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Resistance to second generation of Integrase inhibitors

SWITCHING TO DTG/3TC FDC IS NON-INFERIOR TO TAF-BASED REGIMENS FOR 96 WEEKS: TANGO SUBGROUP ANALYSES

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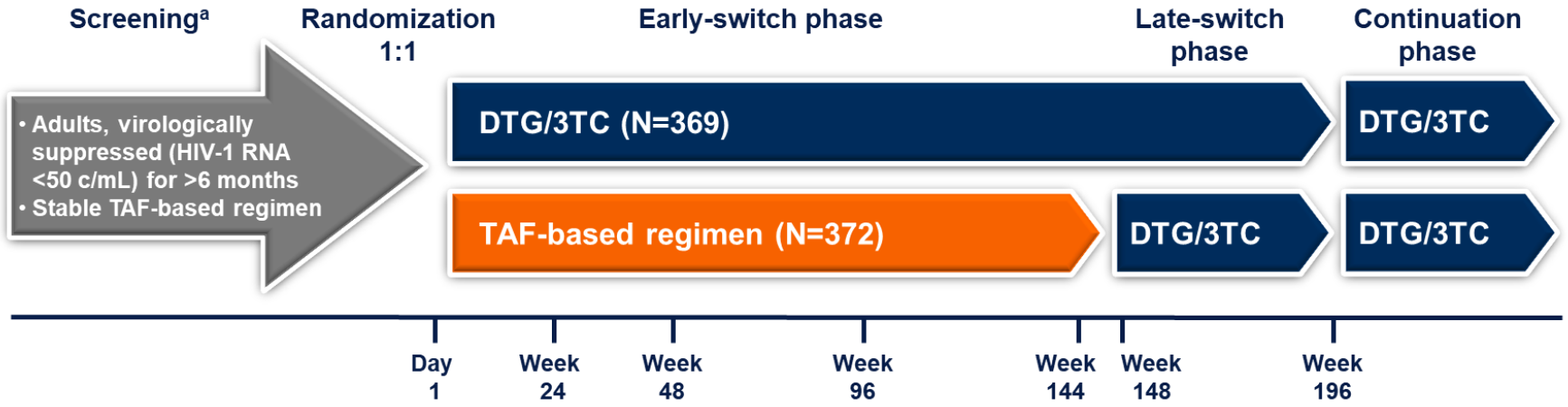
Background

- TANGO (NCT03446573) is an ongoing phase III, non-inferiority trial evaluating efficacy and safety of a switch to DTG/3TC fixed-dose combination in adults with HIV-1 infection who are virologically suppressed on a 3- or 4-drug TAF-based regimen[1]
- In the Week 48 primary analysis and Week 96 analysis of TANGO, switching to DTG/3TC FDC was non-inferior to remaining on a TAF-based regimen in ART-experienced, virologically suppressed adults[2,3]
- Here we present rates of virologic suppression (Snapshot) through **Week 96** by demographic characteristics, baseline third agent class, and disease characteristics

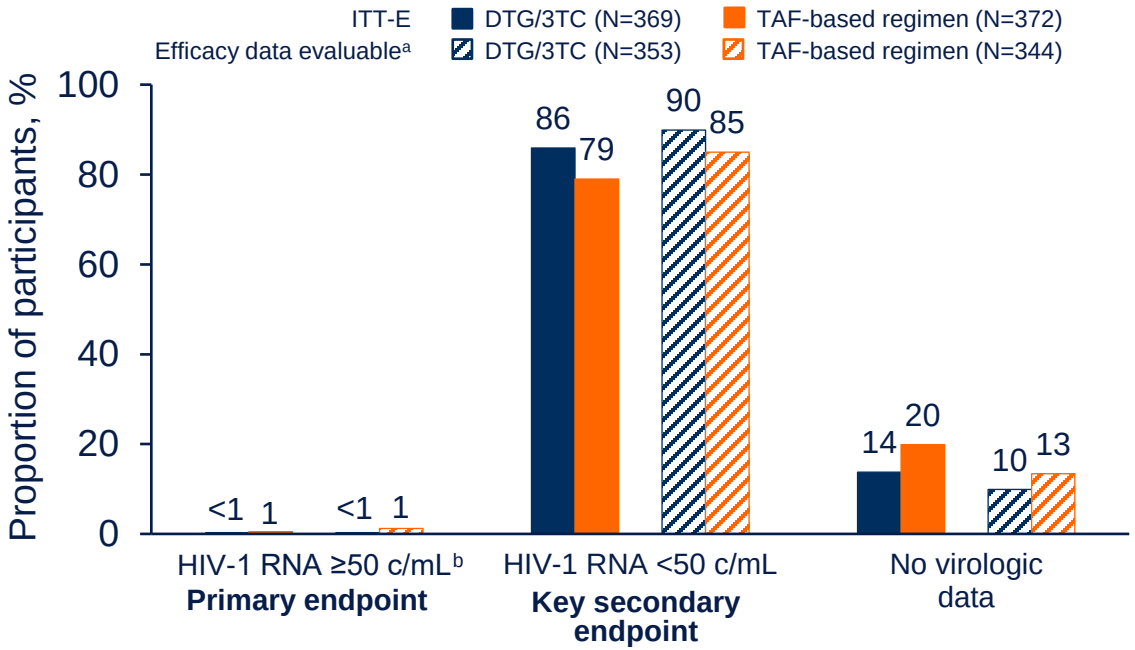


[a]Participants were eligible if they had ≥2 documented HIV-1 RNA measurements <50 c/mL, no HBV infection or need for HCV therapy, no prior VF and no documented NRTI or INSTI resistance, and TAF/FTC + PI or INSTI or NNRTI as initial regimen.

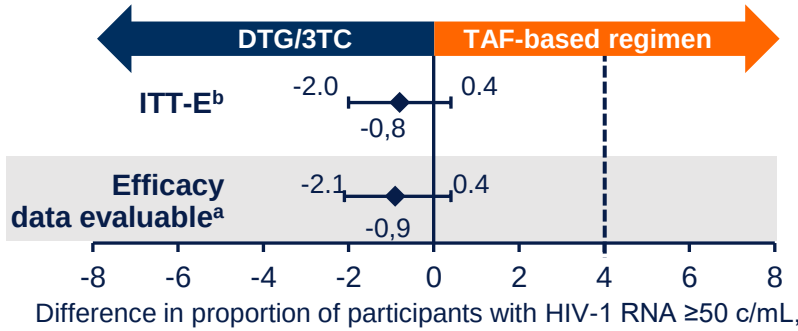
1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03446573. Accessed January 26, 2021. **2.** van Wyk et al. *Clin Infect Dis*. 2020;71:1920-1929. **3.** van Wyk et al. HIV Glasgow 2020; Virtual. Slides O441.

DTG/3TC Is Non-inferior to TAF-Based Regimen at Week 96

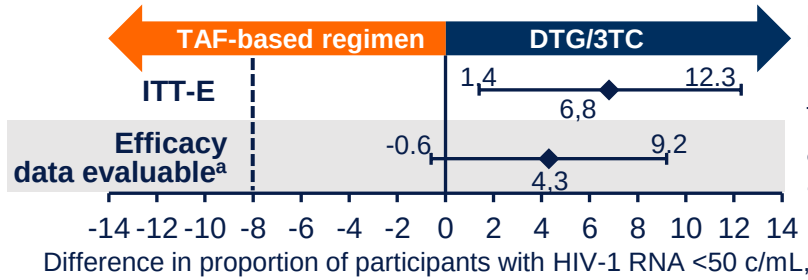
Virologic outcomes (Snapshot analysis)



Adjusted treatment difference (95% CI)[c]



HIV-1 RNA ≥50 c/mL
DTG/3TC is non-inferior to TAF-based regimen at Week 96 based on a 4% non-inferiority margin



HIV-1 RNA <50 c/mL
DTG/3TC is non-inferior to TAF-based regimen at Week 96 based on a −8% non-inferiority margin

- Superiority was demonstrated in the **per-protocol analysis**: 0/348 participants in the DTG/3TC group and 4/351 in the TAF-based regimen group had HIV-1 RNA ≥50 c/mL at Week 96 (adjusted difference, −1.1%; 95% CI, −2.3% to −0.0%; *P*=0.044)
- **In the DTG/3TC group, there were no cases of confirmed virologic withdrawal through Week 96 and 3 cases in the TAF-based regimen group; no resistance mutations were observed**

[a]Sensitivity analysis excluding 16 and 28 participants in the DTG/3TC and TAF-based regimen groups, respectively, because of no Week 96 HIV-1 RNA data due to effects of the COVID-19 pandemic. [b]Primary endpoint (Snapshot virologic non-response, ITT-E). [c]Based on Cochran-Mantel-Haenszel stratified analysis (DTG/3TC − TAF-based regimen) adjusting for baseline third agent class.

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

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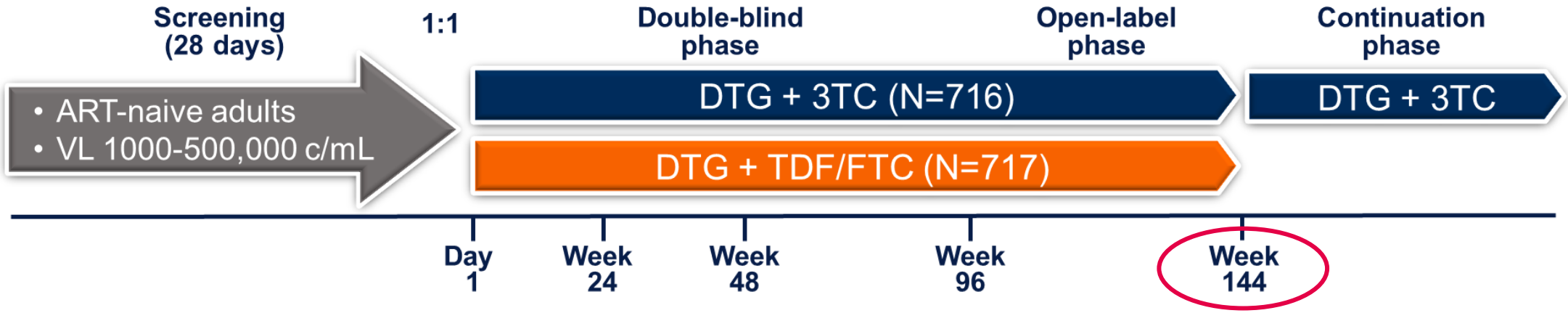
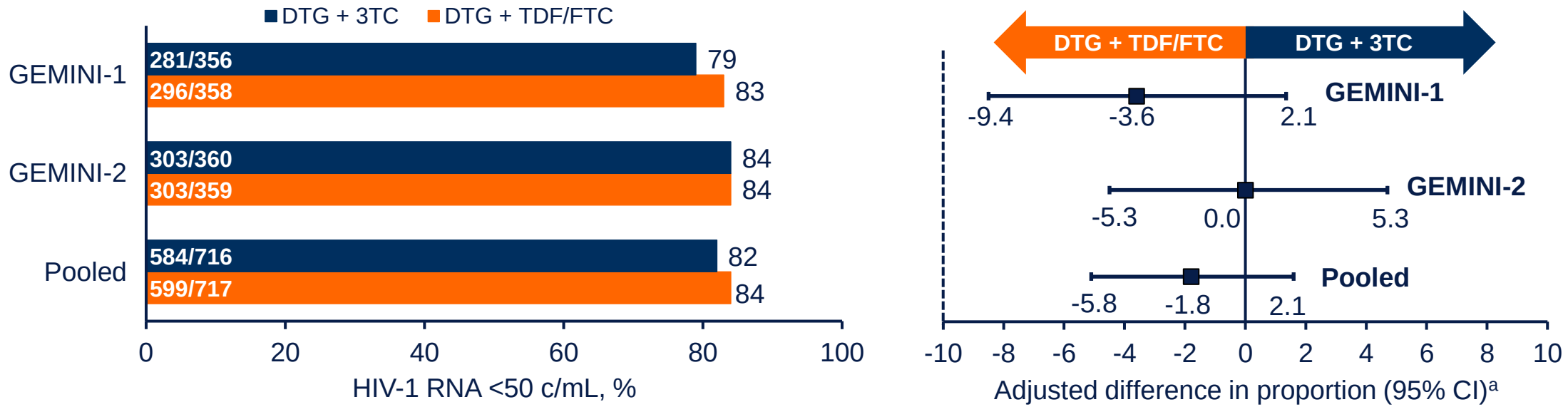
Background

- 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



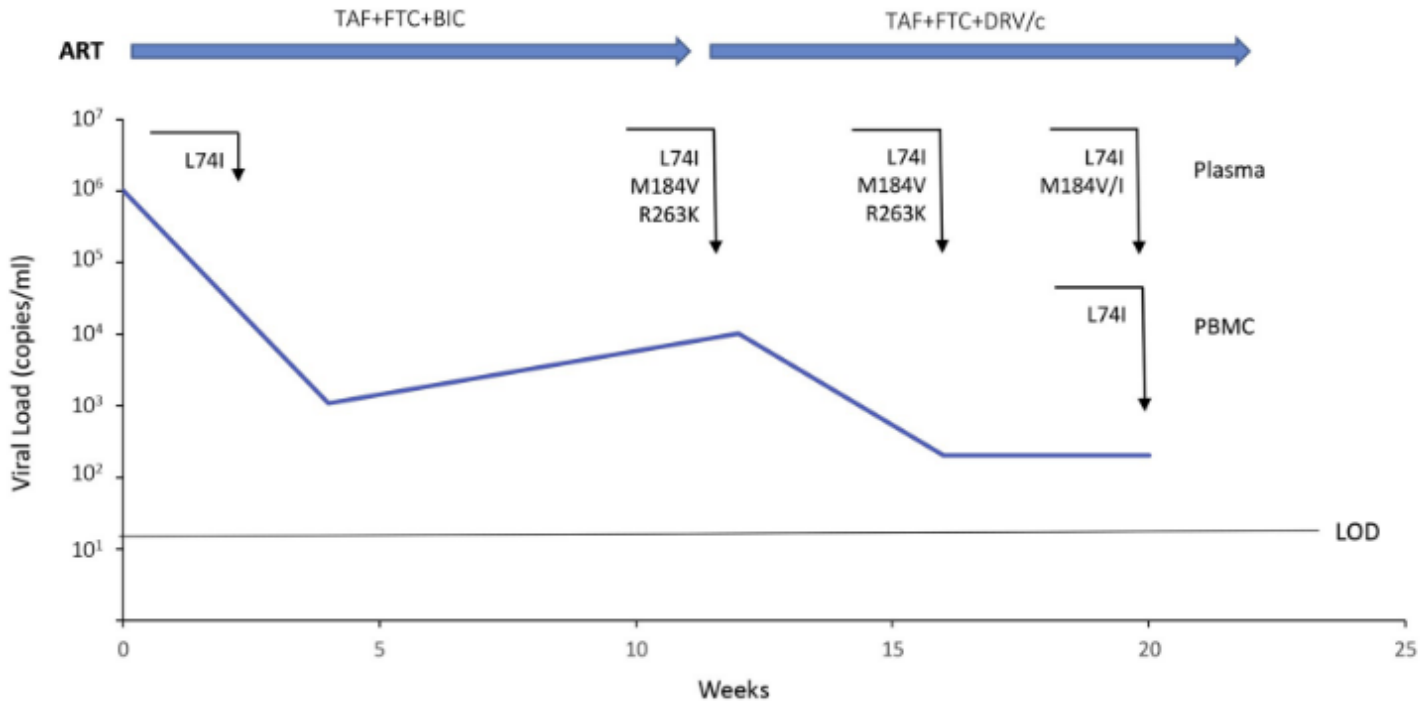
- Through Week 144, 12 participants in the DTG + 3TC group and 9 in the DTG + TDF/FTC group met protocol-defined CVW criteria; there were no treatment-emergent INSTI or NRTI resistance mutations
- **1 non-CVW participant with reported intermittent non-adherence in the DTG + 3TC group developed**
  - **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.

