Characterization of Heavily Treatment-Experienced People With HIV and Impact on Health Care Resource Utilization in US Commercial and Medicare Advantage Health Plans

Julie Priest,[1] Erin Hulbert,[2] Bruce L. Gilliam,[1] and Tanya Burton[2]

[1]ViiV Healthcare, Research Triangle Park, North Carolina, USA, and [2]OptumInsight, Boston, Massachusetts, USA

Background. This retrospective administrative claims study aimed to describe clinical characteristics, health care resource utilization (HCRU), and costs of people with HIV (PWH) in US commercial and Medicare Advantage health plans by antiretroviral treatment (ART) experience and CD4+ cell count.

Methods. Data from the national Optum Research Database between January 1, 2014, and March 31, 2018, for adult PWH continuously enrolled 6 months before and ≥12 months after the first ART identified (follow-up) were summarized by treatment (heavily treatment-experienced [HTE] with limited remaining ART options, treatment-experienced but not HTE [non-HTE], or treatment-naive starting a first antiretroviral regimen) and index CD4+ cell count (<200, 200–500, or >500 cells/mm^3).

Results. Compared with non-HTE (n = 7604) and treatment-naive PWH (n = 4357), HTE PWH (n = 2297) were older (53.5 vs 48.8 and 42.3 years), were more likely to have HIV-related emergency department visits (22.3% vs 12.4% and 18.6%) and inpatient stays (15.8% vs 7.1% and 10.3%), and had a higher mean (SD) daily pill burden (9.7 [7.7] vs 5.1 [5.9] and 3.6 [5.3] pills/d) and a higher mortality rate (5.9% vs 2.9% and 2.3%) during follow-up (all *P* < .001). More HTE (21.8%) and treatment-naive PWH (27.0%) had <200 CD4+ cells/mm^3 vs non-HTE PWH (8.0%; *P* < .001). All-cause and HIV-related costs were higher among HTE PWH in all CD4+ cell count strata and treatment-naive PWH with CD4+ cell counts <200 cells/mm^3 vs non-HTE PWH in all CD4+ cell count strata.

Conclusions. Improved support and clinical monitoring of HTE PWH are needed to prevent worsening outcomes and increased costs.

Keywords. antiretroviral therapy; CD4+ cell count.

Advancements in antiretroviral therapy (ART) have made significant improvements to the health of most people with HIV (PWH) [1], but HIV infection continues to represent a significant burden in the United States. The goals of HIV treatment are to achieve and maintain virologic suppression, restore and preserve immunologic function, reduce HIV-associated morbidity, and prevent disease progression [1]. A subset of PWH are heavily treatment-experienced (HTE), having experienced virologic failure on multiple different treatment regimens, and have limited remaining ART options because of multidrug resistance and intolerance to certain ART agents [1–5]. Treatment of HIV-1 in HTE PWH may be further complicated by factors such as advanced HIV disease with low CD4+ cell count (≤200 cells/mm^3), multiple comorbid medical conditions requiring concomitant medications, and treatment of or prophylaxis for opportunistic infections [1, 2, 5–7]. These individuals may be unable to achieve virologic suppression and are thus at risk of further disease progression and transmission of infection [1].

The risk of HIV disease progression and the likelihood of opportunistic infections are also increased among non-HTE PWH who have low CD4+ cell counts [1, 3, 8]. Delays in diagnosing HIV-1 infection can mean that CD4+ cell counts are already low before ART is started, resulting in a less favorable prognosis in individuals starting their first ART regimen [1].

Data on health care resource utilization (HCRU) and costs are important for health care policy decisions and can improve our understanding of the current and future needs of an aging population of PWH. Both HTE PWH and those with low CD4+ cell counts are likely to have high levels of HCRU and associated costs. Representative real-world databases offer an opportunity to assess HCRU and economic outcomes in large numbers of individuals. This retrospective cohort study used administrative claims for commercial and Medicare Advantage health plan enrollees with evidence of HIV-1 in the Optum Research Database

(ORD). The objectives of the study were to describe the clinical characteristics, HCRU, and costs of PWH according to their antiretroviral treatment experience and index CD4+ cell count.

METHODS

Study Design and Data Sources

This retrospective cohort study used administrative claims data from commercial and Medicare Advantage health plan enrollees with evidence of HIV-1 infection between July 1, 2013, and March 31, 2019, in the geographically diverse ORD (www.optum.com; Optum, Eden Prairie, MN, USA) [9]. The ORD comprises medical and pharmacy claims data (including linked enrollment) since 1993 on >70 million lives in the United States. Data were fully deidentified and Health Insurance Portability and Accountability Act compliant; therefore, institutional review board approval or a waiver of authorization was not required for this study.

Medical claims data included diagnosis codes recorded with the International Classification of Diseases, Ninth and/or Tenth Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) diagnosis codes; procedures recorded with ICD-9-CM and/or ICD-10-CM procedure codes; Current Procedural Terminology or Healthcare Common Procedure Coding System codes; site of service codes; provider specialty codes; revenue codes (for facilities); paid amounts; and other information. Pharmacy claims data included drug name, strength, and dosage form; fill date and number of days of supply; financial information; and deidentified patient and prescriber codes. These data allowed for longitudinal tracking of medication refill patterns and changes in medications. Socioeconomic characteristics generated by a combination of modeling, census data, and a variety of other individual-level and population-level data sources were linked to claims data for analysis. Race/ethnicity was imputed using commercial software (E-Tech, Ethnic Technologies LLC, South

Hackensack, NJ, USA). Mortality data came from the Social Security Administration, in combination with hospital discharge status and use of hospice services in claims.

