Trends in Utilization of Statin Therapy and Contraindicated Statin Use in HIV–Infected Adults Treated With Antiretroviral Therapy From 2007 Through 2015

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Background—HIV is associated with an increased risk for atherosclerotic cardiovascular disease, which may result in many people living with HIV taking a statin. Some statins are contraindicated with certain antiretroviral therapies (ART) and other medications commonly used by HIV-infected patients.

Methods and Results—We analyzed trends in the use of statins, including contraindicated statins, between 2007 and 2015 among HIV-infected patients aged ≥19 years taking ART who had employer-sponsored or Medicare supplemental health insurance in the Marketscan database (n=186 420). Statin use was identified using pharmacy claims. Contraindicated statin use was defined by a pharmacy claim for HIV protease inhibitors, cobicistat, hepatitis C protease inhibitors, anti-infectives, calcium channel blockers, amiodarone, gemfibrozil, or nefazodone followed by a fill for a contraindicated statin type and dosage within 90 days. The percentage of beneficiaries with HIV taking a statin remained unchanged between 2007 (24.6%) and 2015 (24.7%). Among those taking a statin, the percentage taking a contraindicated statin declined from 16.3% in 2007 to 9.0% in 2014 and then increased to 9.8% in 2015. The proportion of contraindicated statin fills attributable to HIV protease inhibitors declined from 63.9% in 2007 to 51.0% in 2015, while those attributable to cobicistat increased from 0% before 2012 to 20.6% in 2015.

Conclusions—Changes in ART regimens resulted in a decline in contraindicated statin use from 2007 to 2014, but this favorable trend was attenuated in 2015 because of increased use of cobicistat-containing ART regimens. (*J Am Heart Assoc*. 2018;7: e010345. DOI: 10.1161/JAHA.118.010345)

Key Words: antiretroviral medications • cobicistat • drug interactions • HIV • hydroxymethylglutaryl-CoA reductase inhibitors • protease inhibitors

The use of antiretroviral therapies (ART) has resulted in a decline in opportunistic infections and increased life expectancy among people living with HIV.[1] As a result, adults with HIV are developing chronic illnesses associated with older age.[2,3] Cardiovascular disease (CVD) has emerged as a major cause of morbidity and mortality in people living with HIV.[3–5]

Statin therapy is a mainstay of atherosclerotic CVD prevention.[6,7] The aging of people living with HIV and the high risk for CVD in this population may have resulted in an increased use of statin therapy in this population. Some statin types and dosages are contraindicated with

medications commonly used to treat people living with HIV as they increase the risk for statin-related adverse events, including muscle problems and acute kidney injury.[8,9] The risk for contraindicated statin use among adults with HIV may have changed over the past decade because of modifications in ART regimens.[10]

The main aim of the current study was to analyze trends in the use of statins and contraindicated statin use among adults living with HIV who were treated with ART between 2007 and 2015. As a secondary aim, we identified factors associated with contraindicated statin use among adults with HIV in 2015. To accomplish these aims, we conducted

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Clinical Perspective

What Is New?

- Contraindicated statin use in people living with HIV have declined between 2007 and 2014 because of less frequent prescriptions for HIV protease inhibitors.
- The decline in the use of contraindicated statins has diminished in the most recent years because of increasing prescriptions for antiretroviral regimens containing cobicistat.

What Are the Clinical Implications?

- There is a need for increased awareness of statin drug interactions in people living with HIV to minimize avoidable adverse events.

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a retrospective cohort study using data from the Marketscan database.

Methods

Study Population

The Marketscan database contains administrative data from individuals enrolled in various employer-sponsored healthcare plans and Medicare supplemental plans. We identified beneficiaries in the Marketscan database who had continuous inpatient, outpatient, and pharmacy insurance coverage for at least 1 full calendar year (ie, from January 1 through December 31) between 2007 and 2015 (hereinafter defined as the "assessment year"). We also required beneficiaries to have continuous inpatient, outpatient, and pharmacy insurance coverage from January 1 through December 31 of the year preceding the assessment year (hereinafter defined as the "baseline year") to identify baseline characteristics. We further restricted the analysis to beneficiaries who lived in the United States for the entire baseline and assessment years, were aged ≥19 years on January 1 of the assessment year and met the definition for HIV infection during the baseline year. HIV infection was defined by (1) ≥1 hospitalization with an *International Classification of Diseases, Ninth Revision* (*ICD-9*) code of 042.x–044.x or V08 in any discharge diagnosis position with ≥1 pharmacy claim for ART or (2) ≥2 pharmacy claims for ART on separate days. Table S1 shows the application of inclusion and exclusion criteria to identify the study population for the current analysis. The current analysis was approved by the Institutional Review Board at the University of Alabama at Birmingham, which waived the requirement to obtain informed consent. The Marketscan database used in the current study is available from Truven

Health Analytics. Other study information is available from the corresponding author.

Beneficiary Characteristics

Beneficiary characteristics analyzed as part of the current analysis included age on January 1 of the assessment year, sex, and region of residence defined using Marketscan beneficiary data. We used claims in the baseline year to determine comorbidities including a history of coronary heart disease (CHD), hypertension, diabetes mellitus, stroke, chronic kidney disease, and liver disease (Table S2).

Use of Statins, ART, and Other Medications With Potential Contraindication With Statins

Use of statins, ART, and other medications with potential contraindications with statins was determined using pharmacy claims during the assessment year. Statins analyzed as part of the current study included atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. ART included nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, entry inhibitors, cobicistat, and integrase inhibitors. As described below, other medications with potential contraindications with statins analyzed as part of the current study included nefazodone, gemfibrozil, amiodarone, calcium channel blockers, antifungal medications, antibiotics, and hepatitis C virus protease inhibitors.

