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

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Abstract Presentation No. 478

## 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**

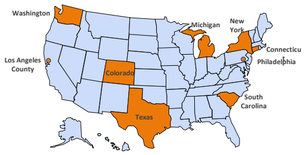



**Figure 2. Characteristics of integrase sequences**

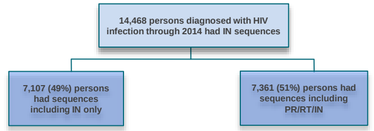



**Figure 3. Trends and timing of integrase (IN) genotypic testing among persons with HIV diagnosis, 9 U.S. jurisdictions, 2010-2014**

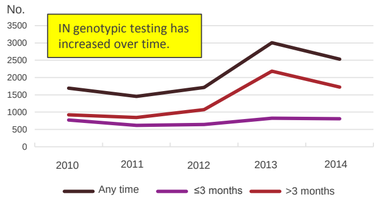
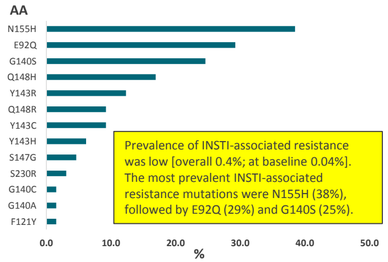



**Figure 4. Prevalence of INSTI-associated resistance mutations among persons with any INSTI DRAMs**




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

1. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/
2. Sierra–The Stanford HIV Web Service (Version 1.1). http://hivdb.stanford.edu/DR/webservices/
3. Wheeler WH, Ziebell RA, Zabina, H, et al. Prevalence of transmitted drug resistance associated mutations and HIV-1 subtypes in new HIV-1 diagnoses, U.S.–2006. AIDS 2010, 24:1203–1212

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*This presentation was made possible with the contributions of HIV surveillance jurisdictions conducting Molecular HIV Surveillance who provided data to CDC*



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