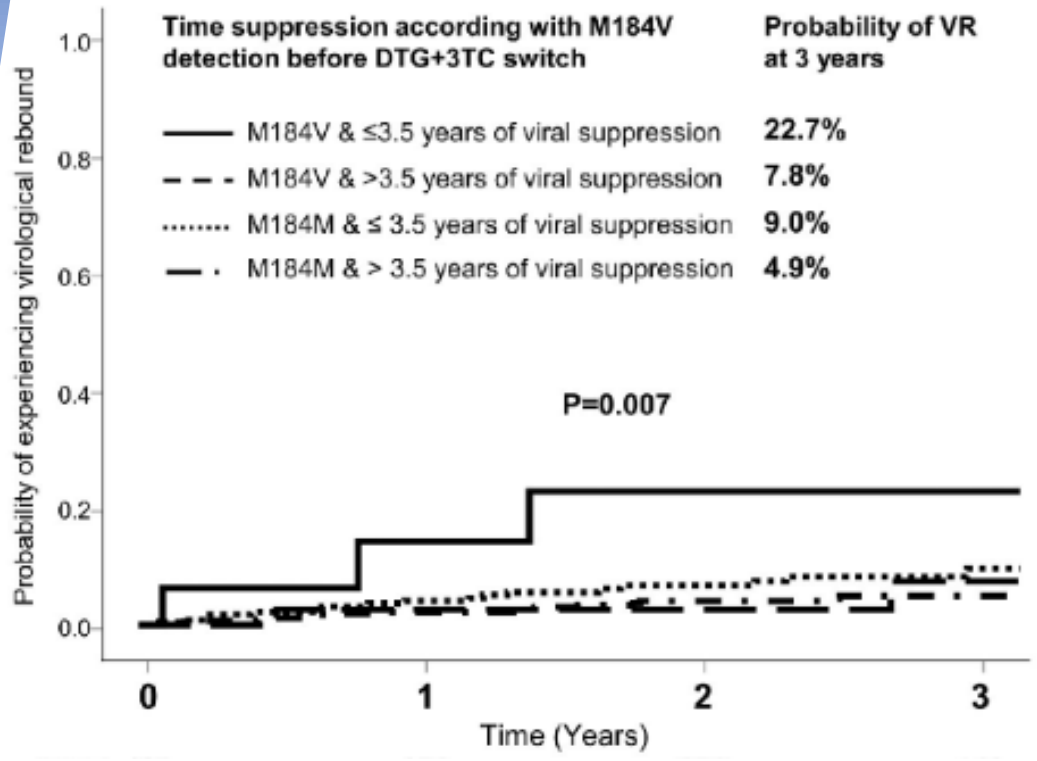
Elisa Teyssou, Cathia Soulie, Antoine Fauchois, Romain Palich, Agathe Nouchi, Sophie Sayon, Basma Abdi, Marc Wirden, Christine Katlama, Valerie Pourcher, Anne-Geneviève Marcelin, **Vincent Calvez**.

Sorbonne University School of Medicine
Sorbonne University -INSERM 1136 research Unit
Department of Virology
Pitié-Salpêtrière Hospital
Paris, France
ANRS AC 43 (Clinical Virology)

Introduction:
M184V disappearance: possible therapeutic impact

- Some retrospective studies evidenced that there is a time effect associated to a treatment success when DTG 3TC was used in switch in patients harboring the M184V mutation in the past

- LAMS RES studies showed that the detection of the M184V mutation
  - less than 3.5 years in the past was associated to a higher risk of virological failure
  - more than 3.5 years: not associated with more virological failure



- **Presence of past detected M184V <3.5 years significantly affects the probability of virological rebound and blips under DTG/3TC ART-line**

(M Santoro et al., JGAR 2022)

➢ Factors associated with the M184V clearance

	2% Univariate analysis			**5% Univariate analysis**	
Characteristic	OR [95% CI]	p value		OR [95% CI]	p value
CD4	0.907 [0.541-1.519]	0.709		0.882 [0.533-1.458]	0.624
FTC/3TC in the current regimen	1.554 [0.539-4.48]	0.414		1.318 [0.474-3.663]	0.597
Mono-Bi versus Tritherapies	0.74 [0.256-2.142]	0.579		0.764 [0.268-2.176]	0.615
Sex	2.741 [0.811-9.26]	0.105		2.595 [0.781-8.619]	0.12
CD4 Nadir	1.661 [1.004-2.749]	0.048		1.569 [0.962-2.559]	0.071
VL Zenit	0.4 [0.209-0.765]	0.006		0.398 [0.209-0.758]	0.005
	2% Multivariate analysis			**5% Multivariate analysis**	
Characteristic	OR [95% CI]	p value		OR [95% CI]	p value
Sex	1.125 [0.826-1.534]	0.455		1.119 [0.839-1.491]	0.445
CD4 Nadir	1.121 [0.909-1.382]	0.284		1.066 [0.876-1.297]	0.524
VL Zenith	0.842 [0.689-1.03]	0.094		0.82 [0.68-0.99]	0.039

Clearance of archived Integrase Stand Transfer Inhibitors resistance mutations in virologically suppressed people with HIV

Basma ABDI[1], Romain PALICH[2], Sophie SEANG[2], Antoine FAUCHOIS[1], Théophile COCHERIE[1], Antoine FAYCAL[2], Sophie SAYON[1], Elisa TEYSSOU[1], Sanaa SALIBA[2], Cathia SOULIE[1], Marc Antoine VALANTIN[2], Valérie POURCHER[2] Christine KATLAMA[2], Vincent CALVEZ[1], Anne-Geneviève MARCELIN[1], Marc WIRDEN[1]

[1]Laboratory of Virology, [2]Infectious diseases department Pitié Salpêtrière Hospital

Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique (IPLESP UMRS 1136)

Paris, France.

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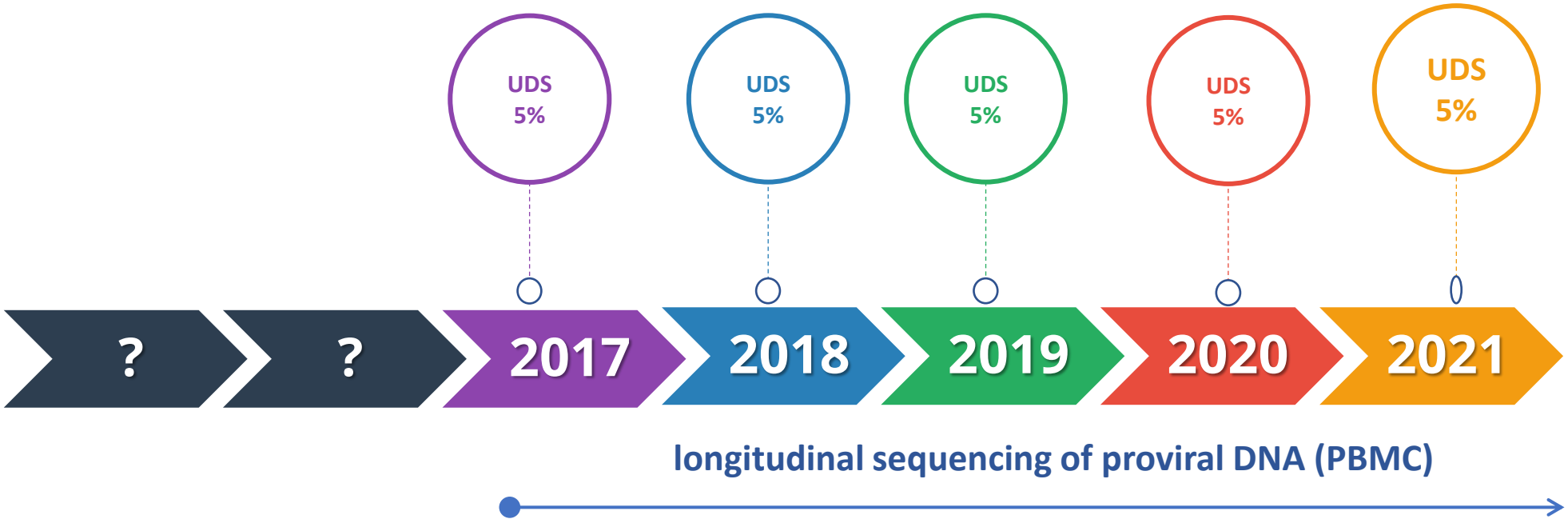
Methods (1/2)

✓ **Retrospective study, monocentric (patients followed up in the department of infectious diseases at Pitié-Salpétrière Hospital, Paris, France).**

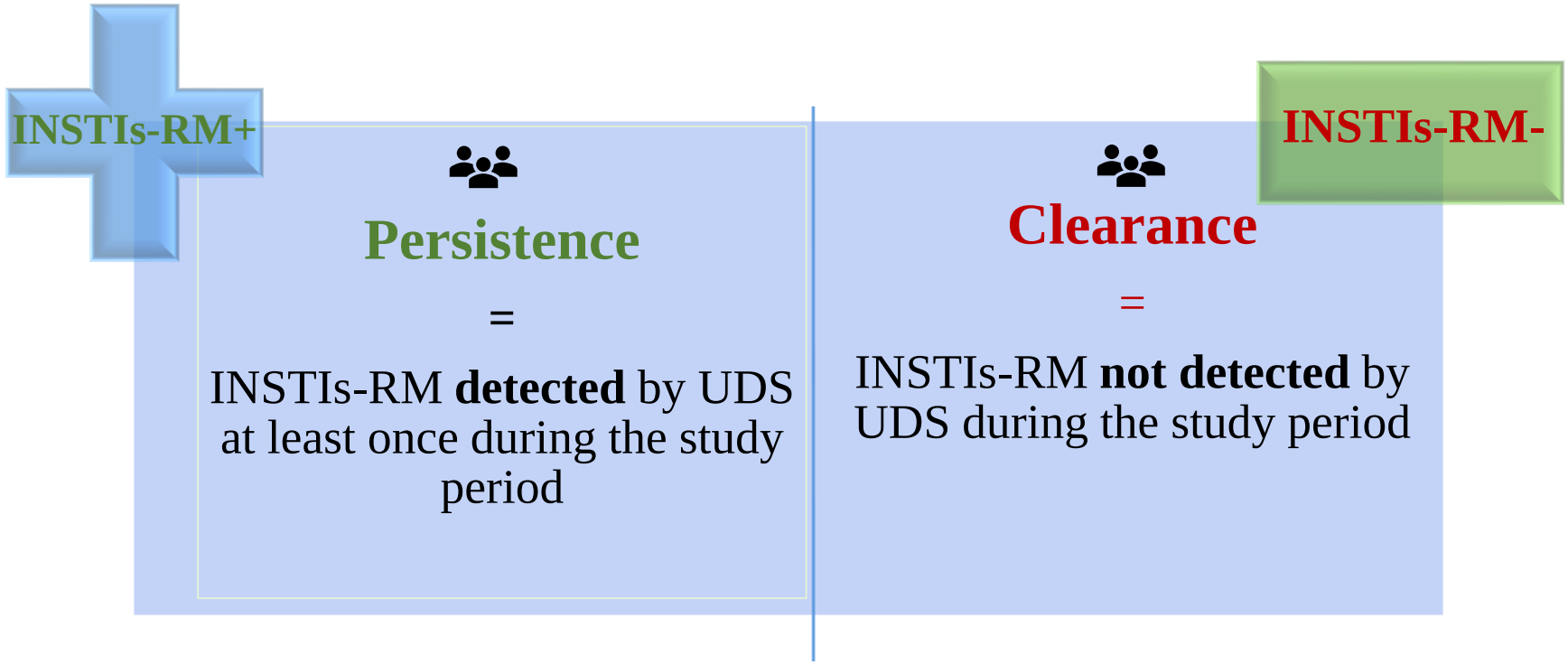
- **Patients with prior VF of INSTIs-based regimen.**
- **INSTIs-RM identified at least once in a previous RNA genotype resistance test.**
- **Plasma HIV-RNA viral load ≤ 20 copies/mL <u>for at least 5 years</u>.**



✓ **Participants' characteristics and HIV medical history were collected at the time of the last available blood sample at inclusion.**

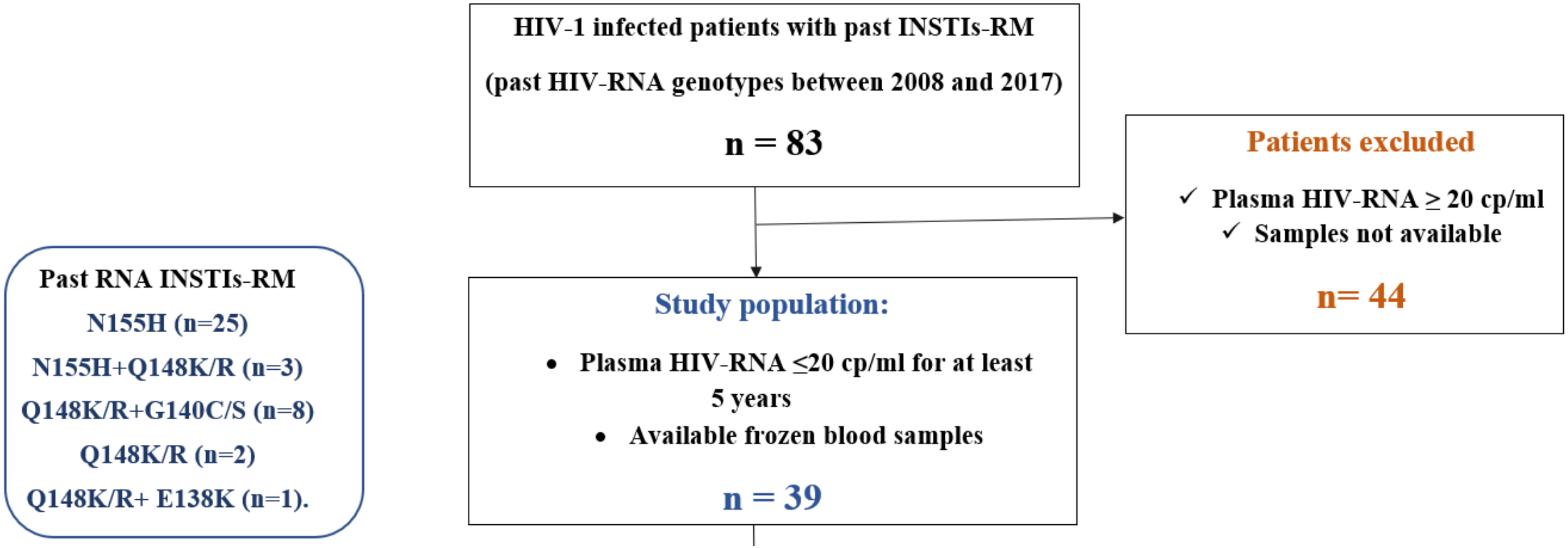
Methods (2/2)

- ✓ **We defined two groups of participants according to INSTIs-RM detection in HIV-DNA between 2017-2021:**

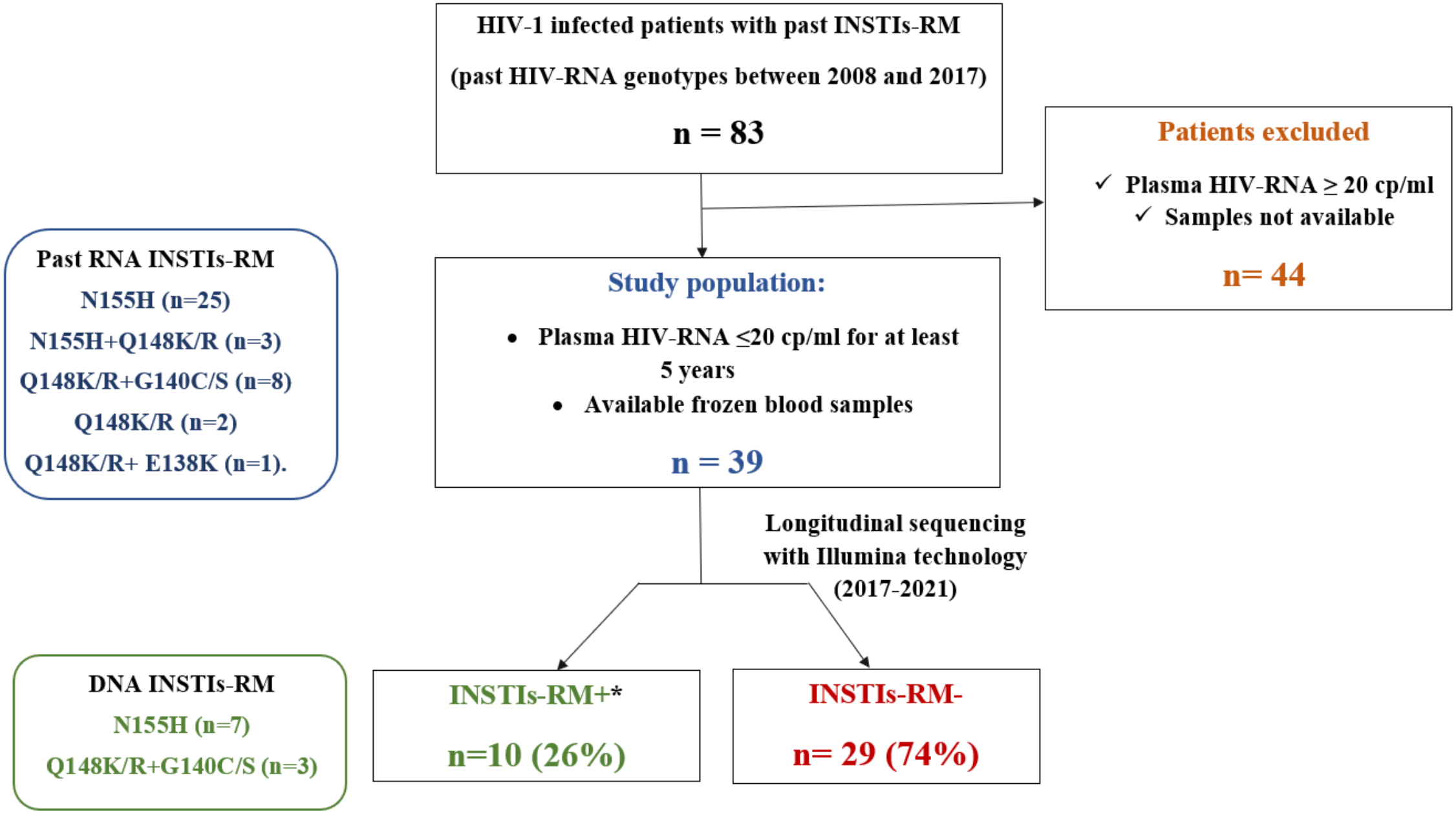


- ✓ **We used the Mann–Whitney test and the Chi2 test for comparison between the two participants' groups.**
- ✓ **We used univariable and multivariable models to identify immune-virological factors associated with the persistence/clearance of INSTIs-RM during time.**

