

GSK Medicine: abacavir/lamivudine/zidovudine
Study No.: WWE113671/WE041/EPI40087, WWE113761/WE042/EPI40088, WWE113660/WE043/EPI40089, WWE113762/WE044
Title: Frequency of Abacavir (ABC) Hypersensitivity Reactions (HSR), Rechallenge, and HSR-Attributable Outcomes are Similar with the Use of Ziagen® or Trizivir®: Final Results from the Trizivir® Epidemiology Study 1.
<p>Rationale:</p> <p>Clinical studies have shown that approximately 5% of subjects receiving Ziagen® develop a hypersensitivity reaction (HSR), which in rare cases can be fatal. HSR is characterized by symptoms indicating multi-organ system involvement. Symptoms usually appear in the first six weeks of treatment with abacavir, with a median time to onset of eleven days. Signs and symptoms of abacavir-related HSR may include fever, rash, gastrointestinal symptoms (nausea, vomiting, diarrhoea, and abdominal pain), lethargy or malaise as well as shortness of breath, cough and sore throat. Less often, HSR is associated with edema, hypotension, and lesions of mucous membranes. The symptoms worsen with continued therapy but usually resolve within 24 hours of treatment discontinuation. Restarting abacavir following a HSR usually results in a return of symptoms within hours.</p> <p>With the introduction of a second GSK formulation, Trizivir®, containing abacavir, there was concern of an increased risk of abacavir rechallenge with Trizivir®, after an initial HSR event attributable to Ziagen®. Recurrence of HSR on rechallenge may be more severe than on initial presentation, and may include life-threatening hypotension and death. Phase IV FDA commitments included conducting an epidemiological program of research to examine the differences between the two abacavir containing products (Trizivir® & Ziagen®) with respect to several outcomes associated with abacavir HSR.</p>
<p>Objectives: An epidemiologic study using four observational databases was designed to answer the following research questions:</p> <ol style="list-style-type: none"> 1. Is the risk (cumulative incidence) of HSR following initiation of Trizivir® equivalent to that for Ziagen®? 2. What is the risk (cumulative incidence) of rechallenge with abacavir following a HSR? In particular, does the availability of Trizivir® tablets increase the risk of rechallenge beyond the risk of rechallenge associated with Ziagen®? 3. What is the risk (cumulative incidence) of HSR-associated hospitalization or HSR-associated death with Trizivir® compared to Ziagen®?
Indication: HIV
Study Investigators/Centers: Rose K. Baker, HIV Insight™; Jennifer S. Fusco, Gregory Fusco, CHORUS; Beth L. Nordstrom, UnitedHealthCare; Larry Mole, Palo Alto Institute for Research and Education on behalf of Veterans Affairs Medical Center
<p>Research Methods: Data were obtained using electronic and primary medical records from HIV Insight™, the Collaborative HIV Outcomes Research / US (CHORUS), United HealthCare (UHC), and the Veterans' Administration HIV/AIDS Service databases (VA). The investigators for each database developed a screening strategy of the electronically available data to identify patients with abacavir discontinuations within 90 days of initiation of abacavir. Data were then abstracted from either the paper-based medical records, electronic medical records (EMR), or both for at least one event consistent with a HSR within 90 days of initiation of abacavir. The medical records of patients who met these screening criteria were abstracted to obtain all pertinent information related to a potential HSR event; this information included historical data, as well as data up to and including 60 days after the date of the potential event.</p> <p>The abstracted information, in its entirety, was presented to the Expert Medical Review Board (EMRB) for case adjudication as a <i>Definite</i>, <i>Probable</i>, <i>Possible</i>, or <i>Not</i> a case. Definite HSR required an HSR response upon abacavir rechallenge. Rechallenge was defined as “first exposure” to an abacavir containing treatment followed by abacavir-sparing period(s), before a “last exposure” to an abacavir containing treatment. Because rechallenge should be avoided, no attempt was made to differentiate between definite HSR and a syndrome that appeared to be HSR but was not confirmed by rechallenge. Thus, events were judged to be either clinically compatible with HSR (HSR-like) or not compatible with HSR.</p> <p>A parallel analysis was performed that restricted the cohorts to patients with a minimum of six months of continuous enrolment prior to the first abacavir dispensing. The six months of observation had to be while the patient was being treated with the current clinician and after the initiation of participation by the clinician in one of the four cohorts.</p>
<p>Data Source(s):</p> <p>Data were obtained using electronic and primary records from HIV Insight™, the Collaborative HIV Outcomes</p>

Research/US (CHORUS), United Health Care/Ingenix and Veterans' Administration HIV/AIDS Service databases.

Study Design:

Multiple Prospective Observational Cohort Studies

Study Population(s):

1) **HIV Insight™**

This was an ongoing longitudinal database that contained clinical data abstracted from outpatient medical charts and entered into an electronic database. The data are from HIV patients from a network of United States physician sites. Patients at risk of an HSR were defined as those patients starting abacavir after January 1, 1999, when abacavir became commercially available, up through December 31, 2003. Ziagen® and Trizivir® use were recorded separately for each patient in the study cohort. Patients were selected into the study cohort according to the following criteria.

Inclusion Criteria: Patients that started on an abacavir course from January 1, 1999 through December 31, 2003. If the first abacavir exposure was Trizivir®, patients were only included if the start date was on or after December 1, 2000 (date Trizivir® became commercially available).

Exclusion Criteria: Patients were excluded if their primary or secondary payer was noted to be United Healthcare (UHC). This was done to avoid duplication with patients identified using UHC data. Patients at HIV clinic sites that dropped out of HIV Insight™ network were excluded. These sites generally had either very few patients meeting study inclusion criteria or a considerable amount of unevaluated data due to incomplete data abstraction. Patients at an HIV clinic site in the HIV Insight™ network that had a large prison population for whom detailed medical records could not be made available were excluded. A patient was excluded if their only documented use of abacavir (Ziagen® or Trizivir®) occurred prior to the patients' first visit at the HIV clinic site. The exclusion was made since detailed information of the events occurring during and the end of abacavir use were less likely to be available for evaluation. A patient was excluded if their only documented use of abacavir (Ziagen® or Trizivir®) occurred prior to when the HIV clinic site began participation in the HIV Insight™ network.

