H2-800

Significant Reductions in the Prevalence of Protease Inhibitor and 3-Class Resistance: Recent Trends in a Large HIV-1 Protease/Reverse Transcriptase Database

Agnes Paquet*, Mark C Evans, Christos Petropoulos, Jeannette Whitcomb, Eoin Coakley, Laura Napolitano and Mojgan Haddad

Monogram Biosciences, Inc.,
South San Francisco, CA, USA

*Corresponding author
Monogram Biosciences, Inc.
345 Oyster Point Blvd.
South San Francisco, CA 94080
apaquet@monogrambio.com

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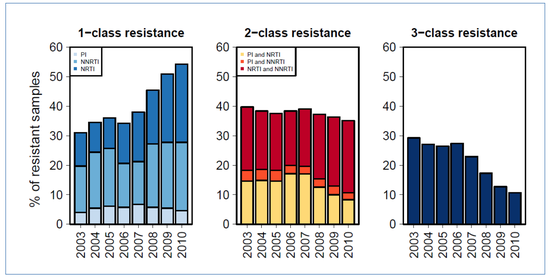
BACKGROUND

- Drug resistance testing for individuals infected with HIV-1 is a key component of the management of antiretroviral (ARV) therapy.
- We examined phenotypic drug resistance patterns in protease- (PI), nucleoside-reverse-transcriptase- (NRTI), and non-nucleoside-reverse-transcriptase-inhibitors (NNRTI) as well as 1-, 2-, and 3-class resistance over time by surveying Monogram Biosciences commercial database.

METHODS

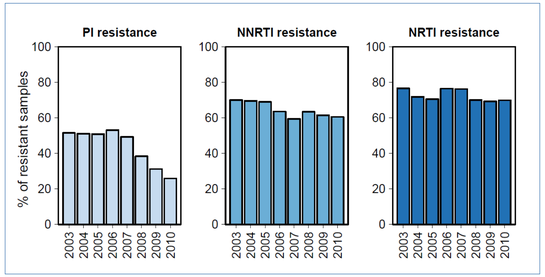
- We examined fully de-identified samples submitted for routine phenotypic and genotypic patient testing that show phenotypic resistance to at least one drug within PIs, NRTIs, and NNRTIs as measured by fold-change of IC50 (FC) ≥ lower cutoff (CO).
- A total of 68587 resistant samples collected from 2003 through 2010 were grouped into specimens that had FC ≥ CO for minimum of 1 drug in each drug-class.
- We studied the temporal trends of % phenotypic resistance and the prevalence of PI, NRTI and NNRTI resistance mutations (RAM) within samples phenotypically resistant to each drug class.
- Jonckheere-Terpstra (JT) test was performed to evaluate the significance of trends.

Figure 1: Trends of phenotypic 1-, 2- and 3-class resistance



Each bar represents the percentage of samples that exhibited reduced phenotypic susceptibility to either one, two, or three drug classes (NRTI, NNRTI, PI) compared to the sum total of all samples that exhibited reduced susceptibility to any drug class (NRTI, NNRTI, PI).

Figure 2: Trends of phenotypic resistance for PIs, NNRTIs and NRTIs



Each bar represents the percentage of samples that exhibited reduced phenotypic susceptibility to any drug from a drug class (NRTI, NNRTI, PI) compared to the sum total of all samples that exhibited reduced susceptibility to any drug class (NRTI, NNRTI, PI).

Table 1: FDA approval dates

Drug Class	Generic Drug Name	FDA Approval (year)
NRTI	Abacavir	1998
	Didanosine	1991
	Emtricitabine	2003
	Lamivudine	1995
	Stavudine	1994
	Tenofovir	2001
	Zidovudine	1987
NNRTI	Delavirdine	1997
	Efavirenz	1998
	Etravirine	2008
	Nevirapine	1996
PI	Atazanavir	2003
	Darunavir	2006
	Fosamprenavir	2003
	Indinavir	1996
	Lopinavir	2000
	Nelfinavir	1997
	Ritonavir	1996
	Saquinavir	1995
	Tipranavir	2005
Combinations	Zidovudine/Lamivudine	1997
	Abacavir/Lamivudine/Zidovudine	2000
	Abacavir/Lamivudine	2004
	Tenofovir/Emtricitabine	2004
	Efavirenz/Tenofovir/Emtricitabine	2006
Fusion-inhibitor	Enfuvirtide	2003
CCR5-inhibitor	Maraviroc	2007
Integrase-inhibitor	Raltegravir	2007