Results (1/4): **Study flowchart**



Results (1/4): **Study flowchart**



*same INSTIs-RM detected in the past

Results (3/4): **Univariable Analysis**

Characteristics	INSTIs-RM- n= 29 (74%)	INSTIs-RM+ n = 10 (26%)	P value
Gender, n (%) Male	21 (72.42)	8 (80)	0.636
Age, years, median (IQR)	58 (55-65)	55 (53-62)	0.221
Time on ART, year, median (IQR)	26 (25-29)	23 (19-26)	0.100
Time to undetectable HIV-RNA , year, median	7.38 (6.17-10.55)	7.30 (5.84-9.88)	0.872
Zenith HIV-RNA viral load ,log_{10} copies/mL,median (IQR)	5.07 (3.99-5.49)	5.56 (5.08-6.00)	0.038
HIV subtype B, n (%)	27.00 (93.10)	10.00 (100.00)	0.695
CD4 nadir, cells/mm^3 ,median (IQR)	147 (78-235)	56 (6-138)	0.097
Last CD4 cells/mm^3, median (IQR)	642 (399-821)	403 (238-616)	0.036
Past INSTIs EVG RAL	 2.00 (6.90) 27.00 (93.10)	 0.00 (0.00) 10.00 (100.00)	0.394
Duration of viral replication under INSTIs, week; median (IQR)	10.57 (3.42-22.14)	32 (6.30-71.43)	0.038
Mean HIV-RNA during viral replication under INSTIs, log10 copies/mL, median (IQR)	2.90 (2.67-3.55)	4.11 (3.40-5.10)	0.007
Time since the last detection of INSTIs-RM, year, median (IQR)	10 (7.00-12.00)	8.00 (7.00-12.00)	0.584
INSTIs as part of ongoing ART, n (%)	13.00 (44.82)	6 .00 (60.00)	0.408

Results (4/4): **Multivariable analysis**

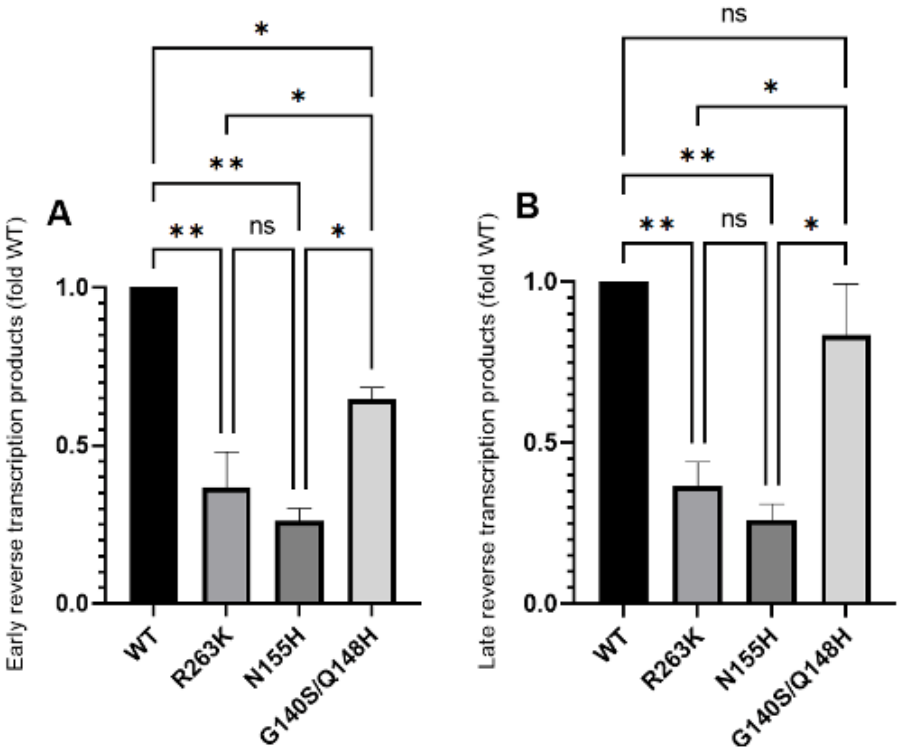
Characteristics	Univariable		Multivariable	
	OR (95%)	P value	OR (95%)	P value
Zenith HIV-RNA VL ,log_{10} copies/mL	1.00 (1.00- 1.00)	0.943		
CD4 nadir, cells/mm^3	1.00 (0.99- 1.03)	0.205		
Last CD4 cells/mm^3	0.99 (0.99- 1.00)	0.344		
Mean HIV-RNA during viral replication under INSTIs, log10 copies/ml	14.97 (1.35- 165.53)	0.027	8.26 (1.46- 46.59)	0.017
Duration of viral replication under INSTIs, (week)	1.07 (1.00- 1.16)	0.041	1.05 (1.00- 1.11)	0.024

- **The duration of viral replication** and **the level of HIV-RNA** during previous INSTIs regimens failure were significantly associated with persistence of INSTIs-RM.

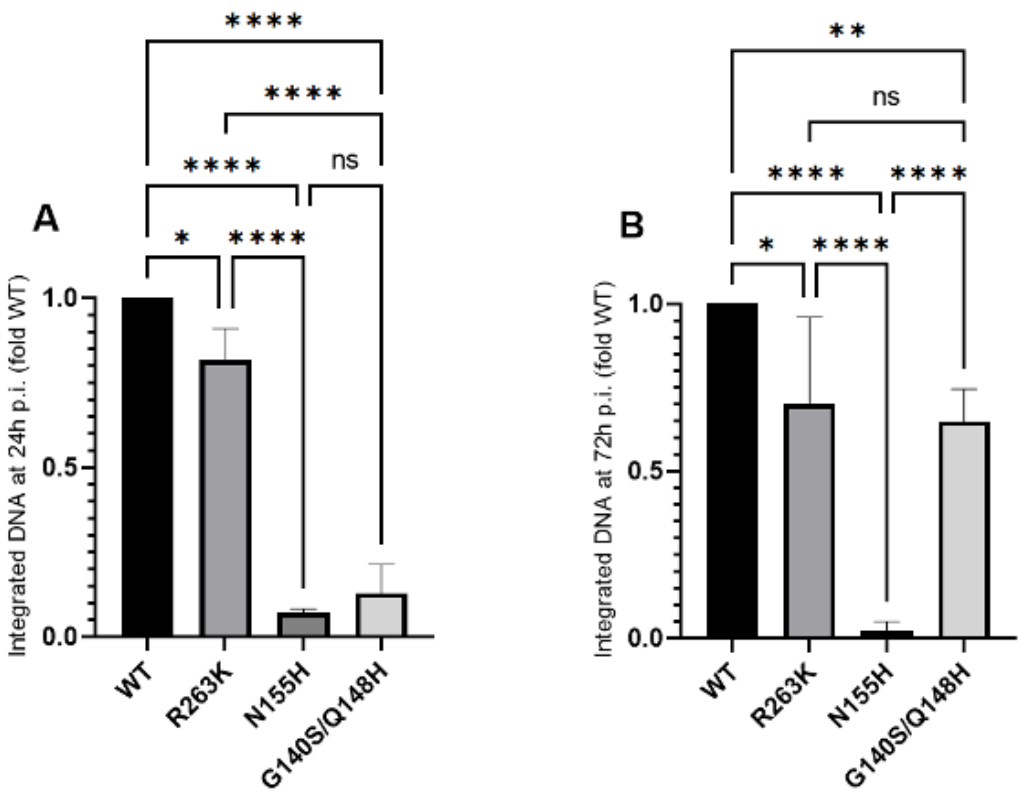
HIV-1 resistance mutations to integrase inhibitors impairboth integration and reverse transcription steps

Pauline Ratouit, Isabelle Malet , Cathia Soulie, Jerome Denis, Ronan Legrand, Elisa Teyssou ,
Anne-Genevieve Marcelin, Vincent Calvez & Vincent Guiraud, *Int J Antimicrob Agents. 2023 Nov*

Vincent Calvez, Pauline Ratouit, Vincent Guiraud , Isabelle Malet , Cathia Soulie, Jerome Denis, Ronan Legrand,
Elisa Teyssou, Anne-Genevieve Marcelin, *CROI Denver 2024*



Impact of INIr mutations on reverse transcription

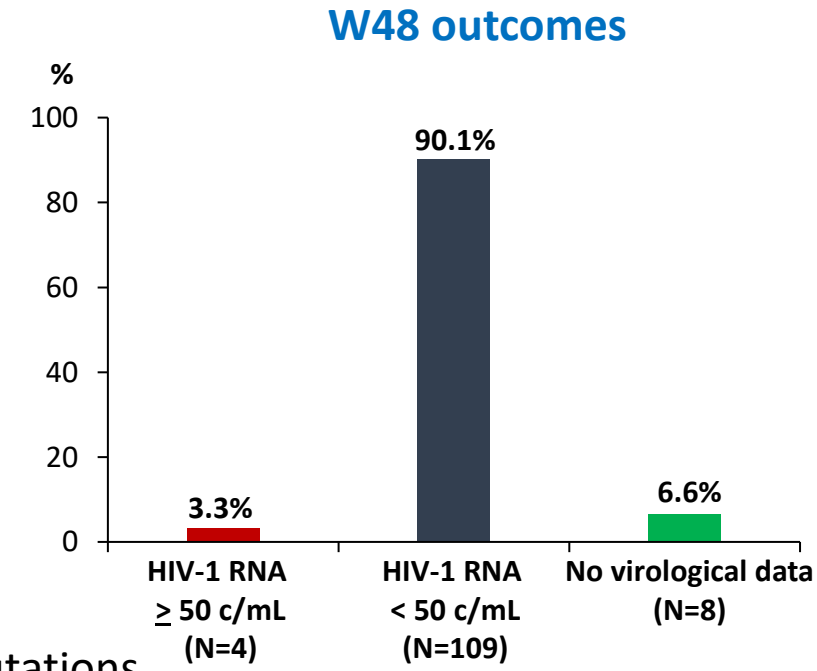


Impact of INIr mutations on integration

Pr V Calvez

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/mm^3
  - Sanger proviral DNA sequencing at screening without 3TC resistance mutations
- Primary endpoint: % HIV RNA ≥ 50 c/mL at W48 (ITT-e, FDA snapshot)
- 121 patients enrolled



Absence d'impact des mutations M184V/I minoritaires dans le maintien de la suppression sous DTG/3TC

- **Sous-étude de l'essai VOLVER** qui avait montré une efficacité > 90 % en switch pour DTG/3TC en cas d'antécédents de résistance confirmée à 3TC mais avec absence de mutation de résistance sur le génotype ADN Sanger avant le switch chez 121 patients *(De Miguel, EACS 2023)*

Mutations minoritaires archivées sur le génotype ADN NGS (seuil : 5 %) sur 107 prélèvements disponibles avant switch et impact sur le contrôle virologique à S48

Génotype ADN NGS avant switch pour DTG/3TC	% sur les 107 prélèvements	CV > 50 c/ml à S48
Absence de mutation	71 %	2,6 %
Mutations M184V/I *	19,6 %	0 %
Mutations M184V	16,8 %	
Mutations M184I	2,8 %	
Autres mutations sur TI (K65R : 1, TAMS : 5, autres : 4)	9,4 %	20 %

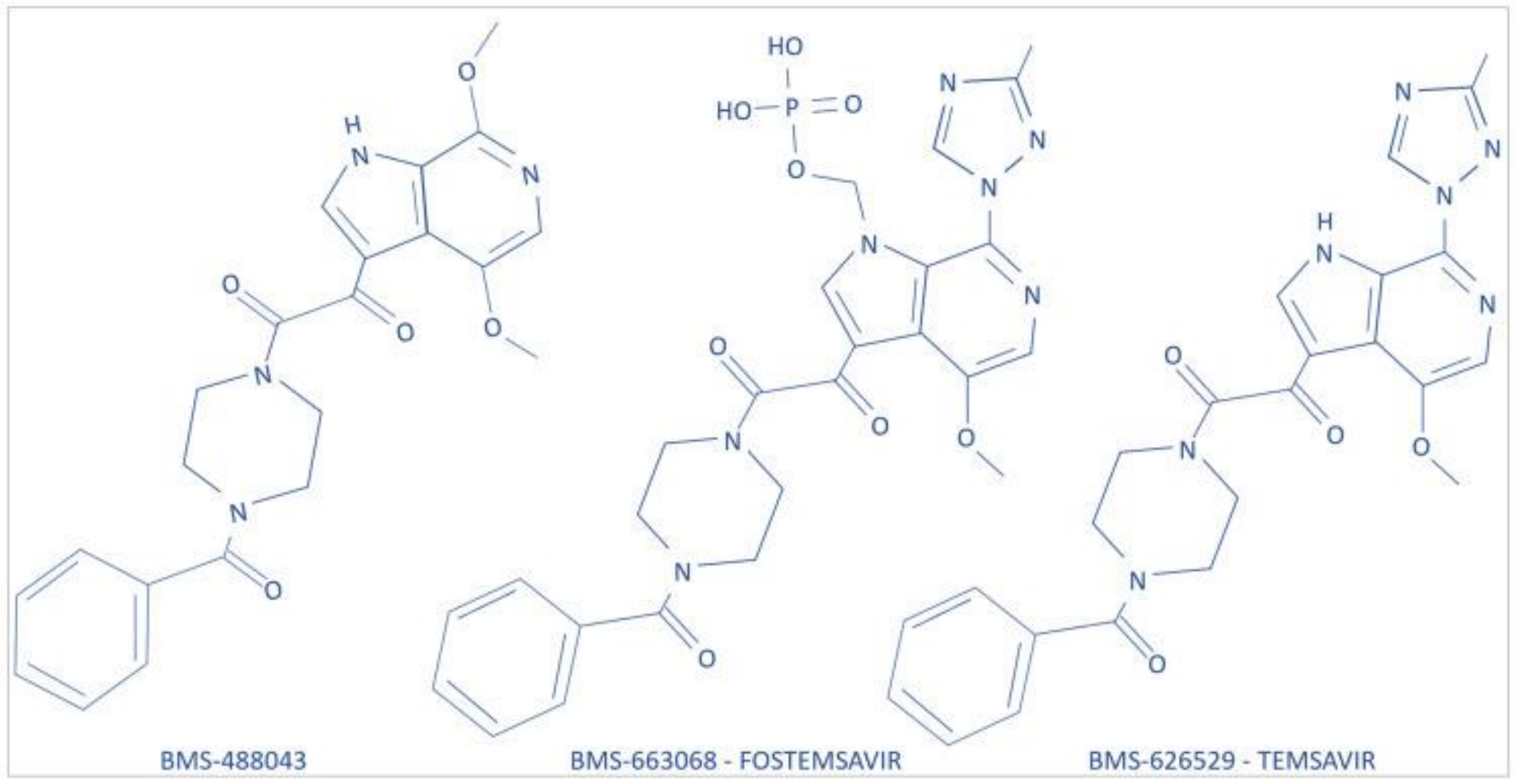
* % médian de la population virale M184V/I : 29 % (extrême : 8-51)

- **Blips** chez les 103 participants avec une CV < 50 c/ml à S48 et un génotype NGS disponible à J0 : 1/21 (4,8 %) participants avec M184V/I sur génotype NGS à J0 vs 9/74 (12,2 %) participants sans cette mutation