2) **CHORUS**

Collaborations in HIV Outcomes Research/US (CHORUS) was an observational study of adults with HIV infection followed for long-term clinical, epidemiologic and humanistic parameters at clinical practices in the United States. Comprehensive patient data were collected using an EMR at the point of care and aggregated monthly to create a research database. At the time of this analysis, the CHORUS study had collected clinical data for patients recruited at 4 sites: Comprehensive Care Center, Nashville, TN, Liberty Medical Group, New York, NY, Pacific Oaks Medical Group, Los Angeles, CA, and Pacific Horizon Medical Group, San Francisco, CA.

Inclusion Criteria: All patients were included if they were prescribed abacavir after consent to participate in CHORUS and on or after January 1, 1999 through December 31, 2003.

Exclusion Criteria: Patients were excluded if their abacavir exposure was known to be part of a clinical trial.

3) **UnitedHealthCare/Ingenix**

The population was obtained from automated health insurance claims data in the Ingenix Research Database. The database contained information on approximately 8,000,000 current and past members of UnitedHealthcare (UHC) from 25 affiliated health plans in the northeast, southeast, midwest, and western United States. Total 2000 enrolment for these plans was approximately 5,000,000 patients, with 95% having pharmacy benefit coverage. The Research Database includes patient demographic information, claims from hospitals, physicians' offices, and other sites that list diagnoses and procedures given to the patient, and outpatient dispensing of drugs. The database is updated frequently with new information about enrolment, pharmacy, and medical claims. Pharmacy claims are included within about eight weeks of their occurrence. Incorporation of medical claims is more variable, with most claims recorded within six months, but up to nine months required to capture 95% of paid claims.

Inclusion Criteria: The UHC/Ingenix study population included data from abacavir users in 17 United Healthcare plans in 14 states. These plans were chosen because of their size, geographical distribution, length of time operating in the United Healthcare system, and accessibility to medical records. The analyses

included patients who received their first dispensing of abacavir between January 1, 1999 and July 31, 2003. All health care claims records for these patients were extracted, including medical and laboratory services, diagnostic procedures, hospitalizations, and drug dispensing, from July 1, 1998 through December 31, 2003.

4) **VA**

The VA's HIV Registry database served as the source for the study population. The VA maintains an EMR system called CPRS (Computerized Patient Record System). This record allows access to a patient's complete medical record including prescription medication use, progress notes, radiology, admissions, procedures and diagnoses regardless of how many VA facilities provided that care. The version of the CPRS system at the time of this study was launched in 1998, shortly before the FDA approval of Ziagen®. As such, there were a few VA facilities that had not fully implemented the EMR for initial cases of Ziagen® exposure. Therefore, all abacavir exposures for these facilities were censored until the EMR was consistently used at the facilities. The population censored amounted to < 2% of the overall VA HIV population in care during 1999.

Inclusion criteria:

Patients who received at least one prescription fill for a FDA approved abacavir containing product (Ziagen® or Trizivir®). Patients with VA EMR covering the period prior to and including the abacavir exposure.

**Exposure Definitions,
Case Screening, Case Abstraction,
Outcome Definitions and Covariates:**

Exposure Definitions (Overall):

All abacavir users identified in each database with exposure to abacavir as either Ziagen® or Trizivir® beginning January 1, 1999 were included in the study. The market introduction of Ziagen® was approximately January 1999 and Trizivir® was approximately December 2000. Exposure capture ended December 31, 2003. Data on abacavir exposure by patients participating in clinical trials or expanded access programs were not routinely collected by all databases in this study. However, a conservative approach was taken to include all patients prescribed abacavir so as not to miss any potential HSR-like events or Rechallenge HSR-like events. Each database categorized patients into one of the following categories based on abacavir formulation and sequencing of the first and last formulation recorded:

Table 1: Study Exposure Definitions and Measures

Group #	Group Name	Description
1	Ziagen® only	Continuous Ziagen® exposure of ≥90 days regardless of number of courses OR <90 days if patient has only a single course
2	Trizivir® only	Continuous Trizivir® exposure of ≥90 days regardless of number of courses OR <90 days if patient has only a single course
3	Ziagen®-Ziagen®	Ziagen® initial course <90 days, break, then 2nd course either ≥ or <90 days of Ziagen® For patients having >2 courses, 2nd exposure must be ≥ 90 days For patients having =2 courses, 2nd exposure any duration
4	Ziagen®-Trizivir®	Ziagen® initial course <90 days, break, then 2nd course either ≥ or <90 days of Trizivir® For patients having >2 courses, 2nd exposure must be ≥ 90 days For patients having =2 courses, 2nd exposure any duration
5	Trizivir®-Trizivir®	Trizivir® initial course <90 days, break, then 2nd course either ≥ or <90 days of Trizivir® For patients having >2 courses, 2nd exposure must be ≥ 90 days For patients having =2 courses, 2nd exposure any duration
6	Trizivir®-Ziagen®	Trizivir® initial course <90 days, break, then 2nd course either ≥ or <90 days of Ziagen®

		For patients having >2 courses, 2nd exposure must be ≥ 90 days For patients having =2 courses, 2nd exposure any duration
7	Other patterns	Initial course <90 days and 2nd course <90 days and 3rd or more courses with any duration and combination of Ziagen® or Trizivir® use

Primary Outcome Definition:

HSR events were judged by the EMRB to be either clinically compatible with HSR (HSR-like) or not compatible with HSR by placing them in the following subcategories: *Definite Case*, *Probable Case*, *Possible Case*, or *Not a Case*. For Rechallenge HSR-like events (or represcription events) the EMRB used the same subcategories. No predetermined criteria for these subcategories were established prior to the EMRB meeting to adjudicating potential cases, but a case definition was provided as guidance, as follows.

