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Diagnostica e meccanismi di resistenza ai nuovi antiretrovirali

Giornate Infettivologiche “Luigi Sacco”

Milano, 29-30 Ottobre 2024

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Conflicts of interest

- Dr. Francesco Saladini has received personal fees for speaker's bureau from ViiV Healthcare

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Recently approved antivirals

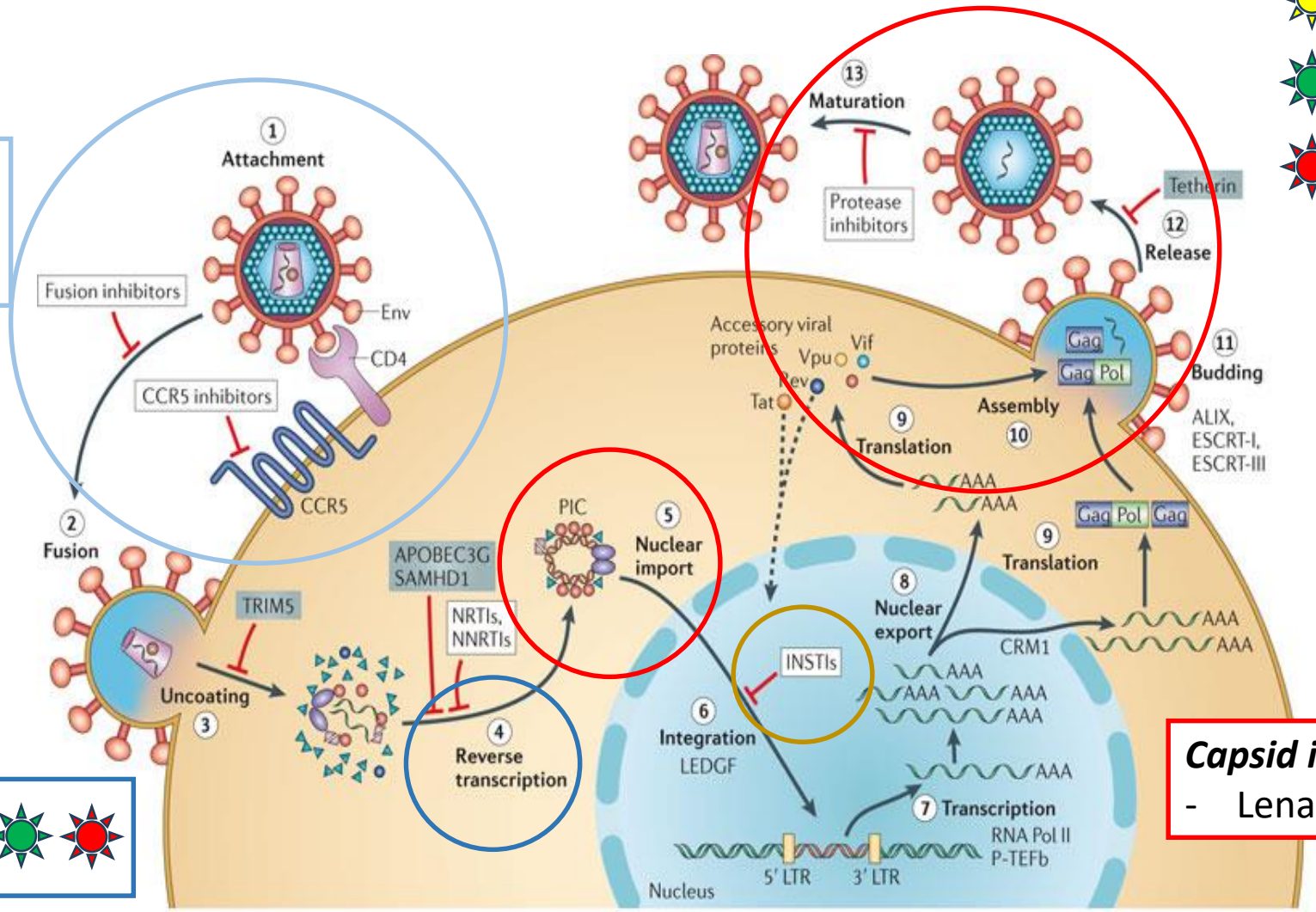
First-line therapy

Mantenance therapy

Salvage therapy

Entry inhibitors:
- Ibalizumab*
- Fostemsavir

* EU marketing withdrawal from January 1, 2023



Nature Reviews | Microbiology

INSTI:
- Cabotegravir (+Rilpivirine LA)

Capsid inhibitor:
- Lenacapavir

NNRTI:
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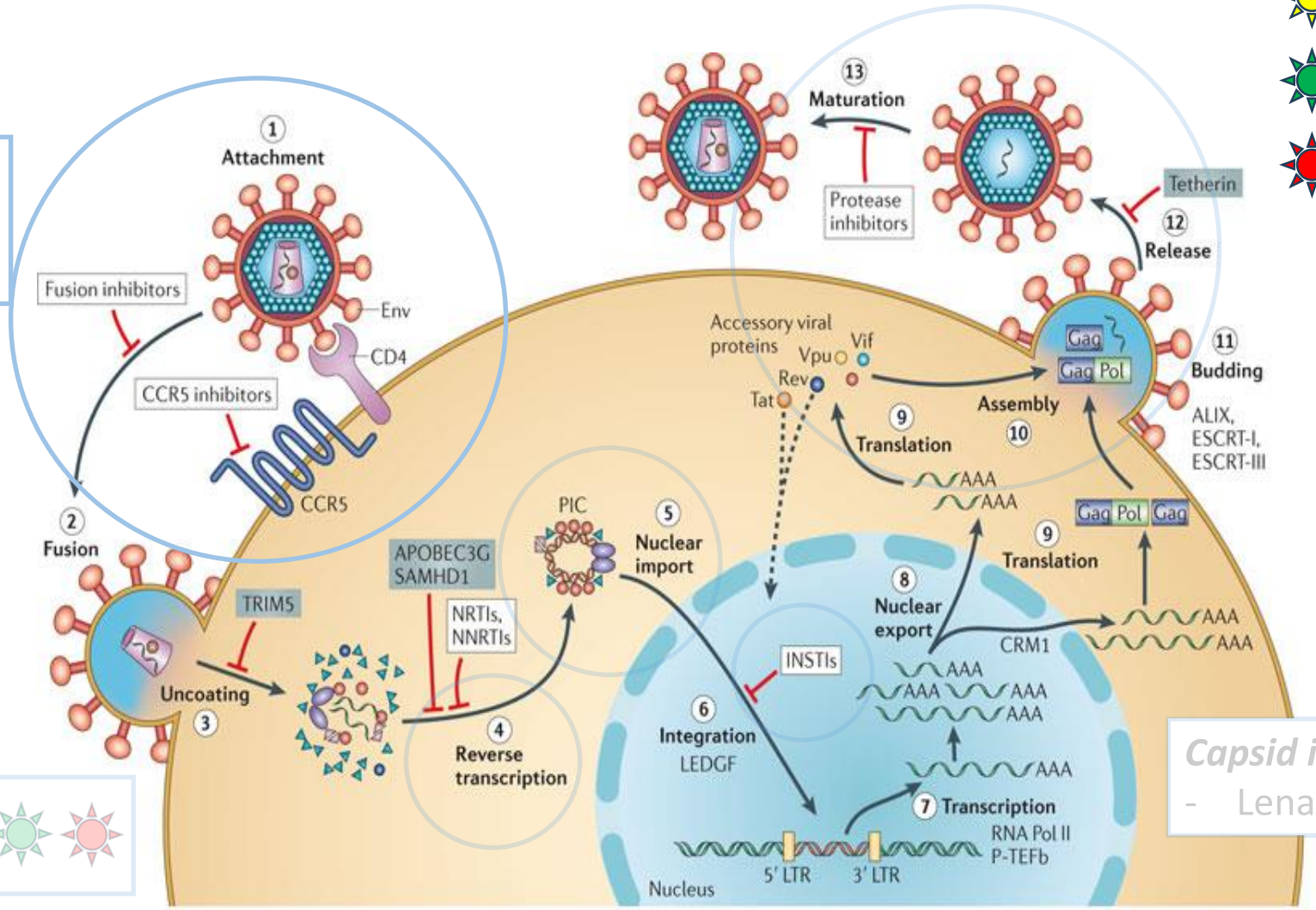

Nature Reviews | Microbiology

INSTI:
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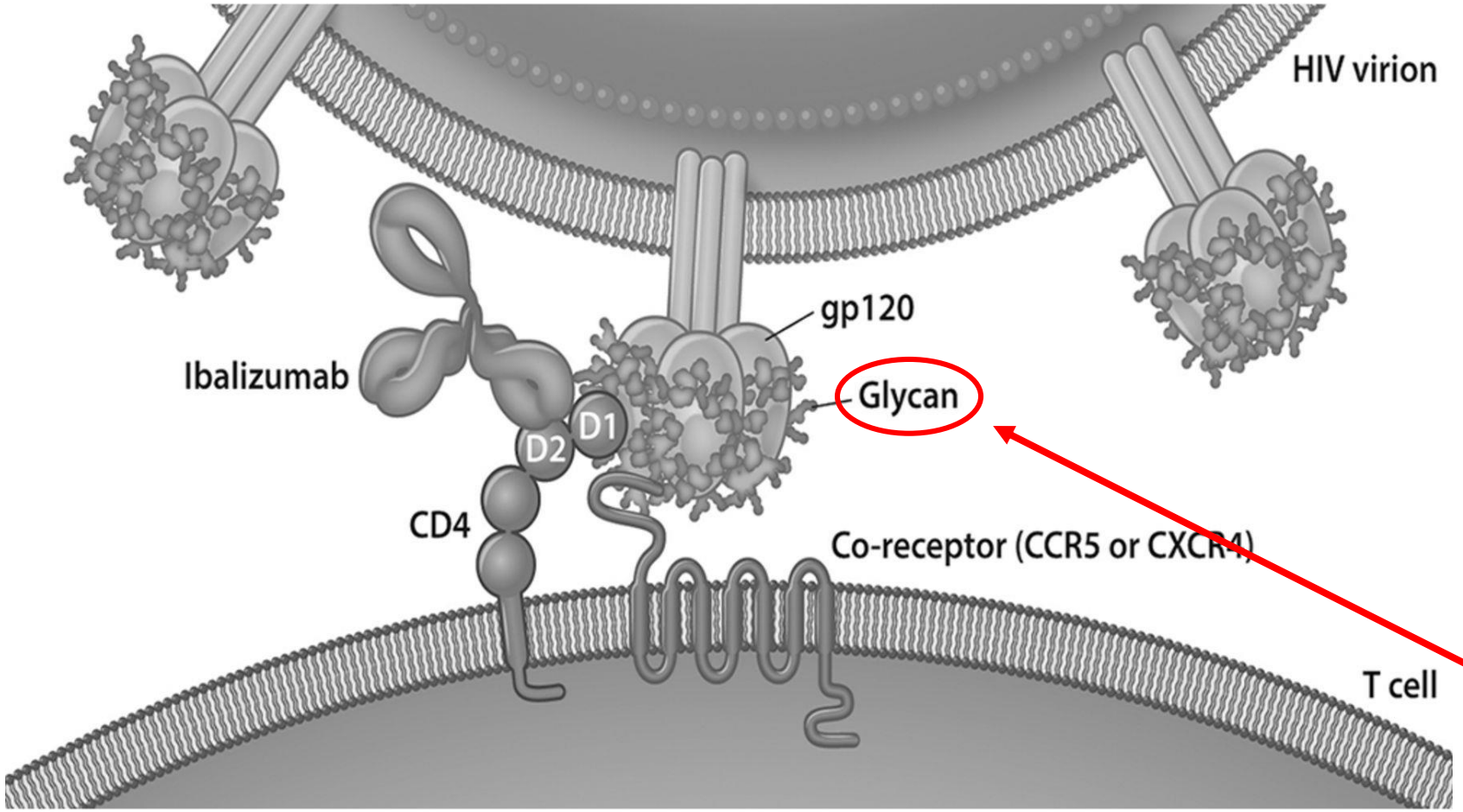
Mechanism of action of Ibalizumab



- Ibalizumab is a recombinant humanized immunoglobulin (Ig) G4 mAb
- Binds to the CD4 T cell extracellular domain 2 at four sites and domain 1 at two sites
- Does not interphere with the binding of MHC-II molecule to domain 1
- Prevents conformational changes leading to the exposure of V3 domain required for co-receptor binding
- HIV gp120 V5 glycans are essential to have IBA block HIV entry following gp120-CD4 binding

