Title

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Journal

AIDS, 34(14)

ISSN

0269-9370

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Publication Date

2020-11-15

DOI

10.1097/qad.0000000000002679

Peer reviewed

HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2021 November 15.

Published in final edited form as:

AIDS. 2020 November 15; 34(14): 2051–2059. doi:10.1097/QAD.0000000000002679.

Significant decline in heavily treatment experienced persons with HIV with limited antiretroviral treatment options in the US, 2000-2017

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Abstract

Objective: Historically, a high burden of resistance to antiretroviral therapy (ART) in heavily treatment experienced (HTE) persons with HIV (PWH) resulted in limited treatment options (LTO). We evaluated the prevalence, risk factors, and virologic control of HTE PWH with LTO throughout the modern ART era.

Design: We examined all ART-experienced PWH in care between 2000-2017 in the Centers for AIDS Research Network of Integrated Clinical Systems cohort.

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Author contributions: KB, RN, JACD, EE, TDM, MY, RM, JE, BR, KM, EG, MS, HC, and MK contributed to study conception, design, and performance. RN and JACD analyzed the data. KB, RN, JACD, HC and MK wrote the first draft of the manuscript. All authors were involved in data interpretation, review, writing and approved the final version of the manuscript.

Presented in part at the 10th International AIDS Society (IAS) Conference on HIV Science, Mexico City, July 2019.

Methods: We computed the annual prevalence of HTE PWH with LTO defined as having ≤2 available classes with ≤2 active drugs per class based on genotypic data and cumulative antiretroviral resistance. We used multivariable Cox proportional hazards models to examine risk of LTO by 3-year study entry periods adjusting for demographic and clinical characteristics.

Results: Among 27,133 ART-experienced PWH, 916 were classified as having LTO. The prevalence of PWH with LTO was 5.2-7.5% in 2000-2006, decreased to 1.8% in 2007, and remained <1% after 2012. Persons entering the study in 2009-2011 had an 80% lower risk of LTO compared with those entering in 2006-2008 (adjusted hazard ratio 0.20; 95% CI: 0.09–0.42). We found a significant increase in undetectable HIV viral loads among PWH ever classified as having LTO from <30% in 2001 to >80% in 2011, comparable to persons who never had LTO.

Conclusions: Results of this large multicenter study show a dramatic decline in the prevalence of PWH with LTO to <1% with the availability of more potent drugs and a marked increase in virologic suppression in the current ART era.

Keywords

Antiretroviral therapy-experienced; HIV; Heavily treatment-experienced; Antiretroviral drug resistance; Limited treatment options

Introduction

Antiretroviral therapy (ART) is highly effective in controlling HIV viremia, decreasing disease morbidity and mortality in persons with HIV (PWH),[1, 2] and preventing HIV transmission.[3] However, the development of antiretroviral (ARV) drug resistance has the potential to limit these therapeutic benefits.[4, 5] Historically, a high burden of ARV drug resistance mutations developed in heavily treatment experienced (HTE) persons through sequential addition of active drugs, incomplete adherence and exposure to lower potency, less tolerable regimens,[6–8] which limited treatment options[9] and posed a significant challenge to disease control. Genotypic resistance testing is recommended before ART initiation and in the setting of virologic failure to guide therapeutic decision making.[9]

The population of HTE PWH has evolved throughout the modern ART era with the introduction of more potent ARV drugs with higher barrier to resistance, less frequent administration, co-formulation, reduced pill burden, and fewer side effects.[10] Information regarding changing prevalence and predictors of HTE PWH, in particular in the setting of contemporary ART, is limited.