The standard definition of an HSR-like event was an event in which conditions in A or B or C were fulfilled where the exclusion criteria did not apply:

- A) Hypersensitivity / anaphylactic reaction / allergic reaction / drug allergy to abacavir was reported by the health care provider. **OR**
- B) Hypersensitivity to abacavir was evident by a positive rechallenge reaction. **OR**
- C) A multi-organ system reaction compatible with hypersensitivity to abacavir was identified by the EMRB. For this to be affirmed, the following needed to be true:

Two or more total symptoms were reported in a discrete time interval during a continuous period of abacavir use (<90 days), within at least two of the following groups:

- Rash
- Fever
- Gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain)
- Constitutional symptoms (lethargy, fatigue, malaise, myalgia, arthralgia, general ill feeling)
- Respiratory symptoms (dyspnea, sore throat, cough)

Any of the following precluded a diagnosis of HSR:

- An alternative cause for the symptoms definitely identified (e.g. clinically diagnosed Herpes Zoster,, or culture proven sepsis); this was determined by EMRB,
- Evidence of a negative rechallenge with abacavir,
- Evidence that symptoms resolved with continued abacavir treatment.

Expert Medical Review Board- Primary Outcome Case Definitions

Event Name	Description
Definite Initial HSR-like event	A case report documenting objective measures of a multi-organ syndrome consistent with an initial hypersensitivity reaction associated with abacavir in which all other explanations have been ruled out.
Probable initial HSR-like event	A case report documenting objective measures of multi-organ syndrome consistent with an initial hypersensitivity reaction associated with abacavir in which other explanations can not be ruled out.
Possible initial HSR-like event	A case report documenting subjective or patient-reported measures of multi-organ syndrome consistent with an initial hypersensitivity reaction associated with abacavir in which other explanations can not be ruled out.
Definite HSR represcription event	A case report documenting objective measures of a severe multi-organ syndrome consistent with a hypersensitivity reaction associated with represcription of abacavir in which a previous initial event is documented and all other explanations have been ruled out.

Probable HSR represcription event	A case report documenting objective measures of a severe multi-organ syndrome consistent with a hypersensitivity reaction associated with represcription of abacavir in which other explanations can not be ruled out or the initial reaction was not recognized.
Possible HSR represcription event	A case report documenting subjective or patient-reported measures of a severe multi-organ syndrome consistent with a hypersensitivity reaction associated with represcription of abacavir in which other explanations can not be ruled out or the initial reaction was not recognized.
Not an event	A case report inconsistent with an initial hypersensitivity reaction or a represcription hypersensitivity reaction associated with abacavir.

For cases where the patient was hospitalized or a death occurred within 90 days of discontinuing abacavir, the EMRB was asked to determine if the hospitalization or death was related to abacavir.

Cohort Specific (Exposure Definition, Case Screening & Case Abstraction)

1. HIV Insight™

Exposure Definition

Patient exposure to abacavir was determined through medical chart documentation of the start and stop dates of use. Transitions between formulations of abacavir (Ziagen® and Trizivir®) were considered a continuous course if no break between formulations took place. A break in abacavir exposure was defined as 7 or more days of no exposure in any form. Treatment courses were categorized by the formulation given first. If dates of use originally entered into HIV Insight™ were found to be in error when completing the HSR forms, the episode would be re-evaluated with the revised dates to determine whether the patient continued to meet the criteria for a potential event, and the HIV Insight™ and study databases were corrected accordingly.

Case Screening

HIV Insight™ screening of potential cases involved the review of retrospective data and prospective data to ascertain abacavir discontinuation. Screening for potential events was performed through algorithms codified in a computer program which was executed on the HIV Insight™ database. If any abacavir treatment was stopped within 90 days, the records of these patients were further examined to determine if there was any evidence of a study outcome of interest. Documentation of any of the following events within 90 days of starting abacavir was coded as a possible event:

- A reason for discontinuing abacavir suggesting a toxic reaction
- A symptom consistent with HSR
- A diagnosis consistent with HSR
- An abnormal lab value consistent with HSR
- Hospitalization or death.

Note that diagnoses that specifically state an abacavir hypersensitivity reaction are searched within 120 days of starting abacavir instead of 90 days. This exception to the 90-day window was made since it was found that some abacavir hypersensitivity diagnoses documented in the HIV Insight™ database did not always occur within the 90 days after starting abacavir.

Case Abstraction

Potential events were summarized on standardized forms containing information specified by GSK. Information needed to complete the forms that were not in the HIV Insight™ database were obtained through abstraction of the patient's medical record, physician recall, and/or hospital discharge record, if applicable.

2. CHORUS

Exposure Definition

In determining the seven exposure patterns, several rules were employed. A course of abacavir was defined as continuous use of the drug without any breaks. For this analysis, a discontinuation of abacavir use for 4 or more days

was considered as a break. Transitions between formulations (e.g. Ziagen® to Trizivir® or vice versa) were not considered a new course as long as the 4-day discontinuation criterion was not violated. Continuous courses that included both formulations were classified under the formulation given first. The risk period was defined to be the first 90 days of continuous exposure to abacavir. All shorter exposures resulted in restarting the clock until 90 days of continuous exposure were reached or abacavir was permanently discontinued.

