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An Informatics Approach to Predicting Rates of Transmitted HIV-1 Drug Resistance

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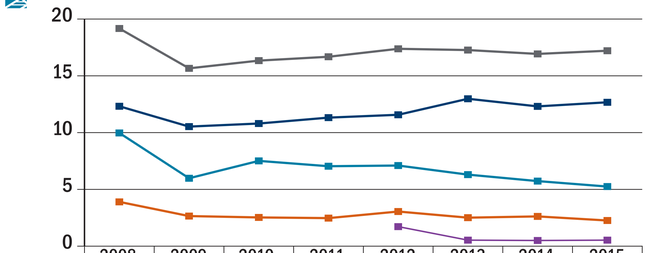
Background

National transmitted HIV-1 drug resistance (TDR) rates are typically monitored through HIV surveillance data and this represents the gold-standard for determining TDR rates in various populations. However, it often requires several years to prepare data for presentation and publication resulting in long lag times between data accumulation and result dissemination. Here we present a computational method using de-identified clinical test results from a large commercial database to infer TDR rates in near real-time.

Methods

A HIPAA-compliant unique Patient ID was assigned to each test result in the LabCorp Clinical Database. New cases of HIV diagnosis were inferred using the linked results from HIV diagnosis, viral load and drug resistance tests. We developed a novel inference model which employs a successive series of filters to derive a subset of resistance assays that were likely to have been performed at the time of initial HIV diagnosis. We used the 2009 surveillance drug resistance mutations (SDRM) list from the Stanford University HIV Drug Resistance Database to determine mutational frequencies. We validated the model by comparing the predicted 2008-2011 NRTI, NNRTI, and PI frequencies to ranges established from prior TDR surveillance studies. We then used our model to calculate rates of TDR for 2012-2015 per drug class, including INIs. This model allows us to assess prevalence rates among several demographic factors.

Figure 1: Predicted TDR Prevalence, 2008-2015



	2008	2009	2010	2011	2012	2013	2014	2015
Any	19.17	15.66	16.34	16.68	17.38	17.27	16.93	17.21
NRTI	9.97	5.98	7.51	7.04	7.10	6.30	5.73	5.25
NNRTI	12.32	10.53	10.80	11.32	11.57	12.98	12.31	12.67
PI	3.9	2.65	2.53	2.47	3.05	2.51	2.62	2.26
INI					1.72	0.53	0.50	0.53

Table 1: Model TDR Predictions Relative to Prior Studies

		Ocfemia[1]	SanDiego[2*]	Buchacz[3†]	Wang[4*]	Low	High	Monogram	n
2008	Any	17.5	12	18.9	17	12	18.9	19.17	1153
	NRTI	7.6	4.0	10.6		4.0	10.6	9.97	
	NNRTI	9.1	4.0	7.8		4.0	9.1	12.32	
	PI	4.5	4.0	4.6		4.0	4.6	3.9	
2009	Any	16.2	22.5	17.5	18.5	16.2	22.5	15.66	1322
	NRTI	6.4	2.7	10.8		2.7	10.8	5.98	
	NNRTI	8	16.2	6.6		6.6	16.2	10.53	
	PI	4.3	2.7	1.8		1.8	4.3	2.65	
2010	Any	17.4	11.8	17.5	15.5	11.8	17.5	16.34	2509
	NRTI	8.9	0.5	10.8		0.5	10.8	7.51	
	NNRTI	6.4	11.8	6.6		6.4	11.8	10.8	
	PI	4.6	0.5	1.8		0.5	4.6	2.53	
2011	Any	18.9	14.8	17.5	19.5	14.8	19.5	16.68	3680
	NRTI	6.4	3.7	10.8		4.5	10.8	7.04	
	NNRTI	10.4	11.1	6.6		6.6	11.1	11.32	
	PI	4.6	3.7	1.8		1.8	4.6	2.47	

TDR rates from prior studies are shown along with the inferred TDR rates Monogram found using the model. Blue highlighting indicates where Monogram's inferred TDR rate fell within the range established from prior studies.
* TDR rates from these studies were approximated from poster figures.
† This study presented the 2009-2011 rates in aggregate and did not break them out by year.

Results

- 8664 putative baseline resistance tests from 2008-2011 were identified. Calculated TDR rates by individual year and by drug class compared favorably to those rates that have previously reported between 2008-2011 (Table 1). INI rates were not included due to lack of comparative data.
- 18,226 putative baseline resistance tests from 2012-2015 were identified. Calculated TDR rates by individual year and by drug class remained comparable to prior years for the NRTI, NNRTI, and PI classes, while TDR for the INI class was low (Figures 1, 2).
- K103N/S was found to be the most frequently transmitted mutation, followed by substitutions at T215 and M184 in the NRTI class (Table 2) when SDRMs were ranked based on observed prevalence.
- In 2015, a higher prevalence of NNRTI mutations was observed in the younger age groups (Figure 3).

Figure 2: Predicted TDR Prevalence, 2012-2015

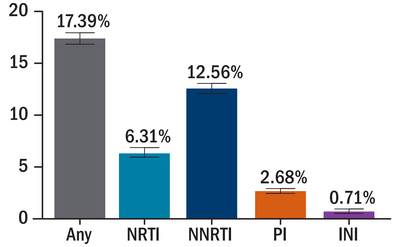


Figure 3: Predicted TDR Prevalence By Age, 2015

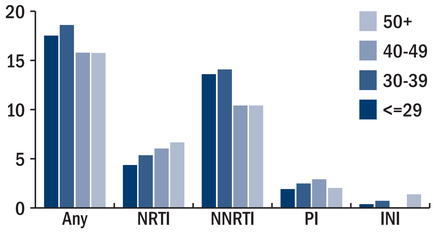


Table 2: Most Frequently Observed TDR Mutations, 2015

NRTI		NNRTI		PI		INI	
Mutation	Freq	Mutation	Freq	Mutation	Freq	Mutation	Freq
T215Y/F/S/C/D/V/E/I	2.26	K103N/S	9.85	M46L/I	1.00	E92Q	0.27
M184V/I	1.74	G190A/E/S	1.21	L90M	0.87	G140S	0.18
M41L	1.48	Y181C/I	1.13	I85V	0.30	Q148H	0.18
K219E/R/Q	0.95	K101E/P	1.00	I54L/V	0.22	N155H	0.18
D67N/G	0.65	Y188H/C/L	0.65	V82L/A/M	0.22	S147G	0.18
K70R/E	0.52	P225H	0.56	D30N	0.13	Y143C	0
L210W	0.48	L100I	0.22	I47V	0.13	T66A/I	0
T69D	0.39	M230L	0.09	I84V	0.13	--	--
L74I/V	0.26	V106A/M	0	V32I	0.09	--	--
K65R	0.22	V179F	0	I50V	0.09	--	--

Conclusions

Our model demonstrates a novel near real-time method for inferring the prevalence of TDR by drug class. This model suggests that national TDR rates for NRTI, NNRTI, and PIs from 2012-2015 have not decreased in a clinically meaningful way relative to prior years which advocates for the continued use of baseline HIV resistance testing. INI TDR rates were surprisingly low, possibly reflective of the efficacy of current antiretroviral regimens which incorporate this class. Near real-time TDR data can facilitate early detection of new drug resistance strains should they arise.

References

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2. Panichsillapakit, T, et al. Poster 600, CROI 2015.
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