INTEGRASE GENOTYPIC TESTING AND DRUG RESISTANCE AMONG PERSONS NEWLY DIAGNOSED WITH HIV IN NEW YORK

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BACKGROUND

Despite HIV treatment guidelines stating that baseline genotypic resistance testing should be obtained at diagnosis, in many cases this testing is not ordered by the clinician or is ordered inconsistently with treatment recommendations.

Integrase strand transfer inhibitors (INSTIs) have emerged as initial regimens for persons newly diagnosed with HIV because of their clinical effectiveness and tolerability.

With widespread use of INSTIs, the concerns of transmitted integrase drug resistance and risk of virologic failure are rising among clinicians.

Transmission of drug-resistant strains poses a great challenge to control the spread of HIV.

OBJECTIVES

The aims of this analysis were to explore:

- The frequency of integrase (IN) testing and factors associated with IN testing.
- The rate of transmitted INSTI drug resistance.
- The common clinically significant INSTI-resistance mutations among persons with newly diagnosed HIV in New York State (NYS).

METHODS

- Persons age 13 and older diagnosed between 2013-2017 and reported to the NYS HIV registry were included in the study.
- The first IN nucleotide sequence for an individual was identified and flagged as an "initial" test if ordered within 3 months of the HIV diagnosis date.
- Persons with 1) incomplete diagnosis or test dates or 2) invalid sequences were excluded.
- Multivariable analysis was used to test the association between IN initial testing and sociodemographic factors.
- Sequences were analyzed using the NYS in-house Resistance Analysis System and compared with the most common clinically significant INSTI-resistance mutations published on Stanford HIVdb Program website.

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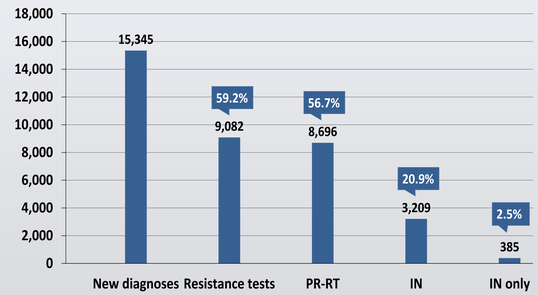
RESULTS – Integrase Testing

- 15,345 persons diagnosed 2013-2017 were included.
- 59.2% had any resistance testing within 3 months of diagnosis.
  - 56.7% had initial PR-RT testing
  - 20.9% had initial IN testing
  - 2.5% had only IN resistance testing
- 88% of persons with initial IN testing also had PR-RT testing.
- Initial drug resistance testing was stable (~60%) from 2013-2017.
- The frequency of initial IN testing among persons newly diagnosed increased significantly from 5.6% in 2013 to 32.4% in 2017 (P<0.0001), but IN testing frequency remained lower than PR-RT testing.

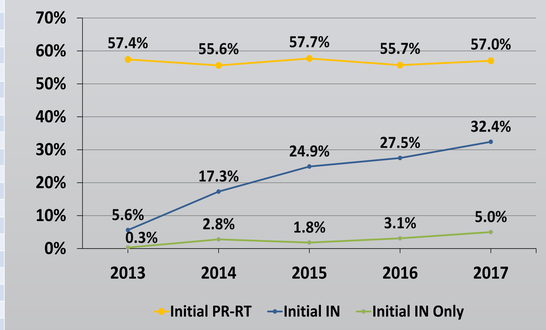
Demographic, Transmission Risk, and Clinical Characteristics of Persons With Initial IN Testing in NYS, 2013-2017

