Poster Number

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HIV Clinical Isolates Containing Mutations Representative of those Selected after First Line Failure with Unboosted GW433908 Remain Sensitive to Other Protease Inhibitors

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Introduction

GW433908 (908) is an investigational protease inhibitor (PI) with demonstrated antiviral efficacy, durability, and tolerability in ART-naïve and -experienced subjects. Although no protease resistance-associated mutations were selected during 48 weeks of treatment with ritonavir-boosted 908 QD (SOLO trial), protease mutations were detected infrequently with unboosted 908 BID (NEAT trial).[1]

In the NEAT trial, the predominant protease (PRO) mutations selected were the V32I+I47V (n = 4) and I54L/M (n = 4) mutations, consistent with an APV-like resistance profile for unboosted 908. In one subject, the I54L-containing virus was replaced with a virus containing the L33F+I50V mutations at a later time-point, after continued treatment with unboosted 908 in the presence of detectable viral load.

To understand the potential patterns of cross-resistance to other PIs, clinical isolates containing the V32I+I47V, I54L/M, or I50V mutations, with or without M46I/L or secondary PRO mutations, were identified from a database of patient samples and susceptibility to all marketed PIs was assessed.

Methods

Approximately 16,000 HIV clinical samples from the ViroLogic database, with matching genotypes and phenotypes, were examined to identify samples with the following primary mutations: V32I+I47V, I54L/M, or I50V.

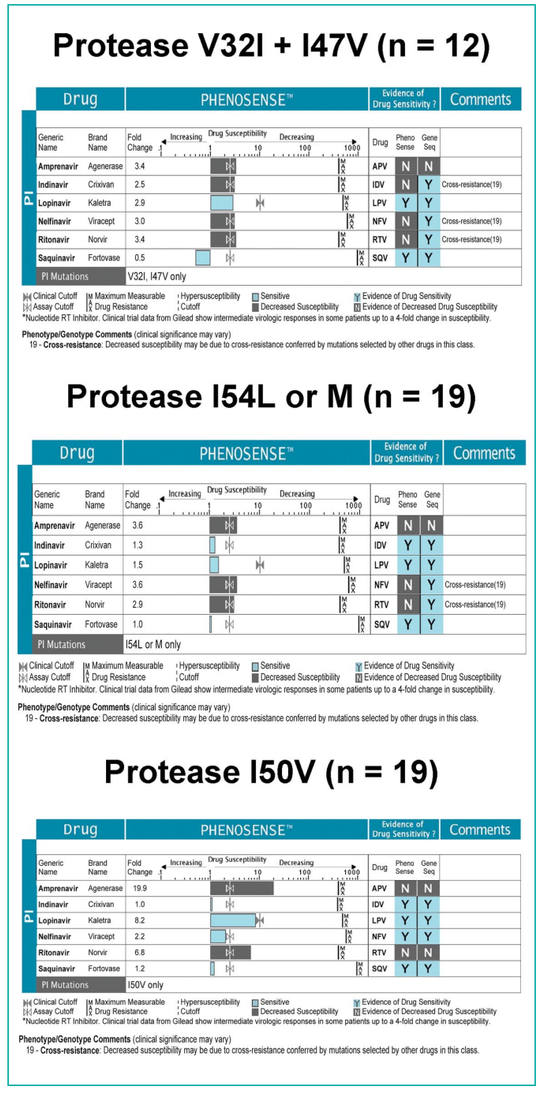
Samples with mixtures at these specific amino acids were excluded, as were samples that also contained certain primary protease mutations (D30N, G48V, V82A/T/S/F, I84V, or L90M) that would indicate exposure to other PIs. The samples described in these analyses were all from clade B viruses.

The median fold-change in susceptibility (IC_{50}) vs the NL4-3 reference was calculated for samples with the specified mutation(s).

Results

Fifty clinical isolates were identified with the indicated primary PI mutations (with or without M46I/L) and no other primary mutations: V32I+I47V (n = 12), I54L/M (n = 13/n = 6), and I50V (n = 19). The primary mutation M46I/L was present at a high frequency with all mutational pathways (67% with V32I+I47V, 37% with I54L/M, and 74% with I50V).

