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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