Health Care Costs in a Cohort of HIV-Infected U.S. Veterans Receiving Regimens Containing Tenofovir Disoproxil Fumarate/Emtricitabine

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ABSTRACT

BACKGROUND: Tenofovir disoproxil fumarate (TDF), a key component in many human immunodeficiency virus (HIV) treatment regimens, is associated with increased renal and bone toxicities. The contributions of such toxicities to treatment costs, as well as the relative differences in treatment costs for various TDF/emtricitabine (FTC) regimens, remains unexplored.

OBJECTIVE: To estimate and compare mean overall and renal- and bone-specific costs, including total, inpatient, outpatient, and pharmacy costs in patients treated with TDF/FTC+efavirenz (EFV) compared with several non-EFV-containing TDF/FTC regimens.

METHODS: We conducted a national cohort study of treatment-naïve HIV-infected U.S. veterans who initiated treatment from 2003 to 2015 with TDF/FTC in combination with EFV, elvitegravir/cobicistat, rilpivirine, or ritonavir-boosted protease inhibitors (atazanavir, darunavir, or lopinavir). Outcomes of interest were quarterly total, inpatient, outpatient, and pharmacy costs using data from the Veterans Health Administration (VHA) electronic medical record and Managerial Cost Accounting System (an activity-based accounting system that allocates VHA expenditures to patient encounters). We controlled for measured confounders using inverse probability of treatment (IPT) weights and assessed differences using standardized mean differences (SMDs). For comparisons where SMDs exceeded 0.1 after IPT weighting, we used the more conservative matching weights in sensitivity analyses. For hypothesis testing, we compared IPT-adjusted differences in quarterly costs between treatment groups using Mann-Whitney U-tests and generalized estimating equation (GEE) regression models.

RESULTS: Of 33,048 HIV-positive veterans, 7,222 met eligibility criteria, including 4,172 TDF/FTC+EFV recipients; mean (SD) age of the cohort was 50.0 (10.0) years; 96.7% were male; 60.1% were black; and 30.1% were white. Quarterly periods of exposure to EFV-containing regimens were 22,499 and of exposure to non-EFV-containing regimens were 11,633. After IPT weighting, absolute SMDs were <0.1 except for a few covariates in the rilpivirine comparison. The per-patient adjusted mean total quarterly costs were \$7,145 for EFV versus \$8,726 for non-EFV ($P<0.001$; Mann-Whitney U-test) and the per-patient adjusted mean difference in total quarterly costs was \$1,419 lower for EFV versus all non-EFV combined ($P<0.001$; GEE model). Corresponding values for outpatient costs (\$2,656 vs. \$2,942; $P<0.001$; difference, -\$254; $P=0.001$), inpatient costs (\$2,009 vs. \$2,614; $P<0.001$), radiology costs (\$213 vs. \$276; $P<0.001$), and pharmacy costs (\$2,480 vs. \$3,170; $P<0.001$; difference, -\$600; $P<0.001$) were all lower for EFV versus all non-EFV combined. Findings based on matching weights were qualitatively similar. Contributions of renal and bone costs to the total costs of treatment were very small, ranging between \$52 and \$94 per patient per quarter for renal outcomes and between \$6 and \$114 for bone outcomes.

CONCLUSIONS: Among 7,222 HIV-treated veterans over an average follow-up of 1.2 years per patient, those patients receiving TDF/FTC+EFV had lower overall health care costs compared with those receiving non-EFV regimens.

J Manag Care Spec Pharm. 2018;24(10):1052-66

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What is already known about this subject

- Efavirenz-based tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) regimens are associated with lower bone and renal toxicity compared with other TDF/FTC regimens.
- A reduced risk of renal and bone adverse events should be associated with lower health care costs with EFV compared with other third agents.

What this study adds

- This study estimated cost burden for various TDF/FTC regimens based on differences in the third agent and estimated the extent to which differences in renal and bone toxicity affected those costs.
- Among 7,222 HIV-treated veterans over an average follow-up of 1.2 years per patient, those patients receiving TDF/FTC+EFV had lower overall health care costs compared with those receiving non-EFV regimens.

Tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) is the most commonly used antiretroviral therapy (ART) backbone for treating human immunodeficiency virus (HIV) worldwide.¹ However, epidemiologic studies have shown increased renal and bone toxicities associated with TDF, contributing to guideline recommendations that TDF should be used with caution or avoided in patients with renal disease and osteoporosis.¹ However, switching patients who are currently stable on TDF/FTC-based regimens, which continue to be recommended in World Health Organization guidelines,² should be approached cautiously, particularly as newer evidence has identified that the renal and bone adverse effects may be attenuated by pairing TDF/FTC with certain third agents. For example, TDF/FTC regimens that include efavirenz (EFV) have been associated with lower rates of adverse renal and bone outcomes compared with the addition of other third agents. EFV, a non-nucleoside reverse transcriptase inhibitor (NNRTI), has been associated with lower risks of both proteinuria and chronic kidney disease (CKD) compared with tenofovir, a nucleoside reverse transcriptase inhibitor³; lower TDF-associated renal impairment in ART combinations that included EFV compared with nevirapine, an NNRTI⁴; and preserved bone mineral density (BMD) compared with atazanavir (ATV), a protease inhibitor (PI).⁵⁻⁸

Estimates of the real-world economic burden of TDF/FTC-associated adverse events (AEs), including renal and bone outcomes, are lacking in the existing literature. Nadkarni et al. (2015) reported that the incidence of hospitalizations for acute kidney injury in patients with HIV doubled from 2002 to 2010, which they attributed to the aging of the HIV population and increases in comorbidities; however, ART effects on acute kidney injury were not examined.⁹ Magoni et al. (2011), who reported the effect of HIV on renal disease in the Italian health care system, also did not evaluate ART effects.¹⁰ Koenig et al. (2010) evaluated the cost-effectiveness of monitoring for renal insufficiency in Haitian HIV patients on ART and found it to be cost prohibitive with negligible clinical benefits in a resource-limited setting.¹¹ In a cost-effectiveness modeling study, Walensky et al. (2016) determined that the reduced renal and bone toxicity of tenofovir alafenamide justified up to a \$1,000/year increase in cost for tenofovir alafenamide versus TDF,¹² largely due to an assumed high cost for hemodialysis of \$87,000 based upon an estimated rate of hemodialysis of 25% in those discontinuing TDF. However, this assumption is not supported by evidence from the Data collection on Adverse events of Anti-HIV Drugs (D:A:D) study demonstrating that end-stage renal disease (ESRD) in patients with HIV infection over a median follow-up of 6 years was associated with diabetes, hypertension, baseline estimated glomerular filtration rate (eGFR), smoking, and current CD4 cell count rather than past or current exposure to TDF.^{13,14}

The real-world cost differences associated with treatment and maintenance of HIV patients across TDF/FTC regimens in combination with different third agents in a U.S. setting remain unknown. The relative contributions of renal and bone adverse outcomes to these costs are also unknown, both on a per-patient basis and on a health-system basis. Given that TDF/FTC regimens that include EFV have demonstrated relatively lower rates of adverse renal and bone outcomes compared with other TDF/FTC regimens,^{3,4,6-8} a reduced risk of these adverse outcomes with EFV may also be associated with lower health care costs with EFV compared to other third agents.