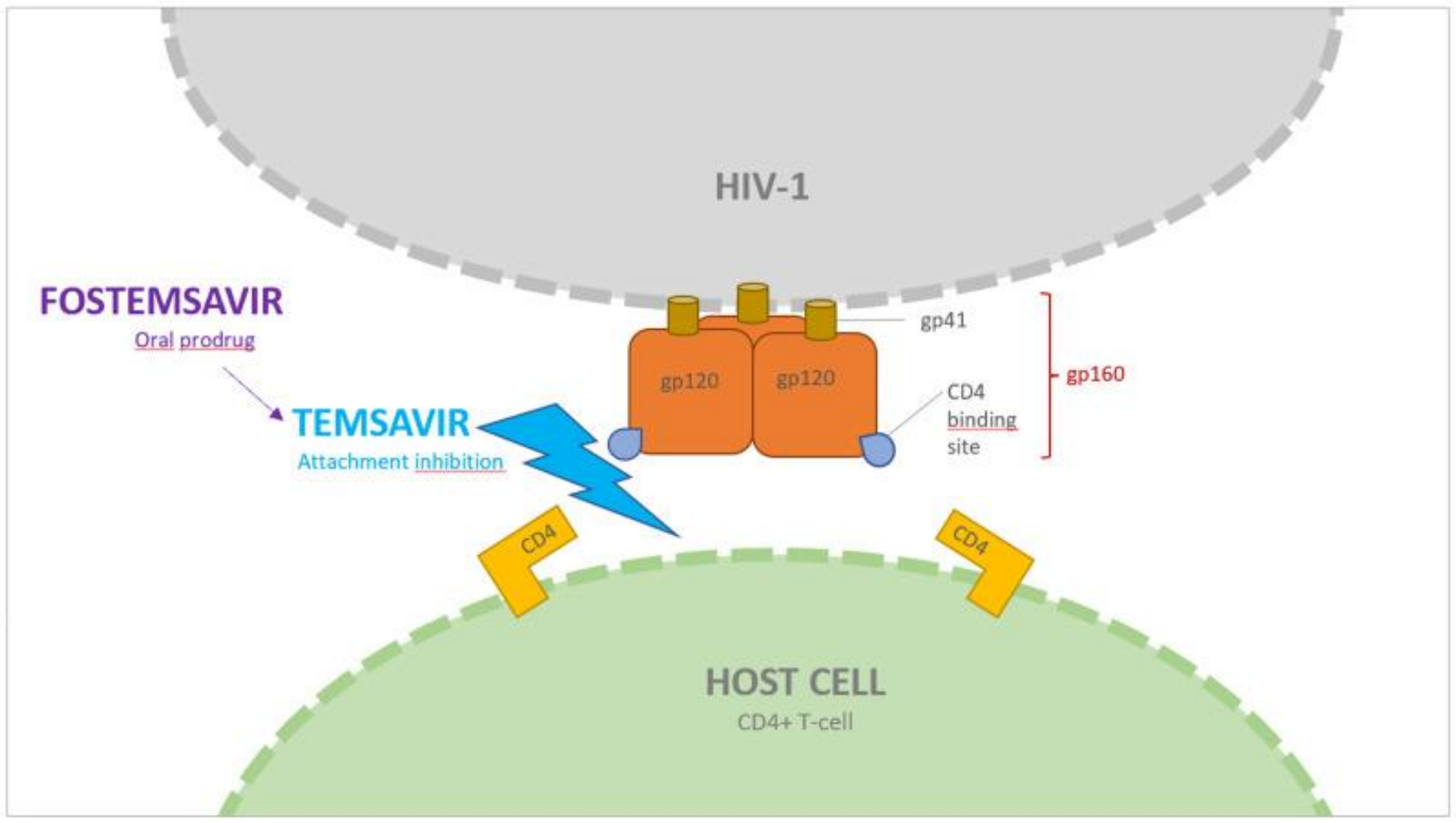
- **Conclusion :** devant l'absence d'impact des mutation M184V/I minoritaires, la réalisation d'un génotype NGS dans le but de guider un switch vers DTG/3TC n'apparait pas utile

De Miguel R, CROI 2024, Abs. 693

Fostemsavir

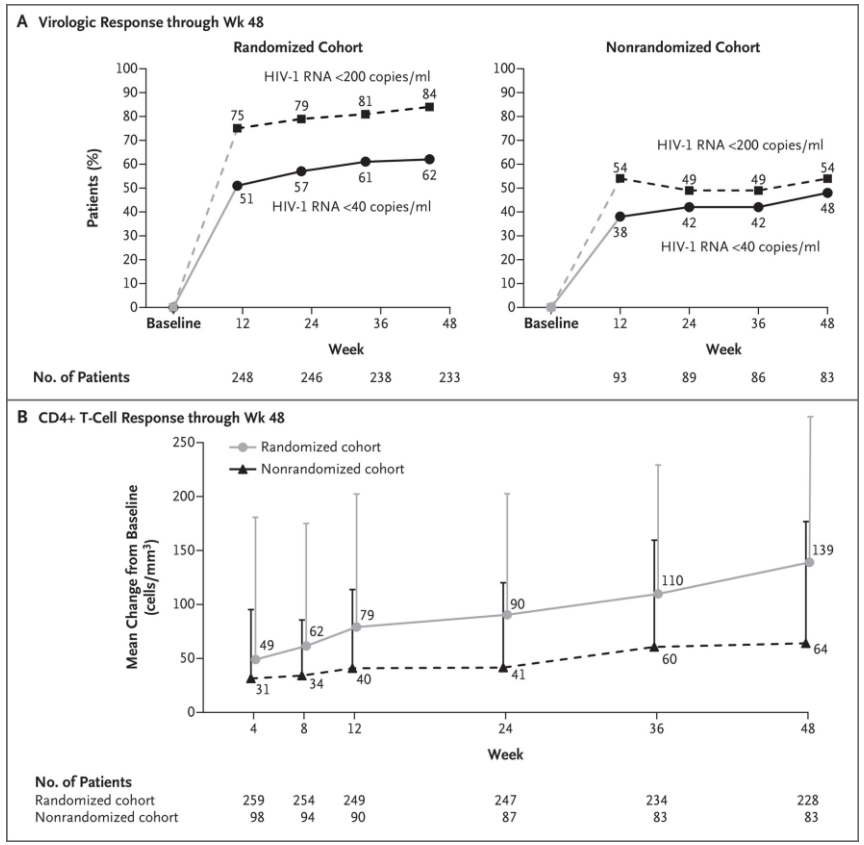


Fostemsavir



Fostemsavir in Adults with Multidrug-Resistant HIV-1 Infection

Michael Kozal, M.D., Judith Aberg, M.D., Gilles Pialoux, M.D., Pedro Cahn, M.D., Melanie Thompson, M.D., Jean-Michel Molina, M.D., Beatriz Grinsztejn, M.D., Ricardo Diaz, M.D., Antonella Castagna, M.D., Princy Kumar, M.D., Gulam Latiff, M.D., Edwin DeJesus, M.D., Mark Gummel, M.S., Margaret Gartland, M.Sc., Amy Pierce, B.S., Peter Ackerman, M.D., Cyril Llamoso, M.D., and Max Lataillade, D.O., for the BRIGHTE Trial Team*



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- **Randomized cohort:**
  - **<u>in 43 %</u>** of failing patients gp120 substitutions occurred during treatment at one or more of the 4 amino acid positions that have been associated with reduced phenotypic susceptibility to temsavir
  - S375N andM426L were the most frequent
  - Median IC 50 increase: 2.3 fold change

- **Nonrandomized cohort**:
  - **<u>in 70%</u>** of failing patients gp120 substitutions occurred
  - Median IC 50 increase: 470 fold change

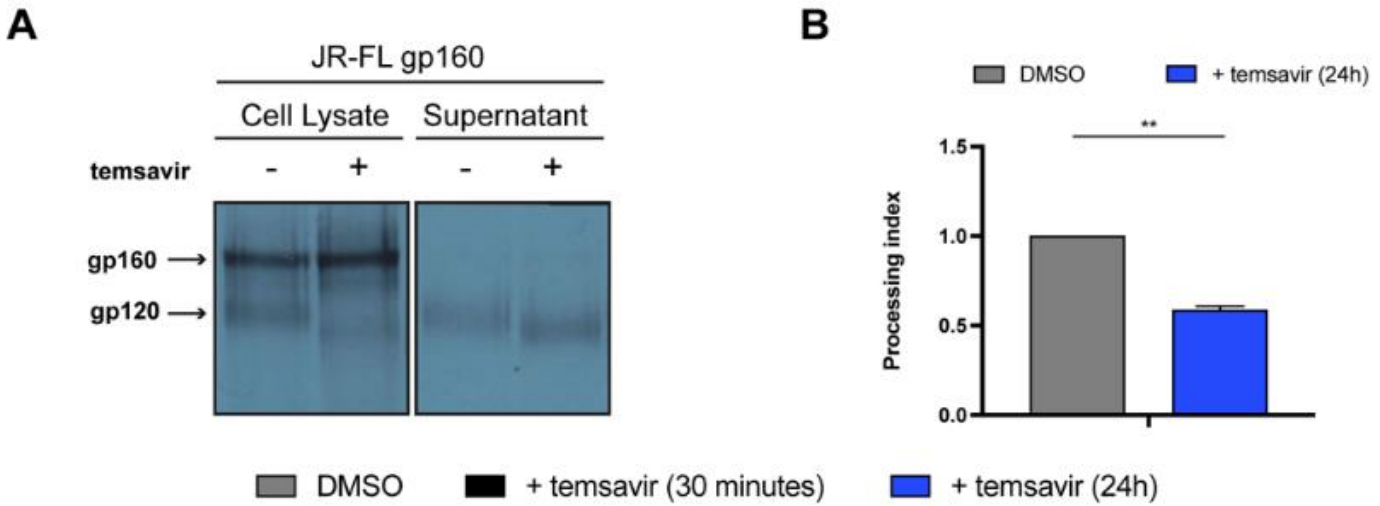
Table S13. Summary of Emergent Viral Genotypic Substitutions of Interest in the gp12
Domain – Protocol-Defined Virologic Failure at Week 48

n (%)*	Randomized Cohort† (N=49)	Non-randomized Cohort (N=46)	Total (N=95)
Sequenced	47 (96)	46 (100)	93 (98)
Substitutions of interest in gp120‡	20 (43)	32 (70)	52 (56)
S375	14 (30)	22 (48)	36 (39)
S375H	0	1 (2)	1 (1)
S375H/N	1 (2)	1 (2)	2 (2)
S375M	0	3 (7)	3 (3)
S375N	7 (15)	8 (17)	15 (16)
S375N/T	1 (2)	2 (4)	3 (3)
S375S/I	0	1 (2)	1 (1)
S375S/M/T	1 (2)	0	1 (1)
S375S/N	3 (6)	6 (13)	9 (10)
S375S/T	1 (2)	0	1 (1)
M426	13 (28)	20 (43)	33 (35)
M426L	8 (17)	12 (26)	20 (22)
M426M/L	6 (13)	8 (17)	14 (15)
M434	4 (9)	4 (9)	8 (9)
M434I	1 (2)	1 (2)	2 (2)
M434M/I	3 (6)	3 (7)	6 (6)
M434M/I/T	1 (2)	0	1 (1)
M475	5 (11)	5 (11)	10 (11)
M475I	4 (9)	1 (2)	5 (5)
M475M/I	1 (2)	4 (9)	5 (5)

Temsavir Treatment of HIV-1-Infected Cells Decreases Envelope Glycoprotein Recognition by Broadly Neutralizing Antibodies

Marianne Boutin,[a,b] Dani Vézina,[a] Shilei Ding,[a] Jérémie Prévost,[a,b] Annemarie Laumaea,[a,b] Lorie Marchitto,[a,b] Sai Priya Anand,[c] Halima Medjahed,[a] Gabrielle Gendron-Lepage,[a] Catherine Bourassa,[a] Guillaume Goyette,[a] Andrew Clark,[d] Jonathan Richard,[a,b] Andrés Finzi[a,b,c]

- Temsavir impacts Env glycosylation and **processing**
- **Could alter** the capacity of several bNAbs to recognize Env present on virions and HIV-1-infected cells.
- Temsavir could **reduce** the capacity of bNAbs to eliminate HIV-1-infected cells by anti-body-dependent cellular cytotoxicity (ADCC)



Resistance to second generation of INIs

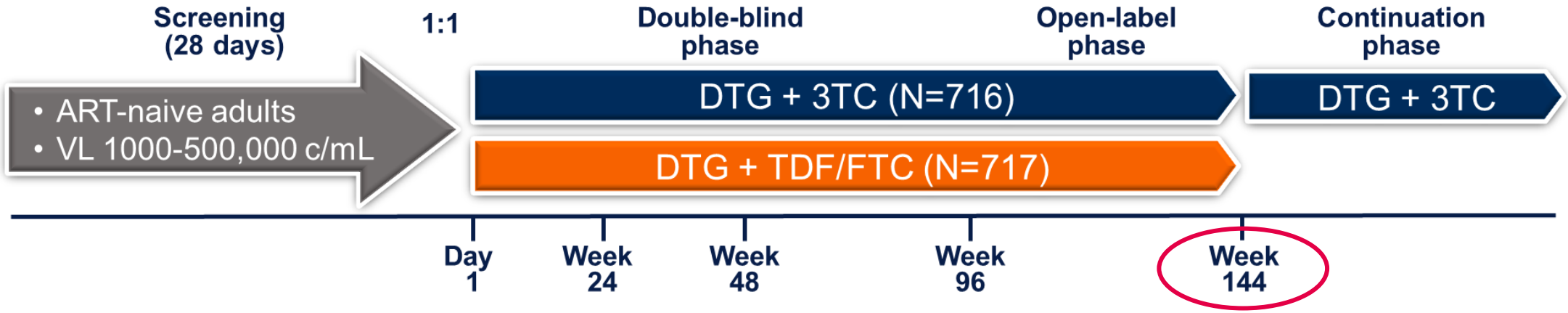
DURABLE EFFICACY OF DTG + 3TC IN GEMINI-1&-2: YEAR 3 SUBGROUP ANALYSES

Chloe Orkin,[1] Norma Porteiro,[2] Mezgebe Berhe,[3] Robin Dretler,[4] Federico Pulido,[5] Shu-Hsing Cheng,[6] Cristiana Oprea,[7] Margaret Johnson,[8] Svetlana Kizhlo,[9] Jörg Sievers,[10] Choy Man,[11] Rimgaile Urbaityte,[12] Mark Underwood,[11] Brian Wynne,[11] Jean van Wyk[10]

[1]Queen Mary University, London, UK; [2]Fundacion IDEAA, Buenos Aires, Argentina; [3]Texas Infectious Diseases Consultants, Dallas, TX, USA; [4]Infectious Disease Specialists of Atlanta, Decatur, GA, USA; [5]Hospital Universitario 12 de Octubre, Madrid, Spain; [6]School of Public Health, Taipei Medical University, Taipei, Taiwan; [7]Carol Davila University of Medicine and Pharmacy Bucharest (at nr 7), Dr. Victor Babes Clinical Hospital for Infectious and Tropical Diseases, Bucharest, Romania; [8]Royal Free Hospital, London, UK; [9]Centre for Prevention and Control of AIDS and Infectious Diseases, St Petersburg, Russia; [10]ViiV Healthcare, Brentford, UK; [11]ViiV Healthcare, Research Triangle Park, NC, USA; [12]GlaxoSmithKline, Stockley Park, UK

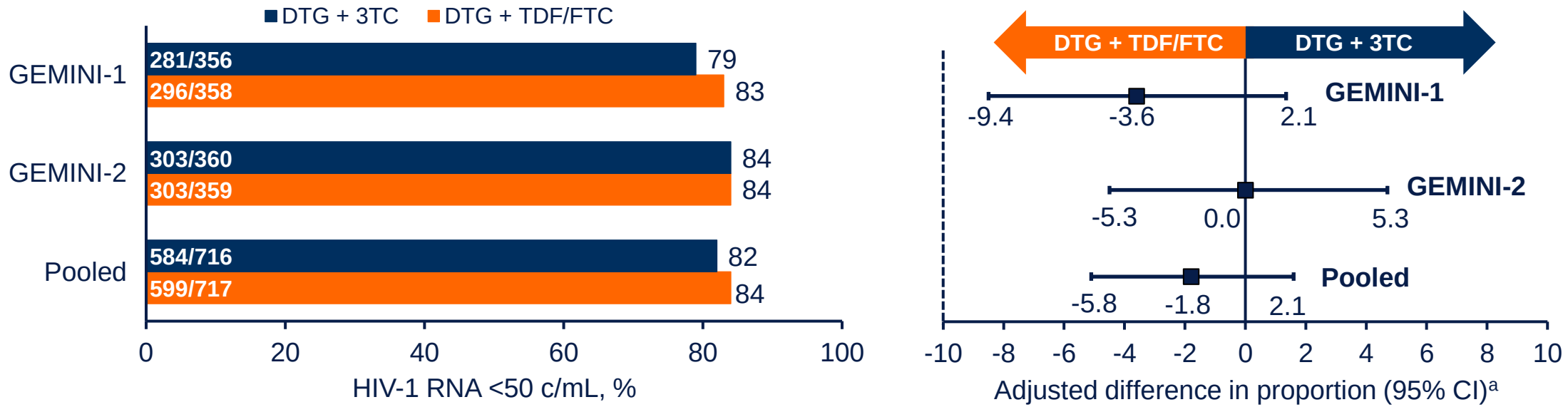
Background

- The GEMINI-1 and -2 studies (NCT02831673 and NCT02831764, respectively) are ongoing phase III, non-inferiority trials evaluating the efficacy and safety of initiating the 2-drug regimen DTG + 3TC in treatment-naive adults with HIV-1 infection compared with the 3-drug regimen DTG + TDF/FTC[1,2]
- In the Weeks 48, 96, and 144 analyses of the GEMINI studies, DTG + 3TC demonstrated non-inferior efficacy vs DTG + TDF/FTC in ART-naive adults through 3 years of treatment[3-5]
- Here we present rates of virologic suppression (Snapshot) and safety results **through Week 144** by demographic and baseline characteristics



1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02831673. Accessed January 27, 2021. **2.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02831764. Accessed January 27, 2021. **3.** Cahn et al. *Lancet*. 2019;393:143-155. **4.** Cahn et al. *J Acquir Immune Defic Syndr*. 2020;83:310-318. **5.** Cahn et al. HIV Glasgow 2020; Virtual. Poster P018.

