

# Inpatient, Outpatient, and Pharmacy Costs in Patients With and Without HIV in the US Veteran's Affairs Administration System

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## Abstract

**Objectives:** To evaluate the association between human immunodeficiency virus (HIV) patients and medical costs (inpatient, outpatient, pharmacy, total) using a national cohort of HIV-infected Veterans and non-HIV matched controls within the Veteran's Affairs (VA) Administration system. **Design:** This study used claims (January 2000 to December 2016) extracted from the VA Informatics and Computing Infrastructure and VA Health Economics Resource Center. Cases included Veterans with an *International Classification of Diseases, Ninth Revision/International Classification of Diseases, Tenth Revision* for HIV with at least 1 prescription for a complete antiretroviral therapy regimen (January 2000 to September 2016). Two non-HIV controls were exact matched on race, sex, month, and year of birth. All patients were followed until the earliest of the following: last date of VA activity, death, or December 31, 2016. **Results:** A total of 79 578 patients (26 526 HIV and 53 052 non-HIV) met all study criteria. The average age was 49.3 years, 38% were black, 32% were white, and 97% were male for both the HIV and control cohorts. Adjusted multivariable logistic regression models demonstrated that HIV was associated with higher odds of incurring a pharmacy cost (odds ratio = 2286.45, 95% confidence interval: 322.79-16 195.82), 4-fold, and 2-fold higher odds of incurring both outpatient and inpatient costs compared to the matched controls, respectively. In adjusted multivariable gamma generalized linear models, HIV-positive patients had an almost 4-fold, 17-fold, and almost 2-fold higher cost than matched controls in total, pharmacy, and outpatient costs, respectively. **Conclusions:** This study found an association between HIV-positive patients having higher odds of incurring a medical cost as well as higher medical costs compared to non-HIV controls.

## Keywords

HIV, inpatient costs, outpatient costs, pharmacy costs

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## Introduction

The utilization of antiretroviral therapy (ART) to manage patients with human immunodeficiency syndrome (HIV) has led to a dramatic increase in life expectancy. There are 1.2 million people living with HIV in the United States and although the incidence of HIV is decreasing, the prevalence is expected to continue increasing.<sup>1,2</sup> The prevalence of HIV is increasing because medications that target HIV have slowed the progression of the virus, reduced hospitalizations, and improved overall survival.<sup>3-5</sup> Millions of years of life have been saved in the United States as a direct result of HIV management.<sup>6-12</sup> In spite of improved survival, HIV-positive patients are prone to experience an increase in comorbidities and even acquire them at an earlier age compared to the general population.<sup>13-15</sup> The survival increase has led to longer

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### What Do We Already Know about This Topic?

For HIV-positive patient, lifetime healthcare costs have increased throughout time, even though the introduction of antiretroviral therapy (ART) reduced the number of HIV-related hospitalizations (17-20). However, some studies report a projected decrease in the cost of health care due to the introduction of ART (19-21). As HIV-positive patients live longer, there may be an increased cost of health-care services throughout their lifetime.

### How Does Your Research Contribute to the Field?

To our knowledge, this is the first longitudinal paper (spanning January 2000 until December 2016 and medical claims data from October 1999 until December 2016) to document costs associated with HIV and compared to a cohort without the disease. Specifically, regression models were utilized to evaluate medical costs over several years.

### What are your Research's Implications Toward Theory, Practice, or Policy?

The research implications have the potential to impact practice and policy in the following ways: (1) Practice. Clinicians can utilize the data to gain or further their understanding of the medical costs associated with managing HIV; and (2) Policy. Payers need clear understanding of the impact of a disease regarding all types of costs (eg, total, pharmacy, inpatient, and outpatient). This paper provides documentation to assist payers in making decisions about their budget and formulary.