Previous studies have used varying approaches to define HTE PWH, often relying on virologic failure and ARV treatment history in the absence of genotypic resistance data, resulting in inconsistent findings.[11–15] Studies that have used genotypic resistance data to more accurately define HTE PWH were largely conducted in the early ART era[6, 8, 16–21] prior to the availability of the integrase strand transfer inhibitor (INSTI) class which has been shown to be highly effective in achieving virologic control in treatment experienced PWH.[22–24] In addition, analyses restricted to PWH undergoing resistance testing[25–27] have been shown to overestimate HTE prevalence.[16, 28] Studies of select sub-populations of PWH and examination of the most recent genotypic test rather than cumulative

resistance[17, 28] have resulted in conflicting estimates of prevalence as well as outcomes related to virologic suppression, disease progression, and mortality among HTE PWH.[5, 12, 14, 29–31]

Furthermore, prior studies have focused on the number of ARV drugs or classes to which a PWH is resistant,[32] rather than how many active drugs they have available, which is the key to achieving virologic suppression.[33] As new drugs and ARV classes become available, the prevalence of PWH with limited treatment options (LTO) may decrease. We conducted this study to examine trends in LTO throughout the modern ART era from 2000 to 2017. We also determined predictors of and clinical outcomes among PWH with LTO defined by cumulative genotypic resistance data and the number of active ARV drugs available.

Methods

Data Source

The Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) is a dynamic prospective clinical cohort of adult PWH receiving care at eight participating academic sites distributed across the United States. Demographic and clinical characteristics of PWH in the CNICS cohort are similar to the overall population of PWH in the United States.[34] Comprehensive clinical data 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.[35] The CNICS Data Management Core at the University of Washington works closely with investigators, clinicians, and data teams at each site to ensure comprehensive capture of ARV drugs and genotypic resistance tests that are processed using the Stanford HIV Drug Resistance Database.[36] Seven of eight CNICS sites collect genotypic resistance data. Institutional review boards (IRBs) at each site approved the cohort protocol.

Study Population

We studied all ART-experienced PWH aged 18 or older in care at the 7 CNICS sites (Case Western Reserve University; Fenway Community Health Center of Harvard University; Johns Hopkins University; University of Alabama at Birmingham; University of California, San Diego; University of North Carolina; University of Washington) with available resistance data between January 1, 2000 and December 31, 2017. We defined ART as a multi-drug regimen including at least 1 drug from the following core classes: non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), or INSTIs. Chemokine coreceptor antagonists and fusion inhibitors were infrequently prescribed and therefore not considered as additional core classes. Participants entered the study in the year of their first CNICS visit between 2000 and 2017 at which they were receiving ART. Drug resistance was ascertained within 4 major classes: nucleoside reverse transcriptase inhibitors (NRTIs), NNRTIs, PIs, and INSTIs. A given drug was considered active if scored by the Stanford algorithm as susceptible (<10 points) and inactive if scored as having potential low-, intermediate-, or high-level resistance (≥10 points).[36] For each individual, resistance mutations were carried forward to assess cumulative ARV drug resistance, including mutations detected in genotypic testing performed prior to ART initiation.

Heavily Treatment Experienced Persons with Limited Treatment Options

We defined individuals with limited treatment options (LTO) as having only 2 active ARV classes available in which there were a limited number of active drugs or ≤1 ARV class available. Three ARV classes were available at the beginning of the study period and were considered limited if there were 2 or fewer active NRTIs or PIs, but as only 2 NNRTIs were available between 2000-2007, this class was considered limited if there were 1 or fewer active drugs available. With the introduction of the first INSTI in 2007, this new ARV class was considered available with 1 active drug. The pool of drugs available in each class per calendar year was defined according to the Food and Drug Administration (FDA) approval dates (Supplemental Table 1).[37]

Statistical Analysis

We examined the annual prevalence as of December 31 of a given year of PWH with LTO among all ART-experienced PWH in care, defined as having had a clinical visit in that year, regardless of HIV RNA level (viral load). Given the approval of new ARV drugs over time within all classes and the introduction of a new ARV class (i.e. INSTI), an individual may contribute to the prevalence of LTO in one calendar year and be classified as non-LTO the following year when a new active drug becomes available.