DTG + 3TC Is Non-inferior to DTG + TDF/FTC at Week 144



- Through Week 144, 12 participants in the DTG + 3TC group and 9 in the DTG + TDF/FTC group met protocol-defined CVW criteria; there were no treatment-emergent INSTI or NRTI resistance mutations
- **1 non-CVW participant with reported intermittent non-adherence in the DTG + 3TC group developed**
  - **M184V at Week 132 (HIV-1 RNA 61,927 c/mL)**
  - **R263R/K at Week 144 (HIV-1 RNA 135 c/mL), conferring a 1.8-fold change in susceptibility to DTG**

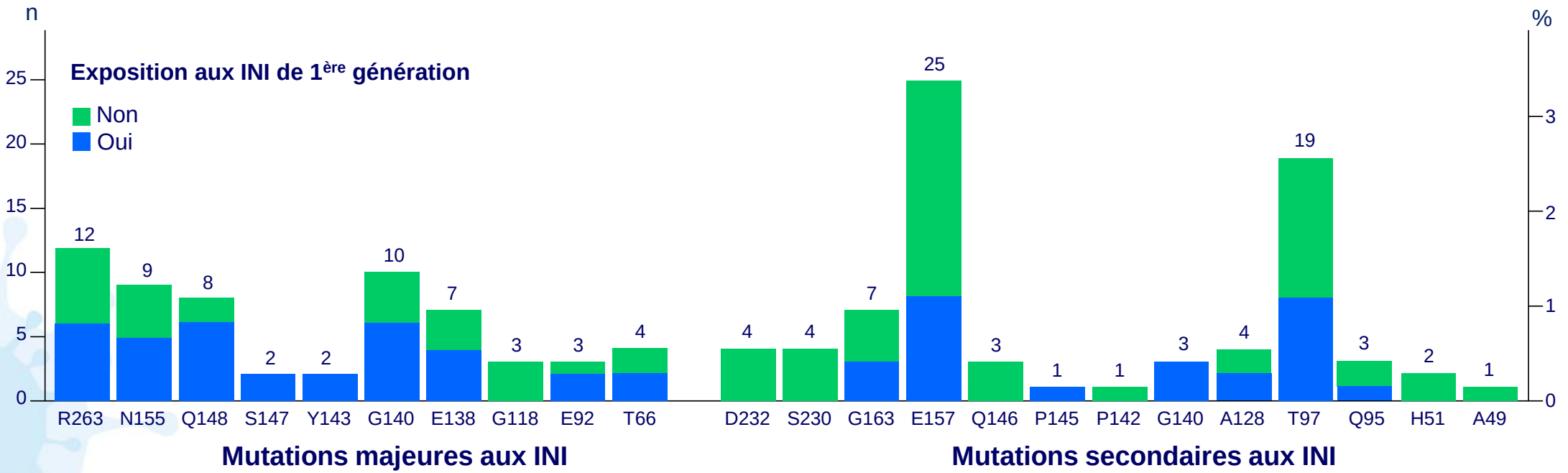
CVW, confirmed virologic withdrawal.
[a]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and baseline CD4+ cell count (≤200 vs >200 cells/mm^3). The pooled analysis was also adjusted for study (GEMINI-1 vs GEMINI-2).
Cahn et al. HIV Glasgow 2020; Virtual. Poster P018.

Orkin et al. CROI 2021; Virtual. Slides 1991.

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 %)

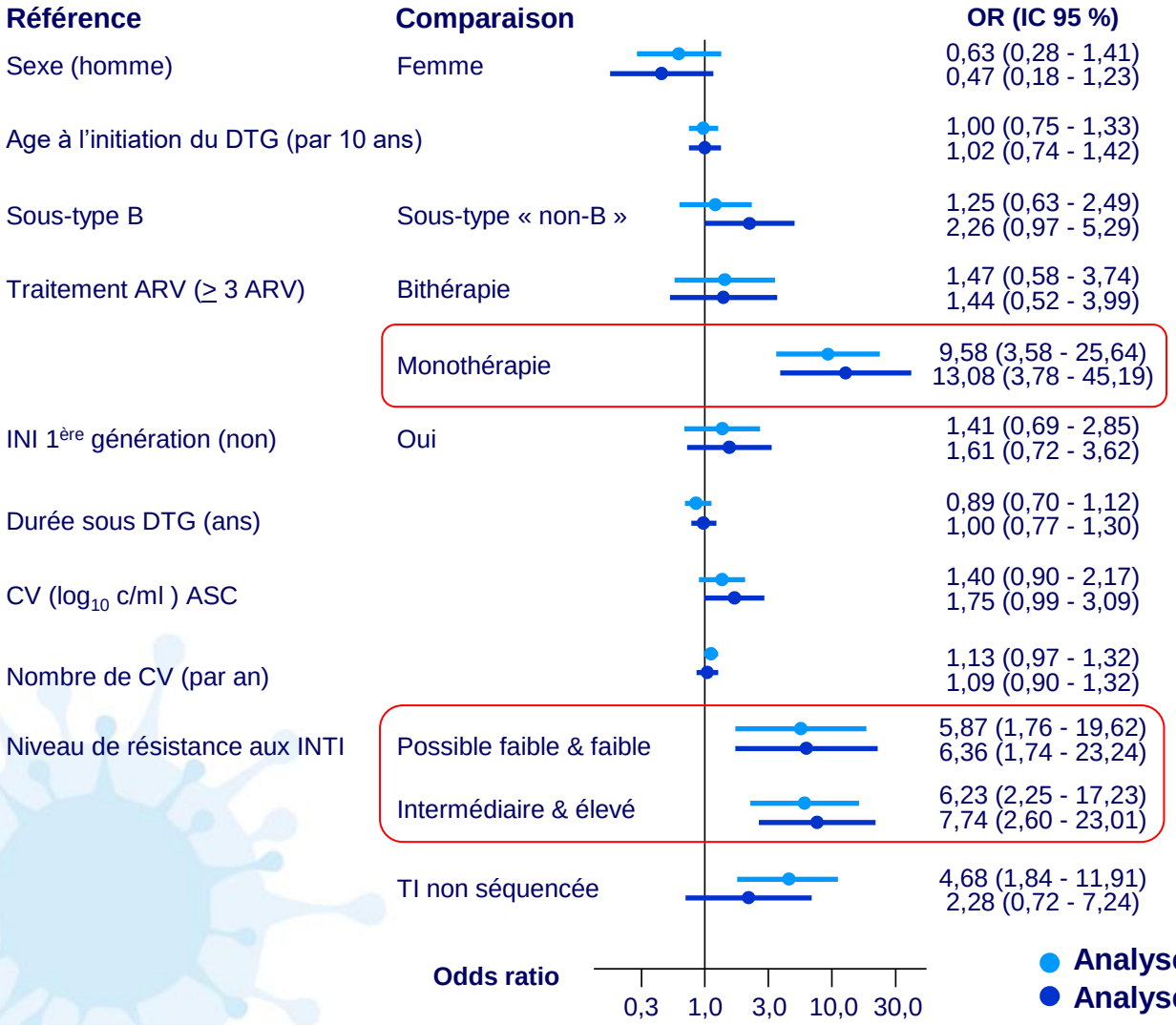
Prévalence de mutations de résistance aux INI



Loosli T, CROI 2023, Abs. 576

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

Facteurs prédictifs d'émergence de mutation de résistance à DTG

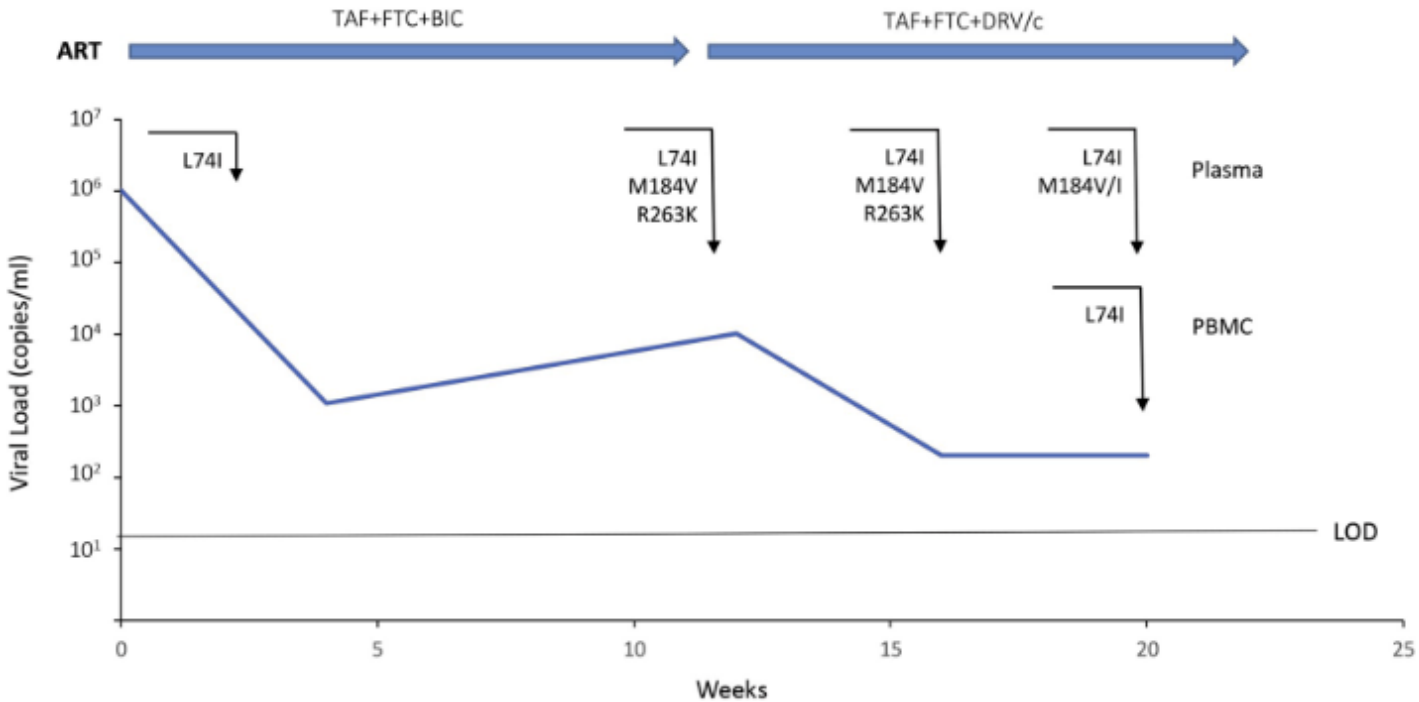


- **Conclusions**
  - Résistance à DTG en cas d'échec est rare (R263K = 1,6 %)
  - Risque augmenté d'émergence de résistance à DTG en cas de monothérapie de DTG (à proscrire en raison du risque très élevé de résistance) et en cas de résistance aux INTI
  - Surveillance nécessaire dans le contexte des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

Loosli T, CROI 2023, Abs. 576

Failure to bictegravir and development of resistance mutations in an antiretroviral-experienced patient

Ana Belén Lozano[a], Natalia Chueca[b,c], Adolfo de Salazar[b,c], Elisa Fernández-Fuertes[a], Antonio Collado[d], Juan Manuel Fernández[a], Marta Álvarez[b,c], Federico García[b,c,*]



Mutation	Wk 0	Wk 12	Wk 16	Wk 20 (Plasma)	Wk 20 (Cells)
		% Prevalence; copies/mL			
M184V	0%; 0	5%; 511	25%; 51	29%; 59*	0%
L74I	52%; 540372	97%; 9925	97%; 198	83%; 169	97%
R263K	0%; 0	96%; 9822	33%; 67	0%; 0	0%

* 8% M184I; 16 copies/mL

Antiviral Research
Volume 179, July 2020

Résistance à DTG et BIC dans les pays à faibles ressources (1)

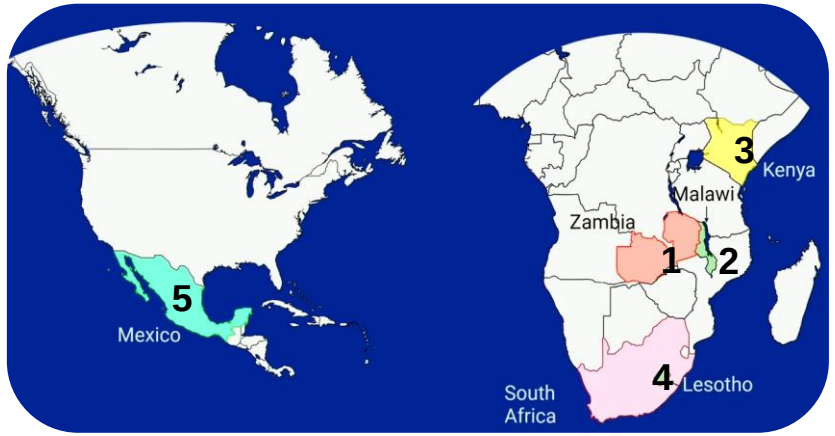
1. Cohorte **Malawi + Zambie** : 2 852 adultes switchés de TAR avec INNTI à TAR avec DTG
CV < 400 c/ml : 95 % au switch. CV ≥ 400 c/ml à 2 ans = 3,3 % (surtout si CV non indétectable au switch)
Mutations majeures de résistance à DTG = 2/45 avec CV > 1 000 c/ml (4,4 %)

2. **Malawi** sept 2023 : 99,9 % des 35 352 enfants sous ARV étaient sous DTG
Evaluation de la résistance chez 133 enfants avec CV confirmée > 1 000 c/ml.
Mutations de résistance majeure aux INI = 16,3 % (DTG = 13,5 %)

3. **Kenya** : programme national de passage au DTG

- 41 patients en 1ère ligne. Après 1,5 ans en médiane, CV > 200 c/ml = 32 %, Mutations majeures de résistance à DTG = 1/12 (8,3 %)
- 190 patients prétraités (INNTI et/ou IP). Après 2,1 ans, CV > 200 c/ml = 28 %, Mutations de résistance majeure à DTG = 7/31 (22,6 %)

4. **Lesotho** : patients ayant switché de INNTI pour DTG, sous DTG ≥ 18 mois avec échec (1 CV ≥ 500 c/ml ou 2 CV ≥ 50 c/ml)
15 299 patients, 151 ayant les critères pour génotype : R à DTG chez 8/78 (10,3 %)



5. Laboratoire de référence, **Mexique**
87 000 patients sous INI de 2ème génération, surtout BIC
Oct 2021-Sept 2023 :

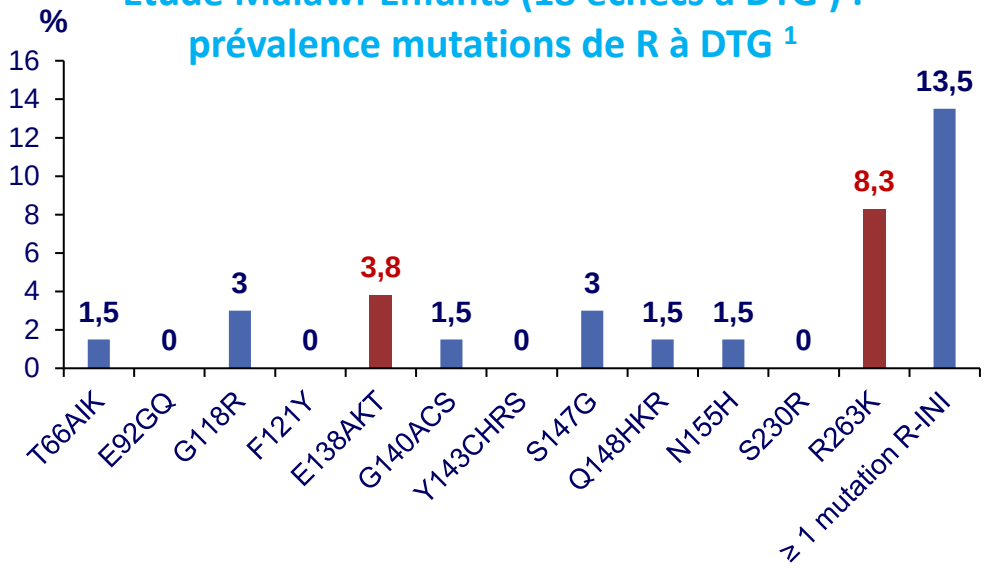
- 100 tests génotypiques réalisés (25 en échec de 1ère ligne, 75 en échec de ≥ 2ème ligne)
- Mutations primaires de résistance à INI : 5/25 et 15/75 (20 %)
- Pas de mutation M184V

1. Whitesell Skrivankova V, CROI 2024, Abs. 676 ; 2. Bello G, CROI 2024, Abs.187LB ; 3. Kingwara L, CROI 2024, Abs. 677 ; 4 Tschumi N, CROI 2024, Abs. 678 ; 5. Soto Ramirez LE, CROI 2024, Abs. 679

Résistance à DTG et BIC dans les pays à faibles ressources (2)

Profils de mutation aux INI

Etude Malawi-Enfants (18 échecs à DTG) : prévalence mutations de R à DTG [1]



	Mutations DTG	n
Résistance élevée	E138K, G140A, S147G, Q148K	2
	G118R, E138K	2
	G118R, R263K	1
	T66I, G188R, E138A	1
Résistance intermédiaire	S147G, N155H	2
	R263K	9
	Q146Q/R, R263/R/K	1

Etude au Kenya [2]	Mutations majeures INI
Echec DTG 1ère ligne (n = 1)	R263K
Echec DTG chez prétraités (n = 7)	E138K E138K, G140A, Q148N E138K, G140A, S147G, Q148R (n = 2) T66I, G118R, E138K (n = 2) E138E/K, S147G, N155H

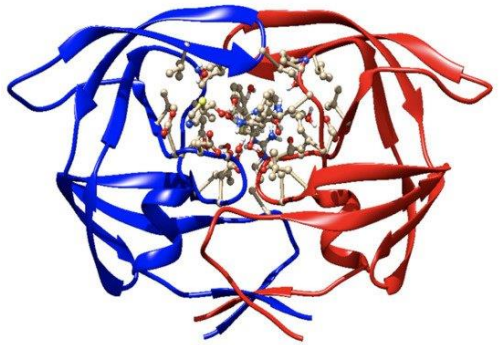
Etude au Lesotho [3]	Mutations majeures INI
Echec DTG chez prétraités (n = 8)	R263K N155H, R263K T66A, G118R, E138K T66A, T97A, G118R, E138K T66I, G118R, E138K, R263K (n = 2) L74M, G118R, E138A, E138K, E157Q, G163K, G163Q H51Y, E92Q

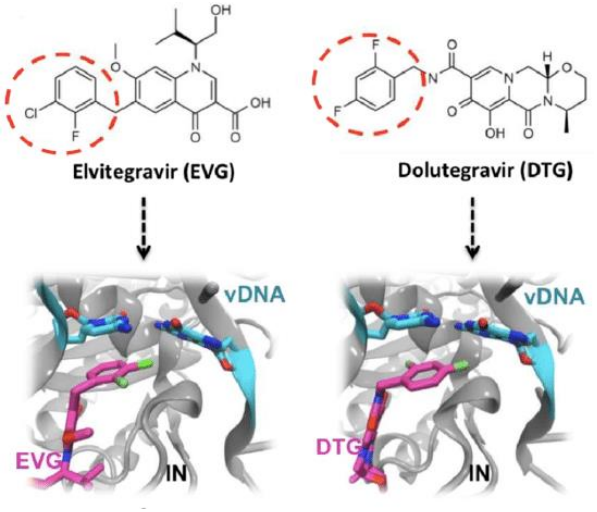
Etude au Mexique (Echecs BIC/F/TAF) [4]	Mutations INI
Echec (n = 9)	R263K, M50I = 4 R263K, M50I, E157Q = 1 E138K = 1 E138K, G140S, Q148H = 1 T97A, E138T, Y143R = 1 T97A, E138T, G140S, Y143R, Q148H = 1

1 Bello G, CROI 2024 , Abs.187LB ; 2 Kingwara L, CROI 2024, Abs. 677 ; 3 Tschumi N, CROI 2024, Abs. 678. ; 4. Soto Ramirez LE, CROI 2024, Abs. 679

Second generation of INIs: boosted PIs behavior ?

