Integrase and Other Transmitted HIV Drug Resistance—23 U.S. Jurisdictions, 2013–2016

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CROI Abstract #3337

Background

- Transmitted drug resistance-associated mutations (TDRMs) have been described for all major classes of antiretroviral therapy (ART) for HIV infection.
- Drug resistance testing for protease (PR) and reverse transcriptase (RT) gene mutations is recommended for all patients at the time of HIV diagnosis[1].
- Testing for integrase (IN) gene TDRMs is recommended when transmitted resistance to integrase strand transfer inhibitors (INSTI) is a concern[1].
- Routine drug resistance testing is based on HIV sequences generated by conventional bulk sequencing methods.
- HIV sequence data from routine drug resistance tests are reported to the U.S. National HIV Surveillance System (NHSS) by state and local health departments.

Objectives & Methods

Objective 1: Characterize HIV Sequence Reporting to NHSS

Characterize reporting of PR/RT and IN sequence data to NHSS from drug resistance tests performed within 3 months of HIV diagnosis for people diagnosed with HIV from 2013–2016.

Objective 2: Characterize TDRMs

Analyze HIV sequences generated by routine drug resistance testing to detect TDRMs for the following drug classes:

Sequence	Drug class
IN	Integrase strand transfer inhibitors (INSTI)
PR/RT	Non-nucleoside reverse transcriptase inhibitors (NNRTI) Nucleoside reverse transcriptase inhibitors (nRTI) Protease inhibitors (PI)

Definition of TDRM: HIV sequence mutation detected by a drug resistance test performed with 3 months of HIV diagnosis in a person with no evidence of prior ART use.

- Mutations detected using the Sierra HIV Web Service[2]
- Relevant mutations defined by the CDC HIV-1 surveillance mutation list[3] for subtype B infection.

Sequences included: All PR/RT and IN sequences reported to NHSS by December 31, 2017 from jurisdictions in which ≥20% of people diagnosed with HIV from 2013-2016 had a drug resistance test within 3 months of HIV diagnosis and no evidence of prior ART use.

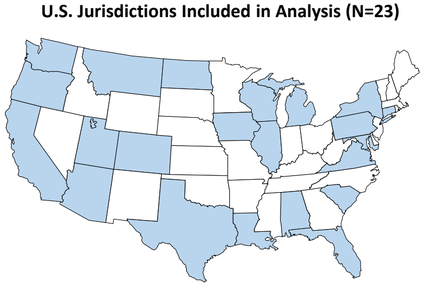
Statistics: Number, percentage, estimated annual percent change (EAPC), and unadjusted prevalence ratios (PR) with 95% confidence intervals (CI) for PR/RT and IN sequences reported and for TDRMs detected, by selected characteristics: sex, age at HIV diagnosis, race/ethnicity, HIV transmission risk, metropolitan statistical area, and U.S region.

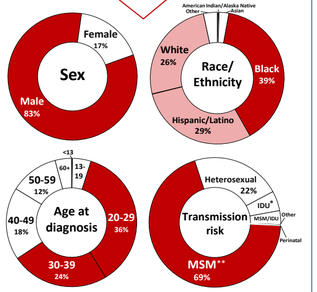
Results

Case Characteristics

These characteristics are similar to those of all people diagnosed with HIV infection in the United States from 2013-2016

U.S. Jurisdictions Included in Analysis (N=23)

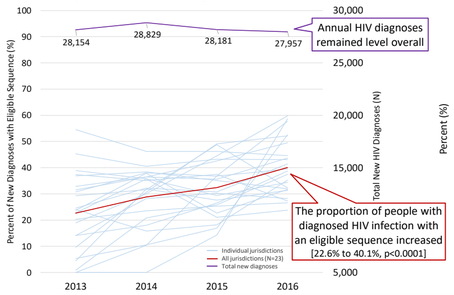




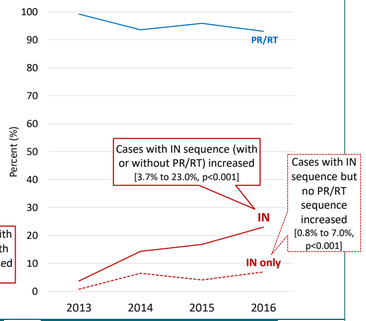
*IDU: Injection drug use
**MSM: Gay, bisexual, and other men who have sex with men

Sequence Reporting

Proportion of People Diagnosed with HIV Infection with an Eligible Sequence Overall and by Jurisdiction, 2013–2016



Proportion of People Diagnosed with HIV Infection with an Eligible PR/RT and/or IN sequence, 2013–2016



TDRMs Overall

40,083 total sequences analyzed (IN + PR/RT)

from

36,288 total cases in the analysis

↓

6,880 (19.0%) cases with ≥1 TDRM

Including cases with TDRMs to:

1 class: 5,905 (16.3%)

2 classes: 865 (2.4%)

3 classes: 110 (0.3%)

4 classes: 0

Any TDRM 6,880 (19.0%) TDRMs

HIGHER prevalence:

- Black/African Americans (19.9%)
  [PR=1.08, 95% CI=1.03–1.14, Ref=White]
- Northeast Region (24.7%)
  [PR=1.08, 95% CI=1.02–1.16, Ref=West Region]
- Metropolitan Areas, pop. 50,000–499,999 (25.4%)
  [PR=1.08, 95% CI=1.01–1.15, Ref: Metropolitan statistical area (MSA), pop. ≥500,000]

LOWER prevalence:

