The Journal of Infectious Diseases

MAJOR ARTICLE

Comorbidities Among US Patients With Prevalent HIV Infection—A Trend Analysis

Joel Gallant,[1] Priscilla Y. Hsue,[2] Sanatan Shreay,[3] and Nicole Meyer[4]

[1]Southwest CARE Center, Santa Fe, New Mexico; [2]University of California San Francisco, San Francisco, and [3]Gilead Sciences, Foster City, California; and [4]Truven Health Analytics, Cambridge, Massachusetts

(See the editorial commentary by van der Valk and Reiss on pages 1481–3.)

Objective. Quantify proportion of human immunodeficiency virus (HIV)–infected patients with specific comorbidities receiving healthcare coverage from commercial, Medicaid, and Medicare payers.

Methods. Data from MarketScan research databases were used to select adult HIV-infected patients from each payer. Treated HIV-infected patients were matched to HIV-negative controls. Cross-sectional analyses were performed between 2003 and 2013 among HIV-infected patients to quantify the proportion with individual comorbidities over the period, by payer.

Results. Overall, 36 298 HIV-infected patients covered by commercial payers, 26 246 covered by Medicaid payers, and 1854 covered by Medicare payers were identified between 2003 and 2013. Essential hypertension (31.4%, 39.3%, and 76.2%, respectively), hyperlipidemia (29.2%, 22.1%, and 49.6%), and endocrine disease (21.8%, 27.2%, and 54.0%) were the most common comorbidities. Comparison of data from 2003 to data from 2013 revealed significant increases across payers in the percentage of patients with the comorbidities specified above ($P < .05$). Across all payers, the proportions of treated HIV-infected patients with deep vein thrombosis, hepatitis C, renal impairment, thyroid disease, and liver disease from 2003 to 2013 was significantly greater ($P < .05$) than for matched controls.

Conclusions. Comorbidities are common among the aging HIV-infected population and have increased over time. There should be a consideration in treatment choices for HIV infection, including the choices of antiretroviral regimens.

Keywords. Prevalent HIV; comorbidity trend; US-specific HIV-infected patients.

Improvements in care, including the introduction of antiretroviral therapy (ART) for the treatment of people infected with human immunodeficiency virus (HIV), have resulted in increased life expectancy [1–8]. With early diagnosis and treatment, patients in resource-rich countries can expect to live into their 70s or beyond, although life-span varies on the basis of the mode of HIV transmission, race, and $CD4^+$ T-cell count at the start of ART [2, 4, 5, 8]. In addition to the increased life-span of diagnosed and successfully treated HIV-infected patients, approximately 15% of incident cases of HIV infection are in persons ≥50 years old. As a result of improvements in patient outcomes and longevity, 30% of prevalent cases of HIV infection are in people ≥50 years old [3, 4, 7].

The longer life-span of the HIV-infected population has introduced a new dynamic into the management of these patients, as providers must contend with comorbidities associated with aging. The term "inflammaging" has been used to describe the process whereby ongoing low-grade inflammation that occurs with aging contributes to the development of various conditions [4]. The chronic immune activation and inflammation caused by HIV infection has been suggested as a factor for accelerated or early aging, whereby HIV-infected patients develop comorbidities at younger ages than persons who are HIV negative [9]. Because certain ART agents have been associated with an increased risk of comorbidity, ART may also contribute to higher rates of comorbidities in HIV-infected patients as compared to age-matched HIV-negative controls [1, 4, 7, 9, 10]. A recent study found that the prevalence of noninfectious comorbidities among ART-experienced HIV-infected persons was similar to findings for HIV-uninfected persons who were 10 years older [11].

HIV-infected patients have been shown to be at higher risk for cardiovascular (CV) disease, hepatic and renal disease, osteoporosis and fractures, metabolic disorders, and several non–AIDS-defining cancers [4, 10, 12–27]. Causal relationships have not been established for all of these associations. Persons with HIV infection have a higher number of comorbidities, compared with HIV-negative people, and the risk for specific comorbidities is higher in older age [9, 12]. A pattern of higher rates of multiple comorbidities has also been observed in older HIV-infected patients who seroconverted at an earlier age as compared to those who were infected at a later age [13].

Received 10 March 2017; editorial decision 26 August 2017; accepted 25 September 2017; published online December 15, 2017.

Presented in part: American Society of Nephrology, San Diego, California, 3–8 November 2015; International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention, Vancouver, Canada, 19–22 July 2015; IDWeek 2015, San Diego, California, 7–11 October 2015; IDWeek 2016, New Orleans, Louisiana, 26–30 October 2016; Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, California, 17–21 September 2015.

Correspondence: N. Meyer, MA, Truven Health Analytics, an IBM Company, 75 Binney St, Cambridge, MA 02142 (nfulcher@us.ibm.com).

The Journal of Infectious Diseases® 2017;216:1525–33

DOI: 10.1093/infdis/jix518

HIV-infected patients receiving ART are now living longer and are likely to acquire chronic conditions related to normal aging, as well as to HIV infection and its treatment. Certain ART regimens have been associated with an increased risk of CV-, renal-, and bone-related adverse events [11, 14, 16, 19, 25, 28]. Recent literature has documented an association between abacavir-based regimens and an increased risk of myocardial infarction in HIV-infected patients, although the association diminished in magnitude and statistical significance after adjustment for traditional risk factors [14, 28]. Tenofovir disoproxil fumarate–based regimens have been associated with reduced renal function [29, 30] and loss of bone mineral density [31, 32]. Some evidence exists indicating tenofovir disoproxil fumarate–associated reductions in bone mineral density may translate into an increase in fracture risk [33]. Thus, optimal treatment for HIV-infected patients requires a focus beyond just viral suppression. Therapeutic management requires targeted efforts to preserve the long-term health of HIV-infected patients as they age and experience an increased duration of ART exposure.

