TITLE PAGE

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
GSK	GlaxoSmithKline
HIPAA	Health Insurance Portability and Accountability Act
HITECH	Health Information Technology for Economic and Clinical Health Act
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
MHC	Major Histocompatability Complex

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2. RESPONSIBLE PARTIES: SPONSOR INFORMATION PAGE

MARKETING AUTHORISATION HOLDER

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Primary Author/ Project officer

Date

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Date

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

Investigator Signature	Date

3. ABSTRACT

Following the identification of a genetic link to abacavir hypersensitivity reaction, HLA-B*5701 testing entered clinical use in 2008 with the demonstration of the clinical utility of HLA screening where it was found that screening eliminated immunologically confirmed hypersensitivity reaction with a negative predictive value of 100% and a positive predictive value of 47.9%. Guidelines subsequently recommended HLA testing for all patients when considering an abacavir-containing regimen.

Objectives:

1) To describe the baseline demographic and clinical characteristics of HIV+ patients initiating an abacavir-based ART regimen.
2) To describe the annual incidence rates and cumulative frequencies of HLA-B*5701 testing before and after June 15, 2008.
3) To describe and compare the annual incidence rates and cumulative frequencies of suspected hypersensitivity reaction among abacavir-exposed patients before and after June 15, 2008.

Study Design:

An observational clinical cohort analysis utilizing prospectively collected electronic medical record (EMR) data obtained from the OPERA® Observational Database will be used to address the study objectives. The observation period will begin on January 1, 1999 (first full year post approval of Ziagen®) with study participants identified through January 1, 2016. Comparison Time Periods are 1) Pre-HLA-B*5701 screening period: January 1, 1999 to June 14, 2008, and 2) Post-HLA-B*5701 screening period: June 15, 2008 to January 1, 2016

Endpoints:

Descriptive statistics will be used to summarize baseline demographics and clinical characteristics of HIV+ patients exposed to an abacavir-containing regimen. Frequencies of HLA testing by year will be summarized. Incidence rates and cumulative frequencies of suspected hypersensitivity reaction to abacavir-containing regimens will be calculated by year of initial exposure to an abacavir-containing regimen.

4. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
<1>	<Date>	<Text>	<Text>	<Text>
<2>	<Date>	<Text>	<Text>	<Text>
<n>	<Date>	<Text>	<Text>	<Text>

5. MILESTONES

Milestone	**Planned date**
Start of data analysis	29-July-2016
Registration in the EU PAS register	28-July-2016
End of data -analysis	15-Aug-2016
Preliminary tables	19-Aug-2016
Draft report of study results	09-Sept -2016
Final report of study results	15-Oct -2016

6. BACKGROUND AND RATIONALE

6.1. Background

Abacavir sulfate, a carbocyclic 2'-deoxyguanosine nucleoside analogue, was approved by the FDA in December 1998, for the treatment of adults and children with HIV infection. The approval of abacavir was based on studies that showed improved CD4 profile and decreased plasma HIV RNA levels in patients who took abacavir in combination with other nucleoside analogues versus those who took antiretroviral regimens without abacavir.[1,2] Abacavir is converted intracellularly by enzymes, into the active compound carbovir triphosphate. This, in turn, competitively inhibits HIV reverse transcriptase and terminates proviral DNA chain extension.[3]

Originally marketed as Ziagen®, abacavir has since been co-formulated with two other nucleoside reverse transcriptase inhibitors, zidovudine and lamivudine (3TC), approved as Trizivir®, followed by co-formulations with lamivudine, approved as Epzicom® and with lamivudine and dolutegravir (DTG), approved as Triumeq®. With all formulations, abacavir is widely used to achieve viral suppression and immunologic improvement in patients with HIV infection. Factors that make abacavir a suitable choice for HIV therapy are its high oral bioavailability (geometric mean of absolute bioavailability is 83%), no significant effect of food on the extent of absorption, pharmacokinetics that support once daily dosing, good central nervous system penetration, no significant drug interactions, and slow development of drug-resistant mutants.[4-8]