cumulative ART exposure per patient and increased cost secondary to age-related diseases.<sup>16</sup> For HIV-positive patients, lifetime health-care costs have increased throughout time, even though the introduction of ART reduced the number of HIV-related hospitalizations.<sup>17-20</sup> However, some studies report a projected decrease in the cost of health care due to the introduction of ART.<sup>19,21</sup> As HIV-positive patients live longer, there may be an increased cost of health care services throughout their lifetime. Previous studies examined the estimated cost of HIV care among different populations such as: (1) a Canadian population,<sup>22</sup> (2) among an Italian population,<sup>23</sup> (3) during nonrecent short periods of time,<sup>24-26</sup> (4) and not comparing to non-HIV-positive patient cost.<sup>18,21,22</sup> Our study utilized a different approach with the goal to evaluate the association between HIV-positive patients and medical costs including inpatient, outpatient, pharmacy, and total costs using a national

cohort of HIV-infected Veterans and non-HIV matched controls within the Veteran's Affairs (VA) Administration system. Supporting over 27 000 people, the Veterans Health Administration (VHA) is the largest single provider of medical care for people living with HIV.<sup>27</sup>

## Methods

### Data Source

This prospective study utilized a historic cohort of HIV infected Veterans using claims data from the Department of VA health-care system. Data were extracted from the VA Informatics and Computing Infrastructure (VINCI) and includes all inpatient, outpatient, and pharmacy claims. The completeness, utility, accuracy, validity, and access methods are described on the VA website, <http://www.virec.research.va.gov>. The study was conducted in compliance with the Department of Veterans Affairs and Dorn Research Institute requirements, received institutional review board (IRB), and Research & Development approval (IRB #993102-4). The IRB approval was expedited because of the use of existing data via a claims data base study; therefore, the retrospective study and the request for the Health Insurance Portability and Accountability Act (HIPAA) waiver was granted.

### Study Design

The HIV cohort included all Veterans with an *ICD-9/10* code of 042.x, V08, B20.x–B24.x, R25.x, or Z21.x with prescriptions for a complete ART regimen. A complete ART regimen was defined as 2 nucleoside/nucleotide reverse transcriptase inhibitors plus a third agent (a non-nucleoside reverse transcriptase inhibitor, a protease inhibitor, or an integrase inhibitor). A complete ART was defined to capture naïve treatment patients and to avoid patients on salvage treatment for resistant HIV. Patients on salvage treatment may have a shorter life expectancy.<sup>14</sup> Veteran Affairs prescription data spanning January 2000 until December 2016 and medical claims data from October 1999 until December 2016 were utilized to complete the analysis. The index date for the HIV-positive patients on ART was defined as the first day patients had all prescriptions for a complete ART. The index dates range from January 2000 to September 2016 and HIV cases were required to have at least 60 days of ART after index. In this study, 2 non-HIV controls were matched for each HIV case. A pool of possible controls was created by selecting, from all patients un-infected with HIV, those who had the same distinct combinations of age, sex, and race of the cases. We then utilized a computer-generated match in which cases were matched to the first 2 controls found with the exact same age, race, and sex. The index date for the control patients was set to the same value as their matched case. Both HIV cases and their associated controls were followed until the earliest time of: last date of VA activity, death, or end of study December 31, 2016.

## Outcome

In this study, the primary outcome is medical costs including inpatient, outpatient, pharmacy, and total costs. Inpatient and outpatient cost data were extracted from VA Health Economics Resource Center data. Pharmacy claims were pulled from the outpatient pharmacy data housed in VINCI and calculated using the unit costs associated with each filled prescription. For each patient, cost data were totaled over the entire follow-up period and then averaged to create an average cost per year for each patient.

## Study Variables

Several covariates were included in the study, including demographic characteristics such as age at index, sex, and race coded as white, black and other/unknown. The Charlson comorbidity index, excluding AIDS diagnoses, was utilized to account for differences in disease burden.<sup>28</sup> The Charlson scores were coded using all claims up to 1 year prior to index. Additional covariates included diabetes, mental health conditions, and drug/alcohol abuse based on *ICD-9* and *ICD-10* codes during any time of the study. Body mass index (BMI) was calculated from the height and weight of the patient and coded as underweight if BMI is less than 18.5, normal if BMI is 18.5 to 24.9, overweight if BMI is 25 to 29.9, and obese if BMI is 30 or more. Hispanic ethnicity, days in study, and index year were also included. Because the study utilized data over several years (2000-2016) and HIV management has changed several times during this time period, we utilized calendar year in the regression models.