- Age ≥30 (18.2%)
  [PR=0.91, 95% CI=0.85–0.97, Ref=Age 20-29]
- Asians (15.2%)
  [PR=0.83, 95% CI=0.70–0.98, Ref=White]

IN Results (N=5,571)

INSTI

42 (0.8%) TDRMs

No difference in prevalence by:

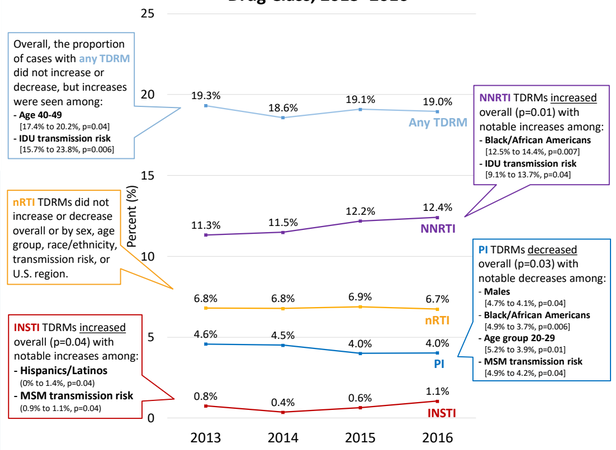
- Sex, race/ethnicity, age group, or transmission risk

HIGHER prevalence:

- Metropolitan Areas (MA), pop. 50,000–499,999 (1.6%)
  [PR=2.36, 95% CI 1.10–5.07, Ref=Metropolitan statistical area, pop. ≥500,000]

TDRM Trends

TDRM Prevalence by Drug Class, 2013–2016



PR/RT Results (N=34,512)

NNRTI **4,103** (11.9%) TDRMs

HIGHER prevalence:

- Black/African Americans (13.5%)
  [PR=1.27, 95% CI=1.18–1.36, Ref=White]
- Midwest Region (13.2%)
  [PR=1.17, 95% CI=1.05–1.30, Ref=West Region]

LOWER prevalence:

- Age ≥30 (10.8%)
  [PR=0.81, 95% CI=0.77–0.86, Ref=Age 20-29]
- Asians (7.8%)
  [PR=0.74, 95% CI=0.58–0.94, Ref=White]

nRTI **2,347** (6.8%) TDRMs

HIGHER prevalence:

- Age ≥30 (7.1%)
  [PR=1.13, 95% CI=1.04–1.23, Ref=Age 20-29]
- Metropolitan Areas (MA) (8.4%)
  [PR=1.17, 95% CI=1.04–1.31, Ref=Metropolitan statistical area, pop. ≥500,000]

LOWER prevalence:

- Black/African Americans (6.4%)
  [PR=0.89, 95% CI=0.81–0.98, Ref=White]
- Midwest Region (6.6%)
  [PR=0.86, 95% CI=0.73–0.998, Ref=West Region]

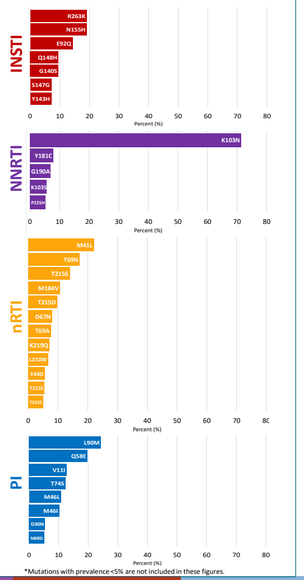
PI **1,469** (4.3%) TDRMs

HIGHER prevalence:

- Midwest Region (5.4%)
  [PR=1.52, 95% CI=1.27–1.83, Ref=West Region]
- Northeast Region (5.4%)
  [PR=1.54, 95% CI=1.32–1.79, Ref=West Region]

Common Mutations

Prevalence of Specific TDRMs by Drug Class, 2013–2016*



*Mutations with prevalence <5% are not included in these figures.

Discussion

- HIV sequence data reporting was new for many jurisdictions in 2013 and reporting increased overall from 2013–2016. Since 2016, many other jurisdictions have begun HIV sequence collection.
- Less than half of HIV diagnoses from 2013–2016 in these 23 jurisdictions had a reported drug resistance test performed <3 months from HIV diagnosis, and an increasing proportion of cases had only an IN sequence reported. Drug resistance testing for PR/RT mutations is needed to detect TDRMs for nRTIs, which remain a critical backbone for ART.
- INSTI TDRM prevalence was low overall, but increased during a period when INSTI use and IN sequence reporting also increased. This indicates a need for ongoing population-level monitoring and additional analysis to identify those most at risk for INSTI TDRMs.
- TDRM prevalence among people who inject drugs (PWID) increased during this time period when U.S. drug overdose deaths also increased and multiple HIV outbreaks occurred among PWID.
- Among people diagnosed with HIV infection attributed to perinatal transmission, 28/71 (39%) sequences had drug resistance mutations. Due to the small sample size, differences in the timing of HIV diagnosis, and uncertainty regarding perinatal ART exposure, this should be interpreted with caution. Additional work is needed to better understand drug resistance detected in the perinatal period.

Limitations

- TDRM prevalence in this analysis might differ from prevalence among all U.S. cases since we included only 23 U.S. jurisdictions and could not include undiagnosed cases or cases with no drug resistance test ordered, performed, or reported to NHSS.
- Cases in the analysis were assumed to be ART-naïve if no evidence of prior ART use was found during case investigation; some cases might have been incorrectly classified as ART-naïve. However, sequences were only included if they were performed within 3 months of diagnosis.
- HIV sequence results from conventional bulk sequencing underestimate the prevalence of drug resistance mutations.

References

1. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.
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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