

Résistances du VIH: Nouvelles molécules, nouvelles combinaisons, nouvelles opportunités

La vision du virologue

Pr Anne-Geneviève Marcelin

Virologie

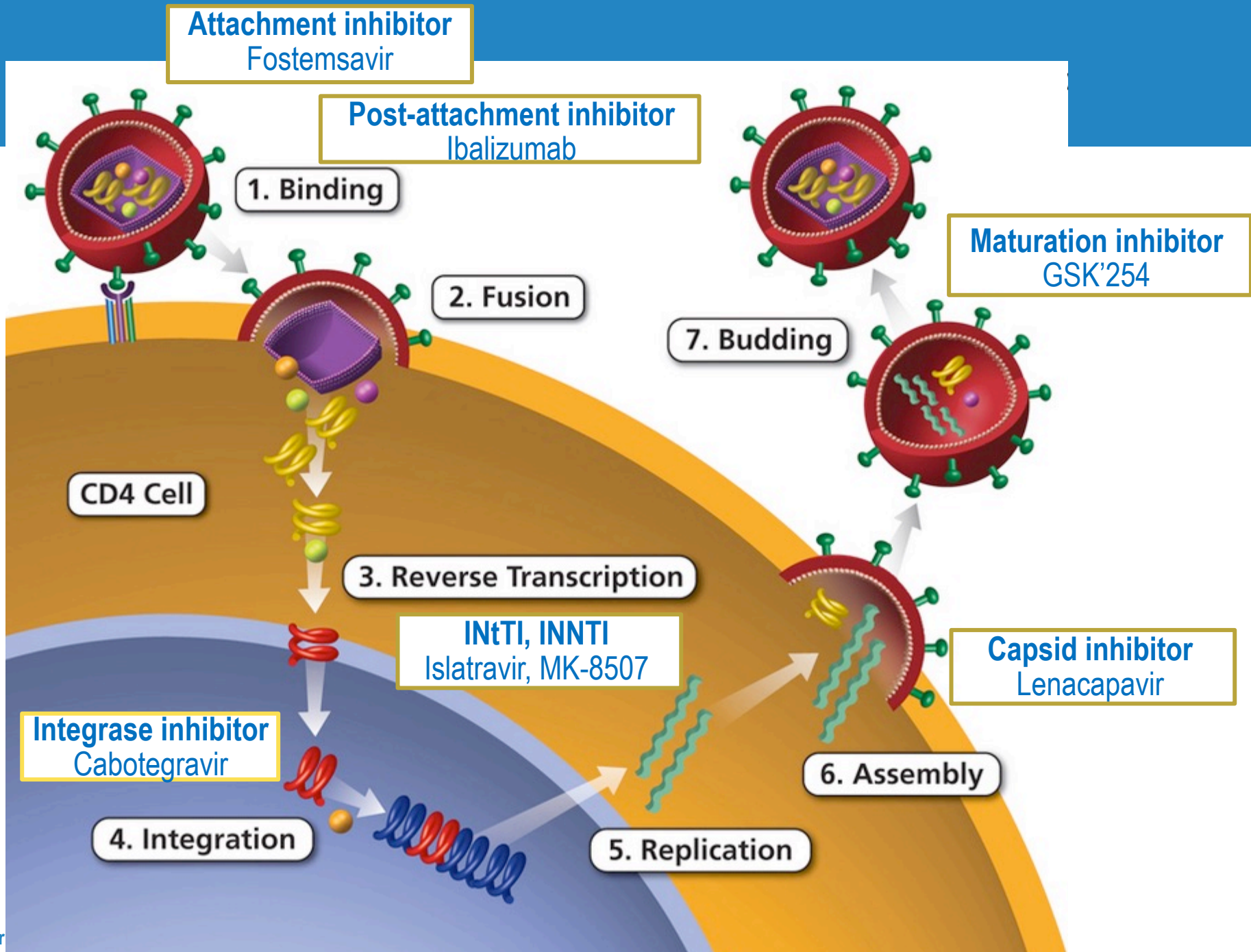
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Déclaration publique d'intérêts

Anne-Geneviève Marcelin a reçu des subventions pour participations à des conférences scientifiques, des honoraires pour des travaux d'expertise et bourses de recherches de différentes firmes pharmaceutiques : Gilead Sciences, Merck, ViiV Healthcare, Theratechnologies, Roche diagnostics, Biorad

« Les présentations des orateurs au cours de cette réunion d'information à caractère exclusivement médical et scientifique organisée par Theratechnologies en France sont destinées à clarifier la prise en charge sur les pathologies, dans un domaine thérapeutique, ou un sujet donné en lien avec les besoins des professionnels de santé et des patients en conformité avec les recommandations thérapeutiques en vigueur. Les informations partagées au cours de cette réunion n'ont pas de vocation promotionnelle. Le Bon usage des classes thérapeutiques éventuellement citées et leur place dans la stratégie thérapeutique doivent toujours être respectés »

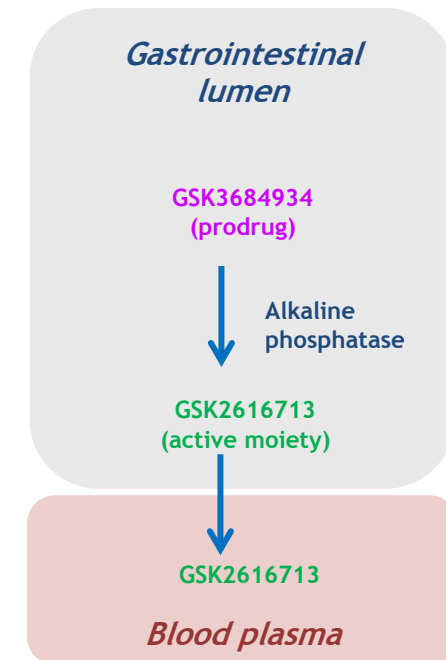


Fostemsavir : GSK3684934

- 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 into the host CD4+ T-cell^{1,2}

