HIV Integrase Genotypic Testing and Resistance in the United States—9 U.S. Jurisdictions

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BACKGROUND

- Since 2012, the U.S. Department of Health and Human Services has recommended antiretroviral therapy (ART) for all HIV-infected persons in the United States[1].
- In 2016, initial combination regimens for the antiretroviral (ARV)-naive patient were updated to include two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third active ARV drug from one of three drug classes:
  - an integrase strand transfer inhibitor (INSTI),
  - a non-nucleoside reverse transcriptase inhibitor (NNRTI),
  - or a protease inhibitor (PI) with a pharmacokinetic (PK) enhancer (booster) (cobicistat or ritonavir).
- Integrase (IN) genotypic testing at entry into HIV care is recommended if transmitted resistance to INSTI is a concern.

OBJECTIVE

- To assess the prevalence of 1) IN genotypic testing and 2) drug resistance-associated mutations (DRAMs) to integrase strand transfer inhibitors (INSTIs) at baseline (i.e., collected ≤3 months after HIV diagnosis) and on any subsequent HIV sequence (i.e., collected >3 months after HIV diagnosis) among persons with diagnosed HIV infection.

METHOD

Population included in analysis:

- Persons with HIV-1 diagnosed through 2014 and reported to the U.S. National HIV Surveillance System (NHSS) by December 2015.
- At diagnosis, persons who resided in 1 of 9 jurisdictions with ≥20% completeness of baseline HIV nucleotide sequences during 2010–2014.

Assessment of IN genotypic testing:

- Described the overall prevalence and timing of IN genotypic tests after HIV diagnosis (i.e., sequence collected ≤3 months and >3 months) by sex, age, race/ethnicity, transmission category, stage of HIV disease, place of birth, population of area of residence at diagnosis.

Assessment of INSTI-associated resistance mutations:

- Used Sierra–the Stanford HIV Web Service[2]–to assess presence of DRAMs to INSTI.
- Applied the CDC HIV-1 surveillance mutation list[3] for subtype B infection.

Statistics:

- Calculated number, percentage and trend of IN genotypic tests among persons with diagnosed HIV by selected characteristics.
- Calculated number, percentage of persons with HIV variants with INSTI-associated resistance mutations in sequences collected ≤3 months and >3 months after HIV diagnosis and most prevalent INSTI-associated resistance mutations

RESULTS

Figure 1. HIV surveillance jurisdictions included in analyses

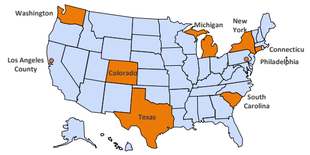


Figure 2. Characteristics of integrase sequences

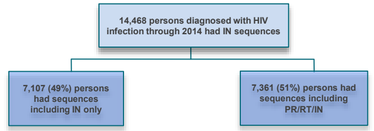


Figure 3. Trends and timing of integrase (IN) genotypic testing among persons with HIV diagnosis, 9 U.S. jurisdictions, 2010-2014

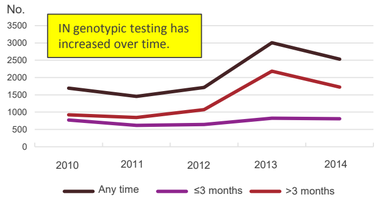
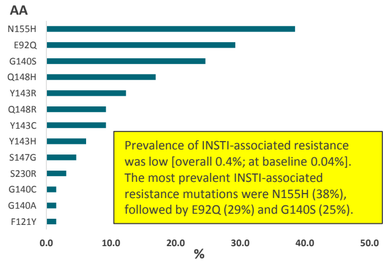


Figure 4. Prevalence of INSTI-associated resistance mutations among persons with any INSTI DRAMs



Mutations with 0.0% prevalence:G118R, Y143G, Y143K, Y143S, Q148K, N155S, N155T, R263K, T66A, T66I, T66K, E92G, E92V

Table 1. HIV integrase genotypic testing among persons with HIV diagnosed through 2014 by selected characteristics, 9 U.S. Jurisdictions