Contraindicated statin use was defined by a pharmacy fill for a statin type and dosage which should not be used because of an increased risk for statin-related adverse events based on the medications filled in the preceding 90 days. Specific statin type and dosages which should not be used by individuals taking HIV protease inhibitors, cobicistat, hepatitis C protease inhibitors, antibiotics, antifungal medications, calcium channel blockers, amiodarone, gemfibrozil, and nefazodone are shown in Table S3. These contraindications were defined in accordance with the guidelines for the management of adults living with HIV from the National Library of Medicine, National Institutes of Health.[11]

Statistical Analysis

The analyses described below were conducted for each calendar year between 2007 and 2015, separately. We calculated baseline characteristics of beneficiaries included in the current analysis and the proportion who were taking ART and other medications with potential statin contraindications during the assessment year. We also calculated the

proportion of beneficiaries taking a statin during the assessment year, overall and by statin type. Among beneficiaries taking a statin, we calculated the proportion taking ART and other medications with a potential statin contraindication. We also calculated the proportion of beneficiaries with contraindicated statin use. Using all contraindicated statin fills, we calculated the proportion attributable to nefazodone, gemfibrozil, amiodarone, calcium channel blockers, antifungal medications, antibiotics, hepatitis C virus protease inhibitors, cobicistat, and HIV protease inhibitors. We also calculated the proportion of all contraindicated statin fills by statin type and dosage.

We used Poisson regression models with robust variance estimators as described by Chen et al to calculate risk ratios and 95% confidence intervals for filling a contraindicated statin during the assessment year associated with calendar year and beneficiary characteristics.[12] Characteristics that were investigated included age, sex, region of residence, and history of CHD, hypertension, diabetes mellitus, stroke, chronic kidney disease, and liver disease. An unadjusted model was conducted as was a model including all factors investigated simultaneously. All

analyses were conducted using SAS v9.4 (SAS Institute Inc, Cary, NC).

Results

Characteristics of Beneficiaries With HIV

A total of 186 420 beneficiaries with HIV met the inclusion criteria for the current analysis. The percentage of beneficiaries with HIV who were aged ≥60 years increased from 9.4% in 2007 to 15.7% in 2015 (Table 1). In each calendar year, >80% of beneficiaries were male and between 42% and 52% resided in the South region of the United States. Also, there was a progressive increase in the prevalence of CHD, hypertension, diabetes mellitus, chronic kidney disease, and liver disease between 2007 and 2015.

Between 2007 and 2015, there was a progressive decline in the proportion of beneficiaries taking HIV protease inhibitors from 50.8% in 2007 to 25.5% in 2015 and fusion inhibitors from 2.2% to 0.1% (Table 2, top panel). The use of cobicistat increased from 0% before 2012 to 15.7% in 2015, while the use of integrase inhibitors increased from 2.0% in

Table 1. Baseline Characteristics of Beneficiaries With HIV Included in the Current Analysis

	2007 (n=9928)	2008 (n=11 713)	2009 (n=19 868)	2010 (n=21 084)	2011 (n=24 781)	2012 (n=28 104)	2013 (n=24 892)	2014 (n=24 225)	2015 (n=21 825)
Age									
<50 y	60.1	58.0	58.9	57.1	54.8	51.8	48.9	47.9	47.3
50 to 59 y	30.5	31.6	31.1	32.1	33.4	34.8	36.0	37.0	37.1
≥60 y	9.4	10.4	10.0	10.8	11.8	13.4	15.1	15.2	15.7
Male	84.8	84.6	84.9	84.6	85.0	84.3	84.4	83.3	83.2
Region									
Northeast	12.2	10.2	12.1	16.4	15.9	18.2	18.4	21.2	20.7
North Central	13.5	13.4	15.4	16.7	15.0	14.4	13.0	13.4	12.8
South	51.8	50.3	47.0	42.3	44.0	43.8	42.4	44.8	47.2
West	22.3	25.7	24.1	24.4	24.2	22.7	25.4	19.3	19.2
Unknown	0.3	0.3	1.4	0.2	0.8	0.8	0.8	1.3	0.1
Comorbidities									
Coronary heart disease	3.2	3.5	3.1	3.7	3.8	3.8	3.9	3.9	3.9
Hypertension	30.6	32.1	31.2	32.1	33.6	34.5	35.1	35.4	35.7
Diabetes mellitus	3.4	4.0	4.2	4.7	5.1	5.4	5.6	6.0	6.7
Stroke	0.4	0.5	0.4	0.5	0.5	0.5	0.5	0.5	0.6
Chronic kidney disease	2.8	3.5	3.3	3.8	4.1	4.4	5.0	5.2	5.9
Liver disease	2.9	3.4	3.7	4.2	4.3	4.3	4.3	4.5	4.9

Numbers in the table represent percentages.

Table 2. Use of ART and Other Medications With Potential Contraindications With Statins Among Beneficiaries With HIV