## Statistical Analyses

The analyses for this study were conducted in multiple steps. First, we used bivariate statistics such as the Wilcoxon rank sum and  $\chi^2$  tests to examine whether there were differences between the HIV cohort and the non-HIV controls. We examined both the baseline characteristics of the samples as well as their mean costs. Second, we utilized logistic regression models to estimate the odds of having a medical cost for persons in the study. Lastly, we used multivariable Gamma generalized linear (GLM) models to estimate the cost ratios (CR) for those patients who incurred costs. All models were adjusted for demographic factors and comorbidities. Data were analyzed using SAS (SAS Institute Inc, SAS 9.1.3, Cary, North Carolina) and R (R Core Team 2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; URL <http://www.R-project.org/>.

## Results

A total of 26 526 HIV-positive patients were identified in the VHA data set who met all the study criteria and were matched to non-HIV controls ( $n = 53\ 052$ ) and comprised the initial sample ( $n = 79\ 578$  patients). The average age was 49.3 years, 38% were black, 32% were white, and 97% were male in both

the HIV and control cohorts. Table 1 displays the baseline sample characteristics for the HIV and non-HIV cohorts. Although the cohorts were matched, the HIV cohort had a higher average Charlson comorbidity index, more patients with hepatitis C, drug/alcohol, mental health, and smoking history. In regard to the costs, the HIV cohort had higher mean total, outpatient, inpatient and pharmacy costs compared to the non-HIV cohort (Table 2). The univariate comparisons within Table 2 demonstrate that HIV-positive patients have higher average: (1) outpatient costs (\$38 164.50 compared to 18 189.62,  $P < .001$ ); (2) inpatient costs (\$43 856.30 compared to \$21 220.30,  $P < .001$ ); (3) pharmacy costs (\$88 297.60 compared to \$4993.10,  $P < .001$ ); and (4) total costs (\$170 318.50 compared to \$44 403.00,  $P < .001$ ).

The odds of having a medical (pharmacy, outpatient, inpatient) cost for the HIV cases and controls were estimated using multivariable logistic regression models shown in Table 3. The multivariable analysis demonstrated that HIV-positive patients had higher odds of having a pharmacy cost than non-HIV controls (odds ratio [OR]: 2286.45, 95% confidence interval [CI]: 322.79-16195.82). HIV-positive patients also had a 4-fold higher odds of having an outpatient cost and a 2-fold higher odds of having an inpatient cost compared to controls (OR outpatient 4.16, 95% CI: 3.67-4.71; OR inpatient 2.26, 95% CI: 2.18-2.35). Age, race, drug/alcohol abuse, mental health, diabetes, BMI, and select index years were also statistically significant covariates in all cost models. Interestingly, while the pharmacy costs were consistent throughout most of the years, all patients had lower odds of an outpatient (2014 and 2015) and inpatient (2001-2016) cost compared to the index year 2000.

The CR for those patients who incurred medical (total, pharmacy, outpatient, inpatient) costs were estimated using multivariable log-link GLM models shown in Table 4. This multivariate analysis for total, pharmacy, and outpatient costs demonstrated that HIV-positive patients had an almost 4-fold, 17-fold, and almost 2-fold higher cost than non-HIV controls, respectively. HIV-positive patients had a nonsignificant 3% higher inpatient cost (CR: 1.03, 95% CI: 0.96-1.11) compared to controls. Because the study utilized data over several years (2000-2016) and HIV management has changed several times during this time period, we utilized calendar year in the regression models. The years in the regression model were accounted for as a covariate to control for the impact a single year or years could have on the results. The GLM model demonstrates that pharmacy costs were higher for the all patients for most years. However, total costs, outpatient costs and inpatient CR demonstrate that by the end of the study period, all patients had a lower cost ratio. The total costs were lower in years 2013 to 2016, the outpatient CR were lower in 2014 and 2015, and the inpatient CR were lower in 2002 to 2016.