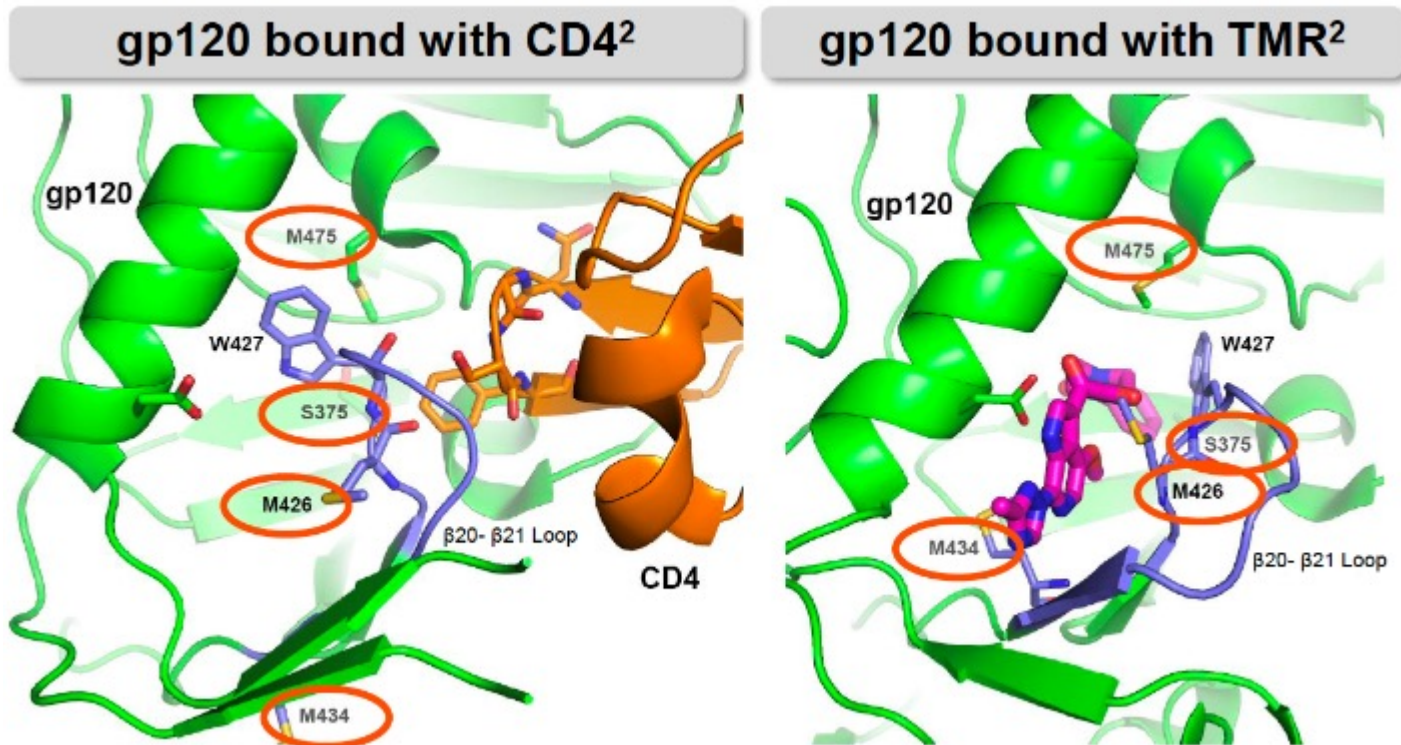
- *In vitro* activity against HIV-1 viruses, with the exception of subtype AE and Group O³
- Active against CCR5-, CXCR4- and dual-tropic (R5X4) strains of HIV-1³⁻⁶
- Unique resistance profile with no *in vitro* cross-resistance to other classes of antiretrovirals^{3,6}

Conversion of GSK3684934 =BMS-663068
to GSK2616713¹= BMS-626529



Fostemsavir : inhibiteur d'attachement

Four polymorphisms involved in TMR-gp120 binding impacting TMR susceptibility



Binding of fostemsavir (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 (6,5%)
 - Similar frequency for subtypes B and CRF02_AG, and lower for subtype B than for subtype D²
- **No difference in frequency of mutations according to viral tropism¹**
- **Necessary to work on an algorithm based on phenotype-genotype correlations to establish the contribution of mutations**

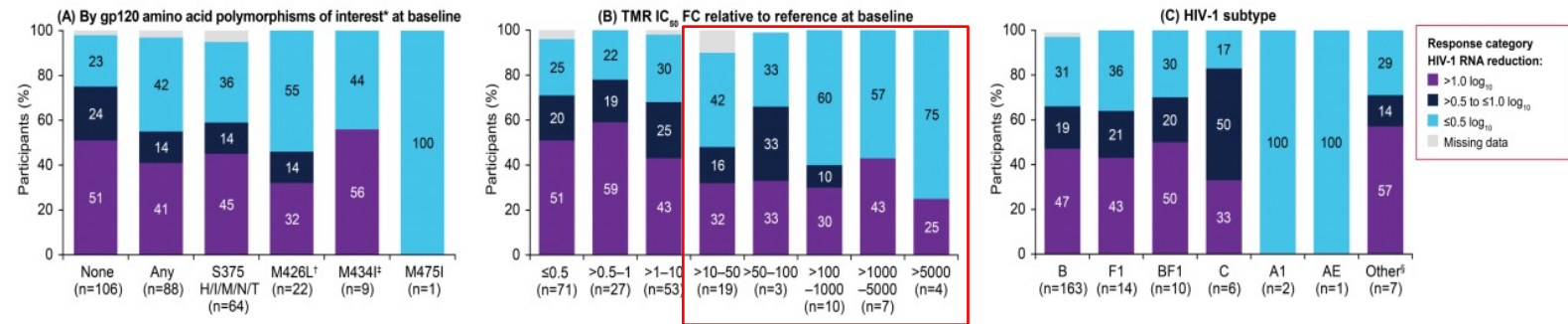
1. Soulié C, et al. JAC 2013; doi:10.1093/jac/dkt018
2. Charpentier C, et al. J Antimicrob Chemother. 2012;67:1459–1461