Many existing studies of comorbidities in the HIV-infected population had a small sample size [7] or were conducted in countries outside the United States [9, 11, 12, 14, 28]. Comorbidities in US HIV-infected patients have not been well documented across different healthcare coverage payers. The objective of this study was to quantify the proportion of US HIV-infected patients with specific comorbidities receiving coverage under commercial, Medicaid, and Medicare payers over time. A more detailed understanding of comorbidity patterns can provide insight into patients at greater risk for poor outcomes and inform selection of ART and treatments for comorbid chronic conditions.

METHODS

Study Design

A retrospective trend analysis was conducted using US administrative claims data to select patients with a prevalent diagnosis of HIV infection. The proportion of patients with specific comorbidities between 2003 and 2013 across various payers was analyzed.

Data Source

Three study populations were selected using data from Truven Health's MarketScan Commercial Claims and Encounters database was used for commercial payer data, the Medicare Supplemental and Coordination of Benefits database was used for Medicare payer data, and the Multi-State Medicaid database was used for Medicaid payer data. These databases contain medical claims for healthcare services performed in the inpatient and outpatient settings, outpatient prescription drug claims, and enrollment data, including demographic information. These administrative claims databases contain standard codes for diagnoses (based on *International Classification of Diseases, 9th Revision, Clinical Modification* [ICD-9-CM] codes), procedures (based on ICD-9-CM codes, *Current Procedural Terminology* codes, and the Healthcare Common Procedure Coding System), and pharmaceuticals (based on National Drug Code identifiers). The claims data are linked to person-level enrollment data through unique enrollee identifiers.

The commercial database contains the healthcare experiences of >35 million enrollees in 2013 covered under a variety of fee-for-service and managed care health plans. The Medicare database includes the healthcare claims for approximately 3.5 million retirees with Medicare supplemental insurance paid for by employers. The Medicaid database contains claims for services provided to approximately 8 million Medicaid enrollees each year from multiple geographically dispersed states.

Because these databases are deidentified in compliance with Health Insurance Portability and Accountability Act regulations, institutional review board approval was not required for this study.

Patient Selection and Analysis Periods

Study patients were required to have at least 1 medical claim (defined as an inpatient or outpatient claim that was not for a procedure that is used to confirm an HIV diagnosis) associated with an ICD-9-CM diagnosis code for HIV (codes 042.xx, 079.53, and v08.xx) from 1 July 2002 through 31 December 2013. Selected patients were required to have at least 6 months of continuous medical and prescription coverage before their first diagnosis of HIV infection (index diagnosis date) and at least 14 days after the index diagnosis. All patients were required to be at least 18 years of age as of the index diagnosis date.

Patients With Prevalent HIV Infection

Analysis of patients with prevalent HIV infection was performed by calendar year. To be included in a given calendar year, patients were required to have continuous enrollment for that specific year. This study reported comorbidity rates for patients with prevalent HIV infection for the individual calendar years of 2003 and 2013. Rates were also reported for the aggregate years of 2003 through 2013. Patients contributed data to the aggregate rate if they had at least 1 year of continuous calendar year eligibility in the time span.

Subset analyses were conducted on treated patients with prevalent HIV infection. Any patient who qualified for inclusion in a given calendar year was considered treated if they had ≥1 ART claim in that calendar year or any time prior. Treated patients were matched to HIV-negative controls (described below), and comorbidity rates were reported for the aggregate years of 2003 through 2013. The proportion of treated HIV-infected patients and HIV-negative controls with specific comorbidities was also determined for each calendar year.

Control Patient Selection

A 10% sample of people who did not have an HIV medical claim or an ART prescription claim between 2002 and 2014 was randomly selected, screened for at least 1 year of continuous

enrollment, and matched to HIV-infected patients by payer, calendar year of index date, 5-year age group, sex, and geographic region (defined by first zip code digit). Controls were assigned to the same index diagnosis date of their matched cases. Potential controls were required to have at least 6 months of continuous enrollment prior to the matched index diagnosis date and at least 14 days of continuous enrollment subsequent to the matched index diagnosis date. Up to 3 controls were selected for each HIV-infected patient.

Variables

Demographic variables measured as of index date included age, sex, race (for Medicaid payer–covered patients only), geographic region (for commercial payer– and Medicare payer–covered patients only), population density (for commercial payer– and Medicare payer–covered patients only), and insurance plan.

Individual comorbidities were measured as the proportion of patients with medical claims with ICD-9-CM diagnosis codes or procedure codes (ICD-9-CM and/or *Current Procedural Terminology* codes) consistent with the specific condition, including CV events (myocardial infarction, coronary artery surgery, peripheral vascular diseases, ischemic stroke, deep vein thrombosis), cardiovascular and renal risk factors (essential hypertension, diabetes, obesity/overweight, hyperlipidemia, hepatitis C, renal impairment, chronic kidney disease, fracture, or osteoporosis), endocrine disease (including diabetes and thyroid disease), cancer, liver disease, rheumatoid arthritis, and alcoholism.

Statistical Analyses

Changes in the observed prevalence of comorbidities in 2003 versus 2013 were analyzed using *t* tests for comparison of proportions. Similarly, proportions were compared among patients with prevalent treated HIV infection and HIV-negative controls, using *t* tests for statistical significance for differences in the proportions of comorbidities observed.

