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hiv resistance response database initiative
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www.hivrdi.org email: info@hivrdi.org

Experienced HIV physicians rate RDI system for predicting response to antiretroviral treatment (ART) as potentially useful treatment tool

Revell A[1], Mican JM[2], Agan B[3], Coe D[1], Wang D[1], Rivera-Goba M[4], Metcalf J[2], Pozniak A[5], Perez Elias MJ[6], Montaner J[7], Lane HC[2], Larder BA[1]

1: HIV Resistance Response Database Initiative (RDI), London, UK; 2: National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA; 3: Infectious Disease Clinical Research Program, Uniformed Services University of the Health Sciences, Bethesda, MD, USA; 4:National Institutes of Health, Clinical Center, Bethesda, MD, USA; 5: Chelsea and Westminster Hospital, London, UK; 6: Ramon Y Cajal Hospital, Madrid, Spain 7: BC Centre for Excellence in HIV/AIDS, Vancouver, Canada

Introduction

- The optimal selection and sequencing of ART is challenging, not least because of the complexity of drug resistance and the range of drugs available.
- In wealthy countries genotyping resistance testing with rules-based interpretation is in widespread use to help make treatment decisions.
- The utility of genotyping is limited by several factors including the categorical nature of most interpretation systems and the difficulty in relating information for individual drugs to the potential response to combination antiretroviral therapy (cART).
- The HIV Resistance Response Database Initiative (RDI) has developed computational models (random forest and artificial neural networks) that make accurate *quantitative* predictions of an individual's virological response to cART.
- These models are being used to power a web-based ART selection tool.
- In this retrospective study, the system was evaluated by HIV-experienced physicians in the USA.

Methods

- 'Sixty-five historical cases of cART failure were anonymised and reviewed by 21 physicians as if a treatment decision were being made at the current time.
- Thirty-nine cases were reviewed by two different physicians giving 104 cases overall.
- The physicians entered the patients' data and their initial treatment decision into the system via the RDI web site.
- They received a report listing the system's predictions of response to the physician's selection and possible alternatives in 'real time', online.
- The physicians entered their final treatment decision following review of the RDI report.
- Finally the physicians completed an online evaluation questionnaire.

Results

- The characteristics of the 65 cases on failing therapy are summarised in Table 1.

Table 1: Baseline characteristics of the 65 cases

Viral load (log10 copies HIV RNA/ml)	CD4 count (cells/ml)	Previous NRTIs (n)	Previous NNRTIs (n)	Previous PIs (n)	NRTI mutations	NNRTI mutations	PI mutations
4.75	322	3.9	1.02	2.6	3.3	1.2	4.5

- The physician's final treatment decision was changed in 33 of 104 cases (32%) following review of the RDI report.
- The responses of the 21 physicians in their evaluation of the system are summarised in Table 2.

Table 2: Physicians' evaluations of the system

Question	Response options with number (%) of the 21 physicians selecting each option				
How easy was it to enter the baseline data?	Very easy	Quite easy	Satis-factory	Quite difficult	Very difficult
	5 (24%)	13 (62%)	2 (10%)	1 (5%)	0 (0%)
How easy to use was the web-based interface overall?	Very easy	Quite easy	Satis-factory	Quite difficult	Very difficult
	4 (19%)	9 (43%)	5 (24%)	1 (5%)	2 (10%)
How easy was it to understand the RDI report?	Very easy	Quite easy	Satis-factory	Quite difficult	Very difficult
	4 (19%)	11 (52%)	6 (29%)	0 (0%)	0 (0%)
How useful was the system in making treatment decisions?	Very useful	Quite	Satis-factory	Not very	Not at all useful
	0 (0%)	5 (24%)	9 (43%)	7 (33%)	0 (0%)
How frequently would you use the system if freely available?	Very frequently	Quite frequently	Sometimes	Infrequently	Never
	1 (5%)	6 (29%)	10 (48%)	3 (14%)	1 (5%)

- 86% of the physicians rated entering baseline data as very or quite easy.
- 86% rated the user interface between very easy and satisfactory to use.
- None of the physicians reported any difficulty understanding the RDI report.
- The system was rated as quite useful or satisfactory by 67%.
- 95% indicated that they would use the system.

Results (continued)

- The system predicted that the regimens finally selected by the physicians and the best of the alternatives on the RDI report would produce significantly greater virological responses than the regimens originally selected by the physicians ($p<0.05$ and $p<0.001$ respectively).
- A frequency analysis of the drugs in the physicians' original and final selections and the alternatives predicted by the system to provide the largest virological response is presented in Table 3.

Table 3: Drug frequency analysis

	Intended treatment			Final selection			RDI top alternative		
	N	%	Rank	N	%	Rank	N	%	Rank
3/FTC	31	30	5	25	24	6	46	44	5
Tenofovir	91	88	1	96	92	1	87	87	2
d4T	0	0	13	0	0	12	7	7	10
Abacavir	16	15	9	14	13	10	1	1	11
ddI	4	4	11	6	6	11	35	34	6
Zidovudine	29	28	6	29	28	4	24	23	8
Efavirenz	21	20	8	18	17	6	19	18	9
Nevirapine	0	0	13	0	0	11	0	0	15
Ritonavir	85	82	2	88	85	2	103	99	1
Lopinavir	12	12	10	17	16	8	56	54	3
Atazanavir	22	21	7	16	15	9	1	1	11
Darunavir	52	50	3	55	53	3	47	45	4
(Fos)amprenavir	0	0	13	0	0	12	1	11	11
Saquinavir	1	1	12	0	0	12	0	0	15
Nelfinavir	0	0	13	0	0	12	1	1	11
Indinavir	0	0	13	0	0	12	0	0	15
Enfuvirtide	36	35	4	30	29	5	25	24	7

Etravirine, maraviroc and raltegravir were excluded from the study due to insufficient long-term follow-up data being available for model development

Conclusions

- **Use of the system was associated with a change in treatment decision in one-third of cases.**
- **The system was judged by most physicians as easy, potentially helpful and likely to be used in practice.**
- **Use of the system may result in a reduction in the number of drugs prescribed and potentially lower treatment costs.**
- **The results suggest that use of the system could improve virological responses in treatment experienced patients.**
- **A randomized, controlled trial will be needed to determine the overall value of adding this tool to standard of care.**
- **An updated version of the system will shortly be available as an experimental tool.**
- **A version that does not require genotypic information is under development for resource-limited settings.**

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