ABACAVIR HYPERSENSITIVITY REACTION

Date of preparation: January 2015

Zinc no: MLT_GIB/HIV/0001/13(1)

REPORTING ADVERSE EVENTS (AEs):

Malta :If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to: GSK (Malta) Limited, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131)

Alternatively, any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system:

Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Ru **D'Argens, Gżira GŻR 1368, MALTA, or sent by email to** postlicensing.medicinesauthority@gov.mt

ViiV Healthcare

DIAGNOSIS OF ABACAVIR HYPERSENSITIVITY

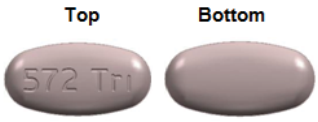
Abacavir Is a Component of Ziagen®, Trizivir®, Kivexa®/Epzicom® and Triumeq ®

- Ziagen®

- Trizivir®

- Kivexa®/Epzicom®

- Triumeq®



[a] Ziagen, Trizivir, Epzicom, Kivexa and Triumeq are registered trademarks of the ViiV Healthcare group of companies

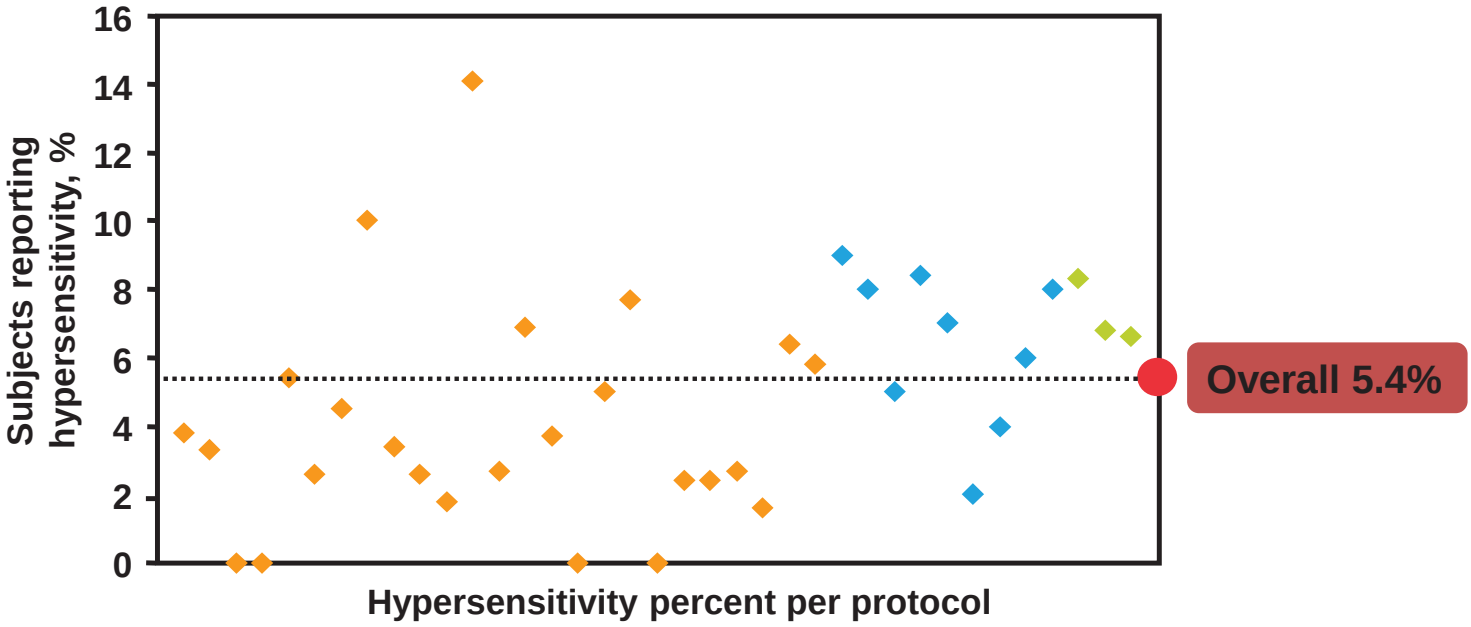
Abacavir Hypersensitivity Reaction

- Idiosyncratic reaction
- Observed in approximately 5% of subjects across clinical studies
- Clinically well characterised
- Manageable by discontinuation of abacavir
- Diagnosis is complicated by
  - Variable presentation with nonspecific symptoms
  - Concomitant use of other antiretroviral medications whose adverse event profiles overlap

Hughes et al. *The Pharmacogenomics J*. 2008;8:365-374.

Frequency of Abacavir Hypersensitivity by Study Protocol

- Occurred in 5.4% of subjects across clinical studies (n=9329)



- July 2001 Risk Factor Analysis (RFA). Symonds et al. *Clin Ther*. 2002;24:565-573.
- May 2003 RFA (Case Report Form Module). Cutrell et al. *Ann Pharmacother.* 2004;38:2171-2172.
- June 2004 RFA. Brothers et al. Poster presented at: 12th Conference on Retroviruses and Opportunistic Infections; February 22-25, 2005; Boston, MA.

Frequency of Suspected Abacavir Hypersensitivity in Select Blinded Clinical Trials Using Non-Abacavir–Containing Regimens

	Abacavir		Zidovudine or indinavir	
Study	Total no.	HSR, n (%)	Total no.	HSR, n (%)
CNA3005[1,2]	268	19 (7%)	265	6 (2%)
CNA30024[2,3]	330	27 (8%)	325	10 (3%)
ACTG A5095[4]	382	37 (10%)	376	28 (7%)
Total	980	83 (8.5%)	966	44 (4.6%)

HSR, hypersensitivity reaction.

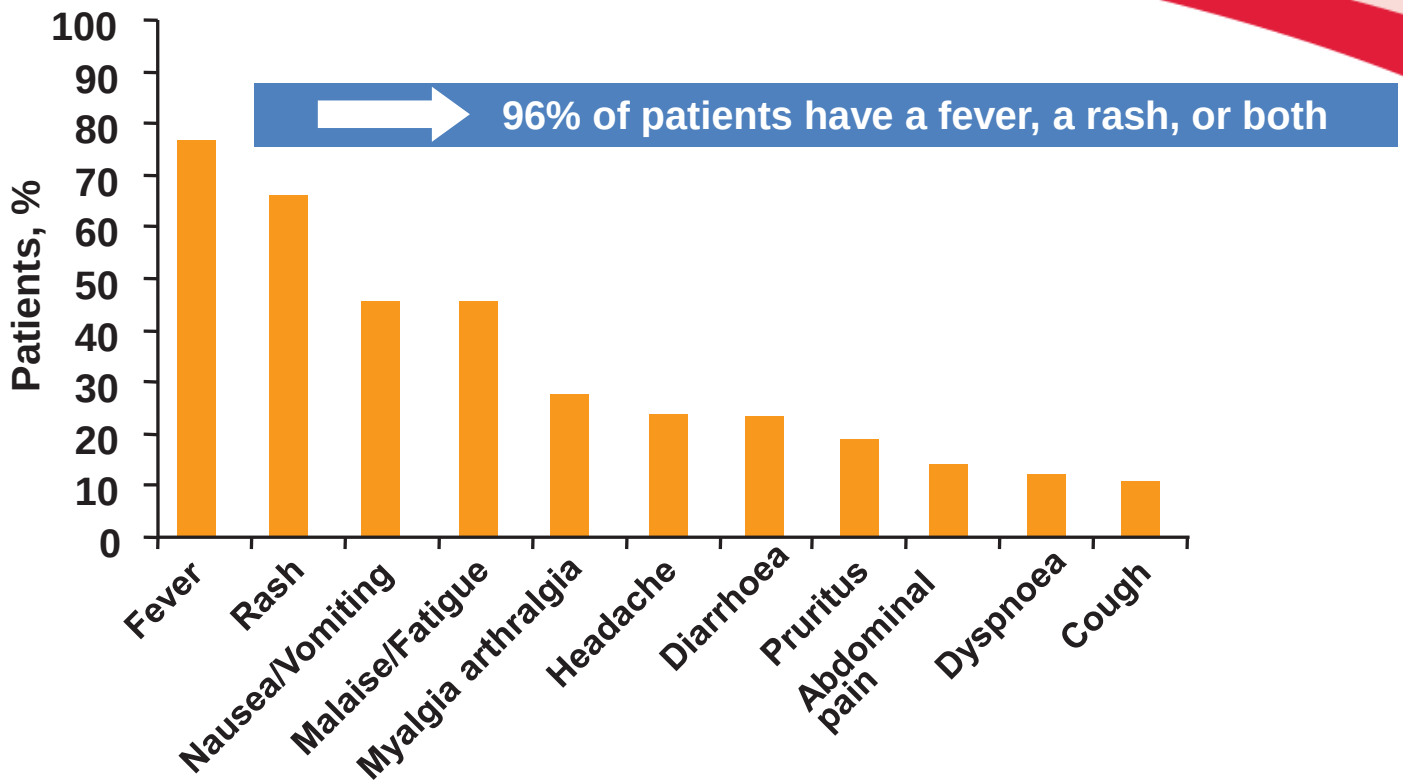
1. Brothers et al. Poster presented at: 12th Conference on Retroviruses and Opportunistic Infections; February 22-25, 2005; Boston, MA. **2.** Hernandez et al. Abstract presented at: 5th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV; July 8-11, 2003; Paris, France. **3.** Wannamaker et al. *Can J Infect Dis Med Microbial*. 2007;18(suppl B):71B. **4.** Gulick et al. *JAMA*. 2006;296:769-781.

