

Identification of abacavir hypersensitivity reaction in health care claims data[†]

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SUMMARY

Purpose Abacavir is associated with an infrequent but potentially serious hypersensitivity reaction (HSR) that can include a wide range of signs and symptoms. Identification of this reaction through medical insurance claims could provide a simple and efficient means of monitoring the incidence of abacavir hypersensitivity in large populations of patients.

Methods Using data from a safety study of 948 abacavir users with 22 hypersensitivity events identified from claims and validated through medical record review, we used a recursive partitioning analysis to construct an algorithm to differentiate between patients with and without validated adverse events. Bootstrap resampling techniques provided validation for the analysis.

Results The analysis produced a classification tree with three decision nodes that comprised the best indicators of HSRs. The predictors included any one of several specific symptoms commonly found with this reaction, a claims diagnosis of adverse effect of drug, anaphylactic shock or unspecified allergy, and a discontinuation in abacavir prior to completing a 90-day course of therapy. The algorithm demonstrated 95% sensitivity and 90% specificity when tested using a bootstrap resampling approach with the current data.

Conclusions A sensitive and specific algorithm for identifying abacavir hypersensitivity from claims was created. This algorithm would permit efficient identification of charts for medical review. Further testing of the algorithm with additional medical claims data for abacavir users will be required to ascertain its validity across databases. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS — antiretroviral therapy; hypersensitivity reaction; classification and regression trees; random forests; claims data

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INTRODUCTION

Abacavir is a nucleoside reverse transcriptase inhibitor used for treatment of HIV. Abacavir causes a hypersensitivity reaction (HSR) in about 4% of recipients,¹ with a range in clinical studies from 0% to 14%.² HSR symptoms indicate multi-organ-system

involvement and usually appear in the first 6 weeks of treatment with abacavir, with a median time to onset of 8 days.³ Signs and symptoms of abacavir-related HSR may include fever, rash, gastrointestinal symptoms (nausea, vomiting, diarrhea, and abdominal pain), and lethargy or malaise as well as shortness of breath, cough, and sore throat.² Less often, HSR may include edema, hypotension, and lesions of mucous membranes.^{4–6} The symptoms worsen with continued therapy but generally resolve within 24 hours after treatment discontinuation.³ HSR symptoms can resemble those related to HIV, opportunistic infections, or adverse reactions to other antiretroviral medications.⁵

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Identification of HSR when it occurs is of critical importance, not only because treatment must be discontinued to prevent the reaction from progressing, but also because of the danger of rechallenge. Reinitiation following an HSR, even a mild reaction and even at low doses of abacavir, usually results in a return of symptoms within hours. The rechallenge reaction may be severe, even fatal.² Recognition of an initial HSR is necessary to avoid rechallenge even in patients with only mild initial reactions.

Health insurance claims data allow screening for potential HSR among large populations of abacavir users, permitting quantitative adverse event surveillance. Unfortunately, there is no specific ICD-9 diagnosis code for HSR, so physicians who note an HSR event have to choose between codes for allergic reactions, adverse drug reactions, and the specific symptoms making up the patient's individual reaction. In the present study, we used recursive partitioning and random forests techniques to develop an algorithm for the identification of HSR from claims data, using HSR events that were validated through medical record review as the 'gold standard.'

METHODS

The present study used data from a larger study conducted in parallel with three other databases to provide postmarketing surveillance for abacavir HSR (unpublished data, GlaxoSmithKline; poster presented at the 3rd IAS Conference on HIV Pathogenesis and Treatment, Rio de Janeiro, Brazil, July 2005). The larger study found no difference in risk of initial and rechallenge HSR, HSR-related hospitalization, and HSR-related death between users of Ziagen[®] (abacavir alone) and Trizivir[®] (abacavir, lamivudine, and zidovudine in a combination tablet). We screened for potential HSR events through the insurance claims data and validated events by an expert panel's review of the abstracted medical record. In order to achieve high sensitivity for detecting HSR, we reviewed a large number of records of persons with claims for any condition that might be a component of HSR. The diagnoses and procedures included in the screening algorithm are shown in Table 1. The present paper reports our further development of an algorithm with similar sensitivity but much better specificity for identifying initial HSR events through claims data.