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

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EUROPEAN MEETING ON HIV & HEPATITIS 2021
TREATMENT STRATEGIES & ANTIVIRAL DRUG RESISTANCE
VIRTUAL MEETING | 26 - 28 MAY 2021

#13

Virological efficacy of switch to 3TC/DTG in a real life cohort of suppressed HIV-1 patients with or without past M184V – The LAMRES Study

Maria M. Santoro[1], Daniele Armenia[2], Elisa Teyssou[3], José Ramón Santos[4], Charlotte Charpentier[5], Sidonie Lambert-Niclot[6], Andrea Antinori[7], Christine Katlama[3], Diane Descamps[5], Carlo F. Perno[8], Vincent Calvez[3], Roger Paredes[4], Francesca Ceccherini-Silberstein[1], Anne Geneviève Marcelin[3], for the LAMRES Study Group

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Disclosure: Maria Mercedes Santoro has received funds for attending symposia, speaking and organizing educational activities from ViiV Health Care, Janssen-Cilag and and Theratechnologies

Background

- **The dual regimen containing dolutegravir (DTG) plus lamivudine (3TC) showed excellent results in registrational studies for its usage as first-line treatment in HIV-1 infected ART-naïve patients and as treatment simplification strategy in virologically suppressed individuals.** *(PADDLE study: Cahn JIAS 2017; ACTG A5353 study: Taiwo et al., CID 2018; GEMINI 1 & 2 studies: Cahn et al., JAC 2020; TANGO study: van Wyk et al., CID 2020)*

- **The presence of pre-existent resistance and in particular of M184V mutation did not affect virological outcome in clinical trials.** *(DOLULAM study: Charpentier et al., JAC 2017; ART-PRO study: De Miguel et al., 2020; Rial-Crestelo et al., 2021)*

- **Considering that patients with previous resistance were often excluded or might be underestimated in clinical trials, only observational studies in real life might provide some additional information, despite their several biases.**

- **However, the impact of previous selection of M184V on virological response to 3TC/DTG in real life is still unclear.**

AIM

To assess the efficacy of 3TC/DTG in a set of virologically suppressed patients with or without past M184V.

Methods

This **European retrospective study** included **several clinical and virological centers** involved in HIV care from **France**, **Italy** and **Spain**.

Patients were included according to the following criteria:

- ✓**To be virologically suppressed** (plasma HIV-RNA ≤50 copies) at **switching to dual therapy including 3TC/DTG**.
- ✓Availability of **at least one previous** HIV-RNA and/or HIV-DNA genotypic resistance test (GRT).
- ✓Virological **follow up after switching** to 3TC/DTG.

Survival analysis was used to evaluate **the role of past M184V on experiencing a virological failure** (**VF**: HIV-RNA >50 cps/mL in 2 consecutive determinations or ≥200 cps/mL in a single determination) or **a blip** (a single HIV-RNA in the range 51-199 cps/mL preceded and followed by ≤50 cps/mL measurements) after 3TC/DTG switch.
Moreover, **demographic, viro-immunological and therapeutical variables** were evaluated **as other potential factors associated with VF or blips**.
Resistance at VF was also evaluated.

Patients' characteristics at 3TC/DTG switch

Demographic characteristics

Variables	Overall (N=533)
Male, n (%)	422 (79.2)
Risk factor, n (%)	
Homosexual	252 (47.3)
Heterosexual	169 (31.7)
Drug abuse	62 (11.6)
Sexual	23 (4.3)
Other/unknown	27 (5.1)
Ethnicity, n (%)	
Caucasian	391 (73.4)
Black	23 (4.3)
Hispanic	18 (3.4)
Other/unknown	101 (18.9)
Adherence, n (%)	
High	130 (24.4)
Medium/Low	22 (4.1)
Unknown	381 (71.5)

Viro-immunological characteristics

Variables	Overall (N=533)
HIV-1 subtype B, n (%)	392 (73.5)
Viremia Zenith (log_{10} copies/mL), median (IQR)	**5.1 (4.5-5.6)**
TND at switch, n (%)	**233 (43.7)**
Time under VS before switch, (years), median (IQR)	5 (3-9)
Nadir CD4 cell count (cell/mm^3), median (IQR)	**266 (133-384)**
Baseline CD4 cell count (cell/mm^3), median (IQR)	691 (514-883)
At least one failure before switch, n (%)	209 (39.2)
INI-failure before switch, n (%)	18 (3.4)

TND: target not detected; VS: virological suppression

Therapeutic characteristics

Variables	Overall (N=533)
Years under cART, median (IQR)	8 (4-15)
N° of previous regimens experienced, median (IQR)	3 (2-5)
N° of ARVs experienced, median (IQR)	
NRTIs	3 (2-4)
NNRTIs	1 (0-1)
PIs	2 (0-3)
INIs	1 (0-1)
Entry Inhibitors	0 (0-0)
Previous 3TC/FTC exposure, n (%)	529 (99.2%)
Previous first generation INI-exposure, n (%)	166 (31.1)
Previous DTG exposure, n (%)	145 (27.2)

Probability of virological failure (VF) after 3TC/DTG switch in a large cohort of virologically suppressed individuals

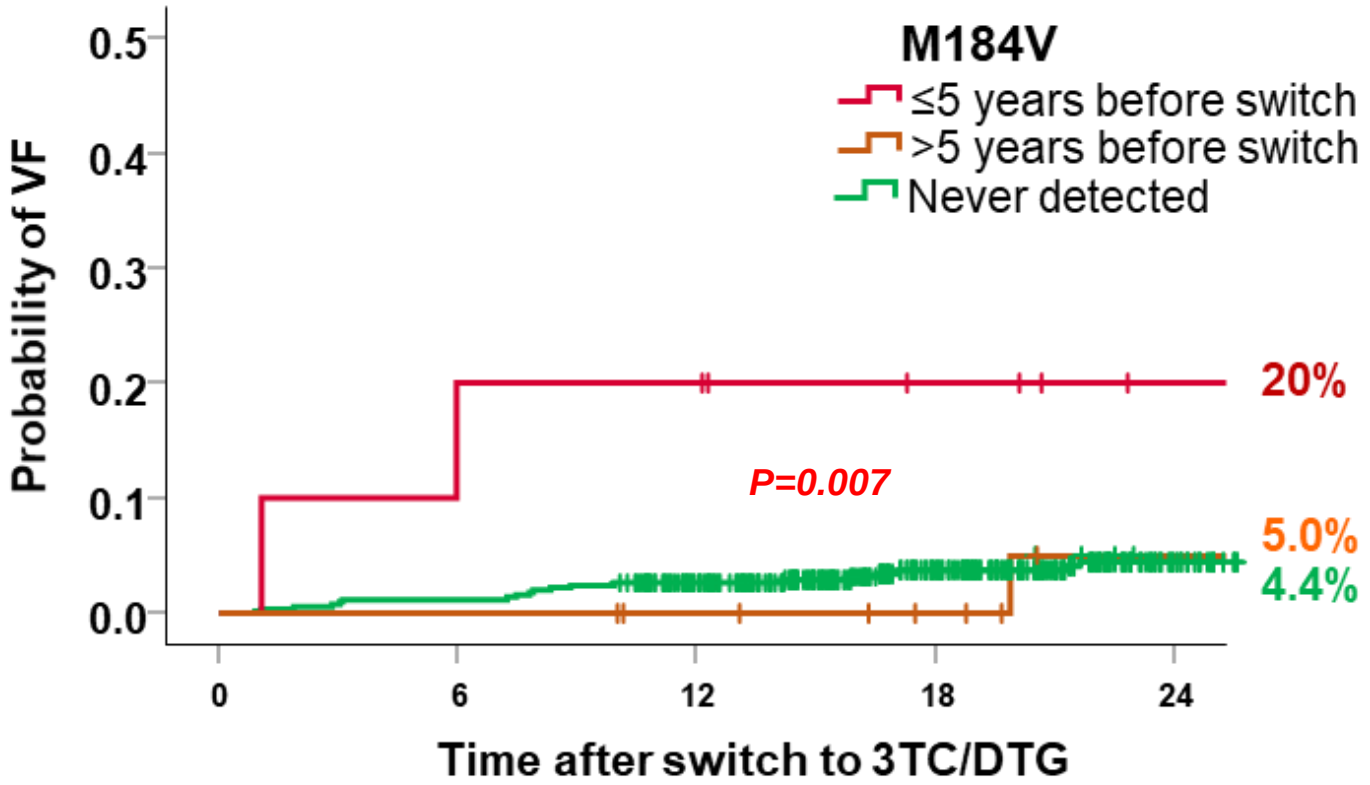
Overall probability at **1 year**: **2.8%**
Overall probability at **2 years**: **4.8%**

No significant difference in the probability of VF was found according to the **presence/absence of M184V (**p=0.345):

- **1 year**: **5.4%** vs. **2.6%**;
- **2 years**: **9.2%** vs. **4.4%**

A significantly higher probability of VF was found in individuals with M184V detected ≤5 years before switch compared to those with M184V detected >5 years and those without M184V.

Kaplan-Meier estimates of VF according to M184V absence/presence and its time of last detection



Factors associated with VF after 3TC/DTG switch

Cox regression analysis confirmed that **past M184V influenced VF only in the context of a more "recent"** (≤5 years) **detection**.

Factors significantly associated with virological failure at uni-multivariable Cox regression analyses

Variables	Hazard ratio (HR, 95% C.I.) to experience VF					
	Crude HR	P value	Adjusted[1] HR	P value	Adjusted[2] HR	P value
Risk factor, n (%)						
Homosexual	1		1		1	
Heterosexual	**4.8 (1.8-13.1)**	**0.002**	**4.6 (1.3-15.8)**	**0.017**	**3.8 (1.1-13.3)**	**0.034**
Drug abuse	2.2 (0.5-9.1)	0.290	2.3 (05-11.7)	0.314	0.9 (0.1-5.4)	0.886
Sexual	2.2 (0.3-18.6)	0.479	2.3 (0.2-20.5)	0.470	2.3 (0.3-21.2)	0.458
Viremia Zenit (copies/mL), n (%)						
<100,000	1		1		1	
100,000-500,000	2.8 (0.9-8.1)	0.063	**3.9 (1.2-12.5)**	**0.020**	3.3 (1.0-11.1)	0.050
>500,000	**4.1 (1.4-12.0)**	**0.010**	**3.3 (1.0-11.0)**	**0.049**	**3.6 (1.1-12.0)**	**0.041**
Cumulative class resistance before switch, n (%)						
None	1		-		1	
1	1.6 (0.6-4.4)	0.366	-	-	1.3 (0.4-3.9)	0.635
2	3 (0.8-10.3)	0.089	-	-	5.1 (0.9-28-6)	0.065
≥3	**7.1 (2-24.7)**	**0.002**	-	-	**23.0 (3.1-168.5)**	**0.002**
Past M184V according to detection time, n (%)						
Never detected	1		1		1	
Detected ≤5 years before switch	**5.6 (1.3-23.7)**	**0.020**	**10.6 (1.6-69.4)**	**0.014**	1.9 (0.3-14.6)	0.518
Detected >5 years before switch	0.7 (0.1-5.6)	0.778	0.5 (0.1-4.0)	0.495	**0.1 (0.0-1.2)**	**0.040**

The following variables have been considered for the Cox regression analysis: sex, age, risk factor, ethnicity; HIV-1 subtype; adherence; time of previous virological suppression before 3TC/DTG switch; number of previous viral blips before 3TC/DTG switch; nadir CD4 cell count; CD4 cell count at 3TC/DTG switch; time under cART before 3TC/DTG switch; 3TC/DTG switch after first-line regimen; at least one virological failure before 3TC/DTG switch; INI-failure before 3TC/DTG switch; class resistance accumulated before 3TC/DTG switch (among PI, NRTI, NNRTI and INI); presence/absence of past M184V; last detection time of M184V before 3TC/DTG switch; percentage of individuals with viremia target not detected (TND) at 3TC/DTG switch. In the table are reported variables that were significant at both uni- and multi-variable models. Two adjusted models are reported: [1] Model adjusted excluding class resistance; [2] Model adjusted also for class resistance.

Resistance at failure

Genotypic resistance test was available for 4/22 individuals who failed 3TC/DTG.

No resistance to INIs and NRTIs was found.

Probability of viral blips after 3TC/DTG switch

Overall probability at **1 year**: **3.6%**
Overall probability at **2 years**: **7.3%**

No statistical association of **M184V with the probability of blips** (p=0.321), neither after considering the time of last M184V detection (p=0.596).

Factors associated with blips after 3TC/DTG switch

By Cox analysis, to be **drug abuser** was positively associated with **viral blips**, while **having viremia target not detected** at switch was negatively associated.

Factors significantly associated with viral blips at uni-multivariable Cox regression analyses

Variables	Crude HR (95% C.I.)	P value	Adjusted HR (95% C.I.)	P value
Risk factor, n (%)				
Homosexual	1			
Heterosexual	**2.1 (1.0-4.3)**	**0.039**	2.1 (1.0-4.3)	0.052
Drug abuser	**3.1 (1.4-6.9)**	**0.006**	**2.9 (1.2-7.1)**	**0.020**
Sexual	1.7 (0.4-7.5)	0.492	1.6 (0.4-7.1)	0.532
Target not detected at switch, n (%)				
No	**1**			
Yes	**0.5 (0.3-0.9)**	**0.018**	**0.4 (0.2-0.7)**	**0.002**

The following variables have been considered for the Cox regression analysis: sex, age, risk factor, ethnicity; HIV-1 subtype; adherence; time of previous virological suppression before 3TC/DTG switch; number of previous viral blips before 3TC/DTG switch; nadir CD4 cell count; CD4 cell count at 3TC/DTG switch; time under cART before 3TC/DTG switch; 3TC/DTG switch after first-line regimen; at least one virological failure before 3TC/DTG switch; INI-failure before 3TC/DTG switch; class resistance accumulated before 3TC/DTG switch (among PI, NRTI, NNRTI and INI); presence/absence of past M184V; last detection time of M184V before 3TC/DTG switch; percentage of individuals with viremia target not detected (TND) at 3TC/DTG switch. In the table are reported only variables that were significant at both uni- and multi-variable models.

HIV With Transmitted Drug Resistance Is Durably Suppressed by B/F/TAF at Week 144

Rima K. Acosta, Grace Q. Chen, Silvia Chang, Ross Martin, Xinxin Wang, Hailin Huang, Diana M. Brainard, Jason Hindman, Sean E. Collins, Hal Martin, Kirsten L. White

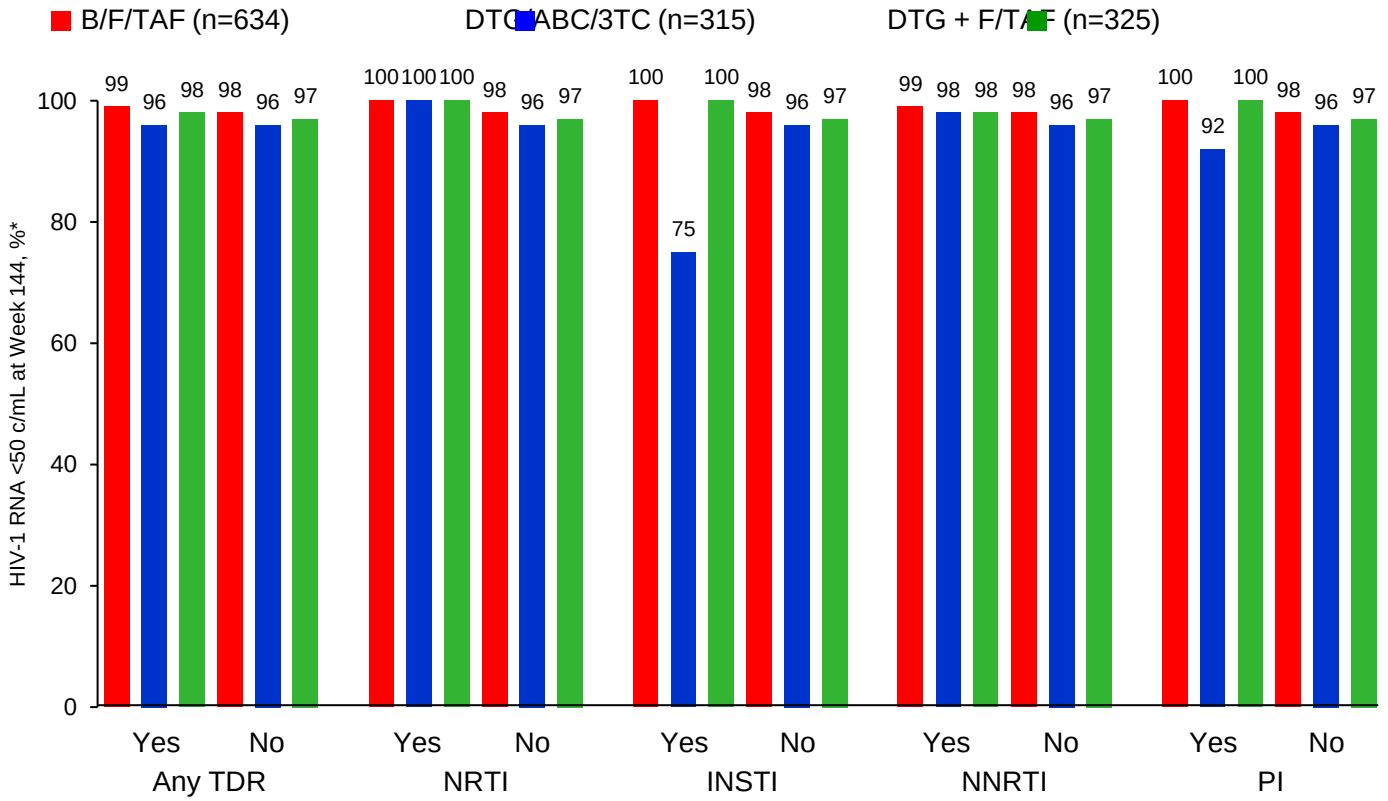
Gilead Sciences, Foster City, CA, USA

Acosta RK, Chen GQ, Chang S, et al. HIV with transmitted drug resistance is durably suppressed by B/F/TAF at Week 144. Presented at: Conference on Retroviruses and Opportunistic Infections; March 6-10, 2021; Virtual. Science spotlight.