Time to Onset of Abacavir Hypersensitivity

- Time to onset was evaluated in studies conducted before the era of prospective screening for hypersensitivity to abacavir
- Median time to onset was ~8 days[1-3]
- Majority of the reported cases (≥90%) occurred within the first 6 weeks of starting abacavir[1,3]
  - Delayed onset (eg, >12 wk) was uncommon (≤6%)

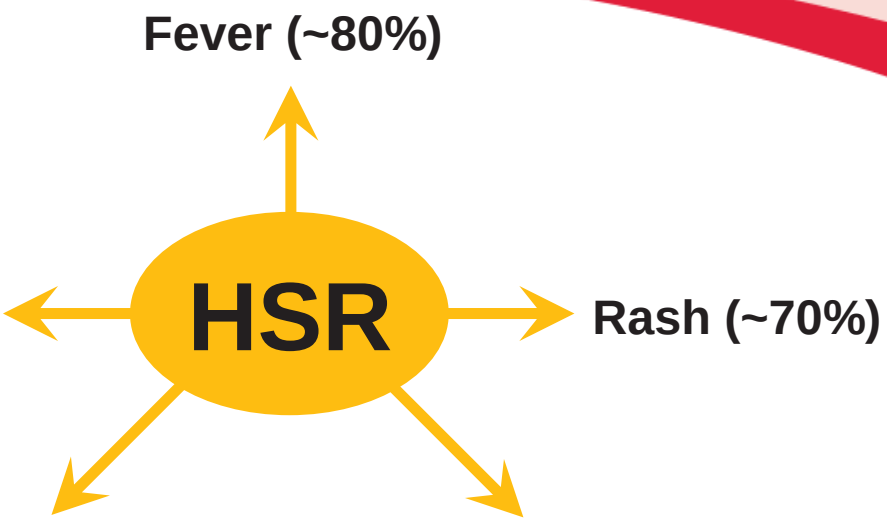
1. Hetherington et al. *Clin Ther*. 2001;23:1603-1614. **2.** Mallal et al. *N Engl J Med*. 2008:358;568-579. **3.** Saag et al. *Clin Infect Dis*. 2008;46:1111-1118.

Hypersensitivity Symptoms Reported With a Frequency ≥10% (n=1803)



Hetherington et al. *Clin Ther*. 2001;23:1603-1614.

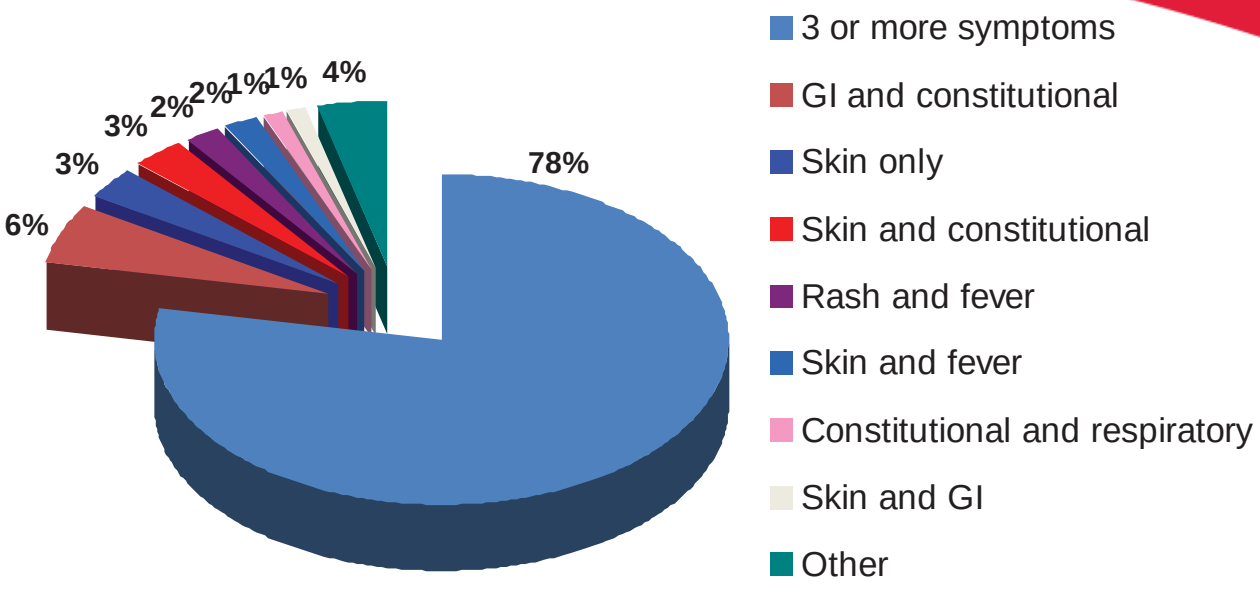
Major Symptoms Associated With Hypersensitivity



HSR, hypersensitivity reaction.

Hetherington et al. *Clin Ther*. 2001;23:1603-1614.

Frequency of Combinations of Abacavir Hypersensitivity Symptoms in Clinical Trials (n=206)



- Multiple symptoms are typical in most cases of hypersensitivity

GI, gastrointestinal.

Hernandez et al. Abstract presented at: 15th International AIDS Conference; July 11-16, 2004; Bangkok, Thailand.

Hypersensitivity Reaction Warning Card

(Where Local Country Labelling aligns with the MAH Global Data Sheet or EU Product Information for the ABC-containing products)

- Patients should contact their physician immediately for advice on whether they should stop taking abacavir if:

1. They develop a skin rash; OR
2. They develop 1 or more symptom from at least 2 of the following groups

  - Fever
  - Shortness of breath, sore throat or cough
  - Nausea or vomiting or diarrhoea or or abdominal pain
  - Extreme tiredness or achiness or generally ill feeling

Hypersensitivity Reaction Warning Card

(Where Local Country Labelling aligns with FDA Prescribing Information and Medication Guides for the ABC-containing products)

- If a patient has a symptom from 2 or more of the following groups while taking an abacavir-containing regimen, he or she should contact a physician immediately to determine whether to stop taking this medicine
  - Group 1: Fever
  - Group 2: Rash
  - Group 3: Nausea, vomiting, diarrhoea, or abdominal (stomach area) pain
  - Group 4: Generally ill feeling, extreme tiredness, or achiness
  - Group 5: Shortness of breath, cough, or sore throat