Data source

Medical and pharmacy claims data were obtained from the Ingenix Research Database, which contained

Table 1. Diagnostic and procedure codes for identification of possible HSR from medical claims data

ICD9	Description
HSR-relevant symptoms	
462	Acute pharyngitis
719.4	Arthralgia
729.1	Myalgia
780.6	Fever
780.7	Malaise and fatigue
780.9	Chills
782.1	Rash
784.0	Headache
786.0	Dyspnea
786.2	Cough
787.0	Nausea and vomiting
787.91	Diarrhea
789.0	Abdominal pain
Syncope and collapse	
780.2	Syncope and collapse
Sudden death	
798.1	Sudden death, cause unknown
Acute allergic reactions/adverse drug events	
961.7	Poisoning by antiviral drugs
977.9	Poisoning by unspecified drug
995.0	Other anaphylactic shock
995.2	Unspecified adverse effect of drug
995.3	Allergy unspecified
Inflammatory conditions of skin and subcutaneous tissue	
693.0	Dermatitis due to drugs and medicines
695.0	Toxic erythema
695.1	Erythema multiforme
695.8	Other erythematous conditions
695.9	Unspecified erythematous conditions
698	Pruritus and related conditions
Acute respiratory syndromes	
518.8	Acute respiratory failure
799.1	Respiratory arrest
Liver disease	
Codes likely to lead to medical record abstraction:	
570	Acute and subacute necrosis of liver
571	Chronic liver disease and cirrhosis
572.2	Hepatic coma
573	Other disorders of liver including 573.3: hepatitis unspecified, including toxic (noninfectious) hepatitis
782.4	Jaundice unspecified, not of newborn
790.4	Nonspecific elevation of transaminase or LDH

(Continues)

Table 1. (Continued)

ICD9	Description
Other liver disease codes worth investigating:	
017.9	Tuberculous hepatitis
070	Viral hepatitis
091.62	Secondary syphilitic hepatitis
095.3	Syphilis of liver
130.5	Hepatitis due to toxoplasmosis
275.0	Disorders of iron metabolism (e.g., pigmentary cirrhosis of liver, hemochromatosis, bronzed diabetes)
572.3	Portal hypertension
572.4	Hepatorenal syndrome
789.1	Hepatomegaly
789.5	Ascites
794.8	Abnormal liver scans
Procedure codes for diagnosis and treatment of liver disease	
CPT	
47000–47015	Biopsy of liver, percutaneous, liver incision
47100–47136	Wedge biopsy of liver, liver excision
47300–47362	Liver repair
47399	Other liver procedures
Intubation, ventilation, and ambulance service	
CPT	
30600–31601	Tracheostomy, planned
31603–31605	Tracheostomy, emergency procedure
31500	Intubation, endotracheal, emergency procedure
31610	Tracheostomy, fenestration procedure with flaps
31612	Tracheal puncture, percutaneous with transtracheal aspiration and/or injection
69433	Ventilating tube insertion
94656	Ventilation assist and management, first day
94657	Ventilation assist and management, subsequent day
ICD-9 v3	
96.01	Insertion of nasopharyngeal airway
96.02	Insertion of oropharyngeal airway
96.04	Insertion of endotracheal tube
96.05	Other intubation of respiratory tract
96.7	Other continuous mechanical ventilation
96.70	Continuous mechanical ventilation of unspecified duration
96.71	Continuous mechanical ventilation for <96 consecutive hours
96.72	Continuous mechanical ventilation for 96+ consecutive hours
93.93	Nonmechanical methods of resuscitations
HCPCS	
A0021–A0050	Ambulance service
A0225–A0999	Ambulance service, specialized services, and supplies

Note: When 3 digits are specified, XXX.00–XXX.99 is implied.
When 4 digits are specified, XXX.X0–XXX.X9 is implied.

data for members of UnitedHealthcare. UnitedHealthcare is one of the largest health insurers in the United States, with more than 300 000 physicians contracted to provide health care services to over 14 million members. The Ingenix database contained detailed information on approximately eight million current and past members, as far back as 1990. Members included in the database belonged to plans in which the costs of pharmaceuticals and health services were reimbursed to providers on an item-by-item basis, so that it is possible to reconstruct nearly all of the members' health care utilization. Approval for this study was granted by the New England Institutional Review Board.

