ABACAVIR HYPERSENSITIVITY REACTION

Abacavir is a component of **Ziagen®, Trizivir®, Kivexa®** and **Triumeq®**

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ViiV Healthcare

Slide Contents

Aim

- The purpose of this slide deck is to provide an educational resource regarding Abacavir Hypersensitivity Reaction (ABC HSR) and support efforts to:
  - Maintain low morbidity and mortality from ABC HSR in general, and to minimise the risk of ABC rechallenge in patients with clinically suspected HSR, regardless of HLA-B*5701 status.
  - Increase understanding and awareness of ABC HSR by Healthcare professionals (HCPs) and expand on the information already included in the product labels.
  - Increase awareness of ABC HSR by patients via the ABC HSR Alert/Warning card and product labelling.

Key Points for Managing Abacavir Hypersensitivity Reaction (HSR)

- Abacavir is associated with a risk for hypersensitivity reactions (HSR) characterised by fever and/or rash with other symptoms indicating multi-organ involvement.
  - Symptoms usually appear within the first 6 weeks although the reaction may occur at any time during therapy.
- Risk of abacavir HSR is higher for patients who test positive for the HLA-B*5701 allele. As such, testing for HLA-B*5701 status should be considered before initiating abacavir treatment. Testing for HLA-B*5701 status is mandated in some markets therefore local requirements and product labelling should be followed.
- However, abacavir HSRs have been reported even in patients who do not carry this allele. The frequency of ABC HSR in these patients is much lower compared with patients who are HLA-B*5701 positive.
- Abacavir **should never be** initiated in patients with a positive HLA-B*5701 status, nor in patients with a negative HLA-B*5701 status who had a suspected abacavir HSR on a previous abacavir-containing regimen.

Key Points for Managing Abacavir Hypersensitivity Reaction (HSR)- continued

- Abacavir must be stopped without delay, even in the absence of the HLA-B*5701 allele, if an HSR is suspected. Delay in stopping treatment with abacavir after the onset of hypersensitivity may result in an immediate and life-threatening reaction.

- After stopping abacavir for a suspected HSR, any product containing abacavir must **never** be re-initiated.

- Restarting abacavir following a suspected HSR can result in a return of symptoms within hours which can be more severe than on initial presentation and may include life-threatening hypotension and death.

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

DIAGNOSIS OF ABACAVIR HYPERSENSITIVITY

Abacavir Hypersensitivity Reaction

- Idiosyncratic reaction
- Approximate reporting rate in clinical trials
  - 1% in trials that excluded participants testing positive for the HLA-B*5701 allele[1]
  - 5% in trials where HLA-B*5701 screening was not performed[2]
  - See slides 16 -18 for further details
- Clinically well characterised[3]
  - Most HSR includes fever and/or rash
  - Other symptoms include respiratory, gastrointestinal and constitutional symptoms such as lethargy and malaise.
  - Multiple symptoms are typical in most cases of hypersensitivity

1. Calculated from published data for four Marketing Authorisation Holder clinical trials: Post F et al. JAIDS. 2010;55 (1):9-57, Young B et al. AIDS. 2008;22(13):1673-1675, Wohl DA et al. *PLoS One*. 2014;9(5):e96187, Walmsley SL et al. *N Engl J Med.* 2013; 369(19):1807-18
2. Cutrell et al. *Ann Pharmacother.* 2004;38:2171-217
3. Hernandez et al. Abstract presented at: 15th International AIDS Conference; July 11-16, 2004; Bangkok, Thailand.

Note: Symptomatology was evaluated from clinical trials where HLA B*5701 screening was not performed

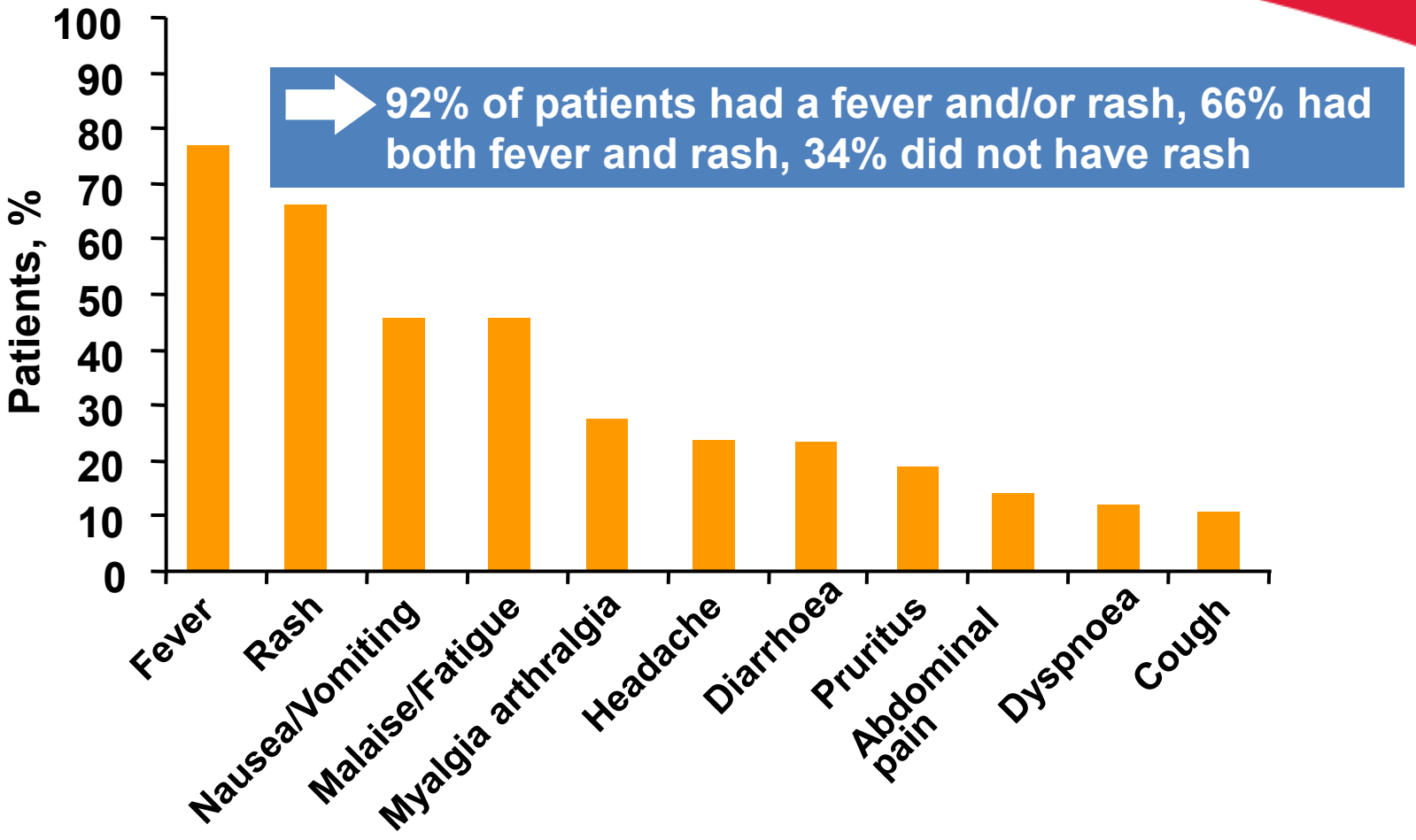
Abacavir Hypersensitivity Reaction - *Continued*

