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BRIEF REPORT

Current Antiretroviral Treatment Among People With Human Immunodeficiency Virus in the United States: Findings from the Centers for AIDS Research Network of Integrated Clinic Systems Cohort

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Among 14 049 people with human immunodeficiency virus in care in 2019–2020, 96% were treated with antiretroviral therapy (ART). Current antiretroviral treatment patterns highlight high uptake of guideline-recommended ART regimens including second-generation integrase strand transfer inhibitors (dolutegravir and bictegravir) and tenofovir alafenamide, especially in antiretroviral-naive individuals initiating ART.

Keywords. ART utilization; ART treatment trends; ART guidelines; integrase inhibitor; tenofovir alafenamide.

Antiretroviral therapy (ART) has rapidly evolved and significantly improved outcomes in people with human immunodeficiency virus (HIV) (PWH). Early fixed-drug combinations and single-tablet regimens (STRs), such as efavirenz–tenofovir disoproxil fumarate (TDF)–emtricitabine (FTC) [1], greatly simplified administration. Historically, antiretroviral (ARV) resistance mutations in heavily treatment-experienced PWH limited drugs available to construct active regimens, but the prevalence of PWH with limited treatment options in the United States declined dramatically to <2% after the introduction of integrase strand transfer inhibitors (INSTIs) with approval of raltegravir in 2007 [2]. Second-generation INSTIs (dolutegravir [DTG] and bictegravir [BIC]) with a higher barrier to resistance have further improved virologic outcomes [1]. Tenofovir alafenamide (TAF), a newer alternative prodrug to TDF with fewer renal and bone adverse effects, was introduced in 2015 [3]. More recent evidence suggests that some 2-drug regimens may be effective under certain circumstances [1, 4]. These improvements have advanced treatment guidelines as contemporary ART has become more effective, easier to take, and less toxic.

Previous studies evaluating ARV treatment patterns were limited to earlier time periods [5–9]. Little is known about current ART use and uptake of newer agents since the introduction of second-generation INSTIs. We evaluated current ARV treatment (2019–2020) and trends in ART (2000–2020) among PWH in care across the United States.

METHODS

The Centers for AIDS Research Network of Integrated Clinic Systems (CNICS) is a prospective observational cohort study of adult PWH in routine care at academic institutions across the United States. Patient-reported outcome measures and comprehensive clinical data, including diagnoses, laboratory results, and medications, collected through electronic medical records and institutional data systems, undergo rigorous quality assessment and are harmonized in a central repository that is updated quarterly [10]. CNICS routinely verifies ART from pharmacy systems through medical record review. The study cohort included all PWH in care, defined as those who attended ≥1 in-person or virtual HIV primary care visit between 1 January 2000 and 30 November 2020 at 7 CNICS sites: Case Western Reserve University; Fenway Community Health Center, affiliated with Harvard University; Johns Hopkins University; University of Alabama at Birmingham; University of California, San Diego; University of North Carolina at Chapel Hill; and University of Washington, Seattle. Institutional review boards at each site approved the CNICS study protocol.

In the primary analysis, we evaluated current ART among all PWH in care, defined as the latest multidrug regimen in 2019–2020 including ≥1 drug from the following core classes: nonnucleoside reverse-transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), or INSTIs. We also examined ARV treatment among the subset of ARV-naive PWH who initiated ART in 2019–2020. In addition, we conducted a serial cross-sectional analysis at the cohort level to evaluate trends in ART among PWH in care between 2000 and 2020, defined as the latest

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multidrug regimen in a given year among those with ≥1 HIV primary care visit during that year. Piecewise linear regression was used to assess trends in INSTIs. Demographic data, including HIV risk factors, were collected at cohort enrollment. Substance use and mental health data were obtained from medical records and the latest patient-reported outcome survey in 2019–2020, which is completed every 4–6 months during HIV primary care visits. Statistical analyses were completed with Stata Statistical Software (release 15; StataCorp).

RESULTS

Among 14 049 PWH in care in 2019–2020, 96% received ARV treatment (N = 13 434). They had a median age of 51 years and were 80% male, 45% black, and 39% white; 56% reported being men who have sex with men, as an HIV risk factor (Supplementary Table 1). While 28% reported current use of methamphetamine, cocaine/crack, or illicit opioids or heroin and 51% had depression or anxiety, the distribution of core ARV classes did not differ by mental health disorders, substance use, demographics, or HIV risk factors (Supplementary Table 1). Compared with all PWH in care in 2019–2020, the 293 ARV-naive PWH who initiated ART in 2019–2020 were younger (median age, 33 years) and more likely to be nonwhite (74% vs 61%, respectively).