Our primary objectives in this analysis were to (a) estimate the adjusted mean total, outpatient, and pharmacy costs of HIV treatment with TDF/FTC in combination with several common base agents and (b) compare adjusted mean differences in total, outpatient, and pharmacy costs. We did this in a cohort of treatment-naïve U.S. veterans initiating treatment with TDF/FTC plus EFV, elvitegravir/cobicistat (EVG/c), rilpivirine (RPV), or boosted PIs. In a supplemental analysis, we also examined the renal- and bone-specific components of costs and use of the Veterans Affairs (VA) health care system.

Methods

Study Design and Datasets

This was a nationwide, historical cohort study of treatment-naïve, HIV-infected patients initiating ART in the Veterans

Health Administration (VHA). The VHA is the largest integrated health care delivery network in the United States, with more than 150 VHA hospitals and 850 outpatient clinics. All datasets were hosted in the VA Veterans Informatics and Computing Infrastructure (VINCI) environment. VINCI is a new initiative to improve researchers' access to VHA data and to facilitate the analysis of that data with integrated tools while ensuring patient privacy and data security in a secure workspace. The University of Utah Institutional Review Board and the Salt Lake City VA Health Care System Office of Research and Development approved this study.

Study Population

Inclusion Criteria. All treatment-naïve HIV-infected adults diagnosed with HIV infection from January 1, 2003, through December 31, 2015, and who received an ART regimen of interest and who had at least 1 VA outpatient encounter 6 months or more before starting their ART regimen were included. HIV infection was identified using diagnosis codes from the *International Classification of Diseases, Ninth/Tenth Revisions, Clinical Modification* (ICD-9/10-CM). The index date was defined as the date the patient received the first ART prescription (any time between January 1, 2003, and December 31, 2015), comprising TDF/FTC with (a) EFV (as EFV/TDF/FTC in fixed-dose combination [FDC] or EFV plus TDF/FTC in FDC); (b) RPV (as RPV/TDF/FTC in FDC or RPV plus TDF/FTC in FDC); (c) EVG/c (as EVG/c/TDF/FTC in FDC); or (d) ritonavir (RTV)-boosted ATV, lopinavir (LPV), or darunavir (DRV; as boosted-PI plus TDF/FTC in FDC).

Exclusion Criteria. Patients were excluded if they had a pharmacy claim for any ART agent in the pre-index period, defined as the 6-month period before the index date. To further ensure each patient was antiretroviral naïve and not receiving continuing ART from previous treatment outside the VHA, we used a validated method for excluding patients who had most likely received previous treatment.²⁰ This method excluded patients if (a) the index regimen was a "salvage" regimen (i.e., composed of both a PI and NNRTI or composed of ≥ 5 agents) or (b) any HIV RNA level < 500 copies per mL during the pre-index period, which suggested prior antiretroviral exposure.²⁰ We also excluded patients who did not have an inpatient or outpatient encounter at least 6 months before the index date to ensure that we captured patients with a pattern of receiving routine care within the VHA.

Follow-up. Patients were followed until they discontinued the ART regimen of interest or until the end of the study period (December 31, 2015), whichever was sooner. We defined discontinuation as a gap of more than 30 days for any 1 of the medications in a patient's ART regimen. The date of discontinuation was the first day of such a gap.

Study Variables

Outcomes/Dependent Variables. Our primary outcome variables included quarterly total, outpatient, inpatient, and pharmacy costs during the period following the index date up to discontinuation of the regimen of interest or the end of the study period. These quarterly costs were calculated by summing all VHA health care costs for inpatient, outpatient, and pharmacy services provided in each quarter after the index date based on data available via the Managerial Cost Accounting System (an activity-based accounting system that allocates VHA expenditures to patient encounters). Quarterly use outcomes were assessed by counting frequencies of outpatient visits and numbers of inpatient days for hospital stays in the VHA during the quarter in which they occurred.

To contrast with the overall costs and use previously described, in supplemental analyses, we calculated quarterly bone- and renal-specific costs and use by summing all VHA health care costs and use associated with an ICD-9/10-CM or Current Procedural Terminology, 4th Edition (CPT-4) code for bone disease (i.e., osteoporosis diagnosis or a vertebral, hip, or wrist fracture) or renal disease (i.e., proteinuria, CKD, or ESRD, including renal transplant and dialysis). All codes for bone and renal disease are available via Web links 1 and 2, respectively.

We used cost per patient-quarter as our unit of measure because duration of follow-up varied substantially between individuals. All cost outcomes were converted to 2015 U.S. dollars (USD) using the personal consumption expenditures index published by the U.S. Bureau of Economic Analysis.²⁴

Exposures/Independent Variables. The exposure of interest was TDF/FTC in combination with EFV compared with TDF/FTC in combination with (a) RPV, (b) EVG/c, or (c) boosted PIs. These 3 TDF/FTC-based FDC regimens were ascertained based on pharmacy claims information.

Covariates/Control Variables. Patient characteristics with a known or theoretical association with exposures and outcomes were identified based on literature search and expert consensus. Identified covariates measured during the pre-index period included demographics (i.e., age, race, body mass index, marital status, sex), disease severity measures (i.e., CD4 count, viral load), measures of comorbid disease (i.e., bone disease, albumin, eGFR, and comorbid conditions), drug exposures (i.e., methadone, proton pump inhibitors, bisphosphonates), and cost. These were assessed in the 6 months before each patient's index date and were used to control for potential confounding.

Bone disease during the pre-index period was defined as a diagnosis of osteoporosis/osteopenia by ICD-9/10-CM diagnosis codes, CPT-4 codes, or classification by BMD test result. Data on patient BMD T-scores were derived from narrative records using a validated natural language processing (NLP)

technique.²¹ NLP can be used to extract clinical data from radiology reports, clinicians' progress notes, and other text reports. This validated technique has been applied in previous studies to extract BMD T-scores from radiology reports.²¹⁻²³ In validation, an examination of test characteristics for the tool revealed that the NLP tool for BMD from radiology reports had an overall accuracy of 92.8% for the anatomic site at which the BMD was measured, 92.8% for the value of the BMD T-score, and 90.4% for the matching the correct BMD T-score value with the correct anatomical site.²¹

Statistical Analysis

Outcomes. We reported patient characteristics during the pre-index period using descriptive statistics and assessed differences between the groups using standardized mean differences (SMDs); absolute SMDs >0.1 were considered meaningful differences.²⁵ To control for confounding by indication and selection bias, we estimated inverse probability of treatment (IPT) weights,²⁶ an extension of the propensity score, which represents the conditional probability of receiving the treatment as predicted by covariates described above. IPT weights were calculated from a propensity score generated using logistic regression that estimated the probability that each patient would initiate TDF/FTC plus EFV.²⁶ In the event that covariate balance using IPT weights was not achieved for any of the comparisons, we conducted a sensitivity analysis using matching weights.²⁷ For our multivariable models, we included a category for "missing" data.²⁸

We compared adjusted costs and use outcomes using IPT-weighted Mann-Whitney U-tests to compare distributions for all pair-wise comparisons versus EFV. We also conducted IPT-weighted generalized estimating equation (GEE) regression models to estimate the adjusted mean differences in quarterly overall outpatient, pharmacy, and total costs and outpatient use associated with exposure to each regimen of interest in the weighted cohort. We identified the most appropriate distribution for the GEE model by using the modified Park test.²⁹ In addition, we used the method of recycled predictions to generate estimates of the marginal effect of each exposure on cost and use in the original scale.³⁰ The relative change in cost associated with EFV-based regimens versus each non-EFV regimen was expressed as the expenditure rate ratio (ERR).