We used multivariable Cox proportional hazards models to examine time from study entry (baseline) to first occurrence of LTO. The primary variable of interest was entry year in 3-year calendar periods. Other variables were measured as of baseline and included age, sex, race/ethnicity, CNICS site, lowest CD4 cell count, maximum HIV viral load, ART naïve at CNICS entry, and mono- dual-NRTI treatment prior to ART initiation. We used multiple imputation with chained equations to address missing lowest CD4 cell count and maximum viral load values. Participants were followed from study entry until incident LTO, loss to follow-up (12 months without a clinic visit) or administrative censoring (December 31, 2017), whichever came first.

In order to determine whether PWH who were ever classified as having LTO achieved viral suppression over time, we calculated the annual percentage of undetectable HIV viral load (<400 copies/mL) tests stratified by LTO status, such that once designated LTO a person remained classified as LTO going forward. We also accounted for loss to follow-up by incorporating inverse probability of censoring weights. In addition, we examined the number of ARV drugs received and the distribution of ARV drug resistance for the study population at the end of follow up by LTO status.

Sensitivity Analyses

While genotypic tests likely capture the majority of PWH who have developed any drug resistance, it is possible that tests were not performed in all instances where resistance had occurred. Previous work has shown that the degree of this type of under-ascertainment is low.[38] To address this potential bias, we conducted a sensitivity analysis using multiple imputation where LTO status was imputed for PWH without genotypic resistance testing who experienced virologic failure (defined as a single HIV viral load >400 copies/mL on ART) followed by any ARV switch within 3 months. We also conducted a sensitivity

analysis classifying a given drug with potential low-level resistance (<15 Stanford score) as active.[36]

In addition, we evaluated the predictive value of virologic failure and ARV treatment history, as used in prior studies that lacked genotypic resistance data, to identify PWH with LTO.[24, 30, 39, 40] We divided our data into a training set used to develop the LTO prediction model, which included 6 of the 7 CNICS sites, and a test set, which included the remaining CNICS site, to evaluate how well the model predicts the outcome. We used a Bayesian Model Averaging[41, 42] approach to identify the optimal model for predicting LTO in 2016 in the development training set of PWH and evaluated potential predictors as of December 31, 2016 including age, sex, race/ethnicity, study entry year, lowest and latest CD4, latest viral load, number of ARV drugs and classes received, and number of virologic failures (defined as a single HIV viral load >400 copies/mL on ART) with any ARV switch within 3 months. We also examined alternative definitions for virologic failure requiring 2 sequential viral loads >400 and >1000 copies/mL respectively followed by any ARV switch within 3 months. Variables with >50% chance of being in the best fitting model were included in a logistic prediction model to estimate their association with risk of LTO in the training set. We assessed the performance of this prediction model via the area under the curve (AUC) of the receiver operating characteristics curve in the test set. We examined the ability of virologic failure with ARV switch as well as the number of ARV drugs received to accurately identify PWH with LTO among participants in the test set. Statistical models were fit using Stata version 14 (Stata-Corp).

Results

There were 27,133 ART-experienced PWH in care between 2000-2017. Genotypic resistance testing was performed after ART initiation in 8,961 PWH, averaging 2.0 tests per individual, totaling 17,803 genotypic tests. The number of ART-experienced PWH in care in a given year increased annually from 3,941 in 2000 to over 13,500 in 2017; half of the entire study population was in care at the end of the 18-year study period. As shown in Table 1, 916 PWH were classified as ever having LTO, the majority of whom were male (85%), white (49%), men who had sex with men as a risk factor for HIV acquisition (54%), with median lowest CD4 71 (interquartile range [IQR] 15 - 182) cells/mm^3, median age 41 years at study entry, and median follow up 4 years (IQR 2 - 7). Almost half (45%) had received mono- or dual-NRTI treatment prior to initiation of ART.

As shown in Figure 1, the annual prevalence of PWH with LTO was 5.2-7.5% in 2000-2006 (514 of 6,857 in care in 2004), declined significantly to 1.8% in 2007 (151 of 8438 in care in 2007), and decreased to less than 1% in 2012 (107 of 13,350 in care in 2014) through 2017.