Case Screening

“Potential case” patients were identified using an algorithm based on the following criteria:

- A physician diagnosis of hypersensitivity.
- A discontinuation of abacavir therapy and one or more symptoms of hypersensitivity within 14 days of the discontinuation of abacavir.
- An indication of allergy to abacavir in the patient’s medical records.
- A discontinuation of abacavir and an entry in the EMR indicating that the reason for discontinuation was an adverse event or probable hypersensitivity reaction.
- An elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) test result within 14 days of the discontinuation of abacavir.
- A diagnosis of a liver disease that could potentially mask an HSR-like event (acute and subacute necrosis of liver; chronic liver disease and cirrhosis, hepatic coma; hepatitis unspecified; jaundice unspecified- not of newborn; tuberculous hepatitis; viral hepatitis; secondary syphilitic hepatitis; syphilis of liver; hepatitis due to toxoplasmosis; disorders of iron metabolism; portal hypertension; hepatorenal syndrome; hepatomegaly; ascites; and abnormal liver scans) within 14 days of the discontinuation of abacavir.
- A hospitalization or emergency room visit within 14 days of the discontinuation of abacavir.
- A death during abacavir use or within 14 days of the discontinuation of abacavir.

Events were identified during the first 90 days of continuous abacavir exposure. Each new abacavir exposure started a new 90-day “at-risk” period during which hypersensitivity and related events were eligible for consideration as outcomes. Therefore, patients with multiple exposures to abacavir had all such exposures evaluated. Events falling outside the 90-day “at risk” period were not included in analysis but were reported in a narrative.

Case Abstraction

Each “potential case” patient identified through the screening process was entered into a CHORUS-specific Medical Record Data Abstraction Form. The form requires all diagnoses, medications, and laboratories prior to and following the abacavir discontinuation event. The form was taken by a trained clinical abstractor to the site to be augmented with any additional information from the written and electronic charts for these patients. Information from note fields in the EMR (not included in the database) and paper notes at the site were used to complete the Medical Record Data Abstraction Form and generated a narrative describing the events around the HSR-like event in chronological order. The completed Medical Record Data Abstraction Forms including the narratives were presented to the EMRB for case determination.

3. United Health Care / Ingenix

Exposure Definition

Abacavir therapy was ascertained from pharmacy dispensing records. A “dispensing” was defined as any provision of abacavir to the patient from the pharmacist. A dispensing can occur either as an initial prescription or a refill. The “days supply”, recorded with each dispensing, was the number of days of therapy contained in the dispensing, assuming that the drug was taken as directed. A “course of abacavir” therapy began on the earliest date of dispensing of abacavir and continued until 14 days had lapsed following the last day of continuous drug supply. An individual patient could have multiple courses of abacavir therapy. A “discontinuation” in therapy was defined as a lapse in abacavir treatment, as identified in the pharmacy claims, of longer than 14 days. A discontinuation marked the end of a course of abacavir. A “new course of abacavir” could occur only after a discontinuation in the previous course of abacavir, as defined above. The new course of abacavir began on the date of first dispensing of abacavir after the end of a preceding course. The date on which the new treatment course began was the date of “reinstitution of therapy”. Thus, intervals between dispensing that were no longer than “days supply” plus 14 days counted as continuations of a course of therapy. Intervals of more than 14 days were counted as discontinuations, which may have been followed by reinstitution of therapy or may have been permanent.

Case Screening

Screening was conducted using combined retrospective and prospective cohort data, with new abacavir initiators added to the cohort in six-month intervals. Screening was based on patients health care claims data reflecting a 90-day course

of abacavir or until the end of the study period. Patients who began abacavir were considered at risk for HSR for 90 days after initiation of a course of therapy. For events occurring within the 90-day risk period, any one HSR-related symptom in the claims qualified as a potential event that warranted further investigation. For patients who had multiple courses of abacavir, all courses were investigated for evidence of potential HSR. Any course of therapy that lasted for at least 90 days, any course following a 90-day event free course, and any course discontinued within 90 days with no evidence of HSR was deemed event-free for all of the primary analyses. Evidence of HSR beyond the risk period was assessed and medical records were abstracted if two or more symptoms of HSR were noted in the claims. Any such events identified outside of the 90-day risk period were intended to be considered separately; a patient having an event only after 90 days (without a prior event) would have been classified in all tables as having no event.

To identify potential HSR events, a search was conducted for any of a broad array of diagnosis and procedure (ICD-9 or CPT) codes possibly consistent with HSR occurring no more than 14 days after a discontinuation of abacavir. The ICD-9 list included codes for dermatologic conditions, acute respiratory syndromes, syncope and collapse, liver disease, acute allergic conditions, adverse drug effect codes, symptom codes consistent with abacavir hypersensitivity, and sudden death. The CPT list included codes related to resuscitation, intubation, liver procedures, and ambulance services.

Case Abstraction

The abstractors recorded all information available in the chart that was requested on the abstraction form and photocopied all lab reports, medication sheets, physician office notes, and hospital admission and discharge summaries that were available from the appropriate time period. A physician who specializes in treatment of patients with HIV used the abstracted medical record information and photocopied records to construct a narrative for each event.

4. V.A.

Exposure Definition

The National HIV Registry database was used to identify all patients that received an outpatient prescription for abacavir as Ziagen® or Trizivir®; these patients were considered as exposed to abacavir. Patients were not removed from this cohort in the event it was discovered, via chart audit, that a patient never received or ingested abacavir. The 90 day inclusion period started with this first prescription fill and exposure was calculated from this date and information contained in the days supply and quantity fields (a prescription coverage period). When the difference between one prescription fill coverage end date and another was at least 7 days, a "GAP" in therapy was identified and the patient began another 90 days interval. Patients who had only one prescription fill for a 90 day supply were considered not to have completed the initial 90 day period. Patients were followed for HSR-like events until they complete at least one 90 day interval without any GAP periods.