Supplemental Analysis. For adjusted mean differences of overall inpatient and radiology costs and use, as well as for adjusted mean differences of any renal and bone cost or use, we used a 2-part model³¹ to calculate the marginal effect associated with each exposure, conditional upon having that cost or use. Specifically, part 1 of the model assessed the odds of having a positive cost (logistic regression) and part 2 assessed the ERR for EFV versus other regimens conditional on having a positive cost (IPT-weighted GEE).

FIGURE 1 Eligibility Criteria for Patient Selection

^aPattern of VA care defined as an inpatient or outpatient encounter at least 365 days before.

^bAs FDC Stribild (Gilead).

^cAs FDC Complera (Gilead) for the vast majority (only 3 patients were taking RPV plus Truvada).

^dAs FDC Atripla (Gilead).

^eAs EFV plus FDC Truvada (Gilead).

ART=antiretroviral therapy; ATV=atazanavir; BMI=body mass index; DRV=darunavir; EVG/c=elvitegravir/cobicistat; FDC=fixed dose combination; HIV=human immunodeficiency virus; LPV=lopinavir; PI=protease inhibitor; RPV=rilpivirine; RTV=ritonavir; TDF/FTC=tenofovir/emtricitabine; VA=Veterans Affairs; VHA=Veterans Health Administration.

Results

Patient Characteristics

Of 33,048 HIV-positive veterans, 13,366 received ART regimens of interest while 7,222 were treatment naive (EFV, n=4,172; non-EFV, n=3,050; Figure 1). The average age of patients in the cohort was 50 years, and 96.5% were male. These patients were followed for an average (standard deviation [SD]) of 13.0 (19.2) months, including 15.0 (21.1), 9.8 (7.6), 9.9 (10.5), and 10.5 (16.7) months for EFV+TDF/FTC,

EVG/c/TDF/FTC, RPV/TDF/FTC, and RTV-boosted PIs+TDF/FTC, respectively. Corresponding median (interquartile range) values were 5.0 (2.0-14.2), 5.7 (2.1-17.9), 4.6 (2.1-10.4), 5.9 (2.8-13.4), and 4.2 (1.8-10.7) months. Patients treated with an EFV regimen had lower mean annual total costs (\$18,000 during the pre-index period) compared with other non-EFV regimens (ranging from \$20,000 for non-EFV and boosted PIs to \$33,000 for EVG/c; Table 1).

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TABLE 1 Unadjusted Characteristics in the Pre-Index Period Among HIV-Infected Veterans Receiving Initial ART with Differing TDF/FTC-Containing Regimens

Characteristic ^a	Initial ART Containing TDF/FTC Plus				
	EFV (n = 4,172)	Non-EFV ^b (n = 3,050)	EVG/c (n = 233)	RPV (n = 173)	RTV-Boosted PI (n = 2,644)
Age, years, mean ± SD	50 ± 10	49 ± 9.8	49 ± 13	48 ± 13	50 ± 9.3
Male	4,033 (96.7)	2,925 (95.9)	222 (95.3)	163 (94.2)	2,540 (96.1)
BMI, kg/m ² , mean ± SD	26 ± 5.0	25 ± 5.1	26 ± 5.6	27 ± 5.3	25 ± 5.1
Married, n (%)	340 (8.1)	224 (7.3)	26 (11.2)	20 (11.6)	178 (6.7)
Race, n (%)					
White	1,256 (30.1)	923 (30.3)	74 (31.8)	48 (27.7)	801 (30.3)
Black	2,509 (60.1)	1,773 (58.1)	124 (53.2)	106 (61.3)	1,543 (58.4)
Hispanic	262 (6.3)	209 (6.9)	19 (8.2)	10 (5.8)	180 (6.8)
Asian	34 (0.8)	28 (0.9)	5 (2.1)	2 (1.2)	21 (0.8)
Other	22 (0.5)	28 (0.9)	2 (0.9)	2 (1.2)	24 (0.9)
CD4+ count, cells/mm ³					
< 200	1,296 (31.1)	1,110 (36.4)	60 (25.8)	23 (13.3)	1,027 (38.8)
200-299	704 (16.9)	481 (15.8)	33 (14.2)	30 (17.3)	418 (15.8)
300-399	639 (15.3)	346 (11.3)	35 (15.0)	11 (6.4)	300 (11.3)
400-499	404 (9.7)	224 (7.3)	24 (10.3)	33 (19.1)	167 (6.3)
≥ 500	597 (14.3)	433 (14.2)	61 (26.2)	65 (37.6)	307 (11.6)
Missing	532 (12.8)	456 (15.0)	20 (8.6)	11 (6.4)	425 (16.1)
HIV viral load, copies/mL					
< 10,000	1,196 (28.7)	959 (31.4)	66 (28.3)	70 (40.5)	823 (31.1)
10,000-100,000	1,445 (34.6)	949 (31.1)	78 (33.5)	67 (38.7)	804 (30.4)
> 100,000	922 (22.1)	691 (22.7)	61 (26.2)	15 (8.7)	615 (23.3)
Missing	609 (14.6)	451 (14.8)	28 (12.0)	21 (12.1)	402 (15.2)
Chronic kidney disease ^c	284 (6.8)	172 (5.6)	16 (6.9)	10 (5.8)	146 (5.5)
eGFR, mL/min/1.73 m ²					
Stage 1, ≥ 90	2,205 (52.9)	1,564 (51.3)	143 (61.4)	110 (63.6)	1,311 (49.6)
Stage 2, 60-89	1,382 (33.1)	997 (32.7)	74 (31.8)	54 (31.2)	869 (32.9)
Stage 3, 30-59	164 (3.9)	124 (4.1)	3 (1.3)	4 (2.3)	117 (4.4)
Stage 4, 15-29	5 (0.1)	7 (0.2)	0 (0.0)	0 (0.0)	7 (0.3)
Stage 5, < 15	39 (0.9)	53 (1.7)	0 (0.0)	0 (0.0)	53 (2.0)
Missing	377 (9.0)	305 (10.0)	13 (5.6)	5 (2.9)	287 (10.9)

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After IPT weighting, all absolute SMDs were <0.10 except for 5 covariates in the RPV comparison, which were between 0.1 and 0.2; these included age, viral load, CKD, cardiovascular disease, and diabetes (Figure 2). After weighting with matching weights, all SMDs were <0.1 (data not shown), meaning the results were qualitatively similar.

Outcomes

Adjusted Mean Total, Inpatient, Outpatient, and Pharmacy Costs. Adjusted mean overall costs were significantly lower for EFV versus all other regimens for every type of cost, including total, outpatient, inpatient, radiology, and pharmacy (all $P < 0.001$; Table 2). Adjusted mean total quarterly cost associated with EFV was \$7,145, compared with \$8,532 with PI-based regimens (the most commonly prescribed drug class of the non-EFV regimens), \$8,726 with all non-EFV regimens combined, \$11,258 with RPV-based regimens, and \$11,728

with EVG/c-based regimens. In the GEE regression, the adjusted mean differences of total quarterly costs were \$1,419 ($P < 0.001$), \$4,488 ($P = 0.012$), \$3,372 ($P = 0.042$), and \$1,303 ($P < 0.001$) lower for EFV regimens versus non-EFV overall, EVG/c, RPV, and PI regimens, respectively (Table 3). Total costs and pharmacy costs were consistently statistically significant, with pharmacy costs being most greatly reduced for EFV in comparison to EVG/c (a reduction of \$1,876; $P < 0.001$). For EFV regimens versus non-EFV regimens, outpatient costs were \$254 ($P = 0.001$) lower, while pharmacy costs were \$600 lower ($P < 0.001$). Compared with all other regimens of interest, ERRs indicated that EFV regimens were associated with significantly lower quarterly expenditure rates for outpatient (9.0%-17.4% lower), pharmacy (20.4%-46.1% lower), or total costs (15.7%-39.5% lower; Table 3). Unadjusted means and standard deviations are presented in Appendix A (available in online article).