RESULTS

Patients With Prevalent HIV Infection

2003–2013

Summary demographic data are presented in Table 1. Three study samples of unique patients with continuous enrollment in one or more calendar years during 2003–2013 were identified: 36 298 commercial payer–covered patients (mean age, 42.2 years, male sex, 78.2%); 26 246 Medicaid payer–covered patients (mean age, 41.6; male sex, 51.3%); and 1854 Medicare payer–covered patients (mean age, 71.5; male sex, 63.8%).

Essential hypertension was the most common comorbidity among patients across all 3 payers (31.4% of commercial payer–covered patients, 39.3% of Medicaid payer–covered patients, and 76.2% of Medicare payer–covered patients), followed by hyperlipidemia (29.2%, 22.1%, and 49.6%, respectively), endocrine disease (including diabetes; 21.8%, 27.2%, and 54.0%, respectively), diabetes (11.0%, 17.8%, and 37.0%, respectively), and renal impairment (8.4%, 14.7%, and 34.7%, respectively).

Table 1. Demographic and Clinical Characteristics of Patients With Prevalent Human Immunodeficiency Virus (HIV) Infection, by Healthcare Coverage Payer: 2003–2013

Characteristic	Commercial (n = 36298)	Medicaid (n = 26246)	Medicare (n = 1854)
Age, y			
Mean ± SD	42.2 ± 10.7	41.6 ± 10.5	71.5 ± 9.2
≥50	24.7	21.5	97.4
Male sex	78.2	51.3	63.8
Race[a]			
White	NA	25.1	NA
Black	NA	55.5	NA
Other/missing	NA	19.4	NA
Cardiovascular events			
Any	6.8	11.3	36.0
Myocardial infarction	1.6	3.2	8.8
Coronary artery surgery	1.4	1.1	5.7
Peripheral vascular diseases	1.8	3.4	17.5
Ischemic stroke	1.4	2.7	9.0
Deep vein thrombosis	2.6	4.1	11.6
Cardiovascular and renal risk factors			
Essential hypertension	31.4	39.3	76.2
Diabetes mellitus	11.0	17.8	37.0
Obesity/overweight	6.4	9.2	6.5
Hyperlipidemia	29.2	22.1	49.6
Hepatitis C	5.1	21.5	4.7
Renal impairment	8.4	14.7	34.7
Chronic kidney disease	4.7	8.2	22.9
Fracture or osteoporosis	7.8	13.3	24.4
Other conditions			
Endocrine disease (including diabetes)	21.8	27.2	54.0
Thyroid disease	6.1	6.4	20.4
Cancer	7.9	9.1	32.7
Liver disease	6.4	11.2	7.4
Rheumatoid arthritis	0.7	1.6	2.8
Alcoholism	3.4	13.8	2.4

Data are percentage of patients, unless otherwise indicated.

Abbreviation: NA, not available.

[a]Race was available from Medicaid payers only.

2003 Versus 2013

The comparison of selected comorbidity rates in 2003 to those in 2013 is reported in Figure 1A–C. Across payers, there were significant increases between 2003 and 2013 in the percentage of patients with renal impairment, essential hypertension, diabetes, obesity/overweight, and hyperlipidemia ($P < .05$ for all comparisons). In addition to the comorbidities specified above, the percentage of Medicare payer– and Medicaid payer–covered patients with any CV event and fracture/osteoporosis also increased significantly over time ($P < .05$ for both comparisons). Among patients