Study Population

The study population included adult (aged ≥18 years in the index year) commercial and Medicare Advantage health plan enrollees with ≥1 nondiagnostic medical claim with a diagnosis code for HIV-1 (ICD-9-CM: 042, V08; ICD-10-CM: B20, Z21) during the study period (July 1, 2013, to March 31, 2019) and ≥1 pharmacy claim for an ART agent during the identification period (January 1, 2014, to March 31, 2018). Those with ≥1 nondiagnostic medical claim with a diagnosis code for HIV-2 at any time during the study period were excluded. Eligible PWH had to be continuously enrolled with medical and pharmacy benefits for 6 months before the index date (baseline) and at least 12 months after the index date, or until evidence of death (12-month fixed and variable follow-up). The index date was based on ART treatment claims during the identification period and was defined according to cohort assignment.

Three mutually exclusive treatment cohorts (HTE, treatment-experienced but not HTE [non-HTE], and treatment-naive) were defined following the criteria in Table 1. Criteria for the HTE cohort were taken from a recent study identifying HTE patients in a large administrative claims database [6] and were based on combination ART regimens typically reserved for PWH at advanced stages of disease based on clinical judgment. For PWH who had claims for ≥1 ART regimen meeting the HTE criteria during the identification period, the earliest regimen meeting the criteria was defined as the HTE index regimen and the index date was defined as the date of the first ART claim included in the HTE index regimen. The non-HTE and treatment-naive cohorts included PWH who had no claims for any ART regimen that met the HTE criteria during the

Table 1. Cohort Identification Criteria

Cohort	Criteria	Index Date
HTE	Any regimen claimed during the study period that is typically reserved for PWH with advanced disease, including: • Dolutegravir BID[a] • Darunavir BID • Enfuvirtide • Etravirine plus maraviroc or 1 of the preceding agents • ≥2 core ART agents[b] *plus* any other ART agent	Date of the first claim during the identification period for an ART agent included in the HTE index regimen[c]
Non-HTE	Any core ART agent[b] not meeting HTE criteria	Date of the first claim during the identification period for a core[b] or backbone[c] ART agent
Treatment naive	No baseline claims for ART agents during the 6-month baseline period (except emtricitabine/tenofovir alone)	

Abbreviations: ART, antiretroviral therapy; BID, twice daily; HTE, heavily treatment-experienced; PWH, people with HIV.

[a]Excluded if coadministered with the UGT1A/CYP3A inducers efavirenz, fosamprenavir/ritonavir, or rifampin.

[b]Core ART agents included those from the following classes: non-nucleoside reverse transcriptase inhibitors; protease, fusion, or entry inhibitors; integrase strand transfer inhibitors; or any combinations of these.

[c]Nucleoside/nucleotide reverse transcriptase inhibitors.

identification period. The index date for these cohorts was defined as the first claim for a core or backbone ART agent during the identification period (Table 1). During the 6-month baseline period before the index date, the non-HTE cohort had ≥1 pharmacy claim for an ART core or backbone agent other than emtricitabine/tenofovir. The treatment-naive cohort had only baseline pharmacy claims for emtricitabine/tenofovir (used for prevention or postexposure prophylaxis) or no claims for ART at all during the 6-month baseline.

Among the subset of individuals with laboratory results submitted to the ORD and a CD4+ cell count result recorded, 3 index CD4+ cell count strata were defined using the laboratory value that was the fewest days from the index date, with priority given to the value taken in the baseline period in the case of a tie (<200, 200–500, or >500 cells/mm^3).

Measures
Demographics, clinical characteristics, and all-cause and HIV-related HCRU and costs were assessed during the 6-month baseline and 12-month follow-up periods. AIDS-defining conditions (listed in Supplementary Table 1) were flagged if there was 1 nondiagnostic medical claim with a diagnosis code for the condition. Health care resource utilization and costs were calculated for ambulatory visits (office and outpatient), emergency department (ED) visits, and inpatient stays. HIV-related HCRU and costs included medical claims with diagnosis codes for HIV and AIDS–defining conditions. Costs were the sum of patient- and health plan–paid amounts and were adjusted using the annual 2018 medical care component of the Consumer Price Index [10].

Treatment pattern variables were measured during the 12-month follow-up period. Average daily pill burden was based on the number of fills and days' supply for all medications during the fixed 12-month follow-up period. All laboratory results for CD4+ cell counts during the study period and closest to the index date were noted. Mortality was assessed during total follow-up, to the earliest of death, end of continuous enrollment, or end of the study period.