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TABLE 1 Unadjusted Characteristics in the Pre-Index Period Among HIV-Infected Veterans Receiving Initial ART with Differing TDF/FTC-Containing Regimens (continued)

Characteristic ^a	Initial ART Containing TDF/FTC Plus				
	EFV (n = 4,172)	Non-EFV ^b (n = 3,050)	EVG/c (n = 233)	RPV (n = 173)	RTV-Boosted PI (n = 2,644)
Comorbidities, n (%)					
CAD/CVD	455 (10.9)	282 (9.2)	28 (12.0)	13 (7.5)	241 (9.1)
Heart failure	134 (3.2)	62 (2.0)	5 (2.1)	2 (1.2)	55 (2.1)
Dyslipidemia	670 (16.1)	419 (13.7)	50 (21.5)	29 (16.8)	340 (12.9)
Hypertension	1,543 (37.0)	921 (30.2)	83 (35.6)	66 (38.2)	772 (29.2)
Diabetes mellitus	567 (13.6)	363 (11.9)	31 (13.3)	19 (11.0)	313 (11.8)
End-stage renal disease ^d	15 (0.4)	13 (0.4)	1 (0.4)	0 (0.0)	12 (0.5)
Viral hepatitis	1,131 (27.1)	909 (29.8)	59 (25.3)	43 (24.9)	807 (30.5)
Tuberculosis	52 (1.2)	46 (1.5)	1 (0.4)	2 (1.2)	43 (1.6)
Psychiatric disorder	1,513 (36.3)	1,396 (45.8)	119 (51.1)	105 (60.7)	1,172 (44.3)
Depression	971 (23.3)	884 (29.0)	83 (35.6)	68 (39.3)	733 (27.7)
Schizophrenia	141 (3.4)	194 (6.4)	12 (5.2)	9 (5.2)	173 (6.5)
Bipolar disorder	647 (15.5)	654 (21.4)	61 (26.2)	63 (36.4)	530 (20.0)
Psychosis	233 (5.6)	310 (10.2)	26 (11.2)	19 (11.0)	265 (10.0)
Posttraumatic stress disorder	372 (8.9)	384 (12.6)	39 (16.7)	53 (30.6)	292 (11.0)
Bone disease ^e	38 (0.9)	27 (0.9)	5 (2.1)	2 (1.2)	20 (0.8)
Tobacco use ^f	1,289 (30.9)	929 (30.5)	70 (30.0)	78 (45.1)	781 (29.5)
Alcohol abuse	957 (22.9)	733 (24.0)	59 (25.3)	51 (29.5)	623 (23.6)
Medications, n (%)					
Methadone	51 (1.2)	72 (2.4)	2 (0.9)	2 (1.2)	68 (2.6)
Proton pump inhibitors	1,191 (28.5)	724 (23.7)	57 (24.5)	24 (13.9)	643 (24.3)
Bisphosphonates	21 (0.5)	18 (0.6)	0 (0.0)	1 (0.6)	17 (0.6)

^aPre-index comorbidities and clinical characteristics were identified in the 6- to 12-month pre-index period.

^bNon-EFV included the EVG/c, RPV, and RTV-boosted PI groups.

^cDefined as either a chronic kidney disease diagnosis or 2 consecutive measures of eGFR < 60 mL per min per 1.73 m² occurring at least 30 days apart.

^dDefined as either a diagnosis of end-stage renal disease, kidney transplant, or dialysis.

^eBone disease defined as diagnosis of osteoporosis/osteopenia or fracture (vertebral, hip, upper arm, forearm, and wrist) by International Classification of Diseases diagnosis codes; Current Procedural Terminology, 4th Edition, codes; or classification by bone mineral density test result.

^fIncluded abuse, dependence, rehabilitation, and toxicity related to tobacco.

ART=antiretroviral therapy; BMI=body mass index; CAD=coronary artery disease; CVD=cerebrovascular disease; EFV=efavirenz; eGFR=estimated glomerular filtration rate; EVG/c=elvitegravir/cobicistat; FTC=emtricitabine; HIV=human immunodeficiency virus; PI=protease inhibitor (atazanavir, darunavir, or lopinavir); RPV=rilpivirine; RTV=ritonavir; SD=standard deviation; TDF=tenofovir disoproxil fumarate.

Adjusted Mean Renal- and Bone-Specific Costs. Adjusted mean renal and bone costs were only a small fraction of the overall costs associated with each exposure. Quarterly renal costs ranged from \$29 on the RPV regimen (vs. \$11,258 total costs on RPV) to \$88 on the EVG/c regimen (vs. \$11,728 total costs on EVG/c). Bone costs ranged from \$6 on the EVG/c regimen (vs. \$11,728 total costs) to \$114 on the RPV regimen (vs. \$11,258 total costs). Differences were statistically significant for many comparisons, with some comparisons favoring EFV and others favoring comparators (Table 2).

Inpatient and Outpatient Utilization. Overall outpatient and inpatient use on EFV regimens were also significantly lower compared with all non-EFV regimens as well as each of the individual regimens (Table 2). The overall total quarterly outpatient encounters were lower with EFV compared with all non-EFV regimens; mean differences were -2.39 ($P < 0.001$),

-5.25 ($P = 0.006$), -9.53 ($P = 0.050$; 95% confidence interval [CI] = -19.08-0.02), and -2.40 ($P = 0.001$) versus non-EFV, EVG/c, RPV, and PI regimens, respectively (Table 3).

Notably, renal and bone use followed the trends of overall use, being generally lower for patients on EFV than on any other regimen and significantly so only in comparisons with EVG/c and RPV regimens (Table 2).

Supplemental 2-Part Models. Because very few patients had zero outpatient or pharmacy costs in the overall analyses, 2-part models were not undertaken for these outcomes in that analysis. In overall 2-part models, the odds of having a positive inpatient or radiology cost were significantly lower for patients on EFV compared with those on PI-based regimens (part 1 models: Appendix B, available in online article). However, among patients who incurred an overall inpatient or radiology cost, none of the mean differences between regimens for such costs

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FIGURE 2

Patient Characteristics in the Pre-Index Period: Verification that IPT Weighting Achieves Covariate Balance Between TDF/FTC-Containing Regimens with EFV Versus All Non-EFV, EVG/c, RPV, and RTV-Boosted PIs

CAD=coronary artery disease; CVD=cerebrovascular disease; EFV=efavirenz; eGFR=estimated glomerular filtration rate; EVG/c=elvitegravir/cobicistat; FTC=emtricitabine; HIV=human immunodeficiency virus; IPT=inverse probability of treatment; PI=protease inhibitor (atazanavir, darunavir, or lopinavir); RPV=rilpivirine; RTV=ritonavir; TDF=tenofovir disoproxil fumarate.