- One of the characteristic of boosted PI:
  - capacity to control replication of HIV with altered backbone
  - many patients with low and mild NRTIs resistance level were treated with NRTIs + r/PIs
- Can we say that second generation of INIs (DTG and BIC) have the same properties ?



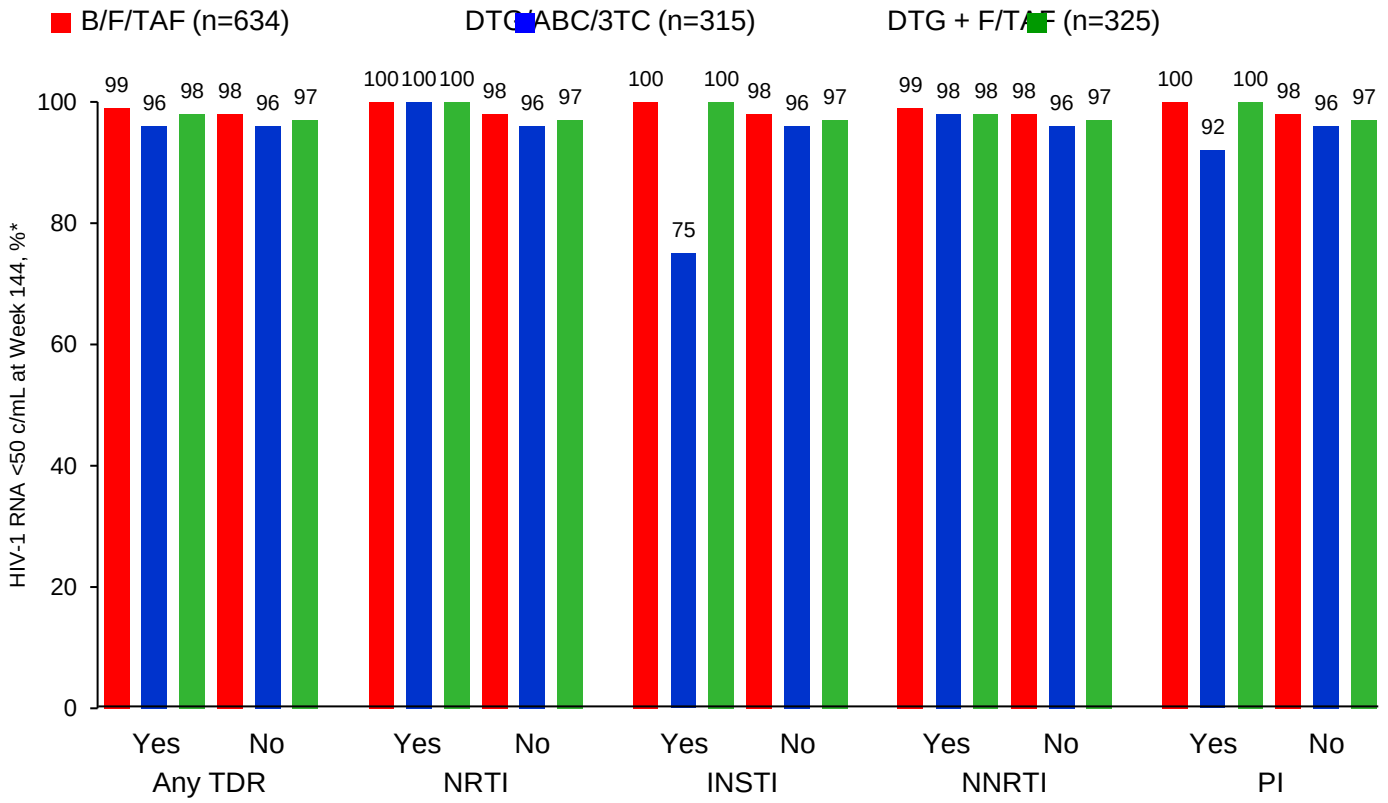


Second generation of INI: boosted PI behavior ?

Preexisting Resistance Substitutions Did Not Alter Virologic Outcomes With B/F/TAF, DTG/ABC/3TC, or DTG + F/TAF Treatment for 144 Weeks

- **Study Design:** Treatment-naive adults with no known resistance to study NRTIs were randomized to receive B/F/TAF, DTG/ABC/3TC, or DTG + F/TAF
  - Resistance analyses were performed at screening and for participants with HIV-1 RNA ≥200 c/mL through Week 144 or at the last visit for those who did not resuppress to HIV-1 RNA <50 c/mL on study
- Preexisting primary NRTI-, PI-, INSTI-, and NNRTI-associated substitutions were found in 2% to 3%, 3% to 4%, 1% to 2%, and 13% to 17% of participants across groups, respectively
- Results at Week 144
  - Of participants with preexisting resistance substitutions, 99% achieved virologic suppression on B/F/TAF, 96% on DTG/ABC/3TC, and 98% on DTG + F/TAF
  - 8, 6, and 7 participants in the B/F/TAF, DTG/ABC/3TC, and DTG + F/TAF groups, respectively, met criteria for resistance testing
    - No treatment-emergent resistance was detected

Impact of preexisting resistance substitutions on treatment outcomes at Week 144



*LOCF outcome analysis did not include 7 B/F/TAF participants and 1 DTG/ABC/3TC participant who had no on-treatment postbaseline HIV-1 RNA data; 1 of these B/F/TAF participants had a primary PI-associated resistance substitution.

V Calvez 2022

Acosta et al. CROI 2021; Virtual. Science spotlight.

NADIA: Wk 96 Results With DTG vs DRV/RTV and TDF vs ZDV as Second-line ART in Africa

Paton. CROI 2022. Abstr 137.

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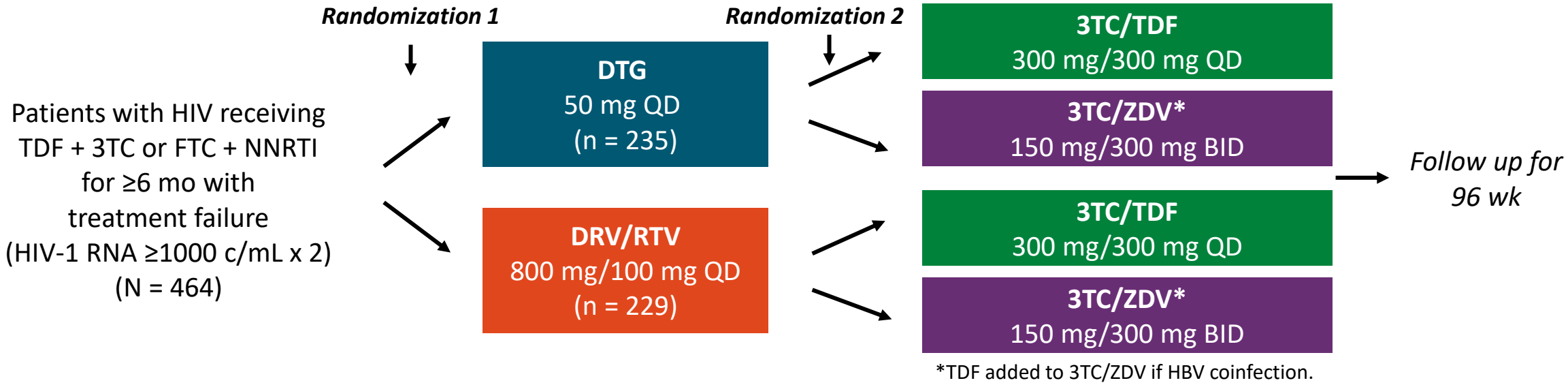
NADIA: DTG vs DRV/RTV and TDF vs ZDV for Second-line Therapy

- Multicenter, 2 x 2 randomized, open-label, noninferiority phase III trial

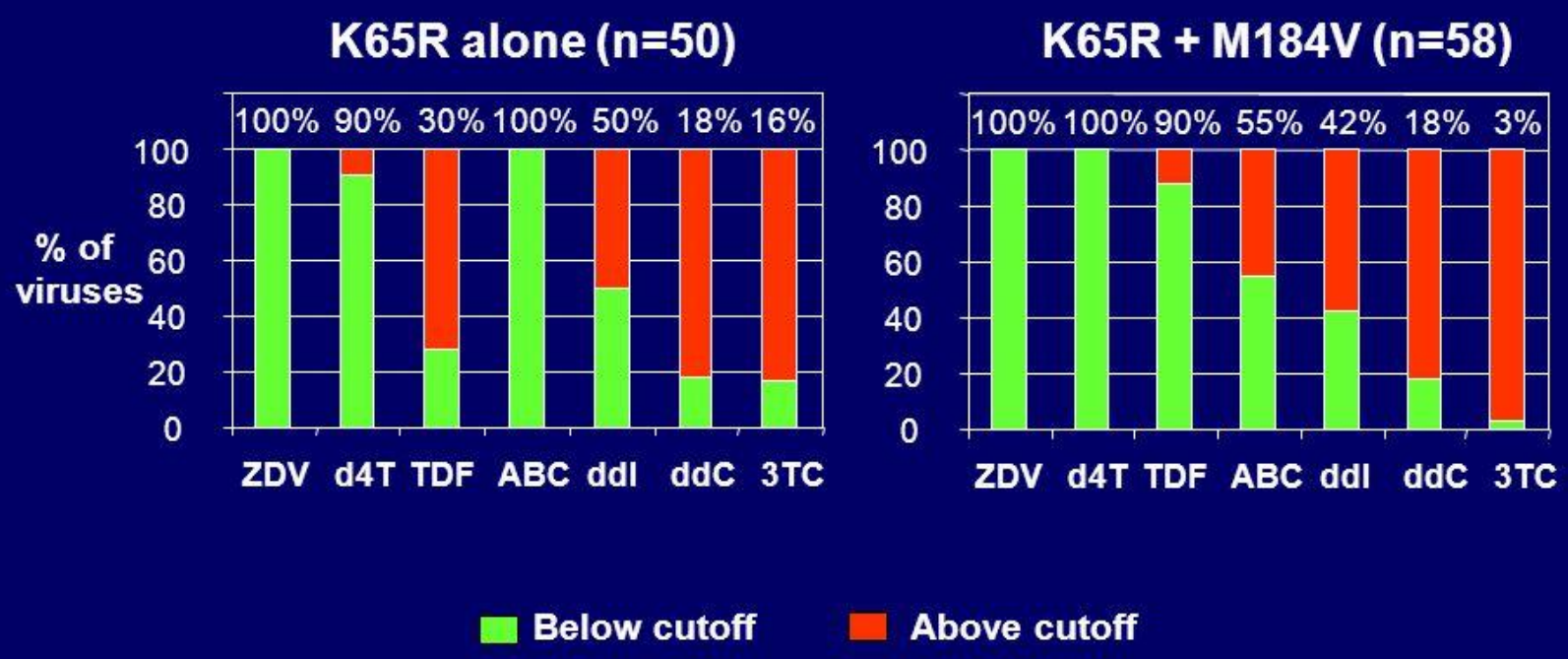


- Study aims: Evaluate noninferiority of DTG to DRV/RTV and of 3TC/TDF to 3TC/ZDV in second line
- Primary outcome: HIV-1 RNA <400 c/mL at Wk 96 by FDA snapshot
- Wk 48 results: DTG was noninferior to DRV/RTV (but 4 cases of DTG resistance); 3TC/TDF was noninferior to 3TC/ZDV

Paton. CROI 2022. Abstr 137. Paton. NEJM. 2021;385:330. NCT03988452.

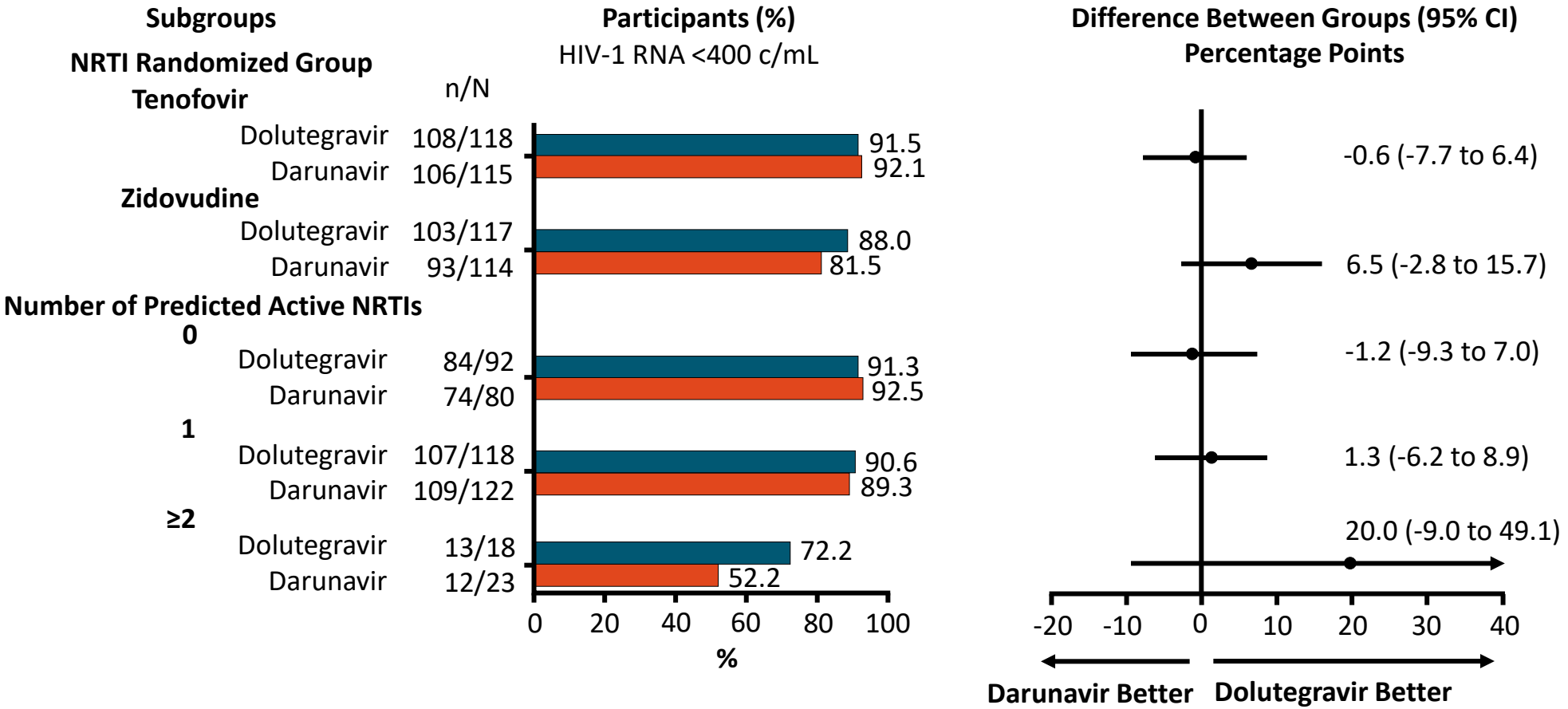
Slide credit: clinicaloptions.com

Phenotypic Susceptibilities of K65R Viruses to NRTIs



Miller MD. 43rd ICAAC, Chicago 2003, #H-904.