Early phase I/II trials with abacavir indicated the occurrence of side effects like headache, gastrointestinal disturbances, rash, malaise, fatigue and asthenia. Like many antiretroviral drugs, abacavir is metabolized by cytochrome P450 in the liver. Therefore, as with other nucleoside analogues, patients who take abacavir are susceptible to lactic acidosis, hepatomegaly and steatosis.[9] Among nucleoside analogues, abacavir is believed to have a lower propensity for causing mitochondrial toxicity. Studies show that switching patients with symptomatic hyperlactatemia or lactic acidosis from stavudine and/or didanosine to abacavir and lamivudine result in less potent levels of hyperlactatemia.[10]

Hypersensitivity is the term used for an extreme form of adaptive immune response. Such responses occur when the immune system reacts inappropriately to certain antigens, and may lead to inflammatory reactions and tissue damage.[11] There are four types of hypersensitivity reactions – I, II, III and IV. Type I hypersensitivity is mediated by immunoglobulin E (IgE), leading to the release of pharmacological mediators which produce an acute inflammatory reaction. Type II hypersensitivity is antibody-dependent (IgG or IgM) and occurs when antibodies bind to self or foreign antigens on cells, causing phagocytosis, killer cell activity or complement-mediated lysis. Type III hypersensitivity develops when large immune complexes cannot be cleared from the reticuloendothelial system. Type IV or delayed type hypersensitivity (DTH) occurs when antigens are trapped in a macrophage and cannot be cleared. As a result, cytokines are released and these mediate a range of inflammatory responses.

The exact mechanism of abacavir hypersensitivity reactions is not clearly understood, although studies suggest the involvement of T-cells and the cytokines interferon-gamma (IFN-γ) and interleukin-4 (IL-4).[12,13] Hypersensitivity to abacavir is a multi-organ syndrome characterized by a sign or symptom in two or more of the following categories:
Group 1: Fever
Group 2: Rash
Group 3: Gastrointestinal (nausea, vomiting, diarrhea or abdominal pain)
Group 4: Constitutional (generalized malaise, fatigue, aches)
Group 5: Respiratory (dyspnea, cough, pharyngitis)

In a review of 9 clinical trials conducted between November 1999 and January 2002 involving 2,670 patients, 8% (range 2-9%) of patients prescribed abacavir reported a suspected hypersensitivity reaction. The median time to onset was 9 days, with 89% presenting symptoms within the first 6 weeks of starting the drug. The vast majority of patients (95%) presented symptoms from two or more of the groups that are described above.[26]

Other symptoms of hypersensitivity include lethargy, myolysis, edema, abnormal chest X-ray, paresthesia, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure and death. Reports of anaphylaxis with initial and re-challenge exposure to abacavir have been documented.[14-17] There have also been isolated case reports of unusual symptoms like anorexia, peri-tonsillar abscess, agranulocytosis, lip ulcers and neuropsychiatric symptoms like night sweats, depression, and auditory hallucinations.[18-20] A retrospective review of data from 200,000 patients who received abacavir through clinical trials or by prescription initially identified a total of 1,803 cases of suspected hypersensitivity to the drug. Upon further review of these cases, the

calculated incidence rate in the clinical trials was determined to be 4.3%. The mortality rate in patients who received abacavir in clinical trials was 0.03%.[21]

Barring rare hypersensitivity reactions with fatal outcomes, in general, the symptoms are reversed after the discontinuation of abacavir. However, hypersensitivity reaction is much more severe and more frequently lethal in patients who, after the resolution of initial symptoms, are reintroduced to abacavir. Following a diagnosis of hypersensitivity, patients must not take abacavir again. Restarting the drug following a hypersensitivity reaction has resulted in cases of life-threatening hypotension and fatal reactions. Additionally, there have been reports of individuals who developed re-challenge hypersensitivity to abacavir after having been asymptomatic following initial use of the drug as well.[15,22] Therefore, it is recommended that all patients receiving abacavir be monitored closely for signs of a hypersensitivity reaction, especially in the initial weeks of treatment.[23]