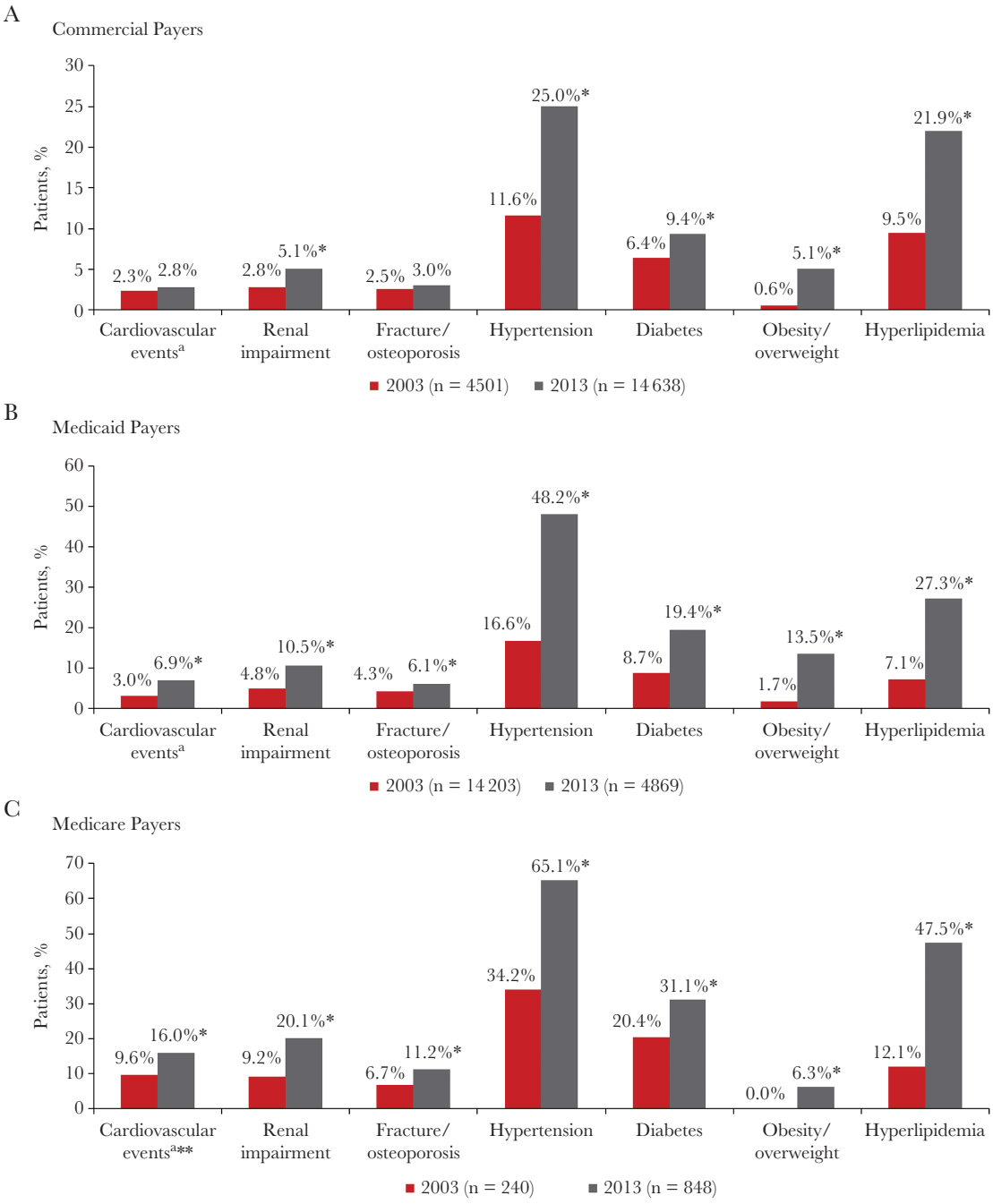

Figure 1. Trends in comorbid conditions among patients with prevalent human immunodeficiency virus (HIV) infection, by healthcare coverage payer, 2003 vs 2013. The percentage of patients with evidence of comorbidities in 2003 and 2013 are reported for commercial, Medicare, and Medicaid payers. [a]Myocardial infarction, coronary artery surgery, peripheral vascular diseases, ischemic stroke, and deep vein thrombosis. *$P < .05$ by the χ^2 test with 1 degree of freedom, for comparisons between 2003 and 2013.

with prevalent HIV infection who were covered by Medicaid payers, the percentage with any CV event and with renal impairment more than doubled between 2003 and 2013 (from 3.0% to 6.9% and from 4.8% to 10.5%, respectively; Figure 1B).

Treated HIV-Infected Patients Versus HIV-Negative Controls

To provide context for changes in comorbidity among HIV-infected patients, a matched set of HIV-negative controls was created, and the populations were compared. A total of 20 519 treated HIV-infected patients and 46 763 HIV-negative controls were identified in the commercial payer–covered population; 16 020 and 36 791, respectively, were identified in the Medicaid payer–covered population; and 461 and 1059, respectively, were identified in the Medicare payer–covered population (Table 2).

In each payer group, statistically significant differences were observed in the proportion of patients with comorbidities among

Table 2. Demographic and Clinical Characteristics of Treated Human Immunodeficiency Virus (HIV)–Infected Patients Versus HIV-Negative Controls, by Healthcare Coverage Payer: 2003–2013

	Commercial			Medicaid			Medicare		
Characteristic/Comorbidity	HIV Infected (n = 20 519)	Controls (n = 46 763)	*P*	HIV Infected (n = 16 020)	Controls (n = 36 791)	*P*	HIV Infected (n = 461)	Controls (n = 1184)	*P*
Age, y									
Mean ± SD	46.2 ± 9.4	46.2 ± 9.2	1.000	44.8 ± 9.4	44.7 ± 9.7	.272	66.8 ± 8.9	66.9 ± 8.9	.838
≥50	13.1	13.0	.753	18.4	17.8	<.001	89.8	89.4	.829
Male sex	84.3	84.3	.934	53.5	53.8	.512	84.2	84.1	.983
Cardiovascular events									
Any	6.7	4.0	<.001	10.4	7.6	<.001	26.9	26.7	.932
Myocardial infarction	1.7	1.0	<.001	3.2	1.7	<.001	8.2	6.7	.266
Peripheral vascular diseases	1.6	1.2	<.001	2.9	3.3	.039	11.3	12.4	.526
Deep vein thrombosis	2.6	1.1	<.001	3.8	1.9	<.001	9.1	5.8	.017
Cardiovascular and renal risk factors									
Essential hypertension	31.2	30.2	.005	37.3	33.8	<.001	65.7	69.8	.106
Diabetes mellitus	10.1	10.2	.704	16.0	18.1	<.001	29.5	33.9	.089
Obesity/overweight	5.6	6.7	<.001	7.6	9.9	<.001	3.5	8.1	<.001
Hyperlipidemia	31.1	30.4	.076	22.4	24.0	<.001	47.9	55.9	.004
Hepatitis C	5.4	0.5	<.001	22.9	3.7	<.001	8.2	1.5	<.001
Renal impairment	8.8	2.8	<.001	15.2	5.9	<.001	31.0	18.2	<.001
Fracture or osteoporosis	7.6	6.4	<.001	13.0	10.0	<.001	18.2	16.4	.372
Other conditions									
Endocrine disease (including diabetes)	20.9	18.1	<.001	26.3	24.5	<.001	43.4	45.4	.452
Thyroid disease	4.7	5.9	<.001	5.5	7.7	<.001	9.3	14.9	.003
Cancer	8.0	4.1	<.001	9.8	4.2	<.001	26.5	20.8	.013
Liver disease	6.2	2.4	<.001	11.3	4.5	<.001	8.9	20.8	.012
Rheumatoid arthritis	0.4	0.6	.001	1.2	1.8	<.001	0.7	3.5	.002
Alcoholism	3.1	1.6	<.001	12.2	5.9	<.001	2.8	2.6	.820

Data are percentage of patients, unless otherwise indicated.

treated HIV-infected patients and HIV-negative controls; some of the statistically significant differences showed higher percentages and some showed lower percentages for HIV-infected patients than their matched HIV-negative controls.