Statistical Analysis
All study measures were summarized descriptively with means, SDs, and medians calculated for continuous variables and frequencies and percentages provided for categorical variables. Results were stratified by treatment cohort (HTE, non-HTE, or treatment-naive) and index CD4+ cell count (<200, 200–500, or >500 cells/mm^3). Differences between treatment cohorts were assessed using Pearson chi-square or 2-sample t tests, differences between CD4+ cell count strata were assessed using Pearson chi-square or F test/analysis of variance, and differences in mortality were assessed using the Kaplan-Meier log-rank test. A multivariable analysis was conducted, using a generalized linear model with a gamma distribution and log

link, to examine the impact of treatment cohort on all-cause and HIV-related costs. Baseline variables were chosen based on significance and/or clinical relevance.

RESULTS

Study Population and Baseline Characteristics
Among 14 258 individuals meeting the inclusion criteria, 2297 (16.1%) were HTE, 7604 (53.3%) were non-HTE, and 4357 (30.6%) were treatment-naive (Table 2). Based on data collected during the 6-month baseline period, compared with non-HTE PWH, HTE PWH were older and were more likely to be enrolled in Medicare, to have a low household income, and to have ≥1 AIDS-defining condition (particularly herpes simplex [4.4% vs 3.3%], encephalopathy [1.3% vs 0.4%], Kaposi's sarcoma [1.2% vs 0.5%], pneumonia [1.1% vs 0.5%], and esophageal candidiasis [0.9% vs 0.1%]) (Table 2; Supplementary Table 1). Prevalence of several common comorbidities was also higher in the HTE cohort compared with the non-HTE cohort, including cardiovascular disease (42.2% vs 27.3%), hypertension (36.0% vs 23.8%), central nervous system disorders (19.9% vs 14.3%), and diabetes (15.2% vs 8.5%) (Supplementary Table 1). The treatment-naive cohort had the lowest mean age at index date (42.3 years) and the greatest proportion of individuals with ≥1 AIDS-defining condition (11.7%) (Table 2).

A total of 5522 (38.7%) individuals had CD4+ cell count results at or close to the index date. Greater proportions of HTE (21.8%) and treatment-naive PWH (27.0%) had CD4+ cell counts <200 cells/mm^3 compared with non-HTE PWH (8.0%; P < .001) (Table 2; Supplementary Table 2). Individuals in the lowest CD4+ cell count strata (<200 cells/mm^3) were also more likely than those in the middle and high strata to be female, live in the South, be African American, have a low household income, and have ≥1 AIDS-defining condition (Supplementary Table 2). Individuals in the lowest CD4+ cell count strata were more likely than those in the middle and high strata to have common comorbidities, including cardiovascular disease (40.3% vs 29.9% and 29.0%, respectively), hypertension (31.9% vs 25.6% and 25.9%), and diabetes (11.9% vs 8.9% and 10.4%) (Supplementary Table 3).

Mortality During Follow-up
The mean (SD) follow-up observation time was 160.6 (80.5) weeks, 192.0 (80.6) weeks, and 124.4 (60.9) weeks in the HTE, non-HTE, and treatment-naive cohorts, respectively.

Mortality was higher in the HTE cohort (135 [5.9%]) than in the non-HTE and treatment-naive cohorts (218 [2.9%] and 99 [2.3%], respectively) (Supplementary Figure 1). Mortality was also higher in individuals in the <200 cells/mm^3 strata (63 [6.4%]) than in those in the middle and high CD4+ cell count strata (90 [2.3%] and 9 [1.4%], respectively).

Table 2. Baseline Demographics and Clinical Characteristics by Treatment Cohort (n = 14 258)