Early studies examining the demographic and clinical predictors of hypersensitivity found higher risks for white race, female gender, elevated baseline CD8 and lower risks for antiretroviral treatment and African American descent.[24-27] Genetic susceptibility factors have been suggested because of the occurrence of the reaction in a small sub-population of patients receiving abacavir, familial disposition, the low incidence of the reaction in patients of African American origin and involvement of the major histocompatibility complex (MHC) alleles in other similar multi-organ hypersensitivity reactions.[28,29] Later studies have found an association between abacavir hypersensitivity and specific human leukocyte antigen (HLA) alleles.[30]

Following the identification of a genetic link to abacavir hypersensitivity reaction, HLA-B*5701 testing entered clinical use in 2008 with the demonstration of the clinical utility of HLA screening where it was found that screening eliminated immunologically confirmed hypersensitivity reaction with a negative predictive value of 100% and a positive predictive value of 47.9%.[30] Guidelines subsequently recommended HLA testing for all patients when considering an abacavir-containing regimen.

6.2. Rationale

With studies showing a negative predictive value of HLA-B*5701 of 100%, treatment guidelines were adjusted after the genetic link was identified and a genetic test became available in 2008. This analysis will assess the use of HLA testing in the general HIV practice setting along with the rates of suspected hypersensitivity reaction due to abacavir in the pre-testing era compared to the post-testing era.

7. RESEARCH QUESTION AND OBJECTIVE(S)

1) To describe the baseline demographic and clinical characteristics of HIV+ patients initiating an abacavir-based antiretroviral therapy (ART) regimen.
2) To describe the annual incidence rates and cumulative frequencies of HLA-B*5701 testing before and after June 15, 2008.

3) To describe and compare the annual incidence rates and cumulative frequencies of suspected hypersensitivity reaction among abacavir-exposed patients before and after June 15, 2008.

8. RESEARCH METHODS

8.1. Study Design

An observational clinical cohort analysis utilizing prospectively collected electronic medical record (EMR) data obtained from the OPERA® Observational Database will be used to address the study objectives.

Period of Observation:

The observation period will begin on January 1, 1999 (first full year post approval of Ziagen®) with study participants identified through January 1, 2016.

Comparison Time Periods:

Pre-HLA-B*5701 screening period: January 1, 1999 to June 14, 2008

Post-HLA-B*5701 screening period: June 15, 2008 to January 1, 2016

8.2. Study Population and Setting

The study sample will be identified from the OPERA Observational Database for analysis. HIV-1 positive patients initiating abacavir-containing treatment for the first time between 1/1/1999 and 1/1/2016 will be included in the study sample if they meet the following inclusion criteria:

1) At least 13 years of age at the index date.
2) Continuous clinical activity in the year prior to abacavir initiation, defined as at least one clinic visit.
3) Continuous clinical activity in the year following abacavir initiation, defined as at least one clinical contact (visit or telephone contact).

Follow-up Period: Patients will be observed from their initiation of abacavir until the first of the following censoring events: a) discontinuation of abacavir, b) cessation of continuous clinical activity, c) death or d) study end (July 31, 2016). Patients failing to meet the continuous clinical activity requirement will be censored 12 months after their last contact.