## Discussion

Antiretroviral therapy has transformed the disease and HIV-positive patients are experiencing increased life expectancy

**Table 1.** Baseline Characteristics for HIV Cases and Controls.

Variable		HIV Cases (N = 26 526)	Controls (N = 53 052)	P Value
Age (mean [SD])		49.27 (10.097)	49.31 (10.098)	.596
Race	Black	10 099 (38%)	20198 (38%)	1.000
	Other/unknown	7841 (30%)	15682 (30%)	
	White	8586 (32%)	17172 (32%)	
Hispanic		1231 (5%)	545 (1%)	<.001
Sex	Male	25 850 (97%)	51700 (97%)	1.000
Days in study (mean [SD])		2780.7 (1594.9)	3170.3 (1622.8)	<.001
Days in study (median, IQR)		2665 (2537)	3180 (2598)	<.001
Charlson comorbidity (mean [SD])		0.66 (1.209)	0.35 (0.938)	<.001
Hepatitis c		7989 (30%)	4400 (8%)	<.001
Diabetes		6520 (25%)	15617 (29%)	<.001
Smoking		14 366 (54%)	22070 (42%)	<.001
BMI	Missing	2984 (11%)	29244 (55%)	<.001
	Normal	10 648 (40%)	4759 (9%)	
	Obese	3914 (15%)	10572 (20%)	
	Overweight	7994 (30%)	8211 (15%)	
	Underweight	986 (4%)	266 (1%)	
Drug/alcohol abuse		8681 (33%)	7624 (14%)	<.001
Mental health		14 424 (54%)	15685 (30%)	<.001
Index year	2000	1876 (7%)	3752 (7%)	1.000
	2001	1796 (7%)	3592 (7%)	
	2002	1784 (7%)	3568 (7%)	
	2003	1759 (7%)	3518 (7%)	
	2004	1819 (7%)	3638 (7%)	
	2005	1935 (7%)	3870 (7%)	
	2006	2174 (8%)	4348 (8%)	
	2007	2144 (8%)	4288 (8%)	
	2008	1800 (7%)	3600 (7%)	
	2009	1727 (7%)	3454 (7%)	
	2010	1734 (7%)	3468 (7%)	
	2011	1528 (6%)	3056 (6%)	
	2012	1327 (5%)	2654 (5%)	
	2013	1268 (5%)	2536 (5%)	
	2014	985 (4%)	1970 (4%)	
	2015	645 (2%)	1290 (2%)	
	2016	225 (1%)	450 (1%)	

Abbreviations: BMI, body mass index; SD, standard deviation.

**Table 2.** Baseline Costs for HIV Cases and Controls: Total and Annualized Costs for Outpatient, Inpatient, Pharmacy, and Total.

	Costs (US\$)	HIV Cases (N = 26 526)	Controls (N = 53 052)	P Value
Total <sup>a</sup>	Outpatient, mean (SD)	38 164.5 (88 480.4)	18 189.62 (42 903.2)	<.001
	Inpatient mean (SD)	43 856.3 (115 494.3)	21 220.3 (171 955.7)	<.001
	Pharmacy mean (SD)	88 297.6 (240 590.1)	4993.1 (14864.3)	<.001
	Total costs mean (SD)	170 318.5 (292 910.8)	44 403.0 (185839)	<.001
Annual <sup>b</sup>	Outpatient mean (SD)	5167.3 (10 677.7)	2061.6 (4806.5)	<.001
	Inpatient mean (SD)	9110.7 (27 373.2)	2817.3 (18 037.4)	<.001
	Pharmacy mean (SD)	11742 (19 600.7)	602.4 (2153.1)	<.001
	Total costs mean (SD)	26 020.5 (36 744.68)	5481.3 (19 947.7)	<.001

Abbreviation: SD, standard deviation.

<sup>a</sup>Total cost represents the average patient cost over the study period.

<sup>b</sup>Annual cost represents each patients total cost divided by the number of years in the study.

which is almost equivalent to non-HIV-positive patients.<sup>29</sup> As all individuals age, health-care costs may increase as a result of the multiple chronic conditions.<sup>23,30</sup> Specifically, HIV-positive

patients experience an increase in comorbidities and these comorbidities can occur at an earlier age compared to non-HIV-positive patients.<sup>13,23</sup> Prior to the introduction of

**Table 3.** Odds of Incurring a Medical Cost for Patient With HIV Compared to Controls for Pharmacy, Outpatient, and Inpatient.

