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Comparative Incidence and Health Care Costs of Medically Attended Adverse Effects among U.S. Medicaid HIV Patients on Atazanavir- or Darunavir-Based Antiretroviral Therapy

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ABSTRACT

Objectives: This is the first study to compare the incidence and health care costs of medically attended adverse effects in atazanavir- and darunavir-based antiretroviral therapy (ART) among U.S. Medicaid patients receiving routine HIV care. **Methods:** This was a retrospective study using Medicaid administrative health care claims from 15 states. Subjects were HIV patients aged 18 to 64 years initiating atazanavir- or darunavir-based ART from January 1, 2003, to July 1, 2010, with continuous enrollment for 6 months before (baseline) and 6 months after (evaluation period) ART initiation and 1 or more evaluation period medical claim. Outcomes were incidence and health care costs of the following medically attended (*International Classification of Diseases, Ninth Revision, Clinical Modification*–coded or treated) adverse effects during the evaluation period: gastrointestinal, lipid abnormalities, diabetes/hyperglycemia, rash, and jaundice. All-cause health care costs were also determined. Patients treated with atazanavir and darunavir were propensity score matched (ratio = 3:1) by using demographic and clinical covariates. Multivariable models adjusted for covariates lacking postmatch statistical balance. **Results:** Propensity-matched study sample included 1848 atazanavir- and 616 darunavir-treated patients (mean age 41 years, 50% women, 69% black). Multivariable-adjusted hazard ratios (HRs) (for darunavir, reference = atazanavir) and per-patient-per-month health care cost differences (darunavir minus atazanavir) were as follows: gastrointestinal, HR = 1.25 ($P = 0.04$), \$43 ($P = 0.13$); lipid abnormalities, HR = 1.38 ($P = 0.07$), \$3 ($P = 0.88$); diabetes/hyperglycemia, HR = 0.84 ($P = 0.55$), \$13 ($P = 0.69$); and rash, HR = 1.11 ($P = 0.23$), \$0 ($P = 0.76$); all-cause health care costs were \$1086 ($P < 0.001$). Too few instances of jaundice (11 in atazanavir and 1 in darunavir) occurred to support multivariable modeling. **Conclusions:** Medication tolerability can be critical to the success or failure of ART. Compared with darunavir-treated patients, atazanavir-treated patients had significantly fewer instances of medically attended gastrointestinal issues and more instances of jaundice and incurred significantly lower health care costs.

Keywords: adverse effects, antiretroviral therapy, atazanavir, darunavir, health care costs, Medicaid.

Introduction

Antiretroviral therapy (ART) adverse effects can have a substantial impact on patients' quality of life, health care resource utilization, and adherence and persistence to therapy [1–4]. Poor ART adherence and discontinuation can result in viral rebound, immune decompensation, and clinical progression. It can also result in the development of drug-resistant virus, which, in turn, can result in the permanent loss of therapeutic options [1,5,6].

Owing to their benefits of optimal and durable virologic efficacy, ease of use, and favorable tolerability and toxicity profiles, atazanavir and darunavir are currently the only protease inhibitors (PIs) that are designated as preferred for first-line ART regimens in the Department of Health and Human Services antiretroviral treatment guidelines [1]. Furthermore, atazanavir and darunavir may also be used as options after the initial failure of a first-line ART regimen [7]. The U.S. Food and Drug Administration approved atazanavir in 2003 and darunavir in 2006.

PIs have been shown to be associated with a variety of adverse effects, including gastrointestinal intolerance, insulin resistance, hepatotoxicity, dyslipidemia, and rash [1,8–10]. Although the common adverse effects of PIs as a class have been established, the current understanding of the variation in adverse effects across specific PIs is based on findings from completed clinical trials, none of which have directly compared darunavir with atazanavir.

ACTG 5257 is a fully enrolled, prospective, randomized trial comparing efficacy and safety in ritonavir-boosted atazanavir + emtricitabine/tenofovir disoproxil fumarate, ritonavir-darunavir + emtricitabine/tenofovir disoproxil fumarate, and raltegravir + emtricitabine/tenofovir disoproxil fumarate for treatment-naive HIV-1–infected volunteers [11]. However, because the results of this trial are not expected until late 2013 or 2014, other sources of data, such as administrative claims, are required to conduct research that compares atazanavir- and darunavir-based ART. Findings from such "real-world" data sources can complement

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the highly internally valid findings from randomized controlled trials because they can offer broad generalizability and provide detailed information on health care costs associated with adverse effect and other forms of medical care that are often not collected in a systematic way within trials.