1. Lataillade et al., EACS 2019. Poster PE3/5; 2. Gartland et al., CROI 2021. Poster 503; 3. Ray et al., J AIDS 2013; 4. Zhou et al., JAC 2014; 5. Lataillade et al., J AIDS 2018

BRIGHTE trial: impact of gp120 polymorphisms, TMR IC₅₀ 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):

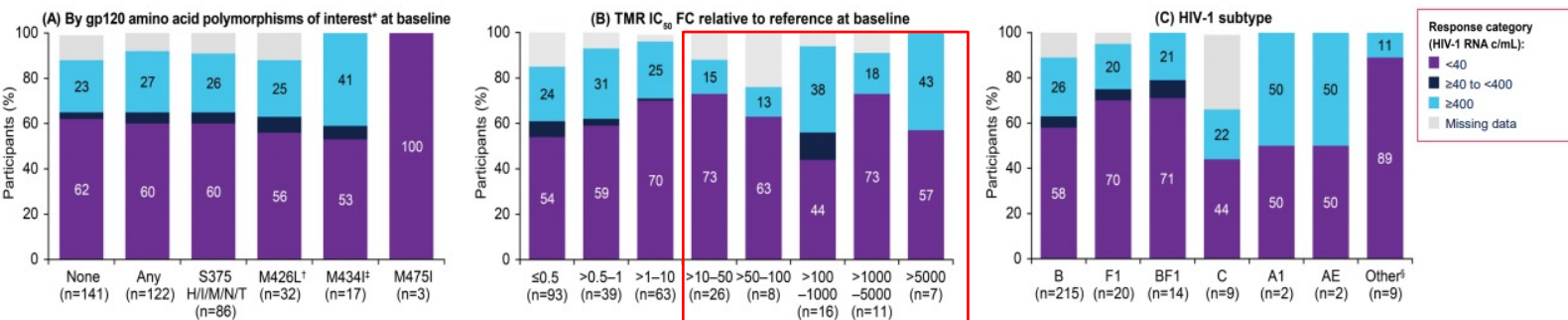


- Broad range of TMR IC₅₀ Fold Change at baseline with 22% of patients in FTR arm with FC > 10 times
- Clear trend to reduced proportion of patients with VL reduction > 0.5 log as FC increases

- Virologic response at Day 8 of FTR functional monotherapy was variable based on the presence of gp120 polymorphisms, TMR IC₅₀ 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):

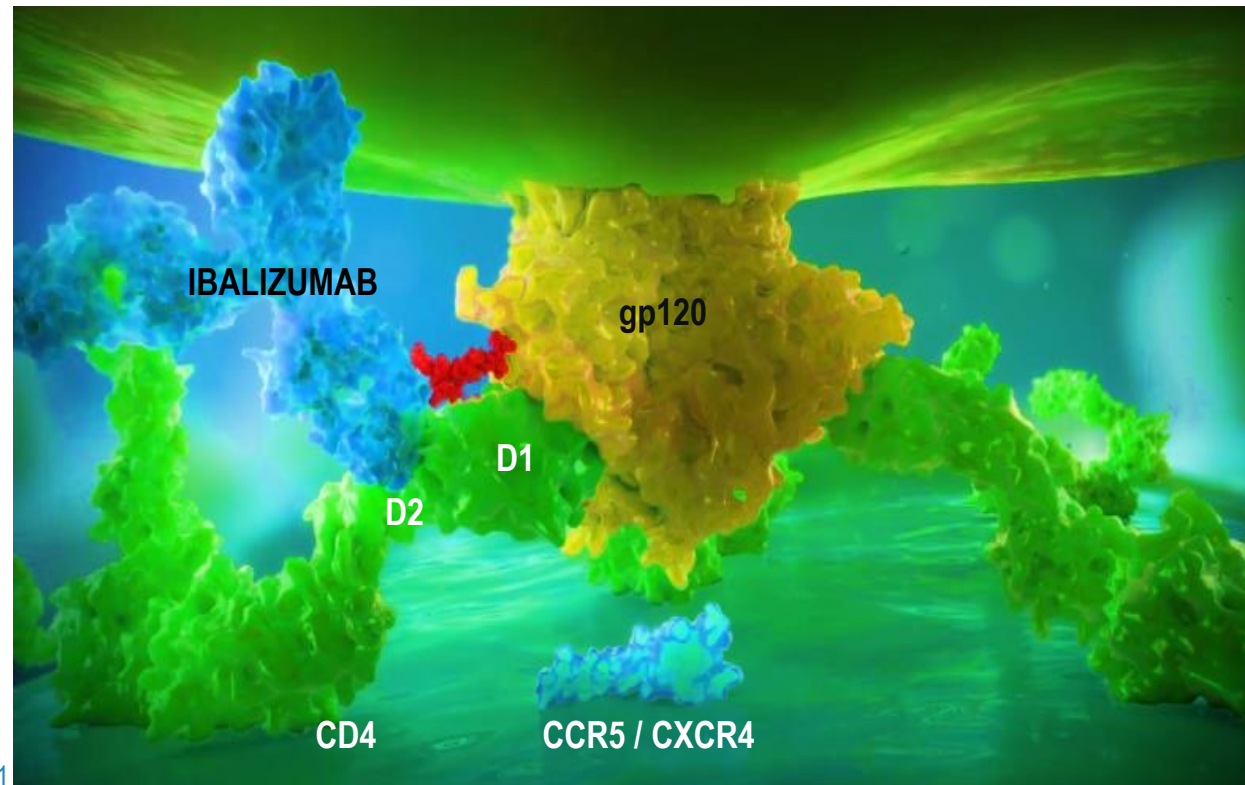


- Broad range of TMR IC₅₀ Fold Change (at baseline 26 % were >10 times)