	HTE (n = 2297)	Non-HTE (n = 7604)	TN (n = 4357)	HTE vs Non-HTE P Value[a]	HTE vs TN P Value[a]
Demographic parameters at index date					
Age at index date, mean (SD), y	53.5 (10.4)	48.8 (11.1)	42.3 (13.1)	<.001	<.001
Age category, No. (%)				<.001	<.001
18–34 y	101 (4.4)	897 (11.8)	1439 (33.0)		
35–49 y	621 (27.0)	2959 (38.9)	1566 (35.9)		
50–64 y	1272 (55.4)	3184 (41.9)	1095 (25.1)		
≥65 y	303 (13.2)	564 (7.4)	257 (5.9)		
Sex, female, No. (%)	379 (16.5)	1096 (14.4)	700 (16.1)	.014	.648
Race/ethnicity, No. (%)				<.001	<.001
White	1140 (49.6)	4116 (54.1)	1595 (36.6)		
African American/Black	592 (25.8)	1855 (24.4)	1159 (26.6)		
Hispanic	265 (11.5)	1114 (14.7)	709 (16.3)		
Other/missing	300 (13.1)	519 (6.8)	894 (20.5)		
Geographic region, No. (%)				.040	<.001
Northeast	336 (14.6)	1151 (15.1)	540 (12.4)		
Midwest	313 (13.6)	1205 (15.8)	667 (15.3)		
South	1292 (56.3)	4037 (53.1)	2594 (59.5)		
West	356 (15.5)	1209 (15.9)	554 (12.7)		
Insurance type, No. (%)				<.001	<.001
Commercial	1391 (60.6)	6212 (81.7)	3804 (87.3)		
Medicare	906 (39.4)	1392 (18.3)	553 (12.7)		
Household income, No. (%)				<.001	<.001
Low (<$40 000)	549 (23.9)	1397 (18.4)	955 (21.9)		
Middle ($40 000–$124 999)	983 (42.8)	3979 (52.3)	1745 (40.1)		
High (≥$125 000)	329 (14.3)	1277 (16.8)	375 (8.6)		
Missing	436 (19.0)	951 (12.5)	1282 (29.4)		
Index year, No. (%)				<.001	<.001
2014	1443 (62.8)	7578 (99.7)	1181 (27.1)		
2015	244 (10.6)	13 (0.2)	1027 (23.6)		
2016	261 (11.4)	6 (0.1)	980 (22.5)		
2017	283 (12.3)	5 (0.1)	952 (21.8)		
2018	66 (2.9)	2 (<0.1)	217 (5.0)		
Index CD4+ cell count, N[b]	1117	2394	2011	<.001	Not calculated
<200 cells/mm^3, No. (%)	244 (21.8)	192 (8.0)	543 (27.0)		
200–500 cells/mm^3, No. (%)	789 (70.6)	1799 (75.1)	1303 (65.0)		
>500 cells/mm^3, No. (%)	84 (7.5)	403 (16.8)	165 (8.2)		
Parameters during the 6-mo pre-index baseline					
Any AIDS-defining conditions during baseline, No. (%)[c]	224 (9.8)	427 (5.6)	511 (11.7)	<.001	.014
All-cause HCRU, No. (%)					
≥1 ambulatory visit	2184 (95.1)	7217 (94.9)	4024 (92.4)	.744	<.001
≥1 ED visit	591 (25.7)	1291 (17.0)	1270 (29.2)	<.001	.003
≥1 inpatient stay	262 (11.4)	298 (3.9)	531 (12.2)	<.001	.350
All-cause HCRU count, mean (SD)					
Ambulatory visits	10.5 (14.3)	7.0 (10.1)	7.3 (8.8)	<.001	<.001
ED visits	0.7 (2.2)	0.5 (2.3)	0.7 (1.8)	<.001	.656
Inpatient stays	0.2 (0.6)	0.1 (0.3)	0.2 (0.5)	<.001	.355

Abbreviations: ED, emergency department; HCRU, health care resource utilization; HTE, heavily treatment-experienced; TN, treatment-naive.

[a]Pearson chi-square test was used for categorical measures; 2-sample t test was used for continuous measures (mean age).

[b]Among the subset of individuals with laboratory results submitted to the Optum Research Database. The index value was the laboratory value taken the fewest days from the index date, with priority given to the value taken in the baseline period in the case of a tie.

[c]AIDS-defining conditions were identified based on diagnostic codes.

Pill Burden During Follow-up

Mean (SD) daily pill burden for HTE PWH was double that of non-HTE and treatment-naive individuals: 9.7 (7.7) pills/d for all medications, 4.2 (2.5) pills/d for ART medications only, and 5.5 (7.0) pills/d for non-ART medications only among the HTE cohort vs 5.1 (5.9) and 3.6 (5.3) pills/d for all medications, 1.9 (1.5) and 1.2 (0.8) pills/d for ART medications only, and 3.2 (5.4) and 2.4 (5.2) pills/d for non-ART medications only among the non-HTE and treatment-naive cohorts, respectively (P < .001 for all comparisons vs HTE PWH).

AIDS-Defining Conditions During Follow-up

Among individuals with no AIDS-defining conditions during the baseline period, 9.4% of the HTE cohort developed 1 AIDS-defining condition during the follow-up period vs 5.4% of the non-HTE cohort ($P < .001$) and 7.2% of the treatment-naive cohort ($P = .003$).

Health Care Resource Utilization During Follow-up

During the 12-month follow-up period, in all treatment cohorts and CD4+ cell count strata, most PWH ($\geq$98%) had $\geq$1 all-cause ambulatory visit. The proportion of PWH who had $\geq$1 HIV-related ambulatory visit was lower for the treatment-naive cohort (94.0%) compared with the HTE cohorts (96.5%; $P < .001$). No differences in ambulatory visits were seen between CD4+ cell count strata. Differences between treatment cohorts and CD4+ cell count strata were more apparent for all-cause and HIV-related ED visits and inpatient stays (Figure 1). A higher proportion of the HTE cohort had all-cause (Figure 1A) and HIV-related (Figure 1B) ED visits and inpatient stays

compared with the other cohorts. Interestingly, proportions of all-cause and HIV-related ED visits and inpatient stays were also higher in the treatment-naive cohort than in the non-HTE cohort. Higher proportions of individuals in the <200 cells/mm^3 strata had all-cause (Figure 1C) and HIV-related (Figure 1D) ED visits and inpatient stays compared with those in the other CD4+ cell count strata. Most inpatient stays were HIV related.