	2007 (n=9928)	2008 (n=11 713)	2009 (n=19 868)	2010 (n=21 084)	2011 (n=24 781)	2012 (n=28 104)	2013 (n=24 892)	2014 (n=24 225)	2015 (n=21 825)
ART									
Nucleoside reverse transcriptase inhibitors	90.7	91.3	91.1	90.9	90.6	90.9	91.8	91.7	91.9
Non-nucleoside reverse transcriptase inhibitors	50.8	54.1	55.1	55.6	56.3	57.7	57.1	54.0	48.5
HIV protease inhibitors	50.8	48.3	45.6	42.6	40.3	37	34.5	30.8	25.5
Fusion inhibitors	2.2	1.2	0.5	0.3	0.2	0.2	0.2	0.1	0.1
Entry inhibitors	0.3	1.0	1.2	1.4	1.7	2.0	2.0	1.8	1.6
Cobicistat	0.0	0.0	0.0	0.0	0.0	1.2	5.0	9.6	15.7
Integrase inhibitors	2.0	7.6	11.1	13.8	16.2	18.4	22.9	29.5	36.2
Other medications with potential contraindications with statins									
Nefazodone	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0
Gemfibrozil	2.9	2.8	2.5	2.2	2.0	1.7	1.5	1.4	1.2
Amiodarone	0.1	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.1
Calcium channel blockers	7.0	7.4	7.2	7.5	7.7	8.2	8.6	9.2	9.5
Antifungal medications	7.6	6.7	6.2	5.7	5.7	5.4	5.1	4.9	5.0
Antibiotics	4.8	3.7	3.6	2.9	2.9	2.5	2.4	2.2	2.3
Hepatitis C virus protease inhibitors	0.0	0.0	0.0	0.0	0.1	0.2	0.1	0.2	0.0

Numbers in the table represent percentages over the total number of beneficiaries. ART indicates antiretroviral therapy.

2007 to 36.2% in 2015. In each year, the most commonly used non-ART medications with potential contraindications with statins were calcium channel blockers, antifungal medications, and antibiotics (Table 2, bottom panel).

Use of Statin Therapy

Statin use remained within 2 percentage points between 2007 and 2015 (Table 3). Atorvastatin was the statin most commonly used among beneficiaries with HIV during this time period, followed by pravastatin and rosuvastatin. Table 4 shows the use of ART and other medications with potential contraindications with statins among beneficiaries with HIV taking statin therapy. Between 2007 and 2015, the use of HIV protease inhibitors and fusion inhibitors decreased while the use of cobicistat and integrase inhibitors increased among beneficiaries with HIV taking statin therapy. Calcium channel blockers, antifungal medications, gemfibrozil, and antibiotics

Table 3. Percentage of Beneficiaries With HIV Taking Statin Therapy During the Assessment Year, Overall and by Statin Type

	2007 (n=9928)	2008 (n=11 713)	2009 (n=19 868)	2010 (n=21 084)	2011 (n=24 781)	2012 (n=28 104)	2013 (n=24 892)	2014 (n=24 225)	2015 (n=21 825)
Any statin	24.6	25.3	25.6	25.4	25.5	26.0	26.4	25.5	24.7
Atorvastatin	13.1	12.6	11.9	10.8	10.3	11.2	12.5	12.4	12.9
Fluvastatin	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1
Lovastatin	0.6	0.5	0.4	0.4	0.4	0.4	0.3	0.3	0.3
Pitavastatin	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.2	0.2
Pravastatin	5.0	5.6	6.0	6.4	6.8	6.6	6.3	5.9	5.4
Rosuvastatin	4.0	4.4	4.9	5.1	5.6	5.9	5.6	5.4	4.8
Simvastatin	3.4	3.6	3.9	4.1	4.0	3.3	2.9	2.4	2.1

Numbers in the table represent column percentages. Within each calendar year, the sum of percentages for each statin type may be higher than the total percentage of beneficiaries taking statin therapy as some beneficiaries may have taken more than one statin type.

Table 4. Use of ART and Other Medications With Potential Contraindications With Statins Among Beneficiaries With HIV Taking Statin Therapy

	2007 (n=2445)	2008 (n=2958)	2009 (n=5084)	2010 (n=5346)	2011 (n=6312)	2012 (n=7318)	2013 (n=6570)	2014 (n=6177)	2015 (n=5386)
ART									
Nucleoside reverse transcriptase inhibitors	91.8	92.2	90.8	90.5	90.4	90.1	90.4	90.4	90.7
Non-nucleoside reverse transcriptase inhibitors	54.4	58.1	58.0	58.3	59.0	60.0	58.8	56.3	52.2
HIV protease inhibitors	54.6	51.8	48.6	46.0	44.3	40.6	38.9	36.0	32.0
Fusion inhibitors	2.9	1.5	0.7	0.4	0.3	0.2	0.2	0.2	0.1
Entry inhibitors	0.3	1.4	1.7	1.7	2.3	2.4	2.6	2.3	2.3
Cobicistat	0.0	0.0	0.0	0.0	0.0	0.8	3.8	6.7	12.3
Integrase inhibitors	2.9	9.5	13.9	17.0	19.7	22.1	26.4	32.3	39.4
Other medications with potential contraindications with statins									
Nefazodone	0.3	0.2	0.1	0.2	0.1	0.1	0.1	0.1	0.0
Gemfibrozil	5.3	5.2	4.5	3.8	3.2	3.1	2.6	2.4	2.4
Amiodarone	0.2	0.1	0.3	0.3	0.4	0.3	0.3	0.3	0.3
Calcium channel blockers	11.2	11.8	11.3	11.9	12.0	12.6	13.0	15.1	15.9
Antifungal medications	6.1	5.7	5.2	4.5	4.5	4.5	4.0	4.0	4.0
Antibiotics	4.9	3.4	4.1	2.8	3.0	2.6	2.1	2.1	2.4
Hepatitis C virus protease inhibitors	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.0