- At W96 FTR + OBT Outcomes were not reliably predicted by the presence of gp120 polymorphisms, TMR IC₅₀ at baseline or HIV-1 subtype

Ibalizumab : Ac anti-CD4 inhibiteur post-attachement

- **Liaison** au **domaine extra-cellulaire 2 (D2)** du récepteur **CD4**
- IBA empêche les changements conformationnels induits par l'interaction gp120/CD4 suite à l'encombrement stérique
- Interférence avec les étapes **post-attachement** requises pour l'entrée du virus dans la cellule



Ibalizumab: propriétés

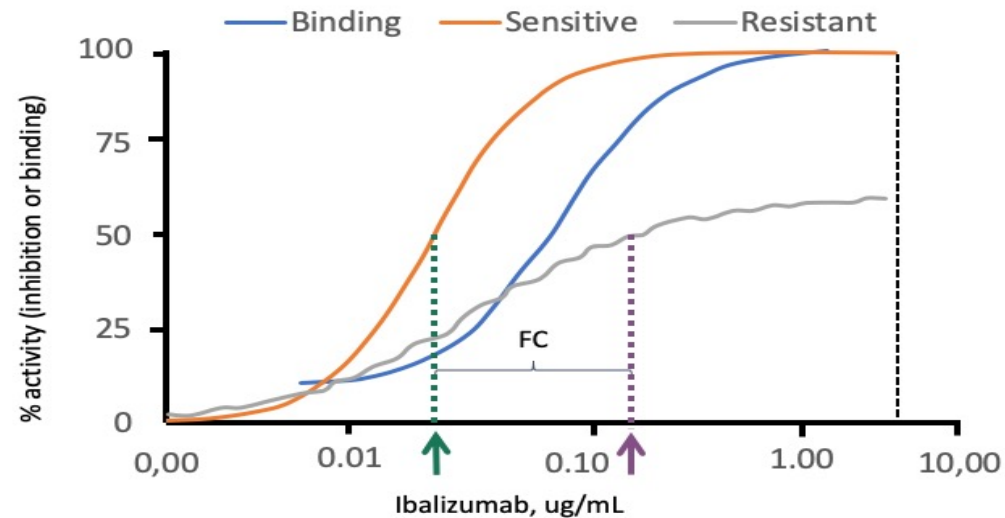
- Actif contre tous les sous-types majeurs du VIH-1
- Actif contre des virus de tropisme CCR5 et CXCR4
- Pas de résistance croisée avec les autres ARV
- Pas d'antagonisme observé avec un autre ARV, synergique avec ENF (in vitro)
- Pas d'interactions avec les ARV actuellement commercialisés
- Pas d'interactions significatives identifiées dans les essais cliniques
- Indiqué, en association avec d'autres médicaments ARV, dans le traitement de l'infection par le VIH-1 multi-résistant chez les adultes pour lesquels il n'est autrement pas possible d'établir un schéma de traitement antirétroviral suppressif

Evaluation de la résistance

- **Inhibiteurs compétitifs du VIH: réduction de sensibilité exprimée par une augmentation de la CI50**
- **Ibalizumab est un inhibiteur non compétitif:**
 - Variation de la CI50
 - Réduction de sensibilité exprimée par un aplatissement de la courbe d'inhibition
 - Réduction du pourcentage maximal d'inhibition (MPI) de l'infection < 100%
 - PhenoSense HIV-1 Entry assay (Monogram Biosciences):
 - Mesure la capacité de pseudovirus (*env*) d'infecter des cellules U87/CD4/CCR5/CXCR4 en présence de dilutions de l'inhibiteur

Reduced Susceptibility to Ibalizumab Is Defined by a Decrease in MPI

- Ibalizumab susceptibility is determined using the PhenoSense® HIV Entry assay¹



← High MPI = sensitive

← Low MPI = partially-sensitive

Even at concentrations associated with maximum binding, ibalizumab becomes only partially active against virus⁵

FC, fold change; MPI, maximum percent inhibition

1. Center for Drug Evaluation and Research. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761065Orig1s000MicroR.pdf; 2. Fessel WJ, et al.

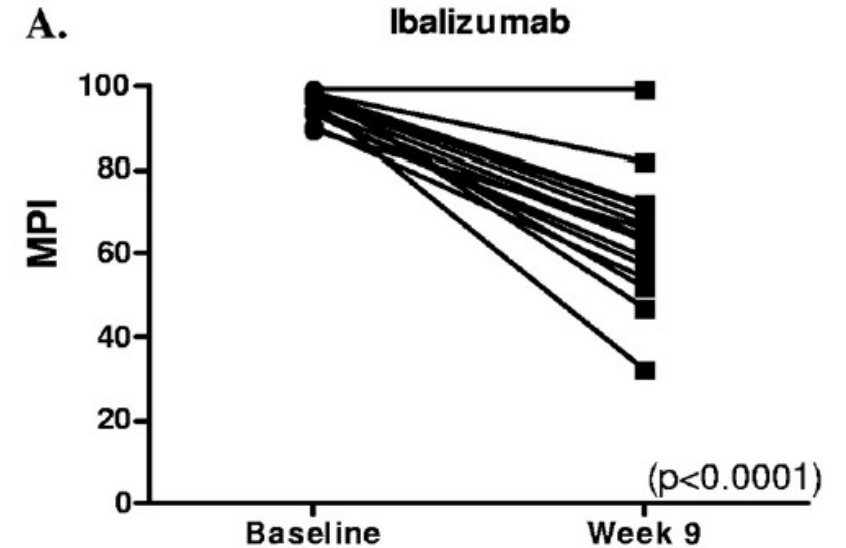
Antiviral Res 2011;92:484-487; 3. Beccari MV, et al. *Antimicrob Agents Chemother* 2019;63; 4. Geretti AM (ed). *Antiretroviral Resistance in Clinical Practice*. 2006.