Health Care Costs During Follow-up

Mean all-cause and HIV-related total health care costs (medical and pharmacy) for the 12-month follow-up period were higher for the HTE cohort than for the non-HTE and treatment-naive cohorts, overall and across all CD4+ cell count strata (Table 3, Figure 2; Supplementary Tables 4 and 5). Medical costs were highest for the HTE cohort in all categories for both all-cause and HIV-related costs, with the greatest differences between treatment cohorts seen in ambulatory and inpatient costs (Supplementary Tables 4 and 5). CD4+ cell
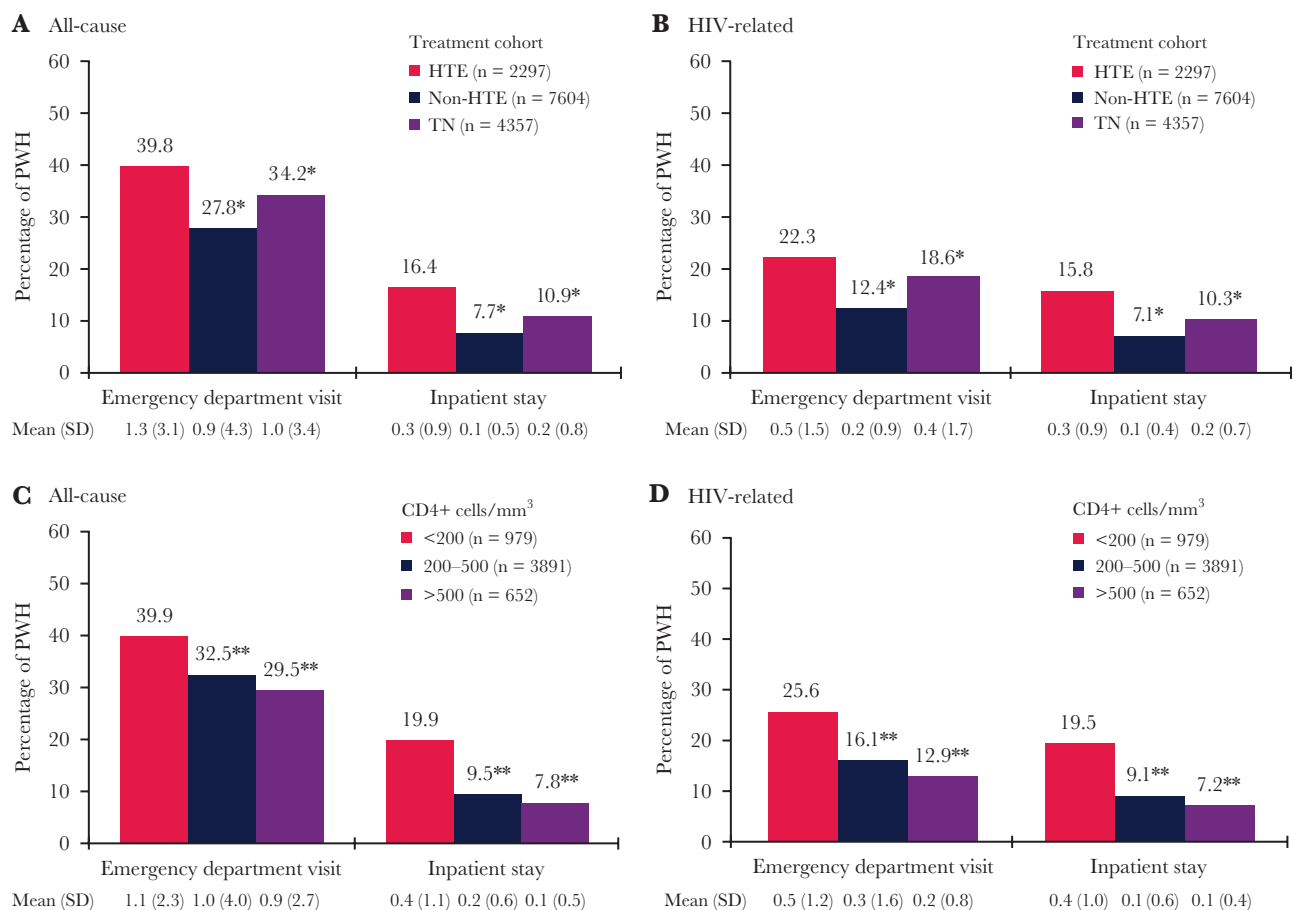

Figure 1. Twelve-month follow-up (A and C) all-cause and (B and D) HIV-related HCRU by treatment cohort and CD4+ cell count strata. Bars show the proportion of PWH with $\geq$1 visit/stay. Numbers under the bars show the mean (SD) number of visits per person for each cohort. HIV-related HCRU included medical claims with diagnosis codes for HIV and AIDS–defining conditions. *$P < .001$ vs HTE cohort (Pearson chi-square test). **$P < .05$ vs <200 cells/mm^3 strata (Pearson chi-square test). Abbreviations: HCRU, health care resource utilization; HTE, heavily treatment-experienced; PWH, people with HIV; TN, treatment-naive.

