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

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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 1,854 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.
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 measures 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: 36298 commercial payer–covered patients (mean age, 42.2 years, male sex, 78.2%); 26246 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).

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 with

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

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

Data are percentage of patients, unless otherwise indicated. Abbreviation: NA, not available.

*Race was available from Medicaid payers only.
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

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**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. aMyocardial infarction, coronary artery surgery, peripheral vascular diseases, ischemic stroke, and deep vein thrombosis. *P < .05 by the \( \chi^2 \) test with 1 degree of freedom, for comparisons between 2003 and 2013.
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.
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 regimens 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

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.
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.
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.

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