Figure 3: PI-Resistance mutations from 2003 to 2010

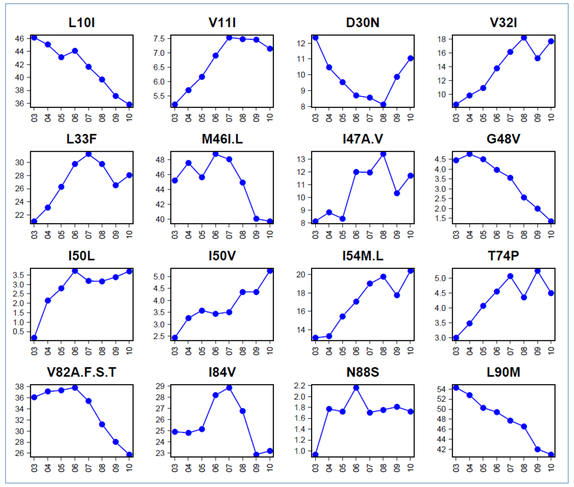


Figure 4: NRTI-Resistance mutations from 2003 to 2010

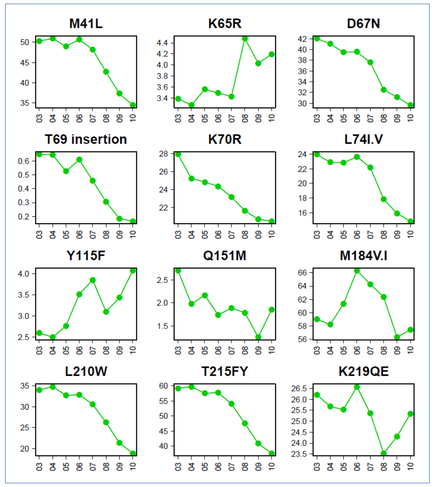
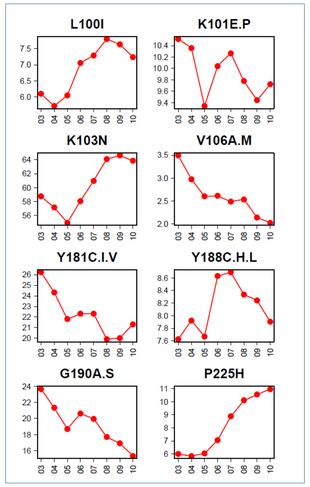


Figure 5: NNRTI Resistance mutations from 2003 to 2010



Each dot represents the percentage of samples that have the specified amino acid at that position, compared to the sum total of all samples that exhibited reduced susceptibility to the drug class of interest.
In cases where more than one amino acid was examined at that position, amino acids are listed alphabetically and separated by a dot (.). “ins” refers to an insertion mutation.

RESULTS

- Marked decrease in the fraction of drug resistant HIV-1 strains with reduced susceptibility to all 3 drug classes since 2007, from **29**% to **11**% (p=0.001).
- Steady increase in reduced susceptibility to a single drug class, from **31**% to **54**% (p=0.0015).
- Double-class resistance remained relatively stable (40% to 35%).
- Decrease in the percentage of resistant viruses that exhibit reduced susceptibility to PIs since 2007, from **49**% in 2007 to **26**% in 2010 (p=0.02).
- Reduced susceptibility to NNRTI and NRTI remained relatively stable: NNRTI decreased from 70% to 61% and NRTI decreased from 77% to 70%.
- The frequency of the PI RAMS associated with first-generation PIs (e.g. L10I, D30N, M46I/L, G48V, V82, L90M) declined, whereas the frequency of mutations V11I, V32I, L33F, I50L/V, I54M/L, T74P and N88S is increasing.
- Major Reverse-Transcriptase (RT) RAMs are declining over time, except for NRTI mutations K65R and Y115F and NNRTI mutations L100I, K103N and P225H.

CONCLUSIONS

- These observations suggest that the downward trend in 3-class drug resistance since 2007 is driven by the decrease in the fraction of resistant viruses with reduced susceptibility to the PI class.
- These trends also highlight a decrease in the number of patients with multi-drug resistant virus: a group for whom very little treatment options were available until 2006.
- The improved efficacy of the standard of care and the continued availability of antiretrovirals utilizing novel anti-HIV targets or with favorable cross-resistance profiles and evolving prescription patterns of PIs, NRTIs, and NNRTIs may have relevance to the decreasing prevalence of multi-drug resistance in this clinical database.
- These results may have important implications for antiretroviral drug selection, clinical trial design as well as future drug discovery and development.

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