8.3. Variables

8.3.1. Exposure definitions

- First exposure to abacavir (Ziagen, Trizivir, Epzicom, Triumeq)

8.3.2. Outcome definitions

- Diagnosis of suspected hypersensitivity reaction to abacavir (HSR)
- Documentation of HLA-B*5701 testing and timing of the test (before starting ABC containing regimen or after)
- Exposure to abacavir post positive HLA testing

8.3.3. Confounders and effect modifiers

Confounding may occur with the use of other ART that causes similar symptoms (e.g. nevirapine and rash) or from other illnesses that could be confused with these symptoms (e.g. influenza season). Effect modification is anticipated to be minimal for this particular analysis insofar as the awareness of HSR associated with abacavir was high in both the pre-2008 and post-2008 periods. Evidence of the level of awareness of HSR with abacavir, especially with potential re-challenges, is available from the Trizivir Epidemiology Program, a post-approval study requirement. In this study, re-challenges with abacavir post HSR diagnoses were minimal, suggesting a high level of awareness of the diagnostic algorithm for HSR and the contraindication of abacavir re-challenge. It is possible that, post-2008, prescriber comfort with abacavir increased due to the availability of HLA testing and its 100% negative predictive value.

8.4. Data sources

The OPERA® (Observational Pharmaco-Epidemiology Research & Analysis) database and research network is a multi-site observational database built from the complete patient health records managed in Electronic Health Record (EHR) systems throughout the U.S.

In total, there are more than 2.5 million documented prospective visits in the EHR systems for HIV+ patients and 2.6 million prescriptions written for ART medications. The average years of follow-up (years of documenting patient visits prospectively in the EHR) for patients in OPERA is 4.2 years and there are 5,479 HIV+ patients who have nine years or more of follow-up.

In addition to HIV treatment, OPERA captures the diagnosis and treatment of co-morbid conditions and diagnoses of HIV negative patients. Epividian analyses other serious comorbid conditions such as Hepatitis C with about 8% of HIV+ patients in OPERA co-infected.

8.5. Study size

As of March 2016, 17,253 patients in OPERA have had an HLA-B*5701 test performed in OPERA. In total, 16,676 patients have been exposed to abacavir in one or more of the various formulations (with a cumulative number of treatment days of 17.2 million). Of these 16,676 patients, 6,638 started an abacavir-containing regimen prior to April 1, 2008.

8.6. Data management

8.6.1. Data handling conventions

Epividian utilizes a number of proprietary algorithms to sort, classify, and aggregate the data pulled from the participating clinics' EHR systems. The process includes automated classification of clinical terms into common clinical terms with review by trained medical staff. The standardization of the data to common terms and application of the Epividian knowledge base are key process steps in gathering data from multiple heterogeneous EHR systems and databases from many locations into a single, homogenous OPERA database for conducting research and commercial analyses. The patient health data gathered, classified and aggregated includes complete medical history & social history, visit dates, vital signs, lab orders and results, medications, problems & diagnoses, and procedures.

Epividian has developed rigorous data management processes that include both automated and manual quality checks. Data quality methods include common techniques such as:

- Detection and reporting of outliers that lead to correction, acceptance, or exclusion of observations; these can include a medical review.
- Detection of potentially missing data (e.g. a patient taking ART medications with no history of HIV infection to determine whether the use was prophylactic or treatment for infection diagnosed elsewhere).
- Data completion using multiple observations and sources (e.g. using diagnoses codes, free text, past medical history, etc. to determine if patient is naive to HIV therapy).
- Detection of observations that are known to be (or likely to be) mutually exclusive for a patient (e.g. record of medications that are typically not administered concurrently).

8.6.2. Resourcing needs

Addressed in contract.

8.6.3. Timings of Assessment during follow-up

Not applicable.

8.7. Data analysis

8.7.1. Essential analysis

Descriptive analyses:

> Demographics: Age, sex, race (African American/non-African American), ethnicity (Hispanic/non-Hispanic), risk of infection (MSM/other), and geographic region

Clinical: ABC formulation (Ziagen/ Trizivir/ Epzicom/ Triumeq), therapy experience (naïve/experienced), concomitant nevirapine use (yes/no), flu season administration (Dec-Mar/other), time period (pre-HLA testing/ post-HLA testing), HLA testing status (yes/no), HLA test results (positive/negative), time from HLA testing to first abacavir exposure. Note: HSR events most commonly occur within 2 weeks of abacavir initiation, events occurring after 6 weeks of initiation of an Abacavir containing regimen will be tabulated separately, as these are often not confirmed as HSR. Time to HSR event tables and Kaplan-Meyer curves will be used to assess the average and median time for the occurrence of suspected HSR.