Characteristics	Total Diagnosis	Persons with initial genotype test		Persons with initial IN test		Adjusted RR (95% CI)
	N	N	%	N	%	
Total	15,345	9,082	59.2%	3,209	20.9%	
Sex at Birth						
Male	12,145	7,383	60.8%	2,699	22.2%	Ref
Female	3,200	1,699	53.1%	510	15.9%	1.12 (0.92, 1.36)
Age at Diagnosis						
13-19	580	364	62.8%	138	23.8%	1.07 (0.89, 1.30)
20-24	2,412	1,407	58.3%	528	21.9%	1.04 (0.93, 1.17)
25-29	2,954	1,834	62.1%	702	23.8%	1.00 (0.90, 1.11)
30-39	3,894	2,301	59.1%	832	21.4%	Ref
40-49	2,717	1,611	59.3%	505	18.6%	0.98 (0.88, 1.10)
50-59	1,900	1,092	57.5%	356	18.7%	1.01 (0.89, 1.16)
60+	888	473	53.3%	148	16.7%	1.01 (0.84, 1.22)
Race/Ethnicity						
Non-Hispanic White	2,805	1,830	65.2%	721	25.7%	Ref
Non-Hispanic Black	5,815	3,187	54.8%	1,022	17.6%	**0.85 (0.76, 0.94)**
Hispanic	5,225	3,169	60.7%	1,149	22.0%	0.93 (0.84, 1.03)
Asian/PI	529	307	58.0%	120	22.7%	0.91 (0.74, 1.12)
Native Am	6	3	50.0%	2	33.3%	1.44 (0.36, 5.80)
Multi Race	965	586	60.7%	195	20.2%	0.90 (0.77, 1.07)
HIV Transmission Risk						
MSM	9,092	5,810	63.9%	2,258	24.8%	**1.29 (1.07, 1.56)**
IDU	381	187	49.1%	54	14.2%	0.96 (0.71, 1.29)
Heterosexual	3,751	3,002	80.0%	598	15.9%	Ref
Pediatric Risk	5	2	40.0%	2	40.0%	-
Unknown	2,116	1,048	49.5%	297	14.0%	1.02 (0.82, 1.26)
Year of Diagnosis						
2013	3,299	1,902	57.7%	185	5.6%	0.00 (0.00, .)
2014	3,349	1,956	58.4%	579	17.3%	Ref
2015	3,099	1,845	59.5%	771	24.9%	**1.41 (1.27, 1.57)**
2016	2,855	1,679	58.8%	786	27.5%	**1.59 (1.43, 1.77)**
2017	2,743	1,700	62.0%	888	32.4%	**1.77 (1.60, 1.97)**
Region						
NYC	11,501	6,770	58.9%	2,430	21.1%	Ref
Rest of State	3,844	2,312	60.1%	779	20.3%	**0.90 (0.82, 0.98)**
Disease Progression						
HIV Only	11,293	6,412	56.8%	2,448	21.7%	Ref
HIV and Later AIDS	1,069	513	48.0%	158	14.8%	1.01 (0.85, 1.19)
Concurrent	2,962	2,152	72.7%	603	20.4%	**0.85 (0.77, 0.94)**
Unknown	21	5	23.8%	0	0.0%	-
Birth Country						
USA	7,982	4,953	62.1%	1,763	22.1%	Ref
Non-USA	4,589	2,584	56.3%	903	19.7%	0.96 (0.87, 1.05)
Unknown	2,774	1,545	55.7%	543	19.6%	0.95 (0.86, 1.05)

Persons Newly Diagnosed with Initial Resistance Testing, 2013-2017



Initial Resistance Testing Among Persons Newly Diagnosed, 2013-2017



Multivariable logistic regression analysis showed:

- The likelihood of having initial IN testing was lower in non-Hispanic blacks compared to non-Hispanic whites (RR:0.85, 95%CI:0.76-0.94), and higher among males with a history of male-to-male sexual contact than persons with heterosexual transmission risk (RR:1.29, 95%CI:1.07-1.56).
- The likelihood of having initial IN testing was lower in residents of rest of state compared to residents of New York City (RR:0.90, 95%CI:0.82-0.98).
- Initial IN testing was less likely in persons with late diagnosis (i.e., concurrent AIDS diagnosis) than HIV only (RR:0.85, 95%CI:0.77-0.94).

RESULTS – Integrase Drug Resistance

- Resistance to ≥1 INSTI drug was seen in 0.7% (24) of 3,209 persons with initial IN testing.
- The most prevalent minor or accessory INSTI drug resistance mutations were E157Q, L74M/I, T97A, G163R/K, H51Y.
- Drug associated mutations were compared to the major INSTI mutation list.

Major INSTI Resistance Mutations (Stanford HIVdb)

	66	92	118	138	140	143	147	148	155	263
Consensus	T	E	G	E	G	Y	S	Q	N	R
Dolutegravir (DTG)	K	Q	R	KAT	SAC			HRK	H	K
Elvitegravir (EVG)	AIK	Q	R	KAT	SAC		G	HRK	H	K
Raltegravir (RAL)	AIK	Q	R	KAT	SAC	RCH		HRK	H	K

Red: mutations associated with the highest levels of reduced susceptibility or virological response.
Bold: reduced INSTI susceptibility or virological response.
Plain: contribute to reduced susceptibility in combination with other INSTI-resistance mutations.

Number of Persons with Major INI Mutations

- Clinically significant INSTI-resistance mutations detected in the initial group included: T66A/I, E92Q, E138K/A, G140S, Y143C/R, Q148H, N155H.
- A high degree of RAL and EVG cross-resistance was observed.
- Moderate clinically significant DTG-associated INST-resistance mutation Q148H was seen in four newly diagnosed persons.

CONCLUSIONS

- Overall, clinician ordering of initial resistance testing lags current treatment guidelines.
- Initial IN testing has increased among persons newly diagnosed with HIV.
- While INSTI drug resistance remains low, the clinically significant INSTI-resistance mutations observed suggests that transmitted INSTI resistance is emerging
- Immediately following diagnosis, it is crucial for clinicians to order resistance testing in general, and IN testing in particular, to make an informed treatment decision.