	Total with IN sequence	Sequence collected ≤3 months of HIV diagnosis				Sequence collected >3 months of HIV diagnosis			
		Total		ARV-Naïve		Total		ARV-Naïve	
	N	N	Row %	N	Row %	N	Row %	N	Row %
Total	**14,468**	**5,240**	**36.2**	**4,631**	**88.4**	**9,228**	**63.8**	**6,129**	**66.4**
Sex									
Male	11,046	4,298	38.9	3,793	88.3	6,748	61.1	4,549	67.4
Female	3,422	942	27.5	838	89.0	2,480	72.5	1,580	63.7
Age at diagnosis (yr)									
<13	232	12	5.2	12	100.0	220	94.8	107	48.6
13–19	894	249	27.9	221	88.8	645	72.1	403	62.5
20–29	5,054	1,741	34.4	1,543	88.6	3,313	65.6	2,191	66.1
30-39	4,471	1,397	31.2	1,252	89.6	3,074	68.8	2,049	66.7
40-49	2,602	1,100	42.3	967	87.9	1,502	57.7	1,030	68.6
50-59	952	559	58.7	473	84.6	393	41.3	288	73.3
>60	263	182	69.2	163	89.6	81	30.8	61	75.3
Race/ethnicity[a]									
American Indian/Alaska Native	25	5	20.0	5	100.0	20	80.0	15	75.0
Asian	185	125	67.6	116	92.8	60	32.4	47	78.3
Black/African American	6,227	1,919	30.8	1,725	89.9	4,308	69.2	2,975	69.1
Hispanic/Latino	3,870	1,636	42.3	1,428	87.3	2,234	57.7	1,341	60.0
Native Hawaiian/Other Pacific Islander	7	2	28.6	2	100.0	5	71.4	5	100.0
White	3,433	1,371	39.9	1,200	87.5	2,062	60.1	1,442	69.9
Other	721	182	25.2	155	85.2	539	74.8	304	56.4
Transmission category[b]: Male[c]									
Male-to-male sexual contact	7,981	3,587	44.9	3,173	88.5	4,394	55.1	3,070	69.9
Injection drug use	1,061	184	17.3	160	87.0	876	82.6	524	59.8
Male-to-male sexual contact and injection drug use	886	170	19.2	147	86.5	717	80.9	429	59.8
High-risk heterosexual contact[d]	1,002	348	34.7	304	87.4	654	65.3	473	72.3
Other[e]	17	3	17.6	3	100.0	14	82.4	7	50.0
Transmission category[b]: Female[c]									
Injection drug use	795	131	16.5	117	89.3	664	83.5	410	61.7
High-risk heterosexual contact[d]	2,478	800	32.3	711	88.9	1,677	67.7	1,101	65.7
Other[e]	17	5	29.4	4	80.0	12	70.6	8	66.7
Transmission category: Child (<13 yrs at dx)									
Perinatal	210	11	5.2	11	100.0	199	94.8	93	46.7
Other[g]	22	1	4.5	1	100.0	21	95.5	14	66.7
Population density of area of residence									
Nonmetropolitan areas (<50,000 population)	374	107	28.6	94	87.9	267	71.4	179	67.0
Metropolitan areas (50,000-499,999 population)	1,628	483	29.7	440	91.1	1,145	70.3	768	67.1
Metropolitan statistical areas (≥500,000 population)	12,426	4,644	37.4	4,094	88.2	7,782	62.6	5,166	66.4
Unknown	40	6	15.0	3	50.0	34	85.0	16	47.1
Place of Birth									
United States	10,332	3,265	31.6	2,869	87.9	7,067	68.4	4,606	65.2
U.S. Dependency	229	55	24.0	46	83.6	174	76.0	83	47.7
Other	2,223	1,000	45.0	916	91.6	1,223	55.0	978	80.0
Unknown	1,684	920	54.6	800	87.0	764	45.4	462	60.5
Stage 3 at diagnosis (AIDS)									
Yes	965	369	38.2	303	82.1	596	61.8	384	64.4
No	13,503	4,871	36.1	4,328	88.9	8,632	63.9	5,745	66.6

[a]Hispanics/Latinos can be of any race.
[b]Data have been statistically adjusted to account for missing transmission category.
[c]Adolescent and adult
[d]Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.
[e]Includes hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or not identified.