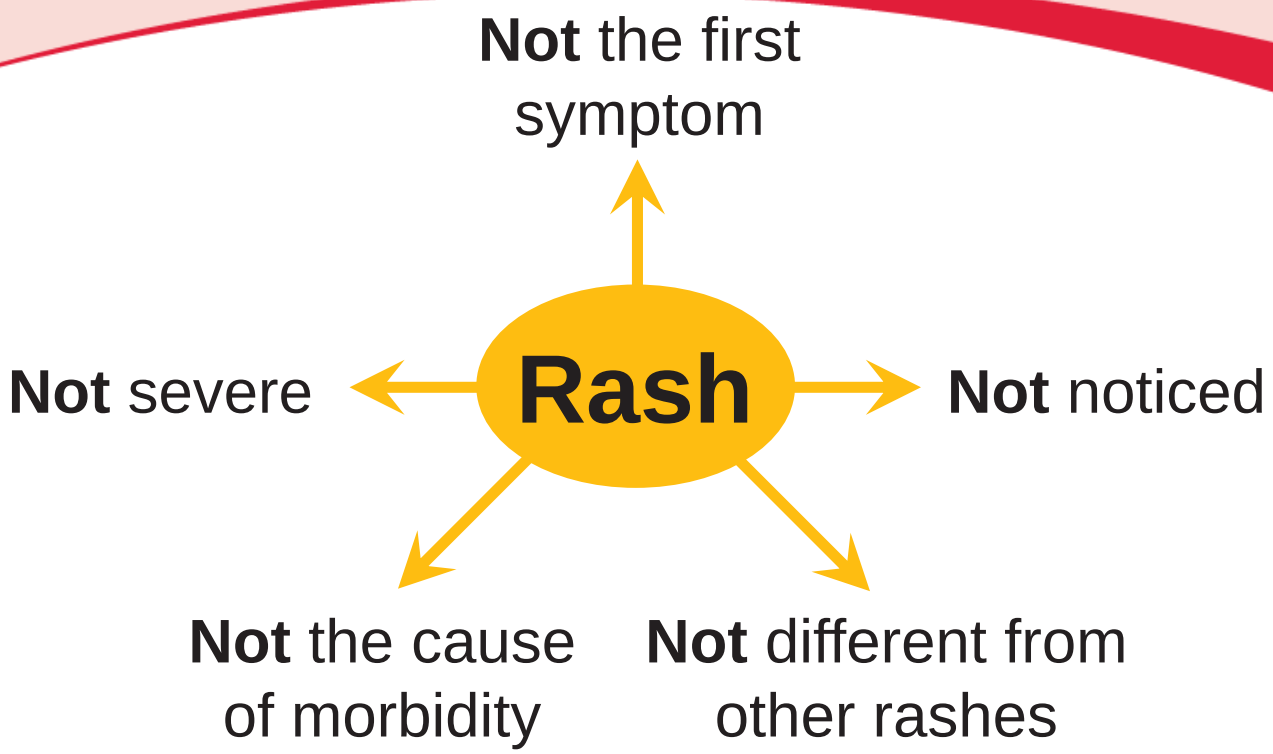
Physical and Laboratory Findings

Physical findings	Possible laboratory abnormalities
Fever	Haematological: lymphopaenia and thrombocytopaenia
Rash: urticarial, maculopapular	Elevated liver enzymes (AST/ALT)
Mucous membrane lesions (pharyngitis, conjunctivitis)	Increased serum creatinine and creatinine phosphokinase
Lymphadenopathy	Chest x-ray normal or diffuse bilateral or lobular infiltrates

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Hetherington et al. *Clin Ther*. 2001;23:1603-1614.

When Present, Rash Is More Distinct for What It Is Not



Thurmond et al. Abstract presented at: 2nd International Workshop on Adverse Drug Reactions & Lipodystrophy in HIV; September 13-15, 2000; Toronto, Canada. Brothers et al. Poster presented at: 12th Conference on Retroviruses and Opportunistic Infections; February 22-25, 2005; Boston, MA.

RISK FACTORS FOR ABACAVIR HYPERSENSITIVITY REACTIONS

Clinical Risk Factors for Abacavir Hypersensitivity

- Not related to CD4+ cell count, viral load, or dose
- No increased risk with protease inhibitor or NNRTI is consistently identified
- Risk of a suspected hypersensitivity reaction is decreased in
  - Patients of African descent
  - Treatment-experienced or CDC category C patients
  - Male patients
- Frequency and clinical presentation are similar in children and adults

CDC, Centers for Disease Control and Prevention.
Cutrell et al. *Ann Pharmacother.* 2004;38:2171-2172.

Interruptions in Abacavir Dosing Are Not Associated With Increased Risk of Hypersensitivity

- On very rare occasions, HSRs have been reported in patients who have restarted therapy and who had no preceding symptoms of an HSR[1]
- However, a study by Thompson et al showed no evidence that interruptions in therapy are associated with an increased risk of abacavir hypersensitivity[2]
  - Therapy gaps of ≥2 days occurred in 74% (119/161) of patients
  - Therapy gaps of ≥5 days occurred in 40% (64/161) of patients
  - Incidence of hypersensitivity (2.5%, 4/161) was consistent with previous reports
  - No increase in severity or mortality rate from abacavir hypersensitivity

HSR, hypersensitivity reaction.

1. Frissen et al. *AIDS*. 2001;15:289. **2.** Thompson et al. Abstract presented at: 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17-20, 2000; Toronto, Canada.

Similar Rates of Suspected Hypersensitivity With Once- or Twice-Daily Dosing of Abacavir

Study	Arm[a]	Hypersensitivity rate, %
CNA30021[1]	ABC BID (+ 3TC + EFV OD)	7
	ABC OD (+ 3TC + EFV OD)	9
EPV40001[2]	ABC BID/3TC BID	8
	ABC BID/3TC OD	2
	ABC OD/3TC BID	8
	ABC OD/3TC OD	4
ESS101822 (ALOHA)[3]	ABC BID + 3TC BID	7
ESS100732 (KLEAN)[4]	ABC OD/3TC OD	6

3TC, lamivudine; EFV, efavirenz.

[a] ABC BID refers to abacavir 300 mg administered twice daily. ABC OD refers to abacavir 600 mg administered once daily.

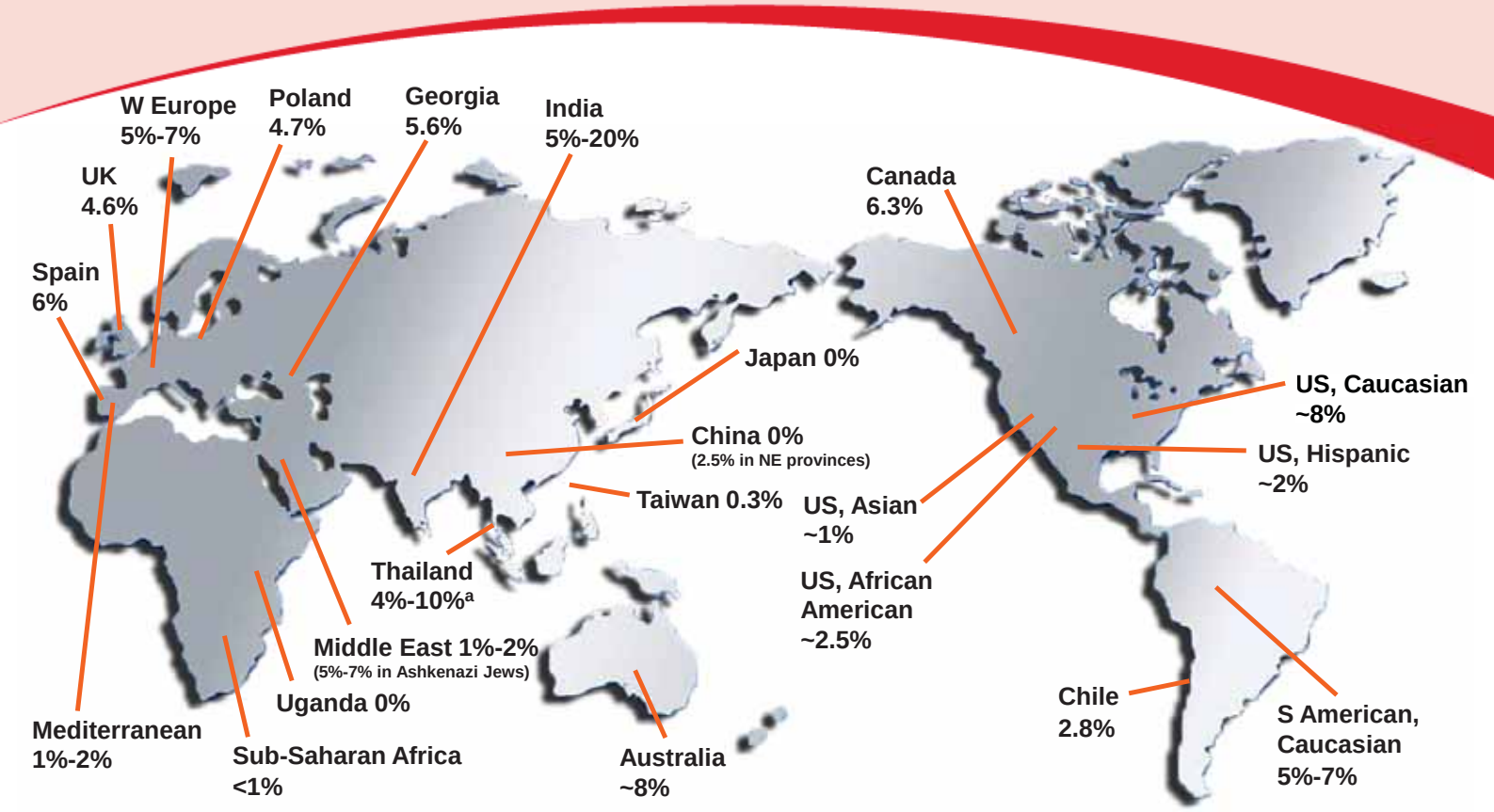
1. Moyle et al. *J Acquir Immune Defic Syndr*. 2005;38:417-425. **2.** Bowonwatanuwong et al. Abstract presented at: 1st International AIDS Society Conference on HIV Pathogenesis and Treatment; July 8-11, 2001; Buenos Aires, Argentina. **3.** Cohen et al. *Pharmacotherapy*. 2008;28:314-322. **4.** Eron et al. *Lancet*. 2006;368:476-482.