Current ARV regimens were predominantly anchored by INSTIs (74% overall among PWH in 2019–2020, 96% of the subset of ARV-naive PWH initiating ART in 2019–2020 [hereafter "ARV-naive"]) and included TAF (overall, 73%; ARV-naive, 94%) (Table 1). The most common INSTI was BIC (overall, 48%; ARV-naive, 87%), which, together with DTG, accounted for 81% of INSTI-based regimens overall and 98% of those initiated in ARV-naive PWH. Among PWH on DTG-based regimens (overall, 33%; ARV-naive, 11%), half took DTG as part of a multitablet regimen (overall, 47%; ARV-naive, 58%). Few PWH were treated with first-generation INSTIs (median start year, 2015–2017), including raltegravir (overall, 2%; ARV naive, 1%) and elvitegravir (EVG) in the STRs EVG/c (EVG with cobicistat)/TDF/FTC and EVG/c/TAF/FTC (overall, 18%; ARV-naive, 2%). Among nucleos(t)ide reverse-transcriptase

Table 1. Current Antiretroviral (ARV) Treatment (ART) by Core Class and Selected Regimens Among People with Human Immunodeficiency Virus in 2019–2020 and the Subset of ARV-Naïve Individuals Initiating ART[a]

ARV Treatment by Core Class and Selected Regimens	Overall (N = 13 434), %	Overall Start Year Median (IQR)	Subset of ARV-Naive Initiating ART in 2019–2020 (N = 293), %
INSTI-based regimen[b]	**74% (n = 9971)**	**2018 (2016–2019)**	**96% (n = 280)**
BIC/TAF/FTC (Biktarvy)[c]	48%	2019 (2018–2019)	87%
Dolutegravir[c]	33%	2016 (2015–2018)	11%
DTG/ABC/3TC (Triumeq)[d]	49%	2016 (2015–2017)	*32%*
DTG/3TC (Dovato)[d]	4%	2019 (2019–2020)	*10%*
EVG/c/TAF/FTC (Genvoya)[c]	17%	2017 (2016–2018)	2%
EVG/c/TDF/FTC (Stribild)[c]	1%	2015 (2014–2016)	0%
Raltegravir[c]	2%	2015 (2012–2018)	1%
PI-based regimen[b]	**6% (n = 824)**	**2016 (2013–2018)**	**1% (n = 4)**
Darunavir[c]	88%	2015 (2012–2018)	100%
DRV/c/TAF/FTC (Symtuza)[d]	*48%*	*2019 (2018–2019)*	*75%*
Atazanavir[c]	12%	2010 (2005–2017)	0%
NNRTI-based regimen[b]	**8% (n = 1137)**	**2015 (2012–2017)**	**1% (n = 3)**
Doravirine[c]	2%	2020 (2019–2020)	0%
RPV/TAF/FTC (Odefsey)[c]	67%	2017 (2016–2018)	100%
RPV/TDF/FTC (Complera)[c]	6%	2013 (2013–2014)	0%
EFV/TDF/FTC (Atripla)[c]	15%	2009 (2005–2013)	0%
Multicore regimen[b]	**11% (n = 1502)**	**2017 (2015–2019)**	**2% (n = 6)**
INSTI and other core drug[c]	96%	2017 (2015–2019)	100%
DTG and DRV[d]	*40%*	*2017 (2015–2019)*	*33%*
DTG/RPV (Juluca)[d]	*15%*	*2019 (2018–2019)*	*17%*
NRTI in combination with any core agent			
TAF[b]	73%	2018 (2016–2019)	94%
ABC[b]	15%	2016 (2015–2017)	4%
TDF[b]	7%	2015 (2012–2017)	1%

Abbreviations: 3TC, lamivudine; ABC, abacavir; ART, ARV treatment; ARV, antiretroviral; BIC, bictegravir; DRV, darunavir; DRV/c, darunavir with cobicistat; DTG, dolutegravir; EVG, elvitegravir; EFV, efavirenz; FTC, emtricitabine; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleos(t)ide reverse-transcriptase inhibitor; PI, protease inhibitor; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a]Drugs and regimens within a core class represent selected regimens of interest and may not add to 100%; totals more than 100% are due to rounding.

[b]Bold core class rows and NRTI drug row percentages are based on corresponding column totals (Overall N = 13 434 or ARV-Naive N = 293).

[c]Drug or regimen row percentages are based on the bold core class total immediately above (eg, DRV is 88% of the 824 people with HIV in PI-based regimens).

[d]Italicized regimen row percentages are a subset of the parent drug total immediately above (eg, DTG/3TC is 4% of the DTG total).

inhibitors, treatment with TDF (overall, 7%; ARV-naive, 1%) and abacavir (overall, 15%; ARV-naive, 4%) in combination with any core agent was limited compared with TAF.

Among all PWH in 2019–2020, 6% of current regimens were PI based (99% boosted), and 8% were NNRTI based (Table 1), while only 1% of ARV-naive PWH initiated a PI-based or NNRTI-based regimen. Most PI-based regimens were anchored by darunavir (88%), with a median start year of 2015. Most NNRTI-based regimens were anchored by rilpivirine (RPV; 73%) as STRs (98%) started between 2009 and 2017. Few PWH were treated with 2-drug regimens, multicore regimens, or regimens not considered first line in guidelines (Table 1).