Table 3.   Twelve-Month Follow-up All-Cause and HIV-Related Health Care Costs by Cohort

Costs	Cohort	Medical + Pharmacy Costs, US Dollars[a]					
		Mean 12-Month Costs			Adjusted for Demographics and Comorbidities[b]		
		Total	Medical	Pharmacy	Predicted Value	Cost Ratio (95% CI)	*P* Value
All-cause costs	HTE	66 845	17 776	49 068	60 027	Reference	
	Non-HTE	41 262	9235	32 028	42 831	0.714 (0.686–0.742)	<.001
	TN	44 368	13 763	30 605	44 310	0.738 (0.706–0.772)	<.001
HIV-related costs[c]	HTE	50 433	10 119	40 314	48 069	Reference	
	Non-HTE	32 344	4746	27 598	33 280	0.692 (0.673–0.712)	<.001
	TN	35 828	8680	27 148	34 876	0.726 (0.700–0.752)	<.001

Abbreviations: HCRU, health care resource utilization; HTE, heavily treatment-experienced; TN, treatment-naive.

[a]Adjusted using the annual medical care component of the Consumer Price Index to reflect inflation to the year 2018 and included estimated amounts paid by Medicare and other payers for the total paid or allowable amount (ie, a coordination of benefits).

[b]Adjusted for age group, sex, race/ethnicity, geographic region and density, household income, and baseline comorbidities and HCRU.

[c]HIV-related HCRU and costs included medical claims with diagnosis codes for HIV and AIDS–defining conditions.

counts <200 cells/mm^3 were associated with higher mean costs in all categories across all treatment cohorts. Mean all-cause total cost among all individuals with CD4+ cell counts <200 cells/mm^3 was 51% higher than for those with CD4+ cell counts >500 cells/mm^3, with medical costs being 207% higher, primarily driven by inpatient stays (Figure 2). Similar trends were seen for HIV-related care. Among individuals in the lowest CD4+ cell count strata (<200 cells/mm^3), average all-cause total cost was highest in the HTE cohort followed by the treatment-naive cohort. In treatment-naive individuals with CD4+ cell counts <200 cells/mm^3, mean medical costs were higher than those in all CD4+ cell count strata for the non-HTE cohort (Figure 2).

A multivariable analysis was conducted to predict 12-month follow-up all-cause and HIV-related health care costs by cohort, adjusted for demographics and baseline comorbidities including age group, sex, race/ethnicity, geographic region and density, household income, and baseline comorbidities and HCRU (Table 3; Supplementary Table 6). The adjusted all-cause and HIV-related total predicted costs for the HTE cohort were ~30% higher than those for the non-HTE cohort, at $60 027 and $48 069 vs $42 831 and $33 280, respectively (*P* < 0.001) (Table 3). Adjusted costs for the treatment-naive cohort were similar to those for the non-HTE cohort.

DISCUSSION

Treatment of HIV-1 in the HTE population can be complicated by multiple clinical and social factors. In this retrospective study based on administrative claims data from >14 000 PWH between July 2013 and March 2019, we found that HTE PWH had a higher disease burden, with an increased prevalence of common comorbidities; a higher daily pill burden; and increased rates of AIDS-defining conditions, mortality, ED visits, inpatient stays, and health care costs compared with the non-HTE population. HTE individuals were also more likely

than non-HTE individuals to have CD4+ cell counts <200 cells/mm^3, which could potentially have contributed to some of these differences in health status. The highest health care costs in this study were seen for HTE PWH with CD4+ cell counts <200 cell/mm^3. These increased costs were principally medical costs rather than HIV pharmacy costs and appear to have been driven by increased hospitalizations, most of which were HIV related. These findings are consistent with those of Gebo et al. [11], who reviewed the medical records of 14 691 PWH receiving care at 10 sites in the US HIV Research Network in 2006 and found that annual average per-person health care costs were greatest for people with CD4+ cell counts ≤50 cells/mm^3 and that the greatest costs for this group were inpatient costs.