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.

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

Long acting agents and new drugs

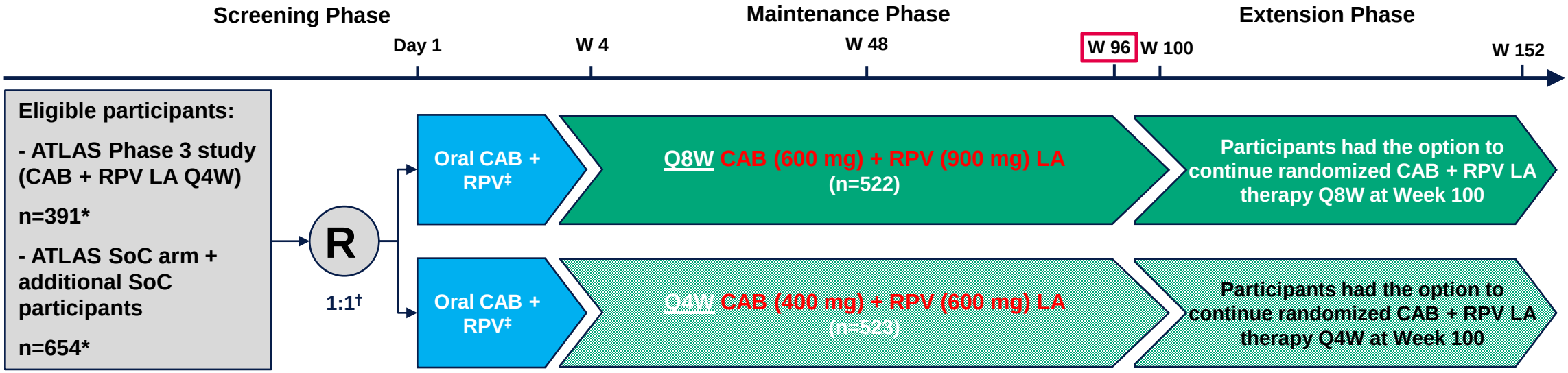
WEEK 96 EFFICACY AND SAFETY OF LONG-ACTING CABOTEGRAVIR + RILPIVIRINE EVERY 2 MONTHS: ATLAS-2M

Hans Jaeger,[1] Edgar T. Overton,[2] Gary Richmond,[3] Giuliano Rizzardini,[4] Jaime Federico Andrade-Villanueva,[5] Rosie Mngqibisa,[6] Antonio Ocampo Hermida,[7] Anders Thalme,[8] Paul D. Benn,[9] Yuanyuan Wang,[10] Krischan J. Hudson,[11] David A. Margolis,[11] Christine Talarico,[11] Kati Vandermeulen,[12] William R. Spreen[11]

[1]MVZ Karlsplatz, HIV Research and Clinical Care Centre, Munich, Germany; [2]University of Alabama at Birmingham, Birmingham, AL, United States; [3]Nova Southeastern University, FL, USA; [4]Fatebenefratelli Sacco Hospital, Milan, Italy; [5]Hospital Civil "Fray Antonio Alcalde", Guadalajara, Mexico; [6]Durban International Clinical Research Site, Enhancing Care Foundation, Durban, South Africa; [7]Department of Internal Medicine, Complexo Hospitalario Universitario de Vigo, Vigo, Spain; [8]Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden; [9]ViiV Healthcare, Brentford, United Kingdom; [10]GlaxoSmithKline, Collegeville, PA, United States; [11]ViiV Healthcare, Research Triangle Park, NC, United States; [12]Janssen Research & Development, Beerse, Belgium

ATLAS-2M Week 96: Study Design

Phase 3b, randomized, multicenter, parallel-group, noninferiority, open-label study



- The primary endpoint was the proportion of participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot, ITT-E)
- Secondary endpoints included the proportion of participants with plasma HIV-1 RNA ≥50 or <50 c/mL at Week 96 (Snapshot, ITT-E)
- Other endpoints assessed at Week 96 included the incidence of CVF (two consecutive plasma HIV-1 RNA levels ≥200 c/mL), incidence of viral resistance in participants with CVF, and safety and tolerability

*ITT-E population. †Randomization was stratified by prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks). ‡Excluding participants with prior CAB + RPV exposure in ATLAS.

For further study design details, please see Overton et al. CROI 2020; Boston, MA. Presentation 3334.[1]

CAB, cabotegravir; CVF, confirmed virologic failure; ITT-E, intention-to-treat exposed; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; R, randomized; RPV, rilpivirine; SoC, standard of care; W, week.

Overton ET, et al. Conference on Retroviruses and Opportunistic Infections 2020; Boston, MA; March 8–11, 2020. Presentation 3334. Available from: www.croiwebcasts.org/p/2020croi/croi/34

ATLAS-2M Week 96: One Participant Met the CVF Criterion Between Week 48 and 96

Overall Summary of CVFs through Week 96

	n	CVFs n (%)	CVFs with RPV RAMs*	RPV RAMs observed at failure	CVFs with IN RAMs*	IN RAMs observed at failure
Q8W	522	**9 (1.7)**	**7/9**	K101E, E138E/K, E138A, Y188L, Y181C	**5/9**	Q148R,† N155H†
Q4W	523	**2 (0.4)**	**1/2**	K101E, M230L	**2/2**	E138E/K, Q148R, N155N/H

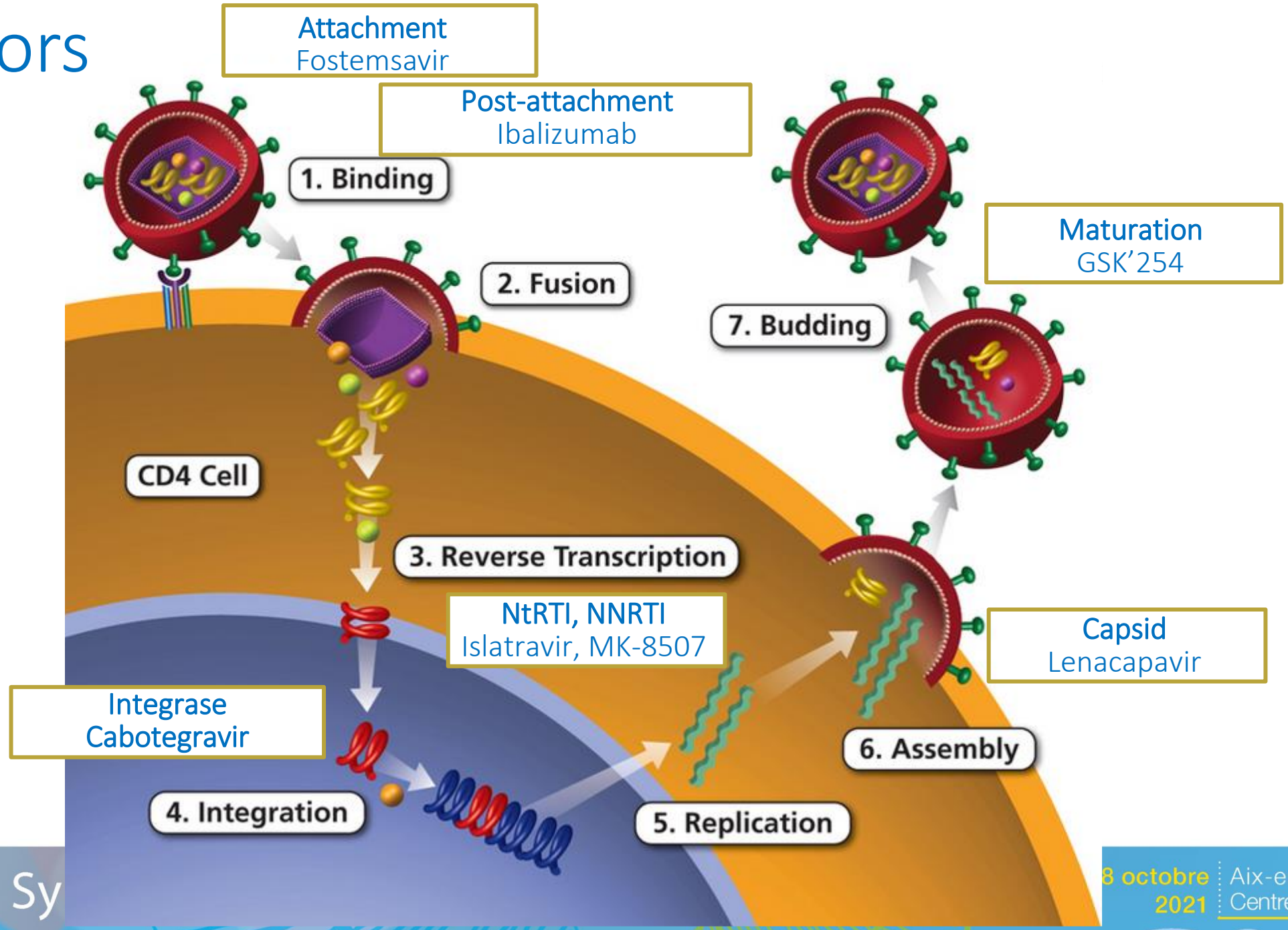
- One additional participant, who was in the Q8W arm, met the CVF criterion between Week 48 and 96 (Week 88)‡
  - NNRTI RAM K103N and RPV RAM Y181C were detected at virologic failure in the plasma sample and retrospectively at baseline in the PBMC sample
  - No INSTI RAMs were present at virologic failure in the plasma sample or in the baseline PBMC sample; IN substitution L74L/I was present at baseline
- 10/11 CVFs resuppressed on alternative regimens (one participant was non-adherent to PI-based ART

*For those with observed RAMs at failure: 7/7 Q8W and 1/1 Q4W CVFs had RPV resistance (fold-change >2), and 3/5 Q8W and 1/2 Q4W CVFs had CAB resistance (fold-change >2.5). †Or mixture.
‡The participant with CVF was a male from the US with a BMI <30 kg/m2 and HIV-1 subtype B. The participant had a viral load of 1916 c/mL at SVF and 9063 c/mL at the confirmatory visit.

ART, antiretroviral therapy; BMI, body mass index; CVF, confirmed virologic failure; IN, integrase; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PBMC, peripheral blood mononuclear cell; PI, protease inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine; SVF, suspected virologic failure.

Jaeger et al. CROI 2021; Virtual. Science Spotlight 1753.

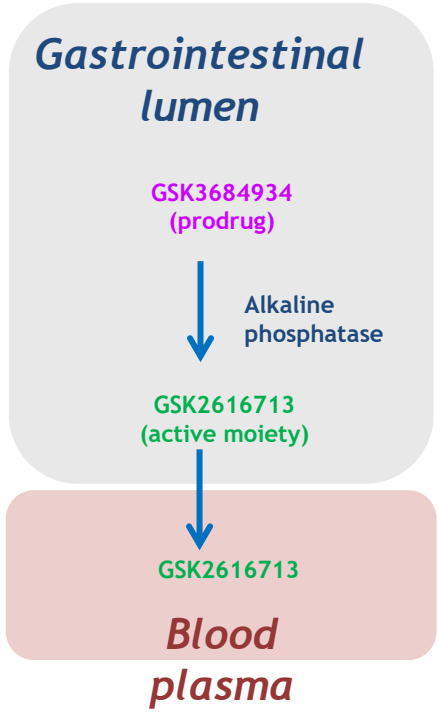
Inhibitors


Attachment
Fostemsavir
Post-attachment
Ibalizumab
1. Binding
2. Fusion
CD4 Cell
3. Reverse Transcription
NtRTI, NNRTI
Islatravir, MK-8507
Integrase
Cabotegravir
4. Integration
5. Replication
6. Assembly
7. Budding
Maturation
GSK'254
Capsid
Lenacapavir

Fostemsavir : GSK3684934

- GSK3684934 (formerly BMS-663068) is a prodrug metabolised to GSK2616713 (formerly BMS-626529), a first-in-class attachment inhibitor that binds to HIV-1 gp120, preventing initial viral attachment and entry of the virus into the host CD4+ T-cell[1,2]
- *In vitro* activity against HIV-1 viruses, with the exception of subtype AE and Group O[3]
- Active against CCR5-, CXCR4- and dual-tropic (R5X4) strains of HIV-1[3–6]
- Unique resistance profile with no *in vitro* cross-resistance to other classes of antiretrovirals[3,6]

Conversion of GSK3684934 =BMS-663068 to GSK2616713[1=] BMS-626529

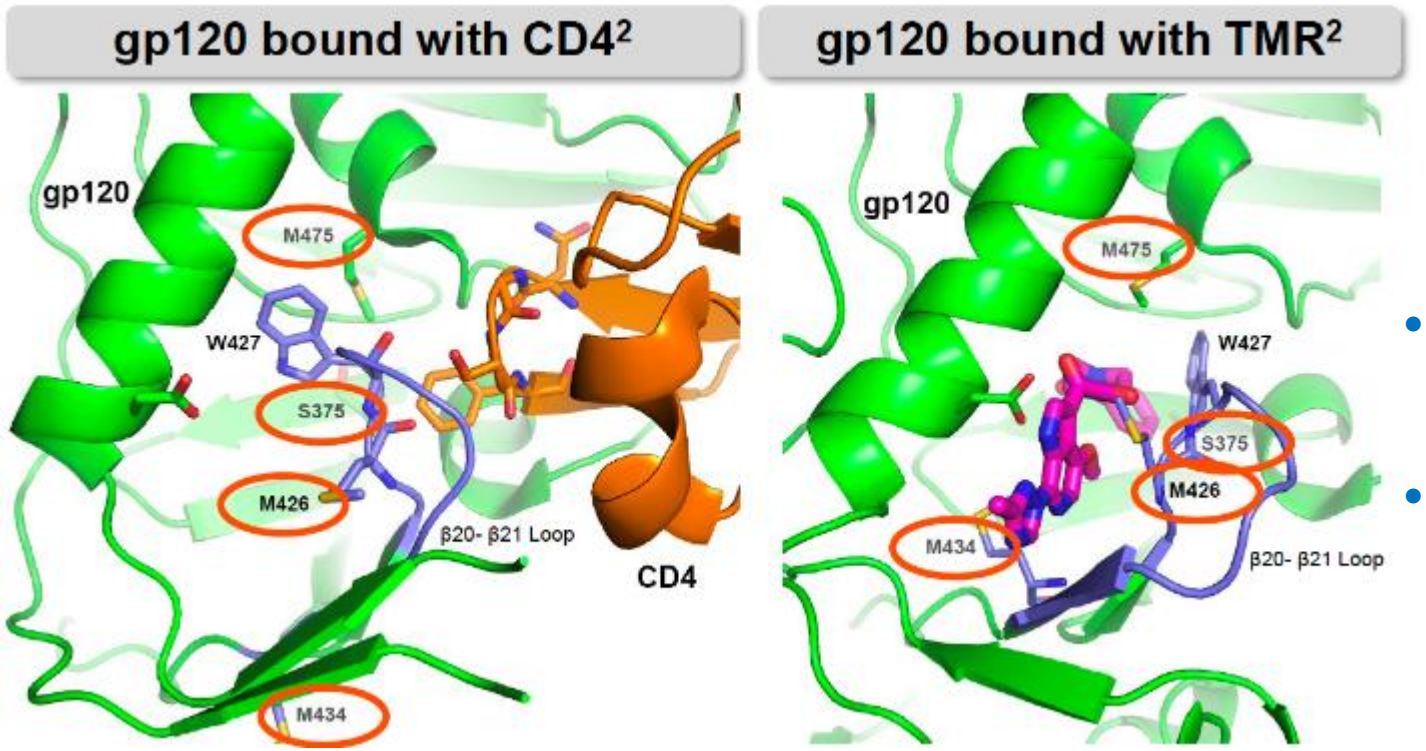


1. Brown J *et al. J Pharm Sci* 2013; 102:1742–17512; 2. Langley DR *et al. Proteins* 2015; 83:331–350;
3. Nowicka-Sans B *et al. AAC* 2012; 56:3498–3507; 4. Ray N *et al. JAIDS* 2013; 64:7–15;
5. Zhou N *et al. JAC* 2014; 69:573–581; 6. Li Z *et al. AAC* 2013; 57:4172–4180.