Figure 1 • Median Fold-change for Protease Inhibitors in Clinical Isolates with Mutations Representative of First Line Unboosted 908 Therapy Failure



Results

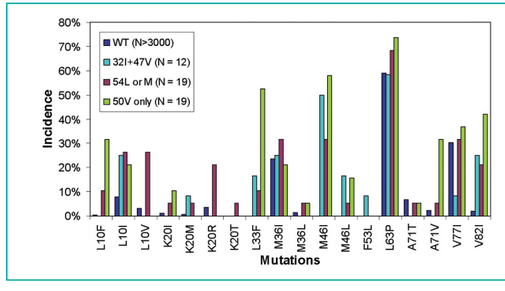
- As seen in Figure 1, for the viruses identified, and in the presence of the M46I/L and/or other secondary protease mutations, viruses with V32I+I47V, I54L/M, or I50V had a median fold-change to amprenavir of 3.4-fold, 3.6-fold, or 20-fold, respectively.
  - For V32I+I47V, I54L/M, and I50V, the median fold-change for saquinavir (0.5, 1.0, and 1.2, respectively) and for indinavir the median fold-change for I54L/M and I50V (1.3 and 1.0, respectively) were below the assay cut-off.
  - The median fold-changes with V32I+I47V, I54L/M, or I50V were also below the clinical cut-off for lopinavir (2.9, 1.5, and 8.2, respectively).
  - With respect to nelfinavir, samples were sensitive or had low-level resistance, with fold-changes of 3.0, 3.6, and 2.2. Low-level cross-resistance was also seen for ritonavir, with fold-changes of 3.4, 2.9, and 6.8.

- Figure 2 compares the incidence of other secondary mutations that were present along with viruses having either V32I+I47V, I54L/M, or I50V to the incidence of secondary mutations present in WT viruses (for which the same primary mutations were excluded).
  - Mutations could be present as mixtures with WT or with other mutant amino acids.
  - Mutations which had an incidence of 0% or were part of the query definition are not shown. 908 was not available for routine clinical treatment, so the mutation pathways shown are presumed to have been selected by APV or by other PIs.

- Although elevations in incidence were seen for the M36I L63P and V77I mutations (Figure 2), the incidences were similar to those seen for WT virus.

- Secondary mutations that were present at an elevated incidence in virus containing V32I+I47V, I54L/M, or I50V compared to WT included mutations at L33F and A71V for the I50V group, and L10, M46, and V82I in all three groups (Figure 2).

Figure 2 • Incidence of Other Resistance Mutations with 32I+47V, 54L/M, or 50V Mutations Compared to WT Viruses



Results

- This secondary mutation profile has some differences with what has been observed for the unboosted 908 treatment arm in NEAT from patients experiencing virologic failure.[1]
  - Unlike the data presented in Figure 2, in which V82I occurs at an increased incidence in the three pathways, there has been no selection for the V82I in patients experiencing virologic failure through 48 weeks or more on therapy in NEAT.[1]
  - L33F and M46I/M have been seen in subjects in NEAT (at Weeks 40 or later). L33F was selected in 2/5 subjects, in one subject at Week 40 (at time of first analysis), and in a second subject at Week 64 at time of last analysis. Similarly, an 46M/I or M46I mix was observed in 2/5 patients at Week 40 or later.

Figure 3 • Most Protease Inhibitors are Still Active in the Presence of Mutations Selected by Unboosted 908

mutation	APV	IDV	LPV	NFV	RTV	SQV	IDV/rtv
32I+47V	3.4	2.5	2.9	3.0	3.4	0.5	2.5
54L or M	3.6	1.3	1.5	3.6	2.9	1.0	1.3
50V	19.9	1.0	8.2	2.2	6.8	1.2	1.0

Full susceptibility
Reduced susceptibility

- Figure 3 demonstrates that selection of 32V+47I, 54L/M, or 50V decreased susceptibility to amprenavir, ritonavir, and nelfinavir (32I+47V and 54L/M only), but maintained susceptibility to lopinavir and saquinavir (median fold-changes shown). The 54L/M and 50V pathways are IDV susceptible but borderline susceptible for the V32I+47V pathway, however, these isolates are all below the clinical cut-off for boosted IDV/rtv.

Conclusions

◆ Clinical isolates with mutational patterns similar to those selected by unboosted 908 remain sensitive to most other protease inhibitors, suggesting that viruses present after treatment failure of an unboosted 908 regimen will respond to second-line PI-containing therapy.

Reference

1. Macmanus S, Yates P, White S, et al. GW433908 in ART-naïve Subjects: Absence of Resistance at 48 Weeks with Boosted Regimen and APV-like Resistance Profile with Unboosted Regimens. *10th Conference on Retroviruses and Opportunistic Infections.* Feb 10-14, 2003. Boston, MA, USA. Abstract 598.