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Prevalence of transmitted HIV drug resistance among recently infected persons in San Diego, California 1996-2013

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Background

- The widespread use of combination antiretroviral therapy (ART) has resulted in the emergence and transmission of drug-resistant HIV strains.
- Transmitted drug resistance (TDR) limits effective treatment options for ART-naïve HIV infected individuals.[1,2]
- Several studies have been reported the estimated prevalence of TDR between 3% and 25% in the USA.[3,4]

Objective

To describe the prevalence, rate of change and phylogenetic relationships of TDR among ART-naïve, recently HIV-infected individuals in San Diego from 1996-2013.

Methods

Study population

- 690 HIV-infected participants, including 496 with clinical or laboratory evidence of primary HIV infection, enrolled in the San Diego Primary Infection Cohort between 1996 and 2013.

Genotypic resistance testing

- At the time of enrollment, population sequencing of the partial HIV-1 *pol* gene was performed.
- Major drug resistance mutations (DRM) were identified using the Stanford HIV Database Calibrated Population Resistance Tool based on the 2009 World Health Organization surveillance of transmitted drug resistant mutations (SDRMs) list.[5]

Transmission cluster analysis

- Putative transmission linkages were inferred when the genetic distance (using the TN93 nucleotide substitution model) between two HIV-1 pol sequences was <1.5%. Multiple linkages were resolved into clusters.

Phylogenetic analysis

- 690 available sequences were used to perform the phylogenetic analysis by using maximum likelihood (ML) approach with general time reversible + Gamma (GTR + G) model of nucleotide substitution in FastTree software.

Results

Table 1. Baseline characteristics of recently HIV-infected individuals

Characteristics		Number of individuals, n (%)
All participants		496 (100)
Sex	Male	478 (96.96)
	Female	15 (3.04)
Age	Mean, years (±SD)	32.49 (±11.13)
Ethnicity	Non-Hispanic or Latino/Americans	230 (63.36)
	Hispanic or Latino/Americans	131 (36.09)
Race	White/Caucasian	379 (77.99)
	Native American	47 (9.67)
	Black/African American	33 (6.79)
HIV risk exposure	MSM/MSM-IDU	464 (94.69)
	Heterosexual	12 (2.45)
CD4 cell count (cell/mm³)	< 200	17 (3.43)
	200 to < 350	88 (17.74)
	350 to < 500	136 (27.42)
	≥ 500	255 (51.41)
	Mean absolute CD4 (±SD)	530 (±222.69)
Viral load	Mean Viral load (log_{10}copies/mL) (±SD)	4.97 (±1.11)

Table 2. Characteristics of recently HIV-1-infected individuals with and without transmitted drug resistance mutations

	Total	TDR	Wild type	Univariate			Multivariate		
				OR	(95%CI)	P-value	OR	(95%CI)	P-value
Participants	496	67 (13.5)	429 (86.5)						
Sex						0.97			0.08
Male	478	65 (13.6)	413 (86.4)	1	Reference		1	Reference	
Female	15	2 (13.3)	13 (86.7)	0.98	0.22-4.43		6.62	0.76-57.8	
Age						0.6			0.46
Mean years (±SD)	32.5 (±11.13)	32.6 (±13.2)	32.5 (±10.8)			0.94[a]			
Ethnicity						0.75			0.58
Non-Hispanic or Latino/A	230	34 (14.8)	196 (85.2)	1	Reference		1	Reference	
Hispanic or Latino/A	131	21 (16)	110 (84)	1.1	0.61-1.99		1.23	0.6-2.53	
HIV risk exposure						0.66			0.58
MSM/MSM-IDU	464	62 (13.4)	402 (86.6)	1	Reference		1	Reference	
Heterosexual	12	2 (16.7)	10 (83.3)	1.30	0.28-6.06		2.45	0.2-30.36	
CD4 count (cells/mm³)						0.23			0.55
<200	17	2 (11.8)	15 (88.2)	1	Reference		1	Reference	
200 to < 350	88	14 (15.9)	74 (84.1)	1.42	0.29-6.90		5.15	0.52-51.06	
350 to <500	136	24 (17.6)	112(82.4)	1.61	0.34-7.50		5.79	0.52-64.89	
≥ 500	255	27 (10.6)	228 (89.4)	0.89	0.19-4.10		5.7	0.36-89.42	
Mean absolute CD4 (±SD)	530 (±222.7)	479 (±172.3)	537 (±228.7)			**0.02[a]**			0.33
Mean log_{10} viral load (±SD)	4.97 (±1.1)	5.23 (±1.1)	4.96 (±1.1)			0.24[a]			0.24
Year of Diagnosis						**0.005**			**0.02**
1996-1999	40	5 (12.5)	35 (87.5)	1	Reference		1	Reference	
2000-2004	200	15 (7.5)	185 (92.5)	0.57	0.19-1.66		0.07	0.01-0.71	
2005-2009	152	32 (21.1)	120 (78.9)	1.87	0.68-5.15		0.23	0.03-2.09	
2010-2013	104	15 (14.4)	89 (85.6)	1.18	0.40-3.49		0.14	0.01-1.29	

