67

TRENDS IN THE DARUNAVIR GENOTYPIC RESISTANCE LANDSCAPE

EW Stawiski, A Paquet, JM Whitcomb, E Coakley, CJ Petropoulos, M Haddad

Presenting Author. Monogram Biosciences, Inc.
345 Oyster Point Blvd., South San Francisco, CA 94080
estawiski@monogrambio.com

17th International HIV Dynamics & Evolution Conference
Monterey, CA
April 25-28, 2010

BACKGROUND

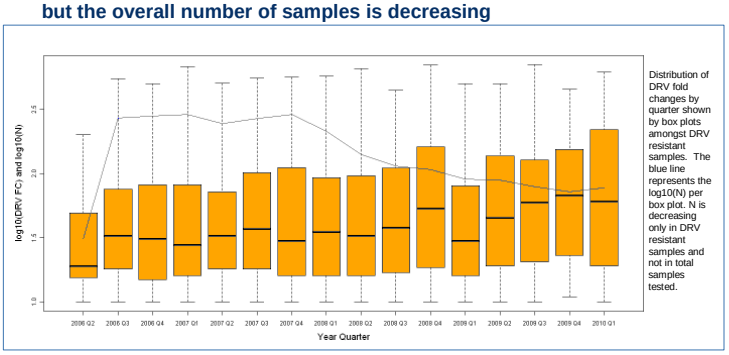
- Darunavir/r (DRV) is a next generation protease inhibitor PI which has shown activity against many HIV-1 strains with multiple PI resistance associated mutations (RAMs).
- International AIDS Society (IAS) guidelines for mutations associated with DRV are commonly used to determine resistance to the drug.
- The purpose of this study was to examine DRV resistance patterns over time by surveying Monogram's patient testing database.

METHODS

- We examined samples submitted for routine phenotypic and genotypic patient testing that had a DRV fold change (FC), fold change of IC50 relative to a reference, greater than the lower clinical cutoff (FC ≥ 10, N=2,665).
- Samples were collected from mid-2006 through March 2010 and were grouped by quarter.
- We considered 11 IAS DRV mutation trends (V11I, V33I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V) with phenotypic response.
- Average frequency of each mutation per quarter was calculated, as well as the mean DRV FC and total count of IAS DRV mutations.
- Significance of trends was evaluated using the Jonckheere-Terpstra test.

RESULTS

Figure 1: Amongst DRV resistant samples, resistance is increasing but the overall number of samples is decreasing



Distribution of DRV fold changes by quarter shown by box plots amongst DRV resistant samples. The blue line represents the log10(N) per box plot. N is decreasing only in DRV resistant samples and not in total samples tested.

Figure 2: Mean DRV FC amongst DRV resistant samples tracks well with an increase in the average number of DRV mutations

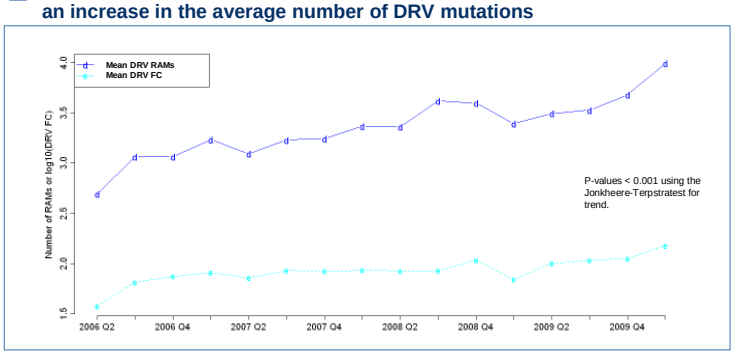


Figure 3: Temporal trends in DRV IAS mutations amongst DRV resistant samples

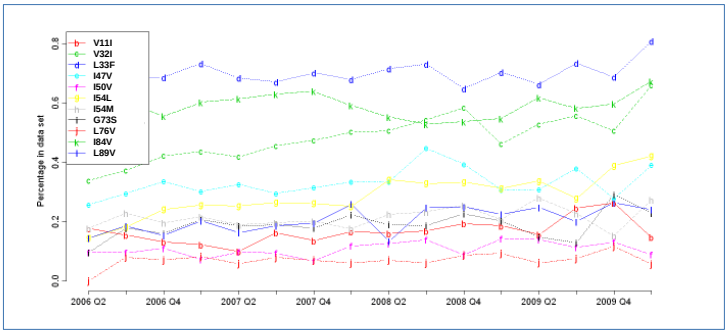


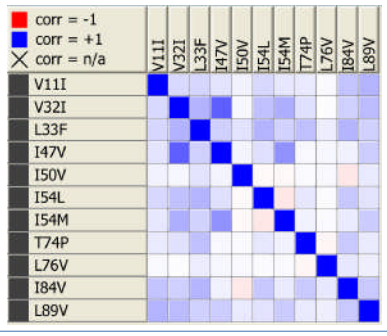
Figure 4: Temporal trends in DRV IAS mutations amongst DRV sensitive samples with a minimum of at least 1 mutation

Table 1: Test for trends amongst DRV IAS mutations

	DRV Resistant		DRV Sensitive	
IAS Mutation	p-value	Trend	p-value	Trend
V11I	0.524		0.645	
V32I	0.001	UP	1.000	
L33F	1.000		1.000	
I47V	0.958		1.000	
I50V	1.000		1.000	
I54L	0.001	UP	0.129	
I54M	0.958		1.000	
G73S	0.645		0.009	DOWN
L76V	1.000		1.000	
I84V	1.000		0.009	DOWN
L89V	0.099	UP	1.000	

DRV IAS mutations tested for trend using the Jonckheere-Terpstra test. P-values were corrected for multiple testing using the Bonferonni method. E35N and V11L were no longer significant with the expanded time points. DRV Sensitive samples were defined as having at least 1 DRV IAS mutation and a DRV FC < 10. Note that repeat patient samples were not removed from the dataset.

Figure 5: Co-variation analysis amongst DRV IAS mutations



Co-variation analysis on the occurrence of DRV IAS mutations using Pearson's chi-square test. Dark blue represents a strong correlation while red represents a negative correlation.

RESULTS

- While the overall number of samples with phenotypic resistance to DRV declined over the last 16 quarters, amongst isolates with DRV FC ≥ 10, the mean number of IAS DRV RAMs increased from 2.7 in Q2 2006 to 4 in Q1 2010 (p-value < 0.001) while DRV FC increased from a mean of 38 to 151 (p-value < 0.001).
- A significant increase in prevalence within IAS mutations was found for V32I, I54L (p-values = 0.001) after correcting for multiple testing.

CONCLUSION

- We observed changes in the DRV resistance landscape over time.
- These results can highlight the potential utility of periodic surveillance of HIV drug resistance to optimize interpretative algorithms.

ACKNOWLEDGEMENTS
We are grateful to the Monogram Biosciences Clinical Reference Laboratory group for performance of PhenoSense and GeneSeq assays.