Pharmacogenetic Risk Factors for Abacavir Hypersensitivity

- HLA-B*5701 is more common among patients who have a suspected hypersensitivity reaction to abacavir compared with those who do not, regardless of race[1-2]
- No other pharmacogenetic markers have been found that identify patients at risk of abacavir hypersensitivity in all ethnic groups and in both sexes[3]

1. Mallal et al. *Lancet*. 2002;359:727-732. **2.** Hetherington et al. *Lancet*. 2002;359:1121-1122. **3.** Martin et al. *Proc Natl Acad Sci USA*. 2004;101:4180-4185.

HLA-B*5701 Carriage Frequency[1-9]



[a] Thailand B*57 carriage: Thai Dai Lue (NE Thai), ~11%; Urban Bangkok, 3.6%; Southern Thai Muslim, 3%.

1. Nolan et al. *J HIV Ther*. 2003;8:36-41. **2.** Lalonde et al. *Tissue Antigens*. 2010;75:12-18. **3.** Poggi et al. *Braz J Infect Dis*. 2010;14:510-512. **4.** Dvali et al. *Georgian Med News*. 2010;12:16-20. **5.** Parczewski et al. *HIV Med*. 2010;11:345-348. **6.** Arrizabalaga et al. *HIV Clin Trials*. 2009;10:48-51. **7.** Sun et al. *J Antimicrob Chemother*. 2007;60:599-604. **8.** Munderi et al. *Trop Med Int Health*. 2011;16:200-204. **9.** Orkin et al. *HIV Med*. 2010;11:187-192.

Rates of Suspected Hypersensitivity Reaction to Abacavir Are Lower Among Black Subjects

Study	N	Black, %	HSR cases, black subjects n (%)	HSR cases, all other subjects n (%)	Overall HSR rate n (%)
KLEAN[a]	879	32	9 (3.3)	44 (7.3)	53 (6.0)
ALOHA	680	34	6 (2.6)	30 (6.7)	36 (5.3)
ACTION[a]	139	32	1 (2.3)	6 (6.3)	7 (5.0)
CNA30024[b]	330	20	2 (3.0)	25 (9.5)	27 (8.2)
CNA30021	770	27	12 (5.7)	52 (9.3)	64 (8.3)
Total	2798	30	30 (3.6)	157 (8.0)	187 (6.7)

- May be related to the low carriage rate of HLA-B*5701 in the black population

HSR, hypersensitivity reaction.

[a] 48-week interim data. [b] Subjects randomised to abacavir only.

Wannamaker et al. *Can J Infect Dis Med Microbial*. 2007;18(suppl B):71B.

HLA-B*5701 Allele and Abacavir Hypersensitivity

- HLA-B*5701–positive patients are likely to experience an abacavir hypersensitivity reaction
- Prospective pharmacogenetic screening for HLA-B*5701 is used to identify patients at high risk for abacavir hypersensitivity
- However, HLA-B*5701 is **not always** present in people who have a suspected abacavir hypersensitivity reaction[1]
  - Therefore, screening patients for the presence of HLA-B*5701 may not predict **everyone** who will experience a hypersensitivity reaction to abacavir

1. Mallal et al. *N Engl J Med*. 2008:358;568-579.

Abacavir Hypersensitivity Risk Factors: Summary

- HLA-B*5701 is the only identified pharmacogenetic marker that is consistently associated with clinical diagnosis of an abacavir hypersensitivity reaction
  - However, some patients with a suspected abacavir hypersensitivity reaction may not have the HLA-B*5701 allele

Recommendations for HLA-B*5701 Screening

- Clinical diagnosis of suspected hypersensitivity to abacavir remains the basis for clinical decision making
- HLA-B*5701 screening for risk of abacavir hypersensitivity should never be substituted for appropriate clinical vigilance and patient management in individuals receiving abacavir
- If abacavir hypersensitivity cannot be ruled out, abacavir should be permanently discontinued, regardless of the results of HLA-B*5701 screening
- Results of pharmacogenetic tests for risk of abacavir hypersensitivity should never be used to support a drug rechallenge decision after a suspected hypersensitivity reaction
- HLA-B*5701 testing must not be used as a diagnostic test after a patient has started treatment with abacavir

Recommendations for HLA-B*5701 Screening (cont)

- In settings where validated screening methods are available, clinicians should screen for HLA-B*5701 in any HIV-infected patient who has not previously been exposed to abacavir
  - Only patients found to lack the HLA-B*5701 allele should begin therapy with the drug.
- Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir.
- Where screening is not available, it is reasonable to initiate abacavir therapy with appropriate clinical vigilance
- In HLA-B*5701–negative patients, and in situations where HLA-B*5701 screening is not available, clinical vigilance remains vital to detect any abacavir hypersensitivity at the earliest stage

MANAGEMENT OF ABACAVIR HYPERSENSITIVITY REACTION

Clinical Management of Abacavir Hypersensitivity

- Regardless of a patient's HLA-B*5701 status
  - When in doubt, stop abacavir therapy
  - Permanently discontinue abacavir after a presumptive diagnosis of hypersensitivity
  - Acute reaction: discontinue abacavir, assess severity, and institute supportive therapy, including fluids, pressors, steroids, and antihistamines
  - Retrieve abacavir from the patient
  - After a patient experiences a hypersensitivity reaction to abacavir, DO NOT substitute with other abacavir-containing regimens or compounds (eg, Ziagen®, Trizivir®, Kivexa®/Epzicom® or Triumeq®)

Clinical Management of Abacavir Hypersensitivity: Restarting Abacavir

- If abacavir therapy is stopped for suspected or confirmed HSR
  - It should not be restarted, regardless of a patient's HLA-B*5701 status
- If abacavir therapy is stopped for reasons other than suspected HSR
  - HLA-B*5701 status of all patients should be verified (by historical review or testing)
    - If a patient is HLA-B*5701 positive, abacavir should not be restarted even if the patient had previously tolerated abacavir
    - If a patient is HLA-B*5701 negative, abacavir may be restarted only if medical care can be accessed readily by the patient or others

HSR, hypersensitivity reaction.

Clinical Management of Abacavir Hypersensitivity: Counseling the Patient

- Make patients (or parents and guardians of children) aware of
  - The signs and symptoms of abacavir hypersensitivity
    - Use the warning card as a tool to initiate discussion
    - Refer to the package leaflet
  - Increased risk of hypersensitivity reaction in individuals who are HLA-B*5701 positive
    - However, HLA-B*5701–negative individuals also may experience an abacavir hypersensitivity reaction
- Have a plan to communicate in the event of a reaction
  - Advise patients to call their doctor immediately if they suspect hypersensitivity or if they develop symptoms consistent with hypersensitivity, regardless of their HLA-B*5701 status

Avoiding Severe Morbidity and Mortality

- Stopping abacavir ➔ rapid resolution of symptoms
- Continued dosing in the face of hypersensitivity reaction ➔ worsening of symptoms
- Restarting any abacavir-containing regimen after the patient experiences a hypersensitivity reaction ➔ more severe, potentially life-threatening events, including hypotension and death

Rechallenge is contraindicated

Diagnosis and Management of Abacavir Hypersensitivity: Summary

- Occurs in approximately 5% of patients
- Symptoms can occur at any time during treatment with abacavir, but usually occur within the first 6 weeks of therapy
- Symptoms are initially mild and evolve over days, becoming more severe with continued abacavir therapy
- Multisystem involvement: Common symptoms include fever, rash, gastrointestinal, malaise, and respiratory symptoms, *but*…
  - No individual symptom will always be present
- Symptoms improve on cessation of abacavir

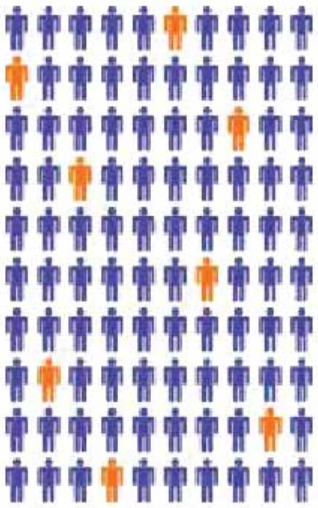
Rechallenge can result in a more rapid and severe reaction, which can be fatal. Rechallenge is contraindicated

If acute illness cannot be differentiated from a hypersensitivity reaction, stop abacavir

HLA-B*5701 TESTING

What Is the HLA-B*5701 Test?