Numbers in the table represent percentages over the total number of beneficiaries taking statin therapy. ART indicates antiretroviral therapy.
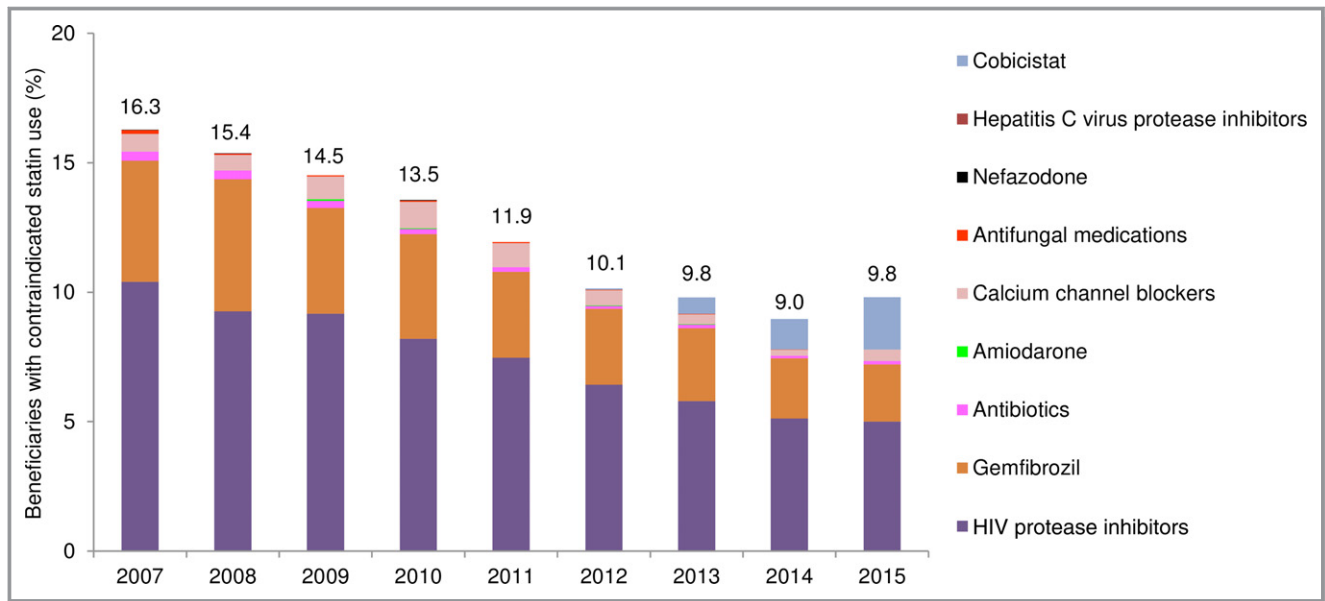
Figure. Contraindicated statin use and relative contribution of ART and other medications among beneficiaries with HIV taking statin therapy. The relative contribution of ART and other medications to contraindicated statin use was calculated using percentages shown in Table 5.

were the most commonly used non-ART medications with potential statin contraindications.

Contraindicated Statin Use

Among beneficiaries taking a statin, the percentage taking 1 with a contraindication declined from 16.3% in 2007 to 9.0% in 2014 and 9.8% in 2015 (Figure). The lower use of contraindicated statins in 2015 versus 2007 was primarily the result of decreased use of HIV protease inhibitors, which accounted for 63.9% and 51.0% of all contraindicated statin fills in 2007 and 2015, respectively (Table 5). The higher use of contraindicated statins in 2015 versus 2014 was primarily attributable to cobicistat, which accounted for 20.6% of all contraindicated statin fills in 2015.

Between 2007 and 2010, simvastatin represented about a third of all contraindicated statin fills and this percentage declined to 13.5% in 2015 (Table 6). The proportion of contraindicated statin fills that were associated with fluvastatin also declined between 2007 and 2015, while those for

Table 5. Contraindicated Statin Fills in the Assessment Year Attributed to ART and Other Medications With Potential Contraindications With Statins

	2007	2008	2009	2010	2011	2012	2013	2014	2015
Contraindicated statin fills, n	1736	1944	3465	3255	3510	3666	2940	2573	2440
ART									
HIV protease inhibitors	63.9	60.2	63.2	60.6	62.5	63.4	59.2	57.2	51.0
Cobicistat	0.0	0.0	0.0	0.0	0.0	0.4	6.5	13.1	20.6
Other medications with potential contraindications with statins									
Nefazodone	0.1	0.1	0.0	0.1	0.0	0.0	0.0	0.0	0.0
Gemfibrozil	28.7	33.2	28.1	29.8	27.8	28.9	28.8	26.0	22.6
Amiodarone	0.0	0.0	0.4	0.2	0.0	0.2	0.2	0.0	0.0
Calcium channel blockers	4.2	3.9	6.1	7.5	7.8	5.8	3.8	2.6	4.5
Antifungal medications	0.9	0.3	0.3	0.4	0.3	0.2	0.2	0.1	0.0
Antibiotics	2.2	2.2	1.9	1.5	1.5	1.1	1.4	1.1	1.3
Hepatitis C virus protease inhibitors	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

With the exception of the first row (contraindicated statin fills, n), the numbers in the table represent column percentages over the total number of contraindicated statin fills (ie, beneficiaries may have multiple contraindicated statin fills in the assessment year). ART indicates antiretroviral therapy.

Table 6. Distribution of Contraindicated Statin Fills in the Assessment Year by Statin Type and Dosage