Llamoso C *et al.* HIV Glasgow 2016; Glasgow, UK. Oral # 335A/B.

Fostemsavir : inhibiteur d'attachement

4 polymorphisms involved in TMR-gp120 binding impacting susceptibility



Binding of temsavir (magenta) to gp120 (green) induces a significant conformational change in the b20-b21 loop (blue) that prevents the binding of CD4 (orange)

- **Mutation M426L**
  - Low frequency in subtype B
  - Similar frequency for subtypes B and CRF02_AG, and lower for subtype B than for subtype D[1]
- **No difference in frequency of mutations according to viral tropism[2]**
- **Necessary to develop algorithm based on phenotype-genotype correlations to establish the contribution of mutations**

1. Charpentier C, et al. J Antimicrob Chemother. 2012

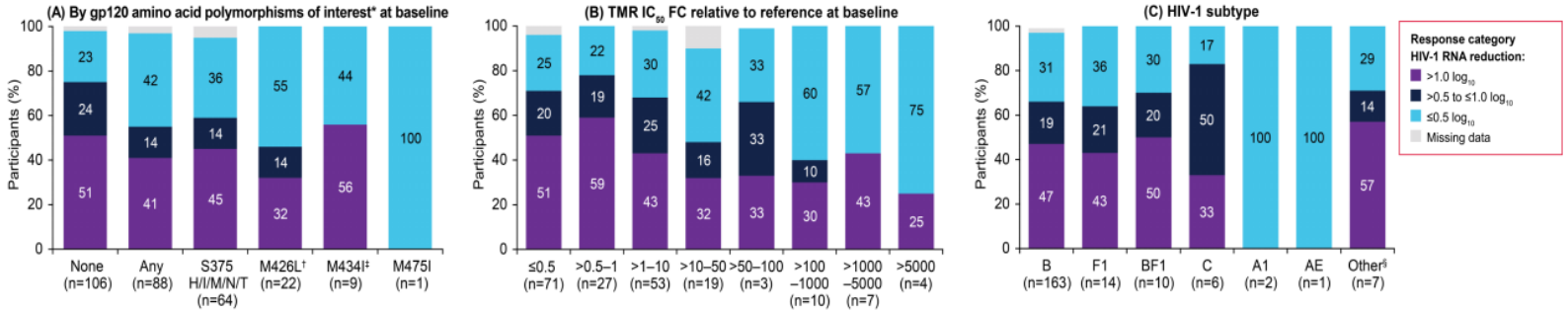
2. Soulié C, et al. J Antimicrob Chemother 2013

Lataillade et al., EACS 2019. Poster PE3/5; Gartland et al., CROI 2021. Poster 503; 3. Ray et al., J AIDS 2013; Zhou et al., JAC 2014; Lataillade et al., J AIDS 2018

BRIGHTE : impact of gp120 polymorphisms, TMR IC_{50} at BL and viral subtype on virological response at D8 and W96

203 failing patients with HIV-1 RNA ≥ 400 c/ml, 1/2 classes remaining active with at least 1 fully active ARV received FTR with a functional monotherapy from D1 to D8

Virologic Response Category at day 8 (Snapshot Analysis):

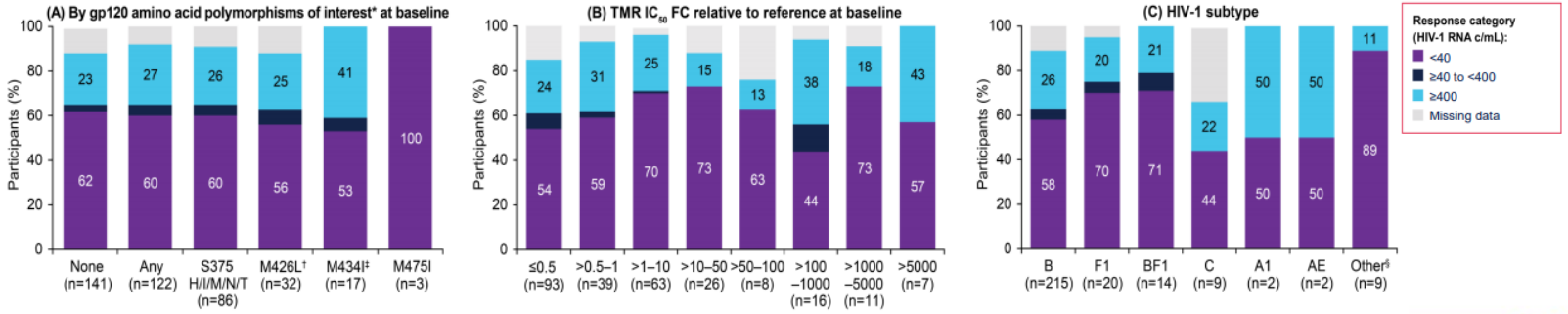


- Broad range of TMR IC_{50} Fold Change at baseline (22% of patients in FTR arm with FC > 10
Clear trend to reduced proportion of patients with VL reduction > 0.5 log as FC increases

Virologic response at Day 8 FTR functional monotherapy was variable based on the presence of gp120 polymorphisms, TMR IC_{50} at baseline or HIV-1 subtype

272 failing patients with HIV-1 RNA ≥ 400 c/ml, 1/2 classes remaining active with at least 1 fully active ARV

Virologic Response Category at Week 96 (Snapshot Analysis):



At W96 FTR + OBT Outcomes were not reliably predicted by the presence of gp120 polymorphisms, TMR IC_{50} at baseline or HIV-1 subtype

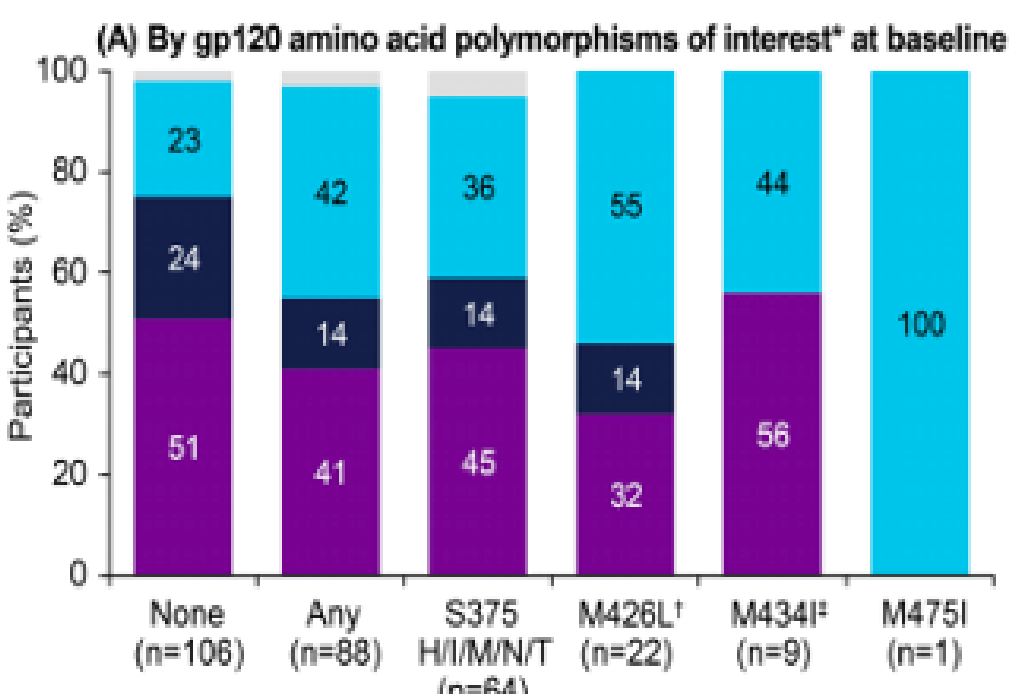
Adapted from Gartland M, et al. HIV Glasgow 2020. P019

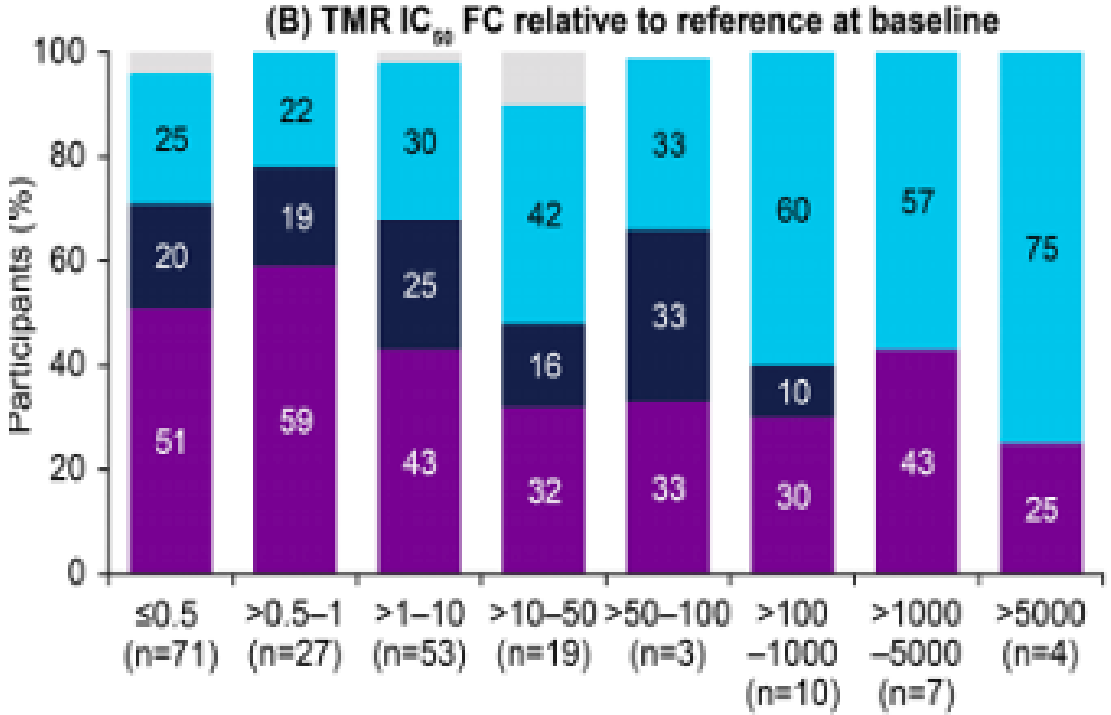
BRIGHTE : impact of gp120 polymorphisms, TMR IC_{50} at BL and viral subtype on virological response at D8 and W96

203 failing patients with HIV-1 RNA ≥ 400 c/ml, 1/2 classes remaining active with at least 1 fully active ARV received FTR with a functional monotherapy from D1 to D8

Virologic Response Category at day 8 (Snapshot Analysis):

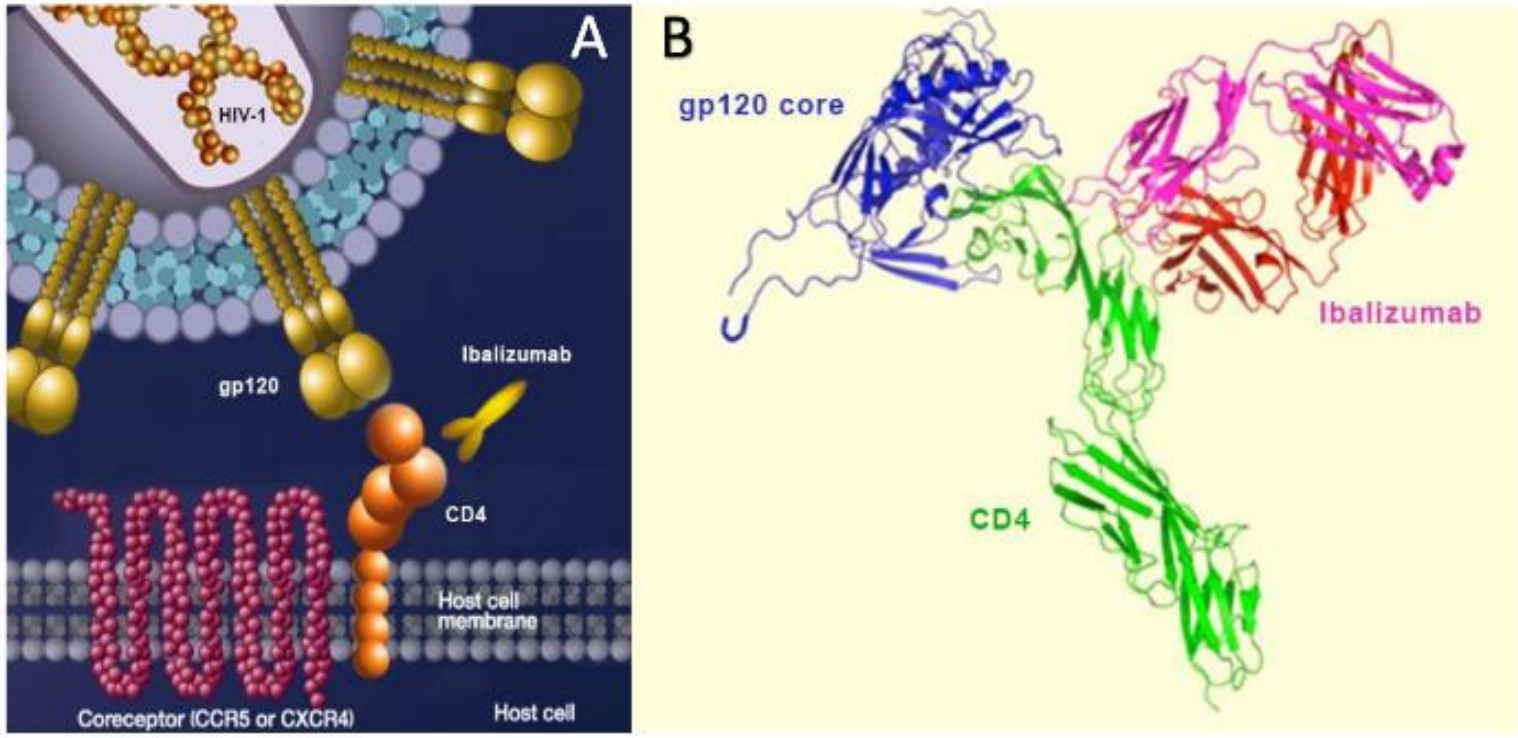
- **Virologic response at Day 8 FTR functional monotherapy** was variable based on the presence of gp120 polymorphisms, TMR IC_{50} at baseline or HIV-1 subtype





Adapted from Gartland M, et al. HIV Glasgow 2020. P019

IBALIZUMAB (IBA): long-acting humanized IgG4 mAb post attachement inhibitor



- Liaison au domaine extra-cellulaire 2 (D2) du récepteur CD4
- Interaction d'un glycane avec la partie N terminale boucle V5 gp120
- Prévient changements conformationels induits par interaction gp120/CD4 (encombrement stérique)

CD4, cluster of differentiation 4; **IgG4,** immunoglobulin G4; **mAb,** monoclonal antibody

Emu B, et al. N Engl J Med 2018;379:645-54 (supplementary appendix)

Baseline phenotypic susceptibility to IBA

VIRAL SENSITIVITY AT BASELINE

Virus	EC_{50} ng/mL	MPI
E03-137817	0.0098	97
E03-137819	0.0154	91
E03-137815	0.0114	96
E03-4328	0.0122	99
E03-4329	0.0169	97
E03-4330	0.0114	99
E03-4331	0.0145	94
E03-4332	0.0166	93
E03-4333	0.012	99
E03-4334	0.0169	89
E03-4335	0.0132	99
E03-4514	0.0098	99
E03-4565	0.0096	99
E03-4682	0.0132	96
E03-4684	0.0091	97
E03-4686	0.0101	98
E03-4569	0.0088	99
Mean ± SD	12 ± 3 ng/mL	97 ± 3
Median	12 ng/mL	97
Range	8.8-16.9 ng/mL	89-99

Baseline sensitivity to IBA:

- Baseline HIV-1 clinical isolates from 17 participants in TNX-355.02 were highly sensitive to IBA with median EC_{50} 12 ng/mL (8.8-16.9 ng/mL) and median MPI 97% (89-99%)
- Similar high sensitivities were observed in baseline samples from TMB-202 and TMB-301, where median MPI was 97% and median IC fold change (relative to reference strain JRCSF) was 0.9 for both studies

In 160 clinical isolates coming from 3 clinical studies, baseline sensitivity to Ibalizumab was high, with a median MPI of 97%