In multivariable analysis, PWH entering the study in 2009-2011 had an 80% lower risk of LTO compared with those entering in 2006-2008 (aHR 0.20; 95% CI: 0.09—0.42), and risk of LTO remained significantly lower in all subsequent calendar periods (Table 2). Lower baseline CD4 count and higher baseline maximum viral load were significantly associated with greater risk of LTO (aHR per 100 higher CD4 cells/mm^3 0.82; 95% CI: 0.78—0.87, aHR per 10-fold higher HIV viral load copies/mL 1.37; 95% CI: 1.26—1.49) as were

increasing age and male sex (aHR per 10 additional years 1.13; 95% CI: 1.05—1.22, aHR female sex 0.72; 95% CI: 0.59—0.87). Participants who had previously received treatment with mono- or dual-NRTIs were more than twice as likely to have LTO compared with those who had not (aHR 2.47; 95% CI: 2.14—2.83).

On average, 90% of PWH in care in a given year had at least one HIV viral load test in that year, including 92% of PWH with LTO, throughout the study period. As shown in Figure 2, fewer than 30% of HIV viral load tests among persons with LTO were undetectable in 2001 compared with more than 50% of tests among PWH who did not have LTO. The proportion of undetectable viral load tests among PWH ever classified as having LTO increased to over 80% in 2011 comparable to persons who never had LTO. Results with and without accounting for loss to follow-up did not differ.

At the end of follow up, PWH with LTO had received twice the number of ARV drugs as PWH who never had LTO (median 11 [IQR 9-13] versus 5 [3-7]) (Table 3). Further, among persons with any ARV drug resistance, PWH with LTO were resistant to 3 times the number of ARV drugs compared to PWH who never had LTO (median 16 [IQR 13-19] versus 5 [3-8]). Among all PWH, as well as those with LTO, the most common ARV resistance was to drugs in the NRTI and NNRTI classes. Notably, 54% of PWH with LTO had no active NNRTIs and no more than 1 NRTI drug available at some point in time.

Results of sensitivity analyses imputing LTO for PWH without genotypic resistance testing who experienced virologic failure and when scoring inactive drugs as ≥15 points did not differ from the main analysis (data not shown). In the Bayesian Model Averaging approaches to evaluate the value of ARV treatment history and virologic failure to predict LTO status, the only significant predictor of LTO in the best fitting model in the training set was the number of ARV drugs received and this was associated with an increased risk of LTO of nearly 70% per additional drug (odds ratio [OR] per drug 1.68; 95% CI: 1.58—1.78). However, when the model was evaluated in the test set, the number of ARV drugs received did not predict LTO status despite excellent model fit (AUC 0.92; 95% CI: 0.86—0.98). Compared with LTO defined by genotypic resistance, identifying potential LTO by receipt of ≥14 ARV drugs had 42% sensitivity, 99% specificity, and a positive predictive value (PPV) of 20%, while receipt of ≥9 ARV drugs had 68% sensitivity, 92% specificity, and a PPV of 5%. Furthermore, compared with LTO defined by genotypic resistance, potential LTO identified by virologic failure with ARV switch had 29% sensitivity, 83% specificity, and a PPV of only 1%. The sensitivity and PPV were also very low for alternative definitions of virologic failure at 21-22% sensitivity and 2% specificity respectively.

Discussion

In this large multicenter study of over 27,000 ART-experienced PWH in care spanning nearly two decades, the prevalence of PWH with LTO declined significantly from 7.5% in 2004 to <2% in 2007 after the introduction of a new ARV class, and since 2012 has remained <1% throughout the current ART era. The availability of new drugs in all ARV classes (i.e. NRTI, NNRTI, PI, INSTI) contributed to the decreasing prevalence of LTO in

PWH throughout the study period. To our knowledge, this study is the first to report the prevalence of PWH with LTO in the most recent time period utilizing longitudinal genotypic resistance data. After accounting for population differences, by 2009 PWH were 80% less likely to have LTO than in previous periods. Most importantly, over the past decade the proportion of PWH in the cohort who ever had LTO and subsequently achieved viral suppression increased dramatically to greater than 80%, which was equivalent to persons who never had LTO. This was likely due to the availability of the INSTI class and NNRTIs and PIs active against resistant HIV variants.[43] These results support growing evidence of the effectiveness of contemporary ART regimens in achieving virologic control in treatment experienced PWH.[22–24]