Case Screening

Any patient that did not complete at least 90 days of abacavir therapy underwent chart review. This constituted about 28% of all exposures to either Ziagen® or Trizivir® by December 31, 2003. In addition, patients with continued intermittent exposure where they never completed 90 consecutive days were reviewed as they were re-exposed to abacavir. Although the exposure was aggregated into any abacavir, the exact formulation the patient received was tracked to permit further analyses by initial and last exposure. Outpatient prescription data were used to identify which patients were prescribed abacavir as Ziagen® or Trizivir®. These records indicate that the medication was "filled" by the pharmacy but it is unknown if the patient actually took at least one dose.

The definition of what constituted a case to be brought to the EMRB for review was modified slightly after the first EMRB meeting once the board understood the quality of the information to be presented. For the initial meeting, a patient was brought to the EMRB for case review if they had at least two symptoms documented in the medical records. For the VA a case was defined as any two symptoms documented in the chart. If the clinician wrote "HSR reaction", it was not enough information without specific symptoms to bring the record up for review. Following this first meeting, the criteria were modified to include patients with at least two symptoms for different organ symptoms or a combination of a laboratory test, radiographic, or vital sign abnormality in conjunction with a symptom.

Case Abstraction

Data were collected during the medical record review and entered into the Microsoft Access® database. All potential patient, institution, or provider identifiers were removed and the generic term abacavir was used to mask the formulation prescribed.

Covariates:

For each patient prescribed abacavir, additional covariates were collected by each database

Covariate Information Collected by Each Database

Covariate	Database			
	HIV/Insight™	CHORUS	UHC/ Ingenix	VA
Patient Characteristics				
Age	+	+	+	+
Gender	+	+	+	+
Race	+	+		
HIV Risk Factors	+	+		
AIDS-defining illness	+	+	+	+
HIV treatment history	+	+	+	+
Provider Characteristics				
Size of practice	+	+		
Practice type	+	+	+	
Provider specialty	+		+	+

Data Analysis Methods:

Following adjudication by the EMRB regarding classification of each potential case, each database analyzed their data using pre-specified table shells, prepared by GSK according to the agreed upon data analysis plan. The data were subsequently aggregated into a combined set of tables, representing data from all databases. The aggregated data findings are presented in this report. Data regarding the number of abacavir users at each site were captured and used as the denominator in calculating the cumulative incidence of EMRB-determined HSR-like events and rechallenge HSR-like events, as well as hospitalizations and deaths attributed to an HSR-like events or Rechallenge HSR-like events. Cumulative incidence of HSR-like events, rechallenge, hospitalizations and deaths were calculated for Ziagen® and Trizivir®. The relative risks of events in the Ziagen® and Trizivir® groups were assessed by calculating unadjusted Odds Ratios (OR) and 95% confidence Intervals (CI) for outcomes using Trizivir® as the reference group. Rechallenge was defined as “first exposure” to an abacavir containing treatment followed by an abacavir-sparing period(s), before a “last exposure” to an abacavir-containing treatment.

A logistic regression model was fit for each of the outcomes described above that considered treatment group (Trizivir® or Ziagen®), treatment status at the time of abacavir initiation (antiretroviral (ART)-naïve or ART-experienced) and disease status at the time of abacavir initiation (non-AIDS diagnosis or AIDS diagnosis). The ability to conduct comparative analyses and model the data using logistic regression was dependent on a sufficient number of events in each treatment group. Two separate analyses were carried out by each database. The first analysis included data from potential cases determined by the EMRB to be a *Definite Case*, *Probable Case*, and *Possible Case* in the numerator of the frequencies and the second included *Definite Cases* and *Probable Cases* in the numerator.

In addition to the primary analysis including all abacavir users, at FDA's request, analyses using the final cumulative data were conducted that restricted the cohorts to patients with at least six months of continuous enrollment prior to the first abacavir dispensing. This parallel analysis was done for the purpose of adjusting for any potential survival bias.

Limitations:

Differences between the individual databases may contribute to different sensitivity in detecting possible HSR events. Data from UHC, which are claims based data, may miss some cases of HSR, but severe events, especially those leading to hospitalization or death should have been identified. CHORUS and the VA have data collected directly from patients' charts with electronic data capture. This capture allows for better sensitivity in detecting HSR events, but would not have clinical events scrutinized at the level of clinical trials. Practice-based databases like HIV Insight™ and CHORUS contain information on HIV patients whose doctors have opted to be part of the database and who were desirable recruitments to the network due to the size of their HIV population. This self-selected group of physicians may tend to be more current in HIV treatment issues than those who either opted not to participate or were not approached due to the size of their HIV patient population. These types of data might tend to bias estimates of the events being measured in this study.

There may be differences in the extent to which physicians in the database use the data collected at their site for case management and/or research. More routine use of the data for case management or research may increase physician awareness of past treatment and outcomes. Physicians also vary to the extent which they record symptom details in the chart, resulting in underreporting of symptoms at some sites.

The parallel subset analysis also had limitations that should be considered in interpreting the observations. The restrictions placed on this analysis were instituted to help increase detection of incident exposures; however, limitations in the observational period may have still allowed individuals with prior abacavir exposure into the study. Additionally, this analysis may be subject to biases imposed by excluding individuals who have an HSR reaction on first exposure to abacavir containing products. These restrictions may have allowed individuals to be classified as 'at risk' when in fact, they were exposed beyond the cumulative amount of time to be considered 'at risk'.

While events rates reported in this study are similar to those reported in clinical trials, biases exist that make a direct comparison to clinical trials difficult. Clinical trial data may be more sensitive in identifying HSR events as scrutiny given to trial patients is predictably greater than in standard medical care.

Study Results:

Patient and Provider Characteristics

The patients' demographic and baseline characteristics as well as the providers' characteristics are a function of the aggregate populations captured by the four observational databases. These characteristics are summarized in Tables 1 and 2 for the primary analysis (i.e., not for the parallel subset analysis).