An unexpected finding was that HCRU and medical costs in the treatment-naive cohort were at least as high as those in the non-HTE cohort. It is likely that PWH in this cohort would have been recently diagnosed. There may be certain costs associated with the first year of treatment that are not seen in later years (and thus not seen in the non-HTE cohort). In addition, in some cases, individuals in the treatment-naive cohort may have been prompted to seek a diagnosis by a clinical event that could have driven some of the initial medical costs. Late diagnosis may also have been a factor, and this is consistent with a relatively high proportion of the treatment-naive cohort having baseline AIDS-defining conditions. Indeed, the proportion of treatment-naive PWH with CD4+ cell counts <200 cells/mm^3 was surprisingly high at 27.0%, suggesting that late diagnosis and/or lack of engagement with services or treatment programs continues to be a problem in the United States. Data from the National HIV Surveillance System of the Centers for Disease Control and Prevention suggest that in 2015 15% of PWH in the United States were unaware of their HIV status and that ~20% of PWH had a CD4+ cell count <200 cells/mm^3 at diagnosis [1, 12]. Our data suggest that this situation may not have improved over recent years and that early integration into HIV care remains a problem to addressed.
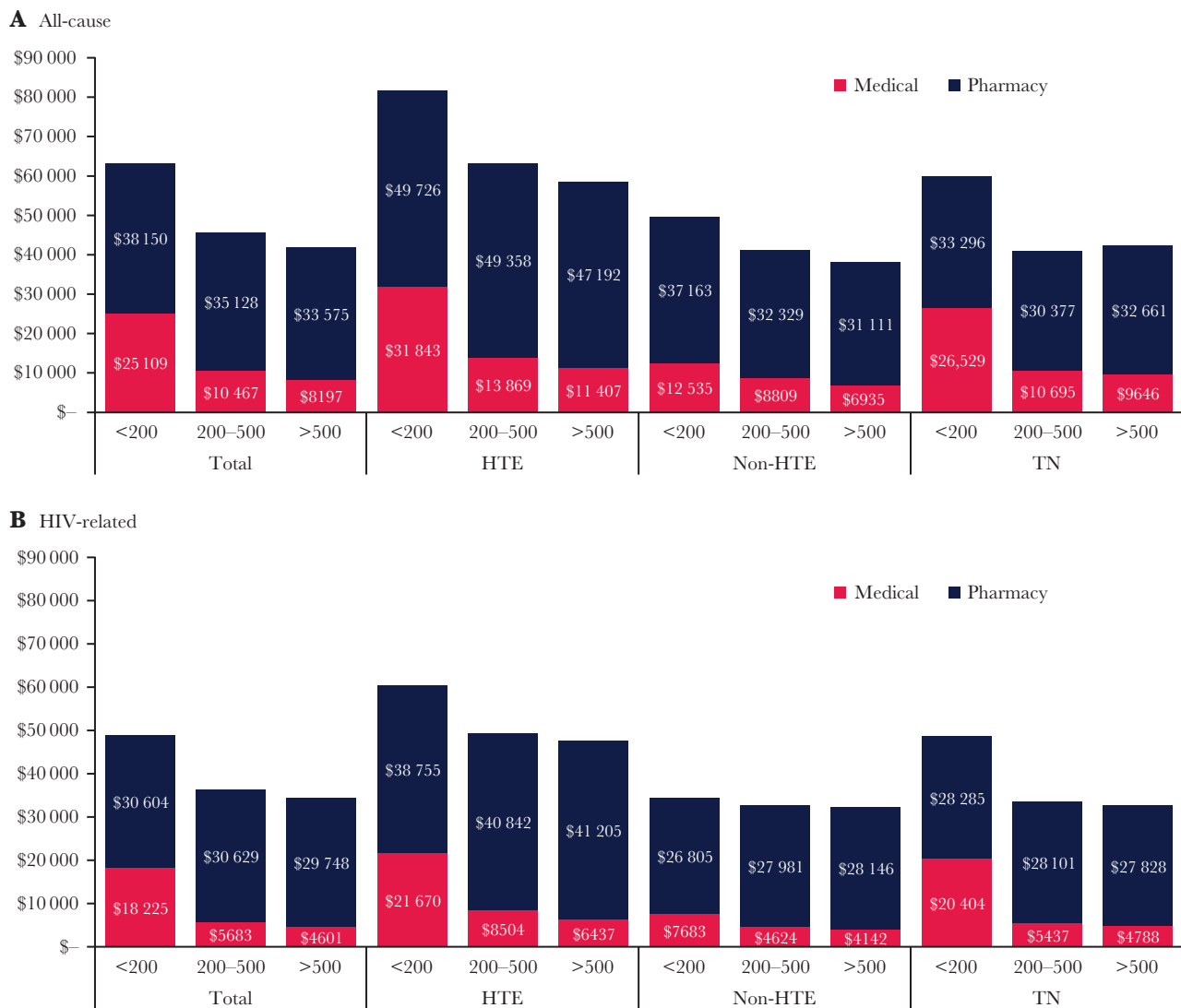
A All-cause

B HIV-related

Figure 2. Mean 12-month follow-up (A) all-cause and (B) HIV-related total health care costs by treatment cohort and CD4+ cell count strata. HIV-related costs included medical claims with diagnosis codes for HIV and AIDS–defining conditions. Abbreviation: HTE, heavily treatment-experienced.

In our study, identification of HTE individuals was based only on claims for treatment regimens typically used in PWH with advanced disease. According to these criteria, 16.1% of the included PWH were classified as HTE. There is no general consensus on the definition of HTE PWH in the literature or guidelines, and multiple descriptions are available based on virologic failure and prior and current ART patterns and/or resistance data [2, 6, 13, 14]. Previous studies in which the definition of HTE included consideration of resistance and/or prior exposure to ART have suggested that the prevalence of HTE PWH in the United States is <6% [6, 13–15]. Our algorithm was limited by the data available in the ORD. Without viral load data, treatment history, or antiretroviral resistance data, the size of the HTE population in our study may have been overestimated or underestimated, with some

treatment-experienced PWH being misclassified into HTE or non-HTE cohorts.