Variable	Pharmacy OR (95% CI)	Outpatient OR (95% CI)	Inpatient OR (95% CI)
(Intercept)	1.95 (1.45-2.64)	10.95 (7.91-15.15)	1.27 (1.07-1.51)
HIV	2286.45 (322.79-16195.82)	4.16 (3.67-4.71)	2.26 (2.18-2.35)
Age	0.99 (0.98-0.99)	0.99 (0.98-0.99)	0.99 (0.99-0.99)
Race (reference = black)			
Other/unknown	0.55 (0.51-0.59)	0.71 (0.65-0.77)	0.46 (0.44-0.48)
White	0.77 (0.72-0.83)	0.84 (0.77-0.91)	0.75 (0.73-0.78)
Hispanic	1.68 (1.13-2.49)	0.79 (0.58-1.07)	1.55 (1.39-1.73)
Sex (reference = female)			
Male	2.14 (1.84-2.48)	1.17 (0.98-1.40)	1.25 (1.13-1.39)
Charlson comorbidity	1.34 (1.24-1.46)	0.96 (0.91-1.00)	1.21 (1.19-1.24)
Drug/alcohol abuse	2.67 (2.25-3.17)	1.51 (1.32-1.72)	1.99 (1.91-2.08)
Mental health	3.02 (2.70-3.38)	2.37 (2.13-2.63)	1.39 (1.33-1.44)
Diabetes	4.39 (4.00-4.82)	2.31 (2.09-2.55)	1.70 (1.63-1.77)
BMI (reference = normal)			
Missing	0.12 (0.11-0.15)	0.19 (0.16-0.21)	0.5 (0.47-0.52)
Obese	1.09 (0.89-1.32)	1.41 (1.18-1.68)	0.75 (0.71-0.79)
Overweight	1.01 (0.83-1.23)	1.4 (1.18-1.66)	0.78 (0.74-0.82)
Underweight	1.17 (0.59-2.31)	0.4 (0.29-0.55)	1.44 (1.26-1.65)
Days in study	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Index year (reference = 2000)			
2001	0.94 (0.80-1.11)	0.67 (0.55-0.83)	0.80 (0.74-0.87)
2002	1.00 (0.85-1.18)	0.75 (0.61-0.92)	0.76 (0.70-0.82)
2003	1.02 (0.87-1.19)	0.83 (0.68-1.01)	0.69 (0.64-0.75)
2004	1.10 (0.94-1.29)	1.19 (0.96-1.46)	0.63 (0.58-0.69)
2005	1.32 (1.12-1.54)	1.06 (0.87-1.29)	0.60 (0.55-0.65)
2006	1.55 (1.33-1.80)	1.28 (1.05-1.56)	0.57 (0.52-0.62)
2007	1.73 (1.48-2.02)	1.34 (1.10-1.62)	0.49 (0.45-0.54)
2008	1.88 (1.60-2.22)	1.35 (1.10-1.64)	0.44 (0.40-0.48)
2009	1.95 (1.65-2.30)	1.34 (1.10-1.64)	0.39 (0.36-0.43)
2010	2.05 (1.73-2.42)	1.21 (0.99-1.47)	0.34 (0.31-0.37)
2011	2.37 (1.98-2.83)	1.19 (0.98-1.46)	0.27 (0.24-0.30)
2012	2.24 (1.86-2.70)	1.06 (0.87-1.31)	0.21 (0.19-0.23)
2013	2.27 (1.88-2.75)	0.95 (0.77-1.17)	0.18 (0.16-0.21)
2014	1.99 (1.62-2.44)	0.61 (0.49-0.75)	0.14 (0.12-0.16)
2015	1.62 (1.28-2.04)	0.09 (0.07-0.11)	0.11 (0.09-0.13)
2016	1.37 (1.00-1.88)		0.05 (0.03-0.07)

Abbreviations: OR, odds ratio; CI, confidence interval.