- People who have the HLA-B*5701 allele are at higher risk of having a hypersensitivity reaction than people who do not have this pharmacogenetic marker
- The one-time HLA-B*5701 test identifies people at high risk for this serious allergic reaction



Screening Methods for HLA-B*5701

- The gold standards for HLA-B*5701 screening are sequence-based genotyping and polymerase chain reaction sequencing of specific oligonucleotide probes
- Blood or saliva samples are collected and tested for genetic sequences coding for the HLA-B*5701 allele

Ma et al. *PLoS Curr*. 2010;2:RRN1203.

Alternative Screening Methods for HLA-B*5701

Screening method	Potential advantages
Capillary electrophoresis assay with fluorescence detection using new sequence-specific PCR primers[1]	Can use noninfective DNA sources (eg, saliva); allows process automation
Genotyping of HCP5 single-nucleotide polymorphism rs2395029[2,3]	Cheaper, more rapid, and easier to perform
Allele-specific PCR melting assay[4]	Minimises post-PCR handling processing
Analysis of sequence variation in HIV reverse transcriptase codon 245[5]	Simple, low-cost screening
Flow cytometric dual staining of B17/CD45[6]	Sensitive, rapid, and cost-effective screening

- Sequenced-based genotyping and PCR sequencing of specific oligonucleotide probes remain the gold standards for HLA-B*5701 screening

PCR, polymerase chain reaction.

1. Giardina et al. *Electrophoresis*. 2010;31:3525-3530. **2.** Rodriguez-Nóvoa et al. *J Antimicrob Chemother*. 2010;65:1567-1569. **3.** Colombo et al. *J Infect Dis*. 2008;198:864-867. **4.** Hammond et al. *Tissue Antigens*. 2007;70:58-61. **5.** Chui et al. *Clin Infect Dis*. 2007;44:1503-1508. **6.** Martin et al. *Pharmacogenet Genomics*. 2006;16:353-357.

What Do the HLA-B*5701 Test Results Mean?

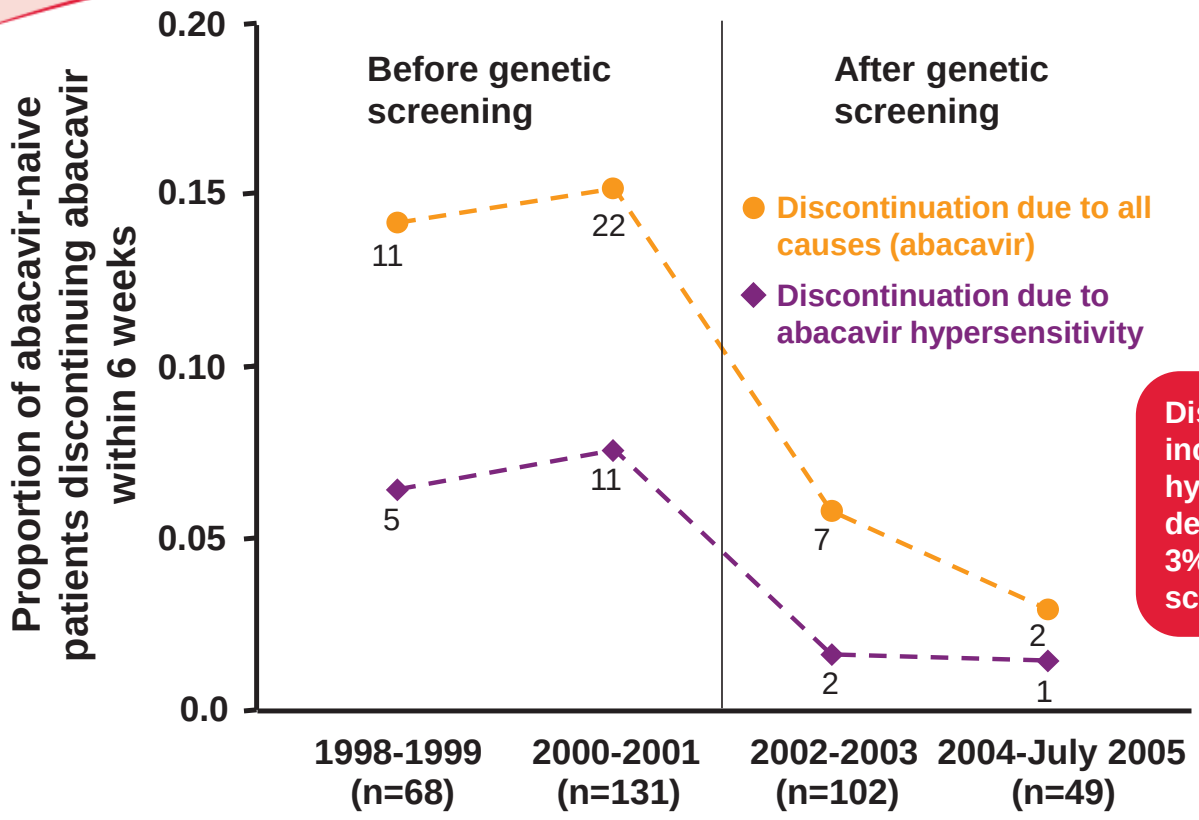
Test result	Meaning	Note
Negative	• Patient is at a lower risk of developing an allergic reaction to abacavir than someone who has tested positive for HLA-B*5701 • Patient may be an appropriate candidate for an abacavir-containing regimen	Patient might still develop a hypersensitivity reaction and should contact his or her healthcare provider if the patient suspects such a reaction
Positive	• Patient is at a higher risk of developing an allergic reaction to abacavir than someone who has tested negative for HLA-B*5701 • Treatment with abacavir is not recommended	

HLA-B*5701 Screening for Risk of Abacavir Hypersensitivity

- The primary goal of HLA-B*5701 screening is to reduce the incidence of abacavir hypersensitivity syndrome
- Data from the Western Australian Cohort suggested that HLA-B*5701 screening was an effective and feasible way to reduce the incidence of abacavir hypersensitivity reaction[1]
- Routine prospective pharmacogenetic testing resulted in a marked reduction in abacavir hypersensitivity[2]
  - Over time, the overdiagnosis of abacavir hypersensitivity caused by another drug or a concurrent disease decreased

1. Mallal et al. *Lancet*. 2002;359:727-732. **2.** Rauch et al. *Clin Infect Dis*. 2006;43:99-102.

Decline in Early Discontinuation of Abacavir After Introduction of Prospective Genetic Screening



Discontinuations due to incidence of abacavir hypersensitivity decreased from 8% to 3% with genetic screening (*P*=0.01)

Rauch et al. *Clin Infect Dis*. 2006;43:99-102. Figure adapted from Rauch et al. *Clin Infect Dis*. 2006;43(1):99-102. With permission.