Multivariable analyses:

Rates of suspected HSR diagnoses by HLA time period.

8.7.2. Exploratory analysis

Assess abacavir exposure rates prior to HLA testing completion in post-06/15/2008 era.

8.7.3. General considerations for data analyses

Missing or incomplete data are not uncommon in the observational setting in which measures are collected through routine clinical care rather than on a set schedule dictated by a protocol associated with a clinical trial.[31] In this setting, data may not be missing at random which can lead to a biased measure of association and overly precise confidence intervals if only those observations with complete data are used in the analysis.[32]

Patients lost to follow up are flagged and their follow up time censored. Sensitivity analyses can be used to elucidate the importance of their contribution to any conclusions.

Stockpiling of medication through incomplete adherence can result in gaps in the medication record. These will be handled by collapsing the medication record across gaps of less than 30 days in which the patient returns to the same medication. A collapse will not occur if it coincides with a suspected hypersensitivity event to allow observation of re-challenge events.

8.8. Quality control and Quality Assurance

Epividian has working practices & procedures governing the use of observational data, the development of analysis specifications and plans, the development of analytical programming, the analytical quality assurance process and the scientific review of reports as well as clinical advisory charters for the clinical review of output intended for public domain. Working practices for the development of analysis specifications include basic identifying information, background material, relevant definitions of key study variables, population definitions, baseline definitions, specific requirements for dataset creation, statistical requirements such as eligibility criteria, exposures, outcomes and model fitting. Working practices for programming include naming conventions, proper code documentation and commentary, content, appearance, efficiencies (i.e. use of macros), and organization of output, maintainability and generalizability. Working practices for programming quality assurance include self-reviews of observational counts, missing

data values, many-to-many merges, variable formatting, numeric-character & character-numeric conversions, uninitialized variables, unresolved macro references, report completeness and report-to-specification correspondence, and system errors and logs. The quality assurance team review may include small sample spot-checking, coding log reviews, complete coding review, selected observations from intermediary dataset reviews, and/or independent programming to reproduce the results. Documentation of non-public domain reports includes market, scientific, statistical, and clinical review. Documentation of scientific protocols, reports and manuscripts intended for public domain follows two sequential steps: an internal-to-Epividian epidemiological, statistical, and clinical review, followed by a clinical/epidemiological external advisory board review.

8.9. Limitations of the research methods

With approximately 7% of the HIV population that is linked to care in the OPERA database (per the CDC estimates), OPERA can provide detailed information on a large portion of the HIV population in the U.S. Even so, issues confronting population-level assessments include such aspects as differential medical care by practice size and specialty, academic and research orientation of the health care practitioner, ethnic-based & gender-based attitudes and geographic regional health care practices. OPERA clinical data is collected at point-of-care and is subject to the record-keeping practices of each healthcare provider and the standards of each clinic or organization. Patients may see multiple physician practices for various conditions, which may result in incomplete case ascertainment. Data is collected for the medical management of patients and is not directly intended for research purposes, but rather for the care and management of individual patients and patient populations.

8.9.1. Study closure/uninterpretability of results

Closure is at report submission.

8.10. Other aspects

The OPERA® Epidemiological and Clinical Advisory Board provides all methodological and clinical oversight.

9. PROTECTION OF HUMAN SUBJECTS

Clinical information is aggregated into the OPERA® Database following the guidelines of HIPAA and HITECH. Data aggregation occurs via a secure and encrypted connection with security and confidentiality maintained through Epividian's validated de-identification algorithms with regular and routine statistical audits of the de-identification process.

9.1. Ethical approval and subject consent

Business Associate Agreements (BAA) in place between Epividian and all medical practices govern, following the guidelines established in HIPAA and HITECH, the encryption, transportation, aggregation, de-identification and use of all clinical data in the

OPERA® Database. All medical practices are responsible for obtaining proper HIPAA consent for their patients. With BAA's in place, a separate informed consent for each individual, non-interventional study is not required.