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TABLE 2 IPT-Adjusted Means and Standard Deviations for Overall, Renal-Specific, and Bone-Specific Quarterly Costs and Use^a

	EFV	All Non-EFV	P Value ^b	EVG/c	P Value ^b	RPV	P Value ^b	RTV-Boosted PI	P Value ^b
Number	4,172	3,050		233		173		2,644	
Quarters	5.6	4.0		3.0		3.9		4.0	
Patient-quarters	23,189	12,073		707		667		10,699	
Overall									
VA cost, \$									
Outpatient	2,656 (26)	2,942 (43)	<0.001	3,068 (179)	<0.001	3,410 (287)	<0.001	3,036 (47)	<0.001
Inpatient	2,009 (81)	2,614 (161)	<0.001	4,253 (1,509)	<0.001	4,399 (1,441)	<0.001	2,583 (153)	<0.001
Radiology	213 (7)	276 (23)	<0.001	258 (35)	<0.001	285 (61)	<0.001	286 (26)	<0.001
Pharmacy	2,480 (39)	3,170 (48)	<0.001	4,407 (181)	<0.001	3,866 (271)	<0.001	3,223 (53)	<0.001
Total cost	7,145 (97)	8,726 (180)	<0.001	11,728 (1,585)	<0.001	11,258 (1,499)	<0.001	8,532 (169)	<0.001
VA use									
Outpatient encounters	18.3 (0.4)	20.7 (0.3)	<0.001	23.1 (17.6)	<0.001	27.6 (2.5)	<0.001	20.4 (0.3)	<0.001
Inpatient days	1.5 (0.1)	1.9 (0.1)	<0.001	1.7 (0.3)	<0.001	1.7 (0.4)	<0.001	1.9 (0.1)	<0.001
Renal									
VA cost, \$									
Outpatient	9 (1)	11 (2)	0.248	14 (5)	<0.001	9 (8)	<0.001	11 (2)	0.239
Inpatient	40 (10)	37 (9)	0.009	74 (57)	<0.001	19 (13)	0.082	36 (9)	0.014
Total	49 (11)	48 (9)	0.35	88 (61)	<0.001	29 (16)	<0.001	47 (10)	0.110
VA use									
Outpatient encounters	0.054 (0.004)	0.062 (0.007)	0.977	0.130 (0.084)	0.007	0.125 (0.036)	<0.001	0.059 (0.007)	0.933
Inpatient days	0.087 (0.009)	0.087 (0.012)	0.182	0.150 (0.045)	<0.001	0.429 (0.196)	<0.001	0.073 (0.010)	0.408
Bone									
VA cost, \$									
Outpatient	10 (3)	8 (2)	0.172	6 (3)	<0.001	27 (23)	0.603	6 (2)	<0.001
Inpatient	20 (8)	14 (7)	0.542	0 (0)	0.008	88 (75)	<0.001	12 (7)	0.008
Total	29 (9)	22 (7)	0.004	6 (3)	<0.001	114 (81)	<0.001	18 (7)	<0.001
VA use									
Outpatient encounters	0.014 (0.003)	0.018 (0.003)	0.023	0.020 (0.009)	0.079	0.058 (0.032)	0.002	0.016 (0.002)	0.105
Inpatient days	0.014 (0.005)	0.03 (0.009)	0.001	0.071 (0.046)	0.029	0.017 (0.015)	<0.001	0.031 (0.012)	0.002

^aCosts are in 2015 U.S. dollars.

^bP value versus EFV. P values are derived from weighted Mann-Whitney U-tests.

EFV = efavirenz; EVG/c = elvitegravir/cobicistat; IPT = inverse probability of treatment; PI = protease inhibitor (atazanavir, darunavir, or lopinavir); RPV = rilpivirine; RTV = ritonavir; SD = standard deviation; VA = Veterans Affairs.

were significant after adjustment (part 2 models: Appendix B). Similarly, the odds of having positive inpatient use were lower with EFV versus all non-EFV regimens; however, among these patients with positive inpatient use, there were no significant adjusted mean differences in inpatient use (Appendix B).

In renal 2-part models, the odds of having a positive pharmacy cost was significantly higher versus EVG/c; however, among these patients with a positive cost, the adjusted mean difference in cost was not significant (Appendix B). The odds of having positive inpatient costs, inpatient use, and outpatient use were significantly lower with EFV versus a number of comparators; however, among these patients with positive costs, significant adjusted mean differences in cost were found for only 2 comparisons (EFV vs. PI for inpatient cost, difference \$10,254, $P=0.041$; and EFV vs. RPV for outpatient encounters, difference 0.69, $P=0.014$; Appendix B).

In bone 2-part models, the odds of having a positive inpatient cost was significantly lower versus RPV; however, among these patients with a positive cost, the adjusted mean difference in cost was not significant (Appendix B). No other bone outcomes showed significantly different odds of having a positive cost.

Discussion

We identified the cost and use effects of different third agents in TDF/FTC ART regimens within a nationwide VHA setting. Adjusted mean quarterly overall costs and use consistently and significantly favored EFV over boosted PIs, EVG/c, and RPV in combination with TDF/FTC, including total, inpatient, outpatient, pharmacy, and radiology costs. We found that patients receiving EFV regimens had quarterly costs that were \$1,419 (95% CI = \$843-\$1,994) lower than those receiving all non-EFV

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TABLE 3 Adjusted Results from IPT-Weighted GEE Model for Quarterly Overall Costs and Utilizations^a

	PQs	ERR (95% CI)	P Value	Mean Difference per PQ \$ (95% CI)	P Value
EFV vs. non-EFV					
Cost					
Outpatient	35,262	0.910 (0.860-0.963)	0.001	-254 (-408--100)	0.001
Pharmacy	35,262	0.795 (0.750-0.842)	<0.001	-600 (-752--447)	<0.001
Total	35,262	0.836 (0.780-0.897)	<0.001	-1,419 (-1,994--843)	<0.001
Utilization					
Outpatient	35,262	0.881 (0.821-0.945)	<0.001	-2.39 (-3.72--1.06)	<0.001
EFV vs. EVG/c					
Cost					
Outpatient	23,896	0.826 (0.703-0.970)	0.020	-520 (-985--54)	0.029
Pharmacy	23,896	0.539 (0.481-0.603)	<0.001	-1,876 (-2,299--1,452)	<0.001
Total	23,896	0.599 (0.433-0.829)	0.002	-4,488 (-7,987--990)	0.012
Utilization					
Outpatient	23,896	0.763 (0.639-0.910)	0.003	-5.25 (-8.99--1.52)	0.006
EFV vs. RPV					
Cost					
Outpatient	23,856	0.903 (0.682-1.195)	0.476	-270 (-1,045-505)	0.494
Pharmacy	23,856	0.645 (0.555-0.750)	<0.001	-1,267 (-1,791--742)	<0.001
Total	23,856	0.675 (0.492-0.926)	0.015	-3,372 (-6,617--128)	0.042
Utilization					
Outpatient	23,856	0.643 (0.448-0.923)	0.017	-9.53 (-19.08-0.02)	0.050
EFV vs. RTV-boosted PIs					
Cost					
Outpatient	33,888	0.898 (0.847-0.953)	<0.001	-286 (-446--126)	<0.001
Pharmacy	33,888	0.796 (0.750-0.846)	<0.001	-579 (-736--422)	<0.001
Total	33,888	0.846 (0.790-0.906)	<0.001	-1,303 (-1,850--756)	<0.001
Utilization					
Outpatient	33,888	0.878 (0.816-0.945)	0.001	-2.40 (-3.77--1.03)	0.001

^aCosts are in 2015 U.S. dollars.