Study population

We included data from abacavir users in health plans in 14 states. We searched the outpatient pharmacy records of all commercial plan members with both medical and prescription drug coverage for abacavir dispensings. The analyses included patients who received their first dispensing of abacavir between 1 January 1999 and 31 July 2003. We required that subjects have a minimum of 6 months of continuous enrollment in the health plan prior to their first dispensing of abacavir in the database. We extracted all health care claims records for these subjects, including medical and laboratory services, hospitalizations, and drug dispensings from 1 July 1998 to 31 December 2003. Drug data include the date, form, dose, quantity, and days supply for each dispensing.

Outcome identification

Identified abacavir initiators were considered at risk for HSR for 90 days after initiation of a course of therapy, because almost all HSR reported to date has occurred during this interval.¹ For completeness, we also searched for potential events associated with discontinuations even beyond the 90-day period. The original claims screening for potential events included any one HSR-related symptom, diagnosis, or procedure, noted in Table 1. The potential event was required to occur during or within 14 days after the period of abacavir exposure and could not be followed by an uneventful refill of abacavir. Potential events identified from the claims were validated through review of medical claims, medical record abstraction, and review by a panel of four clinical HIV specialists. The expert panel evaluated all potential cases, classifying them as definite, probable or possible, or not cases of HSR. Definite events required a

subsequent positive rechallenge, but probable and possible events did not.

Baseline variables

We noted each abacavir user's history of dispensings of other antiretroviral medications and diagnoses of AIDS-defining illnesses during the 6 months preceding the start of abacavir. These variables were coded as dichotomous indicators for prior antiretroviral experience and claims for any one or more AIDS-defining illnesses (based on the CDC's 1993 revised classification system⁶). We also recorded each patient's gender and age on the date of first dispensing of abacavir.

Claims indicators of HSR

A discontinuation in abacavir, with or without symptoms of HSR, that was followed by a reinitiation of the drug without any sign of an adverse reaction was deemed event-free. Symptoms were considered to be potentially abacavir-related only if they occurred during a risk period for HSR that comprised the days from the date of last abacavir dispensing through 14 days following the end of the supply dispensed. The only exception to this rule was one patient who was later rechallenged; because our goal was to characterize initial HSR, we used the last dispensing prior to the initial event to calculate this individual's risk period.

During each subject's risk period, we created flags indicating presence or absence of each of the diagnoses and procedures listed in Table 1. An additional flag indicated the occurrence of a discontinuation in abacavir supply of at least 14 days, in the absence of, or prior to, completing a continuous course of greater than 90 days. To identify non-HSR related diagnoses that might provide alternative explanations for any HSR-related claims, we also searched the claims for all diagnoses given from the date of first potential HSR symptom to 14 days following the latest potential HSR symptom. The 30 most common diagnoses given to patients during this time period were flagged, as were hospitalization and death during the same period. All of the variables that were deemed potential alternative explanations for HSR-related symptoms were entered into the analysis.

Data analysis

We used recursive partitioning⁷ to find the optimal combinations of predictors of HSR. All potential covariates including the baseline variables, HSR-related diagnoses and procedures from during

or within 2 weeks after the patient's last abacavir fill, and alternative diagnoses given during or following the potential event were used in a recursive partitioning analysis using CART software (version 5.0, Salford Systems, San Diego). The classification trees were constructed using 10-fold cross-validation; the data were randomly divided into 10 subsets, with each subset used as a test case against which to judge a tree based on the remaining nine subsets. The final tree was an aggregate of each of the 10 learning trees. In an effort to ensure high sensitivity of the model, we set the cost of misclassification of an HSR event as a non-event to twice as great as the cost of a misclassification of a non-event as an event.

In addition to the 10-fold cross-validation, we used two bootstrap resampling methods⁸ to confirm the variable selection, and sensitivity and specificity estimates. The first used 1000 bootstrap samples of the data (i.e., sampling with replacement) and the tree obtained from the recursive partitioning analysis to obtain 95% confidence intervals around the sensitivity and specificity for that analysis. The second analysis was conducted using random forests with Salford Systems' software. Random forests is an ensemble method in which a large number of trees are constructed. Both individuals and variables are sampled. The ultimate classification of an observation is obtained by a majority vote of the individual trees. Our validation procedure involved taking 1000 bootstrap samples. Each bootstrap sample leaves out on average about one-third of the study population; the individuals who are left out of the bootstrap training sample are used to estimate the accuracy of the tree and the importance of each variable in the model.