Available at: <https://www.ncbi.nlm.nih.gov/books/NBK2239/>; 5. Pace CS, et al. *J Acquir Immune Defic Syndr* 2013;62:1-9.

Image adapted from Pace CS, et al.

Réduction de la MPI à l'échec

- Phase 1b (TNX-355.02): IBA 9 semaines chez PVVIH en échec avec CV > 5000 cp/ml
- Diminution transitoire de la CV
- Mesure de la susceptibilité à IBA à J0 et S9 chez 14 patients
- Tous les pseudovirus exprimant *env* à J0 sont sensibles à IBA
- Réduction significative de la MPI à S9



Recherche de déterminants génotypiques

- Séquençage de la gp160 de 96 clones de 4 patients (J0-S9):
 - Mutations dans *env* et en particulier dans la gp120
 - Pas de mutations au niveau du CD4 binding site
 - Pas de différence de longueur V1/V2 ou autre régions variables
 - Diminution du nombre de sites potentiels de N-glycosylation dans V5

TABLE 2. Lengths and numbers of glycosylation sites in Env variable regions of day 0 and week 9 *env* clones

Subject (identification)	Time point ^c	Length of amino acid sequence in <i>env</i> region ^a						No. of PNGSs in <i>env</i> region ^a					
		gp160	V1	V2	V3	V4	V5	gp160	V1	V2	V3	V4	V5 ^b
1 (004-2-04)	Day 0	835.3	38.0	39.0	35.0	29.8	12.5	30.9	5.1	2.0	1.0	4.9	2.0
	Wk 9	835.3	38.4	39.0	35.0	29.5	12.3	29.9	5.1	2.0	1.0	4.7	1.3
	Day 0/wk 9	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.1	1.5
2 (004-1-07)	Day 0	864.1	38.2	41.8	34.5	34.0	14.3	32.4	5.9	2.5	0.5	5.4	1.8
	Wk 9	844.8	32.3	45.0	34.0	34.2	14.1	31.7	5.0	3.0	0.0	5.9	1.0
	Day 0/wk 9	1.0	1.2	0.9	1.0	1.0	1.0	1.0	1.2	0.8	ND	0.9	1.8
3 (004-1-02)	Day 0	867.3	37.4	46.0	35.0	31.0	15.0	33.3	4.5	4.0	0.3	5.0	1.4
	Wk 9	864.7	36.3	46.0	35.0	31.0	14.3	30.0	4.0	3.8	0.3	4.9	0.3
	Day 0/wk 9	1.0	1.0	1.0	1.0	1.0	1.0	1.1	1.1	1.0	1.0	1.0	4.3
4 (004-2-06)	Day 0	842.8	29.1	43.0	35.0	30.0	17.0	29.7	4.0	3.0	1.7	1.1	2.1
	Wk 9	858.7	28.0	43.0	35.0	30.0	16.7	29.1	4.0	3.0	1.7	1.1	1.0
	Day 0/wk 9	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	2.1
All clones from 4 subjects	Day 0	852.4	35.7	42.5	34.9	31.2	14.7	31.6	4.9	2.9	0.9	4.1	1.8
	Wk 9	850.8	33.8	43.3	34.8	31.2	14.4	30.2	4.5	3.0	0.8	4.1	0.9
	Day 0/wk 9	1.0	1.1	1.0	1.0	1.0	1.0	1.0	1.1	1.0	1.2	1.0	2.0

Corrélation phénotype/génotype

- **Corrélation entre la diminution du nombre de sites de glycosylation dans V5 et la diminution de la MPI**
- **2 sites très conservés de N-glycosylation**

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	<i>P</i> value ^b
2	42	13–100	99	
1	45	<1–100	71	<0.0001
0	9	30–78	40	<0.0001

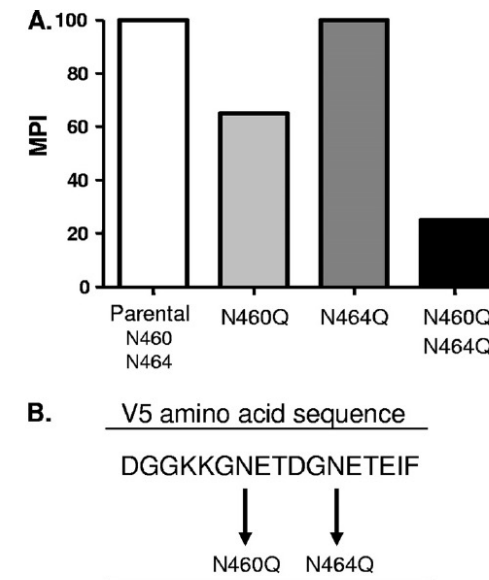


FIG. 5. Effect of V5 N-linked glycosylation sites on ibalizumab susceptibility. (A) Ibalizumab susceptibilities of a parental *env* clone containing site 1 (positions 460 to 462) and site 2 (position 464 to 466) PNGSs and PNGS 1 and 2 knockout clones. (B) V5 amino acid sequences of the parental *env* clone and the PNGS knockout clones.