CI=confidence interval; EFV=efavirenz; ERR=expenditure rate ratio; EVG/c=elvitegravir/cobicistat; GEE=generalized estimating equation; IPT=inverse probability of treatment; PI=protease inhibitor (atazanavir, darunavir, or lopinavir); PQs=patient-quarters; RPV=rilpivirine; RTV=ritonavir.

regimens combined. Furthermore, the adjusted mean differences of pharmacy costs all favored EFV over the other regimens, with pharmacy cost savings ranging from \$579 versus PIs to \$1,876 versus EVG/c. This study is the first to quantify total, inpatient, outpatient, pharmacy, and radiology costs associated with differing third agents in TDF/FTC regimens. These results shed light on the effect of ART regimens on mean quarterly cost from the patient's perspective. The overall cost advantages of EFV regimens (80.3% EFV/FTC/TDF (Atripla, Gilead) and 29.7% EFV+FTC/TDF (Truvada, Gilead; Figure 1) versus non-EFV regimens may be due to several possible reasons. They may be directly related to regimen cost or unmeasured concomitant medications; alternatively, they may be due to unmeasured adverse outcomes from other comorbidities exacerbated by TDF/FTC regimens.

Although renal and bone use followed the trends of overall use in the primary analysis, 2-part models, exploring renal and

bone costs and use in the smaller population of patients who did have positive costs or use, did not consistently follow the overall results. Renal and bone costs were a very small proportion of overall costs, and the CIs in analysis were often wide in these 2-part analyses due to the small sample sizes. Because renal- and bone-specific costs made up such a small proportion of overall costs (<1% according to our data), we concluded that renal and bone disease were not major contributors to the overall cost of long-term HIV treatment in this population.

The disconnect between the overall and the renal and bone costs can likely be attributed to the rarity of renal and bone outcomes but also to other, unmeasured health care needs. HIV drug costs are the main cost for long-term HIV patients, although estimates vary from setting to setting.^{18,32} The cost-effectiveness analysis (CEA) conducted by Simpson et al. (2013) provides a list of other common health care needs for patients with HIV,¹⁸ gleaned from South Carolina

Medicaid data from the early highly active antiretroviral therapy era (i.e., 2002-2003, all inflated to 2011 USD). For example, chronic opportunistic infections requiring ongoing treatment were found to cost anywhere from \$5,052 annually for cytomegalovirus colitis to \$120,000 annually for cytomegalovirus retinitis.¹⁸ Nonserious side effects priced low (from \$0 to \$223 per episode), while serious side effects (including renal failure at \$7,913 per episode) and acute opportunistic infections were more costly, ranging from \$1,336 for an episode of viral infection causing cervical cancer to \$20,248 for a histoplasmosis episode. Although the current relative costs of HIV-related events can only be approximated from this list, due to its age and the fact that it focuses primarily on health care needs of patients on PIs, we can infer the relative frequency, importance, and costliness of renal events compared with other HIV- and ART-related events such as acute and chronic infections, even if it does not provide us with real-world incidences of these needs.

Numerous CEAs that compare various ART regimens, several of which include renal AEs as model inputs, rarely feature renal or bone disease as an outcome associated with ART generally, and none with TDF/FTC specifically.³³⁻³⁵ One CEA by Juday et al. (2013) determined that the FDC TDF/FTC/EVG/c was not cost-effective when compared with the FDC TDF/FTC/EFV at \$100,000/quality-adjusted life years; these results were very sensitive to likelihood of renal AEs.³⁶ Ultimately, most of these analyses considered renal disease as only a contributing factor to the overall cost of HIV or ART, and only one¹² considered bone disease as a contributing factor. Cumulatively, these studies and other CEAs investigating ART generally¹⁵⁻¹⁹ indicate a research need to analyze the economic burden of various components of HIV care associated with different TDF/FTC-based ART regimens.

A key strength of this study can be attributed to the use of VHA datasets. The VHA is the largest integrated provider of HIV care in the United States, allowing a large sample size and to evaluate multiple subgroups.³⁷ The majority market share, single payer, and integrated care attributes of this population enable observations to be made with robust estimates across the HIV continuum of care.

Limitations

Limitations of this study include those typical of observational studies. First, there was an increased risk of residual confounding due to unmeasured differences in patient characteristics during the pre-index period. However, IPT weighting can reliably produce 2 groups that are balanced with respect to measured confounders, allowing valid inferences about treatment

differences to be made. Nonetheless, IPT weighting is unable to control for unmeasured confounders that may affect the choice of initial ART or unmeasured outcomes in the study.

Second, the costs and use captured in our study likely represent an underestimate of total costs and use within the cohort because of health care encounters and costs being limited to those occurring within the VHA; a quarter to nearly one-half of veterans receive some health care in non-VHA facilities.³⁸⁻⁴⁰ Studies comparing demographic and disease characteristics in populations receiving exclusive VHA versus mixed VHA/Medicare services are conflicting; for example, 1 investigation found that patients considered at highest risk were more likely to be receiving mixed VHA and Medicare than exclusive VHA services,⁴¹ and in another investigation, patients with higher indices of socioeconomic advantage were more likely to be receiving mixed versus exclusive VHA services.⁴² However, given the age distribution of our VHA population, less than 5% would have been eligible for Medicare, making it unlikely that dual health care usage affected our conclusions.

Third, because the follow-up time for patients in our cohort varied substantially, we divided the follow-up period into quarters. Alternative statistical methods exist to analyze health care costs in the presence of censoring. For example, Lin et al. (1997) proposed an approach that constructs a survival-adjusted estimator.⁴³ Bang and Tsiatis (2000) improved on this approach by performing inverse probability weighting with survival from censoring probabilities and assuming continuous death and censoring times.⁴⁴ Basu and Manning (2010) extended these methods to allow for estimation of the effect of covariates on survival effects and intensity effects separately.⁴⁵ Future work should apply these methods to estimate the health care costs associated with TDF/FTC ART regimens.

Fourth, the VHA patient population has a small number of females, which limits the generalizability of the results to the wider population of patients with HIV infection, particularly concerning osteoporosis, where disease burden and treatment differ substantially between men and women.⁴⁶ Finally, because the outcomes have been historically obtained rather than gathered prospectively, the lack of ascertainment of non-VHA pharmacotherapies or care limits the generalizability of these findings to non-VHA contexts.

Conclusions

We found that patients on TDF/FTC regimens with EFV had lower overall health care costs and were less likely to have inpatient admissions than those on regimens of TDF/FTC plus RPV, EVG/c, or boosted PIs.

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DISCLOSURES

This study was funded by Bristol-Myers Squibb. Nelson, Ma, Crook, Knippenberg, Nyman, and LaFleur are employees of the University of Utah, which received a grant from Bristol-Myers Squibb to conduct this study. Nyman also discloses honoraria for consulting from Otsuka and for writing a book chapter from Fresenius. La Fleur reports advisory board and consulting fees from Bristol-Myers Squibb outside of this study. Paul and Esker are employees of, and own stock in, Bristol-Myers Squibb.

ACKNOWLEDGMENTS

Medical writing assistance was provided by Julian Martins of Science Communications, Springer Healthcare, which was funded by Bristol-Myers Squibb.

