TRANSMITTED DRUG RESISTANCE IN PEOPLE LIVING WITH DIAGNOSED HIV IN CALIFORNIA

ID: 3184

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Background

Increased antiretroviral (ART) use for treatment and prevention could increase the probability of transmitted drug resistance. We analyzed a population-based dataset of HIV-1 *pol* sequences to estimate the prevalence of transmitted drug resistance-associated mutations (DRAMs) in people living with HIV in California from 2008-2018 and evaluated the transmission potential [1] of identified mutations.

Methods

HIV-1 *pol* sequences reported to the California HIV surveillance system were analyzed with Stanford's HIV Drug Resistance Database using SIERRA [2][3] to determine resistance mutations and COMET [4] to determine subtype. People were classified as ART-naïve if their sequence was obtained within three months of an HIV diagnosis and there was no documentation of prior antiretroviral use.

DRAMs were defined based on CDC's surveillance resistance mutation list [5], which comprised 24 non-nucleoside reverse transcriptase (RT) inhibitor (NNRTI) mutations, 40 nucleoside reverse transcriptase inhibitor (NRTI) mutations, 44 protease inhibitor (PI) mutations, and 26 integrase strand-transfer inhibitor (INSTI) mutations.

We used HIV-TRACE (www.hivtrace.org) [6]-[8] to construct molecular transmission networks. Clustering was defined as two or more sequences that linked with a pairwise genetic distance of ≤ 0.015 substitutions/site. Among ART-naïve people, we compared the frequency of clustering among sequences with a DRAM vs. sequences without a DRAM. We calculated rate ratios and 95% confidence intervals (CIs) to detect positive or negative associations between the presence of a DRAM and clustering frequency.

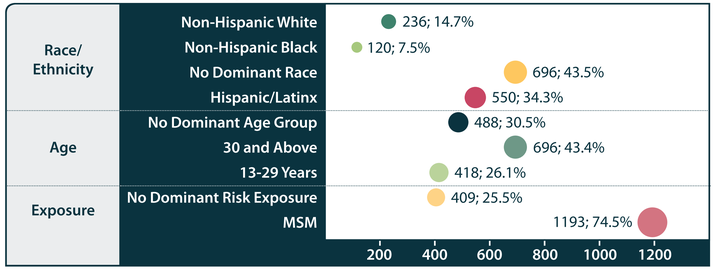
Characteristics of Molecular Clusters

17,468 sequences (93.9% subtype B) obtained within 3 months of HIV diagnosis

15,343 sequenced from persons having no ART use history prior to genotyping

8,371 (54.6%) clustered at or below the 1.5% genetic distance threshold

Figure 1. Molecular Clusters by Predominant[1] Traits (No. and % of Clusters Annotated)



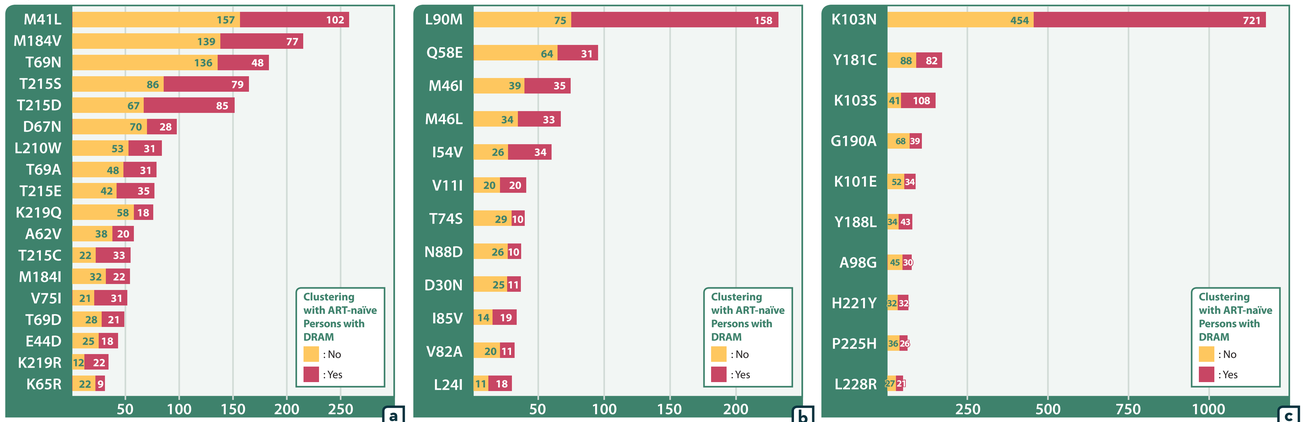
- 54.6% of sequences clustered in **754** dyads and **848** larger clusters ranging from 3 to 116 sequences (median=4).
- In most clusters (74.5%), male-to-male sexual contact was the predominant (≥66%) risk behavior.