Beccari AAC 2019

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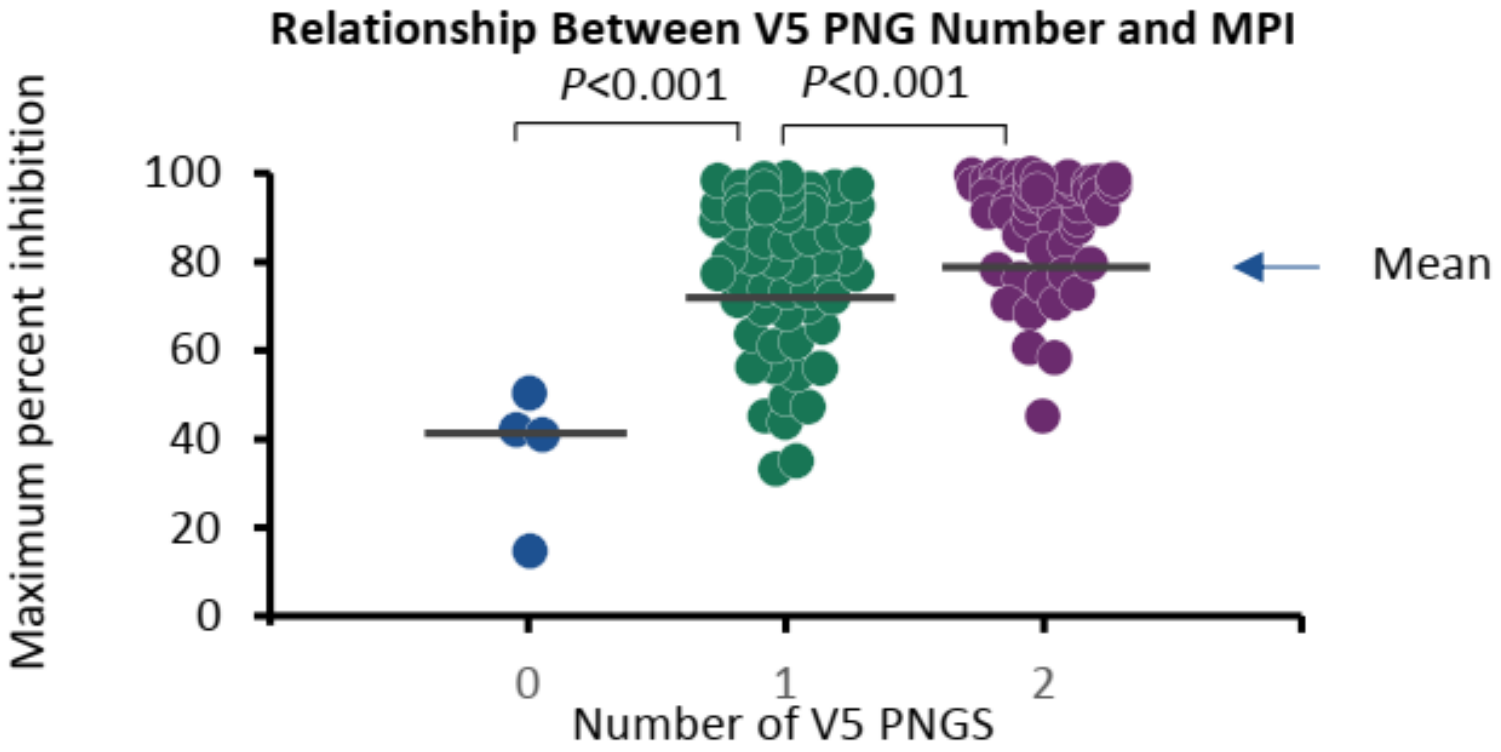
Ibalizumab maximum percentage of inhibition (MPI) and gp120 V5 glycosylation



Potential N-linked glycosylation site (PNGS)

Asn-any-Ser OR **Asn-any-Thr**
N – X – S OR **N – X – T**

- Ibalizumab activity is evaluated by calculating MPI rather than IC_{50} → non-competitive inhibition of HIV infection as other HIV entry inhibitors (e.g., maraviroc)
- 116 HIV-1 pseudotyped viruses tested
  - 107/116 (92.2%) isolates have MPI >50%
  - 76/116 (65.5%) isolates have MPI >80%
- 6.2% of HIV-1 sequences stored in the Los Alamos Database have no PNGS
- CRF01_AE more susceptible to IBA
- Broad MPI range in other subtypes tested

Pace *JAIDS* 2013

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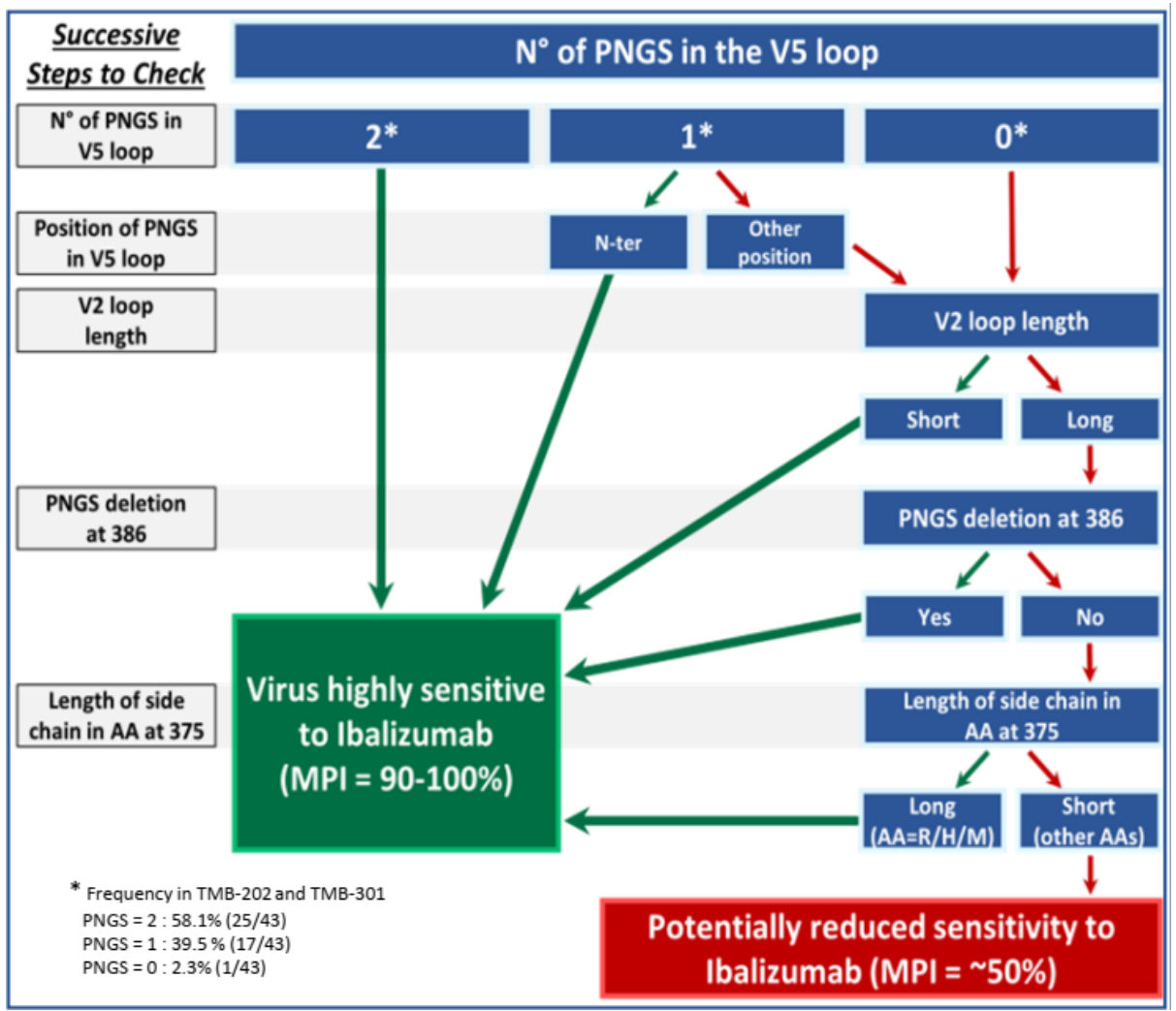
Assessment of genotypic patterns associated with HIV-1 sensitivity to ibalizumab



- Higher susceptibility to IBA associated with **PNGS located closer to the N-terminus of V5**
- HIV with only 1 V5 PNGS can exhibit complete or partial susceptibility to IBA (Pace et al, 2013; Toma et al, 2011; and TMB-202 and TMB-301 studies)
- Higher susceptibility to IBA associated with **shorter V2 regions**, **PNGS deletion at position 386**, or **long side chain AA (H/R/M) at position 375, but only when V5 N-terminal PNGS were absent or deleted**

Jullien, European Meeting on HIV & Hepatitis 2020

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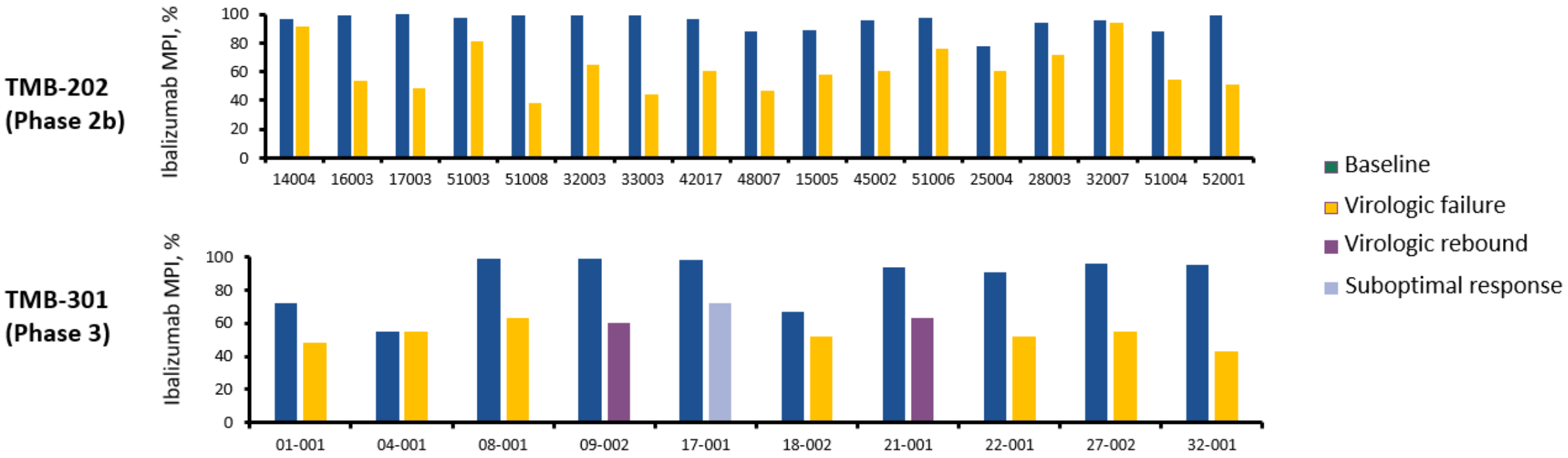
Virological failure or rebound to ibalizumab is associated with reduced ibalizumab activity



- Reduced Maximum Percentage Inhibition at failure/rebound
  - 15/17 in TMB-202, 9/10 in TMB-301 (overall 88.9%)
- Loss of PNGS in the V5 loop of HIV-1 gp120 was the main genetic change associated with reduced susceptibility