In the current study, we used real-world data to compare the incidence and health care costs of medically attended (International Classification of Diseases, Ninth Revision, Clinical Modification [*ICD-9-CM*]-coded or treated) adverse effects in atazanavir- and darunavir-based ART among U.S. Medicaid patients receiving routine HIV care.

Methods

Study Design and Data

This study used a retrospective, observational design with propensity score matching and multivariable statistical analysis techniques. Five specific adverse effects, adapted from those listed within the Department of Health and Human Services treatment guidelines for antiretroviral agents as being common in atazanavir or darunavir, were chosen for study [1]. These were gastrointestinal, lipid abnormalities, diabetes/hyperglycemia, rash, and jaundice.

The data studied were administrative health care claims for Medicaid patients extracted from the 2002 to 2010 years of the Truven Health Analytics MarketScan Multi-State Medicaid (Medicaid) Database. This population was chosen because the Medicaid program covers an estimated 38% to 42% of HIV patients receiving care, making it the single largest source of health insurance for people living with HIV in the United States [12,13]. The Medicaid database comprises inpatient medical, outpatient medical, and outpatient prescription claims and encounter records collected from among patients from 15 geographically dispersed Medicaid states that vary in size and sociodemographic composition. These claims are coded with *ICD-9-CM*, Current Procedural Terminology, National Drug, and Healthcare Common Procedure Coding System codes, which are the current coding standards in the United States. Because of confidentiality agreements between Truven Health Analytics and the states that contribute their data to the Medicaid database, further public disclosure of identifying information about the state Medicaid programs is restricted. The data contained in the Medicaid database are statistically de-identified and fully compliant with the Health Insurance Portability and Accountability Act Privacy Regulations; as such, institutional review board approval and written informed consent were not sought for this study.

Sample Selection Criteria

Patients selected for study were required to have initiated an ART regimen between January 1, 2003, and January 1, 2010, comprising at least two nucleoside reverse transcriptase inhibitors (NRTIs: abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zidovudine, zalcitabine, abacavir/lamivudine, emtricitabine/tenofovir DF, zidovudine/lamivudine, zidovudine/lamivudine/abacavir) in combination with either atazanavir or darunavir, with or without ritonavir boosting; patients with prescription claims for ART prior to initiating atazanavir or darunavir were allowed to enter the study. The study index date was defined as the first observed prescription claim for atazanavir or darunavir.

Patients were required to be aged 18 to 64 years on the index date and have continuous Medicaid enrollment for 6 months before the index date (designated the baseline period) and for 6 months after the index date. Patients were also required to have at least one medical claim during the 6-month period of continuous Medicaid enrollment after the index date to ensure that they had maintained contact with the health care system and thus medically attended adverse effects could be observed.

Patients who had separate episodes of treatment with atazanavir and darunavir, and for whom all study inclusion criteria were met at the time when they initiated each drug, contributed two separate observations to the study analysis, one for the time covered by atazanavir and one for the time covered by darunavir; this was the case for 78 unique patients. Consequently, the study analyses were conducted on an "episode of treatment" unit of observation.

Evaluation Period and Outcomes

The study evaluation period, defined in detail below, was used to measure the incidence and health care costs of medically attended adverse effects as well as all-cause health care costs. All-cause health care costs were defined as health care costs incurred for all inpatient medical, outpatient medical, and outpatient prescription claims during the evaluation period and are not limited to medically attended adverse effects.

Research indicates that PI-related adverse effects frequently occur within the first 3 to 4 months of PI initiation [9,10,14,15]. Accordingly, to capture the majority of adverse effects, the evaluation period was constructed to begin on the index date and end with censoring at the earliest occurrence of either 6 months after the index date or the addition of a different critical agent (PI, non-NRTI, fusion inhibitor, or integrase inhibitor) within the initiated ART regimen. Among the darunavir-treated patients, 78 (12.7%) were coadministered etravirine and 138 (21.8%) were coadministered raltegravir, with coadministration of these drugs being observed almost exclusively in individuals who had claims for ART prior to their index date, suggesting ART experience. Therefore, to allow for such instances of real-world prescribing patterns to be reflected within the study, patients who initiated either of these agents with darunavir were not excluded from the study.

