Changing Rates of Heavily Treatment Experienced Persons with HIV in the United States, 2000-2017

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Background

- Antiretroviral therapy (ART) is highly effective in controlling HIV viremia, decreasing morbidity and mortality, and preventing HIV transmission in persons with HIV (PWH)
- Historically, a high burden of antiretroviral (ARV) drug resistance in heavily treatment experienced (HTxE) persons limited treatment options
- The population of HTxE PWH has evolved in the modern ART era with the introduction of more potent ARV drugs, though information regarding the prevalence and characteristics of this group is limited
- Prior studies have used varying definitions for HTxE, often relying on virologic failure and ARV treatment history in the absence of genotypic resistance data. As a result, reported outcomes related to virologic suppression, disease progression, and mortality among HTxE PWH have been mixed

Objective

- We examined trends in HTxE prevalence throughout the modern ART era from 2000 to 2017 and determined predictors of HTxE PWH defined by cumulative genotypic resistance data

Methods

- We studied all ART experienced adult PWH in care between 2000-2017 in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), a dynamic prospective clinical cohort of >32,000 PWH receiving care at eight participating academic sites across the United States
- Comprehensive clinical data in CNICS are collected through electronic medical records and other institutional data systems, undergo rigorous quality assessment, are harmonized in a central repository, and are updated on a quarterly basis
- Genotypic mutation data were processed using the Stanford HIV Drug Resistance Database and drug susceptibility was defined as a score <10. For each PWH, all identified mutations were carried forward to assess cumulative ARV resistance. HTxE persons were defined as having ≤2 available classes with a limited number of active drugs in each class (≤2 active ARV drugs for NRTIs, NNRTIs, or PIs, and <1 drug for the new INSTI class introduced in 2007)
- We computed the annual HTxE prevalence among all ART experienced persons in care from 2000-2017
- We used multivariable Cox proportional hazards models to examine time from CNICS entry (baseline) to incident HTxE by 3-year calendar periods, adjusting for age, sex, race/ethnicity, CNICS site, baseline nadir CD4 cell count, baseline maximum HIV RNA level, ART-naïve at CNICS entry, and prior single/dual NRTI treatment
- In sensitivity analyses, we examined alternative measures of HTxE including virologic failure (defined as a single HIV RNA >400 copies/mL, or two sequential levels >400 and >1000 copies/mL respectively) followed by ARV drug switch within 3 months, and the number of ARV drugs received among PWH in care in 2016

Results

- Among 27,133 ART experienced PWH, resistance testing was performed in 8,961 persons with 916 PWH classified as HTxE during the study period, the majority of whom were male (85%), white (49%), men who have sex with men as a risk factor for HIV acquisition (54%), with median age 51 years, and median nadir CD4 71 (interquartile range [IQR] 15-182) cells/mm^3 (Table 1)

Table 1. *Distribution of demographic and clinical characteristics among ART experienced PWH by HTxE status, 2000-2017*

Variable	Total N = 27,133	No HTxE N = 26,217	Yes HTxE N = 916
Age at last visit Median, IQR	46 [37-54]	46 [37-54]	51 [44-57]
Female	5173 (19%)	5032 (19%)	141 (15%)
Race/Ethnicity			
White	11709 (43%)	11258 (43%)	451 (49%)
Black	11122 (41%)	10735 (41%)	387 (42%)
Hispanic	3036 (11%)	2980 (11%)	56 (6%)
Other/missing	1266 (5%)	1244 (5%)	22 (2%)
Risk Factor			
Heterosexual	7060 (26%)	6844 (26%)	216 (24%)
IDU	4344 (16%)	4204 (16%)	140 (15%)
MSM	14475 (53%)	13977 (53%)	498 (54%)
Other/unknown	1254 (5%)	1192 (5%)	62 (7%)
First observation year Median, IQR	2008 [2003-2012]	2008 [2003-2012]	2001 [2000-2003]
ART naïve at CNICS entry	11830 (44%)	11558 (44%)	272 (30%)
Prior single/dual NRTI treatment	3971 (15%)	3560 (14%)	411 (45%)
Baseline nadir CD4 cells/mm^3 Median, IQR	234 [82-394]	240 [88-401]	71 [15-182]
Baseline maximum HIV RNA copies/mL Median, IQR	56,255 [5,310-227,500]	53,759 [4,729-218,000]	191,989 [51,234-546,223]