As expected, PWH with lower CD4 and higher HIV viral load, older persons, and those previously treated with mono- or dual-NRTIs were significantly more likely to have LTO. We also found that resistance in the NRTI and NNRTI classes was far more common than in the PI class. Over half of PWH with LTO had no more than 1 NRTI and no active NNRTIs at some time, highlighting treatment challenges posed by limited availability of drugs in these classes needed to construct active 3-drug regimens for HTE PWH. Thus, the historical focus on HTE defined as PWH with triple class resistance did not adequately capture the clinical significance of reverse transcriptase inhibitor resistance in limiting treatment options.[6, 18, 19, 44, 45] Treatment options may be further limited for some patients due to drug intolerance or drug-drug interactions, which were not evaluated in our study.

Studies employing approaches to identify HTE PWH with LTO based on virologic failure or number of prior ARV drug switches, common surrogates for genotypic resistance, are limited by incomplete ARV drug history and lack of information on treatment adherence.[11] We examined the performance of alternative measures of HTE PWH with LTO using three definitions of virologic failure. Irrespective of the definition, virologic failure with ARV switch failed to accurately identify PWH with LTO, but rather resulted in a large proportion of false positive cases as demonstrated by poor PPV. Similarly, the number of ARV drugs received failed to identify PWH with LTO due in part to the low prevalence of PWH with LTO in the contemporary ART era. These findings demonstrate that alternative approaches to identify PWH with LTO in the absence of genotypic resistance data, may have limited clinical utility.

Accurately capturing an individual's resistance profile including archived resistance requires cumulative genotypic test data.[38] Thus prevalence estimates based on the most recent genotypic test[17, 18, 46–48] or in the setting of limited study follow-up[49] can underestimate true prevalence of PWH with LTO. Studies that are restricted to PWH who had resistance testing are known to overestimate prevalence because they examine a select subgroup not representative of the population of PWH on ART in clinical care.[16, 27] Furthermore, analyses based on the number of ARV drugs to which a PWH is resistant rather than how many active drugs they have available, fail to account for decreasing prevalence of LTO as new drugs are introduced. As new treatment approaches including dual drug regimens are utilized, the definition of LTO must continue to evolve while remaining clinically relevant to providers treating HTE PWH.

Strengths of our large multicenter study include comprehensive clinical data on over 27,000 ART-experienced PWH in routine clinical care across the US with extensive follow-up and robust cumulative genotypic resistance data throughout the 18-year study period that includes a decade of INSTI use. Results of sensitivity analyses imputing LTO status suggest lack of genotypic resistance testing in our cohort was not a factor. Whereas previous studies reported variable outcomes with regard to virologic control,[14, 28, 29, 50, 51] we show unequivocally that PWH with LTO have benefitted from the introduction of modern, potent ARV drugs in all classes and have been virally suppressed over the past decade to the same extent as persons who never had LTO. The geographic, racial/ethnic, and clinical diversity of our cohort greatly strengthens the generalizability of our findings to PWH in care in the US.

Results from this large and diverse HIV-infected population demonstrate a dramatic decline in PWH with LTO and a marked increase in virologic control with the introduction of more potent ARV drugs and classes throughout the contemporary ART era. In addition to early and sustained access to ART, new treatment options will be important to support continued improvement in HIV outcomes and prevention of HIV transmission.[1, 3, 52]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

Sources of Support: This project received support from ViiV Healthcare and NIH including CNICS (NIAID grant R24AI067039), and CFARs at the University of Alabama at Birmingham (P30AI027767), University of Washington (P30AI027757), University of California San Diego (P30AI036214), University of California San Francisco (P30AI027763), Case Western Reserve University (P30AI036219), Johns Hopkins University (P30AI094189, U01DA036935), Fenway Health/Harvard (P30AI060354), and University of North Carolina Chapel Hill (P30AI50410). No funders had access to primary data.