Table 1 presents the algorithms, codes, and medication classes used for measuring the five specific adverse effects chosen for this study. Health care costs were summarized as per-patient-per-month (PPPM) units to account for across-patient variability in the duration of the evaluation period and were expressed in 2010 constant dollars, adjusted by using the Medical Care component of the consumer price index [16]. The incidence rates of medically attended adverse effects were calculated as the number of patients with a specific medically attended adverse effect divided by the sum of person-time observed for each patient, where person-time was calculated as the duration of time from the index date until the date of occurrence of the medically attended adverse effect or censoring at the end of the evaluation period.

Covariates

Covariates included patient demographics and clinical characteristics. Patient demographics were defined at the index date and included age, sex, race/ethnicity (black, Hispanic, white, other), insurance plan type (comprehensive, health maintenance organization, preferred provider organization, point of service, point of service with capitation, unknown), index year, urban versus rural residence, and the Medicaid state from which the patient was identified. Clinical characteristics included ART experience (defined as having baseline prescription claims for ART; patients without baseline prescriptions for ART were designated ART naive), presence of ritonavir boosting within the ART regimen at index, NRTIs included within the ART regimen at index, proxy

Table 1 – Algorithms, codes, and medication classes used for measuring medically attended (*ICD-9-CM*–coded or treated) adverse effects.

Adverse effect	Algorithm	*ICD-9-CM*	Medication classes
Gastrointestinal symptoms	One inpatient or one nondiagnostic outpatient claim with an *ICD-9-CM* diagnosis code for diarrhea, nausea, or vomiting OR by at least one outpatient pharmaceutical prescription claim for an antiemetic or an antidiarrhea agent	787.01, 787.02, 787.91	Antiemetics, antidiarrhea agents
Jaundice	One inpatient or one nondiagnostic outpatient claim with an *ICD-9-CM* diagnosis code for jaundice	782.4x	None
Lipid abnormalities*	One inpatient or one nondiagnostic outpatient claim with an *ICD-9-CM* diagnosis code for dyslipidemia OR at least one outpatient pharmaceutical prescription claim for a lipid-lowering therapy	272.0, 272.1, 272.2, 272.3, 272.4	Bile-sequestering resins, statins, niacin, and fibrates
Diabetes/hyperglycemia*	One inpatient or one nondiagnostic outpatient claim with an *ICD-9-CM* diagnosis code for diabetes/hyperglycemia OR at least one outpatient pharmaceutical prescription claim for an antidiabetic medication	250.xx, 792.xx	Alpha-glucosidase inhibitors, biguanides, dipeptidyl peptidase-4 inhibitors, meglitinides, sulfonylureas, thiazolidinediones, insulins, glucagon-like peptide-1 analogs, amylin analog
Rash	One inpatient or one nondiagnostic outpatient claim with an *ICD-9-CM* diagnosis code for rash OR at least one outpatient pharmaceutical prescription claim for a topical glucocorticoid or calamine	692.3, 692.89, 692.9, 693.0, 693.9, 695.0, 695.1, 695.3	Topical glucocorticoids, calamine

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.
* When measuring new-onset adverse effects, patients with baseline period evidence of a given chronic adverse effect (i.e., lipid abnormalities or diabetes/hyperglycemia) were excluded from the calculation of incidence rates for that particular chronic adverse effect. For inpatient claims, the entire cost associated with a claim was included if it had a primary diagnosis code indicative of the adverse effect. If an inpatient claim had a relevant diagnosis code for an adverse effect in a nonprimary position, then only the costs for services associated with that diagnosis code were included. For outpatient claims, the entire cost associated with a claim was included if any diagnosis code indicative of the adverse effect was recorded on the claim.

indices of baseline health status (number of unique three-digit *ICD-9-CM* diagnosis codes, number of unique national drug codes), baseline presence of diagnosed comorbid conditions (hepatitis B, hepatitis C, alcohol or substance abuse, depression, other psychiatric diagnoses), and the baseline presence of each medically attended adverse effect.

Propensity Score Matching and Multivariable Statistical Analyses

To construct atazanavir and darunavir cohorts that were balanced with respect to the measured demographic and clinical characteristics, atazanavir-treated patients were propensity score matched at a 3:1 ratio to darunavir-treated patients. Because patient experience with ART is likely to be strongly correlated with study outcomes, the statistical approach was focused on achieving balance on this covariate. After testing several approaches, it was determined that the optimal balance on this covariate could be achieved only when fitting propensity score models that were stratified by ART experience. Accordingly, two separate propensity score models were fitted: one subset to ART-naive patients and one subset to ART-experienced patients. The resulting matched samples were then combined for analysis.