	2007	2008	2009	2010	2011	2012	2013	2014	2015
Contraindicated statin fills, n	1736	1944	3465	3255	3510	3666	2940	2573	2440
Atorvastatin									
Any dose	37.3	40.2	40.4	37.4	39.1	41.9	52.5	56.7	58.0
10 mg	3.9	4.6	3.7	2.7	3.3	3.4	3.9	2.5	2.7
20 mg	5.9	6.1	4.1	3.9	3.2	2.8	5.6	5.8	5.0
40 mg	21.4	24.7	26.1	21.9	21.7	26.1	31.8	39.1	40.0
80 mg	6.1	4.8	6.5	8.9	10.9	9.6	11.3	9.4	10.3
Fluvastatin									
Any dose	1.2	0.7	0.4	0.2	0.1	0.2	0.0	0.2	0.2
20 mg	0.7	0.6	0.3	0.0	0.0	0.0	0.0	0.0	0.0
80 mg	0.5	0.2	0.1	0.2	0.1	0.2	0.0	0.2	0.2
Lovastatin									
Any dose	2.8	2.1	2.5	1.2	2.3	1.5	2.4	2.3	2.3
10 mg	0.0	0.1	0.0	0.1	0.1	0.1	0.5	0.8	0.7
20 mg	2.0	1.1	1.6	0.3	0.7	0.5	1.1	1.1	1.3
40 mg	0.8	0.8	0.8	0.8	1.5	0.9	0.9	0.5	0.3
Pitavastatin									
Any dose	0.0	0.0	0.0	0.0	0.0	0.2	0.3	0.3	0.7
1 mg	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.0	0.0
2 mg	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.3	0.2
4 mg	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.0	0.5
Pravastatin									
Any dose	8.2	9.8	8.7	8.7	9.3	9.8	8.8	6.8	5.2
10 mg	0.5	0.1	0.4	0.3	1.0	1.1	0.6	0.3	0.1
20 mg	1.3	2.5	2.1	1.8	2.7	1.7	1.9	1.9	1.5
40 mg	4.7	4.8	5.0	4.9	3.4	4.3	4.3	3.0	2.3
80 mg	1.7	2.5	1.3	1.7	2.2	2.7	2.1	1.6	1.4
Rosuvastatin									
Any dose	17.1	17.3	16.9	21.0	20.5	24.8	20.3	18.6	20.0
5 mg	0.2	0.4	0.6	0.9	0.9	1.0	0.8	1.3	1.5
10 mg	0.9	1.0	1.2	1.5	1.4	1.9	2.2	1.5	1.8
20 mg	12.8	11.9	11.6	14.2	14.4	15.9	11.9	11.0	11.1
40 mg	3.2	4.0	3.5	4.5	3.9	6.1	5.5	4.9	5.7
Simvastatin									
Any dose	33.5	29.9	31.1	31.4	28.6	21.6	15.7	15.0	13.5
5 mg	0.2	0.5	0.3	0.6	0.3	0.2	0.1	0.2	0.1
10 mg	3.8	2.4	1.3	2.0	2.0	0.8	1.2	1.2	1.2
20 mg	13.8	11.5	10.9	9.4	8.5	6.8	6.5	5.9	3.6
40 mg	12.2	10.3	12.1	12.1	13.3	12.2	7.0	7.5	8.2
80 mg	3.5	5.3	6.5	7.3	4.5	1.6	0.9	0.2	0.4

With the exception of the first row (contraindicated statin fills, n), the numbers in the table represent column percentages over the total number of contraindicated statin fills (ie, beneficiaries may have multiple contraindicated statin fills in the assessment year).

atorvastatin and rosuvastatin increased. In 2015, atorvastatin and rosuvastatin fills represented 58.0% and 20.0% of all contraindicated statin fills, respectively.

Factors Associated With Contraindicated Statin Use Among Beneficiaries With HIV Taking Statin Therapy

Among beneficiaries with HIV taking statin therapy, contraindications declined between 2007 and 2015, and this association remained statistically significant after multivariable adjustment (Table 7). Older age, male sex, living in the West, North Central, and South versus the Northeast region of the United States, and having a history of CHD, hypertension, diabetes mellitus, and chronic kidney disease were associated with an increased risk for taking a contraindicated statin among beneficiaries with HIV taking statin therapy in unadjusted analyses. With the exception of chronic kidney disease, these factors remained associated with an increased risk for contraindicated statin use after multivariable adjustment.

Discussion

In the current analysis, about 25% of beneficiaries living with HIV were taking a statin and this percentage did not change substantially between 2007 and 2015. The proportion of patients with HIV taking contraindicated statins declined between 2007 and 2014, primarily as the result of the lower use of protease inhibitors. This decline was partially counteracted by the increased use of cobicistat after 2012. As a consequence of the increased use of cobicistat, the proportion of HIV beneficiaries taking contraindicated statins did not continue to decrease through 2015. Factors associated with contraindicated statin use included older age, male sex, living in the North Central, South, and West versus the Northeast region of the United States, and having a history of CHD, hypertension, and diabetes mellitus.

Statins are considered the first-line therapy to lower CVD risk in HIV-infected adults by the National Lipid Association because of their cholesterol-lowering and anti-inflammatory properties.[13] Previous studies suggest that the use of statin therapy is low among HIV-infected adults.[14,15] The current analysis expands on prior studies by showing that the use of statin therapy has not increased between 2007 and 2015 among beneficiaries with HIV. This finding is concerning as factors associated with a higher CVD risk, including older age, history of CHD, diabetes mellitus, and chronic kidney disease have increased among beneficiaries with HIV over this time period.[16–18] These results highlight the need for increasing the appropriate use of statins among patients with HIV. Additionally, studies are needed to identify the barriers preventing statin use among people living with HIV.