Conflicts of Interest:

EFE has received research support to UAB on her behalf from the Gilead HIV Research Scholarship and ViiV Healthcare. MYK has received funding to her institution from ViiV Healthcare and Gilead Sciences. JJE is an ad hoc consultant to Merck, Gilead Sciences, Janssen and ViiV Healthcare, and the University of North Carolina receives funding for clinical trials from Gilead, Janssen and ViiV Healthcare for which he is the site principal investigator. BR has received honoraria from Gilead Sciences and ViiV Healthcare that are not related to his participation in this manuscript. KHM has received unrestricted research grants from Gilead Sciences and Merck to study antiretrovirals for prevention and from Janssen to study HIV vaccines and is on Scientific Advisory Boards for Gilead and Merck. CG is an employee of ViiV Healthcare, sponsor of this study, and owns stock in GSK, parent company of ViiV Healthcare. MSS has received grant support paid to his institution from ViiV Healthcare and Gilead Sciences. HMC has received grant support paid to her institution from ViiV Healthcare. KLB, RMN, JACD, TADM, RDM, EG, and MMK have no conflicts of interest to report.

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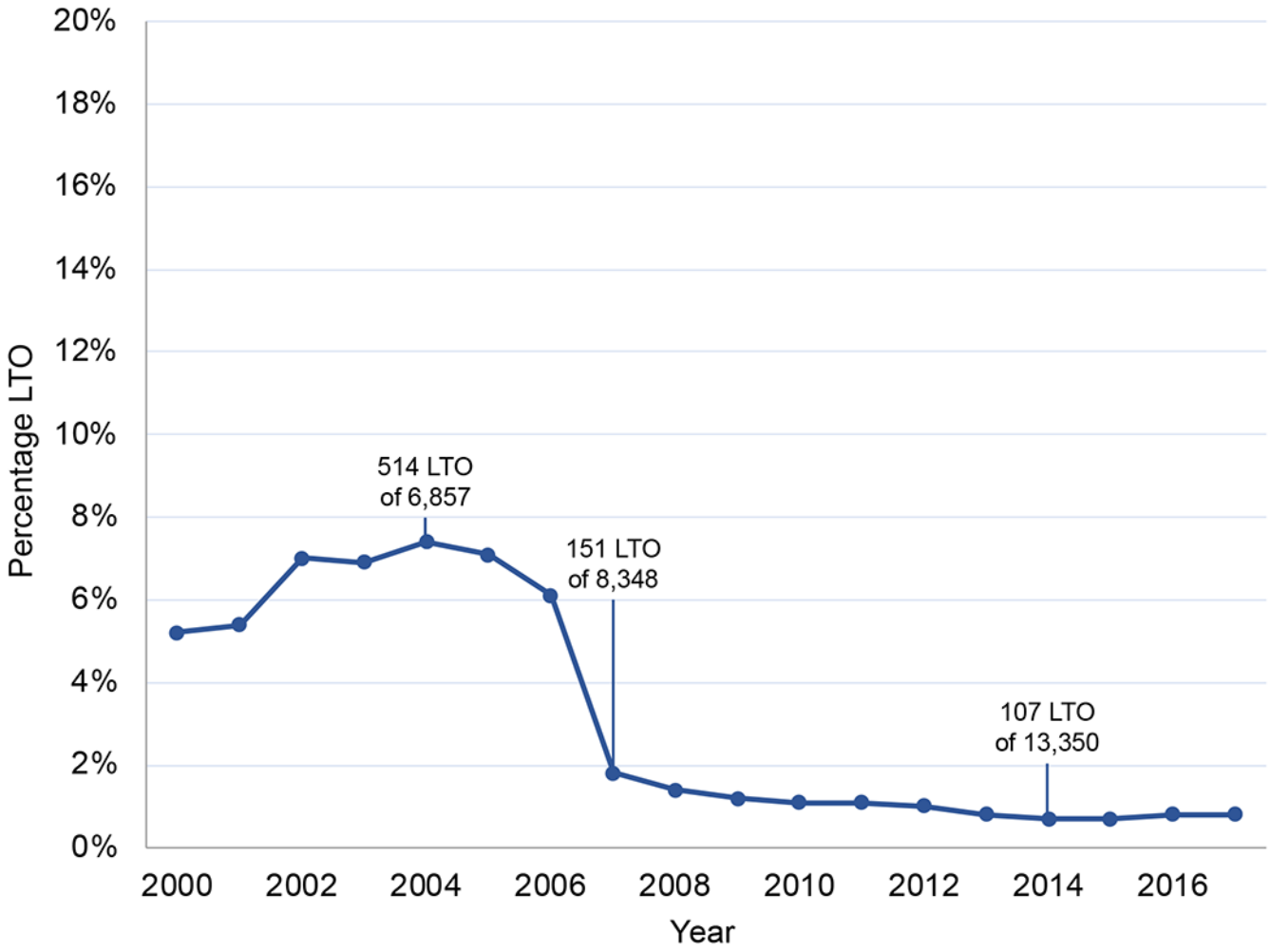