In each of the two propensity score models, multivariable logistic regression was used to predict the probability (i.e., the propensity score) of being in the atazanavir versus darunavir cohorts as a function of patient age, sex, race/ethnicity, insurance plan type, index year, Medicaid state, proxy indices of baseline health status, and baseline presence of diagnosed comorbid conditions. The propensity scores were used to match the atazanavir and darunavir cohorts through nearest neighbor matching, without replacement, within a caliper of 0.25 SDs of the propensity score.

Postmatch multivariable models were used to adjust for the baseline presence of medically attended adverse effects and covariates lacking postmatch statistical balance, as indicated by a standardized difference value of greater than 10 [17]. Multivariable Cox proportional hazards models were used to analyze

the hazard of medically attended adverse effects. A one-part multivariable generalized linear model approach with a log link and gamma error distribution was used to analyze health care costs for all-cause and medically attended lipid abnormality adverse effects. To handle distributions characterized by a large concentration of 0 values, a two-part multivariable generalized linear model approach, in which the first part modeled the probability of incurring any health care costs for a given medically attended adverse effect and the second part modeled differences in health care costs among those with nonzero costs, was used to analyze health care costs for medically attended gastrointestinal, diabetes/hyperglycemia, and rash adverse effects. Finally, because patients who were treated with both atazanavir and darunavir were allowed to contribute two observations to the data set, the Huber-White "sandwich" variance estimator was used to calculate robust variances to address the potential for clustering within the multivariable analyses [18].

Sensitivity Analysis

Two sensitivity analyses were conducted to test the robustness of the results to alternative assumptions about the evaluation period. The first sensitivity analysis addressed the possibility that patients who switch from their index PI to a different PI, non-NRTI fusion inhibitor, or integrase inhibitor in response to adverse effects may wait until after the switch before they fill a prescription for a medication used to treat the adverse effect (e.g., a patient waits a few days to fill a prescription for an antiemetic after switching from a PI that caused gastrointestinal adverse effects). For this sensitivity analysis, a 7-day window after atazanavir or darunavir switches within the evaluation period was allowed for the identification of medically attended adverse effects. The second sensitivity analysis addressed the possibility that the clinical and health care cost impact of an adverse effect could extend beyond the date of a switch in response to an adverse effect (e.g., a patient must remain on lipid-lowering therapies for several months after switching from a PI that caused dyslipidemia). For this sensitivity analysis, if a patient experienced an adverse effect prior to switching from atazanavir or darunavir in the evaluation period, the entire 6-month period was used to measure the health care costs associated with the adverse effect.

Results

Study Sample

During the study period, there were 47,555 episodes of PI treatment among 37,247 patients. Sequentially, exclusions were 4,877 without at least two NRTIs in their ART regimen, 1,757 not aged 18 to 64 years, 3,326 without at least one medical claim in the evaluation period, 9,466 with inadequate baseline continuous enrollment, 4,561 with inadequate evaluation period continuous enrollment, and 3,544 with prior exposure to the initiated PI. Among the remaining 20,024 episodes, 8,038 corresponded to atazanavir and 616 corresponded to darunavir and these were included within the propensity score model. The propensity score models successfully achieved a 3:1 match ratio, matching 1,848 atazanavir-treated patients to all 616 darunavir-treated patients. The discriminant accuracy of the propensity score models, as indicated by the area under the receiver operating curve, was 0.890 among ART-naive patients and 0.873 among ART-experienced patients. The propensity score analyses achieved statistical balance, as indicated by a standardized difference of less than 10, for race, Medicaid state, ART experience, and all

Table 2 – Patient demographics.