Other limitations of this study include those inherent to database claims studies. As information is based on claims data only, some medications may have been missed, such as those provided over the counter, directly by the physician, or as part of a clinical trial. Recorded diagnosis codes may not accurately reflect disease status and lack clinical details, such as duration and severity, that are needed for consistent identification of AIDS-defining conditions. For example, herpes simplex is considered an AIDS-defining condition when it persists for more than 1 month or involves the esophagus or lungs; thus, our study may have overestimated herpes simplex as an AIDS-defining condition when based only on the diagnostic code. Antiretroviral treatment experience was based on pharmacy claims during a

relatively short cross-section of time, so individuals may not have been truly naive to therapy or non-HTE if they experienced a treatment interruption. Medical claims may not capture all conditions that occur, sources used for mortality data may not have captured all deaths occurring during the follow-up period, and socioeconomic data may be missing or inaccurate. Certain clinical variables that influence the choice of treatment, such as disease status, resistance, and toxicity, were not included in the database. Because all PWH were enrolled in either a commercial or Medicare Advantage health plan during the study period, findings from this study may not be applicable to an uninsured population or individuals with Medicaid, which typically includes a significant proportion of PWH. Only 38.7% of the study population had a CD4+ cell count available in the database at or close to the index date, and these individuals may not have been fully representative of the total study population. In addition, there were no HIV-1 RNA measures available, so the level of viral suppression in study cohorts could not be assessed. Despite these limitations, administrative claims remain a powerful source of data for the examination of health outcomes in a real-world setting, away from the highly controlled environment of clinical trials, and offer the advantage of large sample sizes of patients with diverse medical histories.

In conclusion, this study shows that HTE PWH have a high burden of disease with a higher prevalence of common comorbidities; a higher daily pill burden; and increased rates of AIDS-defining conditions, mortality, ED visits, inpatient stays, and health care costs compared with the non-HTE population. Furthermore, a substantial number of both HTE and treatment-naive PWH have CD4+ cell counts <200 cells/mm^3, potentially resulting in more AIDS-defining conditions, higher mortality risk, and higher all-cause and HIV-related HCRU and costs. These data suggest that increased efforts may be needed in the United States to ensure early diagnosis, engagement with health care services, and establishment on effective ART and offer further support to the Ending the Epidemic initiative in the United States [16]. Improved support and clinical monitoring of HTE PWH with more advanced disease are also needed to prevent worsening outcomes and increased costs.

References

1. Department of Health and Human Services, Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. **2019**. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf. Accessed 20 January 2021.
2. Pelchen-Matthews A, Borges AH, Reekie J, et al. Prevalence and outcomes for heavily treatment-experienced (HTE) individuals living with HIV in a European cohort. Poster presented at: 10th IAS Conference on HIV Science; July 21–24, **2019**; Mexico City, Mexico.
3. European AIDS Clinical Society. Guidelines. Version 10.1. **2020**. Available at: https://www.eacsociety.org/files/guidelines-10.1_30032021_1.pdf. Accessed 1 February 2021.
4. Armenia D, Di Carlo D, Flandre P, et al. HIV MDR is still a relevant issue despite its dramatic drop over the years. J Antimicrob Chemother **2020**; 75:1301–10.
5. Cutrell J, Jodlowski T, Bedimo R. The management of treatment-experienced HIV patients (including virologic failure and switches). Ther Adv Infect Dis **2020**; 7:2049936120901395.
6. Henegar C, Vannappagari V, Viswanathan S, et al. Identifying heavily treatment-experienced patients in a large administrative claims database. Poster presented at: 10th IAS Conference on HIV Science; July 21–24, **2019**; Mexico City, Mexico.
7. Lataillade M, Lalezari JP, Kozal M, et al. Safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced individuals: week 96 results of the phase 3 BRIGHTE study. Lancet HIV **2020**; 7:e740–51.
8. Department of Health and Human Services, Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. **2020**. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/Adult_OI.pdf. Accessed 2 June 2021.
9. Optum. Optum claims data. **2021**. Available at: https://www.optum.com/business/solutions/life-sciences/real-world-data/claims-data.html. Accessed 7 October 2021.
10. US Department of Labor, US Bureau of Labor Statistics. Consumer price index. Medical care. Series ID: CUUR0000SAM. Available at: https://data.bls.gov/timeseries/CUUR0000SAM?output_view=pct_12mths. Accessed 20 January 2020.
11. Gebo KA, Fleishman JA, Conviser R, et al; HIV Research Network. Contemporary costs of HIV healthcare in the HAART era. AIDS **2010**; 24:2705–15.
12. Centers for Disease Control and Prevention. Estimated HIV incidence and prevalence in the United States, 2010-2015. HIV Surveillance Supplemental Report. **2018**. Available at: http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Accessed 12 January 2021.
13. Bajema KL, Nance RM, Delaney JAC, et al; Centers for AIDS Research Clinical Network of Integrated Systems (CNICS). Substantial decline in heavily treated therapy-experienced persons with HIV with limited antiretroviral treatment options. AIDS **2020**; 34:2051–9.
14. Hsu R, Henegar C, Fusco J, et al. Identifying heavily treatment-experienced patients in the OPERA cohort. Poster presented at: 22nd International AIDS Conference; July 23–27, **2018**; Amsterdam, the Netherlands.
15. Henegar C, Underwood M, Ragone L, Garges H, Vannappagari V. Trends and characteristics of HIV-1 drug resistance in the United States (2012-2018). Poster presented at: Conference on Retroviruses and Opportunistic Infections; March 8–11, **2020**; Boston, MA.
16. US Department of Health and Human Services, Centers for Disease Control and Prevention. Ending the HIV epidemic: a plan for America. **2020**. https://www.cdc.gov/endhiv/docs/ending-HIV-epidemic-overview-508.pdf. Accessed 26 March 2021.