V5 N-Linked Glycosylation Is the Dominant Determinant of Ibalizumab Reduced Susceptibility (N-term)

- Ibalizumab MPI is significantly associated with the number and position of V5 PNGS in gp120, even in the presence of drug binding¹
- The absence or loss of a PNGS in the V5 loop of HIV-1 gp120 is the primary genetic determinant associated with reduced ibalizumab MPI¹

1. Pace CS, et al. *J Acquir Immune Defic Syndr* 2013;62:1-9.

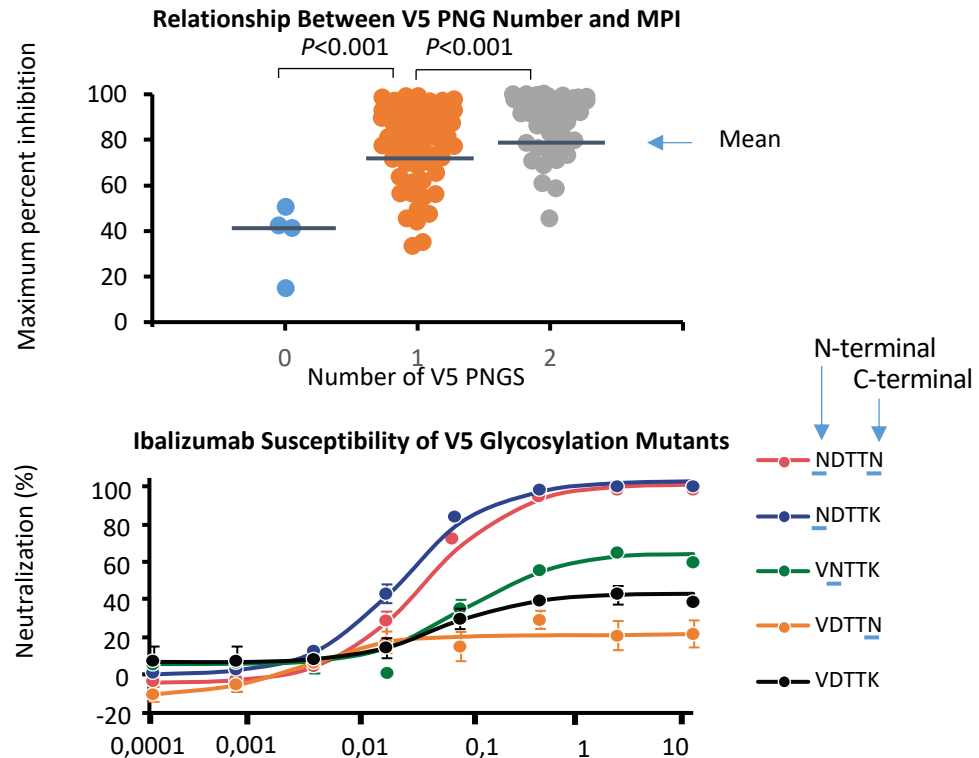


Image adapted from Pace CS, et al.

Ibalizumab Activity Is Conferred by Interactions with a Glycan in the N-Terminus of the V5 Loop

- A glycan linked to a position in the V5 loop fills a void between the V5 loop and the Ibalizumab light chain causing steric hindrance and preventing the conformational change required for viral entry¹

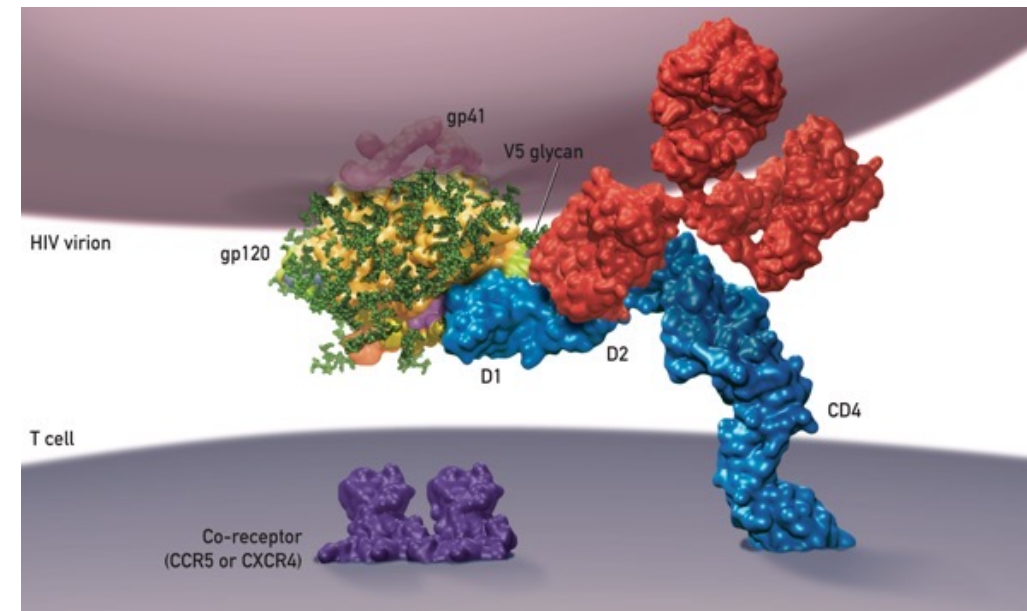
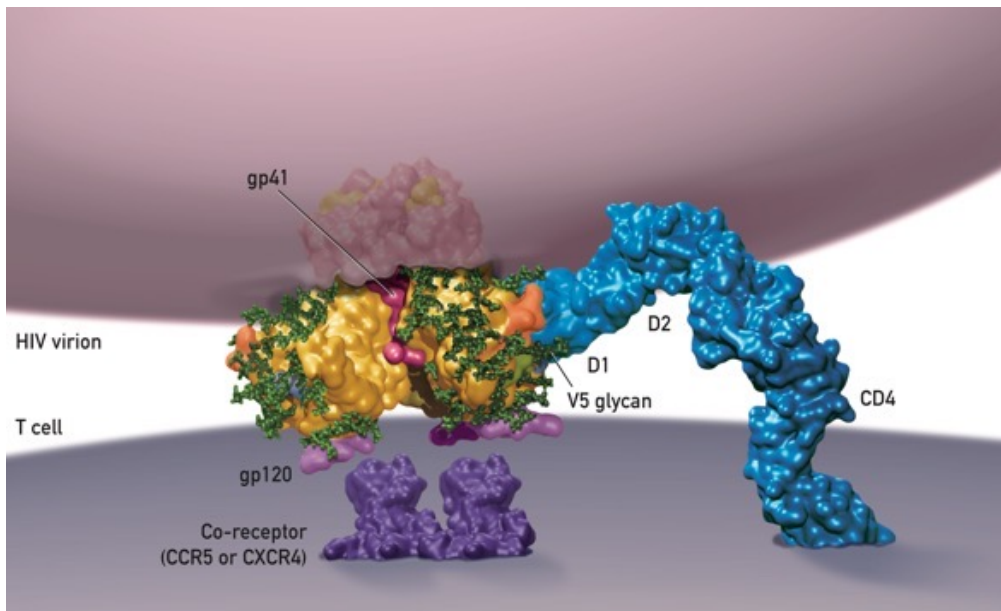