	Atazanavir prematch (n = 8038)	Atazanavir postmatch (n = 1848)	Darunavir (n = 616)
Patient age (y), mean ± SD	42.0 ± 9.0	41.1 ± 9.8	43 ± 9.2
Patient age category (y), n (%)			
18–34	1564 (19.5)	465 (25.2)	111 (18.0)
35–44	3352 (41.7)	671 (36.3)	247 (40.1)
45–54	2455 (30.5)	559 (30.2)	199 (32.3)
55–64	667 (8.3)	153 (8.3)	59 (9.6)
Female patients, n (%)	2872 (35.7)	965 (52.2)	279 (45.3)
Patient race/ethnicity category, n (%)			
Black	3875 (48.2)	1280 (69.3)	410 (66.6)
Hispanic	683 (8.5)	25 (1.4)	17 (2.8)
White	2818 (35.1)	374 (20.2)	125 (20.3)
Other	662 (8.2)	169 (9.1)	64 (10.4)
Patient insurance plan type, n (%)			
Comprehensive	5419 (67.4)	651 (35.2)	221 (35.9)
HMO	1563 (19.4)	660 (35.7)	181 (29.4)
PPO	4 (0.0)	1 (0.1)	0 (0.0)
POS with capitation	943 (11.7)	494 (26.7)	174 (28.2)
Unknown	109 (1.4)	42 (2.3)	40 (6.5)
Index year, n (%)			
2003	1982 (24.7)	0 (0.0)	0 (0.0)
2004	2732 (34.0)	14 (0.8)	0 (0.0)
2005	1553 (19.3)	457 (24.7)	0 (0.0)
2006	384 (4.8)	273 (14.8)	32 (5.2)
2007	381 (4.7)	314 (17.0)	107 (17.4)
2008	502 (6.2)	407 (22.0)	174 (28.2)
2009	393 (4.9)	293 (15.9)	218 (35.4)
2010	111 (1.4)	90 (4.9)	85 (13.8)

HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization.

included comorbid conditions. Covariates for which statistical imbalance remained were adjusted in the postmatch multivariable analyses.

Table 2 displays patient demographic characteristics for the unmatched atazanavir cohort and for the matched atazanavir and darunavir cohorts. After matching, most patients were in the 35 to 44 years of age category, approximately half were men, and most were of black race/ethnicity.

Table 3 displays clinical characteristics for the unmatched atazanavir cohort and for the matched atazanavir and darunavir cohorts. Prior to matching, 83.7% of the atazanavir cohort was ART experienced; after matching, 91.2% of each cohort was ART experienced. Tenofovir and emtricitabine were the NRTIs that were most commonly used as part of the index ART regimen or during the 6-month baseline period. Darunavir-treated patients had numerically higher percentages of patients with baseline medically attended adverse effects.

Incidence and Health Care Costs of Medically Attended Adverse Effects without Multivariable Adjustment

Table 4 displays the duration of the evaluation period in days and unadjusted incidence rates and average PPPM health care costs of medically attended adverse effects during the evaluation period. Compared with atazanavir-treated patients, darunavir-treated patients' incidence rates of medically attended adverse effects were numerically greater for gastrointestinal, lipid abnormalities, and rash and numerically lower for diabetes/hyperglycemia and jaundice. Furthermore, darunavir-treated patients' average PPPM health care costs of medically attended adverse effects were numerically greater for gastrointestinal, numerically lower for jaundice and diabetes/hyperglycemia, and similar for lipid abnormalities and rash.

Average PPPM medically attended gastrointestinal and rash adverse effect health care costs were primarily driven by pharmacy costs. Approximately 99% of the gastrointestinal pharmacy costs were for antiemetics (data not shown). Average PPPM medically attended jaundice, lipid abnormality, and diabetes/hyperglycemia adverse effect health care costs were primarily driven by inpatient care.

In the two sensitivity analyses, the results were not substantively changed and were consistent across the two PIs. When allowing a 7-day window after atazanavir or darunavir switches for the identification of adverse effects, percentage changes in the incidence rates of adverse effects per 1000 person-months ranged from −1% to 8%. When using the entire 6-month period to measure health care costs associated with the adverse effects that occurred prior to atazanavir or darunavir switches, the estimated PPPM costs decreased for acute adverse effects and increased for chronic adverse effects. The largest observed

Table 3 – Patient baseline period clinical characteristics.