combination ART, most of the expenditures for HIV were spent on hospitalizations and the treatment of opportunistic diseases.<sup>19</sup> Subsequent studies evaluated expenditures for the care of HIV-positive patients in the era of combination ART and found discordant results. Studies have demonstrated the cost of providing medical care to HIV-positive patients continues to increase, although the burden of costs has shifted<sup>31</sup> and that aging of HIV-positive patients is leading to increased costs.<sup>22</sup> Other studies have reported an association between use of ART and reductions in overall health-care costs.<sup>25,32</sup> However, HIV management recommendations continues to change and updated data on the cost of HIV are needed, especially since HIV is largely considered a chronic disease within the United States. Because ART has transformed HIV and treated HIV-positive patients are approaching a near normal life span, the overall costs to manage HIV-positive patients compared to a cohort of patients without the disease may have changed since the publication of previous studies. To our knowledge, this

national study among the largest provider of HIV care in the United States is the largest study evaluating cost of HIV-positive patients up to a 16-year period. Furthermore, this study controlled for costs incurred over time by including calendar year in the multivariable regression models. The study results provide information for the basis of clinical and policy decisions as we evaluated the economic impact of ART therapy and the subsequent cost to manage HIV-positive patients. Our study had a very large sample size of HIV-positive patients ( $n = 26\,526$ ) and these patients were exact matched to 2 non-HIV controls ( $n = 53\,052$ ). This study found that compared to non-HIV controls, HIV-positive patients had statistically significantly increased odds of incurring a pharmacy, outpatient, and inpatient cost. However, the outpatient and inpatient costs for all patients were decreasing at the end of the study. Additionally, HIV-positive patients were also found to have higher total, pharmacy, and outpatient costs compared to non-HIV controls, although there was no association found with inpatient costs.

**Table 4.** Multivariable Gamma Generalized Linear (GLM) Models—Estimate the Cost Ratios (CR) for Those Patients who Incurred Costs.

Variable	Total Costs CR (95% CI)	Pharmacy Costs CR (95% CI)	Outpatient Costs CR (95% CI)	Inpatient Costs CR (95% CI)
(Intercept)	37.98 (31.4-45.95)	502.94 (405.48-623.84)	10.44 (9.24-11.79)	173.11 (124.7-240.31)
HIV	3.97 (3.80-4.15)	17.40 (16.59-18.26)	1.95 (1.89-2.00)	1.03 (0.96-1.11)
Age	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Race (reference = black)				
Other/unknown	0.54 (0.51-0.56)	0.70 (0.66-0.74)	0.58 (0.56-0.60)	0.69 (0.63-0.76)
White	0.85 (0.82-0.89)	1.14 (1.08-1.19)	0.85 (0.83-0.87)	0.79 (0.74-0.85)
Hispanic	1.26 (1.11-1.42)	1.08 (0.94-1.23)	1.35 (1.25-1.46)	1.21 (1.02-1.44)
Sex (reference = female)				
Male	1.25 (1.11-1.40)	1.05 (0.92-1.20)	1.01 (0.94-1.09)	1.23 (1.00-1.52)
Charlson comorbidity	1.16 (1.13-1.18)	1.16 (1.14-1.19)	1.16 (1.15-1.18)	1.09 (1.06-1.12)
Drug/alcohol abuse	1.37 (1.31-1.44)	1.03 (0.98-1.09)	1.31 (1.27-1.35)	1.29 (1.20-1.39)
Mental health	1.30 (1.25-1.36)	1.39 (1.33-1.46)	1.33 (1.29-1.36)	1.11 (1.03-1.19)
Diabetes	1.50 (1.43-1.56)	1.34 (1.28-1.40)	1.41 (1.37-1.45)	1.27 (1.19-1.36)
BMI (reference = normal)				
Missing	0.59 (0.56-0.63)	0.7 (0.66-0.75)	0.62 (0.6-0.65)	0.84 (0.76-0.92)
Obese	0.89 (0.84-0.95)	1.04 (0.97-1.11)	0.98 (0.94-1.02)	0.82 (0.75-0.91)
Overweight	0.92 (0.87-0.97)	1.05 (0.99-1.12)	0.98 (0.94-1.01)	0.87 (0.8-0.95)
Underweight	1.12 (0.97-1.3)	0.9 (0.77-1.05)	0.89 (0.81-0.98)	1.16 (0.95-1.41)
Days in study	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Index year (reference = 2000)				
2001	0.94 (0.85-1.03)	1.03 (0.92-1.14)	1.01 (0.95-1.07)	0.90 (0.78-1.04)
2002	0.94 (0.86-1.04)	1.06 (0.95-1.18)	1.05 (0.99-1.12)	0.82 (0.71-0.94)
2003	0.97 (0.88-1.07)	1.16 (1.04-1.29)	1.11 (1.05-1.18)	0.85 (0.73-0.99)
2004	1.07 (0.97-1.18)	1.25 (1.12-1.39)	1.22 (1.15-1.30)	0.86 (0.74-1.00)
2005	1.07 (0.97-1.17)	1.41 (1.27-1.57)	1.29 (1.21-1.37)	0.85 (0.73-0.99)
2006	1.10 (1.00-1.21)	1.49 (1.34-1.65)	1.39 (1.31-1.48)	0.84 (0.73-0.98)
2007	1.08 (0.98-1.19)	1.64 (1.47-1.82)	1.50 (1.41-1.59)	0.76 (0.65-0.88)
2008	1.15 (1.03-1.27)	1.84 (1.64-2.06)	1.54 (1.45-1.65)	0.82 (0.69-0.96)
2009	1.09 (0.98-1.21)	1.83 (1.63-2.06)	1.53 (1.43-1.63)	0.79 (0.66-0.93)
2010	1.07 (0.96-1.19)	2.01 (1.78-2.27)	1.56 (1.46-1.68)	0.72 (0.60-0.86)
2011	0.97 (0.87-1.09)	2.22 (1.95-2.52)	1.42 (1.32-1.53)	0.68 (0.55-0.82)
2012	0.89 (0.79-1.00)	2.11 (1.84-2.41)	1.27 (1.17-1.37)	0.69 (0.55-0.86)
2013	0.75 (0.66-0.85)	2.02 (1.75-2.32)	1.06 (0.98-1.15)	0.57 (0.45-0.72)
2014	0.61 (0.53-0.70)	2.06 (1.77-2.41)	0.75 (0.68-0.82)	0.53 (0.40-0.71)
2015	0.41 (0.35-0.48)	1.63 (1.37-1.95)	0.33 (0.29-0.37)	0.49 (0.34-0.70)
2016	0.15 (0.12-0.19)	0.85 (0.66-1.10)		0.27 (0.13-0.59)

