Correlates of Drug Resistance Mutations in ART-Naive Individuals with HIV Infection

No. 477

Sarah E. Porter[1], Ellsworth Campbell[1], Emily Westheimer[2], Cynthia L. Gay[3], Stephanie E. Cohen[4], Anupama Shankar[1], Jin-fen Li[1], Jeffrey A. Johnson[1], William M. Switzer[1], Philip J. Peters[1]

[1] Centers for Disease Control and Prevention, Atlanta, GA [2]New York City Department of Health and Mental Hygiene, New York, NY [3]University of North Carolina at Chapel Hill, Chapel Hill, NC [4]San Francisco Department of Public Health, San Francisco, CA

Background

- Testing for antiretroviral (ARV) drug resistance is recommended for all persons with a new HIV diagnosis in order to aid selection of an antiretroviral therapy (ART) regimen[1].
- In order to assess the potential of drug resistance testing to inform public health interventions, we evaluated the prevalence and correlates of transmitted drug resistance mutation (TDRM) in ART-naive patients using data from a multi-state study of acute HIV infection.

Methods

Population

- **Data source**. This is a secondary analysis of data from a prospective study of acute HIV testing methods (the STOP study[2]). Participants were persons ≥13 years of age seeking an HIV test at one of 12 public health clinics or community testing sites in North Carolina, New York City, or San Francisco.
- **Inclusion criteria**. This analysis was limited to HIV-infected participants with an HIV-1 polymerase (*pol*) genetic sequence. To ensure individuals had not previously received ART, those with diagnosis >91 days prior to enrollment (identified by HIV case registry record or self-report) were excluded. In total, 540 of 1,326 (41%) HIV-infected study participants were included in this analysis.

Measures

- **Participant characteristics.** Participants self-reported demographic and behavioral information on a written questionnaire.
- **HIV infection status.** Acute HIV infection (AHI) and established HIV infection (EHI) were determined using an HIV testing algorithm that included an antibody-only point-of-care test, a laboratory HIV antigen/antibody combination immunoassay, and HIV-1 RNA testing. AHI was defined as having undetectable HIV antibody and detectable HIV antigen or HIV RNA. EHI was defined as having detectable HIV antibody.
- **Genetic data**. Bulk HIV-1 *pol* sequencing was conducted using TruGene (Siemens Healthcare Diagnostics, Tarrytown, NY) or a CDC in-house assay[3]. Non-polymorphic mutations[4] associated with nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI) were identified using HIVseq[5] and Sierra[6] programs. Allele-specific PCR was used to identify minority K65R mutations (lower limit of mutation detection 0.3%). HIV-TRACE[7] was used to construct genetic networks in which ≤1.5% difference in nucleotide bases was classified as a link.

Statistical analysis

- Logistic regression using SAS v9.3 (Cary, NC) was used to measure association between participant characteristics and TDRM. Results are reported as unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI).

Results

Table 1. Characteristics of participants included in analysis, stratified by HIV infection status

	Total		HIV Infection Status: AHI		EHI	
	n=540		n=132		n=408	
Median Age (IQR)	30 (25-49)		30 (25-41)		30 (24-38)	
Sex, n(%)						
Male*	512	(94.8)	128	(97.0)	384	(94.1)
Female	20	(3.7)	4	(3.0)	16	(3.9)
Transgender female	6	(1.1)	0	(0)	6	(1.5)
Race/Ethnicity, n(%)						
White	189	(35.0)	56	(42.4)	133	(32.6)
Black/African American	171	(31.7)	30	(22.7)	141	(34.6)
Hispanic/Latino	106	(19.6)	31	(23.5)	75	(18.4)
Asian/NHPI	38	(7.0)	12	(9.1)	26	(6.4)
Other/Refused/Missing	36	(6.7)	3	(2.3)	33	(8.1)
Site, n(%)						
North Carolina	133	(24.6)	14	(10.6)	119	(29.2)
New York City	185	(34.3)	47	(35.6)	138	(33.8)
San Francisco	222	(41.1)	71	(53.8)	151	(37.0)
HIV-1 infection subtype, n(%)						
B subtype	508	(94.1)	122	(92.4)	386	(94.6)
Non-B subtype	32	(5.9)	10	(7.6)	22	(5.4)

AHI: Acute HIV infection EHI: Established HIV infection NHPI: Native Hawaiian / Pacific Islander
*Among males, 442 (86%) reported male-to-male sexual contact