	Atazanavir prematch (n = 8038)	Atazanavir postmatch (n = 1848)	Darunavir (n = 616)
ART experienced (nonnaive), n (%)	6731 (83.7)	1686 (91.2)	562 (91.2)
ARVs included in ART regimen or used during 6-mo baseline period, n (%)			
Ritonavir	6827 (84.9)	1645 (89.0)	608 (98.7)
NRTIs			
Tenofovir	6295 (78.3)	1495 (80.9)	536 (87.0)
Emtricitabine	3122 (38.8)	1242 (67.2)	465 (75.5)
Abacavir	2661 (33.1)	571 (30.9)	170 (27.6)
Lamivudine	4936 (61.4)	876 (47.4)	208 (33.8)
Didanosine	2004 (24.9)	198 (10.7)	70 (11.4)
Zidovudine	2710 (33.7)	567 (30.7)	128 (20.8)
Stavudine	1232 (15.3)	126 (6.8)	22 (3.6)
Zalcitabine	16 (0.2)	0 (0.0)	0 (0.0)
Number of three-digit *ICD-9-CM*			
Mean ± SD	11.3 ± 8.9	13.7 ± 10.2	15.2 ± 10.9
Median	9	11	12
Number of unique NDCs			
Mean ± SD	14.8 ± 8.5	13.9 ± 8.5	16.1 ± 9.5
Median	13	12	14
Comorbid conditions, n (%)			
Hepatitis B	144 (1.8)	47 (2.5)	22 (3.6)
Hepatitis C	635 (7.9)	184 (10.0)	62 (10.1)
Alcohol or substance abuse	1006 (12.5)	329 (17.8)	118 (19.2)
Depression	1055 (13.1)	236 (12.8)	74 (12.0)
Any other psychiatric diagnosis	1207 (15.0)	308 (16.7)	111 (18.0)
Cognitive impairment	0 (0.0)	0 (0.0)	0 (0.0)
Medically attended adverse effects, n (%)			
Gastrointestinal	669 (8.3)	172 (9.3)	68 (11.0)
Jaundice	6 (0.1)	2 (0.1)	2 (0.3)
Lipid abnormalities	477 (5.9)	119 (6.4)	68 (11.0)
Diabetes/hyperglycemia	509 (6.3)	144 (7.8)	62 (10.1)
Rash	275 (3.4)	72 (3.9)	26 (4.2)

ART, antiretroviral therapy; ARV, antiretroviral; *ICD-9-CM*, International Classification of Diseases, Ninth Revision, Clinical Modification; NDC, national drug code; NRTI, nucleoside reverse transcriptase inhibitor.

Table 4 – Unadjusted incidence rates and PPPM health care costs of medically attended (*ICD-9-CM*–coded or treated) adverse effects during the evaluation period.

	Atazanavir (n = 1848)	Darunavir (n = 616)
Duration of evaluation period (d)		
Mean ± SD	159 ± 50	151 ± 60
Median	180	180
Gastrointestinal		
Number at risk, n (%)	1848 (100.0%)	616 (100.0%)
Incidence rate (per 1000 person-months)	42.55	59.96
PPPM total health care costs, mean ± SD	$38 ± $387	$73 ± $382
Inpatient costs	$13 ± $349	$17 ± $203
Outpatient costs	$3 ± $23	$7 ± $52
Pharmacy costs	$21 ± $144	$49 ± $298
Jaundice		
Number at risk, n (%)	1848 (100.0)	616 (100.0)
Incidence rate (per 1000 person-months)	1.12	0.32
PPPM total health care costs, mean ± SD	$14 ± $544	$0 ± $4
Inpatient costs	$14 ± $544	$0 ± $4
Outpatient costs	$0 ± $6	$0 ± $1
Lipid abnormalities		
Number at risk, n (%)	1729 (93.6)	548 (89.0)
Incidence rate (per 1000 person-months)	17.49	27.31
PPPM total health care costs, mean ± SD	$28 ± $396	$27 ± $297
Inpatient costs	$21 ± $393	$13 ± $258
Outpatient costs	$2 ± $18	$6 ± $43
Pharmacy costs	$5 ± $26	$8 ± $36
Diabetes/hyperglycemia		
Number at risk, n (%)	1704 (92.2)	554 (89.9)
Incidence rate (per 1000 person-months)	8.4	7.67
PPPM total health care costs, mean ± SD	$96 ± $1253	$62 ± $518
Inpatient costs	$78 ± $1232	$35 ± $459
Outpatient costs	$13 ± $108	$19 ± $125
Pharmacy costs	$6 ± $35	$8 ± $48
Rash		
Number at risk, n (%)	1848 (100.0%)	616 (100.0%)
Incidence rate (per 1000 person-months)	87.11	111.03
PPPM total health care costs, mean ± SD	$6 ± $80	$5 ± $25
Inpatient costs	$2 ± $71	$0 ± $0
Outpatient costs	$1 ± $31	$0 ± $3
Pharmacy costs	$3 ± $11	$4 ± $24
All-cause* health care costs, mean ± SD		
PPPM total health care costs	$3879 ± $6635	$5354 ± $8127
Inpatient costs	$1257 ± $6174	$1520 ± $6875
Outpatient costs	$546 ± $1103	$634 ± $1187
Pharmacy costs	$2076 ± $1829	$3200 ± $4053

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; PPPM, per-patient-per-month.