Abbreviations: CI, confidence interval; CR, costs ratio.

The finding of no-difference of inpatient costs between HIV and non-HIV matched patients is consistent with ART transforming HIV into a chronic disease in the United States. The inpatient cost finding is also consistent with other literature that expenditures for hospitalization have dramatically decreased since the introduction of combination ART.<sup>17,33,34</sup> Additionally, HIV-positive patients are reported to have accelerated aging and more noninfectious comorbidities compared to non-HIV-positive patients and the difference in overall costs in outpatient and total costs support this finding.

Our study results are similar to previously published studies. Guaraldi et al reported a case-control study of data from an HIV outpatient clinic compared to matched non-HIV-positive patients from same geographic area and found that in year 2009 the total cost of medical care was higher in HIV-positive patients.<sup>13,23</sup> The study evaluated noninfectious comorbidities including cardiovascular disease, hypertension, diabetes

mellitus, bone fractures, and renal failure and cost information included pharmacy, outpatient, and inpatient hospital expenditures. The study utilized appropriate modelling, but focused on 1 year of data. Therefore, this study cannot address the financial burden over time. A multiyear study reported data from the Medical Expenditure Panel Survey representing a nationally representative United States civilian population.<sup>35</sup> Using generalized linear modeling, the adjusted direct medical expenditures were evaluated after controlling for confounding factors, including time trend covariates. Data from 342 732 HIV-positive patients from 2002 to 2011 demonstrated the adjusted mean aggregate cost of people living with HIV was almost \$10.7 billion greater than those persons without HIV.<sup>35</sup> A study within the Veterans Affairs Medical Center evaluated the costs of HIV within a clinic in 1999. The cost-effectiveness analysis demonstrated an initial decrease in cost, followed by an increase in total monthly cost of caring for HIV-positive

patients. This small sample size was performed with the Veterans Affairs system (same as our study), while we utilized a national cohort of patients and a vastly larger cohort size.<sup>17</sup>