Image adapted from Song R, et al.

1. Song R, et al. *Nat Biotechnol* 2013;31:1047-1052.

Sensibilité à l'ibalizumab dans 3 essais cliniques

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 EC₅₀ 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%

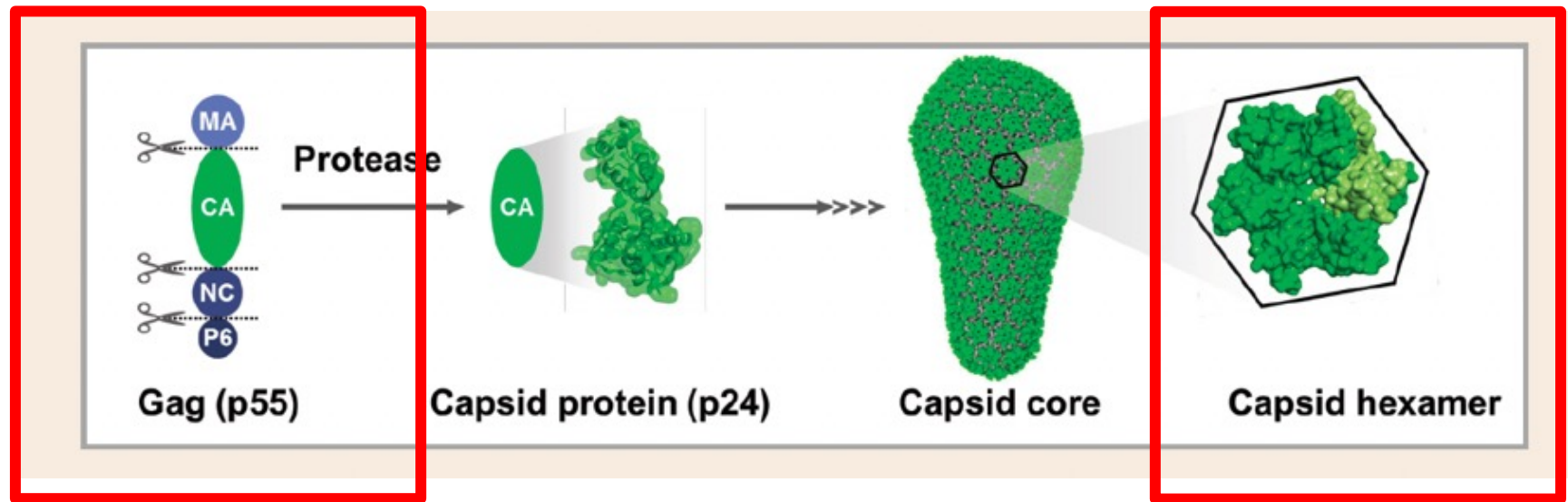
Corrélation entre perte des sites de glycosylation dans V5 et diminution de la MPI

- Analyse génotypique et phénotypique de gp160 sur 45 échantillons collectés à baseline et à l'échec
- Pas d'association entre la réduction de MPI et 36 changements d'AA à 23 positions de la gp160

Ibalizumab: conclusions

- IBA actif sur 92% de virus pseudotypés avec *env* de diverses origine géographique, clade et tropisme
- Déterminant génétique principal de résistance : perte de sites de glycosylation dans V5 (région N-term)
- Mécanisme de résistance probable: capacité des variants résistants à faciliter les changements conformationnels du complexe CD4/gp120 et l'engagement du corécepteur malgré la fixation de l'Ibalizumab.

Inhibiteurs de maturation/capside



Inhibiteurs de clivage

Inhibiteurs d'hexamérisation

Lenacapavir (LEN): potent capsid inhibitor

- Actif contre tous les sous-types majeurs du VIH-1
- Actif contre des 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 seven 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**

Lenacapavir (LEN): potent capsid inhibitor

CAPELLA trial: LEN in heavily treatment-experienced participants with multidrug resistance ⁽¹⁾

LEN-emergent resistance in 2 patients

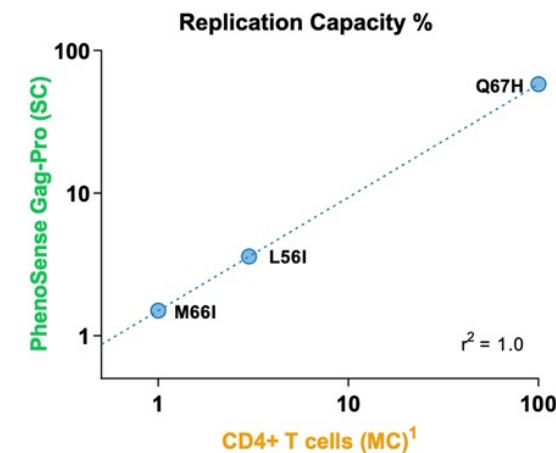
Participants	Fully active agents in OBR	Emergent capsid mutations	At subsequent visits while on LEN
1	None (OBR: MVC, T20, DTG bid, DRV/c, 3TC)	M66I, N74D (W10 : 2 870 c/mL)	Resuppressed with change in OBR
2	DRV/c, DTG, RPV (OBR: TAF/F, DRV/c bid, DTG bid, RPV)	M66I (W26 : 561 c/mL)	Resuppressed with <u>NO</u> change in OBR