ANTIVIRAL ACTIVITY IN CELL CULTURE

Median EC_{50} values against envelope-pseudotyped viruses

Clade	Ibalizumab (µg/mL)
A	0.04
B	0.02
C	0.04
D	0.10
CRF01_AE	0.03
CRF02_AG	0.03
G	0.10
AC	0.23
ACD	0.03
BC	0.07
CD	0.07
Total	0.03

- In vitro IBA neutralised 92% of diverse HIV-1 envelope-pseudotyped viruses representing geography, clade, co-receptor tropism, and stage of infection (neutralisation defined as ≥50% inhibition of infection)
- Median MPI was high and similar across all of the HIV-1 clades assessed in the HIV-1 envelope-pseudotyped virus assay
- Notably, CRF01_AE and CRF02_AG have very high sensitivities to IBA

IBA actif sur 92% de virus pseudotypés avec *env* de diverses origine géographique, sous-types et tropisme

Jullien H et al., European HIV Drug Resistance Meeting 2020, Abstract 27

MPI: Maximum Percentage of Inhibition

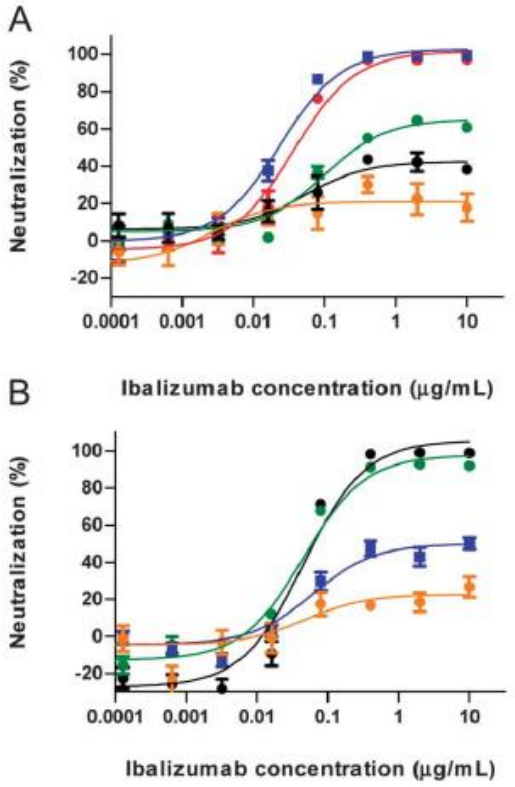
Acquired resistance to IBA and number of potential asparagine-linked glycosylation sites (PNGS) in V5 gp120 loop

Loss of Asparagine-Linked Glycosylation Sites in Variable Region 5 of Human Immunodeficiency Virus Type 1 Envelope Is Associated with Resistance to CD4 Antibody Ibalizumab[▽]

TABLE 3. The presence of V5 N-linked glycosylation sites is associated with ibalizumab susceptibility

No. of V5 PNGSs[a]	No. of clones	MPI of ibalizumab		
		Range	Median	*P* value[b]
2	42	13–100	99	
1	45	<1–100	71	<0.0001
0	9	30–78	40	<0.0001

Anti-CD4 Monoclonal Antibody Ibalizumab Exhibits Breadth and Potency Against HIV-1, With Natural Resistance Mediated by the Loss of a V5 Glycan in Envelope



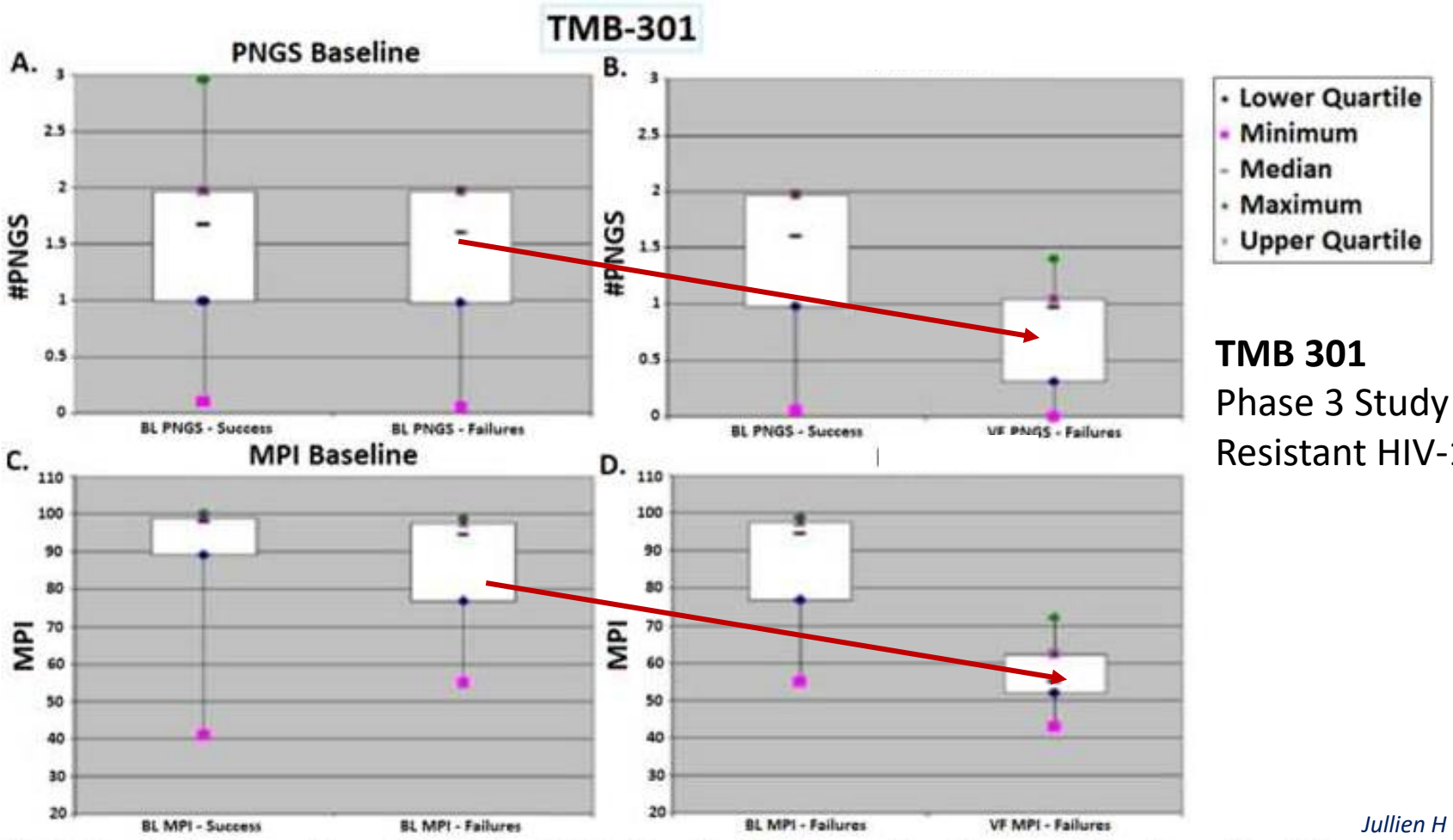
Symbol	RHPA4259.7	V5 sequence	number of V5 PNGS	nV5 PNGS position
●	VK0.16NN	**N**DTT**N**	2	0.16
■	V0.16N	**N**DTTK	1	0.16
◆	D0.33N	V**N**TTK	1	0.33
▲	K0.83N	VDTT**N**	1	0.83
●	wt	VDTTK	0	1

Symbol	AC10.0.29	V5 sequence	number of V5 PNGS	nV5 PNGS position
●	wt	RG**N**QTD**N**QT	2	0.3
◆	N0.3D	RG**N**QTDDQT	1	0.3
■	N0.7D	RGDQTD**N**QT	1	0.7
▲	NN-DD	RGDQTDDQT	0	1

- **Déterminant génétique principal de résistance** : perte de sites de glycosylation dans V5 (gp120 région N-term)
- **Mécanisme de résistance probable**: capacité des variants résistants à faciliter les changements conformationels du complexe CD4/gp120 et l'engagement du corécepteur malgré la fixation de l'IBA

1. Toma et al., J Virol, 2011; 2. Pace et al., J AIDS 2013

IBA: evolution of number of PNGS and MPI between BL and VF in samples from patients included in the IBA TMB 301 clinical trial

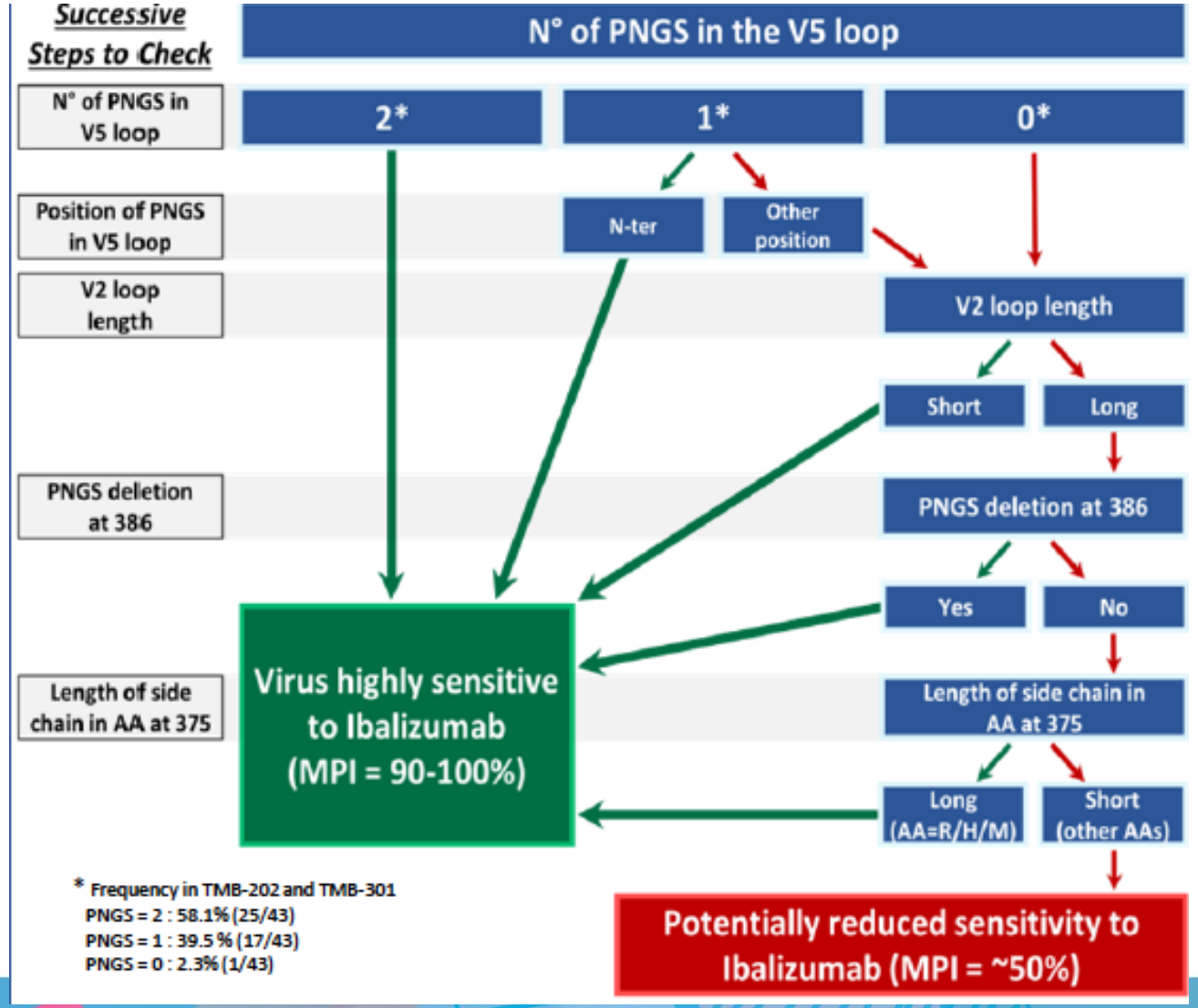


TMB 301
Phase 3 Study of Ibalizumab for Multidrug-Resistant HIV-1

Jullien H et al., European HIV Drug Resistance Meeting 2020, Abstract 27

TMB-301 analysis : Comparison of # PNGS and MPI at baseline in failing patient Vs successful patients (A and C). Comparison of # PNGS and MPIs in failing patients at baseline and PDTF (B and D)

Decisional tree to genotypically predict susceptibility to IBA



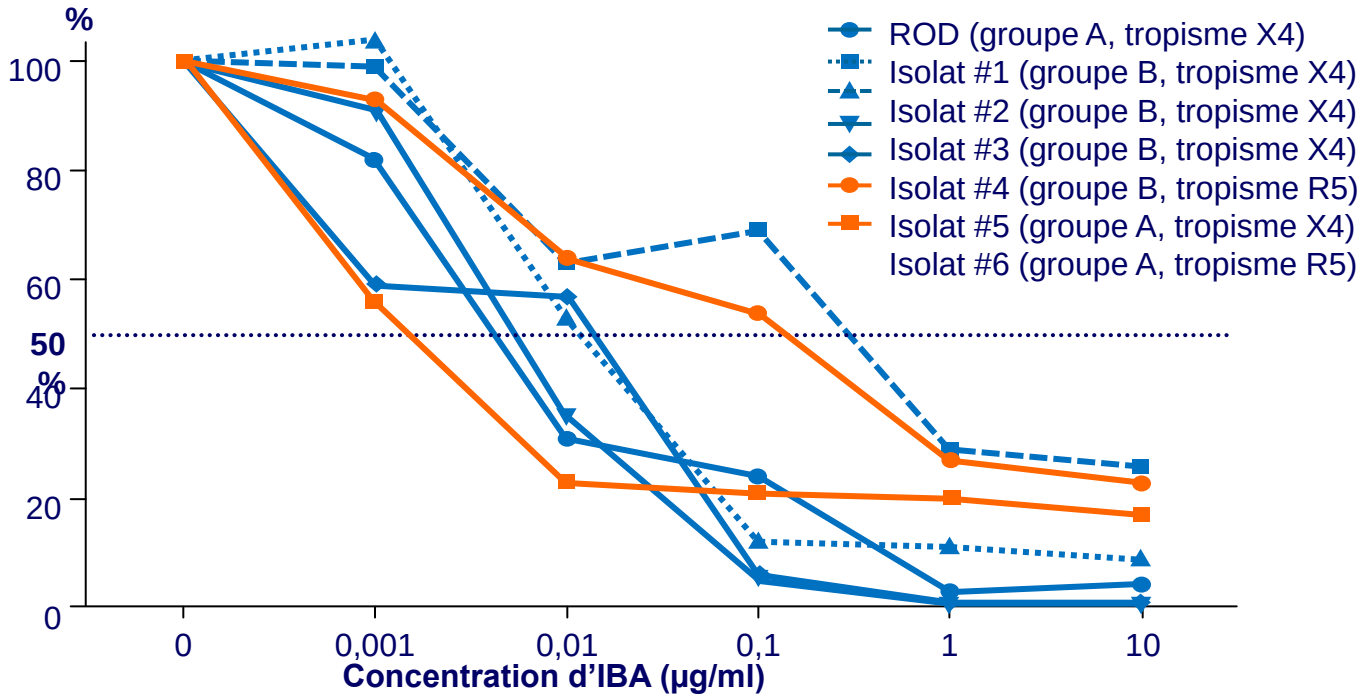
- Number of PNGS in the V5 gp120 loop
- V2 loop length (associated with the number of V2 PNGS)
- Side chain of residue 375 (H/R/M)

- *1. Jullien H et al., European HIV Drug Resistance Meeting 2020, Abstract 27*

VIH-2 : Efficacité antivirale d'IBA *in vitro*

- Détermination de la CI_{50} de IBA de 7 isolats cliniques VIH-2 issus de pts naïfs d'IBA (test phénotypique PBMC)
- CI_{50} comprise entre 0,002 et 0,18 µg/ml, similaire à celle du VIH-1 (CI_{50} = 0,06 µg/ml)
- Le % maximum d'inhibition (MPI) était > 90 % (n=4) entre 80 et 90 % (n=1) et < 80 % (n=2)

Sensibilité phénotypique à IBA (% inhibition)