[1]*Predominant trait defined as characteristics shared by at least two-thirds of members of a cluster.*

Prevalence of Transmitted DRAMs

The prevalence of any DRAM in a sequence from an antiretroviral-naïve person was 19.8%; **NNRTI, NRTI, and PI** mutations were detected in **11.5%, 8%, and 4%** of sequences, respectively. The integrase region was sequenced in a subset of 1734 persons and an **integrase** DRAM was detected in **1.2%** of sequences.

Figure 2. Selected NRTI (a), PI (b), and NNRTI (c) Mutations with Population Prevalence of 0.2% or Higher and INSTI Mutations (d; Clustering Frequencies Not Shown)



d INSTI Mutations (N): N155H (6); Q148R (3); S147G (3); E92G (2); G140S (2); T66I (2); E92Q (1); G118R (1); N155S (1); S230R (1); T66A (1); and Y143R (1)

Clustering Frequencies of Specific DRAMs

- Of the 134 DRAMs comprising drug resistance surveillance list, 68 were found in the treatment-naïve population with ≥ 0.1% prevalence.
- Compared to sequences without a mutation, a higher proportion of sequences with an NNRTI mutation clustered (rate ratio [RR] 1.06), whereas a lower proportion of NRTI mutations clustered (RR=0.80).
- Enhanced clustering tendencies were detected in strains containing NNRTI and PI mutations, among which K103N, K103S, and L90M had relative clustering rates significantly greater than one.

Table. DRAM Prevalence by ART Class and Select Mutations[1] and Frequency of Clustering with ART-naïve HIV-infected People

DRAM Class and Selected Mutations	Total N	Prevalence	Clustering N	Clustering %	Rate Ratios of Clustering (95% CIs)
Any DRAM	3035	19.8%	1604	52.9%	0.96 (0.93-1.00)
NNRTI Mutation*	**1770**	**11.5%**	**1028**	**58.1%**	**1.06 (1.01-1.10)**
NRTI Mutation~	1234	8.0%	544	44.1%	0.80 (0.75-0.86)
PI Mutation~	609	4.0%	299	49.1%	0.89 (0.82-0.97)
INSTI Mutation[2]	21	1.2%	8	38.1%	0.69 (0.40-1.20)
K103N (NNRTI)*	**1175**	**7.7%**	**721**	**61.4%**	**1.13 (1.08-1.19)**
Y181C (NNRTI)	170	1.1%	82	48.2%	0.89 (0.76-1.04)
K103S (NNRTI)*	**149**	**1.0%**	**108**	**72.5%**	**1.34 (1.21-1.48)**
M41L (NRTI)~	259	1.7%	102	39.4%	0.71 (0.61-0.83)
M184V (NRTI)~	216	1.4%	77	35.6%	0.64 (0.54-0.77)
T69N (NRTI)~	184	1.2%	48	26.1%	0.47 (0.37-0.60)
T215S (NRTI)	165	1.1%	79	47.9%	0.86 (0.74-1.01)
T215D (NRTI)	152	1.0%	85	55.9%	1.01 (0.87-1.16)
K65R (NRTI)~	31	0.2%	9	29.0%	0.52 (0.30-0.91)
L90M (PI)*	**233**	**1.5%**	**158**	**67.8%**	**1.24 (1.13-1.35)**

[1]A prevalence cutoff of 1% was used for selecting mutations included in the table; [2]The subset of 1734 sequences screened in the integrase region was used for estimating INSTI DRAM prevalence; * denotes significantly higher clustering rates than wildtype clustering at the 0.05 significance level; and ~ denotes significantly lower clustering rates.

Conclusions

- This population-based drug-resistance analysis demonstrated sustained DRAM transmission, particularly of NNRTI mutations, among antiretroviral-naïve people.
- **K103N**, **K103S**, and **L90M** mutations were associated with more clustering, a proxy for increased further transmission. These mutations do not have a significant replication fitness cost to the virus which can allow the mutation to persist in the absence of ART exposure and transmit among ART-naïve people. The association with increased transmission could be attributable to transmission network or viral characteristics. Fortunately these common DRAMs do not impact preferred treatment regimens.
- Although reassuring that the NRTI mutations M184V and K65R were associated with less clustering, a proxy for reduced further transmission, this finding should continue to be monitored as exposure to NRTIs increases with the expansion of pre-exposure prophylaxis.
- INSTI DRAMs remain uncommon despite the wide use of INSTIs for HIV treatment. These DRAMs were not associated with clustering but this finding should be monitored as exposure to INSTIs for HIV treatment and post-exposure prophylaxis continues to increase.

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The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the California Department of Public Health or the Centers for Disease Control and Prevention.

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