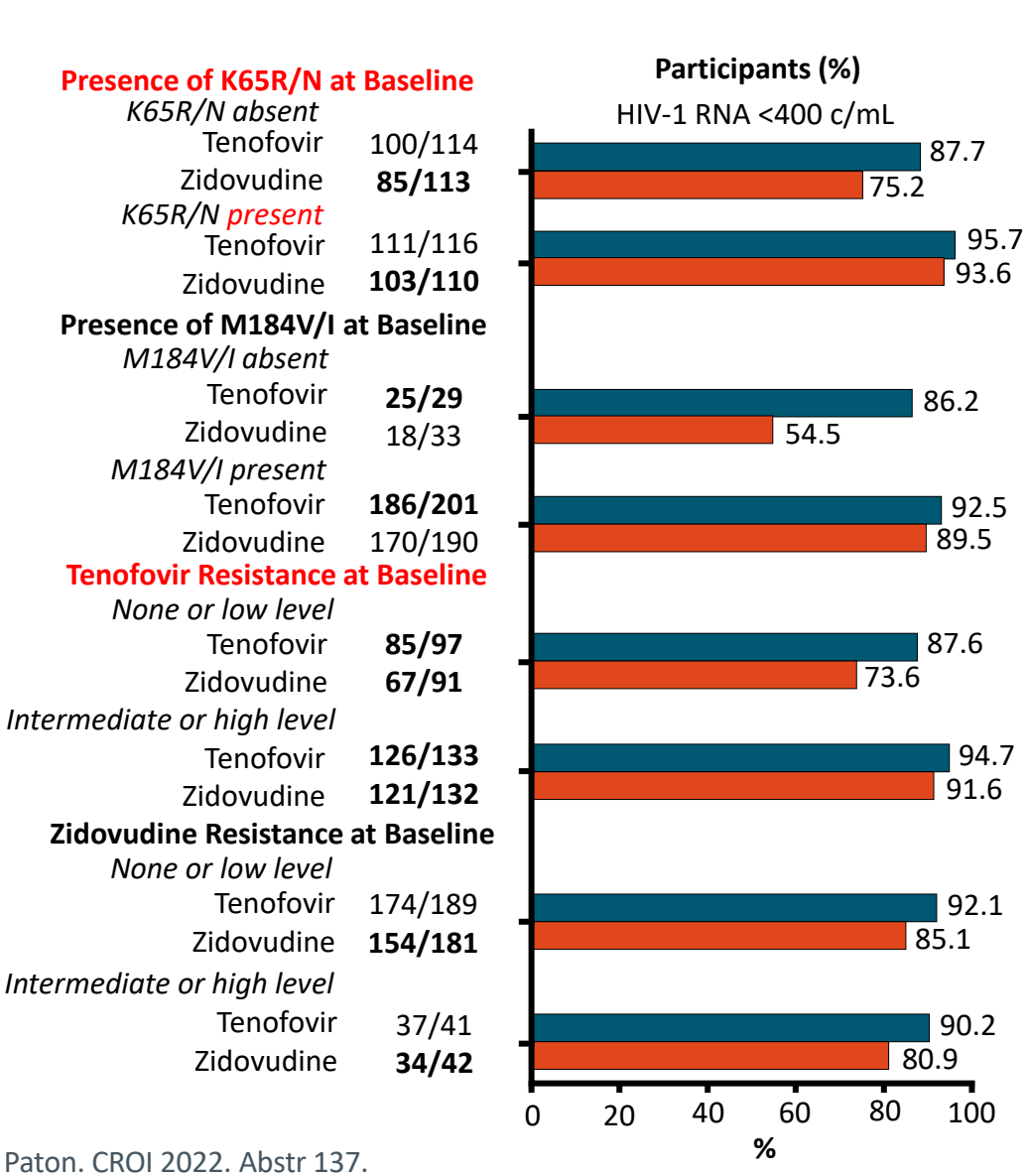
NADIA: Wk 96 Efficacy Subgroup
DTG = DRV/RTV

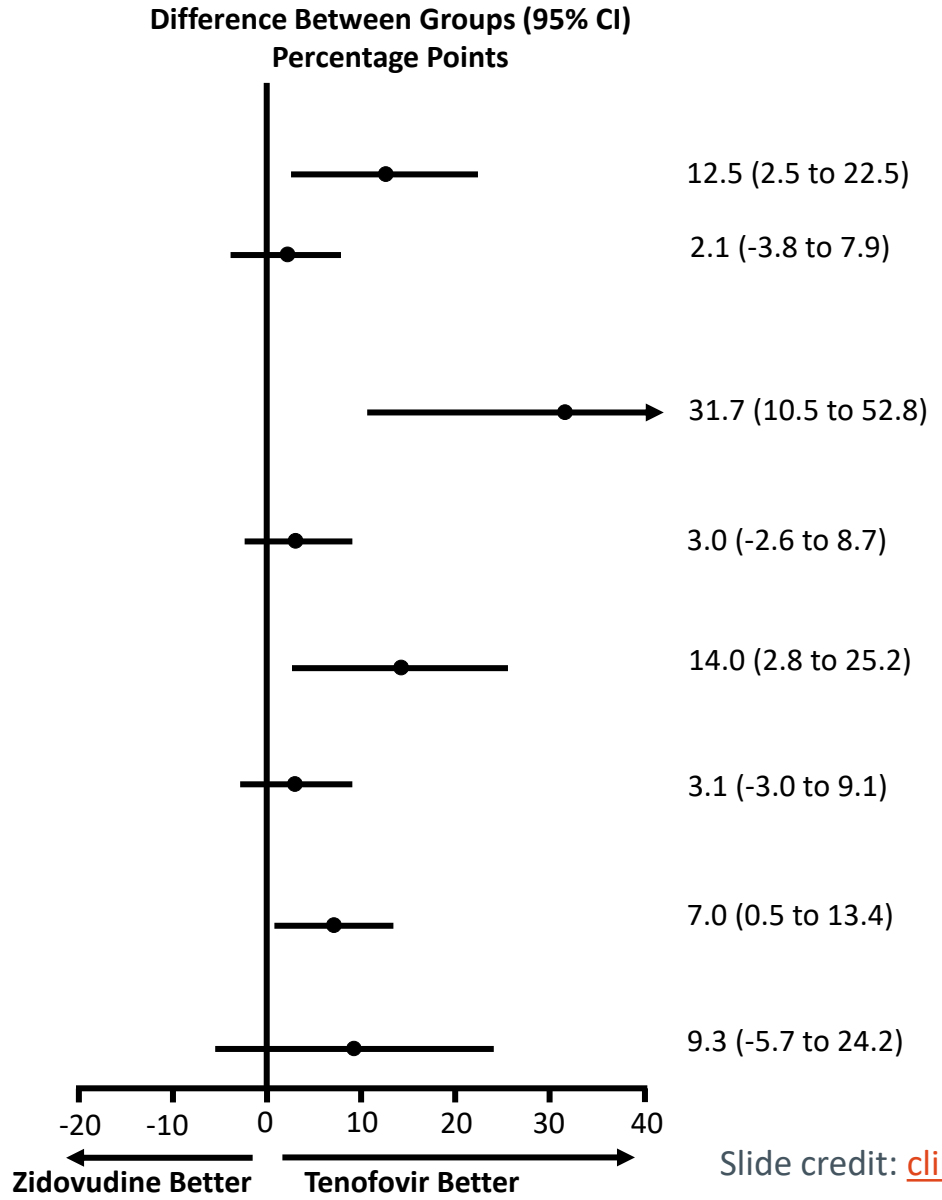


Paton. CROI 2022. Abstr 137.

Slide credit: clinicaloptions.com

NADIA: Wk 96 Efficacy Subgroup Analysis of TDF vs ZDV





Paton. CROI 2022. Abstr 137.

Slide credit: clinicaloptions.com

NADIA: Wk 96 DTG Resistance Mutations at Virologic Failure

- Frequent resistance at failure
- ≠ pathways driven by
  - NRTI used ?
  - Level of VL at failure ?

Patients With Resistance by NRTI Backbone	HIV-1 RNA at Rebound, c/mL	DTG Resistance Level by Stanford Algorithm	DTG Mutations*
3TC/ZDV			
▪ 1	≥1000	High	T66TA, G118R, E138K, G149GA, G163GR
▪ 2	≥400	High	T66TAIV, T97A, G118R, E138K
▪ 3	≥1000	High	T66I, G118R, E138K, G149GA
▪ 4	≥1000	High	T66A, G118R, E138K
▪ 5	≥1000	High	E138K, G140A, Q148R
▪ 6	≥1000	Intermediate	R263RK
3TC/TDF			
▪ 1	≥1000	Intermediate	M50I, R263K
▪ 2	≥1000	Intermediate	M50I, R263RK
▪ 3	≥400	Intermediate	M50I, R263RK

*Sequences acquired from 48/55 patients.

Paton. CROI 2022. Abstr 137.

Slide credit: clinicaloptions.com

Cabo Rilpivirine

ATLAS-2M: Phase 3b, randomized, open-label study (international)

13 Participants with Confirmed Virologic Failure in ATLAS-2M through W152

	Study Arm	Sex, BMI kg/m^2, Country, HIV-subtype	Viral load at SVF (c/mL)	Baseline RAMs*		On-Treatment RAMs SVF Timepoint	
				NNRTI	INSTI	NNRTI	INSTI
BL-W48[3]	Q8W	F, ≥ 30, South Africa, C	267	V108V/I, Y181Y/C, H221H/Y	None	**K103N**	None
	Q8W	F, ≥ 30, Russia, Complex	141,132	None	None	**K101E**	**Q148R**
	Q8W	F, ≥ 30, South Africa, C	938	Y188Y/F/H/L	G140G/R	Y188L	**N155N/H, Q148Q/R**
	Q8W	M, < 30, Spain, B	737,830	None	None	None	None
	Q8W	F, ≥ 30, Canada, A1	16,205	Y188L, P225H	None	Y188L, P225H	Analysis failed
	Q8W	F, < 30, Russia, A	211,639	E138E/A	T97T/A	**K101E, E138A**	T97A, N155H
	Q8W	M, ≥ 30, US, B	5687	E138A, K103N, V108V/I	None	E138A, K103N	**N155H**
	Q8W	M, < 30, Russia, A1	296	None	None	**E138E/K**	**Q148Q/R, N155N/H**
	Q4W	M, < 30, France, B	121,233	None	None	None	**N155N/H**
	Q4W	M, < 30, US, B	9627	None	None	**K101E, M230L**	**E138E/K, Q148R**
W48-96[2]	Q8W	M, < 30, US, B	1916	K103N, Y181C	None	K103N, Y181C	None
W96-152[1]	Q8W	M, < 30, Germany, B	24,221	None	None	**E138A, M230M/L**	**Q148R**
	Q8W	M, < 30, Russia, A6	59,467	None	None	**E138A, Y181Y/C**	**Q148R**

*Baseline resistance associated mutations were assessed in peripheral blood mononuclear cells (HIV-1 proviral DNA). **Red bolded text** indicates treatment emergent RAMs
RAM, resistance-associated mutation; SVF, suspected virologic failure

1. Overton ET, et al. CROI 2022, Poster 479; 2. Jaeger H et al. CROI 2021; Abstract 401; 3. Overton T, et al. Lancet 2021;396:1994-2005

CAB/RPV q8s comme stratégie de switch en Afrique : résultats S48 de l'essai CARES (1)

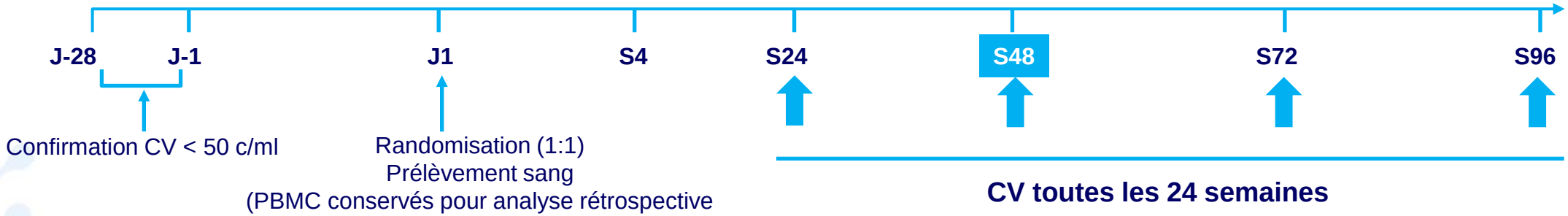
- Essai randomisé Phase 3b, ouvert, multicentrique, de non infériorité
- 8 sites Afrique sub-saharienne (Ouganda, Kenya, Afrique du Sud)
- 1 039 personnes screenées, 512 randomisées (527 exclusions dont 375 pour anti-HBc+ et 33 Ag HBs+)

- **512 adultes VIH+**
- **Sous traitement ARV oral stable : TDF + 3TC/FTC + DTG/NVP/EFV**
- **CV < 50 c/ml 4 à 12 mois avant et au moment du screening**
- **Pas d'antécédent d'échec thérapeutique**
- **Pas d'infection VHB**

Traitement oral (SOC)
TDF + 3TC/FTC + DTG/NVP/EFV
(n = 256)

CAB + RPV oral (optionnel)

CAB (600 mg) + RPV (900 mg) LA IM q8s
(n = 256)



- **Critère principal** : % CV < 50 c/ml à S48 (Snapshot FDA), non infériorité sur population ITT (marge 10 %)

Kityo CM, CROI 2024, Abs.122LB

CAB/RPV q8s comme stratégie de switch en Afrique : résultats S48 de l'essai CARES (2)

Caractéristiques à l'inclusion

	CAB + RPV LA (n = 256)	Traitement oral (SOC) (n = 257)	Total (n = 512)
Femmes	57 %	58 %	58 %
IMC ≥ 30 kg/m^2	22,4 %	19,8 %	21,1 %
Durée de 1ère ligne ARV, médiane (IQR)	8 ans (4-13)	7 ans (4-13)	8 ans (4-13)
Exposition préalable à INNTI	73 %	74 %	74%
Traitement avec INI au screening	91 %	93 %	92 %
Traitement avec INNTI au screening	9 %	7 %	8 %
Analyse ADN J0 (sur PBMC conservés)			
Sous-type viral A1	56 %	57 %	56 %
Mutations de résistance à RPV	12,5 % (25/200)	14,7 % (26/177)	13,5 % (51/377)
Résistance intermédiaire/élevée* à RPV	8,5 % (17/200)	11,9 % (21/177)	10,1 % (38/377)
Mutations de résistance à CAB	15,8 % (15/95)	16,5 % (14/85)	16,1 % (29/180)
Résistance intermédiaire/élevée* à CAB	10,5 % (10/95)	5,9 % (5/85)	8,3 % (15/180)

* Selon algorithme de Stanford

Kityo CM, CROI 2024, Abs.122LB

Table S4 Resistance profile at baseline *

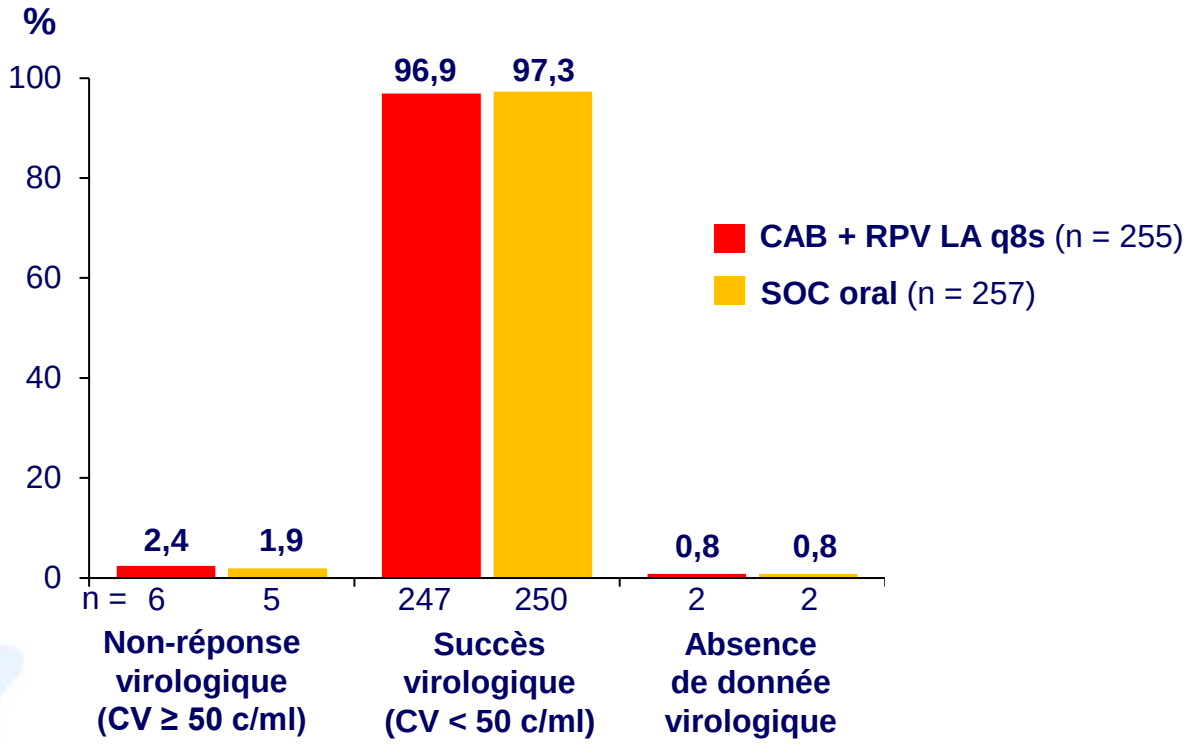
	Long-acting therapy (N=255)	Oral Therapy (N=257)	Overall (N=512)
NNRTI resistance mutations			
Participants with RT sequence	200	177	377
Mutations to rilpivirine			
Any	25 (12)	26 (15)	51 (14)
L100I/F	0	1 (1)	1 (<1)
K101E/P	0	2 (1)	2 (1)
E138A/G/K ‡	14 (7)	8 (5)	22 (6)
V179L	0	0	0
Y181C/I/V	2 (1)	2 (1)	4 (1)
Y188L	0	1 (1)	1 (<1)
H221Y	0	1 (1)	1 (<1)
F227C	0	0	0
M230I/L	10 (5)	12 (7)	22 (6)
Mutations to any NNRTI †	54 (27)	44 (25)	98 (26)
K103N/S mutation	18 (9)	13 (7)	31 (8)
INSTI resistance mutations			
Participants with INSTI sequence	95	85	180
Mutations to cabotegravir §			
Any	15 (16)	14 (16)	29 (16)
T66K	0	0	0
T97A	5 (5)	7 (8)	12 (7)
G118R	0	1 (1)	1 (1)
E138A/K/T	3 (3)	1 (1)	4 (2)
G140A/C/R/S	7 (7)	2 (2)	9 (5)
Q148H/K/R	1 (1)	1 (1)	2 (1)
S153F/Y	1 (1)	1 (1)	2 (1)
N155H	0	0	0
R263K	2 (2)	1 (1)	3 (2)
Mutations to any INSTI †	16 (17)	14 (16)	30 (17)
NRTI resistance mutations			
Participants with RT sequence	200	177	377
Mutations to any NRTI †	23 (12)	25 (14)	48 (13)
M184V/I mutation	19 (10)	20 (11)	39 (10)
K65R/E/N mutation	0	1 (1)	1 (<1)

A previous pooled analysis of long-acting therapy trials identified a strong association between the presence of archived rilpivirine resistance mutations before the start of long-acting therapy and the risk of subsequent virological failure on this regimen.