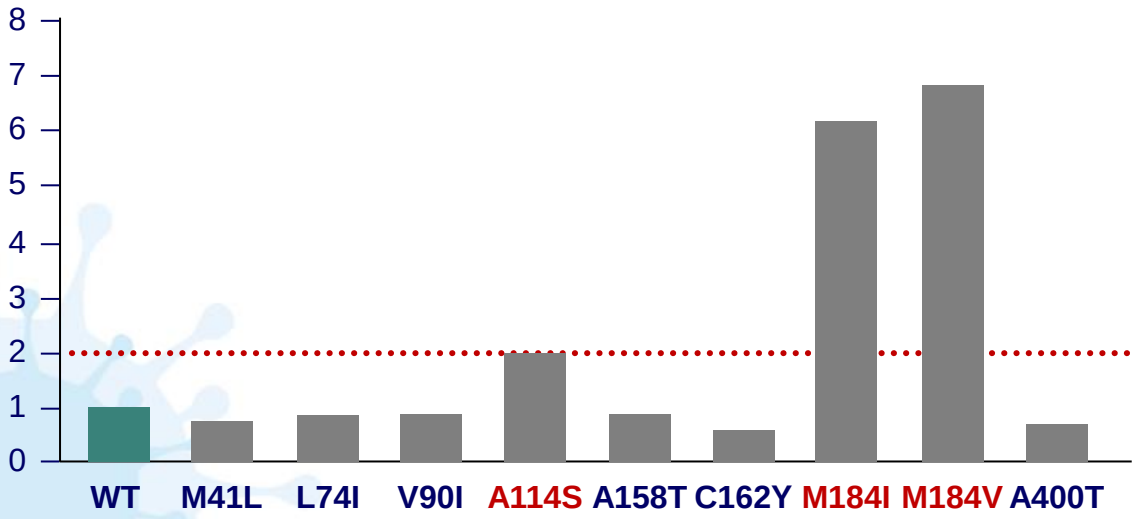
- **Résultats**
  - IBA est actif *in vitro* sur les 2 groupes du VIH-2, quelque soit le tropisme du virus
  - IBA peut constituer une nouvelle option thérapeutique chez les patients VIH-2 porteurs de virus multirésistants

Le Hingrat Q, WAIDS 2020, Abs. PEB0122

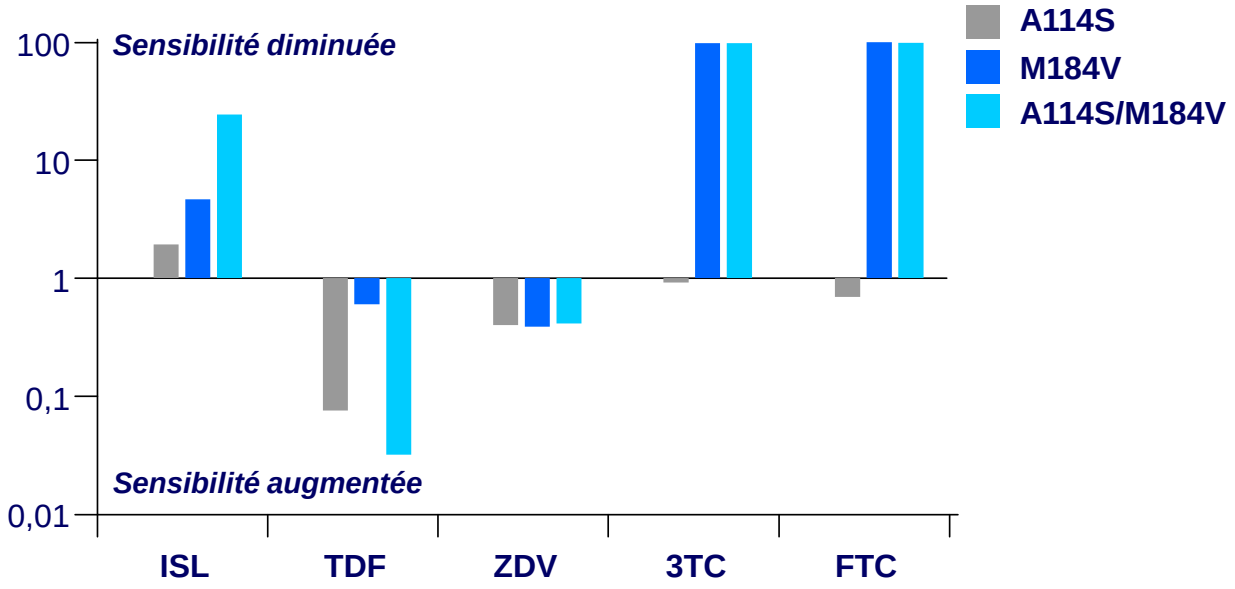
Islatravir : sélection de résistance *in vitro* (1)

- **Méthode :** sélection de résistance in vitro avec ISL sur cellules MT4 à partir de virus de sous-type A, B et C
- **Résultats**
  - Résistance toujours associée aux mutations M184I ou M184V (sous-types A, B, et C)

FC à ISL des mutations identifiées par sélection *in vitro*



FC à ISL et autres INTI des mutations identifiées par sélection in vitro



Diamond T, HIV Glasgow 2020, Abs. P120

Development of Human Immunodeficiency Virus Type 1

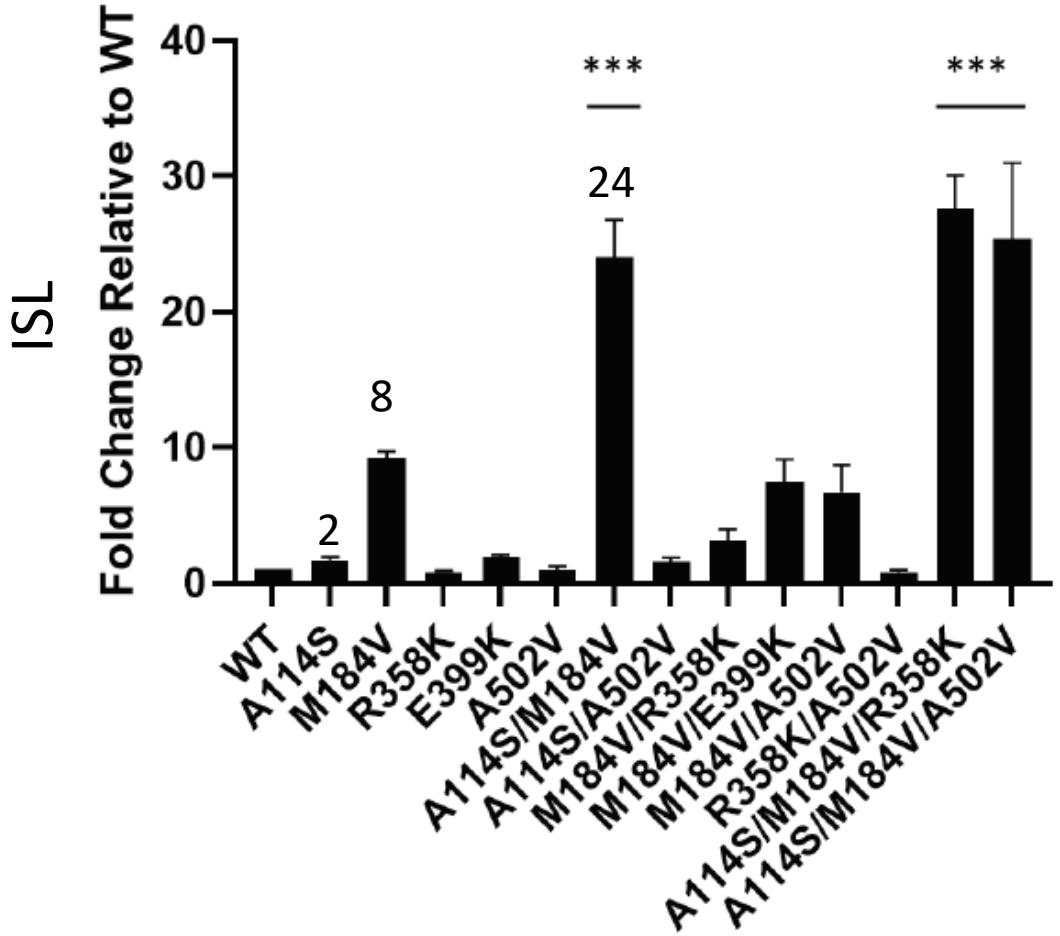
Resistance to 4'-Ethynyl-2-Fluoro-2'-Deoxyadenosine (EFdA)

Starting with Wild-Type or Nucleoside Reverse Transcriptase Inhibitor Resistant-Strains

Running Title – HIV resistance to EFdA

Maria E. Cilento[a,*], Aaron B. Reeve[b,*], Eleftherios Michailidis[c,$], Tatiana V. Ilina[b], Eva Nagy[b], Hiroaki Mitsuya[d], Michael A. Parniak[b,†], Philip R. Tedbury[a], Stefan G. Sarafianos[a,#],

AAC Accepted Manuscript Posted Online 13 September 2021
Antimicrob Agents Chemother doi:10.1128/AAC.01167-21



- Using recombinant viruses, we validated the role for M184V as the primary determinant of EFdA resistance
- A novel EFdA resistance mutational pattern that included A114S was identified in the background of M184V. A114S/M184V exhibited higher EFdA resistance (~24-fold) than M184V (~8-fold) or A114S alone (~2-fold).

229

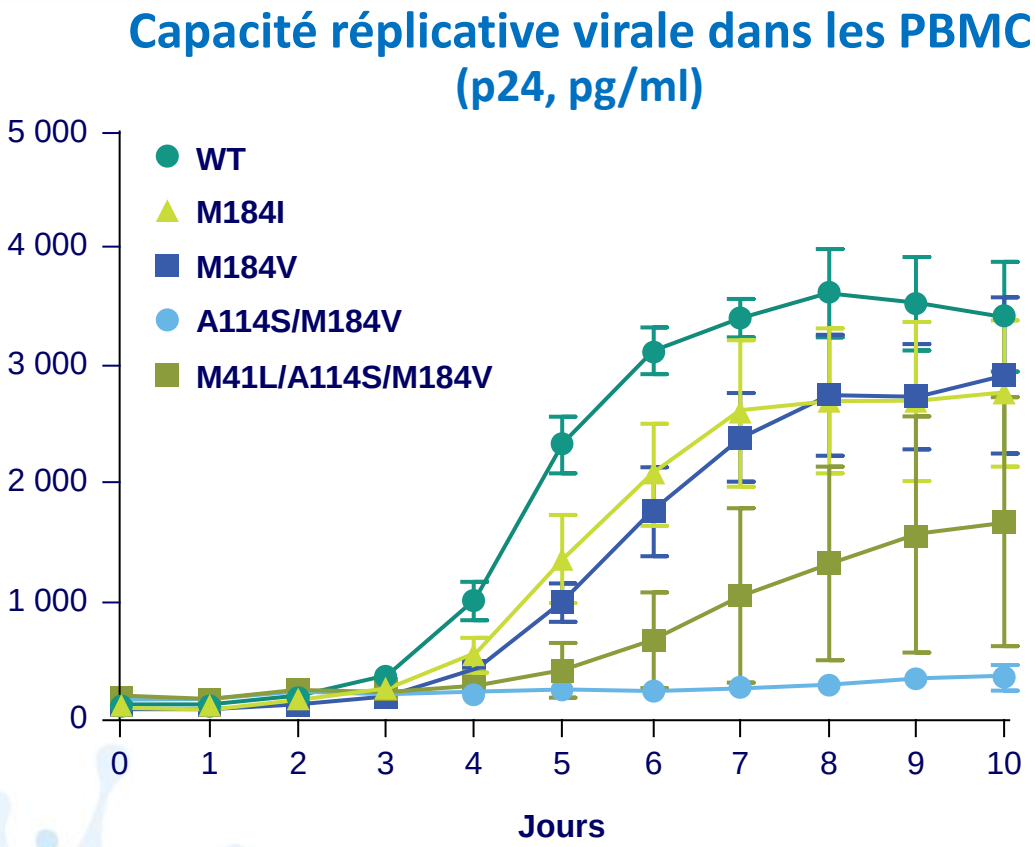
230 **FIGURE 3.** Resistance to EFdA of HIV-1 mutants selected during passaging. Mutations

231 were introduced into pNL4-3. TZM-GFP cells were pre-treated with EFdA and infected

232 after 24h. GFP positive cells (infected cells) were counted in varying concentrations of

233 EFdA. Mutants were normalized to WT infection to produce fold change. EFdA dose

Islatravir : études de sélection de résistance in vitro (2)



Capacité réplicative

- nulle pour le double-mutant A114S-M184V
- très abaissée (36 % du virus WT) pour le triple-mutant M41L-A114S-M184V

- **Conclusions**
  - En présence d'ISL, sélection in vitro des mutations M184I/V (pour sous-types A, B et C)
  - Seule autre mutation avec un impact sur la sensibilité phénotypique à ISL : A114S (FC = 2), mais si elle est associée à M184V, le virus est résistant mais n'est plus *fit*

Diamond T, HIV Glasgow 2020, Abs. P120

J Antimicrob Chemother 2021; **76**: 2137–2142
doi:10.1093/jac/dkab126 Advance Access publication 14 April 2021

Journal of Antimicrobial Chemotherapy

Cell culture selections reveal favourable drug resistance profiles for doravirine and islatravir

Bluma G. Brenner[1]*, Maureen Oliveira[1], Ruxandra-Ilinca Ibanescu[1], Jean-Pierre Routy[2] and Réjean Thomas[3]

Table 1. Cell culture selections of resistance using doravirine (DOR), DOR + islatravir (ISL), and DOR + lamivudine (3TC)

			Week 8		Week 24	
Virus	Subtype	Drug(s) (baseline EC_{50})[a]	[Drug][a]	Acquired mutations	[Drug][a]	Acquired mutations
14637	B	DOR (0.003)	0.005[a]	V108I	2.5	V108I, F227F/L, M230L, L234I
14969	B	DOR (0.001)	0.005	V108I	1	V108I, A62V, V106I, E138K, H221Y
5326	B	DOR (0.006)	0.025	V106A	10	V106A, A62A/V, V108I/V, F227L, Y318F
4742[b]	C	DOR (0.009)	0.0025	(E138A), V108I	2.5	(E138A), V108I, V106M, Y318F
6343	CRF01_AE	DOR (0.0004)	0.0025	None	2.5	V108I, H221Y, L234I
96USSN20[c]	CRF02_AG	DOR (0.006)	0.005	Y318F	10	Y318F, V106A, F227L
pNL4.3	B	DOR (0.001)	0.010	V108I	2.5	V108I, F227L, M230L, Y318F/Y
16347	B	DOR + ISL	0.0025/0.01	None	0.01/0.05	V108I
14969	B	DOR + ISL	0.005/0.01	None	0.01/0.05	V108I/V, H221Y
5326	B	DOR + ISL	0.01/0.05	None	0.05/0.5	V108I
4742	C	DOR + ISL	0.001/0.01	(E138A)	0.01/0.1	(E138A), V108I/V, Y188Y/H
6343	CRF01_AE	DOR + ISL	0.0025/0.025	None	0.005/0.05	None
96USSN20	CRF02_AG	DOR + ISL	0.01/1.01	None	0.25/2.5	V108I, M184M/I. Y318F
pNL4.3	B	DOR + ISL	0.005/0.05	None	0.025/0.25	V108I
16347	B	DOR + 3TC	0.01/0.05	V106A/V	0.025/0.1	V106A, M184M/I
14969	B	DOR +3TC	0.01/0.05	None	0.01/0.05	None
5326	B	DOR + 3TC	0.005/0.05	V106A/V	0.05/0.5	V106A
4742	C	DOR + 3TC	0.0025/0.025	(E138A)	0.025/0.25	(E138A), V108I
6343	CRF01_AE	DOR + 3TC	0.01/0.05	None	0.01/0.1	V108I, H221Y, L234I
96USSN20	CRF02_AG	DOR + 3TC	0.01/0.1	None	0.025/0.25	F227F/V, Y318F/Y
pNL4.3	B	DOR + 3TC	0.01/0.1	V108I/V	0.025/0.25	V108I