Prospective Screening for Abacavir Hypersensitivity

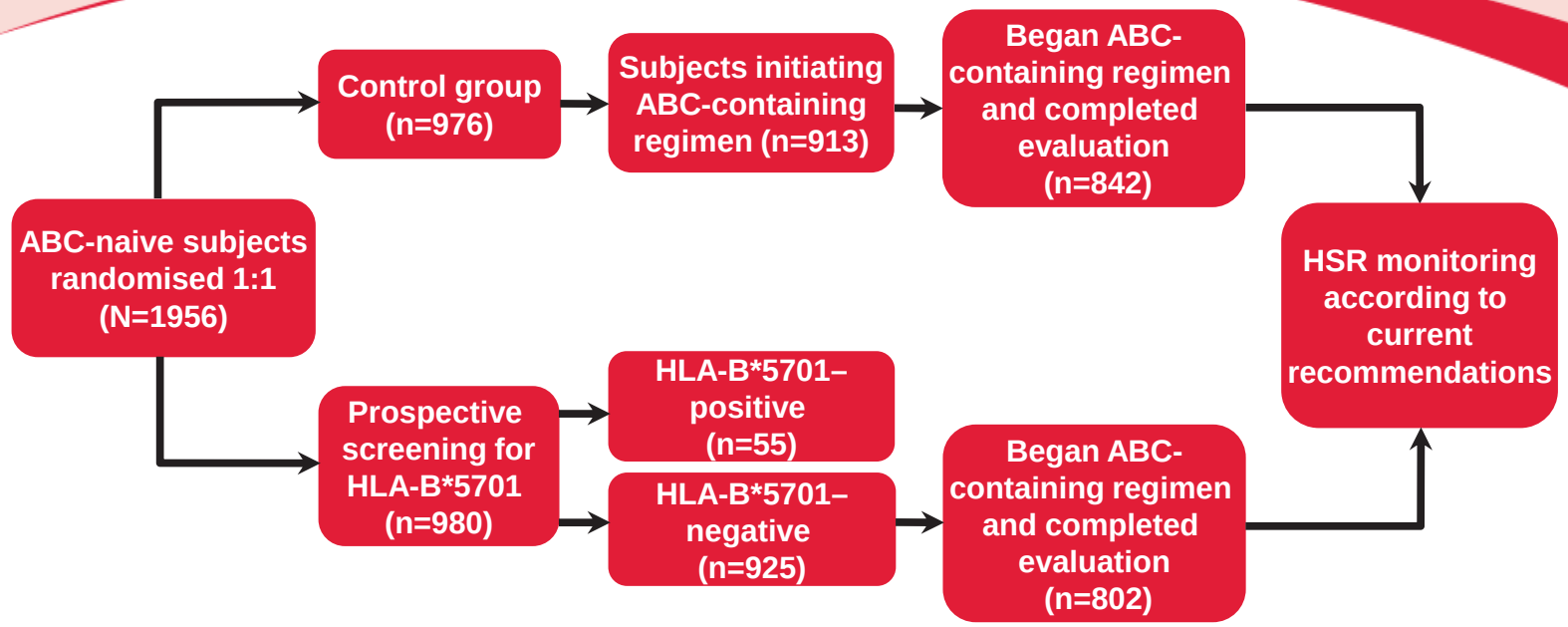
- After the data from Western Australia were observed, some treatment centres introduced HLA-B*5701 screening for abacavir hypersensitivity
- However, there was still a requirement to validate HLA-B*5701 screening in a fully powered, prospective clinical trial
- The role of the HLA-B*5701 allele as a predictive marker for abacavir hypersensitivity was therefore evaluated in the PREDICT-1 study
- In addition, supporting data were provided by a retrospective study (SHAPE) conducted in the United States

PREDICT-1: Study Objectives

- To determine whether prospective screening for HLA-B*5701, before treatment with abacavir, resulted in
  - A significantly lower incidence of clinically suspected abacavir hypersensitivity
  - A significantly lower incidence of immunologically confirmed abacavir hypersensitivity as determined by epicutaneous (skin) patch testing

Mallal et al. *N Engl J Med*. 2008:358;568-579.

PREDICT-1: Study Design



ABC, abacavir; HSR, hypersensitivity reaction.

Mallal et al. *N Engl J Med*. 2008:358;568-579.

PREDICT-1: Demographics

	Prospective Screen[a] ITT (EV1) (n=803)	Control ITT (EV1) (n=847)
Male, n (%)	595 (74)	602 (71)
Female, n (%)	208 (26)	245 (29)
Mean age, y (range)	42 (18-77)	42 (18-76)
Self-reported race, n (%)[b]		
White: White/Caucasian/European heritage	665 (83)	702 (83)
African American/African heritage	96 (12)	96 (11)
White: Arabic/North African heritage	12 (2)	13 (2)
American Indian or Alaskan native	8 (1)	10 (1)
Mixed race	7 (1)	11 (1)
Other[c]	14 (2)	15 (2)
Antiretroviral naive, n (%)	147 (18)	149 (18)
Antiretroviral experienced, n (%)	656 (82)	698 (82)

ITT (EV1), intention-to-treat evaluable population.

[a] HLA-B*5701–negative. [b] One subject in the prospective pharmacogenetics screening arm failed to provide information on race. [c] Other includes all race categories for which there were <1% of subjects in either study arm (ie, South East Asian heritage, East Asian heritage, Central/South Asian heritage, native Hawaiian or other Pacific islander, and white mixed race.

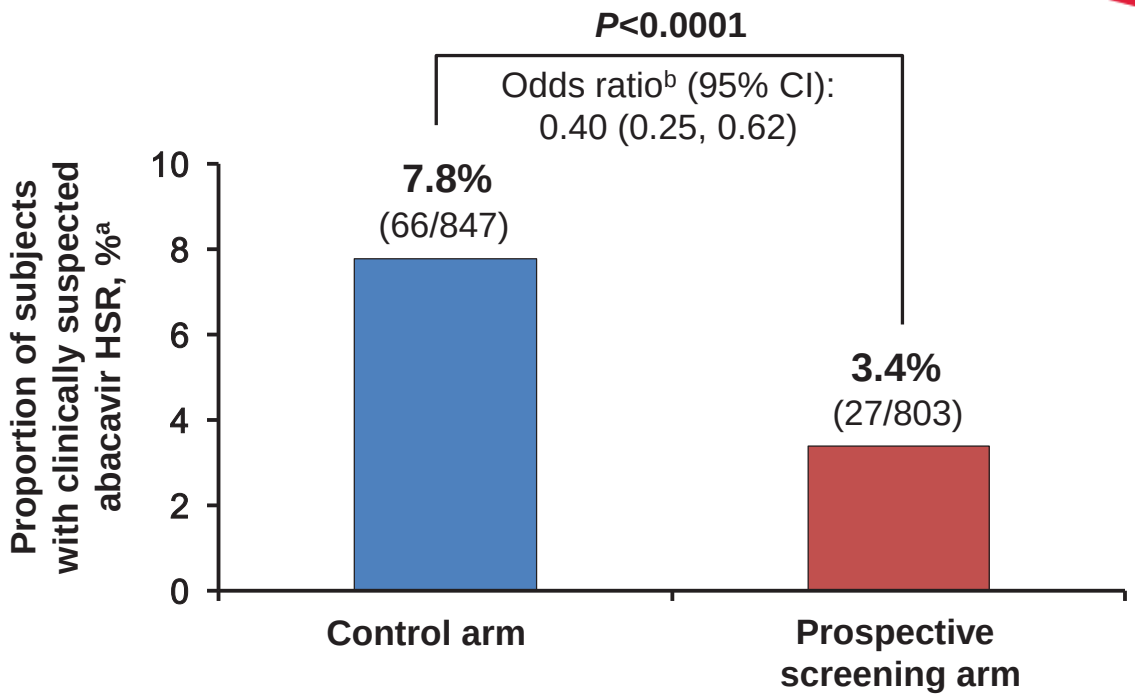
Mallal et al. *N Engl J Med*. 2008:358;568-579.

PREDICT-1: HLA-B*5701 Status by Race

- Incidence of an HLA-B*5701–positive screen in the white population was 106/1650 (6%), whereas incidence in the African American/African heritage group was 1/232 (<1%)
- No other race category was reported by more than 1% of subjects in either the HLA-B*5701–positive or –negative groups, so no conclusions can be drawn

Mallal et al. *N Engl J Med*. 2008:358;568-579.

PREDICT-1: Incidence of Clinically Suspected Abacavir Hypersensitivity

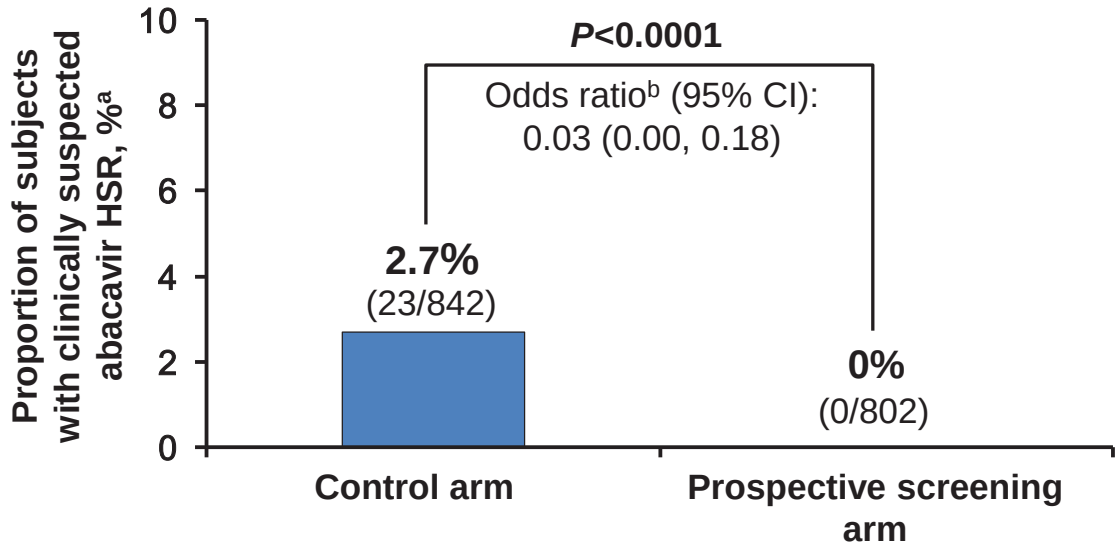


HSR, hypersensitivity reaction.