Primary Analysis – Number of Patients with Study Drug Exposures and Potential HSR-like Events Evaluated by the EMRB; for Definite, Probable, and Possible Cases

Abacavir exposure was identified in 11,586 patients. The databases identified 8,877 patients with a first drug exposure to Ziagen® and 2,709 with a first exposure to Trizivir®. There were 8,724 patients with a last exposure to Ziagen® and 2,862 with a last exposure to Trizivir®. Seven-hundred fifty-five patients with their first exposure to Ziagen® and 201 to Trizivir® were reviewed as potential HSR-like events by the EMRB.

HSR-like Events

In the analysis that considered all *Definite*, *Probable*, and *Possible Cases*, the frequency of HSR-like events was 3.6% and 3.1% for Ziagen® and Trizivir® first exposures, respectively. (Table 3) The unadjusted Odds Ratio for HSR-like events comparing the exposure odds of Ziagen® to Trizivir® was 1.17 (95% CI: 0.92, 1.49). The adjusted Odds Ratio for HSR-like events comparing Ziagen® to Trizivir® was 1.04 (95% CI: 0.80, 1.34) by adjusting covariates of gender, age, ART experience and AIDS defining illness using analysis of pooled data from the four databases. Thirty-three (0.4%) hospitalizations among patients with first exposure to Ziagen® and 10 (0.4%) hospitalizations among patients with initial exposure to Trizivir®, were attributed to a *Definite*, *Probable* or *Possible* HSR-like event. The unadjusted Odds Ratio for hospitalizations attributed to an HSR-like event, comparing the exposure odds of Ziagen® to Trizivir® was 1.01 (95% CI: 0.5, 2.05). No deaths were identified.

In the analysis that considered only *Definite* and *Probable* HSR-like events (Table 4), the observed frequency was 0.7% for Ziagen® and 0.4% for Trizivir®. The unadjusted Odds Ratio for HSR-like events comparing Ziagen® to Trizivir® was 1.48 (95% CI: 0.79, 2.76). Seventeen hospitalizations among patients with first exposure to Ziagen® (0.2%) and 3 among those with first exposure to Trizivir® (0.1%) were attributed to a *Definite* or *Probable* HSR-like event. The unadjusted odds ratio for hospitalizations, comparing Ziagen® or Trizivir® was 1.73 (95% CI: 0.51, 5.91).

Rechallenge HSR-like Events

Thirteen *Definite*, *Probable*, and *Possible* Rechallenge HSR-like events (0.1%) occurred among patients who were last exposed to Ziagen® and 5 among patients who were last exposed to Trizivir® (0.2%). (Table 5) The unadjusted Odds Ratio for Rechallenge HSR-events comparing the exposure odds of Ziagen® to Trizivir® was 0.85 (95% CI: 0.30, 2.39). Four hospitalizations among patients with a last exposure to Ziagen® (0.05%) and 2 among those with last exposure to Trizivir® (0.1%) were observed. The unadjusted Odds Ratio for hospitalizations attributed to a Rechallenge HSR-like event, comparing the exposure odds of Ziagen® to Trizivir® was 0.66 (95% CI: 0.12, 3.58). No deaths were identified.

For only *Definite* and *Probable* Rechallenge HSR-like events 7 (0.1%) occurred among patients who were last exposed to Ziagen® and 3 among patients last exposed to Trizivir® (0.1%). (Table 6) The unadjusted Odds Ratio for Rechallenge HSR-like events comparing Ziagen® to Trizivir® was 0.77 (95% CI: 0.20, 2.96). Three hospitalizations among patients with a last exposure to Ziagen® (0.03%) and 2 among those with a last exposure to Trizivir® (0.1%) were attributed to a *Definite* or *Probable* Rechallenge HSR-like event. The unadjusted Odds Ratio for hospitalizations attributed to a Rechallenge HSR-like event comparing Ziagen® to Trizivir® was 0.49 (95% CI: 0.08, 2.95).

There were too few Rechallenge HSR-like events, hospitalizations attributed to either an HSR-like event or Rechallenge HSR-like event and no associated deaths to permit the calculation of adjusted Odds Ratios in these analyses. An adjusted Odds Ratio was calculated for *Definite/Probable/Possible* HSR-like events in the primary analysis only.

Parallel Subset Analysis

See Tables 7 through 11.

Table 1

Demographics /Baseline Characteristics, and Drug Use Pattern for all Abacavir Patients ¹		
	Total (n=11,586)	
	n	%
Race		
Caucasian	5124	44.2
Black	3527	30.4
Hispanic	711	6.1
Asian	53	0.5
Other/Undefined	631	5.4
Missing	1540	13.3
Gender		
Male	10732	92.6
Female	854	7.4
Age		
<36 years	1933	16.7
36-54 years	7982	68.9
>54 years	1671	14.4
Treatment History		
ART-Naïve	2489	21.5
ART-Experienced	9097	78.5
Risk factors		
MSWM	4258	36.8
Multiple Partners-Heterosexual	1267	10.9
IV Drug User	1152	9.9
Other/Unknown	3369	29.1
Missing	1540	13.3
Aids Defining Illness/patient		
None	7315	63.1
≥ 1	4271	36.9
Drug Use Patterns		
1. Ziagen® Only ²	6936	59.9
2. Trizivir® Only ²	2014	17.4
3. Ziagen®- Ziagen®	878	7.6
4. Ziagen® – Trizivir®	69	0.6
5. Trizivir® – Trizivir®	298	2.6
6. Trizivir® – Ziagen®	33	0.3
7. Other Patterns	1358	11.7
¹ Population includes only patients with abacavir start date in time to collect the data for primary analysis; characteristics summarized at start of first course of abacavir. ² Includes patients who eventually initiate another course of abacavir (either Ziagen® or Trizivir®), but only after successfully completing at least 90 days on the initial course. ART= Antiretroviral therapy; MSWM= Men having sex with men; IV Drug User= Intravenous Drug User		