- The mutation conferred high level LEN resistance: >884 and 138 fold-change in EC50 (vs WT)
- M66I mutation significantly impairs viral replication (1,5% replication capacity vs WT)

LEN Resistance Mutations are associated with reduced viral fitness ⁽²⁾

PhenoSense Gag-Pro (Single-cycle) vs. CD4+ T cell (Multi-cycle)

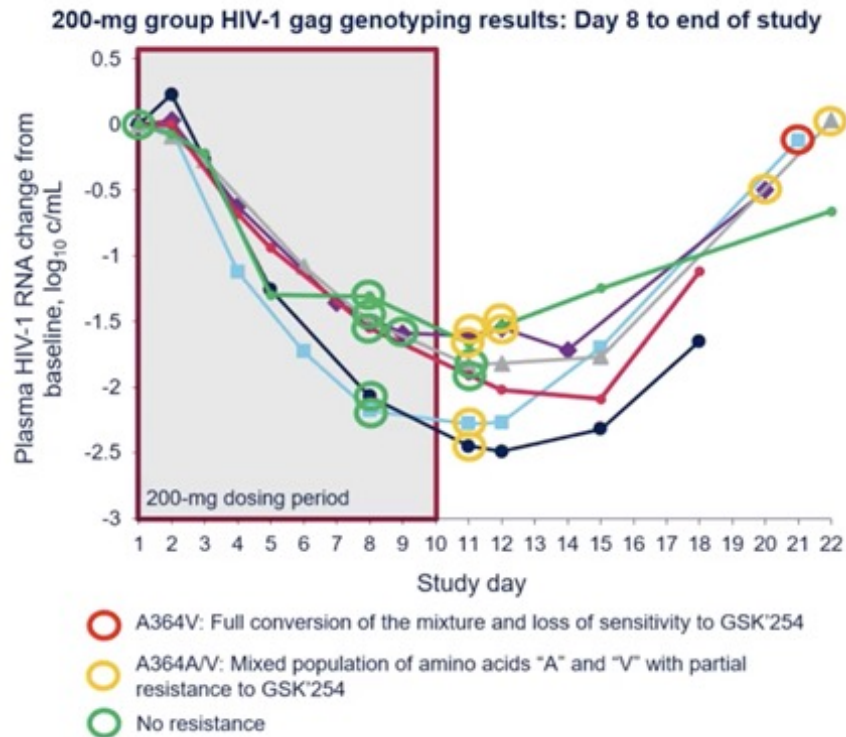
HIV-1 Capsid Sequence	PhenoSense Gag-Pro (SC)	
	LEN Fold-Resistance ^a	Replication capacity, % WT ^b
T107N	3.8	32
Q67H	4.8	58
N74D	16	ND
Q67H+N74S	20	15
Q67H+T107N	87	ND
L56I	204	3.6
Q67H+M66I	1,594	ND
Q67H+N74D	>2,700	ND
M66I	>2,700	1.5



MC, multi-cycle; ND, not determined; SC, single cycle.
a. Ratio of Mutant/WT EC₅₀, determined with SC reporter HIV-1 in PhenoSense Gag-Pro assay.
b. Percentage of reference strain, determined with SC reporter HIV-1 in PhenoSense Gag-Pro assay.
1. Link, Nature 2020; Yant, IAS 2019. Gag-Pro: overlapping data with CD4+ T cell MC assay available for 3 of 9 mutants.

Maturation inhibitor GSK'254

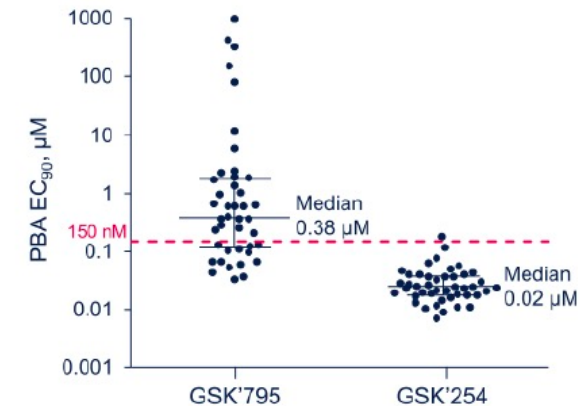
Phase IIA proof of concept trial of next generation maturation inhibitor (1)



Effect of Gag polymorphisms on GSK'254 IC₅₀ (2)

Viral genotype	EC ₅₀ , μM	Fold change vs wild-type	Maximal percent inhibition, %
Wild-type	0.0023	1.0	99
V370A	0.0018	0.8	99
V370M	0.0014	0.6	98
V362I	0.0026	1.1	96
ΔV370/T371A	0.0026	1.1	99
ΔV370	0.0058	2.4	94
ΔV370A/R286K	0.0038	1.6	93
A364V	>3	>630	37

GSK'254 IC₅₀ of 35 chimeric subtypes B/C with diverse Gag sequences (2)



New ARV and HIV-1 non M and HIV-2

Drug	HIV-1 group O	HIV-2
Fostemsavir	Resistance¹	Resistance²
Ibalizumab	Ongoing	Susceptible³
Lenacapavir	Susceptible⁴	Ongoing
Cabotegravir	Susceptible⁵	Susceptible⁶
GSK'254	No data	No data