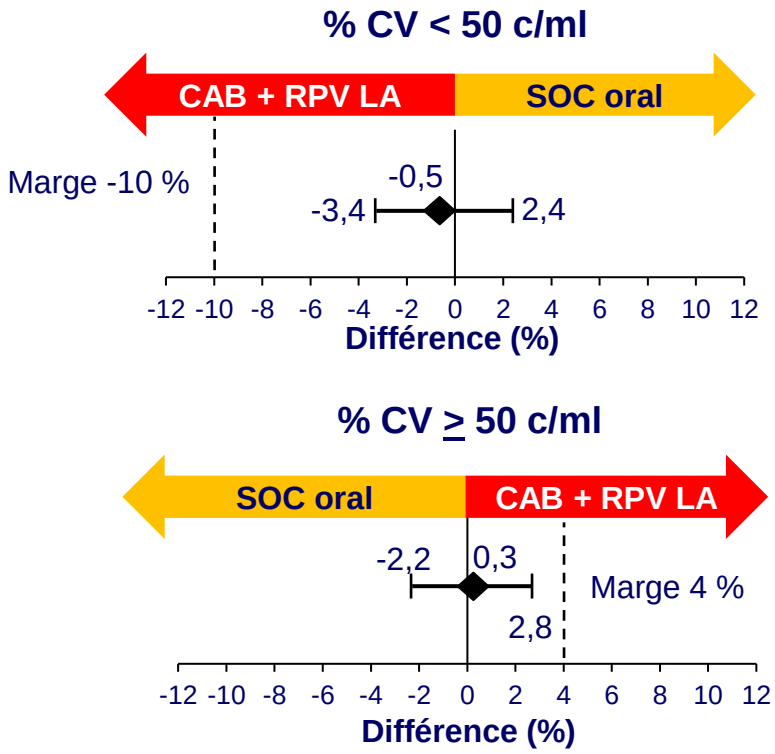
Our finding of a low rate of virological failure despite the high proportion of participants with previous NNRTI exposure and baseline resistance mutations provides important reassurance that extensive programmatic use of NNRTIs in the past does not preclude consideration of future use of longacting therapy as an option for the public health approach.

CAB/RPV q8s comme stratégie de switch en Afrique : résultats S48 de l'essai CARES (3)

Devenir virologique à S48



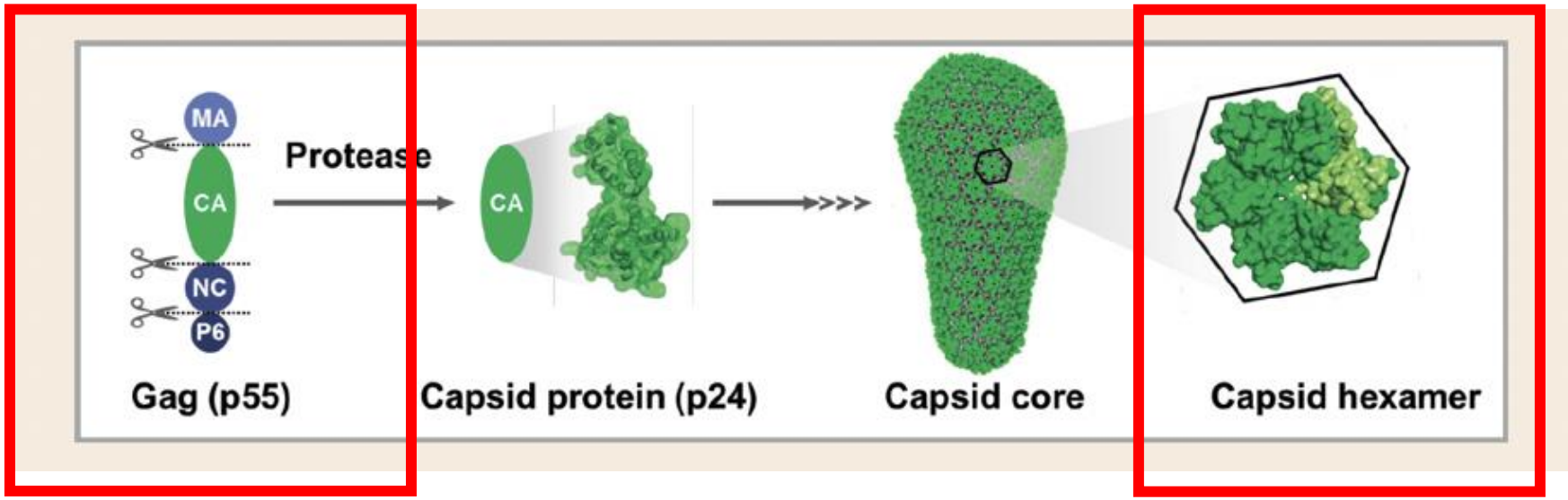
Différence ajustée (IC 95 %)



- **2 échecs virologiques dans le bras CAB + RPV LA**, 0 dans le bras SOC oral :
  - 1 confirmé (2 CV ≥ 200 c/ml) à S48 : 8 608 c/ml, pas d'injection retardée, sous-type A1, IMC 26 kg/m^2, pas de R à J0, émergence de R à RPV (V108I, E138K, V179L) et intermédiaire à CAB (E92V, N155H, L74M), re-suppression sous TDF/3TC/DTG
  - 1 non confirmé (décès avant re-test) à S48 : 44 984 c/ml, pas d'injection retardée, sous-type D, IMC 22 kg/m^2, à J0 : R faible RPV (K103N/S, E138A) et pas de mutation INI, à l'échec R faible RPV (K103N/S, V106A, E138A) et R élevée à CAB et intermédiaire à DTG (G118R)

Kityo CM, CROI 2024, Abs.122LB

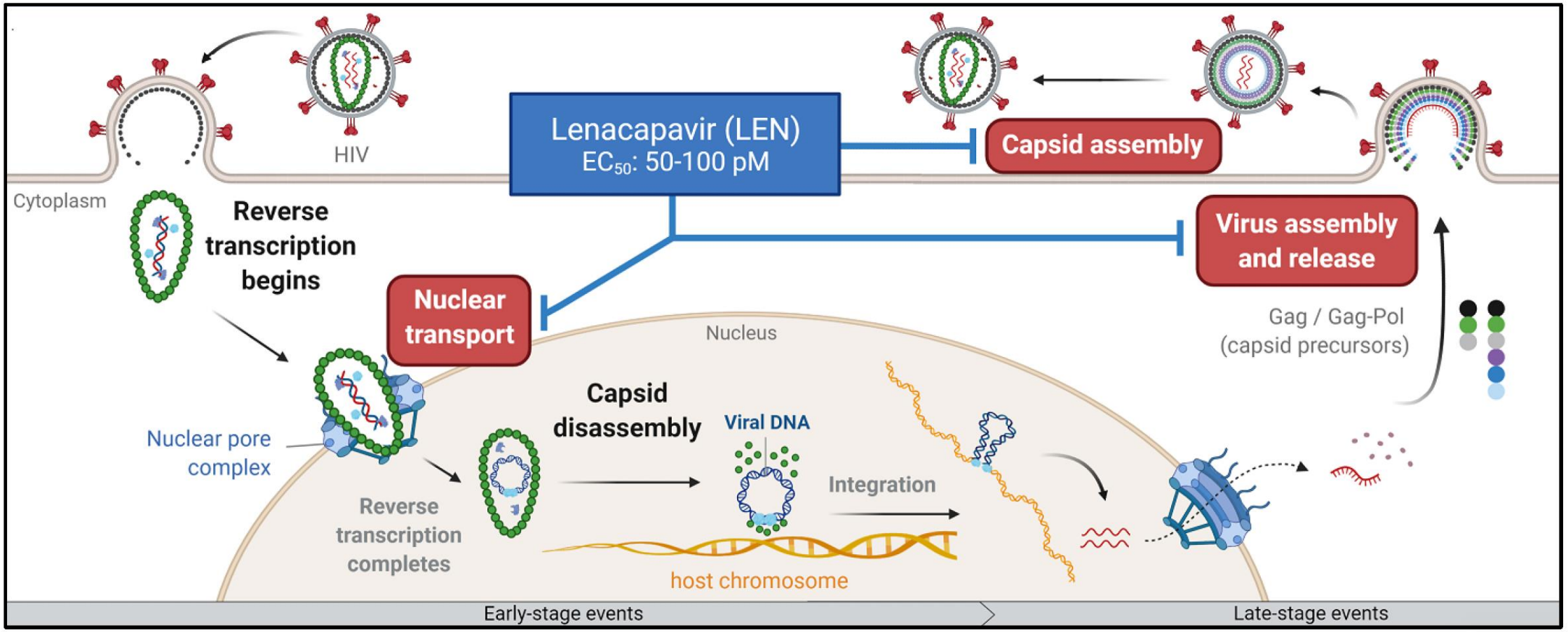
Inhibiteurs de capside



Inhibiteurs de clivage

Lenacapavir

LEN : Capsid inhibitor targets multiple stages of HIV replication cycle

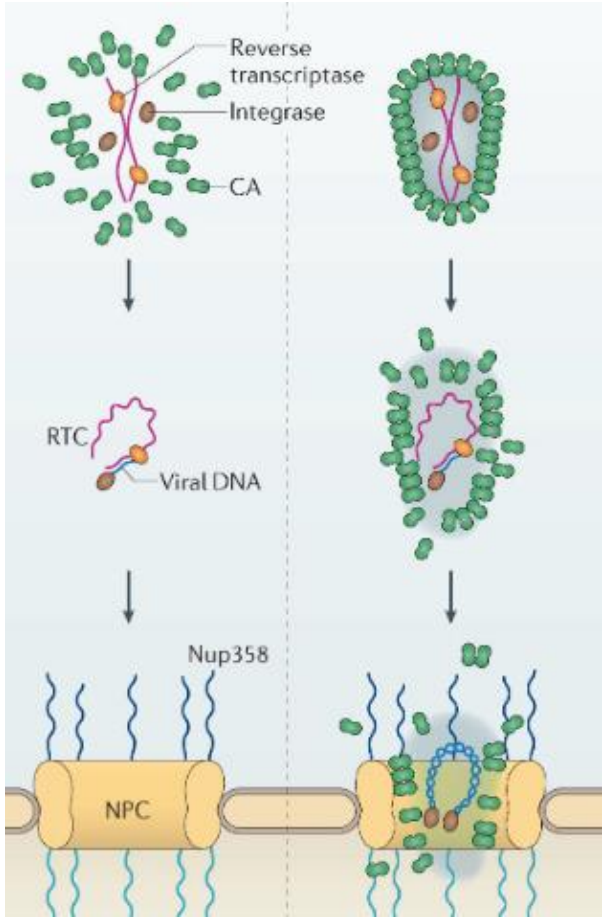


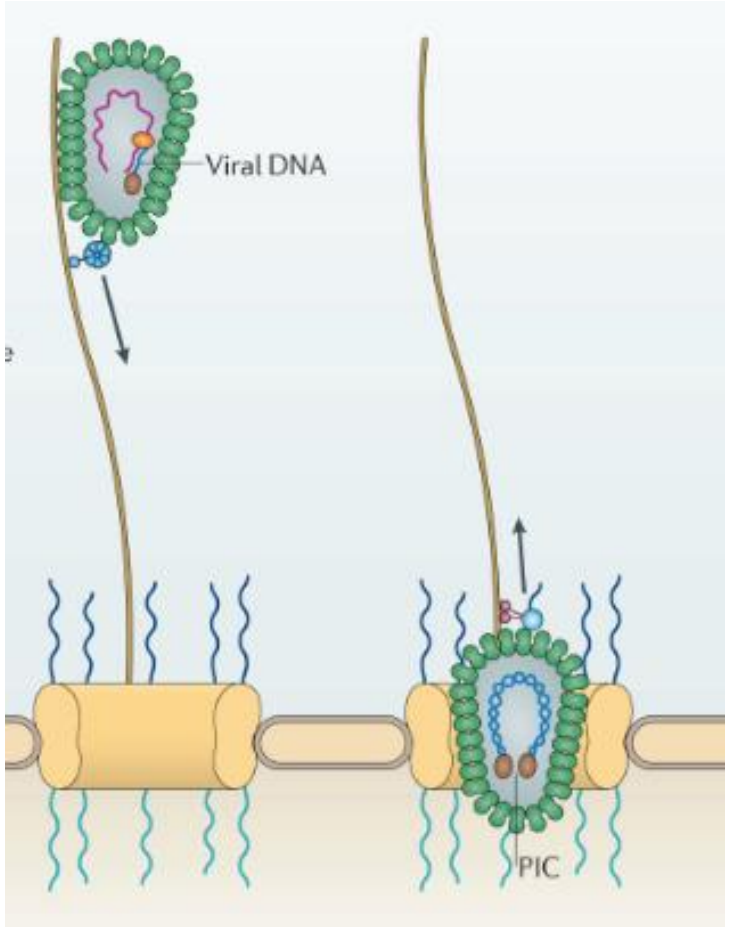
Link JO et al. Nature 2020 ; Bester et al. Science 2020

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

Past four decades

HIV uncoating occurs in the cytoplasm



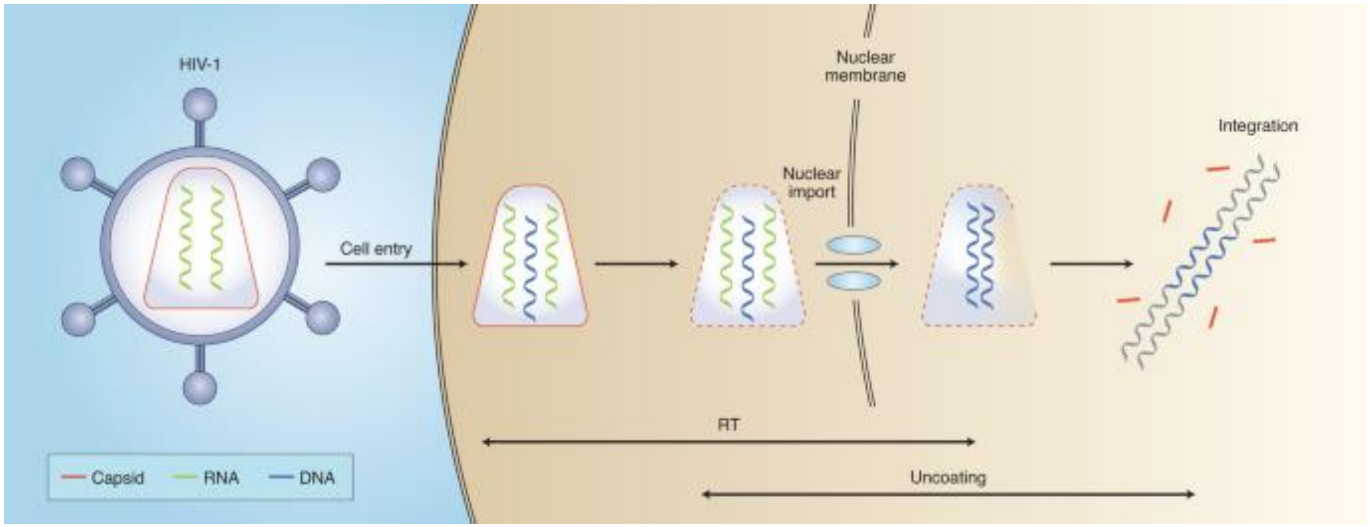


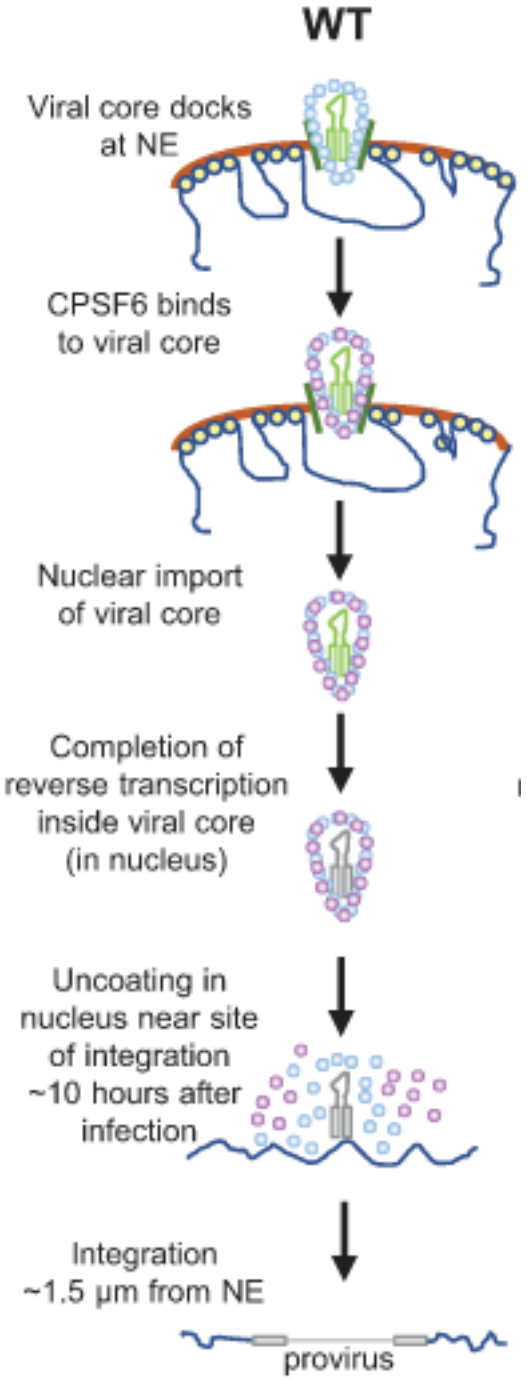
HIV-1 uncoats in the nucleus near sites of integration

Ryan C. Burdick[a], Chenglei Li[a], MohamedHusen Munshi[a], Jonathan M. O. Rawson[b], Kunio Nagashima[c], Wei-Shau Hu[b], and Vinay K. Pathak[a,1]

[a]Viral Mutation Section, HIV Dynamics and Replication Program, Center for Cancer Research, National Cancer Institute at Frederick, Frederick, MD 21702; [b]Viral Recombination Section, HIV Dynamics and Replication Program, Center for Cancer Research, National Cancer Institute at Frederick, Frederick, MD 21702; and [c]Electron Microscopy Laboratory, Cancer Research Technology Program, Leidos Biomedical Research, Inc., Frederick National Laboratory for Cancer Research (FNLCR), Frederick, MD 21702

- This study showed:
  - nearly intact viral cores enter the nucleus
  - reverse transcription is completed in the nucleus before uncoating
  - uncoat before integration near their genomic integration sites.