[a] Intention-to-treat evaluable population. [b] Prospective screen versus control adjusted for actual strata of race, ART status, introduction of NNRTI, and concurrent PI use.

Mallal et al. *N Engl J Med*. 2008:358;568-579.

PREDICT-1: Incidence of Immunologically Confirmed Abacavir Hypersensitivity



HSR, hypersensitivity reaction.

[a] Intention-to-treat evaluable population. [b] Prospective screen versus control adjusted for actual strata of race, ART status, introduction of NNRTI, and concurrent PI use.

Mallal et al. *N Engl J Med*. 2008:358;568-579.

PREDICT-1: Association Between HLA-B*5701 Status and Skin Patch Test Results

- In the control arm of the study, 30 subjects who had a clinically suspected abacavir hypersensitivity reaction were also HLA-B*5701 positive upon subsequent testing
- Of these, 23 had a positive skin patch test, but 6 subjects had a negative skin patch test result (the remaining subject did not receive a skin patch test)

These data emphasise that skin patch testing should not be used as a clinical tool for diagnosis or to justify abacavir rechallenge

Mallal et al. *N Engl J Med*. 2008:358;568-579.

PREDICT-1: Conclusions

- In PREDICT-1, prospective HLA-B*5701 screening and avoidance of abacavir therapy in subjects with a positive test result
  - Dramatically and significantly reduced the incidence of a clinically suspected abacavir hypersensitivity reaction
  - Completely eliminated the incidence of skin patch test–confirmed abacavir hypersensitivity
- HLA-B*5701–positive subjects were likely to have a suspected clinical diagnosis of abacavir hypersensitivity
- HLA-B*5701–negative subjects were unlikely to have a clinical diagnosis of abacavir hypersensitivity

Mallal et al. *N Engl J Med*. 2008:358;568-579.

SHAPE: Study Rationale

- Several studies have suggested that HLA-B*5701 is highly associated with abacavir hypersensitivity in Caucasians
- The low sensitivity of this marker in black subjects may relate to the use of clinical data alone to define abacavir hypersensitivity[1]
- SHAPE was a retrospective case-control study to estimate the sensitivity of HLA-B*5701 in both white and black subjects, using skin patch testing to supplement clinical diagnosis of abacavir hypersensitivity[2]

1. Hughes et al. *Pharmacogenomics*. 2004;5:203-211. **2.** Saag et al. *Clin Infect Dis*. 2008;46:1111-1118.

SHAPE: Inclusion Criteria

- Subjects had retrospectively identified, clinically suspected abacavir hypersensitivity
  - Documented abacavir use and hypersensitivity event
    - Within 6 weeks of treatment initiation
    - Symptoms in ≥2 categories (rash, fever, gastrointestinal, constitutional)
    - Improvement or resolution upon discontinuation of abacavir
  - HLA-B*5701 determination and abacavir skin patch testing
- Controls
  - Retrospectively identified with no evidence of abacavir hypersensitivity after ≥12 weeks of abacavir use
  - Pharmacogenetic blood sample and consent collected as part of a previous study
  - Did not undergo skin patch testing

Saag et al. *Clin Infect Dis*. 2008;46:1111-1118.

SHAPE: Demographics

	Skin patch test–positive hypersensitivity reaction		Clinically suspected hypersensitivity reaction		Controls	
	White (n=42)	Black (n=5)	White (n=130)	Black (n=69)	White (n=202)	Black (n=206)
Mean age, y (range)	44 (23-57)	47 (32-57)	45 (22-73)	45 (22-76)	41 (19-72)	41 (19-73)
Sex, n (%)						
Male	38 (90)	5 (100)	106 (82)	41 (59)	187 (93)	146 (71)
Female	4 (10)	0	24 (18)	28 (41)	15 (7)	60 (29)

Saag et al. *Clin Infect Dis*. 2008;46:1111-1118.

SHAPE: Results

White Subjects

	SPT-positive HSR (n=42)	SPT-negative HSR (n=85)[a]	All HSR (n=130)[a]	Controls (n=202)
HLA-B*5701 positive, n	42	15	57	8
HLA-B*5701 negative, n	0	69	72	194
Sensitivity (95% CI)	1.0 (0.92, 1.00)	—	0.44 (0.35, 0.53)	—
Specificity (95% CI)	—	—	—	0.96 (0.92, 0.98)

Black Subjects

	SPT-positive HSR (n=5)	SPT-negative HSR (n=63)	All HSR (n=69)[b]	Controls (n=206)
HLA-B*5701 positive, n	5	5	10	2
HLA-B*5701 negative, n	0	58	59	204
Sensitivity (95% CI)	1.0 (0.48, 1.00)	—	0.14 (0.07, 0.25)	—
Specificity (95% CI)	—	—	—	0.99 (0.97, 1.00)

- Immunologically confirmed HSR cases (SPT+) odds ratio = 1945 [110, 334352; white]; 900 [38, 21045; black]
- All clinically suspected HSR cases odds ratio = 19 [8, 48; white]; 17 [3, 164; black]

HSR, hypersensitivity reaction; SPT, skin patch test.

[a] One subject did not have HLA-B*5701 result; 3 subjects did not have results for skin patch tests. [b] One subject had unknown skin patch test.

Saag et al. *Clin Infect Dis*. 2008;46:1111-1118.

SHAPE: Conclusions

- In this study, sensitivity of HLA-B*5701 in white and black subjects with skin patch test–confirmed abacavir hypersensitivity was 100%
- Lower sensitivity of HLA-B*5701 screening was observed when abacavir hypersensitivity was defined by clinical diagnosis alone
- Not all HLA-B*5701–positive subjects had a positive skin patch test result
- Data from this retrospective study suggest that prospective HLA-B*5701 screening may reduce abacavir hypersensitivity rates in white and black subjects
- The presence of the HLA-B*5701 allele is associated with increased risk of abacavir hypersensitivity, regardless of race

Saag et al. *Clin Infect Dis*. 2008;46:1111-1118.

Overview of Results From PREDICT-1 and SHAPE Studies

- The presence of the HLA-B*5701 allele is associated with increased risk of abacavir hypersensitivity, regardless of race
- Screening for HLA-B*5701 before starting treatment with abacavir may identify subjects at increased risk of a hypersensitivity reaction
- Avoiding treatment with abacavir in subjects with the HLA-B*5701 allele was shown to significantly reduce the incidence rate of clinically diagnosed cases of hypersensitivity
  - HLA-B*5701–negative subjects are unlikely to experience an abacavir hypersensitivity reaction
  - HLA-B*5701–positive subjects are likely to experience an abacavir hypersensitivity reaction

ARIES: First Large, Open-label Prospective Study Using HLA-B*5701 Screening

- This study of subjects beginning ABC therapy excluded HLA-B*5701–positive individuals from enrollment
- The rate of abacavir hypersensitivity reaction among HLA-B*5701–negative subjects (N=517) was assessed
- At 30 weeks, 4 individuals (0.8%) were diagnosed with clinically suspected abacavir hypersensitivity reaction
  - Skin patch tests for all 4 subjects were negative
  - The absence of HLA-B*5701 and the negative skin patch test results suggest that the symptoms may not have been related to ABC

ABC, abacavir.
Young et al. *AIDS*. 2008;22:1673-1675.

HLA-B*5701: Who Should Be Tested?

- This one-time screening test is recommended for most people with HIV as one of their routine lab tests
- Those who should be tested include
  - People who have not yet started HIV treatment
  - People who have started HIV treatment but who have never taken an abacavir regimen
  - People of unknown HLA-B*5701 status who have stopped an abacavir-containing regimen and did not have a hypersensitivity reaction **and** who are going to restart an abacavir regimen

People who have been diagnosed with an abacavir hypersensitivity reaction should not receive abacavir. HLA-B*5701 testing is not necessary for these people

Recommendations for HLA-B*5701 Screening

- Clinical diagnosis of suspected hypersensitivity to abacavir remains the basis for clinical decision making
- HLA-B*5701 screening for risk of abacavir hypersensitivity should never be substituted for appropriate clinical vigilance and patient management in individuals receiving abacavir
- If abacavir hypersensitivity cannot be ruled out, abacavir should be permanently discontinued, regardless of the results of HLA-B*5701 screening
- Results of pharmacogenetic tests for risk of abacavir hypersensitivity should never be used to support a drug rechallenge decision after a suspected hypersensitivity reaction
- HLA-B*5701 testing must not be used as a diagnostic test after a patient has started treatment with abacavir

Recommendations for HLA-B*5701 Screening (cont)

- In settings where validated screening methods are available, clinicians should consider screening for HLA-B*5701 in any HIV-infected patient who has not previously been exposed to abacavir
  - Only patients found to lack the HLA-B*5701 allele should begin therapy with the drug
- Where screening is not available, it is reasonable to initiate abacavir therapy with appropriate clinical vigilance
- In HLA-B*5701–negative patients, and in situations where HLA-B*5701 screening is not available, clinical vigilance remains vital to detect any abacavir hypersensitivity at the earliest stage

Summary

- The one-time HLA-B*5701 test
  - Helps identify patients who are at higher risk of a serious allergic reaction to abacavir
  - May help patients and physicians be more informed about treatment decisions
  - Personalises HIV treatment
- If unsure of a patient's HLA-B*5701 status, discuss testing
  - This simple blood test can help determine whether an abacavir-containing regimen is appropriate
- HLA-B*5701 screening for risk of ABC HSR should never be substituted for appropriate clinical vigilance and patient management in individuals receiving ABC
  - Clinical diagnosis of suspected ABC HSR remains the basis for clinical decision making

ABC, abacavir; HSR, hypersensitivity reaction.