Table 2

Provider Characteristics ¹		
	Total (n=11586)	
	n	%
Practice		
Hospital-based	6384	55.1
Office-based	5202	44.9
Public clinic	0	0.0
Missing	0	0.0
Physician/Provider		
ID Physician	1640	14.2
Other Physician	1447	12.5
NP or PA	112	1.0
Missing	8387	72.4
Size of HIV Practice		
< 10 active patients	4	0.0
10-50 active patients	218	1.9
>50 active patients	9824	84.8
Missing	1540	13.3

¹Characteristics summarized at start of first course of abacavir.
ID Physician = Infectious Disease Physician; NP = Nurse Practitioner; PA = Physician Assistant

Primary Analyses

Table 3

Summary of Initial Course of Ziagen® and Trizivir®: All Abacavir Patients ¹						
Primary Analysis- (Definite, Probable & Possible cases)	Ziagen® First Exposure ² (n=8877)		Trizivir® First Exposure ² N=2709		Unadjusted Odds Ratio 95% CI	
	n	%	n	%	OR	95% CI
Screened but not evaluated	4	0.0	1	0.0	N/A	N/A
Data unavailable	46	0.5	11	0.4	N/A	N/A
Abstracted & evaluated	755	8.5	201	7.4	N/A	N/A
HSR-like event	320	3.6	84	3.1	1.17	0.92 – 1.49
HSR-like hospitalization	33	0.4	10	0.4	1.01	0.5 – 2.05
HSR-like death	0	0.0	0	0.0	NA	NA

¹ Population includes only patients with abacavir start date in time to collect the data for this analysis.
² Ziagen® and Trizivir® exposure groups are a mutually exclusive classification based on regimen groups 1, 3, 4, and part of 7 for the "Ziagen® First Exposure" group and groups 2, 5, 6 and part of 7 for the "Trizivir® First Exposure" group.
OR=Odds Ratio; CI= Confidence Interval; HSR= Hypersensitivity Reaction

Table 4

Summary of Initial Course of Ziagen® and Trizivir®: All Abacavir Patients ¹						
Primary Analysis- (Definite & Probable Cases)	Ziagen® First Exposure ² N=877		Trizivir® First Exposure ² N=2709		Unadjusted Odds Ratio 95% CI	
	n	%	n	%	O.R.	95% CI
Screened but not yet evaluated	4	0.0	1	0.0	N/A	N/A
Data unavailable	46	0.5	11	0.4	N/A	N/A
Abstracted & evaluated	755	8.5	201	7.4	N/A	N/A
HSR-like event	58	0.7	12	0.4	1.48	0.79 – 2.76
HSR-like hospitalization	17	0.2	3	0.1	1.73	0.51 – 5.91
HSR-death	0	0.0	0	0.0	N/A	N/A

¹ Population includes only patients with abacavir start date in time to collect the data for this analysis.
² Ziagen® and Trizivir® exposure groups are a mutually exclusive classification based on regimen groups 1, 3, 4, and part of 7 for the "Ziagen® First Exposure" group and groups 2, 5, 6 and part of 7 for the "Trizivir® First Exposure" group.
OR=Odds Ratio; CI= Confidence Interval; HSR= Hypersensitivity Reaction

Table 5

Summary of Final Course of Ziagen® or Trizivir®: All Abacavir Patients ¹						
Primary Analysis- (Definite, Probable, & Possible Cases)	Ziagen® Last Exposure ² (n=8724)		Trizivir® Last Exposure ² (n=2862)		Unadjusted Odds Ratio 95% CI	
	n	%	n	%	O.R.	95% CI
Rechallenge HSR	13	0.1	5	0.2	0.85	0.30 – 2.39
Rechallenge HSR hospitalization	4	0.0	2	0.1	0.66	0.12 – 3.58
Rechallenge HSR death	0	0.0	0	0.0	NA	NA

¹ Population includes only patients with abacavir start date in time to collect the data for this analysis.
² Ziagen® and Trizivir® exposure groups are a mutually exclusive classification based on regimen groups 1, 3, 6, and part of 7 for the "Ziagen® Last Exposure" group and groups 2, 4, 5, and part of 7 for the "Trizivir® Last Exposure" group.
OR=Odds Ratio; CI= Confidence Interval; HSR= Hypersensitivity Reaction

Table 6

Summary of Final Course of Ziagen® or Trizivir®: All Eligible Abacavir Patients ¹						
Primary Analysis- (Definite and Probable Cases)	Ziagen® Last Exposure ² N=8724		Trizivir® Last Exposure ² N=2862		Unadjusted Odds Ratio 95% CI	
	n	%	n	%	O.R.	95% CI
Rechallenge HSR	7	0.1	3	0.1	0.77	0.20 – 2.96
Rechallenge HSR hospitalization	3	0.0	2	0.1	0.49	0.08 – 2.95
Rechallenge HSR death	0	0.0	0	0.0	N/A	N/A

¹ Population includes only patients with abacavir start date in time to collect the data for this analysis.
² Ziagen® and Trizivir® exposure groups are a mutually exclusive classification based on regimen groups 1, 3, 6, and part of 7 for the "Ziagen® Last Exposure" group and groups 2, 4, 5, and part of 7 for the "Trizivir® Last Exposure" group.
OR=Odds Ratio; CI= Confidence Interval; HSR= Hypersensitivity Reaction

Parallel Subset Analyses

Table 7

Usage Patterns of Ziagen® and Trizivir®: All Abacavir Patients ¹		
Parallel Substudy –(Definite, Probable & Possible Cases)	Number Ever Receiving Abacavir N=8976	
Pattern	n	%
1. Ziagen® Only ²	5255	58.5
2. Trizivir® Only ²	1510	16.8
3. Ziagen®-Ziagen®	730	8.1
4. Ziagen®-Trizivir®	61	0.7
5. Trizivir®-Trizivir®	242	2.7
6. Trizivir®-Ziagen®	27	0.3
7. Other Patterns	1151	12.8