ART – antiretroviral therapy; HTxE - heavily treatment experienced; IDU – injection drug user; IQR – interquartile range; MSM – men who have sex with men; NRTI – nucleoside reverse transcriptase inhibitor

- Annual prevalence of HTxE PWH was 5.2-7.5% in 2000-2006, after which it declined significantly to 1.8% in 2007 with the addition of a new ARV class (INSTI), and remained <1% after 2012 (Figure 1)
- PWH entering care in 2009-2011 had an 80% lower risk of becoming HTxE compared to those entering in 2006-2008 (aHR 0.20, 95% CI 0.09-0.42) (Table 2)
- Lower baseline CD4 nadir and higher baseline maximum HIV RNA level were significantly associated with greater risk of becoming HTxE (aHR per 100 CD4 cells/mm^3 increase 0.82, 95% CI 0.78-0.87; aHR per 10-fold HIV RNA copies/mL increase 1.37, 95% CI 1.26-1.49)

Figure 1. *Annual prevalence of HTxE PWH among all antiretroviral experienced PWH in care between 2000–2017*

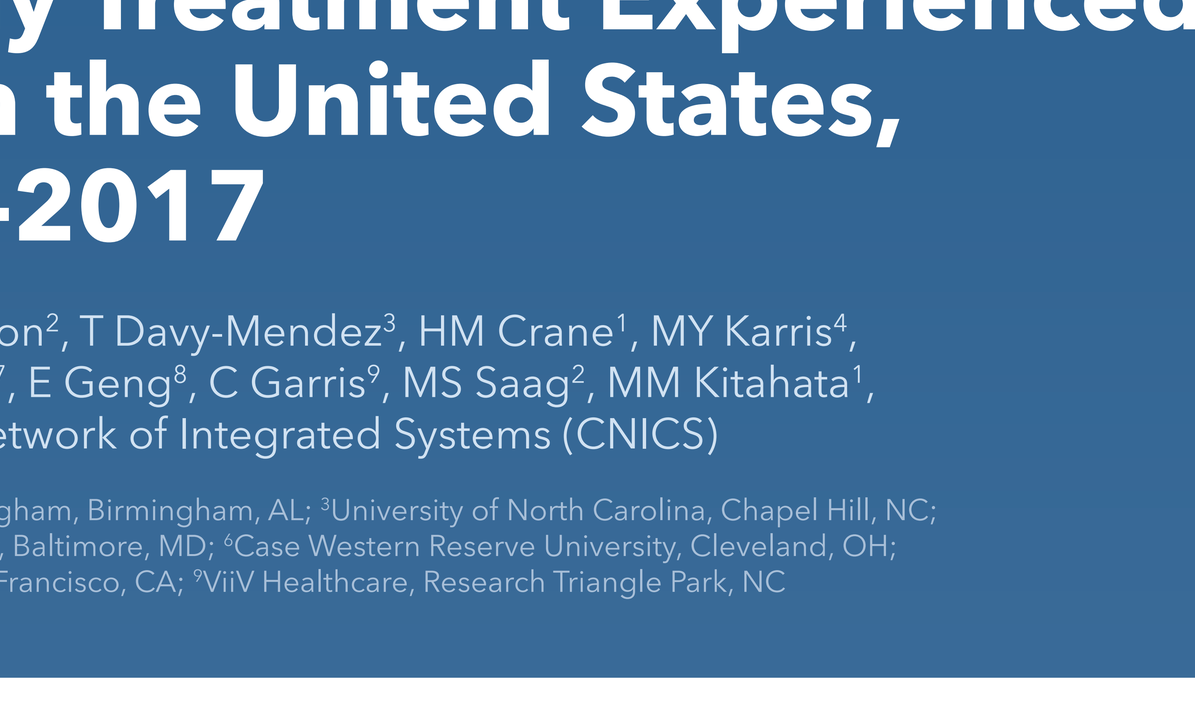

Table 2. *Adjusted hazard ratios (aHR) of incident HTxE PWH according to calendar period, demographic and clinical characteristics**