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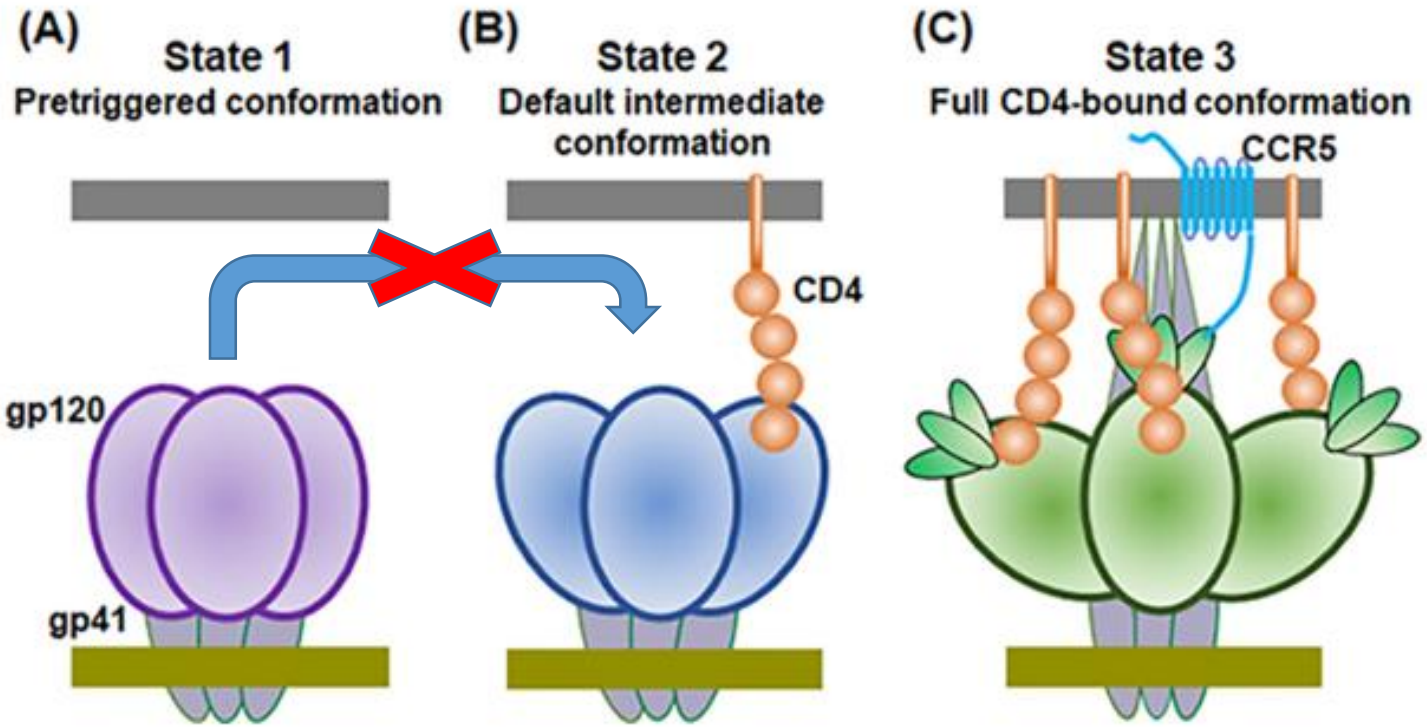
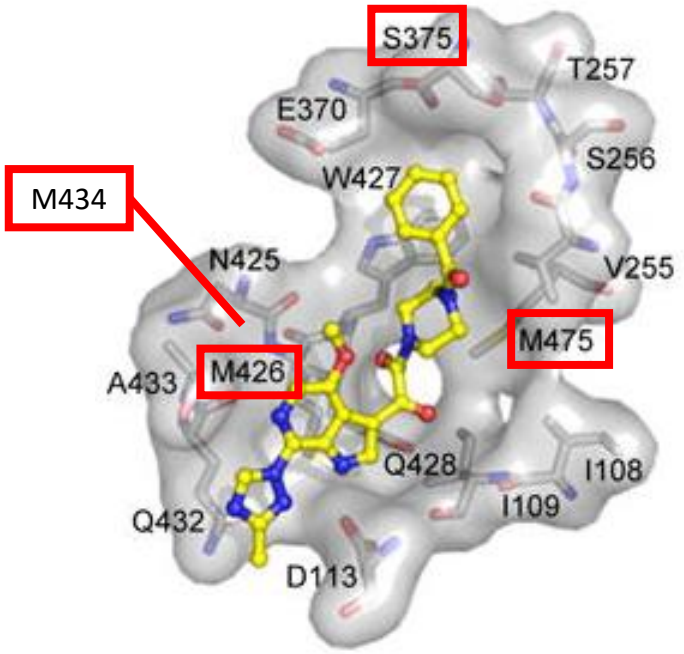
Mechanism of action of fostemsavir (FTR)

- **Temsavir, the active compound of the pro-drug fostemsavir,** binds to a conserved pocket under the β20–21 loop of gp120, close to the CD4 binding site
- Stabilize a prefusion-closed conformation of Env and block Env glycoprotein transitions critical for entry
- Broad range of natural susceptibility within each subtype
  - CRF01 naturally resistant to FTR

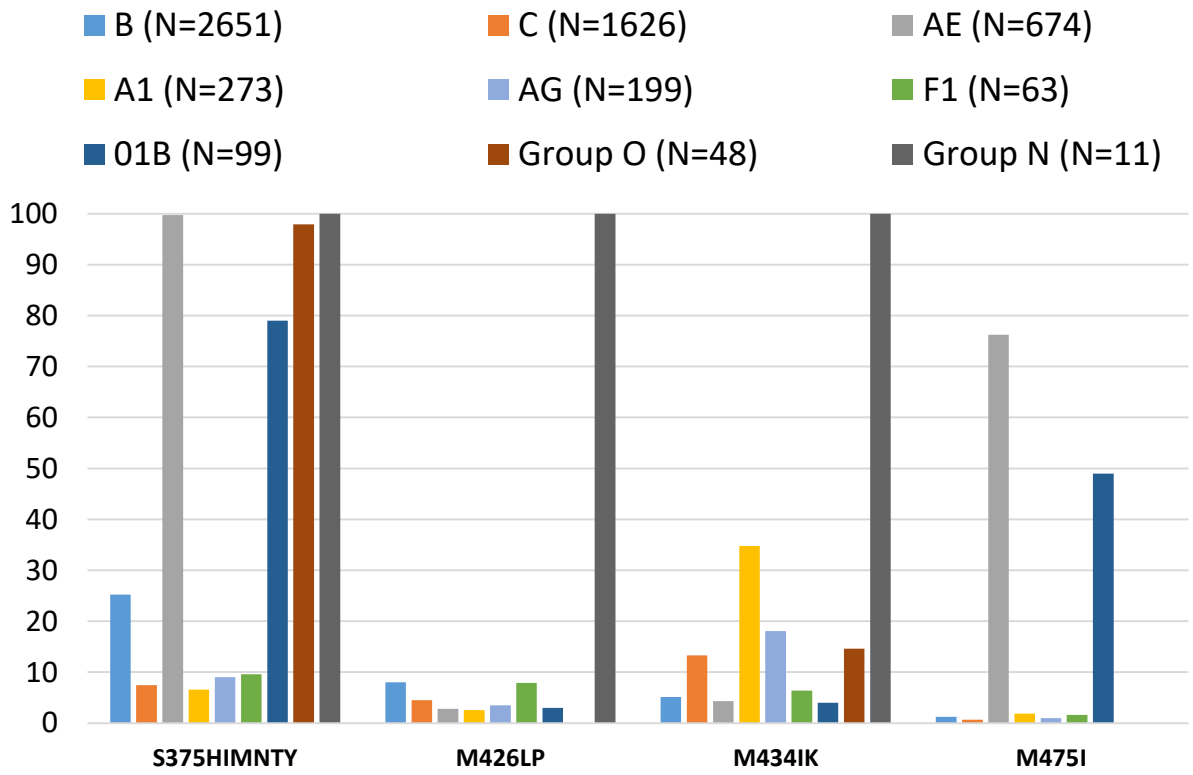


Resistance to fostemsavir

Positions associated with emerging mutations *in vivo*



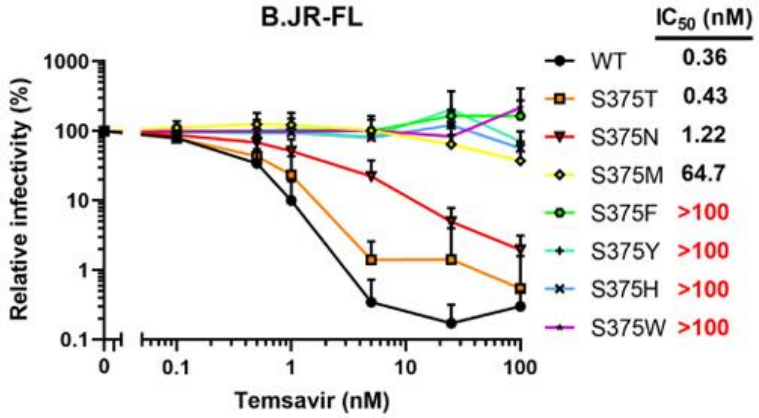
Adapted from Pancera *Nat Chem Biol.* 2017



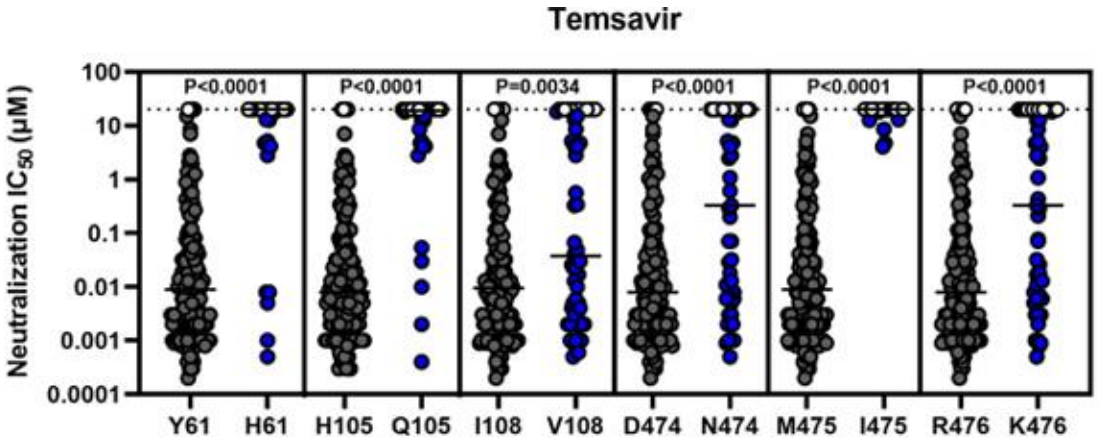
- Most mutations associated with resistance to FTR are natural polymorphisms
- **S375H** and **M475I** predominant among **CRF01_AE** (S375H, 99.3%; M475I, 76.3%)

Adapted from Gartland *J Antimicrob Ther* 2021

Resistance to fostemsavir

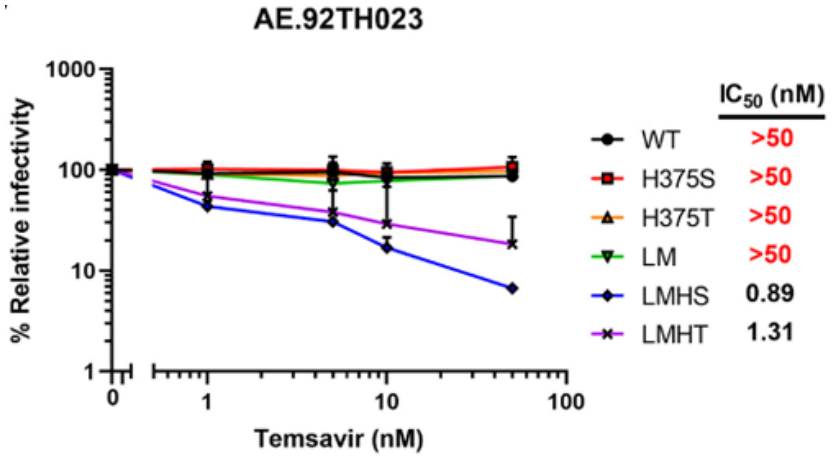


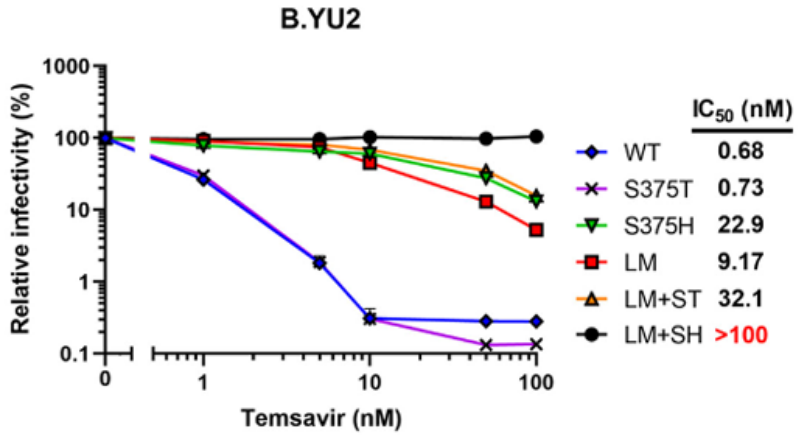
The activity of temsavir inversely correlated with the size of residue 375



S375

H375





Inner layer mutations (LM: H61, Q105, V108, N474, I475, K476;) coevolve with H375 and contribute to temsavir resistance

LM are necessary for CD4 binding in presence of H375 (Zoubchenok *J Virol* 2017)