Figure 1.
Annual prevalence of PWH with limited treatment options (LTO) among ART-experienced persons in care by year (2000–2017)

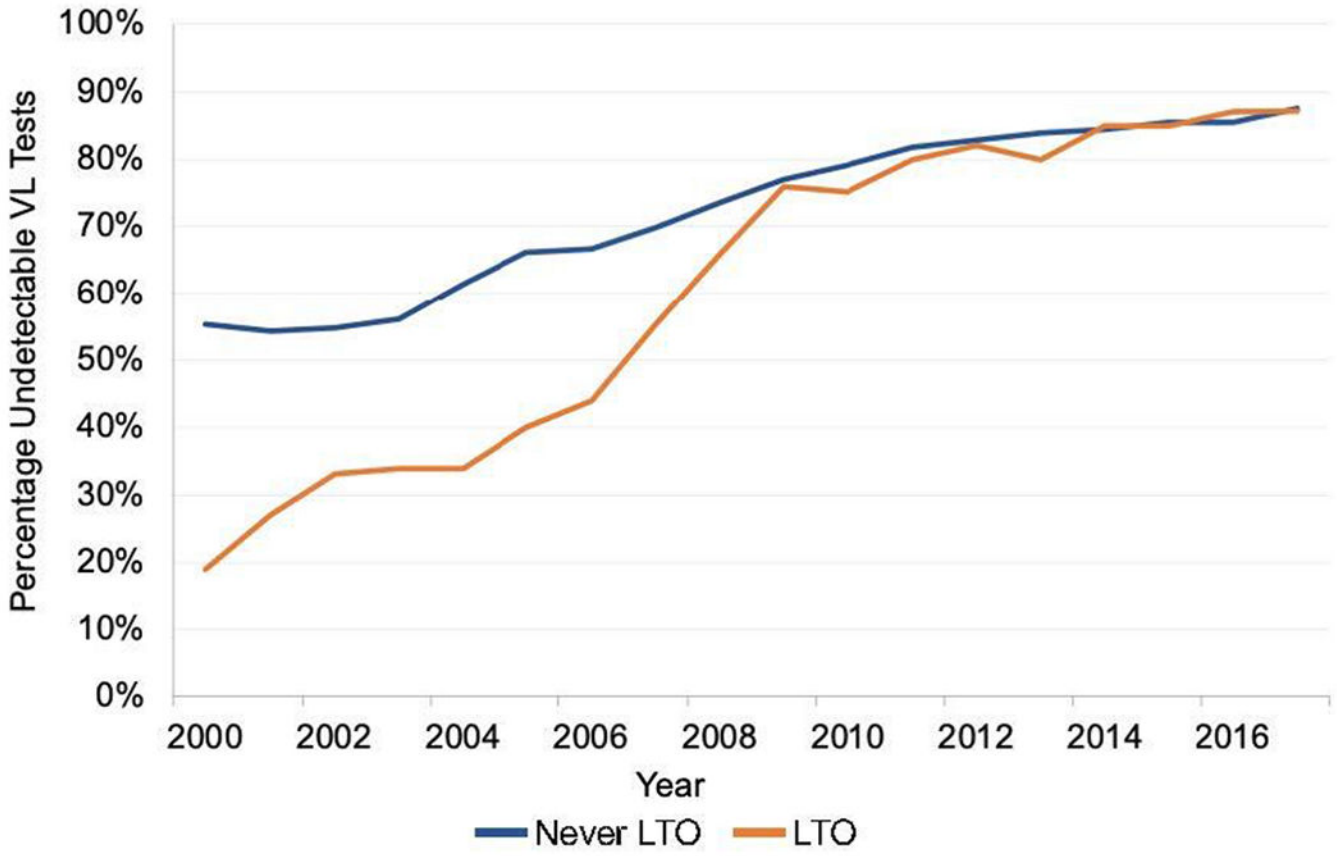

Figure 2.

Percentage of undetectable HIV viral load tests by year among antiretroviral-experienced PWH by limited treatment option (LTO) status* (2000-2017)

*Once designated LTO, a person remained classified as LTO going forward in this analysis, which accounted for loss to follow-up using inverse probability of censoring weights

Table 1.

Distribution of demographic and clinical characteristics among antiretroviral therapy experienced PWH by limited treatment options (LTO) status, 2000-2017

Variable	Total N = 27,133	Never LTO N = 26,217	Ever LTO N = 916
Age Median, IQR	40 [33-47]	40 [33-47]	41 [36-46]
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%)
Study entry year			
2000-2002	6284 (23%)	5698 (22%)	586 (64%)
2003-2005	4461 (16%)	4204 (16%)	257 (28%)
2006-2008	4060 (15%)	4012 (15%)	48 (5%)
2009-2011	4495 (17%)	4486 (17%)	9 (1%)
2012-2014	4774 (18%)	4764 (18%)	10 (1%)
2015-2017	3059 (11%)	3053 (12%)	6 (1%)
Median study entry year	2008	2008	2001
IQR	[2003-2012]	[2003-2012]	[2000-2003]
Lowest CD4 cells/mm^3 Median, IQR	234 [82-394]	240 [88-401]	71 [15-182]
Maximum viral load copies/mL Median, IQR	56255 [5,310-227,500]	53759 [4,729-218,000]	191989 [51,234-546,223]
ART naïve at CNICS entry	11830 (44%)	11558 (44%)	272 (30%)