RESULTS

A total of 948 individuals initiated abacavir during the study period and met the enrollment criterion of a minimum of 6 months of continuous enrollment prior to the start of abacavir. A total of 101 patients had one or more events flagged by our initial claims screening as potential HSR. Medical records for 14 of these individuals were not available for abstraction; these 14 patients were dropped from all further analyses, leaving 934 subjects. Based on information from both claims and abstracted medical records, 22 subjects had an event that was judged by the expert medical review board to be possible or probable HSR, with no events judged definite HSR. Table 2 presents baseline characteristics of patients with and without subsequent HSR events. Most subjects were male (85%), received other antiretroviral treatments in the 6 months prior to

Table 2. Baseline characteristics of study population

Characteristic	No HSR event (<i>n</i> = 912)		HSR event (<i>n</i> = 22)		<i>p</i> -value*
Age	Mean = 41.0	SD = 8.2	Mean = 38.3	SD = 8.9	0.13
Male gender	<i>N</i> = 777	85.2%	<i>N</i> = 21	95.5%	0.12
Prior antiretroviral therapy	<i>N</i> = 611	67.0%	<i>N</i> = 17	77.3%	0.31
At least one AIDS-defining illness	<i>N</i> = 216	23.7%	<i>N</i> = 7	31.8%	0.38

**p* values obtained from a *t*-test for age and chi-square or Fisher exact tests for categorical variables.

initiating abacavir (67%), and had no AIDS-defining illnesses during the 6-month baseline period (76%). The mean age was 41 years with a standard deviation of 8.2. None of these characteristics differed significantly between patients with and without an HSR event.

The frequencies of claims indicators of HSR and other diagnoses given during the risk period, and *p* values obtained from chi-square or Fisher exact tests comparing patients with and without HSR events, are presented in Table 3. A preliminary recursive partitioning model had seven decision nodes and

Table 3. Diagnoses and procedures from the date of last dispensing of abacavir through 14 days after the end of supply

Diagnosis or procedure	No HSR event (<i>n</i> = 912)		HSR event (<i>n</i> = 22)		<i>p</i> value*
	Count	Percent	Count	Percent	
Acute pharyngitis	6	0.7	0	0.0	0.87
Arthralgia	7	0.8	1	4.5	0.16
Myalgia	3	0.3	2	9.1	0.005
Fever	18	2.0	11	50.0	<0.001
Headache	5	0.5	3	13.6	<0.001
Nausea (with or without vomiting)	12	1.3	4	18.2	<0.001
Malaise	25	2.7	7	31.8	<0.001
Chills	5	0.5	0	0.0	0.89
Rash	9	1.0	3	13.6	0.002
Dyspnea	15	1.6	1	4.5	0.27
Cough	7	0.8	0	0.0	0.85
Diarrhea	21	2.3	2	9.1	0.08
Abdominal pain	21	2.3	1	4.5	0.32
Unspecified allergy	1	0.1	5	22.7	<0.001
Adverse effect of drug or anaphylactic shock	7	0.8	11	50.0	<0.001
Skin reaction	4	0.4	2	9.1	0.007
Respiratory failure/arrest	7	0.8	1	4.5	0.16
Hepatitis and other liver diseases	16	1.8	2	9.1	0.06
Abnormal liver findings	7	0.8	1	4.5	0.16
Tracheostomy	4	0.4	0	0.0	0.91
Intubation/ventilation	3	0.3	0	0.0	0.93
Ambulance services	6	0.7	2	9.1	0.01
Agranulocytosis	6	0.7	1	4.5	0.14
Electrolyte disorders	15	1.6	4	18.2	<0.001
Anemia	16	1.8	3	13.6	0.008
Depression	7	0.8	0	0.0	0.85
Gastroenteritis	4	0.4	1	4.5	0.11
Pneumonia	8	0.9	0	0.0	0.83
Acute renal failure	4	0.4	2	9.1	0.007
Lymphoma	6	0.7	0	0.0	0.87
Septicemia	8	0.9	0	0.0	0.83
Death (all causes)	11	1.2	0	0.0	0.77
Any hospitalization	37	4.1	5	22.7	0.002
Discontinuation in abacavir	483	53.0	22	100.0	<0.001
Fever, headache, nausea, malaise, or rash	55	6.0	18	81.8	<0.001
Adverse effect of drug, anaphylactic shock, or unspecified allergy	8	0.9	14	63.6	<0.001