Prevost *Nat Commun* 2023

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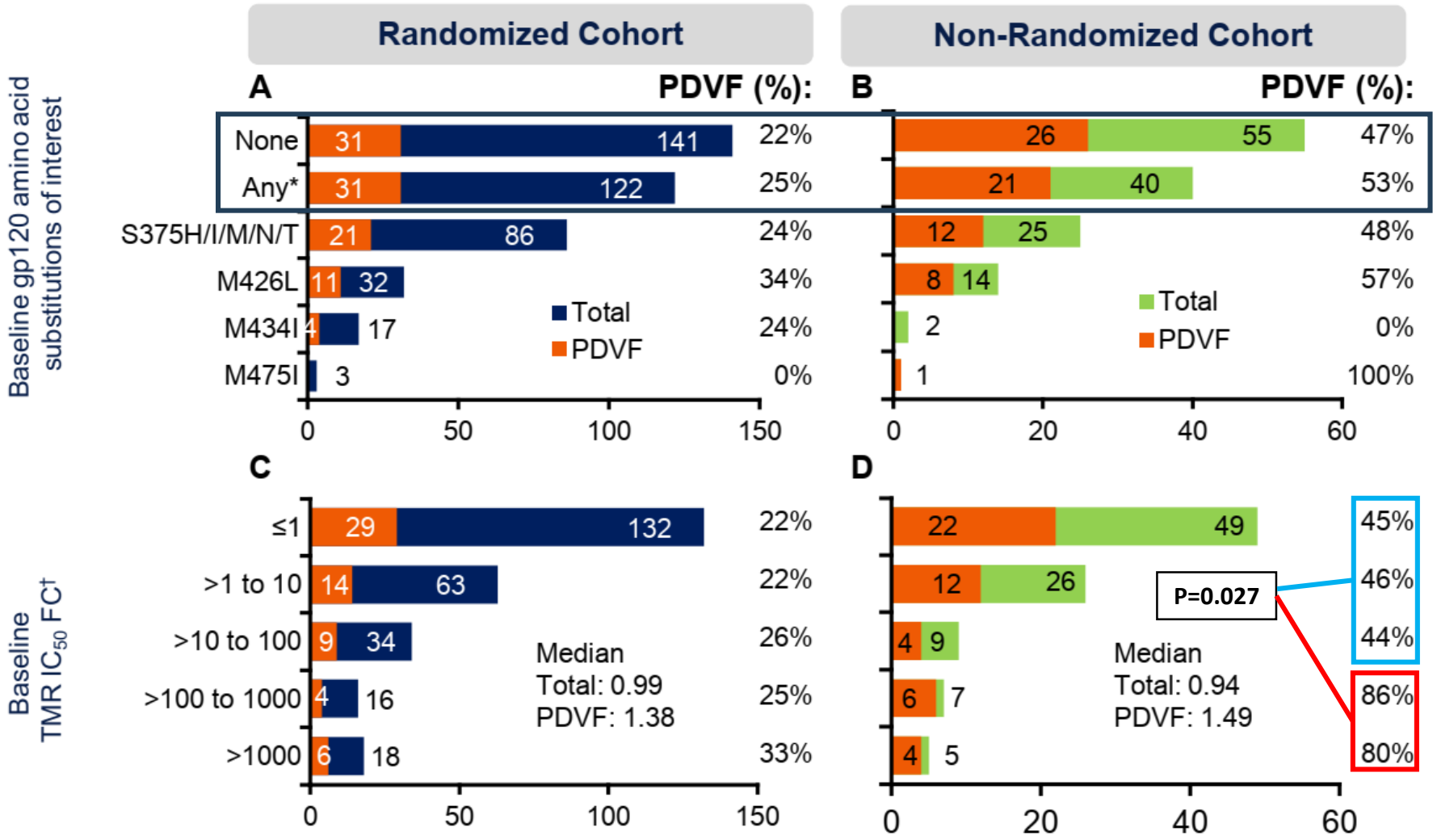
Genotypic vs. Phenotypic screening of FTR susceptibility in the BRIGHTE study



PDVF Through Week 96 for Randomized and Non-Randomized Cohorts by **Baseline gp120 Substitutions of Interest** (A and B) and **temsavir IC_{50} FC** (C and D)

No correlation between baseline genotypic resistance and response

Correlation between baseline phenotypic resistance (>100 FC IC_{50}) and response limited to the non-randomized cohort

Gartland *AAC* 2022

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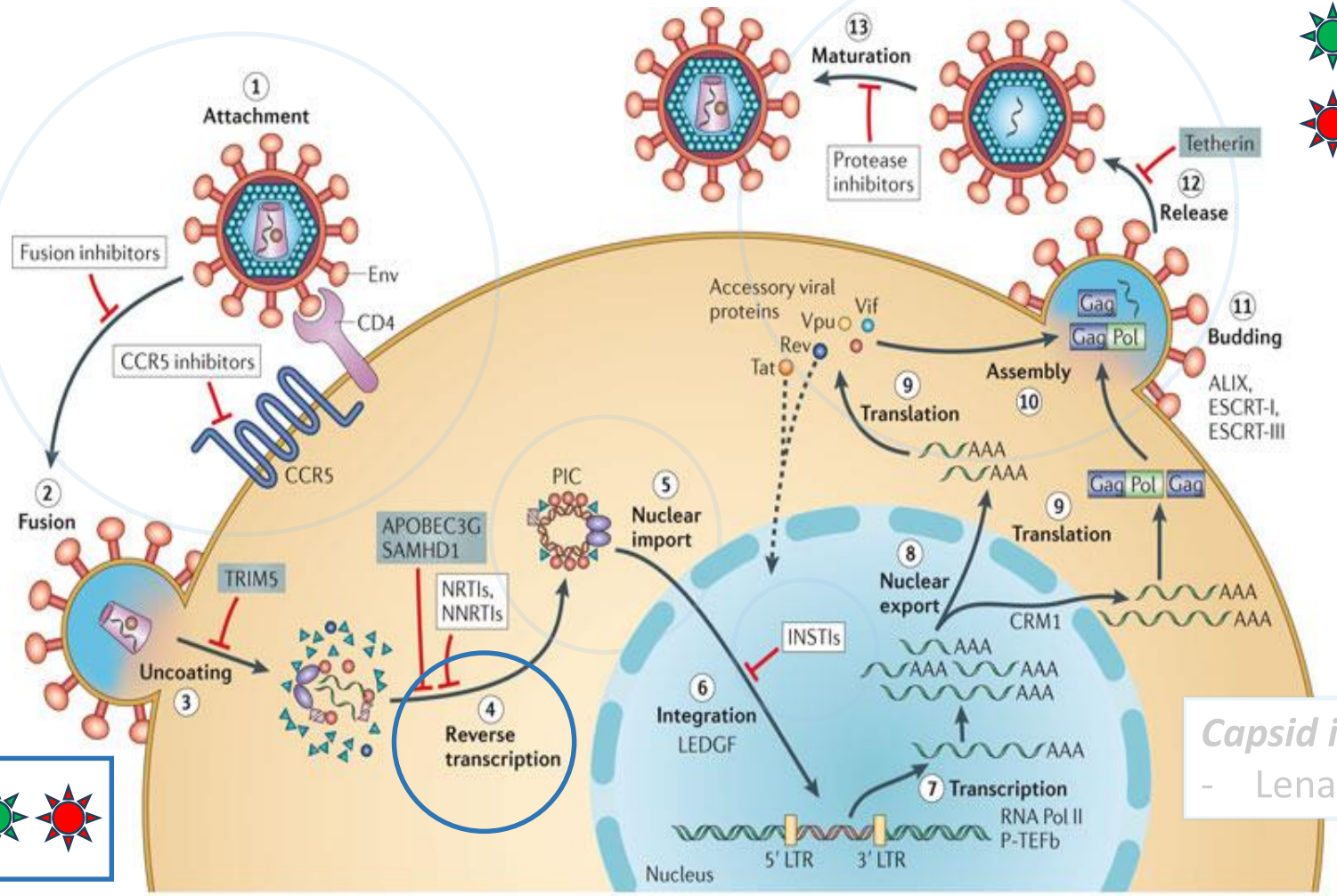

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Impact of HIV-1 Resistance-Associated Mutations on Susceptibility to Doravirine: Analysis of Real-World Clinical Isolates

Asante-Appiah, AAC 2021

TABLE 1 Prevalence of clinical isolates bearing a common NNRTI RAM and respective doravirine susceptibility

Common NNRTI RAM[a]	Prevalence, n (%)[b] (N = 4,070)	Doravirine fold-chan median (IQR)[c]
K103N	580 (14.3)	1.3 (0.8–2.4)
V106I	218 (5.4)	1.3 (0.8–2.7)
Y181C	214 (5.3)	2.2 (1.2–4.6)
V108I	126 (3.1)	2.2 (1.3–5.5)
K101E	123 (3.0)	1.5 (1.0–2.3)
G190A	99 (2.4)	1.8 (1.0–4.1)
E138K	56 (1.4)	1.6 (0.9–2.4)
K103N+Y181C	53 (1.3)	3.1 (1.2–5.1)

[a]NNRTI RAMs present in over 50 isolates were classed as common.
[b]Prevalence of isolates with RAMs (n) irrespective of presence of any other NNRTI RAMs in total of clinical isolates.
[c]Relative to wild type.
IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation.

- DOR is active against most common single NNRTI RAMs
- High level resistance observed with single NNRTI RAMs Y188L or Y318F

TABLE 2 Prevalence of clinical isolates bearing a single unique NNRTI RAM and respective doravirine susceptibility

Single unique NNRTI RAM	Prevalence, n (%) (N = 4,070)	Doravirine fold-change, median (IQR)[a]
K103N	237 (5.8)	1.0 (0.7–1.3)
V90I	104 (2.6)	0.9 (0.6–1.3)
V106I	102 (2.5)	0.8 (0.6–1.3)
E138A	61 (1.5)	1.0 (0.8–1.4)
K103R	49 (1.2)	0.9 (0.6–1.2)
V179D	45 (1.1)	0.5 (0.4–0.6)
V108I	26 (0.6)	1.6 (1.0–2.2)
Y181C	21 (0.5)	1.6 (1.2–1.8)
K101E	17 (0.4)	1.0 (0.9–1.1)
A98G	16 (0.4)	1.5 (0.9–1.9)
Y188L	15 (0.4)	41.0 (25.0–250.0)
P225H	11 (0.3)	1.2 (0.7–1.8)
K103S	10 (0.3)	1.5 (1.1–1.8)
E138G	9 (0.2)	1.0 (0.7–1.1)
E138K	7 (0.2)	1.4 (1.1–1.7)
G190A	6 (0.2)	1.2 (1.0–1.4)
E138Q	5 (0.1)	0.8 (0.6–1.1)
H221Y	4 (0.1)	1.2 (0.8–1.5)
Y318F	3 (<0.1)	11.0 (3.0–14.1)
Y188H	2 (<0.1)	0.8 (0.5–1.2)

[a]Relative to wild type.
IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation.

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Impact of HIV-1 Resistance-Associated Mutations on Susceptibility to Doravirine: Analysis of Real-World Clinical Isolates

Asante-Appiah, AAC 2021

TABLE 3 Prevalence of clinical isolates according to the number of NNRTI RAMs and respective susceptibility to doravirine

No. of RAMs	Prevalence, n (%) (N = 4,070)	Doravirine fold-change, median (IQR)	*P*-value[a]
1	953 (23.4)	0.9 (0.6–1.3)	<0.0001
2	398 (9.8)	1.3 (0.8–2.4)	<0.0001
3	219 (5.4)	2.3 (1.2–7.7)	<0.0001
4	108 (2.7)	3.0 (1.4–13.2)	<0.0001
≥5	68 (1.7)	5.6 (2.4–33.6)	<0.0001

[a]*P*-value from the Mann-Whitney U to test whether fold-change from a randomly selected group of X number of RAMs is significantly greater or less than the fold-change from a randomly selected group without any RAMs (wild-type).

IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation.

- The higher the number of NNRTI RAMs, the higher the resistance to DOR

Isolates with FC values above the 3–fold DOR biological cutoff

- DOR remains susceptible in nearly half of isolates resistant to each of other NNRTI
- DOR resistant isolates retain limited susceptibility to EFV and NVP and partial susceptibility to ETR and RPV

TABLE 5 Proportion of NNRTI-resistant clinical isolates that are susceptible to other NNRTIs

	Percentage of resistant samples susceptible to other NNRTIs, %				
NNRTI	Doravirine-resistant[a]	Efavirenz-resistant	Etravirine-resistant	Nevirapine-resistant	Rilpivirine-resistant
Doravirine-susceptible[a]		62.2	44.7	65.8	45.0
Efavirenz-susceptible	17.1		31.0	18.7	28.1
Etravirine-susceptible	45.2	68.8		65.0	24.4
Nevirapine-susceptible	9.3	1.6	6.0		8.7
Rilpivirine-susceptible	31.9	59.4	5.6	57.4	

[a]A doravirine cutoff 3-fold was used for this comparison.

NNRTI, nonnucleoside reverse transcriptase inhibitor.