Table 2. Frequency of selected HIV-1 *pol* TDRM in NNRTI, NRTI, or PI classes (N=540)

Drug resistance mutation	n(%)	
NNRTI, NRTI, or PI class	**95**	**(17.6)**
NRTI class	**31**	**(5.7)**
T215 D, S, C, E, or I	18	(3.3)
M41 L	4	(0.7)
M184 V or I	5	(0.9)
V75 I	3	(0.6)
K65 R	0	(0)
K65 R – minority*	4	(0.8)
Other†	5	(0.9)
NNRTI class	**62**	**(11.5)**
K103 N or S	48	(8.9)
Y181 C or I	10	(1.9)
H221 Y	8	(1.5)
G190 A or E	3	(0.6)
Other‡	4	(0.7)
PI class	**21**	**(3.9)**
L90 M	9	(1.7)
M46 I or L	6	(1.1)
D30 N	4	(0.7)
Other§	3	(0.6)

*474 persons were tested for minority resistance to K65R
†Other NRTI: T69N, K70R, L210W
‡Other NNRTI: A96G, E138Q, K101E, P225H
§Other PI: I50V, N88S, V82A

Table 3. Association between participant characteristics and HIV-1 *pol* TDRM in NNRTI, NRTI, or PI classes (N=540)

Characteristic	TDRM n/N (%)	Odds Ratio (95% CI)[5]
Study site geographic location		
North Carolina	13 / 133 (9.8)	Ref
New York City	31 / 185 (16.8)	1.9 (0.9, 3.7)
San Francisco	51 / 222 (23.0)	**2.8 (1.4, 5.3)**
Race/Ethnicity		
White	34 / 189 (18.0)	Ref
Black/African American	18 / 171 (10.5)	**0.5 (0.3, 1.0)**
Hispanic/Latino	21 / 106 (19.8)	1.1 (0.6, 2.1)
Asian/NHPI	15 / 38 (39.5)	**3.0 (1.4, 6.3)**
Other/Refused/Missing	7 / 36 (19.4)	1.1 (0.4, 2.7)
Age group (years)		
≤25 years	25 / 153 (16.3)	Ref
26-35 years	36 / 209 (17.2)	1.1 (0.6, 1.9)
36-45 years	22 / 110 (20.0)	1.3 (0.7, 2.4)
>45 years	11 / 54 (20.4)	1.3 (0.6, 2.9)
HIV infection status*		
Established	69 / 408 (16.9)	Ref
Acute	26 / 132 (19.7)	1.0 (0.6, 1.7)
Genetic cluster size*		
1 individual	68 / 422 (16.1)	Ref
2 individuals	8 / 63 (12.7)	0.7 (0.3, 1.7)
≥3 individuals	19 / 55 (34.5)	**2.7 (1.4, 5.4)**
Male-to-male sexual contact*†‡		
No	13 / 85 (15.3)	Ref
Yes	81 / 442 (18.3)	0.8 (0.4, 1.7)
Met last sexual partner online*†		
No	41 / 233 (17.6)	Ref
Yes	32 / 202 (15.8)	0.9 (0.5, 1.5)
Missing	22 / 105 (21.0)	1.3 (0.7, 2.4)
Sex with known HIV+ partner*†		
No	76 / 411 (18.5)	Ref
Yes	19 / 129 (14.7)	0.8 (0.4, 1.3)
≥3 sexual partners*†		
No	29 / 156 (18.6)	Ref
Yes	47 / 302 (15.6)	0.8 (0.4, 1.3)
Missing	19 / 82 (23.2)	1.0 (0.5, 2.1)

TDRM: Transmitted drug resistance mutation associated with NNRTI, NRTI, or PI classes
Ref: Reference group
*Adjusted for age, race/ethnicity, and study site.
†Risk behaviors are self-reported and describe behavior in the 12-month period prior to interview. A subset of participants did not complete all risk behavior assessments and are reported as missing.
‡Reference group includes females and males who did not report sexual contact with males.
§Significant associations (α=0.05) shown in bold.