* All-cause health care costs are health care costs incurred for all inpatient medical, outpatient medical, and outpatient prescription claims during the evaluation period and are not limited to medically attended adverse effects.

change was for jaundice in the atazanavir cohort where the estimated PPPM health care cost decreased from $14 to $2.

Incidence and Health Care Costs of Medically Attended Adverse Effects with Multivariable Adjustment

Table 5 displays the postmatch multivariable-adjusted hazard ratios and PPPM health care cost differences for medically attended adverse effects during the evaluation period.

Compared with atazanavir-treated patients, darunavir-treated patients had significantly greater hazards of medically attended gastrointestinal adverse effects, insignificantly greater hazards of medically attended lipid abnormalities and rash adverse effects, and insignificantly lower hazards of medically attended diabetes/hyperglycemia adverse effects.

Compared with atazanavir-treated patients, darunavir-treated patients had significantly greater PPPM all-cause health care costs and insignificantly greater ($0 difference in the case of rash) PPPM medically attended adverse effect health care costs for all the specific medically attended adverse effects.

Too few instances of jaundice (11 in atazanavir and 1 in darunavir) occurred to support multivariable modeling. No multivariable adjustment was conducted for the sensitivity analyses.

Discussion

This is the first study to compare the incidence and health care costs of medically attended adverse effects in U.S. Medicaid patients receiving atazanavir- or darunavir-based ART. Therefore, these data provide valuable insights into the real-world experience of a large segment of the U.S. HIV population.

One of the reasons for studying gastrointestinal adverse effects currently is that to date, studies comparing darunavir with atazanavir with regard to this adverse effect have been equivocal. In the CASTLE (comparison of atazanavir/ritonavir in naive subjects in combination with tenofovir-emtricitabine versus lopinavir/ritonavir in combination with tenofovir-emtricitabine to assess safety and efficacy), ARTEMIS (AntiRetroviral Therapy with TMC114 ExaMined In naïve Subjects), BMS-045 (Bristol Myers Squibb Study 045), and TITAN (TMC114/r In Treatment-experienced pAtients Naive to lopinavir) trials, atazanavir and darunavir were separately demonstrated to have favorable gastrointestinal tolerability compared with lopinavir in treatment-naive patients and treatment-experienced patients, respectively [19]. In each of the trials, the relative risk of grades 2 to 4 diarrhea and nausea for atazanavir tended to be lower than that for darunavir, when both were compared with lopinavir. However, across-trial differences in procedures and populations limit the ability to draw a meaningful conclusion on the comparative gastrointestinal tolerability of atazanavir and darunavir. In a randomized exploratory study of the metabolic effects of darunavir/ritonavir and atazanavir/ritonavir in treatment-naive HIV patients over 48 weeks, one darunavir-treated patient and no atazanavir-treated patient experienced grades 2 to 4 diarrhea related to treatment [20]. This study, however, was small (65 subjects), with meaningful differences in baseline characteristics between the treatment groups, again limiting the ability to draw a meaningful conclusion. Therefore, the current real-world data that show a significantly higher hazard ratio of medically attended gastrointestinal adverse effects for darunavir compared with atazanavir are of interest, particularly because gastrointestinal intolerance is a known risk factor for treatment failure [21].

Medically attended jaundice adverse effects were the least frequently occurring of the examined adverse effects. While the small number of events that occurred (12 in total) precluded multivariable analysis, the descriptive differences in the number

Table 5 – Postmatch multivariable-adjusted hazard ratios and PPPM health care cost differences for medically attended (*ICD-9-CM*–coded or treated) adverse effects during the evaluation period.*

	Hazard ratio* (atazanavir = reference)		PPPM health care cost difference* (darunavir − atazanavir)	
Gastrointestinal	1.251	$P = 0.043$	$43	$P = 0.132$
Lipid abnormalities	1.375	$P = 0.072$	$3	$P = 0.879$
Diabetes/hyperglycemia	0.843	$P = 0.552$	$13	$P = 0.693$
Rash	1.108	$P = 0.233$	$0	$P = 0.760$
All-cause† health care costs	NA	NA	$1086	$P < 0.001$

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NA, not available/applicable; PPPM, per-patient-per-month.