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Emerging resistance to doravirine in phase 3 clinical trials

- Overall, DOR treatment-emergent variants were detected in 16 (1.3%) of 1249 participants of DRIVE-FORWARD (DF) and DRIVE-AHEAD (DA)

Subject, study	PDVF type or early discontinuation (D/C)	PDVF, week	Subtype	VL BL	VL PDVF	Emerging DOR RAM	FC	Emergin NRTI RAM	Predicted resistance to RPV	Predicted resistance to ETR	Predicted resistance to EFV
1, DA	Non-response	24	B	164,149	13,380	V106I, H221HY, F227C	>102.28 (R)	M184M/V (S)	R	I	I
2, DA	Non-response	24	B	130,969	34,944	A98G, V106VI, H221HY, F227C	>109.9 (R)	M184V (R)	R	R	R
3, DA	Non-response	24	B	71,777	14,791	A98AG, F227FC	>97.8 (R)	V75VI, M184V (R)	R	I	R
4, DA	Non-response	24	B	202,090	106,092	V106A, P225H, Y318YF	>210.82 (R)	K65R (R)	S	S	R
5, DA	Non-response	24	C	148,905	32,799	V106M/T, F227CR	>98.16 (R)	K65KR, M184V (R)	I	I	R
6, DA	Non-response	36	C	20,664	7,498	Y318YF	0.35 (S)	A62V (S)	S	S	S
7, DA	Rebound	48	CRF01_AE	27,034	1,256	Y188L	>181.58 (R)	M41L, M184V (R)	R	S	R
8, DF	Rebound	60	B	120,765	1,591	V106A, P225H	>95.05 (R)	V118I, M184I (R)	S	S	R
9, DF	Rebound	116	B	90,989	401	A98G, V106VI	1.66 (S)	none	I	I	I
10, DF	Rebound	116	B	27,030	5,192	V106VM, Y318F	20.0 (R)	none	S	S	R
11, DF	Rebound	116	A1	96,420	428	V108VI	17.0 (R)	A62AV, M184MV (R)	S	S	I
12, DA	Rebound	116	B	94,058	476	V106A, F227FL	>106.47 (R)	None	S	S	R
13, DA	Rebound	192	B	94,050	976	V106A, Y318YF	11.0 (R)	M184I (R)	S	S	I
14, DF	D/C	4	F1	28,432	472	V106I	0.84 (S)	None	S	S	S
15, DF	D/C	24	B	388,431	55,708	V106I, H221Y, F227C	>96.61 (R)	M184V (R)	R	I	I
16, DA	D/C	116	b	269,274	1,575	V106VA, F227FCLR	2.33 (S)	None	I	I	R

Legend. S = susceptible; I = intermediate resistance; R = high-level resistance.

Residual phenotypic susceptibility to doravirine in multidrug-resistant HIV-1 from subjects enrolled in the PRESTIGIO Registry

RV ID	NNRTI RAMs	NNRTI exposure at sample collection	Previous exposure to NNRTI	FC values			Stanford HIVdb predicted susceptibility		
				DOR	ETR	RPV	DOR	ETR	RPV
1	A98G, K103N, Y181C, P225H	ETR	EFV, NVP	17.9	100	100	R	I	R
2	L100I, K103N, V179VI, K238N	ETR	EFV	12.2	37.8	100	I	I	R
3	K103N, Y181V	ETR	NVP	7.4	100	100	LLR	R	R
4	K103KNRS, Y181C, **G190S**, H221HY	ETR	none	22.5	48.0	100	R	R	R
5	E138Q, V179E, Y181C	none	EFV, NVP	0.9	26.0	12.2	PLLR	I	R
6	V108I, Y181C	none	EFV, ETR, NVP	3.7	3.2	30.6	I	I	I
7	V106I, **Y188L**, K238N	none	EFV	100	2.9	100	R	LLR	R
8	Y181C, H221Y, M230I	RPV	ETR	80.1	100	100	I	I	R
9	A98G	none	NVP	3.4	0.5	3.7	LLR	PLLR	LLR
10	L100I, E138R, V179L	ETR	None	21.9	100	100	LLR	I	R
11	K103N, Y181I	none	EFV, ETR, NVP	0.2	0.4	3.9	LLR	R	R
12	K103N, E138A, P225H, **M230L**	none	ETR	100	14.1	100	R	I	R
13	K101E, Y181C, G190A	none	EFV, ETR	5.3	22.7	100	I	R	R
14	L100V, K101H, V179F, Y181C, G190A	ETR	NVP, RPV	100	100	100	I	R	R
15	K101E, Y181C, G190A	ETR	None	1.3	2.2	14.4	I	R	R
16	E138K, **G190E**	ETR	EFV, RPV	100	100	100	R	I	R
17	K103N	none	EFV, ETR, NVP	0.4	0.2	0.6	S	S	S
18	V108I, E138A, Y181V	ETR	EFV, NVP	14.9	100	100	I	R	R
19	Y181I	ETR	None	1.2	100	100	LLR	R	R
20	L100I, K103N, E138G	none	EFV, ETR	7.0	100	100	I	I	R
21	A98G, L100I, K103N, E138Q	none	ETR	27.1	100	100	I	I	R
22	K103N, Y181C	none	ETR	4.4	4.0	19.1	LLR	I	I
		Median FC (IQR)		**9.8 (2.9-40.4)**	**42.9 (3.1-100)**	**100 (17.9-100)**			

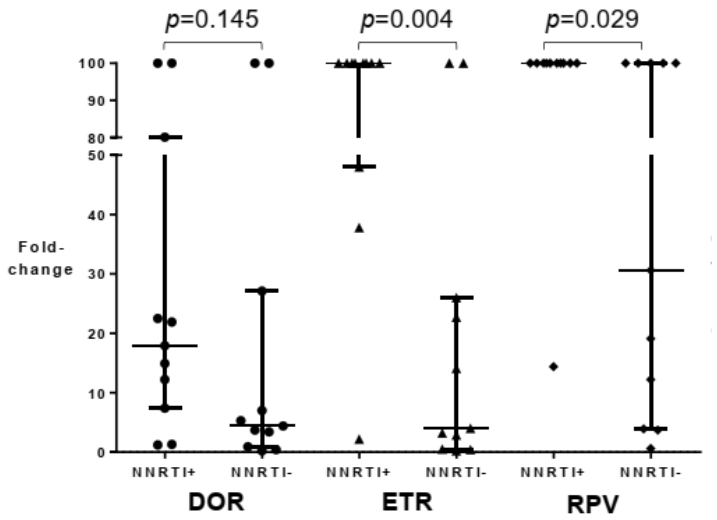
Susceptible | Intermediate resistance | High-level resistance

Fold-change (FC) cut-off values associated with reduced susceptibility:

- DOR >3 (biological)
- RPV >2.5 (biological)
- ETR 2.9 (lower) – 10 (upper) (clinical)

Stanford HIVDB DOR RAMs in bold, IAS-USA DOR RAMs underlined

- 5/22 (23%) isolates are full susceptible to DOR
- Median DOR FC values were higher in samples collected in individuals exposed to NNRTI at sample collection



Saladini, Int J Antimicrob Agents 2023

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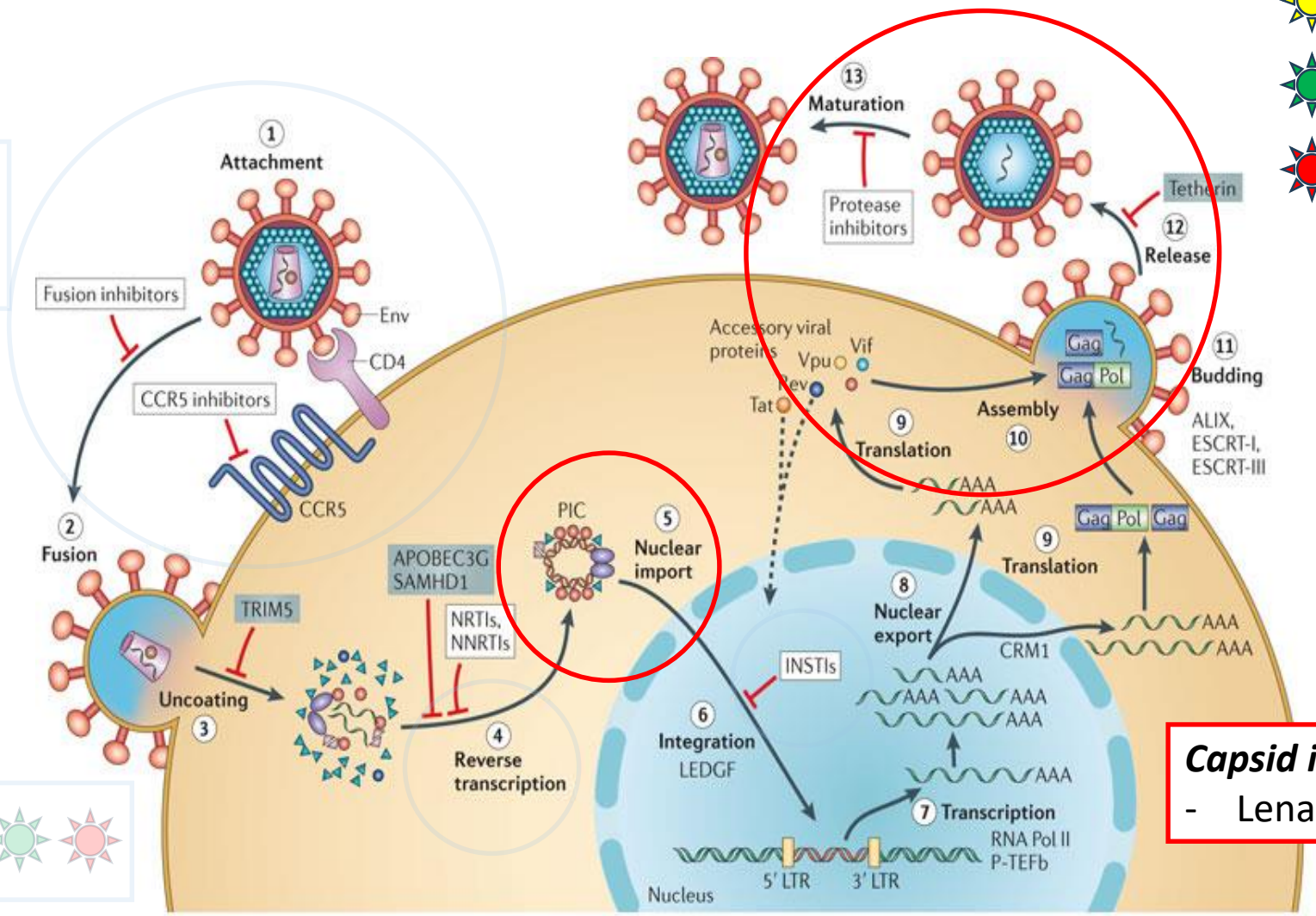

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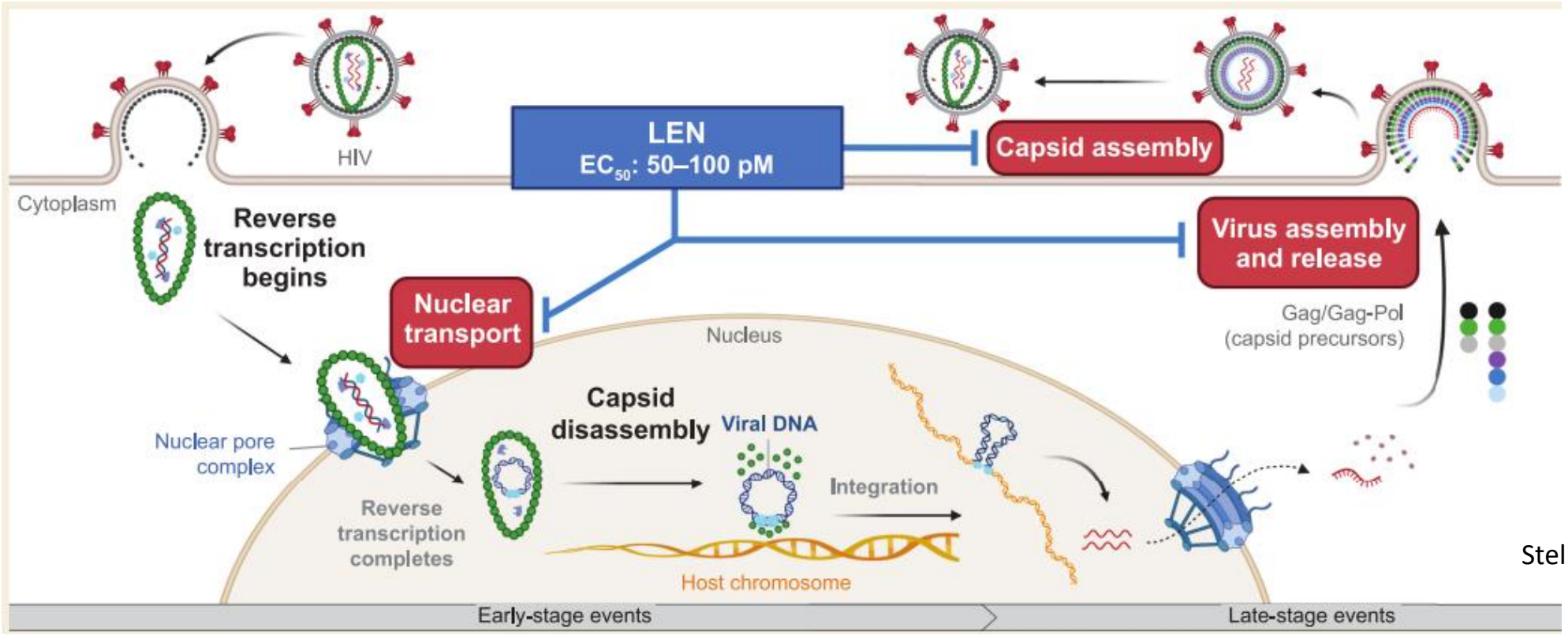
Lenacapavir mechanism of action