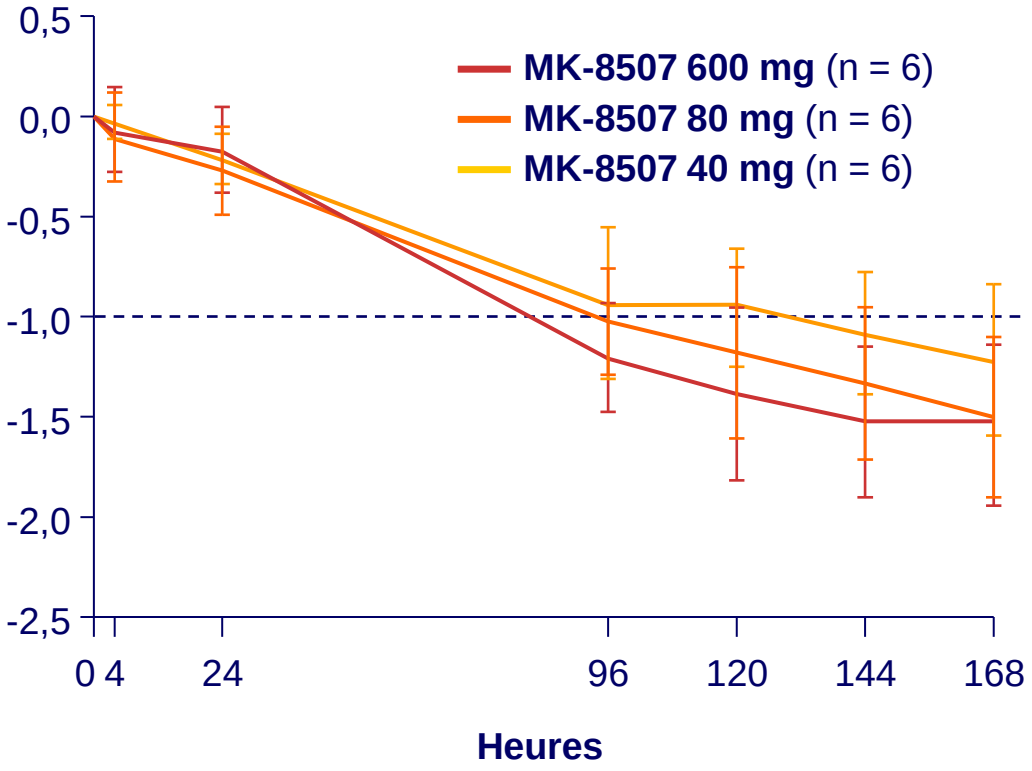
[a]The genotype of acquired resistance mutations and drug concentrations reached for doravirine (μM), lamivudine (μM) and islatravir (nM) are shown for weeks 8 and 24.
[b]Isolate 4742 is a subtype C strain with a baseline natural polymorphism of E138A in a treatment-naive patient.
[c]Isolate 96USSN20 had baseline D67D/N, T69D and K70R mutations associated with resistance to thymidine analogues.

le meilleur ...de CROI 2021

MK-8507, nouveau INNTI : profil de résistance (1)

- CI_{50} : 51,3 nM
- Demi-vie plasmatique moyenne : 70 h
- Administration per os 1 fois/semaine envisageable
- Dose orale unique de 40 mg de MK-8507
  ➔ baisse de CV >1 log_{10} c/ml à J7
- Essai de phase 2 : MK-8507 + ISL qs en cours
- **Actif sur les sous-types de VIH-1**
  A, A1, CRF01_AE, CRF02_AG, B, BF, C, D, F1, G, H
- **FC sur simples mutants**
  K103N (FC = 4,7)
  Y181C (FC = 2,9)
  G190A (FC = 3,7)

Baisse moyenne de CV après une dose unique de MK-8507 (log_{10} c/ml ± ET)

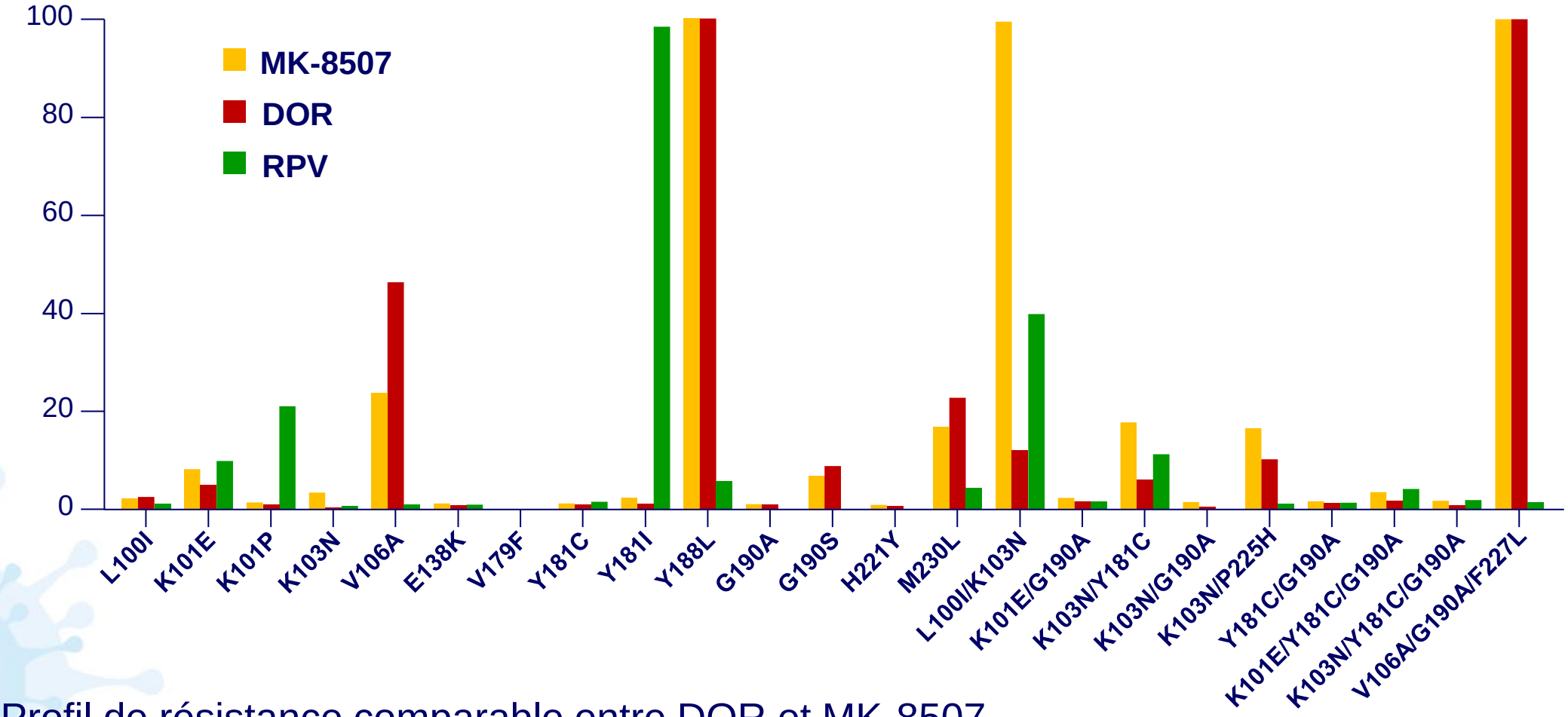


Diamond TL, CROI 2021, Abs. 129

le meilleur ...de CROI 2021

MK-8507, nouveau INNTI : profil de résistance (2)

Détermination du FC de résistance à différents INNTI



- Profil de résistance comparable entre DOR et MK-8507

Diamond TL, CROI 2021, Abs. 129

le meilleur ...de CROI 2021

MK-8507, nouveau INNTI : profil de résistance (3)

- Les cultures in vitro sous pression de sélection conduisent à l'émergence de mutations communes entre DOR et MK-8507
- Emergence de la mutation V106A avec sous-type B

Emergence de mutations sous pression de sélection *in vitro*

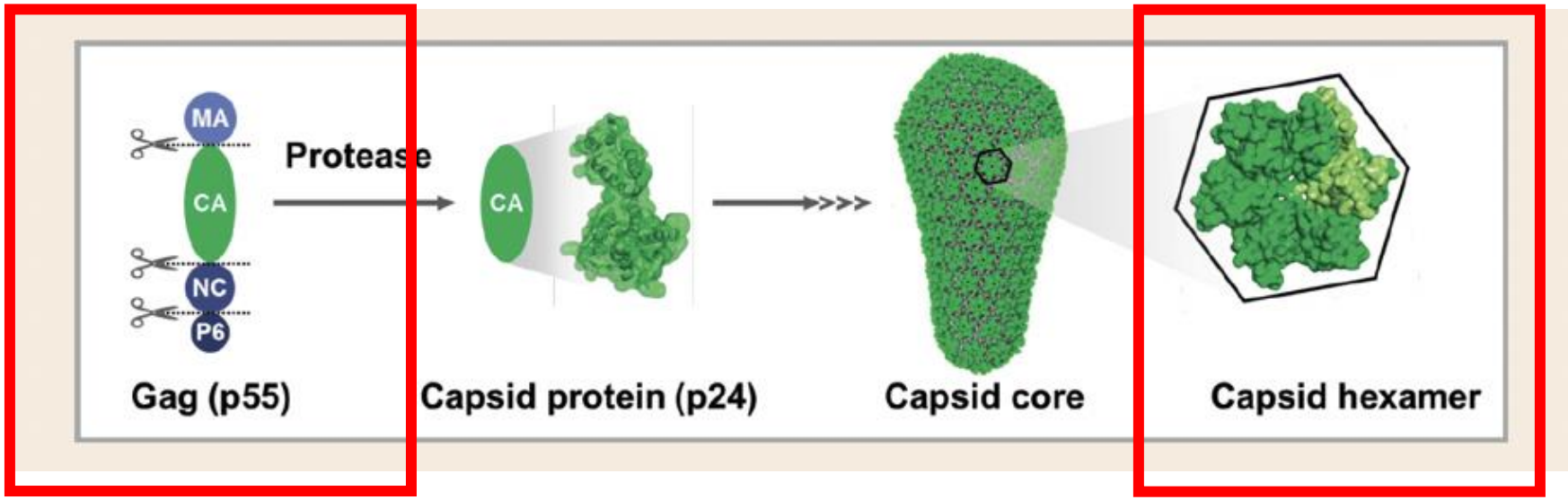
MK-8507	**V106A**	→ V106A/P225H → V106A/H221Y → V106A/P236L	
	V106A	→ **V106A/F227L**	→ **V106A/F227L/L234I** → V106A/F227L/Y318F
	V106A/Y318F	→ V106A/P225H/Y318F → V106A/H221Y/Y318F → V106A/F227L/Y318F	
DOR	**V106A**	→ **V106A/F227L**	
	V106A	→ V106A/L234I	→ **V106A/F227L/L234I**

Analyses phénotypiques (FC)

Mutation	MK-8507	DOR
V106A	8,9	15,6
V106I	1,7	1,8
Y188L	> 100	> 100
P225H	1,7	4,3
F227C	26	70
F227L	0,9	4,7
F227V	1,9	11,6
M230L	37,4	52,7
L234I	3,1	10,8
Y318F	7	10,3

Diamond TL, CROI 2021, Abs. 129

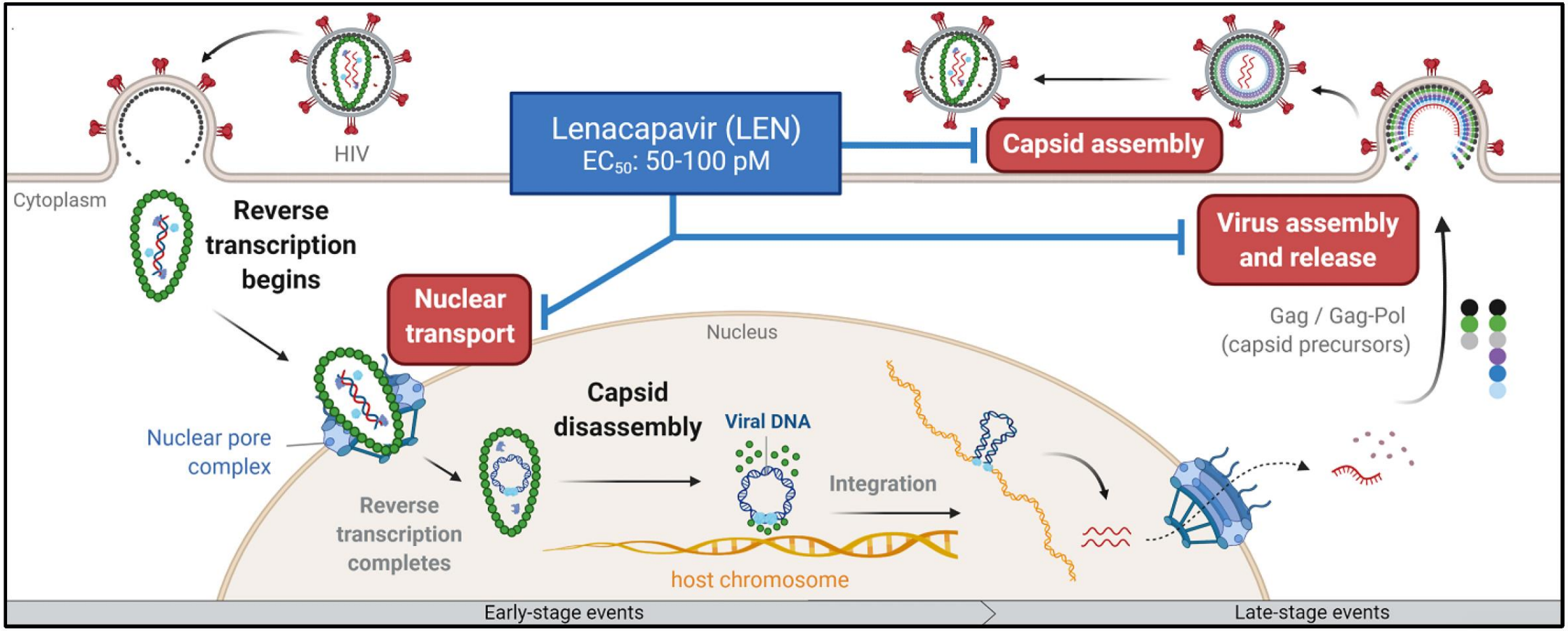
Inhibiteurs de capside



Inhibiteurs de clivage

Inhibiteurs d'hexamérisation

LEN : Capsid inhibitor targets multiple stages of HIV replication cycle



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

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

Phenotype and fitness of HIV-1 encoding emergent LEN-selected variants (1)

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 (2)

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

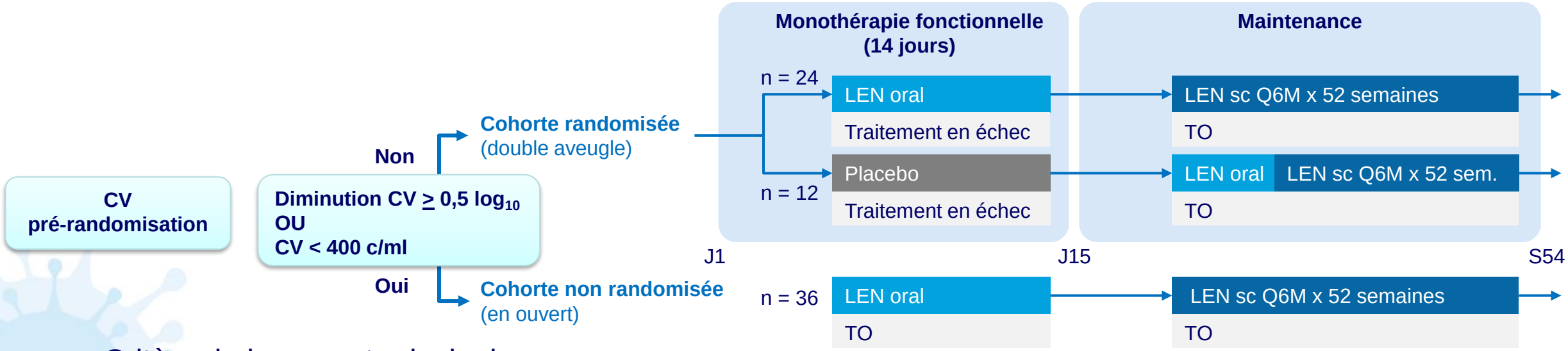
- **Conclusion: Absence of naturally occurring LEN resistance mutations**

(1) Yant SR, et al. IAS 2019. Poster TUPEA075; (2) Marcelin A-G, et al. JAC 2020;75:1588–1590

le meilleur ...de IAS 2021

Essai CAPELLA : lenacapavir chez des PVVIH lourdement prétraités avec multirésistance (1)

- Essai international de phase 2/3 chez des PVVIH lourdement prétraités avec multirésistance
- Critères d'éligibilité principaux (screening) :
  - CV > 400 c/ml
  - Résistance à, au moins, 2 ARV de 3 des 4 principales classes (INTI, INNTI, IP et INI)
  - ≤ 2 ARV pleinement actifs
- Selon l'évolution de la CV (CV répétée en pré-randomisation) inclusion dans la cohorte randomisée ou dans la cohorte non randomisée



- Critère de jugement principal : diminution CV ≥ 0,5 log_{10} c/ml à J15

LEN oral : 600 mg J1 et J2, 300 mg à J8
LEN sc : 927 mg (2 x 1,5 ml) à J15 puis tous les 6 mois
TO : traitement optimisé (ARV en évaluation autorisés, ARV non autorisés : ATV, EFV, ETR, NVP, TPV)

Segal-Maurer S, CROI 2021, Abs. 127 ; Molina JM, IAS 2021, Abs. OALX01LB02

le meilleur ...de IAS 2021

Essai CAPELLA : lenacapavir chez des PVVIH lourdement prétraités – Résultats à S26 (3)