Variable	aHR*	P-value	95% CI	
Age at entry (per 10 years)	1.13	0.001	1.05	1.22
Female	0.72	0.001	0.59	0.87
Race/Ethnicity (reference: White)				
Black	0.92	0.29	0.78	1.07
Hispanic	0.82	0.19	0.62	1.10
Other/Missing	0.77	0.24	0.50	1.19
Entry year				
2000-2002	5.75	<0.001	4.25	7.78
2003-2005	4.20	<0.001	3.07	5.75
2006-2008 (reference)	--	--	--	--
2009-2011	0.20	<0.001	0.09	0.42
2012-2014	0.26	<0.001	0.13	0.51
2015-2017	0.36	0.02	0.15	0.84
Baseline nadir CD4 (per 100 cells/mm^3 increase)	0.82	<0.001	0.78	0.87
Baseline maximum HIV RNA (per 10-fold increase copies/ml)	1.37	<0.001	1.26	1.49
ART naive at CNICS entry	0.34	<0.001	0.29	0.40
Prior single/dual NRTI treatment	2.47	<0.001	2.14	2.83

* N=887 events due to censoring

Table 3. *Distribution of ARVs received and ARV resistance among all ART experienced PWH by HTxE status*

Variable	Total N = 27,133	No HTxE N = 26,217	Yes HTxE N = 916
Total number of ARVs received by class, Median, IQR			
All ARV	5 [3-7]	5 [3-7]	11 [9-13]
NRTI	3 [2-4]	3 [2-4]	5 [4-6]
NNRTI	1 [0-1]	1 [0-1]	1 [1-2]
PI	1 [0-2]	1 [0-2]	4 [3-5]
INSTI	0 [0-1]	0 [0-1]	1 [0-1]
Number of PWH with any ARV resistance	7022 (26%)	6106 (23%)	916 (100%)
Number of ARVs resistant to, Median, IQR	6 [3,10]	5 [3, 8]	16 [13,19]
Number of PWH with ARV resistance by class			
Any NRTI	4686 (17%)	3779 (14%)	907 (99%)
Any NNRTI	4618 (17%)	3800 (14%)	818 (89%)
Any PI	2050 (8%)	1306 (5%)	744 (81%)
Any INSTI	357 (1%)	313 (1%)	44 (5%)
Number of PWH by common ARV resistance			
Didanosine	4591 (17%)	3686 (14%)	905 (99%)
Nevirapine	4473 (16%)	3658 (14%)	815 (89%)
Efavirenz	4239 (16%)	3429 (13%)	810 (88%)
Abacavir	3935 (15%)	3035 (12%)	900 (98%)
Lamivudine/Emtricitabine	3518 (13%)	2651 (10%)	867 (95%)
Stavudine	3051 (11%)	2212 (8%)	839 (92%)
Rilpivirine	2782 (10%)	2169 (8%)	613 (67%)
Etravirine	2771 (10%)	2160 (8%)	611 (67%)
Zidovudine	2538 (9%)	1713 (7%)	825 (90%)
Tenofovir	2059 (8%)	1262 (5%)	797 (87%)

ARV – antiretroviral; HTxE - heavily treatment experienced; IQR – interquartile range; INSTI – integrase inhibitor; NRTI – nucleoside reverse transcriptase inhibitor; NNRTI – non-nucleoside reverse transcriptase inhibitor; PI – protease inhibitor

- Among persons with any ARV drug resistance, HTxE PWH were resistant to 3 times the number of ARV drugs compared to PWH who were not HTxE (median 16 [13-19] versus 5 [3-8] no HTxE) (Table 3)
- Compared with HTxE PWH identified by genotypic resistance, HTxE defined by virologic failure (>400 copies/mL) with ARV switch had 29% sensitivity, 83% specificity, and a positive predictive value (PPV) of 1%. The PPV for HTxE defined by other definitions of virologic failure or the number of ARV drugs ranged from 1-20%

Conclusions

- HTxE prevalence declined dramatically after 2006-2008 and has remained <1% in the contemporary ART era, suggesting the decrease is due to the availability of more potent ARV drugs with a higher barrier to resistance
- Neither virologic failure with ARV switch nor number of ARV drugs received accurately identified HTxE PWH
- The decline in HTxE has important implications for improved virologic control and survival, as well as reduced HIV transmission