**p* values obtained from chi-square or Fisher exact tests, as appropriate.

demonstrated excellent sensitivity and specificity (95% and 93%, respectively). The variables used to partition the sample fell into two main groups: diagnoses of specific symptoms that can occur with HSR and diagnosis codes that were presumably meant to indicate a diagnosis of HSR. The five specific symptoms that were identified, which included fever, headache, nausea, malaise, and rash, each contributed to the model individually (i.e., not as interactions) and all were low in prevalence. To construct a more parsimonious model, we created a combined variable indicating the presence of any one or more of the five symptoms. Similarly, the diagnoses of adverse effect of drug, anaphylactic shock, and unspecified allergy formed a combined flag that was set to one if any of the three diagnoses were present.

Figure 1 shows the final classification tree obtained by using the combined variables. The first predictor selected was the presence of any of the five symptoms of fever, headache, nausea, malaise, and rash. The 73 patients with at least one of these symptoms split on whether they had a discontinuation of abacavir dispensings prior to completion of a 90-day course; 18 of 22 HSR events met both of these criteria. Patients lacking any of the five symptoms were classified as having HSR if they had a diagnosis of adverse effect of drug, unspecified allergy, or anaphylactic shock; this criterion correctly classified three of the remaining four events. Only one HSR

event failed to be identified by any of the predictors in the model. The three variables found in the decision nodes carried almost all of the importance in the model; in rank order from most to least important, the variables were the five specific symptoms, adverse drug event or allergy, and discontinuation in abacavir. The model correctly classified 21 of 22 (95.5%) HSR events and 863 of 912 (94.6%) non-events. Application of the tree to 1000 bootstrap samples of the data produced 95% confidence intervals of 83.3% to 100.0% for sensitivity and 93.1% to 96.1% for specificity.

The random forests bootstrap resampling approach, which was performed using all of the variables that were entered into the recursive partitioning model, obtained the same three most important variables as the recursive partitioning model, with the same order of importance. The random forests procedure, which provides unbiased estimates of sensitivity and specificity,⁸ showed the same level of sensitivity as the recursive partitioning model (95.5%) and slightly lower specificity (90.4%).

DISCUSSION

The recursive partitioning analysis was successful in creating a highly sensitive and specific algorithm for identifying HSR from claims data alone. Bootstrap

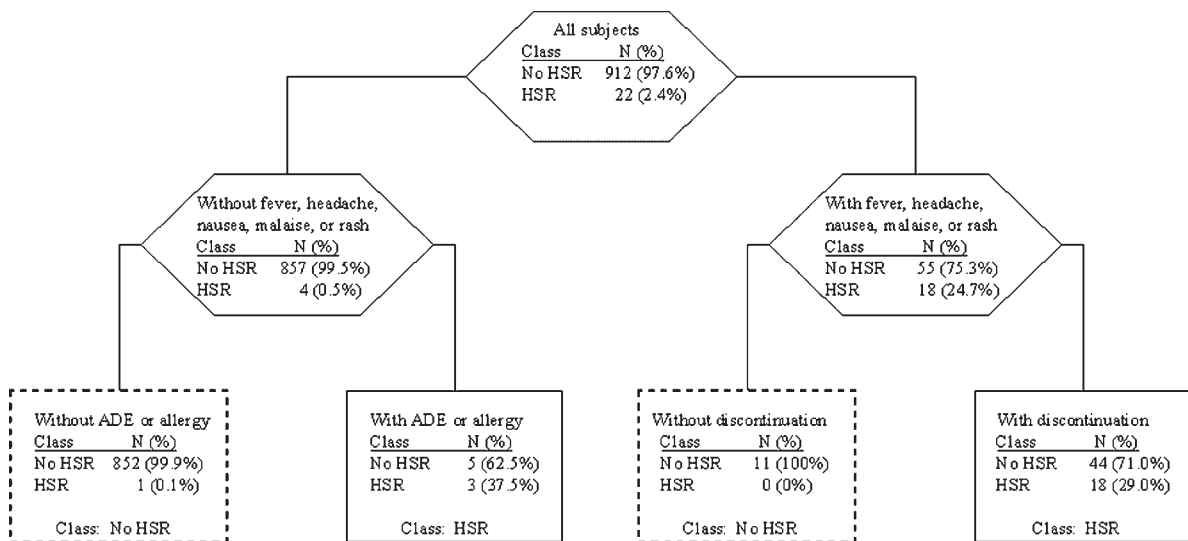


Figure 1. Classification tree showing the algorithm for claims identification of HSR obtained via recursive partitioning. The hexagonal boxes represent decision nodes and the rectangular boxes show the final classification of patients predicted from the algorithm, with dashed borders indicating a prediction of no event and solid borders indicating a predicted HSR event. Each of the classification boxes shows the number of patients correctly and incorrectly classified by the algorithm