Stellbrink, EACS 2021

First-in-class capsid (CA) inhibitor approved for the treatment of multidrug resistant HIV-1

Picomolar potency (EC_{50} = 50-100 pM)

No natural resistance observed in large dataset (Marcelin, *JAC* 2020; Nka, *JAC* 2023)

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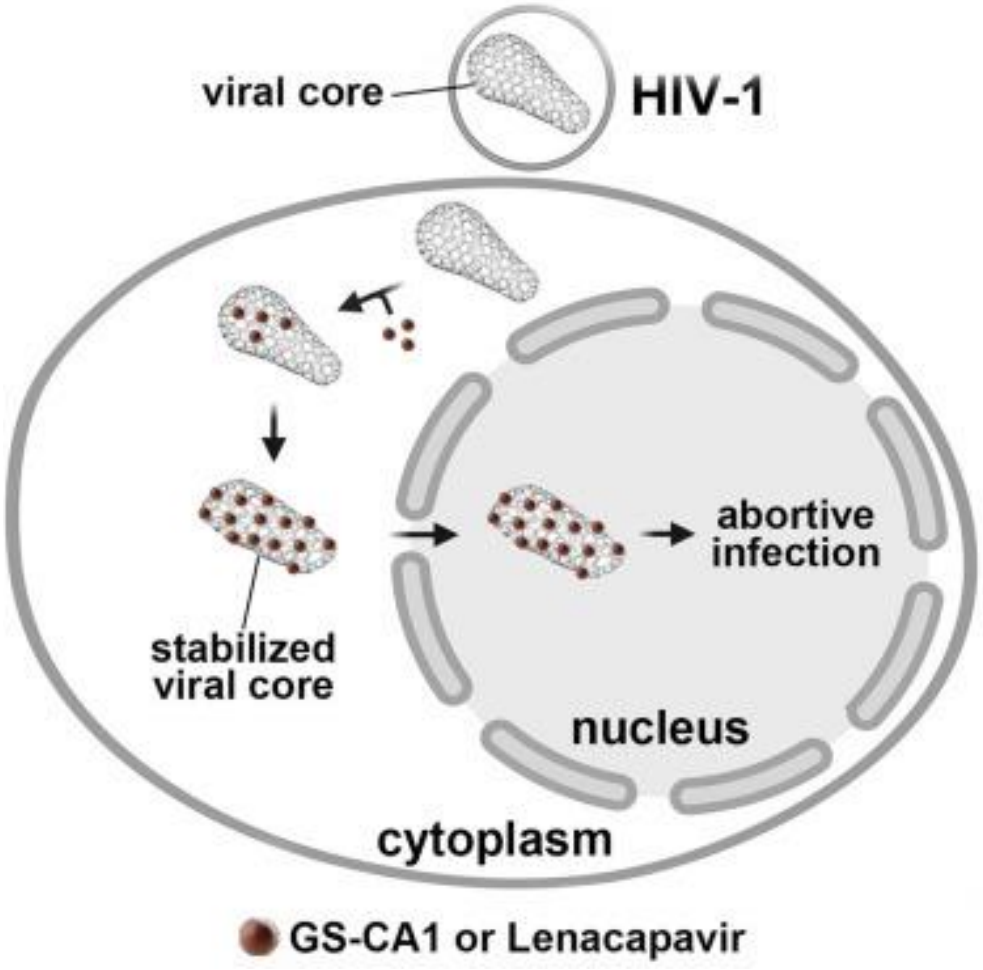
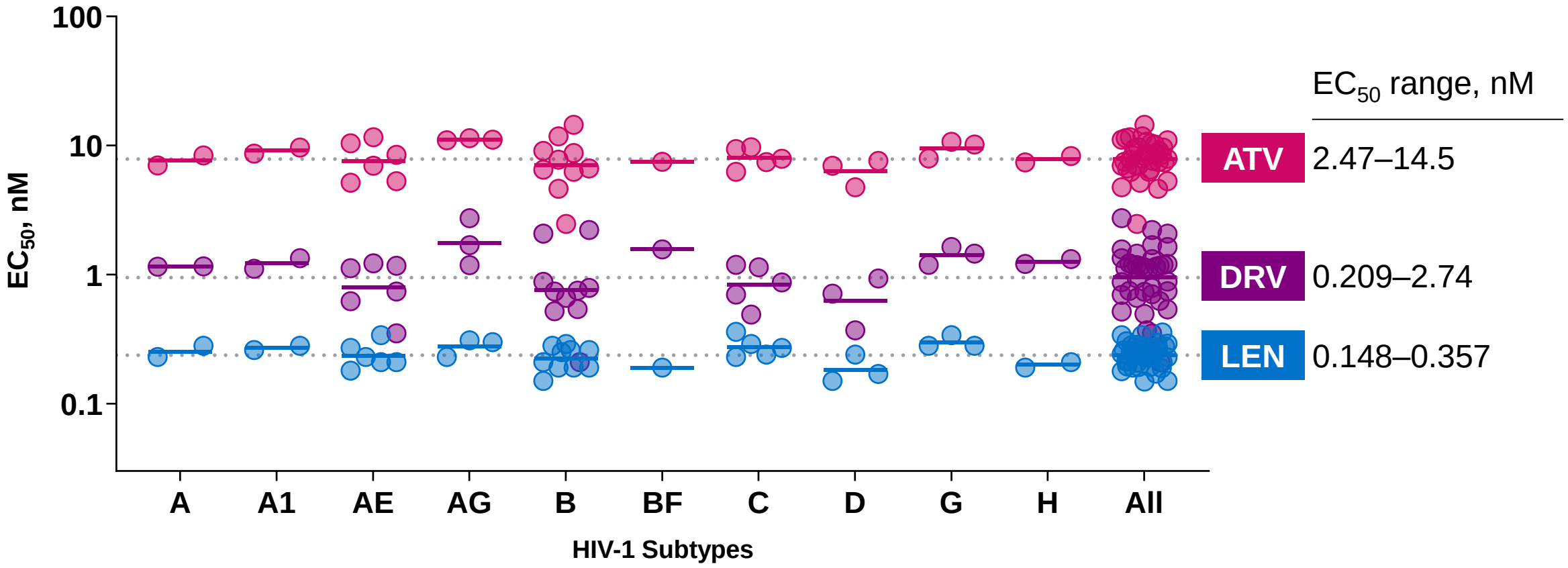
Lenacapavir mechanism of action in the early phases of HIV-1 replication cycle



- Lenacapavir doesn’t prevent nuclear entry of HIV-1 viral core
- Lenacapavir stabilized the structure of the viral core preventing uncoating
- Lenacapavir doesn’t inhibit the reverse transcription but prevent the integration of viral DNA in the host genome

Selyutina, iScience 2022

Lenacapavir is active against all HIV-1 subtypes



EC_{50} values determined with PhenoSense Gag-Pro assay. n=37 clinical isolates.
Each dot represents an individual isolate; solid lines represent geometric mean EC_{50} for each subtype; dotted lines indicate geometric mean EC_{50} for all subtypes tested.

VanderVeen L, et al. vCROI 2021. Oral #128

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Emergent resistance to lenacapavir at week 104 in the CAPELLA study

CA residue	L56	M66	Q67	K70	N74	A105	T107
In vivo	–	I	H/K/N	H/N/R/S	D/H	T/S	A/C/N/S
In vitro	I	I	H	N	D/S	–	N

Category, n (%)	CAPELLA (N=72)
Resistance analysis population	**27** (38)
LEN RAM emergence	**14** (19)
M66I	6 (8)
Q67H/K/N	8 (11)
K70H/N/R/S	7 (10)
N74D/H/K	3 (4)
A105T/S	4 (6)
T107A/C/N/S	3 (4)
No LEN RAM emergence	**13** (18)

Margot, EACS 2023

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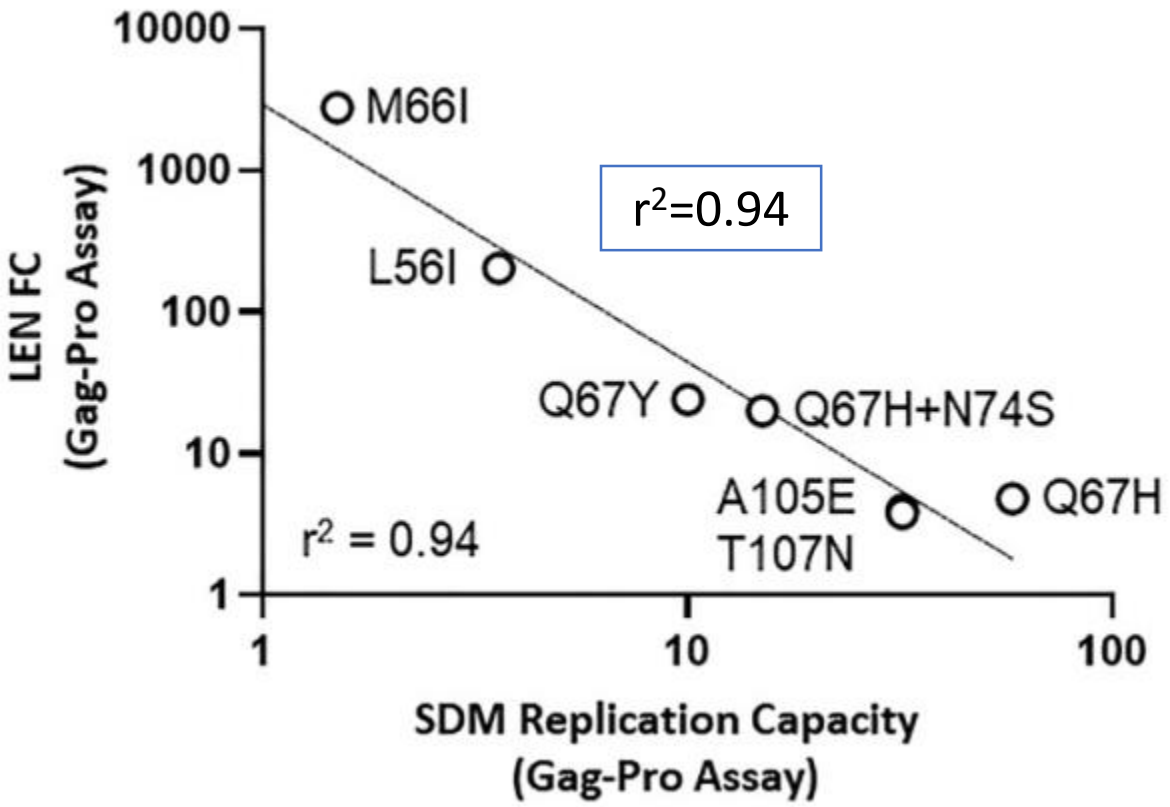
Resistance vs. fitness with Lenacapavir selected mutants



Correlation between replication capacity and fold change in lenacapavir susceptibility in the Gag-Pro assay.

Replication capacity (RC) and lenacapavir change in susceptibility for the seven mutants with dual data in the single-cycle Gag-Pro assay are plotted and analysed by linear regression. **An inverse relationship was observed between RC and susceptibility to lenacapavir**.

FC, fold change; LEN, lenacapavir; SDM, site-directed mutant.

