Temporal trends of transmitted HIV drug resistance following seroconversion

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INTRODUCTION

- Transmitted drug resistance (TDR) may increase with wider use of combination antiretroviral therapy (cART)
- TDR can contribute to cART failure
- In seroprevalent cART naïve individuals, it has been shown that TDR has decreased with calendar time
- It has yet to be established if this decrease can be attributed to lower TDR as the data used are from naïve nucleotide samples opposed to nucleotide samples near HIV seroconversion

AIMS

- To analyse the time trends of TDR among individuals with nucleotide sequence data near HIV seroconversion

METHODS

DATA

- CASCADE data on HIV-1 positive individuals with negative and positive HIV test dates ≤3 years apart
- Inclusion criteria (4,183 individuals)
  - Seroconverted in the cART era (≥1996)
  - Seroconverted before December 31, 2012
  - ≥1 cART naïve nucleotide sequence ≤1 year of HIV seroconversion

ANALYSIS

- Identify the most common (>10%) TDR mutations by drug class according to the WHO criteria (surveillance drug resistance mutations - SDRMs)
- Virus considered resistant if at least one SDRM mutation was present
- Logistic regression was used to examine the association between TDR and calendar time adjusting for sex, HIV transmission risk group, HIV diagnoses during acute HIV infection (HIV test interval < 30 days or laboratory evidence of acute HIV infection) and age at seroconversion
- We used the Stanford HIV db algorithm to determine susceptibility to cART drugs

RESULTS

Table 1: Baseline characteristics

Seroconversion year		2007 (2004, 2010)
Age at seroconversion (years)		33 (27, 39)
RISK GROUP	MSM - N (%)	3341 (80%)
	IDU - N (%)	113 (3%)
	MSW - N (%)	636 (15%)
	Other/Unknown - N (%)	93 (2%)
Acute HIV infection - N (%)		1270 (30%)
SUBTYPE	B - N (%)	3052 (73%)
	A - N (%)	315 (8%)
	C - N (%)	264 (6%)
	G – N (%)	69 (2%)
	Recombinant - N (%)	152 (4%)
	CRF02_AG	84 (2%)
	Other CRF	52 (1%)
	Other/Unknown	195 (5%)
TDR Mutations - N (%)		457 (11%)
NRTI - N (% of TDR)		251 (55%)
41L - N (% of NRTI)		78 (31%)
215S - N (% of NRTI)		53 (21%)
215D - N (% of NRTI)		38 (15%)
184V - N (% of NRTI)		30 (12%)
NNRTI - N (% of TDR)		157 (34%)
103N- N (% of NRTI)		104 (66%)
PI - N (% of TDR)		125 (27%)
90M- N (% of PI)		32 (26%)
46 I- N (% of PI)		27 (22%)
46L - N (% of PI)		21 (17%)
82A - N (% of PI)		16 (13%)
85V - N (% of PI)		13 (10%)

Values are median (IQR) unless otherwise stated. Abbreviations: MSM – men who have sex with men; IDU – injection drug use; MSW – sex between men and women.

- 457 (11%) individuals had ≥1 TDR related mutation, 66 (2%) with TDR to ≥2 classes and 10 (<1%) with TDR to ≥3 classes
- Proportion of TDR (any class) has decreased over time starting at 23% in 1996, 12% in 2003 and 9% in 2012
- TDR has significantly decreased in NRTI, PI, and has moderately decreased in NNRTI drug classes
- 251 (6%) individuals had ≥1 TDR mutation related to high/intermediate resistance (Stanford Score ≥4), 31 (<1%) with TDR to ≥2 classes and 8 (<1%) with TDR to ≥3 classes
- 84 (2%), 137 (3) and 75 (2%) had high/intermediate resistance mutation to an NRTI, NNRTI and PI, respectively
- High/intermediate TDR decreased with calendar time, significantly so for NRTI drug class (data not shown)

Figure: Prevalence 95%CI of TDR over time by drug class

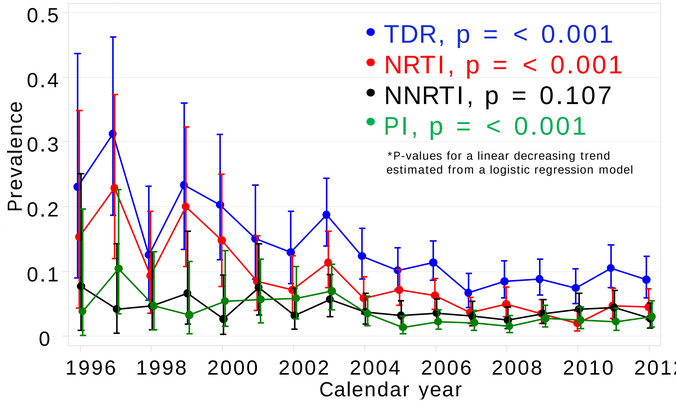


Table 2: Predictors of any TDR

Covariate	HR (95 % CI)	P- value
Females	1.01 (0.60, 1.71)	0.96
Risk Group		0.08
MSM	1	
IDU	0.68 (0.35, 1.31)	
MSW	0.62 (0.42, 1.66)	
OTH/Unknown	0.82 (0.41, 1.66)	
Age Group (years)		0.86
15-24	1	
25-34	1.09 (0.82, 1.47)	
35-44	1.02 (0.74, 1.39)	
45+	1.11 (0.76, 1.63)	
Seroconversion year	0.92 (0.89, 0.94)	<0.001
Acute Infection	1.18 (0.96, 1.46)	0.12

CONCLUSION

- Transmitted drug resistance has decreased over calendar time which is a realistic estimation of the actual decrease in TDR due to the inclusion nucleotide sequence data close to HIV seroconversion
- Moderate evidence of an association between risk of TDR and diagnoses during acute infection may suggest TDR impacts presentation to care during acute infection (e.g. seroconversion illness) or that we underestimate TDR if not tested immediately following seroconversion.

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