Table 7. Risk Ratios (95% Confidence Intervals) for a Contraindicated Statin Use During the Assessment Period Associated With Calendar Year and Beneficiary Characteristics Among Beneficiaries With HIV Taking Statin Therapy

	Beneficiaries With HIV Taking Statin Therapy (n=47 596)	
	Unadjusted	Multivariable-Adjusted
Age		
<50 y	1 (reference)	1 (reference)
50 to 59 y	1.24 (1.13, 1.35)	1.23 (1.12, 1.35)
≥60 y	1.23 (1.10, 1.37)	1.18 (1.04, 1.33)
Male	1.30 (1.13, 1.49)	1.26 (1.10, 1.45)
Year		
2007	1 (reference)	1 (reference)
2008	0.94 (0.87, 1.03)	0.92 (0.85, 1.01)
2009	0.89 (0.81, 0.98)	0.89 (0.81, 0.98)
2010	0.83 (0.75, 0.92)	0.82 (0.74, 0.91)
2011	0.73 (0.66, 0.82)	0.71 (0.64, 0.79)
2012	0.62 (0.56, 0.69)	0.60 (0.54, 0.67)
2013	0.60 (0.54, 0.67)	0.57 (0.51, 0.64)
2014	0.55 (0.49, 0.62)	0.53 (0.47, 0.59)
2015	0.60 (0.54, 0.68)	0.57 (0.50, 0.64)
Region		
Northeast	1 (reference)	1 (reference)
North Central	1.28 (1.10, 1.50)	1.21 (1.03, 1.41)
South	1.22 (1.07, 1.39)	1.18 (1.04, 1.35)
West	1.36 (1.18, 1.56)	1.29 (1.12, 1.48)
Unknown	1.04 (0.67, 1.61)	1.04 (0.67, 1.60)
Comorbidities		
Coronary heart disease	1.49 (1.34, 1.65)	1.34 (1.20, 1.50)
Hypertension	1.28 (1.18, 1.40)	1.16 (1.06, 1.27)
Diabetes mellitus	1.43 (1.29, 1.58)	1.38 (1.24, 1.54)
Stroke	1.13 (0.88, 1.45)	1.01 (0.78, 1.30)
Chronic kidney disease	1.28 (1.14, 1.44)	1.12 (0.99, 1.27)
Liver disease	0.88 (0.70, 1.10)	0.82 (0.66, 1.03)

The multivariable adjusted model includes adjustment for all variables in the table simultaneously.

In the current analysis, the use of contraindicated statins among beneficiaries with HIV declined between 2007 and 2014. This decline was mainly the result of the lower use of protease inhibitors. Results from the current analysis also suggest that cobicistat, a pharmacokinetic booster/enhancer, has counteracted some of the decline in contraindicated statin use. Cobicistat is a potent inhibitor of the cytochrome P-450 3A4 (CYP3A4) and increases the concentration of

statins metabolized through this enzyme system.[19,20] Cobicistat may also increase the serum concentration of statins by inhibiting the permeability glycoprotein, the breast cancer resistance protein, and the organic anion-transporting polypeptides 1B1 and 1B3.[19,20] Cobicistat was initially approved by the Food and Drug Administration in a fixed-dose combination with elvitegravir, emtricitabine, and tenofovir disoproxil in August 2012.[21] After its approval, the use of cobicistat increased substantially among adults with HIV.[10] In the current analysis, the use of contraindicated statins attributable to taking cobicistat increased substantially between 2012 and 2015. This finding suggests a lack of awareness of contraindications for statin therapy associated with cobicistat. Increasing physicians' awareness and implementing electronic prescription systems with drug-drug interaction checks may reduce the contraindicated use of statins attributed to cobicistat among HIV patients.[22,23] Patients with HIV taking cobicistat who initiate statin therapy should be prescribed atorvastatin or rosuvastatin at the lowest dosages and these medications should be titrated with close monitoring for adverse reactions.[8,24]

Non-ART therapies commonly prescribed in adults with HIV also contribute to the use of contraindicated statins. In the current analysis, gemfibrozil accounted for 22.6% of contraindicated statin use in 2015. Elevated triglycerides levels are common among HIV patients, particularly in those taking protease inhibitors.[25] In HIV patients requiring triglyceride-lowering therapy, fenofibrate and omega-3 fatty acids should be preferred over gemfibrozil given their lower risk for rhabdomyolysis when combined with statins.[26,27] In the current analysis, the use of calcium channel blockers increased between 2007 and 2015, presumably because of the higher prevalence of hypertension in more recent years. In 2015, calcium channel blockers accounted for 4.5% of contraindicated statin use. Among HIV patients with hypertension taking statins, the use of antihypertensive medication classes other than calcium channel blockers should be considered. The 2017 American College of Cardiology/American Heart Association blood pressure guideline recommends thiazide diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers in addition to calcium channel blockers for adults initiating antihypertensive medication.[28] Future surveillance on the use of calcium channel blockers and statins among HIV patients is warranted as this population is aging.

Simvastatin and lovastatin should be avoided in HIV-infected adults as these medications are contraindicated with several ARTs including protease inhibitors.[9,11,13] Use of atorvastatin, rosuvastatin, or pitavastatin is preferable in HIV patients, although dosing adjustments may be required.[9,13] In the current analysis, there was a decline in the proportion of contraindicated statin attributable to simvastatin, particularly after 2010. Several factors could have contributed to this decline in the use of simvastatin, including increasing awareness about the contraindication with ART, increased concerns about adverse muscle events associated with this medication,[29,30] and the availability of low-cost atorvastatin after becoming generic in 2011.[31] In 2015, 58.0% and 20.0% of contraindicated statin use was attributable to atorvastatin and rosuvastatin, respectively. These results suggest a lack of awareness on the need for dosing adjustment when using atorvastatin and rosuvastatin in people with HIV.

The use of contraindicated statins was higher in subgroups with high CVD risk, including older patients, men, and those with CHD, hypertension, or diabetes mellitus. This finding may be explained by the use of high-intensity statin dosages in these groups. The use of contraindicated statins was also higher in beneficiaries with HIV living in the South and West versus the Northeast US region. Given the high proportion of HIV-patients living in the South and West regions of the United States,[32] increased awareness of contraindicated statins by healthcare professionals who care for HIV patients in these regions is warranted.