However, fitness can be fully restored depending on the individual virus genetic context

Margot, JAC 2022

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Resistance vs. fitness with Lenacapavir selected mutants

Outcome After VF	VF participants with LEN RAMs (n=14)	
	Non-adherence to OBR (had at least 1 fully active agent)	Suboptimal OBR (had no fully active agents)
Resuppressed	1. Q67H 2. K70N + N74K 3. M66I + K70S 4. N74D 5. Q67H **Low fitness of mutant virus likely playing a role in allowing resuppression without OBR change**	11. M66I + Q67H + N74D + A105T 12. M66I + T107A With OBR Change
Did not resuppress	6. M66I + N74D + A105T 7. Q67H + K70R + A105T 8. Q67K + K70H 9. Q67H + K70R + T107N 10. Q67H + K70R	13. M66I + A105T 14. M66I + Q67H + K70R + T107C

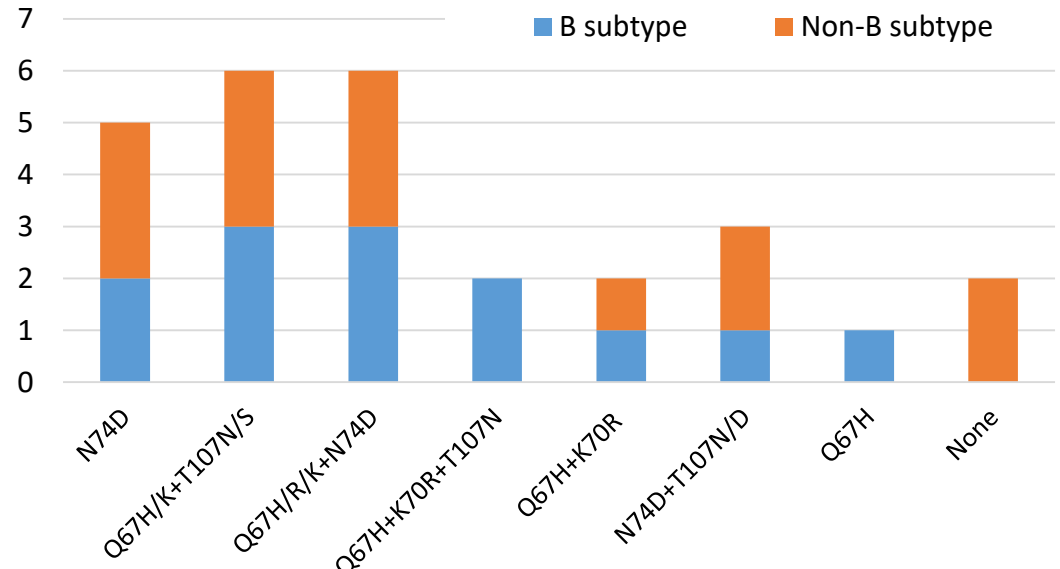
- *Post* VF, 7 of 14 participants with LEN RAMs achieved HIV-1 RNA <50 c/mL on LEN + OBR

Margot, EACS 2023

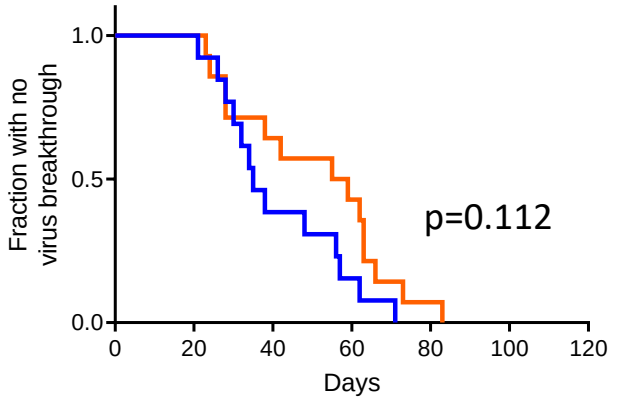
Resistance to lenacapavir

- In vitro study including 26 gag-PR recombinant viruses using samples from therapy naïve (TN, n. 15) or heavily treatment-experienced (HTE, n. 11) PWH from the PRESTIGIO Registry

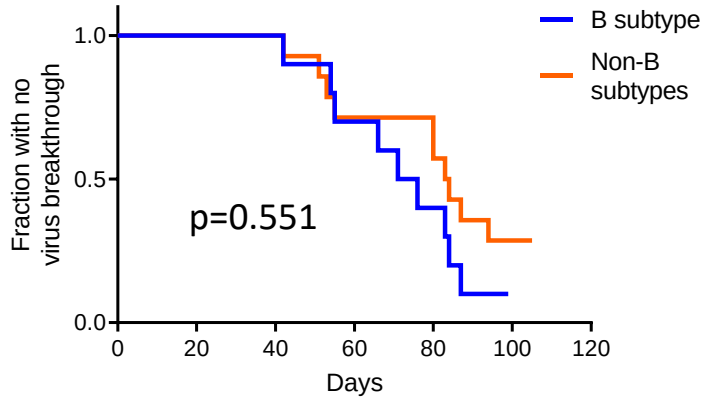
- 13 non-B subtype (CRF02_AG and F1 in three cases each, while A1, C, D, G, CRF01_AE, CRF06_cpx, B/F URF in one case each)

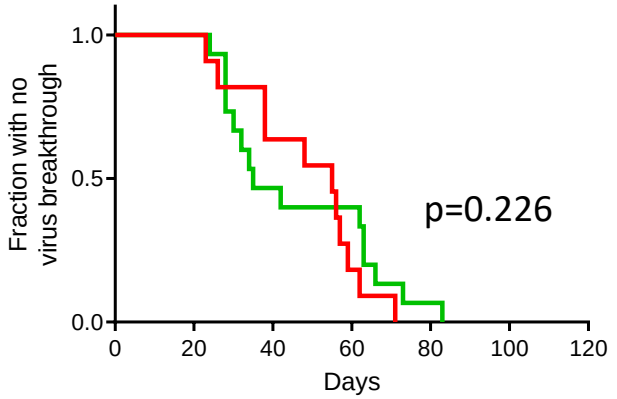


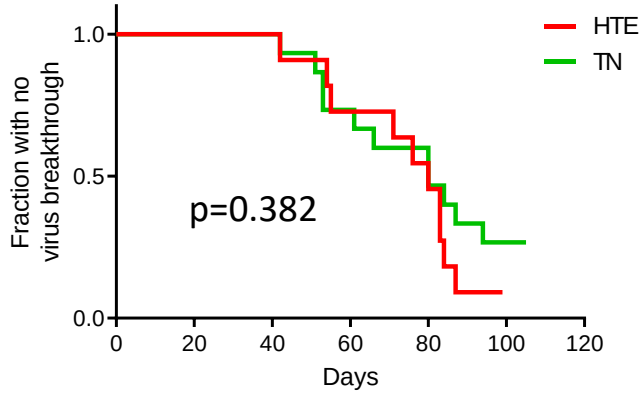
LEN 10X IC_{50}



LEN 100X IC_{50}







- **Phenotypic baseline susceptibility and time to viral breakthrough was comparable among B vs. non-B subtypes and HTE vs. TN PWH**
- **No difference in the selection of LEN RAMs between B and non-B subtypes**

Paletti oral communication ICAR 2024

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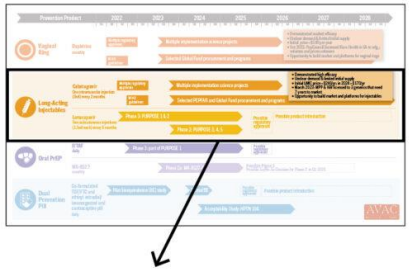
Lenacapavir for PrEP trials

- Initial data
- Possible data
- Possible earliest regulatory submissions
- Possible earliest regulatory approval and market entry with product from Gilead
- Possible earliest generic manufacturer(s)



Trial	Population	Location	Size	2022	2023	2024	2025	2026	2027	2028	2029
PURPOSE 1 Phase 3 Injectable lenacapavir & oral F/TAF	Cisgender adolescent girls and young women	South Africa and Uganda	**5,010**	Initial results released in June 2024 demonstrated no infections in the LEN arm							
PURPOSE 2 Phase 3 Injectable lenacapavir	Cisgender men who have sex with men, Transgender women, Transgender men, Gender non-binary	US, South Africa, Peru, Brazil, Mexico, Argentina, and Thailand	**3,000**			Fully enrolled; initial results expected late 2024 or early 2025					
PURPOSE 3 **HPTN 102** Phase 2 Injectable lenacapavir	Cisgender women	US	**250**			Currently recruiting; estimated study completed date early 2028					
PURPOSE 4 **HPTN 103** Phase 2 Injectable lenacapavir	People who inject drugs	US	**250**			Currently recruiting; estimated study completed date mid-2027					
PURPOSE 5 Phase 2 Injectable lenacapavir	Cisgender men who have sex with men, Transgender women, Transgender men, Gender non-binary	France and UK	**262**			Enrollment expected to begin in the second half of 2024					

AVAC
Advocacy. Access. Equity.

Updated June 2024

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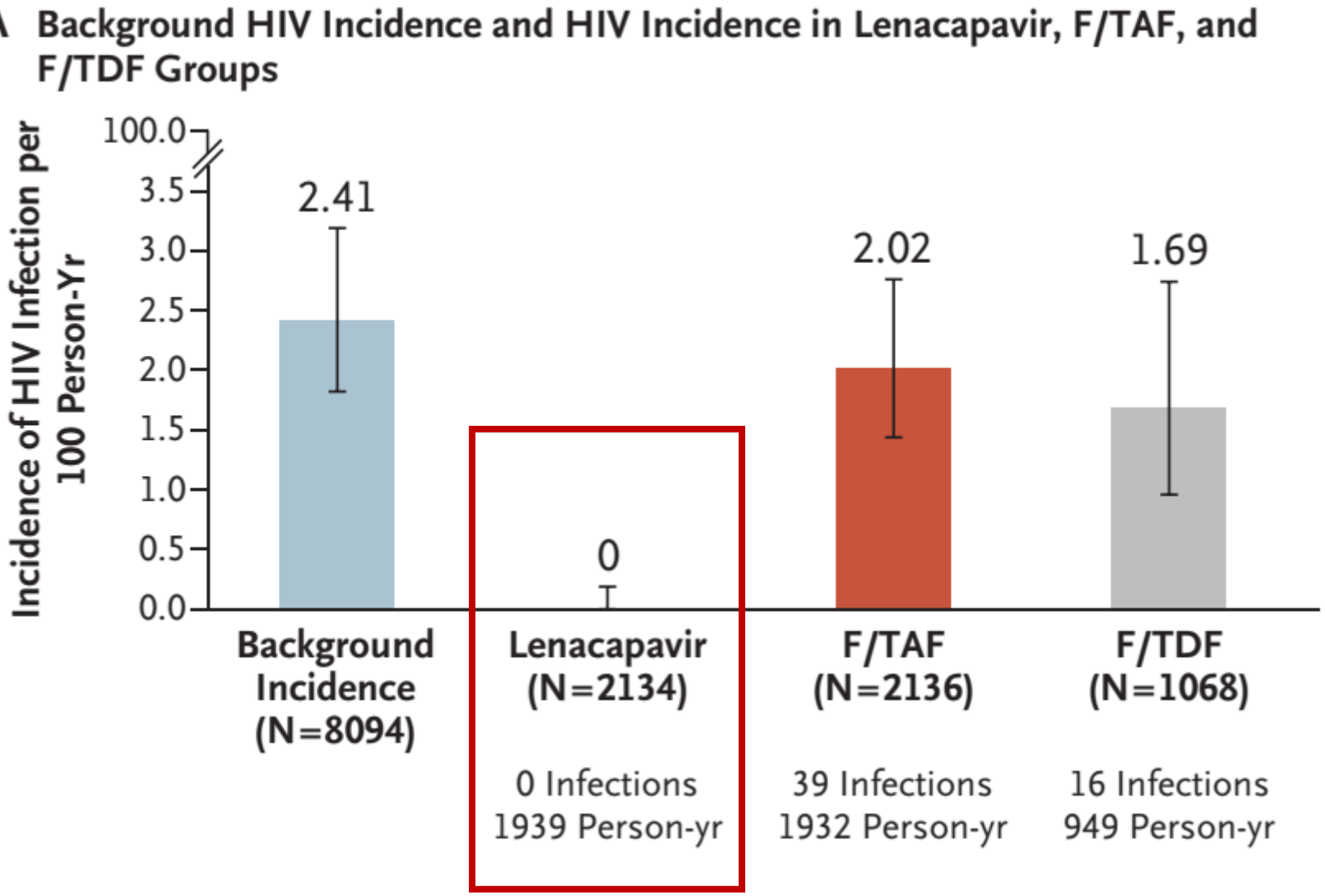
Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women



Bekker, N Engl J Med 2024

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Recently approved antivirals