Among the commercial payer–covered population, the differences between HIV-infected patients and HIV-negative controls were significant for all comorbidities except diabetes and hyperlipidemia ($P < .05$). Among patients covered by commercial payers, a higher proportion with treated HIV infection had any CV event, myocardial infarction, deep vein thrombosis, peripheral vascular disease, hypertension, hepatitis C, renal impairment, fracture/osteoporosis, endocrine disease (including diabetes), cancer, liver disease, and alcoholism, compared with HIV-negative controls ($P < .001$ for all comparisons). A higher proportion of HIV-negative controls were obese/overweight, had thyroid disease, and had rheumatoid arthritis, compared with HIV-infected patients ($P < .001$ for all comparisons). Although statistically significant differences were observed between HIV-infected patients and HIV-negative controls for some comorbidities (eg, hypertension and hyperlipidemia), the absolute differences in prevalence were small. For example, among commercial payer–covered patients, 31.2% of HIV-infected patients had hypertension as compared to 30.2% of HIV-negative controls ($P = .005$).

Comparisons between HIV-infected patients and HIV-negative controls covered by Medicaid payers were similar with the exceptions of a higher percentage of HIV-negative controls having peripheral vascular diseases, diabetes, and hyperlipidemia. Among the cohorts with Medicare payer coverage, a higher proportion of treated HIV-infected patients had deep vein thrombosis, hepatitis C, renal impairment, and cancer, compared with HIV-negative controls ($P < .05$ for all comparisons). The proportion of patients covered by Medicare payers who were obese/overweight, had hyperlipidemia, had thyroid disease, and had liver disease was greater among HIV-negative controls, compared with HIV-infected patients ($P < .05$ for all comparisons).

Figure 2A–C and Figure 3A and 3B present comparisons of HIV-infected patients to their matched HIV-negative controls by calendar year from 2003 through 2013 with regard to the prevalence of hypertension, diabetes, renal impairment, hyperlipidemia, and any CV event. Data for renal impairment (Figure 2C) were the most consistent, showing a higher proportion of treated HIV-infected patients with this comorbidity

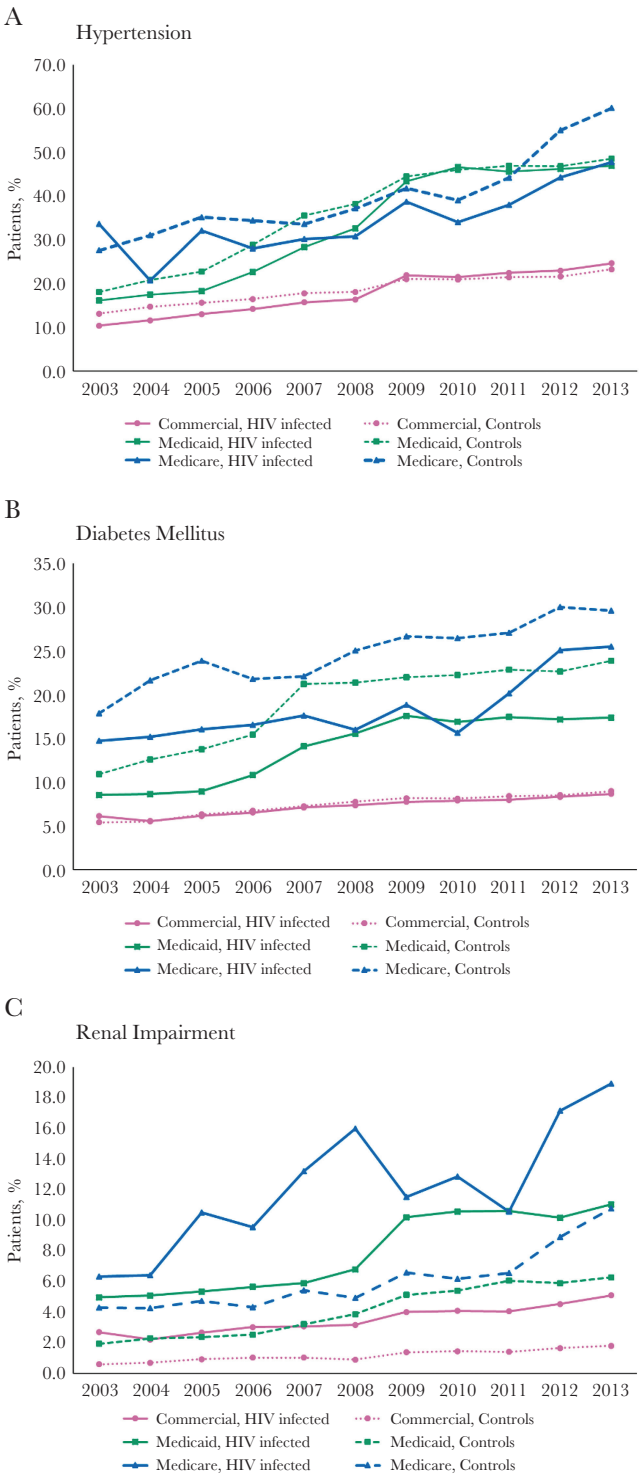

Figure 2. Trends in essential hypertension, diabetes mellitus, and renal impairment are reported by healthcare coverage payers among treated human immunodeficiency virus (HIV)–infected patients and HIV-negative controls during 2003–2013.