Prior mono- dual-NRTI treatment	3971 (15%)	3560 (14%)	411 (45%)

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

Table 2.

Adjusted hazard ratios for PWH with limited treatment options according to calendar period and baseline demographic and clinical characteristics, N=27,133*

Variable	aHR†	P-value	95% CI	
Age (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	0.5	1.19
Study 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
Lowest CD4 (per 100 cells/mm^3)	0.82	<0.001	0.78	0.87
Maximum viral load (per 10-fold increase copies/ml)	1.37	<0.001	1.26	1.49
ART naïve at CNICS entry	0.34	<0.001	0.29	0.40
Prior mono- dual-NRTI treatment	2.47	<0.001	2.14	2.83

*877 events due to censoring;

†aHR – adjusted hazard ratio (model adjusted for all variables in table and site);

ART– antiretroviral therapy; CI –confidence interval; NRTI – nucleoside reverse transcriptase inhibitor.

Table 3.

Distribution of ARVs received and ARV resistance among ART-experienced PWH at the end of follow up by limited treatment options (LTO) status

Variable	Total N = 27,133	Never LTO N = 26,217	Ever LTO 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 NNRT	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 with most 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; IQR – interquartile range; INSTI – integrase inhibitor; NRTI – nucleoside reverse transcriptase inhibitor; NNRTI – non-nucleoside reverse transcriptase inhibitor; PI – protease inhibitor