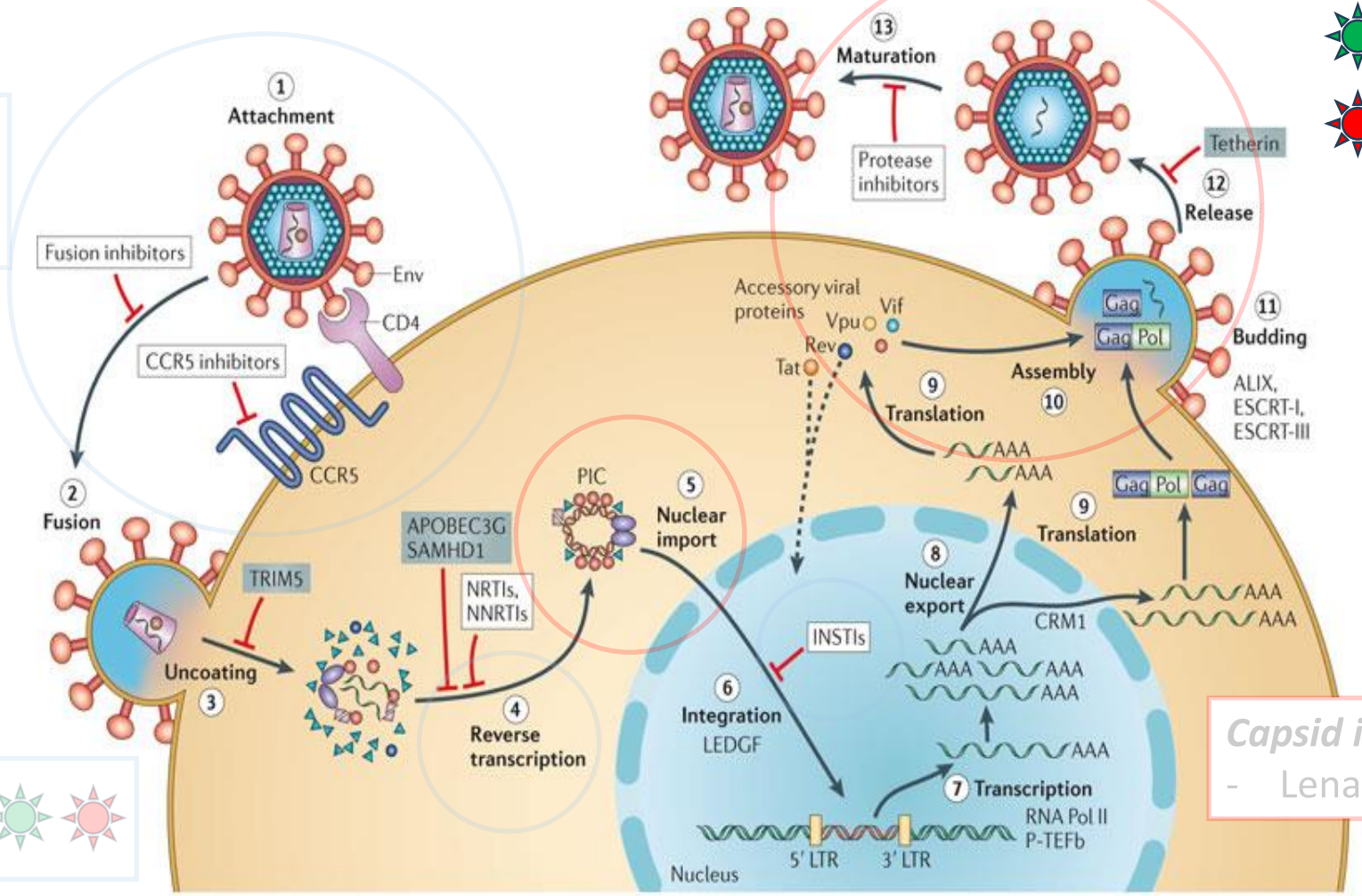
First-line therapy

Mantenance therapy

Salvage therapy

Entry inhibitors:
- Ibalizumab*
- Fostemsavir

* EU marketing withdrawal from January 1, 2023



Nature Reviews | Microbiology

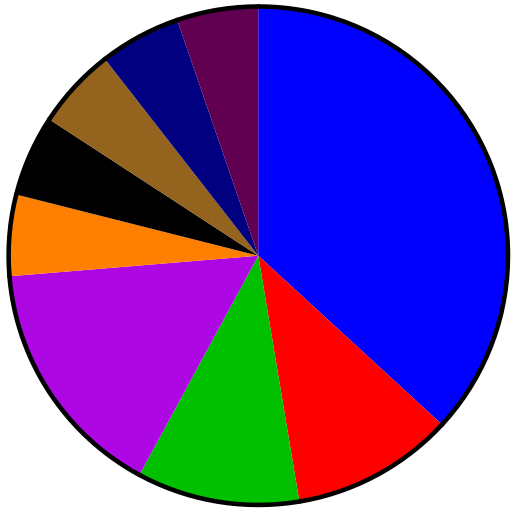
INSTI:
- Cabotegravir (+Rilpivirine LA)

Capsid inhibitor:
- Lenacapavir

NNRTI:
- Doravirine

Emerging resistance to CAB under CAB/RPV LA virological failure in clinical studies

- Data from clinical studies FLAIR, LATTE-2, ATLAS, ATLAS-2M, LATITUDE, SOLAR, CARES including 2,588 PWH
- Globally, 19 virological failures with emerging resistance to INSTI



Total=19

- 7 Q148R
- 2 E138K + Q148R
- 2 Q148Q/R + N155N/H
- 3 N155H
- 1 T97A + N155H
- 1 E92V + N155H
- 1 G140R
- 1 G118R + G140R
- 1 E138K + G140S + Q148K

Q148R in 57.8% of cases, mostly associated with low-level/intermediate resistance to DTG

N155H alone or with 1 INSTI RAM (excepting Q148R) in 26.3% of cases, mostly associated with minimal or absent reduction of the susceptibility to DTG

High level resistance to DTG

Close monitoring of CAB/RPV might allow to identify early treatment failure and reduce the risk of high-level INSTI class resistance

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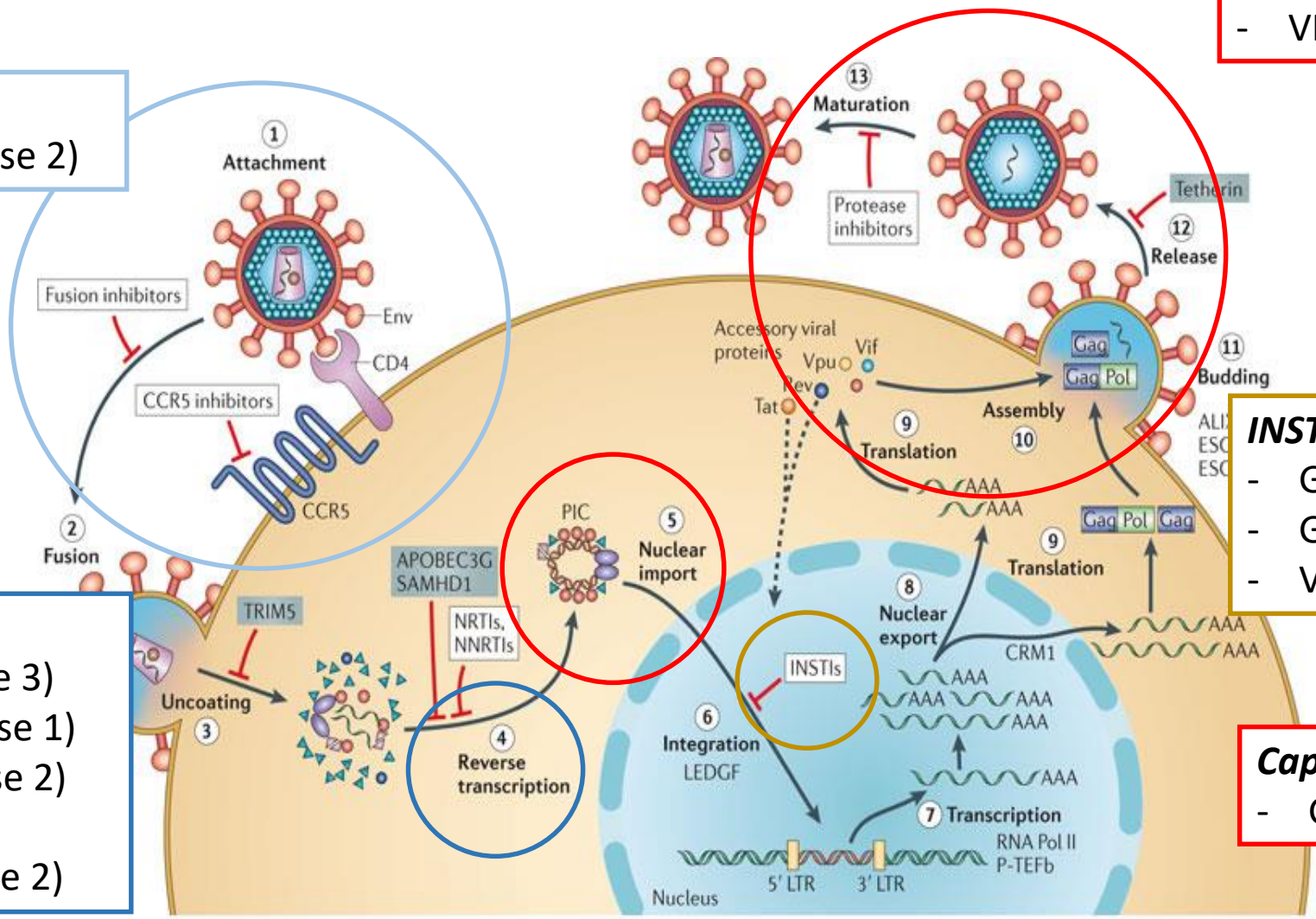
Investigational ARVs on the way

Maturation inhibitor:
- VH-…937 (QW, phase 1)

Entry inhibitors:
- bNAbs (Q6M, phase 2)



INSTI:
- GS-1720 (QW, phase 1)
- GS-6212 (Q3M, phase 1)
- VH-…184 (QD, phase 1)

NRTTI:
- Islatravir (QW, phase 3)
- GS-1614 (Q3M, phase 1)
- MK-8527 (QM, phase 2)

NNRTI
- MK-8507 (QW, phase 2)

Capsid inhibitor:
- GS-4182 (QW, phase 1)

Nature Reviews | Microbiology

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HIV-1 drug target regions

Capsid inhibitor
- LEN

PI
- DRV, ATV, LPV

NRTI
- 3TC, FTC, TDF/TAF, ABC

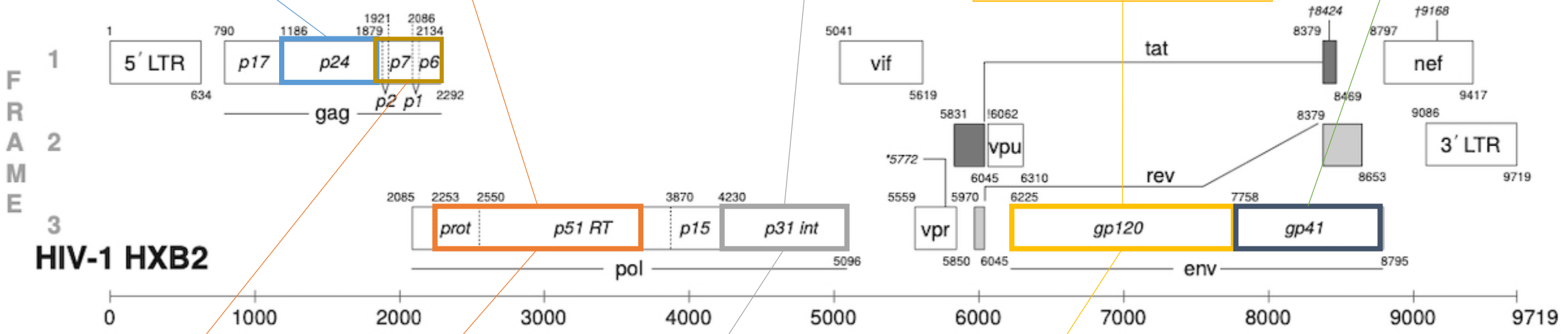
NNRTI
- RPV, ETR, DOR, EFV, NVP

INSTI
- 1° gen RAL, EVG,
- 2° gen DTG, BIC, CAB

Licensed ARVs

Entry inhibitors
- MVC (V3 domain)
- FTR
- IBA (V5 domain)

Fusion inhibitor
- ENF



Maturation inhibitors

NRTTI

3° gen INSTI

Entry inhibitors
- bNAbs

Investigational ARVs

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Take home messages

- **Natural susceptibility to new drugs is good/excellent**
  - Reduced susceptibility to fostemsavir in CRF01_AE
- **Emergent resistance to new drugs at treatment failure is less reassuring**
  - None may be labelled as high genetic barrier, promising data from some investigational drugs (e.g., ISL, VH-184)
- **Genotype may predict drug susceptibility with good/high accuracy**
  - …except for FTR
- **Phenotyping may help to evaluate drug activity**
  - To be considered in deep salvage with complex MDR
  - To improve the accuracy of genotype-based prediction algorithms