as compared to HIV-negative controls for each calendar year across all payers. Among patients with commercial payer coverage, HIV-infected patients also had a higher rate of any CV event (Figure 3B), compared with controls, for each year.

DISCUSSION

The current study examined the evolution of comorbidities in HIV-infected patients across different payers between 2003 and 2013. Although the proportion of HIV-infected patients with specific comorbidities differed between study populations covered by commercial, Medicaid, and Medicare payers, comorbidities were common regardless of payer.

This analysis of a population with prevalent HIV infection found frequent occurrences of CV and renal risk factors, including essential hypertension, diabetes, and hyperlipidemia. The percentage of Medicaid payer– and Medicare payer–covered patients with any CV event or with renal impairment nearly doubled over the decade. Previously published studies have reported an association between certain ART regiments and renal or CV adverse events. Regimens including tenofovir disoproxil fumarate and certain protease inhibitors have been associated with an increased risk of renal impairment, while abacavir-based regimens have been linked with an increased risk of CV events [21, 34, 35]. The increased use of certain ART regimens for longer durations may have contributed to the observed increases in renal- and CV-related comorbidities among HIV-infected patients over the years, and these trends merit additional study.

There were more comorbidities observed in HIV-infected patients as compared to their matched HIV-negative controls for many of the conditions evaluated. Hepatitis C and renal impairment were elevated across patients from all payers, and renal impairment was consistently elevated for each calendar year. For both HIV-infected patients and HIV-negative controls, the proportions with specific comorbidities increased from 2003 to 2013. These increases in prevalence may be partially explained by improved access to preventive screening as a result of provisions in the Patient Protection and Affordable Care Act (PPACA) [36]. Among patients with prevalent HIV infection, there were significant increases in both groups with regard to the percentages with hypertension, diabetes, obesity/overweight, and hyperlipidemia from 2003 to 2013.

Previously published studies on comorbidities in HIV-infected patients have found similar increases in comorbidities. Schouten et al performed a prospective cross-sectional comparison of HIV-infected patients to HIV-negative controls ≥45 years old from outpatient clinics in Amsterdam and found significantly greater occurrence of hypertension, myocardial infarction, and impaired renal function in HIV-infected patients [9]. Onen et al performed a prospective cross-sectional study of HIV-infected patients ≥50 years old from 2 US urban clinics and matched controls from the National Health and Nutrition Examination Survey and found that HIV-infected patients had a higher prevalence of hypertension, hypertriglyceridemia, low bone mineral density, and lipodystrophy but a similar prevalence of coronary heart disease, diabetes, chronic viral hepatitis, and non–AIDS-defining malignancies [7]. The Swiss HIV

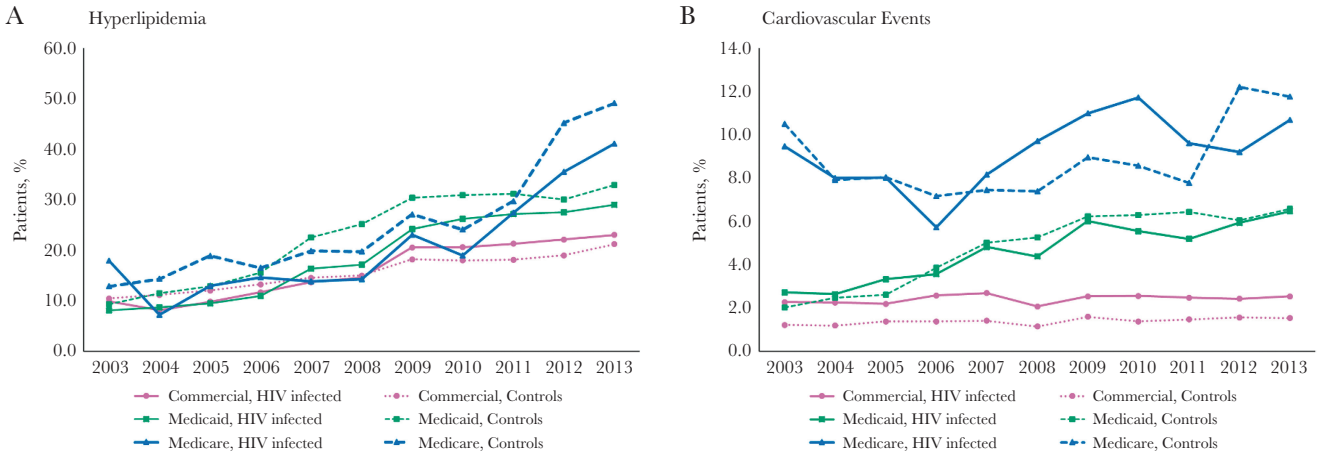

Figure 3. Trends in hyperlipidemia and cardiovascular events by payer among treated human immunodeficiency virus (HIV)–infected patients and HIV-negative controls during 2003–2013. Cardiovascular events include myocardial infarction, coronary artery surgery, peripheral vascular diseases, ischemic stroke, and deep vein thrombosis.