Over the last 20 years, the proportion of PWH receiving ART increased from 68% in 2000 to >90% since 2012. Treatment with INSTI-based regimens increased significantly after the introduction of DTG in 2013, at a rate of 10% per year in 2013–2020, compared with 3% per year in 2007–2013 ($P < .001$), with corresponding declines in the use of NNRTI- and PI-based regimens (Supplementary Figure 1*A*). Treatment with TAF increased sharply after the introduction of TAF in 2015 (Supplementary Figure 1*B*). The proportion of PWH treated with STRs increased each year, to 71% in 2020 (Supplementary Figure 1*C*), but STRs anchored by drugs with a lower barrier to resistance, such as EVG and RPV, plateaued in 2018, while BIC/TAF/FTC increased in uptake to become the most common STR in 2020 (Supplementary Figures 1*C*, 1*D*, and 2*A*).

DISCUSSION

Advances in ART including drugs with higher barrier to resistance, less toxicity, simpler administration, and new treatment paradigms have significantly improved HIV treatment over the last 20 years. Among >14 000 PWH in routine care in 2019–2020, 96% received ART, the majority of whom were treated with an INSTI-based regimen anchored by BIC or DTG. Treatment with TAF rose substantially after its introduction in 2015, with TAF replacing TDF as the predominant form of tenofovir. Few ARV-naive individuals were started on regimens not recommended as first-line treatment, and treatment with 2-drug regimens was limited despite growing evidence of efficacy [1, 4]. While overall STR use increased, few PWH continued to take STRs anchored by drugs with lower barrier to resistance, such as EVG and RPV started in earlier calendar periods. The most common STR in 2020 was BIC/TAF/FTC. To our knowledge, the current study reports the latest ART patterns in the United States and provides much-needed information on the current use of second-generation INSTIs and newer ARV treatment in accordance with ART treatment guidelines.

The introduction of INSTIs led to a substantial decrease in PWH with limited treatment options [2]. Newer INSTIs with a higher barrier to resistance (DTG and BIC) improved virologic suppression, further simplified treatment, and facilitated rapid initiation of ART [1]. Before DTG was introduced in an STR, it was commonly used in multitablet regimens, likely owing to a greater barrier to HIV resistance than available STRs anchored by agents with a lower barrier to resistance (eg, NNRTIs and first-generation INSTIs). Our findings are consistent with earlier reports of decreasing use of NNRTI-based regimens [5, 6, 9]. Decreased treatment with boosted PIs may be due to greater drug-drug interactions and adverse effects compared with INSTIs. Lags in guideline uptake, patient or provider preferences, insurance coverage, and concerns regarding adherence may contribute to continued use of older regimens [11]. Patterns of ARV treatment will continue to evolve as we gain greater understanding of adverse effects with prolonged and expanded use of newer agents, such as the metabolic and weight effects of second-generation INSTIs and TAF [1].

Strengths of our study include up-to-date, comprehensive data on ARV treatment in a large and diverse cohort of PWH in routine care with demographic and clinical characteristics, similar to the overall population of PWH in the United States [12]. While results may not necessarily be generalizable to all clinical settings, CNICS includes 8 geographically distributed HIV clinics across the United States.

Our findings regarding current ARV treatment highlight the high uptake of second-generation INSTIs, TAF, and guideline-recommended regimens, especially among ARV-naive individuals initiating ART. As ART continues to evolve, continued study of ARV treatment patterns will be needed, regarding the role of new drugs and implementation of guidelines to improve clinical outcomes for all PWH.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. K. C. is a member of the medical advisory board for Gilead Sciences and reports grants or contracts from Gilead Sciences to their institution, outside the submitted work. G. A. B. has received research grant support from Merck Foundation and Eli Lilly, consulting fees from Med IQ, and payment or honoraria from StateServ and the University of Kentucky. J. K. reports a past relationship with the American Board of Internal Medicine, as an infectious disease specialty board member. J. J. E. reports contracts to their institution from ViiV Healthcare, Gilead Sciences, and Janssen; is an ad hoc consultant to Merck, Gilead Sciences, ViiV, and Janssen; and is an investigator for clinical trials at the University of North Carolina, which receives funding from Gilead, ViiV, and Janssen. E. R. C. has received unrestricted research grants paid to UC Reagents from Gilead Sciences for an unrelated hepatitis C virus project and from Merck

Sharp & Dohme for an unrelated project and has received payment or honoraria from Gilead Science. M. S. S. reports money paid to their institution from ViiV and Gilead for clinical trials that are now closed, outside the submitted work; reports participation on the data science monitoring board for the I-SPY COVID trial; and reports serving on the board of directors for International Antiviral Society-USA. H. M. C. has received research grant support from ViiV and the Agency for Healthcare Research and Quality paid to their institution, outside the submitted work, and reports participation on the National Institutes of Health Office of AIDS Research Advisory Council.

All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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