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N	4,172		3,050		233		173		2,644	
Quarters	5.6		4.0		3.0		3.9		4.0	
Patient-quarters	23,189		12,073		707		667		10,699	
Overall										
VA cost, \$										
Outpatient	2,612	(3,619)	2,999	(4,737)	3,201	(4,258)	3,222	(4,558)	2,971	(4,778)
Inpatient	1,927	(11,639)	2,736	(17,995)	4,979	(45,276)	3,752	(20,487)	2,525	(14,267)
Radiology	215	(1,031)	271	(2,278)	276	(1,218)	298	(1,477)	269	(2,371)
Pharmacy	2,444	(6,625)	3,234	(5,183)	4,472	(4,499)	3,814	(4,805)	3,116	(5,235)
Total	6,983	(14,361)	8,969	(19,988)	12,652	(46,960)	10,788	(22,318)	8,612	(16,524)
VA use										
Outpatient encounters	17.5	(26.77)	21.29	(32.08)	24.80	(39.03)	27.11	(43.01)	20.70	(30.70)
Inpatient days	1.35	(7.55)	2.08	(9.72)	1.91	(7.88)	3.13	(12.79)	2.02	(9.60)
Renal										
VA cost, \$										
Outpatient	10	(230)	10	(208)	11	(103)	7	(100)	10	(218)
Inpatient	38	(1,451)	40	(1,032)	53	(1,103)	81	(1,278)	36	(1,010)
Radiology	9	(9)	0	(12)	0	(0)	0	(0)	0	(12)
Pharmacy	2	(14)	3	(166)	1	(4)	2	(8)	3	(177)
Total	48	(1,483)	49	(1,084)	64	(1,179)	88	(1,366)	46	(1,057)
VA use										
Outpatient encounters	0.06	(0.60)	0.06	(0.78)	0.10	(1.61)	0.12	(1.25)	0.06	(0.65)
Inpatient days	0.09	(1.34)	0.09	(1.45)	0.17	(1.26)	0.30	(3.64)	0.08	(1.20)
Bone										
VA cost, \$										
Outpatient encounters	11	(502)	8	(311)	4	(52)	51	(1,108)	6	(179)
Inpatient	20	(1,255)	15	(751)	0	(0)	78	(1,367)	12	(720)
Radiology	0.04	(5.64)	0.11	(11)	0	(0)	0	(0)	0.13	(12)
Pharmacy	0.45	(16)	0.53	(16)	0.04	(0.44)	0.02	(0.54)	0.60	(17)
Total	32	(1,373)	24	(828)	4	(52)	129	(1,858)	19	(745)
VA use										
Outpatient encounters	0.01	(0.26)	0.02	(0.33)	0.03	(0.38)	0.07	(0.92)	0.02	(0.24)
Inpatient days	0.01	(0.72)	0.03	(1.25)	0.11	(2.00)	0.01	(0.24)	0.03	(1.22)

^aCosts are in 2015 U.S. dollars.

EFV = efavirenz; EVG/c = elvitegravir/cobicistat; PI = protease inhibitor (atazanavir, darunavir, or lopinavir); RPV = rilpivirine; RTV = ritonavir; SD = standard deviation; VA = Veterans Affairs.

Health Care Costs in a Cohort of HIV-Infected U.S. Veterans Receiving Regimens Containing Tenofovir Disoproxil Fumarate/Emtricitabine

APPENDIX B Adjusted Results from IPT-Weighted 2-Part Model for Overall, Renal-Specific, and Bone-Specific Inpatient Quarterly Costs and Use and Radiology Costs^a

	Part 1: Positive Cost vs. No Cost ^b				Part 2: EFV vs. Other Regimens Conditional on Having a Positive Cost ^c						
	PQs	Odds Ratio (95% CI)		P Value	PQs	ERR (95% CI)		P Value	Mean Difference (95% CI)		P Value
Overall											
EFV vs. non-EFV											
Inpatient cost	35,262	0.863	(0.778-0.958)	0.006	2,975	0.914	(0.804-1.039)	0.171	-2,265	(-5,566-1,035)	0.179
Radiology cost	35,262	0.932	(0.869-0.999)	0.046	11,088	0.817	(0.672-0.993)	0.042	-154	(-313-6)	0.059
Inpatient use	35,262	0.876	(0.797-0.964)	0.006	3,754	0.966	(0.829-1.125)	0.654	-0.56	(-3.02-1.90)	0.655
EFV vs. EVG/c											
Inpatient cost	23,896	0.880	(0.638-1.213)	0.434	1,855	0.612	(0.344-1.089)	0.095	-14,809	(-36,405-6,788)	0.179
Radiology cost	23,896	0.990	(0.784-1.251)	0.936	7,362	0.840	(0.638-1.107)	0.216	-128	(-341-86)	0.242
Inpatient use	23,896	0.744	(0.567-0.977)	0.033	2,975	1.159	(0.836-1.607)	0.377	1.99	(-2.21-6.19)	0.354
EFV vs. RPV											
Inpatient cost	23,856	0.604	(0.321-1.138)	0.119	1,857	0.890	(0.555-1.426)	0.627	-3,119	(-16,581-10,343)	0.650
Radiology cost	23,856	0.953	(0.636-1.427)	0.814	7,349	0.897	(0.496-1.620)	0.718	-79	(-529-371)	0.731
Inpatient use	23,856	0.624	(0.422-0.922)	0.018	2,220	1.405	(0.876-2.255)	0.158	4.13	(-0.78-9.03)	0.099
EFV vs. RTV-boosted PIs											
Inpatient cost	33,888	0.856	(0.768-0.954)	0.005	2,829	0.945	(0.834-1.070)	0.371	-1,413	(-4,536-1,710)	0.375
Radiology cost	33,888	0.926	(0.861-0.995)	0.036	10,659	0.815	(0.662-1.004)	0.054	-154	(-325-16)	0.076
Inpatient use	33,888	0.844	(0.765-0.932)	0.001	3,556	0.955	(0.811-1.119)	0.572	-0.73	(-3.271-8.2)	0.576
Renal											
EFV vs. non-EFV											
Cost											
Outpatient	35,262	0.867	(0.636-1.180)	0.364	406	0.903	(0.525-1.553)	0.712	-88	(-562-386)	0.715
Inpatient	35,262	0.593	(0.363-0.968)	0.037	70	1.794	(1.088-2.960)	0.022	10,821	(260-21,381)	0.045
Radiology ^d	35,262				5						
Pharmacy	35,262	1.013	(0.882-1.163)	0.859	5,432	0.524	(0.167-1.639)	0.267	-10	(-35-14)	0.417
Total	35,262	0.851	(0.638-1.137)	0.275	5,708	1.004	(0.566-1.779)	0.990	1	(-192-195)	0.990
Utilization											
Outpatient	35,262	0.979	(0.772-1.242)	0.861	268	0.891	(0.646-1.229)	0.483	-0.23	(-0.89-0.43)	0.489
Inpatient	35,262	0.878	(0.683-1.128)	0.308	37	1.199	(0.553-2.600)	0.645	3.43	(-10.75-17.62)	0.635
EFV vs. EVG/c											
Cost											
Outpatient	23,896	0.675	(0.295-1.547)	0.353	277	1.031	(0.652-1.630)	0.895	24	(-340-389)	0.895
Inpatient	23,896	0.446	(0.061-3.282)	0.428	40	1.250	(0.867-1.804)	0.232	4,691	(-3,874-13,256)	0.283
Radiology ^d	23,896				0						
Pharmacy	23,896	2.445	(1.507-3.967)	0.000	3,900	1.897	(0.892-4.038)	0.096	7	(-1-14)	0.089
Total	23,896	0.737	(0.324-1.677)	0.467	4,073	0.310	(0.054-1.793)	0.191	-538	(-1,748-672)	0.384
Utilization											
Outpatient	23,896	0.768	(0.507-1.164)	0.213	635	0.360	(0.094-1.383)	0.137	-3.33	(-10.08-3.42)	0.334
Inpatient	23,896	0.553	(0.380-0.805)	0.002	248	1.321	(0.885-1.972)	0.173	2.09	(-0.65-4.84)	0.135
EFV vs. RPV											
Cost											
Outpatient	23,856	0.726	(0.186-2.834)	0.645	273	1.911	(1.325-2.758)	0.001	374	(107-640)	0.006
Inpatient	23,856	1.542	(0.351-6.769)	0.566	41	1.303	(0.848-2.003)	0.228	5,790	(-4,875-16,455)	0.287
Radiology ^d	23,856				0						
Pharmacy	23,856	0.711	(0.288-1.760)	0.461	3,943	0.775	(0.361-1.665)	0.513	-3	(-15-8)	0.572
Total	23,856	0.765	(0.199-2.938)	0.696	4,112	2.965	(1.077-8.164)	0.035	197	(34-360)	0.018
Utilization											
Outpatient	23,856	0.544	(0.300-0.986)	0.045	652	1.532	(1.008-2.329)	0.046	0.69	(0.14-1.24)	0.014
Inpatient	23,856	0.450	(0.266-0.762)	0.003	246	1.077	(0.614-1.891)	0.795	0.61	(-3.74-4.96)	0.784