In contrast, utilizing Medicaid data on HIV-positive patients at John Hopkins in Maryland in the mid-1990s, Gebo and colleagues reported a lower number of hospitalizations for HIV-positive patients receiving ART compared to those untreated and significantly lower hospital inpatient and community care costs.<sup>25</sup> Another study demonstrated decreased health-care costs among HIV-positive patients. Gardner et al utilized data on 325 patients initiating therapy from 1997 to 2003 and demonstrated that for adherent patients, ART was associated with decreased health-care costs. However, because of the cost of ART, total medical costs were increased as almost 61% of total costs were related to ART.<sup>19</sup> A Canadian study utilized data from southern Alberta between 1995 and 2001 and included pharmacy, inpatient, outpatient, and home health costs. The study found an increase in direct cost of medical care between 1995 and 2001 for HIV-positive patients primarily from the growing cost of ART drug costs.<sup>31</sup> The cost of therapy has distributed differently because of the introduction of combination ART. The increase in overall costs was driven by pharmacy costs.

Our study adds to the literature about the cost of HIV. Specifically, our study has a very large sample size and represents current data that can be utilized by clinicians and payers involved in the care of HIV-positive patients. In addition to our longitudinal study, our multivariable regression model controls for cost per year. Although our study has strengths, the study also exhibits limitations common to observational claims database analyses that may affect the generalizability to other patient populations. First, this study was a retrospective observational study of US Veteran HIV-positive patients; therefore, the ART utilization patterns may not be generalizable to patients of different groups. For example, patients were included in the study if they were prescribed a complete ART regimen. The ART regimen was required only at study entry. However, if patients were switched to another ART treatment or ART treatment was no longer continued their respective costs were included in the models. Therefore, a salvage ART regimen could be in the treatment of pharmacy and overall costs and could impact the outcomes. Additionally, we cannot exclude unmeasured confounding factors that may influence ART utilization. Specifically, the study population was predominantly middle-aged males with HIV; therefore, our findings may not be generalizable to patients of different age groups or genders. Also, the experience of providers may affect expenditures, as HIV-related costs have been demonstrated to be 50% higher among providers whose practices included few HIV-positive patients.<sup>21</sup> This study did not account for the experience of the provider and this may have impacted the results. We utilized the VINCI to conduct the study to capture claims data that occurred within the Department of Veterans Affairs. It is possible that a patient(s) may have utilized care outside the VA system and this encounter would not be captured and could impact the outcome(s). However, we followed

patients until the study end date, death, or last date of activity in the VA system. If patients, particularly, the controls, sought health care from an outside provider and did not use VA services anymore they would be excluded after their last VA activity date. Additional factors that could have influenced the results include: (1) Viral suppression and select/individual HIV medications were not evaluated (nor controlled for) and could have influenced the results of this study; (2) CD4 levels were also not evaluated and could have influenced the results as CD4 counts less than 200 cells/mm<sup>3</sup> have been associated with higher costs<sup>36</sup>; and (3) adherence was not evaluated in the analysis and this could impact the results as adherence can decrease health-care utilization and associated costs.<sup>19</sup> Nevertheless, our study consisted of a sample representative of a national population of diverse patients and providers with long-term follow-up information. This information should be utilized by health-care systems to ensure they are equipped with resources to handle the unique treatments of HIV-positive patients. Since HIV is a chronic disease in the United States, the long-term costs associated with ART will most likely remain. However, because of improved survival and accelerated aging, costs of HIV-positive patients compared to non-HIV-positive patients may increase. This analysis demonstrated the potential economic burden of the improved survival and accelerated aging by documenting a substantial difference in HIV costs. However, the costs were largely driven by HIV medications and early years of data and by the end of the study period the outpatient and inpatient costs were lower for all patients.

## Conclusions

Our study documents the association of medical (inpatient, outpatient, pharmacy, and total) costs from a national cohort of HIV-positive patients compared to non-HIV controls within the VA system, the largest single provider of care to HIV-infected individuals in the United States. This research found an association between HIV-positive patients having higher odds of incurring a medical cost as well as higher medical costs compared to non-HIV controls. The financial burden of HIV resulting from longer lifespans is considerable and this study highlights the costs associated with HIV management.

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