We analyzed trends and factors associated with contraindicated use of statins as this increases the risk for adverse events associated with this medication.[9,13] Some medications commonly used among HIV patients may reduce the efficacy of statin therapy.[9] Non-nucleoside reverse transcriptase inhibitors may reduce serum concentrations of statins metabolized through the CYP3A4 enzyme system.[9] Because non-nucleoside reverse transcriptase inhibitors do not increase the risk for statin-related adverse events, these medications were not considered a contraindication in the current analysis. However, clinicians should be aware of possible drug-drug interactions when prescribing statins in HIV-patients taking non-nucleoside reverse transcriptase inhibitors.[8]

Strengths of the current study include the availability of data on ART and statin use in a large cohort of HIV patients from all regions of the United States. The pharmacy data we used included medications and dosages. The current study has several known and potential limitations. Misclassification of the use of statins, ART, and other medications with contraindications with statins is possible given that we relied on pharmacy fill data. These data indicate that beneficiaries filled a prescription but not whether they took it. Also, using administrative claims data may result in misclassification of baseline characteristics and HIV infection status if diagnosis codes for these conditions are not used or incorrectly used. We lacked data on estimated glomerular filtration rate, which prevented us from determining additional contraindications with specific statin doses resulting from renal impairment. Also, we did not have data on socioeconomic status and race/ethnicity. These data are not available in Marketscan.

Conclusion

In conclusion, in this large population with health insurance, the percentage of beneficiaries living with HIV that was taking a statin did not increase between 2007 and 2015 despite aging and a higher prevalence of CHD, hypertension, diabetes mellitus, and chronic kidney disease. The use of contraindicated statins declined between 2007 and 2014, primarily because of lower use of protease inhibitors. However, the increased use of cobicistat attenuated this decline. The current study supports the need to increase the appropriate use of statins among people living with HIV consistent with clinical practice guidelines. Also, clinicians should be vigilant in prescribing statin types and dosages with no or minimal contraindications among adults living with HIV.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Cascade of beneficiaries with HIV included in the current analysis.

Criteria	2007	2008	2009	2010	2011	2012	2013	2014	2015
Had medical coverage in the assessment and baseline years	18,796,150	18,719,527	27,745,990	27,705,972	29,198,060	32,689,682	25,426,912	24,692,985	17,247,365
Had pharmacy coverage in the assessment and baseline years	13,910,859	15,162,188	21,150,244	22,253,050	23,467,368	26,232,014	21,177,823	19,752,611	16,301,118
Alive on December 31 of the assessment year	13,903,998	15,152,507	21,135,925	22,236,418	23,447,148	26,212,571	21,161,279	19,738,038	16,290,590
Lived in the United States in the assessment and baseline years	13,903,661	15,152,374	21,135,125	22,232,988	23,443,764	26,212,386	21,161,188	19,737,964	16,290,370
Age ≥19 years on January 1 of the assessment year	10,865,088	11,839,144	6,380,286	17,235,998	18,333,731	20,587,102	16,703,634	15,545,306	12,850,818
Had ≥1 HIV inpatient diagnosis code or ≥2 pharmacy fills for ART in the baseline year	10,135	11,939	20,218	21,390	25,113	28,443	25,113	24,420	21,985
Had ≥1 pharmacy fill for ART in the baseline year	9,928	11,713	19,868	21,084	24,781	28,104	24,892	24,225	21,825

ART: antiretroviral therapy; HIV: human immunodeficiency virus.

Table S2. Definitions for patient characteristics.

Characteristics	Definition
Coronary heart disease[1]	Any of the following: • ≥1 hospitalization or physician evaluation and management visit with a diagnosis code of MI (ICD-9-CM diagnosis code of 410.xx or 412.xx) in any discharge diagnosis position • ≥1 hospitalization or physician visit with a procedure code for revascularization (ICD-9-CM procedure codes 00.66, 36.0, 36.01-36.19, 36.2, ICD-9-CM diagnosis codes V45.81 or V45.82, or CPT codes 33510-33519, 33521-33523, 33530, 33533-33536, 92980-92982, 92984, 92995, 92996) • ≥1 inpatient or physician evaluation and management visit with another CHD-related code (ICD-9-CM code of 411.xx, 413.xx, or 414.xx)
Hypertension[2,3]	Any of the following: • ≥1 hospitalization with a discharge diagnosis code of 401.xx in any discharge diagnosis position • ≥ 2 physician evaluation and management visits with an ICD-9-CM diagnosis code of 401.xx in any position at least 7 days apart • ≥1 pharmacy for an antihypertensive medication
History of diabetes[2-4]	Any of the following: • ≥1 hospitalization with a discharge diagnosis code of diabetes (ICD-9-CM diagnosis codes 250.xx, 357.2, 362.0x, or 366.41) in any discharge diagnosis position • ≥2 physician evaluation and management visits with a diagnosis code of diabetes (ICD-9-CM diagnosis codes 250.xx, 357.2, 362.0x, or 366.41) in any position occurring at least 7 days apart • ≥1 pharmacy for an oral hypoglycemic medication or insulin
History of stroke[5]	Any of the following: • ≥1 hospitalization with a discharge diagnosis code of stroke (ICD-9-CM discharge diagnosis code of 430.xx, 431.xx, 433.x1, 434.x1 or 436.x) in any discharge diagnosis position • ≥1 physician evaluation and management visit with a diagnosis code of stroke (ICD-9-CM discharge diagnosis code of 430.xx, 431.xx, 433.x1, 434.x1 or 436.x) in any position
Chronic kidney disease[6]	Any of the following: • ≥1 hospitalization with a discharge diagnosis code of chronic kidney disease (ICD-9-CM diagnosis code of 016.0x, 095.4, 189.0, 189.9, 223.0, 236.91, 250.4x, 271.4, 274.1x, 283.11, 403.x1, 403.x0, 404.x2, 404.x3, 404.x0, 404.x1, 440.1, 442.1, 447.3, 572.4, 580–588, 591, 642.1x, 646.2x, 753.12–753.17, 753.19, 753.2x, or 794.4) in any discharge diagnosis position • ≥1 physician evaluation and management visit with a diagnosis code of chronic kidney disease (ICD-9-CM diagnosis code of 016.0x, 095.4, 189.0, 189.9, 223.0, 236.91, 250.4x, 271.4, 274.1x, 283.11, 403.x1, 403.x0, 404.x2, 404.x3, 404.x0, 404.x1, 440.1, 442.1, 447.3, 572.4, 580–588, 591, 642.1x, 646.2x, 753.12–753.17, 753.19, 753.2x, or 794.4) in any position
Liver disease[2,3]	Any of the following:

Characteristics	Definition
	• ≥1 hospitalization with a discharge diagnosis code of liver disease (ICD-9-CM diagnosis codes 070.0, 070.1, 070.20–070.23, 070.30–070.33, 070.41–070.44, 070.49, 070.51–070.54, 070.59, 070.6, 070.70, 070.71, 070.9, 275.0x, 275.1, 456.0, 456.1, 456.20, 456.21, 571.0–571.3, 571.40–571.42, 571.49, 571.5, 571.6, 571.8, 571.9, 572.2–572.4, 572.8, 573.3, 573.5, 573.8, 576.1, 576.8, 782.4, E947.9, V02.60, V02.61, V02.62, V02.69, or V42.7) in any discharge diagnosis position • ≥2 physician evaluation and management visits with a diagnosis code of liver disease (ICD-9-CM diagnosis codes 070.0, 070.1, 070.20–070.23, 070.30–070.33, 070.41–070.44, 070.49, 070.51–070.54, 070.59, 070.6, 070.70, 070.71, 070.9, 275.0x, 275.1, 456.0, 456.1, 456.20, 456.21, 571.0–571.3, 571.40–571.42, 571.49, 571.5, 571.6, 571.8, 571.9, 572.2–572.4, 572.8, 573.3, 573.5, 573.8, 576.1, 576.8, 782.4, E947.9, V02.60, V02.61, V02.62, V02.69, or V42.7) in any position occurring on separate days

CPT: Current Procedure Terminology; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; MI: myocardial infarction.
Physician evaluation and management visits include ambulatory visit, emergency department, inpatient face-to-face and nursing home.

Table S3. Medications with statin contraindications.

Contraindicated medication group	Contraindicated medication	Contraindicated statin dose
Nefazodone	Nefazodone	Lovastatin any dose Simvastatin any dose
Gemfibrozil	Gemfibrozil	Atorvastatin any dose Fluvastatin any dose Lovastatin any dose Pitavastatin any dose Pravastatin any dose Rosuvastatin any dose Simvastatin any dose
Amiodarone	Amiodarone	Lovastatin >40 mg daily Simvastatin >20 mg daily
Calcium channel blockers	Amlodipine	Simvastatin >20 mg daily
	Diltiazem	Lovastatin >20 mg daily Simvastatin >10 mg daily
	Verapamil	Lovastatin >20 mg daily Simvastatin >10 mg daily
Antifungal medications	Fluconazole	Fluvastatin > 40 mg daily
	Itraconazole	Atorvastatin >20 mg daily Lovastatin any dose Simvastatin any dose
	Posaconazole	Atorvastatin any dose Lovastatin any dose Simvastatin any dose
	Voriconazole	Lovastatin any dose Simvastatin any dose
Antibiotics	Clarithromycin	Atorvastatin >20 mg daily Lovastatin any dose Simvastatin any dose Pravastatin >40 mg daily Simvastatin any dose
	Erythromycin	Lovastatin any dose Pitavastatin >1 mg daily Simvastatin any dose
	Rifampin	Pitavastatin >2 mg daily
	Telithromycin	Atorvastatin >20 mg daily Lovastatin any dose Simvastatin any dose
Hepatitis C virus protease inhibitors	Boceprevir	Atorvastatin >40 mg daily Lovastatin any dose Simvastatin any dose
	Simeprevir	Atorvastatin >40 mg daily

	Telaprevir	Atorvastatin any dose
		Lovastatin any dose
		Simvastatin any dose
Cobicistat	Cobicistat	Atorvastatin any dose (if in combination with atazanavir)
		Atorvastatin >20 mg daily (if in combination with darunavir or elvitegravir)
		Lovastatin any dose
		Rosuvastatin >10 mg daily (if in combination with atazanavir)
		Rosuvastatin >20 mg daily (if in combination with darunavir)
		Simvastatin any dose
Human immunodeficiency virus protease inhibitors	Atazanavir	Lovastatin any dose
		Simvastatin any dose
	Darunavir	Lovastatin any dose
		Simvastatin any dose
	Fosamprenavir	Atorvastatin >20 mg daily
		Lovastatin any dose
		Simvastatin any dose
	Indinavir	Lovastatin any dose
		Simvastatin any dose
	Nelfinavir	Atorvastatin >40 mg daily
		Lovastatin any dose
		Simvastatin any dose
	Ritonavir	Lovastatin any dose
		Simvastatin any dose
	Ritonavir-boosted atazanavir	Rosuvastatin >10 mg daily
	Ritonavir-boosted darunavir	Atorvastatin >20 mg daily
	Ritonavir-boosted fosamprenavir	Atorvastatin >20 mg daily
	Ritonavir-boosted lopinavir	Rosuvastatin >10 mg daily
	Ritonavir-boosted saquinavir	Atorvastatin >20 mg daily
	Saquinavir	Lovastatin any dose
		Simvastatin any dose
	Tipranavir	Atorvastatin any dose
		Lovastatin any dose
		Simvastatin any dose

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