Cohort Study, a prospective observational study, found elevated rates of stroke, myocardial infarction, diabetes, bone fractures, osteoporosis, and non–AIDS-defining malignancies for older HIV-infected patients as compared to younger HIV-infected patients [12]. Variation in the prevalence rates of comorbidities across these studies can be attributed to differences in methods and patient characteristics.

Cross-sectional studies provide data for a particular point in time, and the length of the period analyzed can affect findings. The number of diagnoses appearing on claims is limited by the format of the claim form, and chronic conditions are less likely to appear on a consistent basis unless they are the reason for a patient visit. This may, in part, explain differences in findings in the current study. Patients who were eligible for >1 calendar year had a greater opportunity to contribute to a comorbid count in the 2003–2013 analysis than to the comorbid count for a specific calendar year analysis.

Clinically, while older age by itself contributes to the increased occurrence of comorbidities, underlying HIV infection and its treatment are also important variables. HIV infection may result in metabolic complications, renal toxicity, hepatotoxicity, and osteoporosis [4]. Similarly, depending on the ART regimen used, side effects can include lipodystrophy, nephrotoxicity, hepatotoxicity, bone loss, and increased risk of CV events [4, 14].

Limitations of the analyses should be noted. As with any administrative claims data, the potential for misclassification of HIV infection and comorbidities due to miscoding of claims is a possibility. Second, this study did not examine causal relationships. Third, while controls were screened for absence of HIV diagnosis and HIV therapy, this cannot ensure a completely HIV-negative comparison group. In addition, the study criterion requiring 12 months of continuous enrollment in a calendar year may introduce an immortality bias, especially among Medicare payer–covered patients. The nature of claims data means that requiring ≥12 months of continuous enrollment may result in a more stable population than is typical, especially among HIV-infected patients. Furthermore, because patients could be followed for multiple years, patients with enough follow-up data available could appear in both 2003 and 2013;, thus, statistical comparisons between 2003 and 2013 were not truly independent for a subset of patients. Among HIV-infected patients evaluated during 2013, approximately 30% covered by commercial payers, 10% covered by Medicaid payers, and 12% covered by Medicare payers were also evaluated during 2003. Of the HIV-negative controls in 2013, 11% covered by Medicaid payers and 14% covered by Medicare payers were also present in 2003. In addition, the study did not attempt to evaluate trends over time for comorbidities with multivariable regression analysis. This study was not able to ensure comparability between treated HIV-infected patients and their matched HIV-negative controls with regard to lifestyle-related factors that might have influenced results. Also, results may not be generalizable to HIV-infected patients who were covered by payers other than commercial, Medicaid, or Medicare payers or who were uninsured. The population covered by Medicare payers in this study only included the subset who had employer-provided supplemental insurance and, thus, may not be representative of all Medicare payer–covered patients. Finally, it is worth noting that, between 2003 and 2013, the implementation of the PPACA and other changes encouraging the use of electronic health records may have increased documentation, resulting in potentially more reporting and giving the appearance of greater comorbidity prevalences.

As the HIV-infected population ages, it is becoming increasingly important to identify and manage comorbidities that may increase the risk of CV complications, kidney disease, osteoporosis, and bone fracture. The comorbidities will influence the choice of ART and are thus an important consideration in optimizing the selection of HIV treatment.

Notes

Acknowledgments. We thank Laurie Costa, for her support in building the study database, and Michele Shaw, for her writing assistance in preparing the initial draft of the manuscript.

Gilead worked with the authors to define the goals and objectives and to draft the study protocol. The authors had access to summary tables of the data as they were being produced, including demographic summaries, initial counts, and percentages. As the statistical analyses were conducted, tables of results and draft figures were provided for author review and comment. Final results prior to manuscript were provided for review and comment to all study authors.

Financial support. This work was supported by Gilead Sciences.