Emergence de résistance à LEN dans la cohorte randomisée (n = 36)

Participants avec critère pour tests de résistance : 11 (31 %)
[CV confirmée ≥ 50 c/ml à S4, rebond ≥ 50 c/ml ou ↗ CV > 1 log_{10} c/ml à partir du nadir]

Pas d'émergence de résistance à LEN : 7 (19 %)

Emergence de résistance à LEN : 4 (11 %)

M66I	4
Q67H	1
K70N/R/S	1
N74D	1

- Les 4 participants avec émergence de résistance au LEN sont restés sous LEN
  - 3 participants : CV < 50 c/ml à une visite ultérieure (2 sans et 1 avec un changement du TO)
  - 1 participant sans ARV pleinement actif dans le TO n'a jamais eu de CV < 50 c/ml (baisse maximale CV de 1,7 log_{10} c/ml)

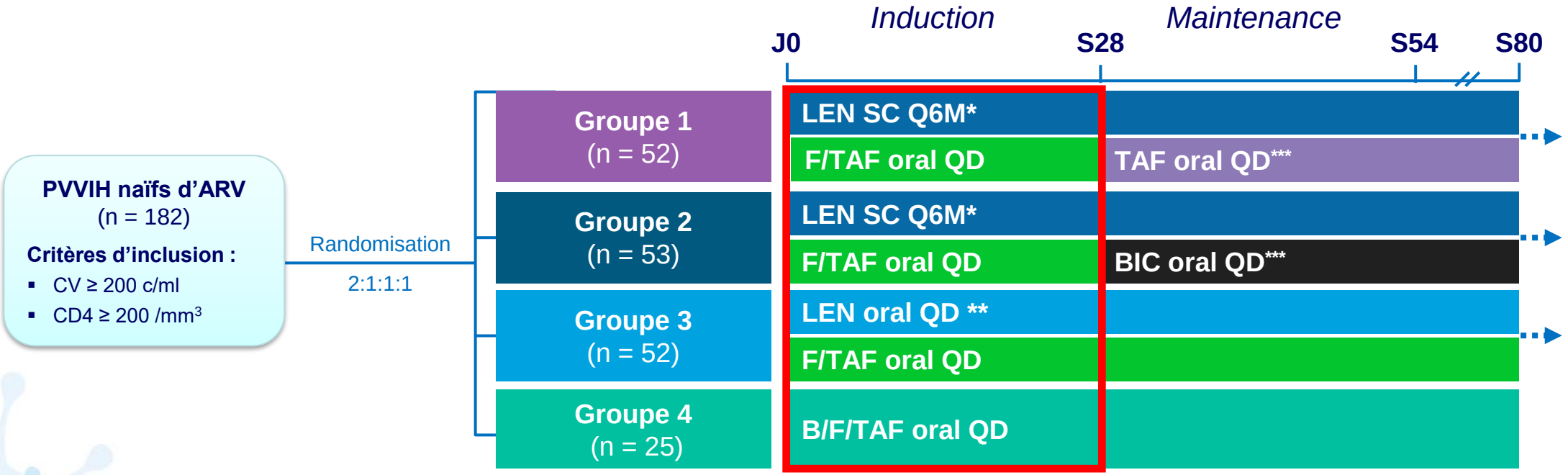
- Aucun participant n'a développé de résistance additionnelle aux ARV du TO

Molina JM, IAS 2021, Abs. OALX01LB02

le meilleur ...de IAS 2021

Essai CALIBRATE : lenacapavir chez des PVVIH naïfs d'ARV, phase 2 induction-maintenance – Résultats à S28 (1)

- Essai de phase 2, randomisé, ouvert chez des PVVIH naïfs d'ARV
  - Induction : 28 semaines de trithérapie : 3 groupes avec LEN vs B/F/TAF
  - Puis 2 groupes de bithérapie avec LEN vs 1 groupe trithérapie avec LEN vs B/F/TAF



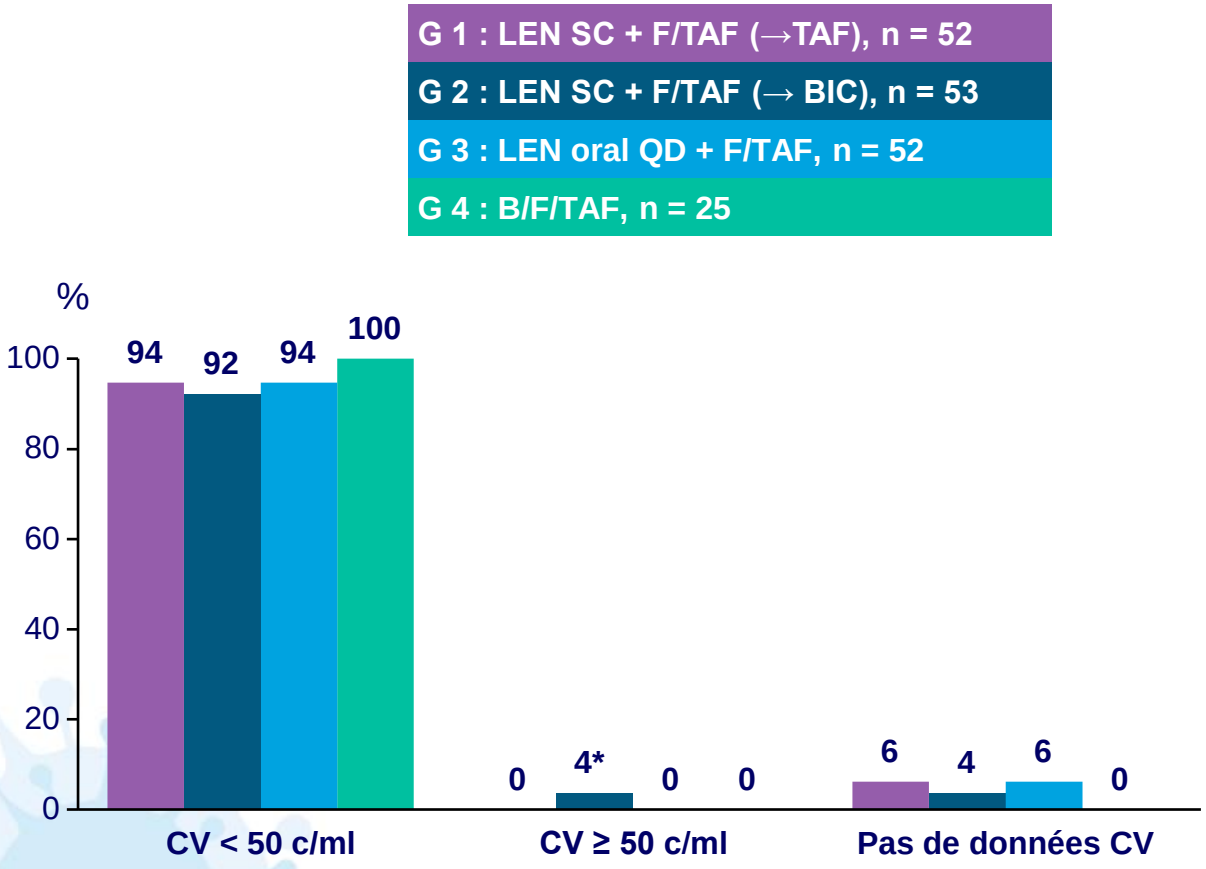
- **Caractéristiques à l'inclusion**
  - Age médian : 29 ans ; femmes : 7 % ; noirs : 52 %
  - CV médiane : 4,37 $\log_{10}$ c/ml (IQR : 3,86 à 4,74) ; CV > 100 000 c/ml : 15 %
  - CD4, médiane : 437/mm^3 (IQR : 332 à 599)

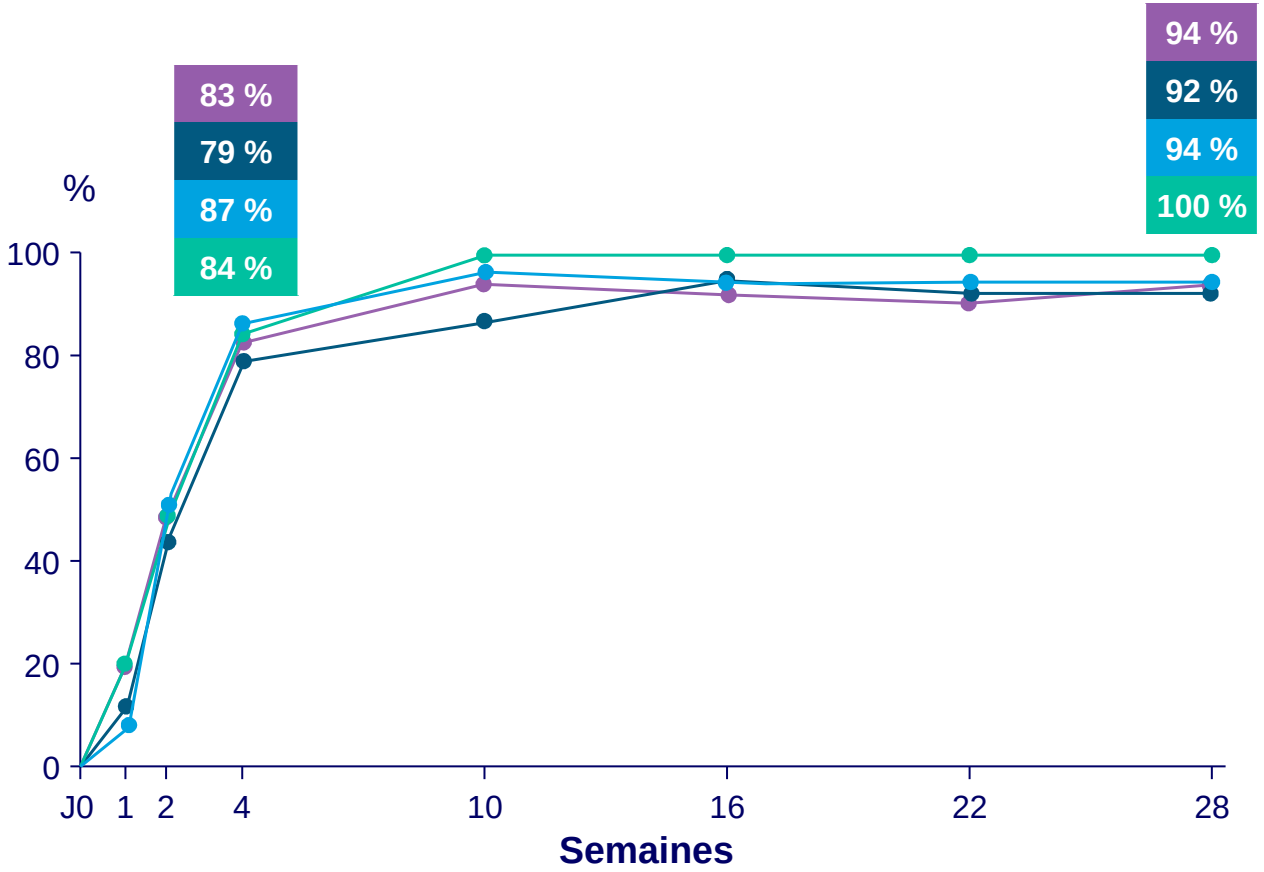
* LEN oral lead-in (600 mg J1 et J2, 300 mg à J8) puis LEN sc : 927 mg (2 x 1,5 ml) à J15 puis tous les 6 mois
** LEN oral 600 mg J1 et J2, puis 50 mg/j à partir de J3
*** Les participants des groupes 1 et 2 pour poursuivre l'étude au-delà de S28 avec TAF oral 25 mg (G1) ou BIC oral 75 mg (G2) devaient avoir à S16 et S22 CV < 50 c/ml

Gupta SK, IAS 2021, Abs. OALB0302

Essai CALIBRATE : lénacapavir chez des PVVIH naïfs d'ARV, phase 2 induction-maintenance – Résultats à S28 (2)

Résultats virologiques à S28 (ITT, snapshot)





*1 arrêt pour du critère du protocole "CV < 50 c/ml avant S28" non atteint ; 1 arrêt à J2

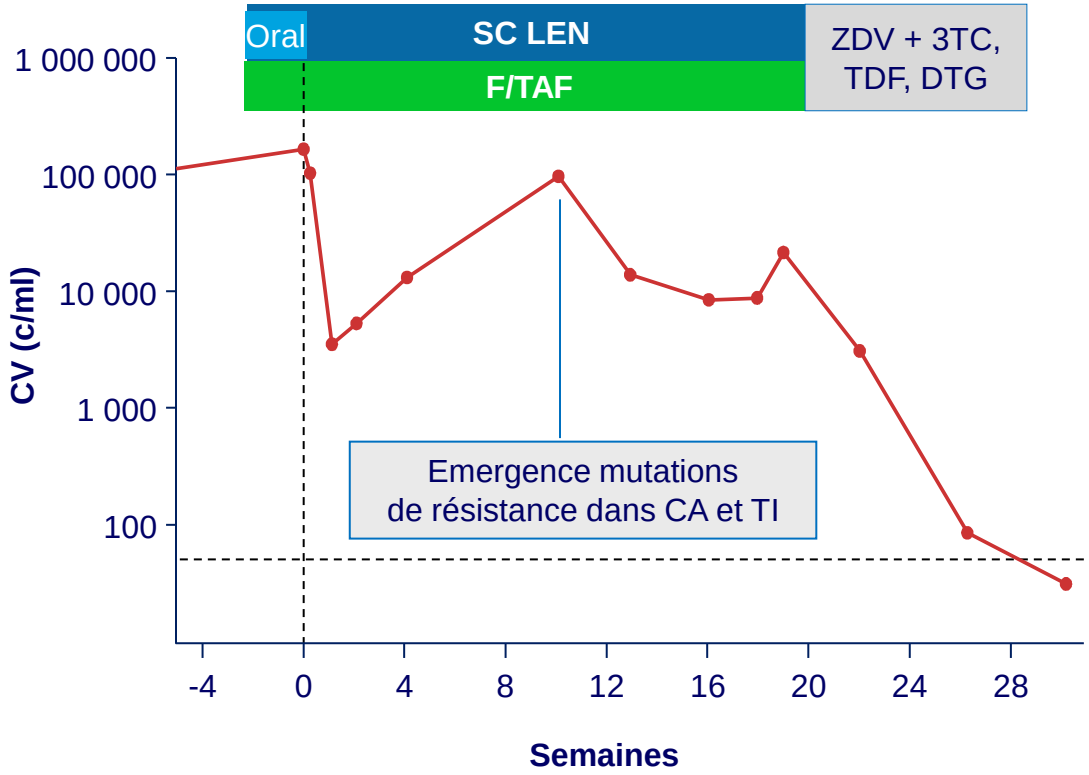
Gupta SK, IAS 2021, Abs. OALB0302

Essai CALIBRATE : lenacapavir chez des PVVIH naïfs d'ARV, phase 2 induction-maintenance – Résultats à S28 (3)

- **Analyse de la résistance**
  Une analyse de résistance était prévue chez les participants avec soit :
  - CV ≥ 50 c/ml et une réduction < 1 $\log_{10}$ c/ml de J1 à S10
  - en cas de rebond avec CV ≥ 50 c/ml
  - une augmentation de CV > 1 $\log_{10}$ c/ml à partir du nadir

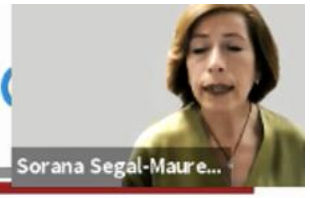
- **Emergence de mutations de résistance à S10 chez un participant du groupe 2**
  - **CA : Q67H + K70R (LEN fold change = 20)**
  - **TI : M184M/I**

- **Les concentrations plasmatiques de LEN étaient constamment dans les valeurs cibles**



Gupta SK, IAS 2021, Abs. OALB0302

Treatment-emergent Resistance



Participant	Fully active agents in OBR*	At Prior Visits while on LEN	Emergent Capsid Mutations	At Subsequent Visits while on LEN
#1	None	Suppressed	M66I, N74D (at Wk10: 2870 copies/mL)	Resuppressed with change in OBR
#2	DRV/COBI, DTG, RPV	Suppressed	M66I (at Wk26: 561 copies/mL)	Resuppressed with **no** change in OBR

- Among 72 heavily treatment-experienced participants with multidrug resistance and failing therapy at baseline who received SC LEN, 2 had emergent capsid mutations
  - The mutations conferred high level LEN resistance: >884 and 138 fold-change in EC_{50} (vs WT)
  - M66I mutation significantly impairs viral replication (1.5% replication capacity vs WT)
    - See oral presentation 1781: VanderVeen *et al* for additional information
- Further analyses are ongoing

Merci de votre attention