resampling, using two different methods, confirmed the variable importance levels, and the high sensitivity and specificity. Patients with a claims diagnosis of fever, headache, nausea, malaise, or rash and who also had a discontinuation in abacavir without having completed a continuous 90-day course were very likely to have had a validated HSR event. Patients with none of the five symptoms but who had a diagnosis of adverse effect of drug, unspecified allergy, or anaphylactic shock were also likely to have an HSR event.

Although we had included numerous diagnoses that occurred during or after the potential HSR event in an effort to identify alternative explanations for HSR-related diagnoses and symptoms that were not in fact reflective of HSR, none of these diagnoses appeared to be an important differentiator in the recursive partitioning model. Instead, only symptoms and diagnoses that are clearly relevant to a positive diagnosis of HSR entered the final model. Some diagnoses, such as pneumonia or septicemia, appeared only in noncases and thus could be considered as indicating differential diagnoses, but they may have been too infrequent and/or occurred only in patients lacking the positive predictors of HSR used in the model and hence did not help to differentiate noncases from cases.

The number of validated HSR cases on which the present algorithm was built was small. It is thus quite possible that additional claims flags for HSR could be identified in a larger sample of events. Only one case failed to be identified from the five characteristics in the algorithm, but 49 nonevents were predicted by the algorithm to be events. The positive predictive value of the algorithm was 30%, indicating that 70% of predicted cases were false positives. Patients flagged by this algorithm as having HSR should therefore be considered to be at substantial likelihood having suffered HSR but not as definite cases. These individuals would be highly appropriate candidates for medical chart review. Our estimate of sensitivity of the model may be an overestimate, because we did not abstract medical records for individuals who had no claims for any of the diagnoses or procedures listed in Table 1.

The diagnoses of adverse drug effect, anaphylactic shock, and allergy are those we had believed most likely to be used by physicians attempting to note an observed HSR event in the claims. Although only three HSR events were classified in the tree on the basis of one of these diagnoses, a count of patients with HSR who received such a diagnosis either with or without one of the five symptoms revealed that the

majority (64%) had one of the HSR-indicating codes. This high proportion suggests that physicians were likely to have recognized and made an effort to record in the claims the incidence of the adverse reaction. Over a third of the HSR events found in the present study, however, were indicated only by one or more of the symptoms that were components of the individual patient's reaction. The physicians may have failed to recognize the event as an abacavir HSR or may not have chosen a diagnosis code for the claims that directly signaled an adverse or allergic reaction. Since medical claims are being used more and more for research into drug safety and other important public health issues, it may be beneficial for physicians prescribing abacavir to receive additional guidance regarding the most appropriate claims diagnoses to use in cases of HSR.

The ultimate goal of an algorithm such as this is to provide a means of easily monitoring the claims of abacavir users for potential HSR, not only among United Healthcare members but in other claims databases as well. Before reaching this goal, the algorithm needs to be tested in one or more additional databases to determine the extent to which it accurately captures events that have been validated through medical records or other external sources of information. If the algorithm performs well, our algorithm or a refinement of it based on additional data may be helpful in ongoing surveillance for cases of abacavir HSR. Such large-scale surveillance efforts can allow monitoring for changes in the incidence of this adverse event; by linking to other information in the claims data, possible causes for any increase or decrease in incidence can be found. Definitive ascertainment of HSR events will of course require supplemental information, but a generalizable claims algorithm can generate timely signals for potential public health problems or improvements with regard to abacavir adverse reactions.

KEY POINTS

- Identification of HSR to abacavir is important to avoid rechallenge.
- Claims data allow monitoring of large numbers of antiretroviral drug users.
- We developed a sensitive and specific algorithm for the identification of abacavir HSR from claims data.

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