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HIV-1 from antiretroviral-naïve and experienced patients lack capsid substitutions associated with GS-6207 *in vitro* resistance

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INTRODUCTION

- The viral capsid protein (CA, p24) provides multiple essential functions throughout the HIV replication cycle, making it an attractive target for antiviral intervention
- GS-6207 is a first-in-class HIV CA inhibitor with a unique, multi-stage mechanism of action, including the inhibition of CA disassembly, nuclear transport, new virion production and CA assembly[1]
- *In vitro* characterization of the CA inhibitor GS-6207 revealed the high potency of the compound (EC_{50} = 0.1 nM)[2]
- Phase 1b clinical study showed that single subcutaneous (SC) doses of GS-6207 from 50 to 450 mg resulted in potent antiviral activity in people living with HIV (PLWH), with mean maximum HIV-1 RNA declines ranging from 1.8 to 2.2 $\log_{10}$ copies/mL over 10 days[3]
- GS-6207 exhibits a unique *in vitro* resistance profile with full activity against NRTI, NNRTI, INSTI or PI resistant mutants. In *in vitro* resistance studies, GS-6207 selected the CA variants L56I, M66I, Q67H, K70N, N74D, N74S and T107N (alone and in combinations), with Q67H and N74D being the most predominantly observed variants[4]
- All GS-6207-selected variants showed reduced susceptibility to GS-6207 and all but Q67H showed reduced infectivity in MT-2 cells and impaired replication capacity in primary human CD4+ T-cells[4]
- Genetic variations in gag naturally occur depending on the HIV subtypes, immune pressure (CTL epitopes), and prior use of HIV protease (PR) inhibitors (PIs), as gag is the substrate for PR
- Here we studied the prevalence of CA mutations associated with *in vitro* resistance to GS-6207 in antiretroviral therapy (ART)-naïve or -experienced PLWH

METHODS

- Sanger sequencing was used to study the presence of GS-6207 *in vitro*-selected mutations (L56I, M66I, Q67H, K70N, N74D, N74S, and T107N in CA)
- We studied 1500 PLWH in 3 large groups: 500 ART-Naïve, 500 ART Experienced without PI use, and 500 ART-Experienced with a history of PI failure with or without major PI resistance mutations (IAS-USA definition)[5]
- All these patients were followed according to the local standard of care and resistance testing was performed following the French national recommendations: systematic resistance testing in any new HIV-1 diagnostic and in any ART failure (defined by the occurrence of 2 consecutive plasma HIV-1 viral load > 50 copies/mL)

RESULTS

- Among the 1500 patients studied, the most prevalent HIV-1 subtypes were B and CRF 02 AG. The other subtypes observed were in accordance with the HIV-1 epidemiology in west Africa (**Table 1**)

Table 1: Characteristics of HIV-1 subtypes

HIV-1 Subtype Distribution, % (n)	ART-Naïve (n=500)	ART-Experienced no PI use (n=500)	ART-Experienced PI failure history (n=500)
B	37.0% (185)	42.0% (210)	56.0% (280)
CRF 02 AG	46.0% (230)	48.0% (240)	37.0% (185)
F1	4.6% (23)	2.4% (12)	-
CRF 06	4.4% (22)	3.8% (19)	3.4% (17)
A1	2.8% (14)	-	1% (5)
D	2.2% (11)	2.2% (11)	1.6% (8)
Other non-B	3.0% (15)	1.6% (8)	1.0% (5)

ART: antiretroviral therapy; PI: protease inhibitor

- The majority of ART-experienced patients with history of PI failure had at least 1 major PI resistance mutation (**Table 2**)

Table 2: Major PI resistance associated mutations (RAMs)

Number of Major PI RAMs, % (n)	ART-Naïve (n=500)	ART-Experienced no PI use (n=500)	ART-Experienced PI failure history (n=500)
0	99.4% (497)	99.6% (498)	47.2% (236)
1	0.6% (3)	0.4% (2)	22.4% (112)
2	-	-	16.4% (82)
3	-	-	10.4% (52)
4	-	-	3.6% (18)

ART: antiretroviral therapy; PI: protease inhibitor
Major PI RAMs (IAS-USA definition): D30N, V32I, M46I/L, I47A/V, G48V, I50L/V, I54L/M, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, and L90M in PR

- None of the seven GS-6207 resistance mutations identified in *in vitro* selection experiments was detected among the 1500 patients studied regardless of the subtypes analyzed or history of PI failure (**Table 3**)

Table 3: Prevalence of HIV-1 sequences with GS-6207 and PI RAM

	Mutations	ARV-Naïve (n=500)	ARV-Experienced no PI use (n=500)	ARV-Experienced PI failure history (n=500)
GS-6207 RAM (*in vitro*-selected)	L56I	-	-	-
	M66I	-	-	-
	Q67H	-	-	-
	K70N	-	-	-
	N74D	-	-	-
	N74S	-	-	-
	T107N	-	-	-
PI-RAM	Any from IAS USA list	0.6%	0.4%	52.8%

ART: antiretroviral therapy; PI: protease inhibitor; RAM: resistance associated mutation

CONCLUSION

- In our database (n=1500) of ART-naïve and experienced PLWH with various subtypes, no mutations associated with *in vitro* resistance to GS-6207 were observed
- Therefore, previous PI failure and emergence of PI resistance mutations are not anticipated to affect the activity of GS-6207 against HIV-1 CA
- This suggests a very low likelihood (<1 in 1500) of pre-existing resistance mutations against GS-6207 in the PLWH population at-large
- Treatment with GS-6207 has the potential to be effective in ART-naïve and experienced PLWH regardless of treatment history, including prior PI use

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