Potential conflicts of interest. J. G. has received research funding from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen Therapeutics, Merck, Sangamo BioSciences, and ViiV Healthcare/GlaxoSmith Kline; has received consulting fees from Bristol-Myers Squibb, Gilead Sciences, Janssen Therapeutics, Merck, Theratechnologies, and ViiV Healthcare/GlaxoSmith Kline. P. H. has received research funding from Pfizer, has received honoraria from Gilead, and is a paid consultant to Gilead Sciences. S. S. is an employee and shareholder of Gilead Sciences. Nicole Meyer is an employee of Truven Health Analytics. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Althoff KN, McGinnis KA, Wyatt CM, et al.; Veterans Aging Cohort Study (VACS). Comparison of risk and age at diagnosis of myocardial infarction, end-stage renal disease, and non-AIDS-defining cancer in HIV-infected versus uninfected adults. Clin Infect Dis **2015**; 60:627–38.
2. Cahill S, Valadéz R. Growing older with HIV/AIDS: new public health challenges. Am J Public Health **2013**; 103:e7–e15.
3. Centers for Disease Control and Prevention (CDC). HIV/AIDS among persons aged 50 and older, CDC HIV/AIDS facts. Atlanta, CDC: **2008**.
4. Guaraldi G, Prakash M, Moecklinghoff C, Stellbrink HJ. Morbidity in older HIV-infected patients: impact of long-term antiretroviral use. AIDS Rev **2014**; 16:75–89.
5. Health Resources and Services Administration. Ryan White HIV/AIDS Program Population Fact Sheet, Older Adults, December **2014**. http://hab.hrsa.gov. Accessed 26 March 2016.
6. Krentz HB, Gill MJ. Increased costs of HIV care associated with aging in an HIV-infected population. HIV Med **2015**; 16:38–47.
7. Onen NF, Overton ET, Seyfried W, et al. Aging and HIV infection: a comparison between older HIV-infected persons and the general population. HIV Clin Trials **2010**; 11:100–9.
8. Samji H, Cescon A, Hogg RS, et al.; North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. PLoS One **2013**; 8:e81355.
9. Schouten J, Wit FW, Stolte IG, et al.; AGEhIV Cohort Study Group. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. Clin Infect Dis **2014**; 59:1787–97.
10. Brothers TD, Kirkland S, Guaraldi G, et al. Frailty in people aging with human immunodeficiency virus (HIV) infection. J Infect Dis **2014**; 210:1170–9.
11. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. Clin Infect Dis **2011**; 53:1120–6.
12. Hasse B, Ledergerber B, Furrer H, et al.; Swiss HIV Cohort Study. Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. Clin Infect Dis **2011**; 53:1130–9.
13. Guaraldi G, Zona S, Brothers TD, et al. Aging with HIV vs. HIV seroconversion at older age: a diverse population with distinct comorbidity profiles. PLoS One **2015**; 10:e0118531.
14. Sabin CA, Worm SW, Weber R, et al.; D:A:D Study Group. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. Lancet **2008**; 371:1417–26.
15. Esser S, Gelbrich G, Brockmeyer N, et al. Prevalence of cardiovascular diseases in HIV-infected outpatients: results from a prospective, multicenter cohort study. Clin Res Cardiol **2013**; 102:203–13.
16. Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. JAMA Intern Med **2013**; 173:614–22.
17. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab **2007**; 92:2506–12.
18. Achhra AC, Mocroft A, Ross MJ, et al.; International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) START Study Group. Kidney disease in antiretroviral-naïve HIV-positive adults with high CD4 counts: prevalence and predictors of kidney disease at enrolment in the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. HIV Med **2015**; 16(Suppl 1):55–63.
19. Islam FM, Wu J, Jansson J, Wilson DP. Relative risk of renal disease among people living with HIV: a systematic review and meta-analysis. BMC Public Health **2012**; 12:234.

20. Mallipattu SK, Wyatt CM, He JC. The New Epidemiology of HIV-Related Kidney Disease. J AIDS Clin Res **2012**; Suppl 4:001.
21. Mocroft A, Lundgren JD, Ross M, et al.; D:A:D study group; Royal Free Hospital Clinic Cohort; INSIGHT study group; SMART study group; ESPRIT study group. Development and validation of a risk score for chronic kidney disease in HIV infection using prospective cohort data from the D:A:D study. PLoS Med **2015**; 12:e1001809.
22. Ryom L, Mocroft A, Kirk O, et al.; D:A:D Study Group. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. J Infect Dis **2013**; 207:1359–69.
23. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. AIDS **2006**; 20:2165–74.
24. Hansen AB, Gerstoft J, Kronborg G, et al. Incidence of low and high-energy fractures in persons with and without HIV infection: a Danish population-based cohort study. AIDS **2012**; 26:285–93.
25. Triant VA, Brown TT, Lee H, Grinspoon SK. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. J Clin Endocrinol Metab **2008**; 93:3499–504.
26. Womack JA, Goulet JL, Gibert C, et al.; Veterans Aging Cohort Study Project Team. Increased risk of fragility fractures among HIV infected compared to uninfected male veterans. PLoS One **2011**; 6:e17217.
27. Yin MT, Kendall MA, Wu X, et al. Fractures after antiretroviral initiation. AIDS **2012**; 26:2175–84.
28. Palella FJ, Althoff KN, Moore RD, et al. Abacavir use and risk for myocardial infarction in the NA-ACCORD [poster]. Presented at: Conference on Retroviruses and Opportunistic Infections, Seattle, Washington, 23–26 February **2015**. http://www.natap.org/2015/CROI/croi_175.htm. Accessed 1 March 2017.
29. Mocroft A, Kirk O, Reiss P, et al.; EuroSIDA Study Group. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. AIDS **2010**; 24:1667–78.
30. Yombi JC, Pozniak A, Boffito M, et al. Antiretrovirals and the kidney in current clinical practice: renal pharmacokinetics, alterations of renal function and renal toxicity. AIDS **2014**; 28:621–32.
31. Childs K, Welz T, Samarawickrama A, Post FA. Effects of vitamin D deficiency and combination antiretroviral therapy on bone in HIV-positive patients. AIDS **2012**; 26:253–62.
32. Mills A, Crofoot G Jr, McDonald C, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate in the first protease inhibitor-based single-tablet regimen for initial HIV-1 therapy: a randomized phase 2 study. J Acquir Immune Defic Syndr **2015**; 69:439–45.
33. Bedimo R, Maalouf NM, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. AIDS **2012**; 26:825–31.
34. Friis-Møller N, Ryom L, Smith C, et al.; D:A:D study group. An updated prediction model of the global risk of cardiovascular disease in HIV-positive persons: The Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study. Eur J Prev Cardiol **2016**; 23:214–23.
35. Costagliola D, Lang S, Mary-Krause M, Boccara F. Abacavir and cardiovascular risk: reviewing the evidence. Curr HIV/AIDS Rep **2010**; 7:127–33.
36. Patient Protection and Affordable Care Act, 42 USC §18001 et seq (**2010**).