Recent Trends in a Large HIV-1 Protease/Reverse Transcriptase and Co-receptor Tropism Database

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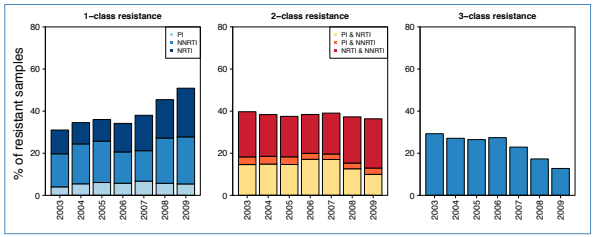
BACKGROUND

- Drug resistance testing and co-receptor tropism determination are key components of the management of antiretroviral therapy for individuals infected with HIV-1.
- The purpose of this study was to examine phenotypic drug resistance patterns in protease- (PI), nucleoside-reverse-transcriptase- (NRTI), and non-nucleoside-reverse-transcriptase-inhibitors (NNRTI) over time, as well as prevalence of co-receptor usage by surveying Monogram's commercial patient testing database.

METHODS

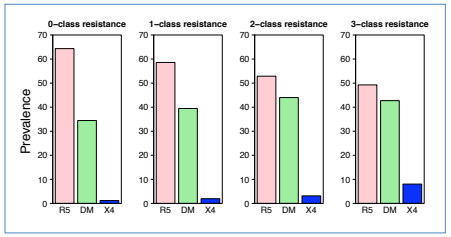
- We examined fully de-identified samples submitted for routine phenotypic and genotypic patient testing that show phenotypic resistance to at least one drug within PIs, NRTIs, and NNRTIs as measured by fold-change of IC50 (FC) ≥ lower cutoff (CO).
- A total of 62,323 resistant samples collected from 2003 through 2009 were grouped into specimens that had FC ≥ CO for minimum of 1 drug in each drug-class.
- We studied the temporal trends of % phenotypic 1-, 2-, and 3-class resistance and the prevalence of PI, NRTI and NNRTI resistance mutations (RAM).
- Furthermore, we examined the prevalence of CCR5 (R5) and CXCR4 (X4) using viruses among 6,949 samples that had genotypic PI, NRTI, and NNRTI resistance information as well as co-receptor tropism as determined by Monogram's Trofile assay.
- 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 (i.e. NRTI, NNRTI, PI).

Figure 2: Tropism distribution by genotypic class resistance



CXCR4-mediated entry is more prevalent among patient viruses with multiple drug class resistance (NRTI, NNRTI, and PI). DM (Dual-Mixed) refers to viral populations that utilize CCR5 and CXCR4 to enter CD4+ cells.

Figure 3: Temporal trends of PI-Resistance mutations

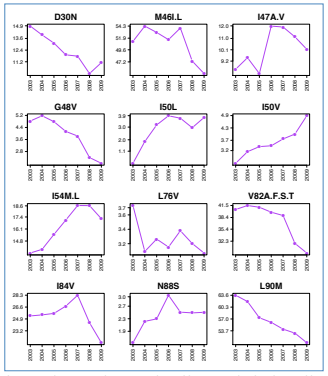


Figure 4: Temporal trends of NRTI-Resistance mutations

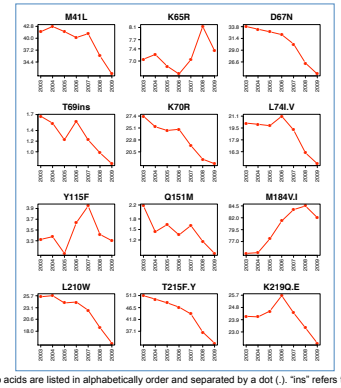
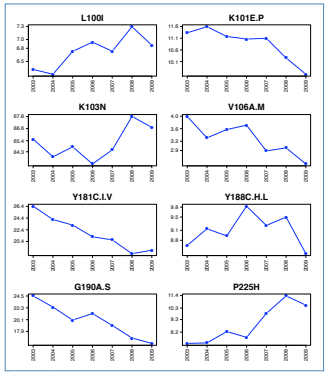


Figure 5: Temporal trends of NNRTI-Resistance mutations



In cases where more than one amino acid was examined at that position, amino acids are listed in alphabetically order and separated by a dot (.). "ins" refers to an insertion mutation.

RESULTS

- Among samples that show any phenotypic drug resistance, percentage of samples with single-class resistance increased from **31%** in 2003 to **51%** in 2009 while double-class resistance remained relatively stable (**40%** to **36%**), and triple-class resistance declined from **29%** to **13%**.
- This observation is linked to a significant increase in single-class NRTI resistance (p=0.005).
- Prevalence of CXCR4 using viruses (DM + X4) among samples with matched PR/RT genotype was **35.7%**, **41.4%**, **47.1%**, and **50.7%** for 0-, 1-, 2-, and 3-class resistance, respectively.
- The increase of X4 usage with increasing number of class resistance was statistically significant (p=0.02).
- The frequencies of major mutations associated with resistance to PI, NRTI and NNRTI are declining over time, except for RT positions **65** and **184** (NRTI RAM), RT positions **100**, **103** and **225** (NNRTI), and PR positions **50**, **54** and **88**.

CONCLUSIONS

- A strong trend (2003-2009) of decreasing prevalence of 3-class resistance (NRTI, NNRTI, and PI) was identified in the Monogram Biosciences' commercial database.
- This was associated with an increased prevalence of single-class resistance.
- CXCR4-mediated entry was more prevalent among patient viruses with multiple drug class resistance.
- This trend may be due to the more advanced disease stage of treatment experienced patients.

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