9.2. Subject confidentiality

All clinical data is de-identified as per HIPAA and HITECH. The OPERA® Clinical Advisory Board provides clinical and methodological review & oversight.

All clinical data is de-identified as per HIPAA and HITECH in OPERA® with all reports submitted at the aggregated population level. No personally identifiable information is available in the OPERA® Database.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The study design is to analyse the patient level information recorded in the OPERA database from electronic health records in an aggregate manner. Reporting of adverse events by Epividian to competent authorities is not applicable as the healthcare information used in this study will not contain physician attribution of adverse event causality to any medicinal product.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

Health care practitioners, regulatory authorities

11.2. Study reporting and publications

Final report to be submitted to sponsor. Study results will be submitted to a peer reviewed journal.

12. REFERENCES

1. Staszewski S, Katlama C, Harrer T, Massip P, Yeni P, Cutrell A, Tortell SM, Harrigan RP, Steel H, Lanier RE, Pearce G. A dose-ranging study to evaluate the safety and efficacy of abacavir alone or in combination with zidovudine and lamivudine in antiretroviral treatment-naive subjects. AIDS 1998; 12 (16): F197-202.
2. Saag MS, Sonnerborg A, Torres RA, Lancaster D, Gazzard BG, Schooley RT, Romero C, Kelleher D, Spreen W, LaFon S. Antiretroviral effect and safety of abacavir alone and in combination with zidovudine in HIV-infected adults. Abacavir Phase 2 Clinical Team. AIDS 1998; 12 (16): F203-9.
3. Hervey PS, Perry CM. Abacavir: a review of its clinical potential in patients with HIV infection. Drugs. 2000; 60 (2): 447-79.
4. Chittick GE, Gillotin C, McDowell JA, et al. Abacavir (1592U89): absolute bioavailability and effect of food. Pharmacotherapy 1999; 19:932-42.
5. McDowell JA, Lou Y, Symonds WS, Stein DS. Multiple-dose pharmacokinetics and pharmacodynamics of abacavir alone and in combination with zidovudine in human immunodeficiency virus-infected adults. Antimicrob Agents Chemother 2000;44: 2061-67.
6. Weller S, Radomski KM, Lou Y, Stein DS. Population pharmacokinetics and pharmacodynamics modeling of abacavir (1592U89) from a dose-ranging, double-blind, randomized monotherapy trial with human immunodeficiency virus-infected subjects. Antimicrob Agents Chemother 2000; 44:2052-60.
7. Wang LH, Chittick GE, McDowell JA. Single-dose pharmacokinetics and safety of abacavir (1592U89), zidovudine, and lamivudine administered alone and in combination in adults with human immunodeficiency virus infection. Antimicrob Agents Chemother 1999; 43: 1708-15.
8. Tisdale M, Alnadaf T, Cousens D. Combination of mutations in human immunodeficiency virus type 1 reverse transcriptase required for resistance to the carbocyclic nucleoside 1592U89. Antimicrob Agents Chemother 1997; 41: 1094-98.
9. Bleeker-Rovers CP, Kadir SW, van Leusen R, Richter C. Hepatic steatosis and lactic acidosis caused by stavudine in an HIV-infected patient. Neth J Med; 57 (5): 190-3.
10. Lonergan JT, Barber RE, Mathews WC. Safety and efficacy of switching to alternative nucleoside analogues following symptomatic hyperlactatemia and lactic acidosis. AIDS 2003; 17 (17): 2495-9.
11. Brostoff J, Hall T, Male D, Hay F, Barnetson RS, Gawkrodger D, Britton W. (1996) in *Immunology* ed. Roitt I, Brostoff J, Male D (Mosby Publishing).
12. Vilar FJ, Naisbitt DJ, Park BK, Pirmohamed M. Mechanisms of drug hypersensitivity in HIV-infected patients: the role of the immune system. J HIV Ther 2003; 8 (2): 42-7.
13. Vyakarnam A, King D, Tomkins S, Easterbrook P, Raffi F, Thurmond L, Thorborn D, Kemeny M. Immunological components of hypersensitivity to abacavir. 8th European Conference on Clinical Aspects and Treatment of HIV Infection, Athens, October 28-31, 2001. Abstract # 332.
14. Walensky RP, Goldberg JH, Daily JP. Anaphylaxis after rechallenge with abacavir. AIDS 1999; 13 (8): 999-1000.
15. Frissen PH, de Vries J, Weigel HM, Brinkman K. Severe anaphylactic shock after rechallenge with abacavir without preceding hypersensitivity. AIDS 2001; 15 (2): 289.