Figure 1. Transmitted drug resistance was associated with geographic location and race/ethnicity

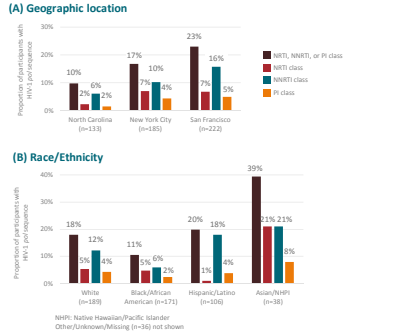
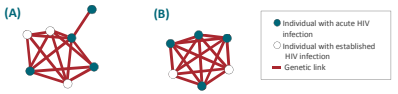


Figure 2. Transmitted drug resistance was associated with being part of a genetic cluster

Examples of large genetic clusters (≥6 individuals) with shared TDRM



(A) All 7 individuals in this cluster had a K103N mutation (associated with NNRTI resistance).[5]
(B) All 6 individuals in this cluster had a T215D mutation (revertant of T215 Y/F, may predispose to virological failure on NRTI AZT- or d4T-containing regimen).[5]

- 45 genetic clusters with 2-9 individuals were identified. Overall, 118 (22%) participants were part of a genetic cluster.
- 10 (22%) genetic clusters had ≥1 individual with TDRM.
- In 3 of 4 (75%) large clusters (≥6 individuals), all sequences within the cluster shared the same TDRMs.

See "Phylodynamic Analysis Aids Partner Services by Identifying Unreported Transmission" (E. Campbell et.al., Poster 592) for further analysis of STOP transmission clusters.

Summary

- 18% of newly diagnosed participants had ≥1 TDRM associated with NNRTI, NRTI, or PI drug classes. NNRTI-associated TDRM was the most common in all study sites (12%), followed by TDRM associated with NRTI (6%) and PI (4%) drug classes.
- TDRM was not associated with acute HIV infection or the HIV risk behaviors assessed in this analysis.
- Individuals from a San Francisco study site, of Asian/Native Hawaiian/Pacific Islander race/ethnicity, or genetic clusters of ≥3 individuals had greater odds of TDRM. Black/African American individuals had lower odds of TDRM.
- Geographic and demographic differences in TDRM may indicate differences in ART use by partners of participants in this analysis.
- Association between TDRM and cluster size was driven by shared resistance mutations in large genetic clusters (≥6 individuals).
- Given the association between TDRM and large genetic clusters, enhanced partner services may be warranted for persons with TDRM to improve HIV case finding.

Limitations

- This secondary analysis was limited to the study sub-population of individuals with HIV-1 *pol* sequence data.
- HIV-1 *pol* sequence data was only collected from individuals without prior diagnosed HIV infection; therefore, genetic clusters do not represent participants' partners with known HIV infection.

References

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV–1–infected adults and adolescents. Department of Health and Human Services. Available at ww.aidsinfo.nih.gov/ContentFiles/dultandAdolescentGL.pdf. Accessed February 1, 2017.
2. Peters, P. J., Westheimer, E., Cohen, S., et al. (2016). Screening yield of HIV antigen/antibody combination and pooled HIV RNA testing for acute HIV infection in a high-prevalence population. Jama, 315(7), 682-690.
3. Jasuja, S., Thompson, N. D., Peters, P. J., et. al. (2012). Investigation of hepatitis B virus and human immunodeficiency virus transmission among severely mentally ill residents at a long term care facility. PLoS One, 7(8), e43252.
4. Wheeler, W. H., Ziebell, R. A., Zabina, H., et al. (2010). Prevalence of transmitted drug resistance associated mutations and HIV-1 subtypes in new HIV-1 diagnoses, US–2006. AIDS, 24(8), 1203-1212.
5. Stanford HIV Drug Resistance Database. https://hivdb.stanford.edu
6. Sierra-The Stanford HIV Web Service. https://hivdb.stanford.edu/DR/webservices/
7. HIV-TRACE, Viral Evolution Group, UC San Diego. http://github.com/veg/hivtrace/

Acknowledgments

We thank the individuals who participated in this study, as well as STOP study researchers and staff at NYC Department of Health and Mental Hygiene, UNC Chapel Hill, San Francisco Department of Public Health, and CDC.

Contact

Sarah E. Porter, MPH
Epidemiology Branch, Division of HIV/AIDS Prevention,
Centers for Disease Control and Prevention
seporter@cdc.gov

www.cdc.gov | Contact CDC at: 1-800-CDC-INFO or www.cdc.gov/info
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of HIV/AIDS Prevention