¹ Population includes only patients with abacavir start date in time to collect the data for primary analysis.
² Includes patients who eventually initiate another course of Abacavir (either Ziagen® or Trizivir®), but only after successfully completing at least 90 days on the initial course

Table 8

Summary of Initial Course of Ziagen® and Trizivir®: All Abacavir Patients ¹						
Parallel Substudy- (Definite, Probable & Possible Cases)	Ziagen® First Exposure ² N=6887		Trizivir® First Exposure ² N=2089		Unadjusted Odds Ratio 95% CI	
	n	%	n	%	O.R.	95% CI
Screened but not yet evaluated	3	0.0	0	0.0	N/A	N/A
Data unavailable	43	0.6	7	0.3	N/A	N/A
Abstracted & evaluated	641	9.3	160	7.7	N/A	N/A
HSR-like event	286	4.2	70	3.4	1.25	0.96 - 1.63
HSR-like hospitalization	30	0.4	7	0.3	1.30	0.57 - 2.97
HSR-like death	0	0.0	0	0.0	N/A	N/A

¹ Population includes only patients with abacavir start date in time to collect the data for this analysis.
² Ziagen® and Trizivir® exposure groups are a mutually exclusive classification based on regimen groups 1, 3, 4, and part of 7 for the "Ziagen® First Exposure" group and groups 2, 5, 6 and part of 7 for the "Trizivir® First Exposure" group.
OR=Odds Ratio; CI= Confidence Interval; HSR= Hypersensitivity Reaction

Table 9

Summary of Initial Course of Ziagen® and Trizivir®: All Abacavir Patients ¹						
Parallel Substudy- (Definite & Probable Cases)	Ziagen® First Exposure ² N=6887		Trizivir® First Exposure ² N=2089		Unadjusted Odds Ratio 95% CI	
	n	%	n	%	O.R.	95% CI
Screened but not yet evaluated	3	0.0	0	0.0	N/A	N/A
Data unavailable	43	0.8	7	0.3	N/A	N/A
Abstracted & evaluated	641	9.3	160	7.7	N/A	N/A
HSR-like event	56	0.6	10	0.5	1.70	0.87 - 3.35
HSR-like hospitalization	16	0.2	2	0.1	2.43	0.56 - 10.58
HSR-like death	0	0.0	0	0.0	N/A	N/A

¹ Population includes only patients with abacavir start date in time to collect the data for this analysis.
² Ziagen® and Trizivir® exposure groups are a mutually exclusive classification based on regimen groups 1, 3, 4, and part of 7 for the "Ziagen® First Exposure" group and groups 2, 5, 6 and part of 7 for the "Trizivir® First Exposure" group.
OR=Odds Ratio; CI= Confidence Interval; HSR= Hypersensitivity Reaction

Table 10

Summary of Final Course of Ziagen® or Trizivir®: All Eligible Abacavir Patients ¹						
Parallel Substudy- (Definite, Probable & Possible Cases)	Ziagen® Last Exposure ² N=6751		Trizivir® Last Exposure ² N=2225		Unadjusted Odds Ratio 95% CI	
	n	%	n	%	O.R.	96% CI
Rechallenge HSR	12	0.2	5	0.2	0.79	0.28 - 2.25
Rechallenge HSR hospitalization	3	0.0	2	0.1	0.49	0.08 - 2.96
Rechallenge HSR death	0	0.0	0	0.0	N/A	N/A

¹ Population includes only patients with abacavir start date in time to collect the data for this analysis.
² Ziagen® and Trizivir® exposure groups are a mutually exclusive classification based on regimen groups 1, 3, 6, and part of 7 for the "Ziagen® Last Exposure" group and groups 2, 4, 5, and part of 7 for the "Trizivir® Last Exposure" group.
OR=Odds Ratio; CI= Confidence Interval; HSR= Hypersensitivity Reaction

Table 11

Summary of Final Course of Ziagen® or Trizivir®: All Eligible Abacavir Patients ¹						
Parallel Substudy- (Definite & Probable Cases)	Ziagen® Last Exposure ² N=6751		Trizivir® Last Exposure ² N=2225		Unadjusted Odds Ratio 95% CI	
	n	%	n	%	O.R.	95% CI
Rechallenge HSR	7	0.1	3	0.1	0.77	0.20 - 2.98
Rechallenge HSR hospitalization	3	0.0	2	0.1	0.49	0.08 - 2.96
Rechallenge HSR death	0	0.0	0	0.0	N/A	N/A

¹ Population includes only patients with abacavir start date in time to collect the data for this analysis.
² Ziagen® and Trizivir® exposure groups are a mutually exclusive classification based on regimen groups 1, 3, 6, and part of 7 for the "Ziagen® Last Exposure" group and groups 2, 4, 5, and part of 7 for the "Trizivir® Last Exposure" group.
OR=Odds Ratio; CI= Confidence Interval; HSR= Hypersensitivity Reaction

Conclusion:

Of the 11,586 abacavir users included in this study, there was an overall percentage of HSR-like events between 3.1 and 4.2, depending on enrolment restrictions. The overall frequency of *Definite/Probable/Possible* HSR-like events was consistent with published frequencies of abacavir related HSR. Few hospitalizations attributed to HSR-like events were observed. Rechallenge HSR events were uncommon in both Ziagen® and Trizivir® treatment groups. No deaths attributable to HSR or to Rechallenge HSR-like events were observed. There were no differences between Ziagen® and Trizivir® in any of the analyses of these data regardless of the inclusion of *Possible* events in the primary analyses or in the parallel analyses.