Lenacapavir (LEN)

- Actif contre
  - tous les sous-types majeurs du VIH-1
  - virus de tropisme CCR5 et CXCR4
- Pas de résistance croisée avec les autres ARV

In-vitro resistance selection assays in MT-2 cells and human peripheral blood mononuclear cells identified Q67H and N74D as the major resistance-associated mutations. Additional variants included L56I, M66I, K70N, Q67H/N74S and Q67H/T107N.

HIV-1 Capsid Sequence	WT	T107N[d]	Q67H	N74D	K70N	Q67H N74S	Q67H T107N	L56I	Q67H N74D	M66I
Fold Resistance to GS-6207[a]	1	4	6	22	24	32	62	239	1,099	>3,200
Infectivity in MT-2 cells (% WT)[b]	100	50	95	48	7	34	41	9	29	6
Replication Capacity in Primary CD4+ T-cells (% WT)[c]	100	ND	100	1	ND	ND	28	3	<1	<1

Prevalence of capsid substitutions associated with LEN in vitro resistance in HIV-1 from ARV-naive and ART-experienced patients

Table 1. Distribution of HIV-1 subtypes among studied patients

HIV-1 subtype distribution	ART naive ($N = 500$), % (n)	ART experienced without PI use ($N = 500$), % (n)	ART experienced with history of PI failure ($N = 500$), % (n)
B	37 (185)	42 (210)	56 (280)
CRF02_AG	46 (230)	48 (240)	37 (185)
F1	4.6 (23)	2.4 (12)	—
CRF06	4.4 (22)	3.8 (19)	3.4 (17)
A1	2.8 (14)	—	—
D	2.2 (11)	2.2 (11)	1.6 (8)
Other non-B	3.0 (15)	1.6 (8)	1.0 (5)

Among the samples from the 1 500 patients studied, none of the LEN (GS-6207) resistance mutations identified during in vitro selection experiments were detected, regardless of HIV subtype or treatment history

- **Conclusion: Absence of naturally occurring LEN resistance mutations**

Marcelin A-G, et al. JAC 2020;75:1588–1590

le meilleur ... de IAS 2023

Analyse de la diversité du gène de la capside

- Cohorte Ougandaise UARTO chez des patients naïfs d'ARV
- Séquences de capside à partir de prélèvements obtenus entre 2002 et 2010
- Mutations capside analysées associées à la résistance à LEN :
  - L56I, M66I, Q67H, K70N/S/R, N74D/S, A105T et T107N (Liste mutations IAS-USA)
  - Q67K/N, K70H, N74H, A105S et T107A/C *(Ogbuagu et al., 2022 ; Margot et al., 2022)*

- **Résultats**
  - n = 546 séquences de capside
  - Sous-types : A1 (51 %), D (30 %), A1/D (11 %), C (4 %)

Prévalence des mutations de résistance à LEN

L56I	M66I	Q67H/K/N	K70H/N/S/R	N74D/H/S	A105S/T	T107A/C/N
0	0	0	1 K70R (0,2 %)	0	0	7 T107A (1,3 %)

  - Analyses phylogénétiques : pas de clusters entre les 8 séquences porteuses de mutations

- **Conclusion :** très faible prévalence de polymorphismes dans la capside pouvant impacter la sensibilité phénotypique à LEN

Omoding D, IAS 2023, Abs. EPB0274

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 ≥ 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

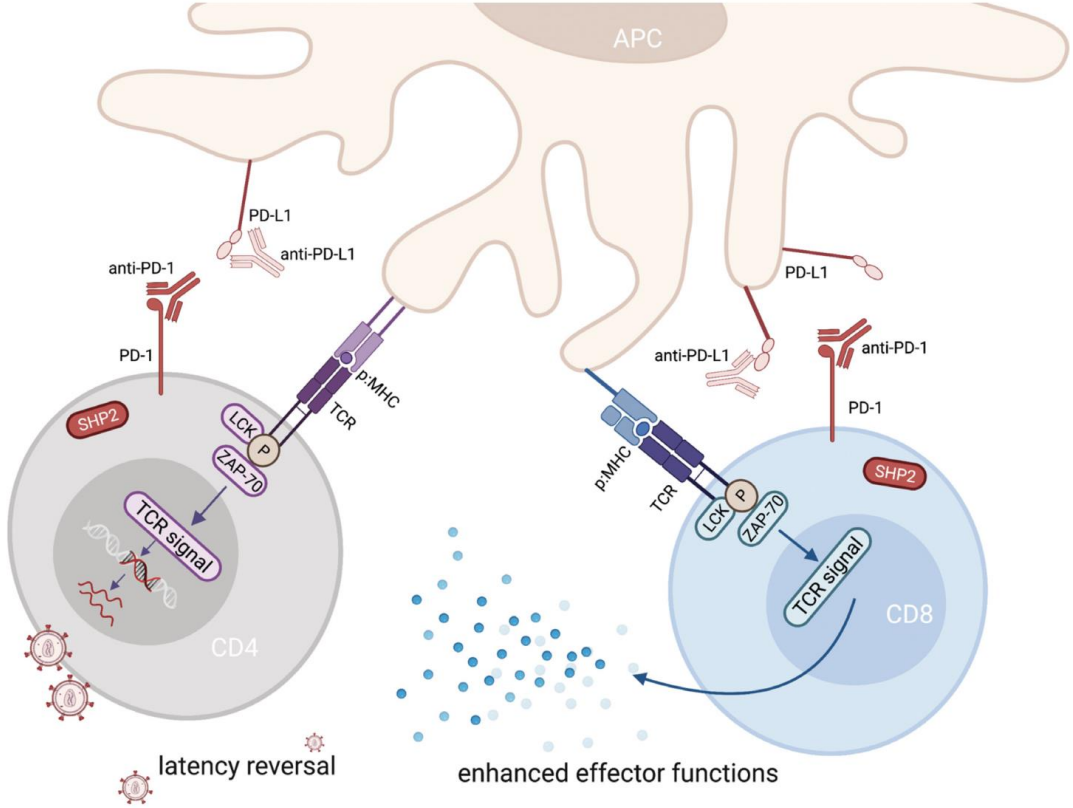
Nicolas Margot, Vamshi Jogiraju, Laurie VanderVeen, Vidula Naik, Hadas Dvory-Sobol, Martin S. Rhee, and Christian Callebaut

Patient Clones and Site-Directed Mutants

#	Genotype	RC (%)[a]	LEN FC[a]	LEN FC MT-2[b]
A.	M66I	0.6	>869.0	*Non-infectious*
B.	M66I A105T	1.2	>869.0	*Non-infectious*
C.	M66I	1.5	>869.0	*Non-infectious*
D.	M66I Q67H K70R	3.1	>869.0	*Non-infectious*
E.	M66I	12.0	>869.0	*Non-infectious*
F.	M66I T107S	24.0	>869.0	*Non-infectious*
G.	M66I K70S	*AF*	*AF*	*Non-infectious*
H.	A105T	*AF*	*AF*	*Non-infectious*
I.	K70R	9.7	1.2	*Non-infectious*
J.	K70H	9.8	154.2	*Non-infectious*
K.	K70H	37	84.8	345
L.	K70S	*AF*	*AF*	*Non-infectious*
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

Immune checkpoints and HIV

- Achieving long term control of HIV in the absence of ART will likely require potent T cell function
- chronic HIV infection is associated with immune exhaustion that persists even on ART
- This is driven by elevated expression of immune checkpoints that provide negative signalling to T cells
- Immune checkpoint antibodies have two distinct effects in the setting of HIV on ART
  - and they activate HIV expression in latently infected CD4+ T-cells
  - they enhance HIV-specific CD8+ T-cell function.



V Calvez 2023

Safety, Pharmacokinetics, and Exploratory Efficacy of the PD-1 Inhibitor Budigalimab in ART-Suppressed People Living With HIV-1: Preliminary Analysis of 2 Phase 1b Studies Including an Analytical Treatment Interruption

Moti Ramgopal,[1] Jay Lalezari,[2] Ana Gabriela Pires dos Santos,[3] Preethi Krishnan,[3] Tanaya Vaidya,[3] Fei Zhou,[3] Nael M. Mostafa,[3] Till Geib,[3] Heide Betman,[3] Patrick Dorr,[3] Maria L. Alcaide,[4] Jean-Pierre Routy[5]

[1]Midway Immunology & Research Center, Fort Pierce, FL, USA; [2]Quest Clinical Research, San Francisco, CA, USA; [3]AbbVie, Inc., North Chicago, IL, USA; [4]University of Miami Miller School of Medicine, Miami, FL, USA; [5]McGill University Health Centre, Montreal, QC, Canada

19th European AIDS Conference, 18–21 October 2023, Warsaw, Poland

abbvie

Budigalimab is an anti-PD-1 mAb and is rationalized to enhance immune control of HIV

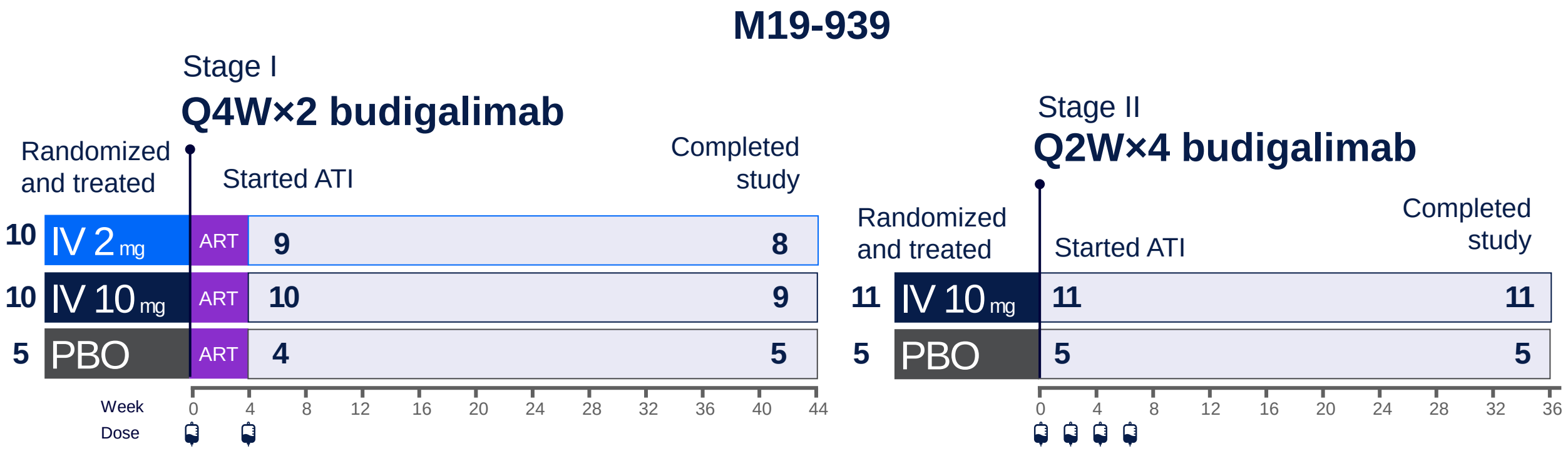
- Chronic HIV disease results in immune exhaustion and dampened T-cell responses through upregulation of inhibitory co-receptors or "immune checkpoints," such as PD-1[1]
- PD-1 inhibitors are approved as cancer immunotherapies. In HIV infection they offer a potential approach to achieve durable viral control without ART through reversal of T-cell exhaustion, restoration of T-cell functionality, and possible viral latency reversal[2-5]
- Budigalimab (ABBV-181) is a humanized, recombinant Fc mutated IgG1 monoclonal antibody targeting programmed cell death 1 (PD-1) receptor L234A L235A mAb; results from phase 1 trials in solid tumors suggest that 250 mg IV Q2W or 500 mg IV Q4W has a similar efficacy and safety profile for cancer patients as that of approved PD-1 inhibitors[6,7]
- Studies M19-939 (NCT04223804) and M19-972 (NCT04799353) are phase 1b randomized double-blind studies to investigate very low-dose (≤20 mg) budigalimab in PLWH

Objective:
Identify an efficacious dose and regimen of budigalimab with a favorable safety profile in PLWH

Outcomes:
Safety, pharmacokinetics and bioavailability, PD-1 receptor saturation, biomarkers, viral load kinetics

1. Fenwick C, et al. *Immunol Rev.* 2019;292(1):149-163; 2. Fromentin R, et al. *Nat Commun*. 2019;10(1):814; 3. Gay CL, et al. *J Infect Dis.* 2017;215(11):1725-1733; 4. Mylvaganam GH, et al. *JCI Insight.* 2018;3(18):e122940; 5. Uldrick TS, et al. *Sci Transl Med.* 2022;14(629):eabl3836; 6. Powderly J, et al. *Clin Transl Sci.* 2021;14(1):277-287; 7. Italiano A, et al. *Cancer Immunol Immunother.* 2022;71(2):417-431.
ART, antiretroviral therapy; IgG1, immunoglobulin gamma 1; IV, intravenous; mAb, monoclonal antibody; PD-1, programmed cell death protein; PLWH, people living with HIV; Q2W, every 2 weeks; Q4W, every 4 weeks.

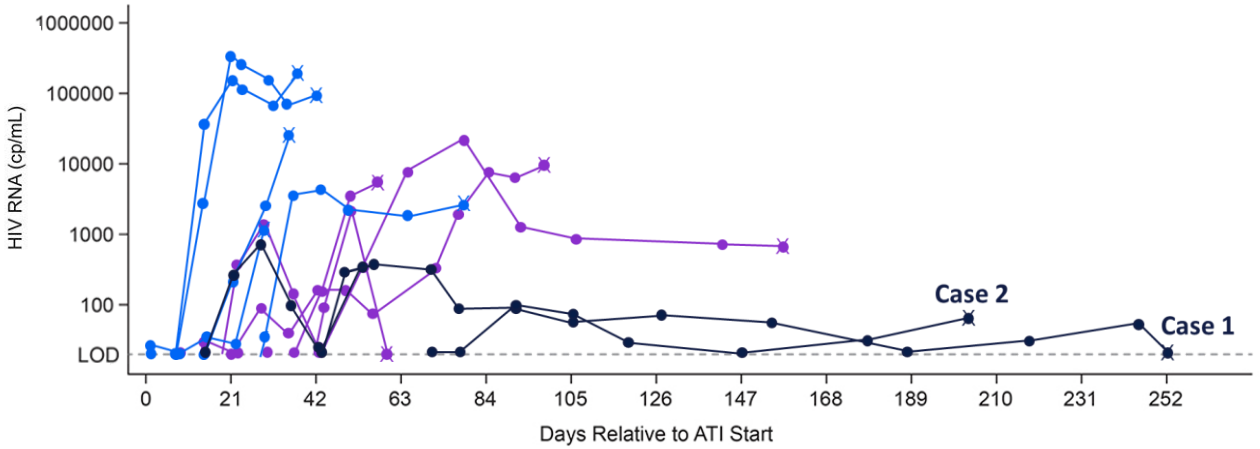
M19-939 and M19-972: Phase 1b randomized double-blind studies of budigalimab in PLWH



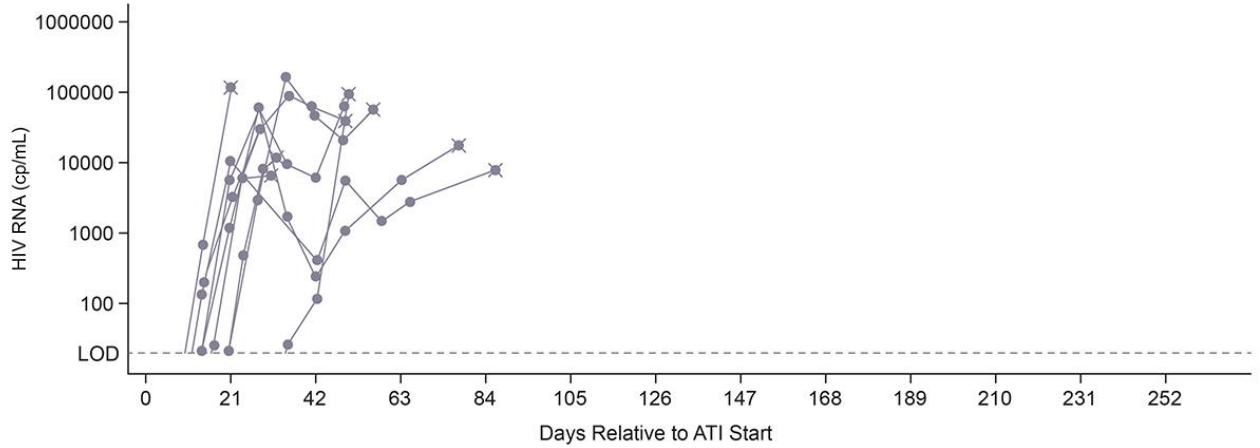
Week 0 indicates baseline/start of treatment.
ART, antiretroviral treatment; ATI, analytical treatment interruption; IV, intravenous; PBO, placebo; PLWH, people living with HIV; Q2W, every 2 weeks; Q4W, every 4 weeks.

Exploratory efficacy: Viral load kinetics during ATI (M19-939)

10-mg Q2W×4 Budigalimab (n=11)



Pooled Placebo (n=9)



Legend

- Case 1 and 2
- With delayed viral rebound or off-ART viral control[a]
- Without delayed viral rebound or off-ART viral control[a]
- Placebo
- Last observed data point before ART restart

	Pooled Placebo (n=10)	10-mg Q2W×4 Budigalimab (n=11)
Median time to viral rebound (90% CI), days	21 (21–24)	29 (21–49)

Left graphs in log scale; day 0 corresponds to baseline; in stage II, 2 participants discontinued study drug: 1 for protocol violation (prohibited live vaccination); 1 for AE (grade 1 reversible hyperthyroidism).
[a]Defined as experiencing delayed viral rebound (>21 days) and/or off-ART viral control (<1000 cp/mL).
ART, antiretroviral therapy; ATI, analytical treatment interruption; LOD, limit of detection (20 cp/mL); Q2W, every 2 weeks.