IN genotypic testing was more common among males, persons aged 20-29 years, blacks, persons residing in areas with a population of ≥500,000, persons born in the United States and persons who were not stage 3 of HIV disease (AIDS); by transmission category, more common among males with HIV infection attributed to male-to-male sexual contact and among females with infection attributed to high-risk heterosexual contact.

Table 2. Prevalence of INSTI-associated resistance mutations among persons with HIV diagnosed through 2014 by selected characteristics, 9 U.S. Jurisdictions

	Total with IN sequence	Sequences with DRAMs			
		Overall		>3 months of diagnosis	
	N	N	Row %	N	Row %
Total	**14,468**	**65**	**0.4**	**63**	**96.9**
Sex					
Male	11,046	41	0.4	39	95.1
Female	3,422	24	0.7	24	100.0
Age at diagnosis (yr)					
<13	232	2	0.9	2	100.0
13–19	894	1	0.1	1	100.0
20–29	5,054	21	0.4	21	100.0
30-39	4,471	30	0.7	29	96.7
40-49	2,602	7	0.3	7	100.0
50-59	952	3	0.3	2	66.7
>60	263	1	0.4	1	100.0
Race/ethnicity[a]					
Black/African American	6,227	33	0.5	32	97.0
Hispanic/Latino	3,870	14	0.4	13	92.9
White	3,433	10	0.3	10	100.0
Other[b]	938	8	0.9	8	100.0
Transmission category[c]: Male[d]					
Male-to-male sexual contact	7,981	29	0.4	28	96.6
Injection drug use	1061	4	0.4	3	75.0
Male-to-male sexual contact and injection drug use	886	3	0.3	3	100.0
High-risk heterosexual contact[e]	1002	5	0.5	5	100.0
Other[f]	17	0	0.0	0	100.0
Transmission category[c]: Female[d]					
Injection drug use	795	3	0.4	3	100.0
High-risk heterosexual contact[e]	2478	19	0.8	19	100.0
Other[f]	17	0	0.0	0	100.0
Transmission category: Child (<13 yrs at dx)					
Perinatal	210	2	1.0	2	100.0
Other[f]	22	0	0.0	0	100.0
Population density of area of residence					
Nonmetropolitan areas	374	3	0.8	3	100.0
Metropolitan areas	1,628	5	0.3	5	100.0
Metropolitan statistical areas	12,426	56	0.5	54	96.4
Unknown	40	1	2.5	1	100.0
Place of Birth					
United States	10,332	49	0.5	48	98.0
U.S. Dependency	229	2	0.9	2	100.0
Other	2,223	7	0.3	7	100.0
Unknown	1,684	7	0.4	6	85.7
Stage 3 at diagnosis (AIDS)					
Yes	965	9	0.9	9	100.0
No	13,503	56	0.4	54	96.4

[a]Hispanics/Latinos can be of any race.
[b]Includes other races
[c]Data have been statistically adjusted to account for missing transmission category.
[d]Adolescent and adult
[e]Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.
[f]Includes hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or not identified.

Prevalence of INSTI-associated resistance mutations among all IN sequences was extremely low (65/14,468; 0.4%).

LIMITATIONS

- Analysis was based on a convenience sample of 9 jurisdictions with minimum completeness of nucleotide sequence data.
- Collection of integrase sequence was limited during the period assessed.
- Sequences were obtained from specimens collected at any time after HIV infection.
- Sequences were obtained by conventional bulk sequencing, which underestimates the prevalence of resistance mutations.
- Sequences analyzed were assumed to have been obtained from persons who were ART-naïve if no evidence of prior ART was found during the HIV case investigation, and some persons might have been incorrectly classified as ART-naïve.
- NHSS does not collect HIV drug regimen information; therefore, no assessment of DRAM and regimen is possible.

DISCUSSION

- NHSS provides an opportunity to monitor IN genotypic testing and prevalence of INSTI-associated resistance at a population level.
- A majority of genotypic testing for resistance to INSTIs occurs more than 3 months after HIV diagnosis, likely after initiation of antiretroviral therapy.
- INSTI-resistant mutations are rare and indicate that current INSTI-based regimens remain effective.
- Systematic HIV drug resistance testing and reporting supports monitoring DRAMs at a population level.

REFERENCES

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