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Health Care Costs in a Cohort of HIV-Infected U.S. Veterans Receiving Regimens Containing Tenofovir Disoproxil Fumarate/Emtricitabine

APPENDIX B Adjusted Results from IPT-Weighted 2-Part Model for Overall, Renal-Specific, and Bone-Specific Inpatient Quarterly Costs and Use and Radiology Costs^a (continued)

	Part 1: Positive Cost vs. No Cost ^b				Part 2: EFV vs. Other Regimens Conditional on Having a Positive Cost ^c						
	PQs	Odds Ratio (95% CI)		P Value	PQs	ERR (95% CI)		P Value	Mean Difference (95% CI)		P Value
EFV vs. RTV-boosted PIs											
Cost											
Outpatient	33,888	0.856	(0.620-1.181)	0.343	390	0.917	(0.521-1.614)	0.764	−75	(−573-422)	0.767
Inpatient	33,888	0.599	(0.360-0.999)	0.049	65	1.781	(1.080-2.937)	0.024	10,254	(431-20,078)	0.041
Radiology ^d	33,888				5						
Pharmacy	33,888	0.995	(0.863-1.147)	0.946	5,245	0.499	(0.154-1.618)	0.247	−11	(−38-15)	0.409
Total	33,888	0.833	(0.617-1.125)	0.234	5,509	1.001	(0.565-1.775)	0.996	0.49	(−188-189)	0.996
Utilization											
Outpatient	33,888	0.935	(0.820-1.066)	0.314	871	0.886	(0.694-1.131)	0.331	−0.27	(−0.83-0.28)	0.338
Inpatient	33,888	0.912	(0.808-1.031)	0.140	246	1.077	(0.614-1.891)	0.795	0.61	(−3.74-4.96)	0.784
Bone											
EFV vs. non-EFV											
Cost											
Outpatient	35,262	0.934	(0.656-1.328)	0.703	235	1.476	(0.663-3.287)	0.341	522	(−610-1,653)	0.366
Inpatient	35,262	0.813	(0.333-1.982)	0.648	21	1.668	(0.711-3.915)	0.240	15,435	(−12,793-43,664)	0.284
Radiology ^d	35,262				4						
Pharmacy	35,262	1.231	(0.663-2.284)	0.510	293	1.175	(0.478-2.892)	0.725	10	(−48-68)	0.731
Total	35,262	1.055	(0.729-1.527)	0.775	523	1.487	(0.603-3.667)	0.389	799	(−1,093-2,691)	0.408
Utilization											
Outpatient	35,262	0.941	(0.803-1.103)	0.453	268	0.891	(0.646-1.229)	0.483	−0.23	(−0.89-0.43)	0.489
Inpatient	35,262	0.512	(0.240-1.093)	0.084	37	1.199	(0.553-2.600)	0.645	3.43	(−10.75-17.62)	0.635
EFV vs. EVG/c											
Cost											
Outpatient	23,896	0.663	(0.272-1.619)	0.367	152	2.943	(1.480-5.852)	0.002	1,277	(23-2,532)	0.046
Inpatient	23,896				13						
Radiology ^d	23,896				0						
Pharmacy	23,896	0.844	(0.200-3.562)	0.818	193	15.078	(8.496-26.759)	0.000	107	(29-185)	0.007
Total	23,896	0.835	(0.306-2.283)	0.726	337	7.786	(2.992-20.267)	0.000	3,179	(431-5,928)	0.023
Utilization											
Outpatient	23,896	0.803	(0.300-2.152)	0.663	176	0.933	(0.384-2.267)	0.879	−0.14	(−1.97-1.70)	0.882
Inpatient	23,896	0.265	(0.058-1.205)	0.086	19	0.761	(0.303-1.912)	0.561	−6.34	(−30.46-17.77)	0.606
EFV vs. RPV											
Cost											
Outpatient	23,856	0.851	(0.293-2.473)	0.767	155	0.396	(0.092-1.706)	0.214	−2,661	(−9,013-3,691)	0.412
Inpatient	23,856	0.138	(0.030-0.641)	0.011	16	1.574	(0.686-3.610)	0.284	11,023	(−7,737-29,782)	0.249
Radiology ^d	23,856				0						
Pharmacy	23,856	2.377	(0.317-17.857)	0.400	187	4.430	(2.587-7.589)	0.000	84	(9-159)	0.028
Total	23,856	1.512	(0.543-4.209)	0.428	333	0.140	(0.058-0.341)	0.000	−11,975	(−21,971-−1,979)	0.019
Utilization											
Outpatient	23,856	0.680	(0.218-2.127)	0.508	174	0.336	(0.133-0.849)	0.021	−4.19	(−10.51-2.13)	0.194
Inpatient	23,856	0.197	(0.037-1.049)	0.057	18	4.097	(3.054-7.817)	0.000	11.55	(3.88-19.22)	0.003
EFV vs. RTV-boosted PIs											
Cost											
Outpatient	33,888	1.007	(0.691-1.468)	0.971	222	1.914	(0.881-4.157)	0.101	806	(−330-1941)	0.164
Inpatient	33,888	1.118	(0.398-3.143)	0.832	18	1.521	(0.584-3.966)	0.391	13,678	(−19,471-46,827)	0.419
Radiology ^d	33,888				4						
Pharmacy	33,888	1.290	(0.673-2.473)	0.443	285	1.014	(0.440-2.336)	0.974	1	(−50-51)	0.974
Total	33,888	1.109	(0.750-1.638)	0.605	503	1.873	(0.683-5.136)	0.223	1,171	(−837-3,180)	0.253
Utilization											
Outpatient	33,888	0.904	(0.576-1.419)	0.661	252	0.986	(0.133-0.849)	0.021	−0.03	(−0.62-0.57)	0.930
Inpatient	33,888	0.608	(0.266-1.389)	0.238	32	1.036	(0.436-2.464)	0.936	0.70	(−16.40-17.81)	0.936

^aCosts are in 2015 U.S. dollars.

^bLogistic regression analysis.

^cIPT-weighted generalized estimating equations analysis.

^dNot enough patients with radiology costs to analyze.

CI = confidence interval; ERR = expenditure rate ratio; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; IPT = inverse probability of treatment; PI = protease inhibitor (atazanavir, darunavir, or lopinavir); PQs = patient-quarters; RPV = rilpivirine; RTV = ritonavir.