Validation of New Informatics Systems for Routine HIV-1 Genotypic and Virtual Phenotypic Antiviral Drug Resistance Analyses in Clinical Laboratories

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Background

- Clinical laboratories performing testing for detection and analyses of HIV-1 genotypic drug resistance need reliable and up-to-date software and database solutions to optimally analyze Sanger sequencing-generated data for interpretative reporting of results.

Methods

- Through a retrospective analysis of HIV-1 reverse transcriptase (RT) and protease (PR) sequences generated from the Trugene *HIV-1* Genotyping assay (**TG**; Siemens Healthcare Diagnostics Inc., Tarrytown, NY), for 100 selected unique clinical plasma specimens obtained from HIV-1-infected patients, we evaluated 2 analytical informatics systems (Fig. 1):
  - A newly FDA-registered data processing module software application (**DPM** v1.0; Advanced Biological Laboratories S.A., Luxembourg) based on several external drug resistance (**DR**) databases, including Stanford HIVdb (**SD**) and Geno2Pheno (**G2P**)
  - A research-use-only **ViroScore-HIV** (VS) software application.
- Results of drug resistance to NRTI, NNRTI and PI were compared with the Guidelines version 17 interpretation generated from TG.
- HIV-1 tropism and DR to integrase inhibitors were not evaluated (not available in TG).

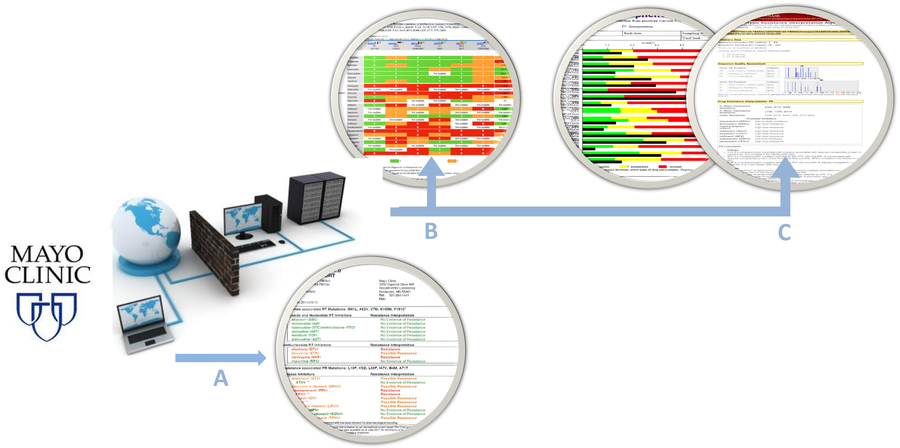

Fig. 1: Overview of the workflow of analyses for Trugene HIV-1 (A), ViroScore® (B), and DPM (C).

Results

- Among 100 selected TG sequences generated at the Mayo Clinic laboratory from March 2013 through May 2014, agreement of DR interpretative results between DPM v1.0 and VS was >99.9%.
- Agreement between TG and SD and between TG and G2P were both only 17%.
- Median % agreement in DR interpretation between TG and SD, TG and G2P, SD and G2P are showed in Table 1.
- Detailed % agreement for each drug or drug combination are shown in Table 2.
- With TG as the reference result, SD and G2P generated:
  - "Positive" minor discordance, defined as susceptible S vs. intermediate I, or I vs. resistant R to ≥1 drug, in 66% and 56% of results, respectively;
  - "Negative" minor discordance (I vs. S, or R vs. I) in 32% and 54%
  - major discordance (S vs. R) in 6% and 15%
  - and major discordance (R vs. S) in 1% and 19% of subjects, respectively.

Table 1: Overall agreements of drug resistance interpretations between Trugene, ViroScore SD HIVdb and ViroScore Geno2Pheno.

	TOTAL**	PI	NRTI**	NNRTI**
Median Correlation ratio TruGene / VS-HIVDB	0,89	0,86	0,95	0,95
Median Correlation ratio TruGene / VS-G2P	0,83	0,84	0,81	0,82
Median Correlation ratio VS-HIVDB / VS-G2P	0,83	0,82	0,92	0,81
	** RPV, D4T, AZT, DDI Excluded			

Table 3: Types of discordances observed in drug resistance interpretations between Trugene and results obtained via DPM from SD HIVdb and Geno2Pheno.

Number of samples with at least X **moderate positive** switch for DPM-HIVdb compared to TruGene	66
Number of samples with at least X **moderate positive** switch for DPM-G2P compared to TruGene	56
Number of samples with at least X **high positive** switch for DPM-HIVdb compared to TruGene	6
Number of samples with at least X **high positive** switch for DPM-G2P compared to TruGene	15
Number of samples with at least X **moderate negative** switch for DPM-HIVdb compared to TruGene	32
Number of samples with at least X **moderate negative** switch for DPM-G2P compared to TruGene	54
Number of samples with at least X **high negative** switch for DPM-HIVdb compared to TruGene	1
Number of samples with at least X **high negative** switch for DPM-G2P compared to TruGene	19

Table 2: Agreements of drug resistance interpretations between Trugene, ViroScore SD HIVdb and ViroScore Geno2Pheno for each drug or drug combination.

	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	NFV	SQV/r	TPV/r	3TC	ABC	AZT	D4T	DDI	FTC	TDF	EFV	ETR	NVP
Correlation ratio TruGene / DPM-HIVDB	0,89	0,87	0,82	0,90	0,78	0,96	0,86	0,81	0,99	0,79	0,83	0,76	0,80	0,98	0,91	0,95	0,64	0,96
Correlation ratio TruGene / DPM-G2P	0,80	0,94	0,84	0,90	0,94	0,83	0,82	0,47	0,99	0,63	0,84	0,52	0,60	0,98	0,62	0,87	0,58	0,82
Correlation ratio DPM-HIVDB / DPM-G2P	0,83	0,86	0,81	0,81	0,81	0,83	0,87	0,41	0,99	0,84	0,88	0,65	0,71	0,99	0,61	0,89	0,58	0,81

Conclusions

- DPM v1.0 and VS were reliable to analyze RT and PR sequences in HIV-1 drug resistance testing for both research and routine clinical use.
- Differences in interpretation of drug resistance observed were most likely due to differences in the interpretive guidelines used by these databases.