* The multivariable models adjusted for covariates within the propensity score model that lacked postmatch statistical balance; the baseline presence of each specific adverse effect was also included in its respective individual model. For the two-part health care cost models (gastrointestinal, diabetes/hyperglycemia, and rash), *P* values were developed by using bootstrapping with 500 repetitions. Too few instances of jaundice (11 in atazanavir and 1 in darunavir) occurred to support multivariable modeling.

† All-cause health care costs are health care costs incurred for all inpatient medical, outpatient medical, and outpatient prescription claims during the evaluation period and are not limited to medically attended adverse effects.

of patients with medically attended jaundice adverse effects favored darunavir. The low incidence rates observed in the present study are consistent with results from prior clinical trials showing that jaundice is relatively uncommon with both atazanavir/ritonavir and darunavir/ritonavir treatment [22,23]. The PPPM health care costs associated with medically attended jaundice were relatively low in atazanavir-treated patients, ranging from $2 in the sensitivity analyses to $14 in the primary analyses. This is likely due to the nature of jaundice associated with atazanavir that occurs in some patients who have atazanavir-associated hyperbilirubinemia. This hyperbilirubinemia is not associated with hepatitis and reverses upon discontinuation of atazanavir without any additional treatment [24].

There were no differences between atazanavir and darunavir for all other studied adverse effects. While there was a numerically lower hazard of medically attended diabetes/hyperglycemia adverse effects, this was not significantly different and was inconsistent with numerically higher adjusted health care costs for medically attended diabetes/hyperglycemia in darunavir-treated patients.

The present study also found that darunavir-treated patients incurred significantly higher all-cause health care costs than did atazanavir-treated patients, a result of increased costs across all settings of care (inpatient, outpatient, and pharmacy), with the majority of the difference being driven by pharmacy costs. These pharmacy costs are not strictly related to the management of HIV but also include costs for all outpatient prescriptions used to manage comorbidities, adverse effects, and any other medical needs that are treated with pharmacotherapy. This $1086 PPPM difference translated into an annual health care cost difference of approximately $13,000 per patient. Although the present study did not explore the detailed drivers of these differences in costs, future research could help to elucidate this matter by examining underlying differences in the services utilized in each setting of care, the diagnosis coding recorded for those services, and the various classes of medications that patients used. Given the substantial magnitude of the all-cause cost differences, such additional research is warranted.

This study was subject to limitations. First, administrative claims data are not collected for research purposes and may be subject to errors in diagnostic coding. Second, this study specifically examined medically attended adverse effects and therefore less severe adverse effects, specifically those for which the severity did not motivate medical attendance, would not have been captured. Third, because we defined ART experience as having prescription claims for ART during the 6-month baseline period, we cannot rule out the possibility of misclassification for those patients who may have had claims for ART more than 6 months prior to their index date. Fourth, because this database contains data for patients covered through Medicaid within 15 states, the findings may not be generalizable to the whole U.S. HIV population. Fifth, because this study used an observational study design, we cannot exclude the possibility of residual confounding from unmeasured factors. The most relevant unmeasured factors in this study are clinical data, such as CD4 and viral load values or history of AIDS, which are not available in the data used for this study. These factors are likely to correlate with patients' economic and clinical outcomes. If atazanavir or darunavir is prescribed in a manner that systematically favors patients with a history of AIDS or low CD4 and viral load values beyond what was accounted for through stratification of the propensity score models by ART experience, the present study results could be confounded by such prescribing behavior. As such, we can establish associations, but not causal relationships, between treatments and outcomes.

Because this study is one of the first of its kind, future research is warranted to corroborate these findings and advance the understanding of the adverse effects of atazanavir and darunavir in various populations. Within the present study, most (91.2%) patients were ART experienced. Because these agents have become more frequently prescribed in ART-naive patients, future studies that include such patients are needed to address these matters in this important segment of the HIV population.

Conclusions

In the present study of the incidence and health care costs of medically attended adverse effects in Medicaid patients receiving routine HIV care, atazanavir-treated patients had significantly fewer instances of medically attended gastrointestinal issues and more instances of jaundice and incurred significantly lower health care costs than did darunavir-treated patients. Source of financial support: Bristol-Myers Squibb sponsored this study.

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