Table 2: Data are presented as number (%) of patients, unless otherwise indicated. ORs were estimated using simple (unadjusted) and multiple (adjusted) logistic regression. a=Two-sample t test. We found a statistically significant increase in TDR and this significance remains when controlling for potential confounders. In a univariate analysis, mean baseline CD4 cell count was significantly lower among individuals with TDR (p = 0.02), but after adjusting for confounding fators, no significant association became evident in multivariate analyses. There was no statistical association between TDR and other population demographics.

Figure 1. Prevalence of transmitted drug resistance mutations by drug class among treatment-naïve, recently HIV-infected individuals

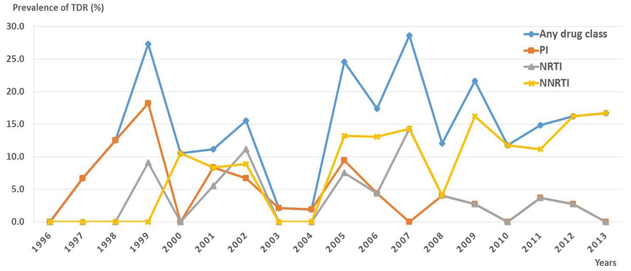

Figure 1: TDR prevalence was as follows: any drug (13.5%), PI (4.4%), NRTI (3.8%), NNRTI (8.5). We found that the prevalence of TDR to NNRTIs significantly increased over the entire study period (p for trend = 0.005).

Figure 2. Phylogenetic tree of all HIV-1 *pol* sequences

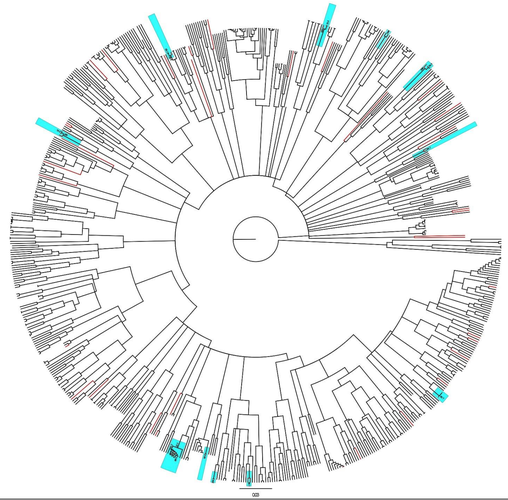

Figure 2: The maximum likelihood phylogenetic tree of all 690 HIV-1 *pol* sequences using GTR + Gamma model in FastTree software. Red branches represent sequences with K103N mutation and blue boxes indicate identified clusters which contain at least two individuals sharing the same resistance mutation. We identified 103 transmission clusters (295 individuals, 43% of the cohort), of which 24 included at least one individual with a DRM. Of these 24 clusters, 11 (45.8%) included at least 2 individuals carrying the same resistance mutation, and the K103N was the concordant mutation found in 9 out of these 11 clusters.

Figure 3. Prevalence of common specific resistance mutations in treatment-naïve, recently HIV-infected individuals

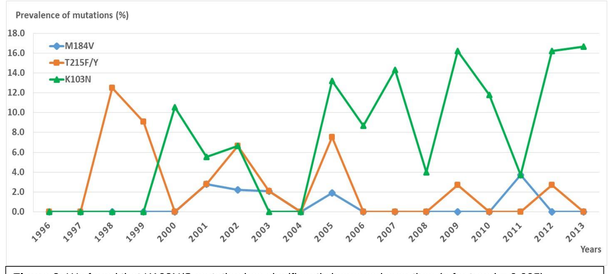

Figure 3: We found that K103N/S mutation has significantly increased over time (p for trend = 0.005).

Conclusions

- We identified that the prevalence of TDR has significantly increased over the past 18 years (1996-2013) among ART-naïve, recently HIV-infected individuals in San Diego, specifically for TDR to NNRTIs.
- We also found evidence of TDR within transmission clusters, suggesting that TDR may be driven by individuals transmitting to others during primary HIV infection.
- Current trends suggest that NNRTI based regimens should not be prescribed for new diagnoses without prior resistance testing
- These findings highlight the value of close monitoring the epidemiologic trends of TDR in order to detect clustering of infected individuals, and to provide information on TDR to guide future therapeutic decisions for treatment and prevention of HIV.

Acknowledgments

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