SKIN PATCH TESTING

Skin Patch Testing Is Not a Substitute for HLA-B*5701 Screening

- Skin patch testing may be a sensitive and specific procedure to supplement the diagnosis of abacavir hypersensitivity in a research setting
- In the PREDICT-1[1] and SHAPE[2] studies, reducing misdiagnosis of hypersensitivity was critical to primary outcomes, and skin patch test results were interpreted by expert dermatologists
- As shown in PREDICT-1 and SHAPE, a negative skin patch test result is not a signal that it is safe to treat a patient with abacavir[1,2]
  - Several subjects (6/847, 0.7%) had a clinical diagnosis of abacavir hypersensitivity, a positive HLA-B*5701 screening result, **but a negative skin patch test result**[1]
  - A negative result from a skin patch test, followed by subsequent rechallenge with abacavir, may result in a severe life-threatening reaction and possible death

These data do not support the use of skin patch testing in routine clinical practice

1. Mallal et al. *N Engl J Med*. 2008:358;568-579. **2.** Saag et al. *Clin Infect Dis*. 2008;46:1111-1118.

Limitations of Skin Patch Testing

- Skin patch testing cannot be used as a screen for patients who have not previously received abacavir
- Regardless of the outcome of a skin patch test, patients must stop treatment with abacavir if hypersensitivity is suspected clinically
- Skin patch test results must **never** be used to support reinitiating abacavir in the routine clinical setting
- Skin patch testing should **never** change a clinical diagnosis of abacavir hypersensitivity

HYPERSENSITIVITY CASE STUDIES

Case Presentation #1

- A 46-year-old woman, newly diagnosed with HIV infection, initiated therapy with abacavir, lamivudine, and efavirenz
  - HLA-B*5701 status unknown
- On day 8 of therapy, her physician noted a mild pruritic rash on her neck and trunk
  - The patient was afebrile, had no gastrointestinal symptoms, and felt well
  - She did not have any muscle or joint aches, respiratory symptoms, or tenderness or swelling of the lymph nodes
  - She had not taken any other medications
- Differential diagnoses include
  - A reaction to efavirenz
  - Abacavir hypersensitivity
  - Immune reconstitution syndrome

Case Presentation #1 (cont)

- Course of action
  - Patient has a single mild symptom, so closely monitor for resolution or progression before making a decision
    - Review symptoms of hypersensitivity
    - Instruct patient to continue all medications and immediately contact physician if other symptoms develop
    - Reevaluate patient after 24 hours
- Follow-up
  - Patient continued all medications
  - Rash improved over the next 4 days with no further symptoms
- Conclusion
  - Patient had a transient efavirenz-related rash (ie, not a hypersensitivity reaction)

Case Presentation #1: Alternative Scenario

- After noticing the rash 3 days before, the patient discontinued all medications; the rash has since resolved
- Course of action
  - Permanently discontinue abacavir: Although the reaction may have been an efavirenz rash, by stopping all drugs it is no longer possible to differentially diagnose an abacavir hypersensitivity reaction without exposing the patient to the risk of rechallenge

Case Presentation #1: Summary

- A single symptom is not sufficient for a diagnosis of hypersensitivity
  - **Drug interruption after a single symptom should be avoided**
    - Resolution of symptom off-drug makes a differential diagnosis impossible
  - However, if abacavir **is** interrupted, **it should not be restarted**
    - Resolution of symptom may represent aborted evolution of a multisymptom hypersensitivity reaction
    - Reinitiation puts the patient at risk for a rechallenge reaction
    - Abacavir should be retrieved from patient to avoid the risk of rechallenge
- Take a careful history, and review for other symptoms
- Continue to monitor the patient
- Avoid corticosteroids in case they mask the development of additional symptoms
- Use antihistamines if necessary for the patient's comfort

Case Presentation #2

- 29-year-old male with a history of HSV and syphilis
- Newly diagnosed with HIV, low CD4 (<200 cells/mm^3), and high viral load
- Negative screening result for HLA-B*5701
- Initiated abacavir, lamivudine, and lopinavir/r
- Concomitant medications
  - Valacyclovir (chronic medication) initiated before antiretroviral therapy
  - Co-trimoxazole initiated with antiretrovirals

HSV, herpes simplex virus.

Case Presentation #2 (cont)

- **Day 8:** Patient noted myalgias and low-grade fever peaking at 37.8°C
- **Day 9:** Patient noted faint rash with low-grade fever peaking at 39°C approximately 9 hours after morning dose
- **Day 10:** Patient experienced same symptoms at the same time after morning dose, but fever peaked at 38°C with fewer myalgias
- **Day 11:** Patient was evaluated in clinic
  - Temperature 37°C
  - Generalised fine urticarial rash
  - Asymptomatic

Case Presentation #2 (cont)

- Course of action
  - Symptoms appear to have been resolving each day despite continued abacavir dosing over several days
  - Symptom resolution and the patient's negative HLA-B*5701 screening status suggest another aetiology
  - Continue abacavir dosing with close monitoring and discontinue co-trimoxazole
- Follow-up
  - Co-trimoxazole is stopped on day 11; subject is seen in the clinic on days 12 and 13, and symptoms continue to decline in severity
  - Patient is given topical steroids and antihistamines for the rash
  - By day 15, rash and myalgias have resolved and patient remains afebrile on abacavir, lamivudine, and lopinavir/r
- Conclusion
  - Co-trimoxazole allergy

Case Presentation #2: Alternative Scenario

- Patient is seen on days 12 and 13; symptoms continue but do not increase or decrease in severity
- Patient is given topical steroids and antihistamines for the rash
- By day 15, rash is resolving but myalgias continue; patient complains of malaise
- Course of action
  - Permanently discontinue abacavir if no other cause of the patient's symptoms is identified; in this case, abacavir hypersensitivity cannot be definitively ruled out

Case Presentation #2: Summary

- Consider other causes for rash and fever when patient is taking concurrent medications known to be associated with these symptoms or with allergies, particularly if screening suggests a low risk of abacavir hypersensitivity
- However, a negative HLA-B*5701 screen does **not** definitively rule out the possibility of a hypersensitivity reaction
  - If a diagnosis of abacavir hypersensitivity cannot be excluded, then abacavir must be permanently discontinued, regardless of the results of any test

Case Presentation #3

- 45-year-old male initiated treatment with abacavir, lamivudine, and boosted fosamprenavir
  - HLA-B*5701 status unknown
- **Day 5:** Onset of vomiting
- **Day 6:** Onset of diarrhoea; nausea worsens with more frequent vomiting
- **Day 7:** Development of fever to 39˚C and general weakness; gastrointestinal symptoms continue without further increase in severity; careful search revealed no rash

Case Presentation #3 (cont)

- Course of action
  - Permanently discontinue abacavir
    - Cumulative, multiorgan symptomatic onset indicates a high probability of a developing abacavir hypersensitivity reaction
- Follow-up
  - Within 24 hours of abacavir discontinuation, patient is afebrile and gastrointestinal symptoms are resolving
- Conclusion
  - Patient experienced abacavir hypersensitivity

Case Presentation #3: Summary

- Rash is very common in abacavir hypersensitivity; however, just as rash alone would not be sufficient for a diagnosis of a hypersensitivity reaction, neither is the absence of rash a reason to exclude a diagnosis of hypersensitivity in the presence of other consistent symptoms; rash may occur late or even after discontinuation of abacavir
- Other features point towards the diagnosis of a hypersensitivity syndrome
- Patient developed multiorgan involvement, including constitutional and gastrointestinal symptoms
  - Even in the absence of a rash, patient's symptoms point to a possible diagnosis of abacavir hypersensitivity
- Symptoms did not all appear at once but in a stepwise manner