16. Shapiro M, Ward KM, Stern JJ. A near-fatal hypersensitivity reaction to abacavir: case report and literature review. AIDS Read 2001; 11 (4): 222-6.
17. Clay PG, Rathbun RC, Slater LN. Management protocol for abacavir-related hypersensitivity reaction. Ann Pharmacother 2000; 34 (2): 247-9.
18. Colebunders R, Hilbrands R, De Roo A, Pelgrom J. Neuropsychiatric reaction induced by abacavir. Am J Med 2002; 113 (7): 616.
19. Aquilina C, Mularczyk M, Lucas F, Viraben R. Unusual clinical presentation of hypersensitivity reaction to abacavir. AIDS 2003; 17 (16): 2403-4.
20. Sankatsing SU, Prins JM. Agranulocytosis and fever seven weeks after starting abacavir. AIDS. 2001; 15 (18): 2464-5.
21. Hetherington S, McGuirk S, Powell G, Cutrell A, Naderer O, Spreen B, Lafon S, Pearce G, Steel H. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. Clin Ther 2001; 23 (10): 1603-14.
22. El-Sahly HM. Development of abacavir hypersensitivity reaction after rechallenge in a previously asymptomatic patient. AIDS 2004; 18 (2): 359-60.
23. Clay PG. The abacavir hypersensitivity reaction: a review. Clin Ther 2002; 24 (10): 1502-14.
24. Easterbrook PJ, Waters A, Murad S, Ives N, Taylor C, King D, Vyakarnam A, Thorburn D. Epidemiological risk factors for hypersensitivity reactions to abacavir. HIV Med 2003; 4 (4): 321-4.
25. Cutrell AG, Hernandez JE, Fleming JW, Edwards MT, Moore MA, Brothers CH, Scott TR. Updated clinical risk factor analysis of suspected hypersensitivity reactions to abacavir. Ann Pharmacother 2004; 38 (12): 2171-2.
26. Symonds W, Cutrell A, Edwards M, Steel H, Spreen B, Powell G, McGuirk S, Hetherington S. Risk factor analysis of hypersensitivity reactions to abacavir. Clin Ther 2002; 24 (4): 565-73.
27. Hewitt RG. Abacavir hypersensitivity reaction. Clin Infect Dis 2002; 34 (8): 1137-42.
28. Martin AM, Nolan D, Gaudieri S, Almeida CA, Nolan R, James I, Carvalho F, Phillips E, Christiansen FT, Purcell AW, McCluskey J, Mallal S. Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and a haplotypic Hsp70-Hom variant. Proc Natl Acad Sci U S A 2004; 101 (12): 4180-5.
29. Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, Sayer D, Castley A, Mamotte C, Maxwell D, James I, Christiansen FT. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet 2002; 359 (9308): 727-32.
30. Mallal S, Phillips E, Carosi G, et. al. HLA-B*5701 Screening for Hypersensitivity to Abacavir. N Engl J Med 2008;358:568-79.
31. PCORI 2013 http://www.pcori.org/assets/2013/11/PCORI-Methodology-Report.pdf p37.
32. 13. Sterne 2009 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2714692/