- Symptoms usually appear within the first 6 weeks of starting abacavir[1]
  - Median time to onset of 11 days
  - However, reactions can occur at any time during therapy
- Diagnosis is complicated by
  - Variable presentation with nonspecific symptoms
  - Concomitant use of other medications including antiretroviral medications, with overlapping adverse event profiles
- Symptoms improve on cessation of abacavir

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

Note: Data for time to onset was evaluated from clinical trials where HLA B*5701 screening was not performed

Hypersensitivity Symptoms Reported With a Frequency ≥10%



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

Note: Symptomatology was evaluated from clinical trials where HLA B*5701 screening was not performed

Additional Physical and Laboratory Findings

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

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

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

Hypersensitivity Reaction Alert Card – GDS/EU SmPC

(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 abdominal pain
   - Extreme tiredness or achiness or generally ill feeling

Hypersensitivity Reaction Warning Card – FDA

(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

PHARMACOGENETIC TESTING

Pharmacogenetic Risk Factor for Abacavir HSR

- HLA-B*5701 allele is more common among patients who have a suspected HSR to abacavir compared with those who do not.
- No other pharmacogenetic markers have been found that identify patients at risk of abacavir HSR.
- Prospective pharmacogenetic screening for HLA-B*5701 can be used to identify patients at high risk for abacavir HSR.
- HLA-B*5701 is not always present in people who have a suspected abacavir HSR
  - Therefore, clinical diagnosis of suspected HSR to abacavir remains the basis for clinical decision making
  - HLA-B*5701 screening for risk of abacavir HSR should never be substituted for appropriate clinical vigilance and patient management in individuals receiving abacavir

Recommendations for HLA-B*5701 Screening

- **Testing for HLA-B*5701 status should be considered before initiating abacavir treatment.** Testing for HLA-B*5701 status is mandated in some markets therefore local requirements and product labelling should be followed.
- Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir.
- HLA-B*5701 status must always be documented and explained to the patient prior to initiating therapy.
- Results of pharmacogenetic tests for risk of abacavir HSR should never be used to support a drug rechallenge decision after a suspected HSR
- HLA-B*5701 testing must not be used as a diagnostic test after a patient has started treatment with abacavir

Supporting study data for HLA-B*5701 screening

PREDICT-1 (CNA106030): pivotal, double blinded, randomised clinical trial to establish the effectiveness of the HLA-B*5701 allele as a predictive marker for abacavir (ABC) hypersensitivity reaction (HSR)[1]

- 1,956 ABC naive participants randomised 1:1 in a double blinded fashion to:
  - Arm A) Retrospective HLA-B*5701 testing after starting ABC therapy (Controls)
  - Arm B) Prospective HLA-B*5701 screening; positive patients excluded pre- ABC therapy
- Retrospective epicutaneous patch testing (EPT) in all cases of clinically suspected ABC HSR

ABC HSR[2]	Arm A	Arm B	p value	OR (95% CI)[3]
Clinically Suspected	7.8% (66/847)	3.4% (27/803)	<0.001	0.40 (0.25–0.62)
Immunologically (EPT) Confirmed	2.7% (23/842)	0.0% (0/802)	<0.001	0.03 (0.00–0.18)

- Estimated that 48% - 61% of patients with HLA-B*5701 will develop HSR on ABC-containing therapy vs. 0% to 4% of patients who do not have the allele

1. Mallal et al. N Engl J Med. 2008:358;568-579. 2. Intention-to-treat evaluable population. 3. Odds ratio (OR); Confidence interval (CI); Prospective screen versus control adjusted for actual strata of race, ART status, introduction of NNRTI, and concurrent PI use.

Supporting study data for HLA-B*5701 screening

SHAPE (ABC107442): a retrospective case-control study to estimate the sensitivity and specificity of the HLA-B*5701 allele in self-reported White and Black participants with and without suspected ABC HSR, using EPT to supplement clinical diagnosis of abacavir hypersensitivity[1]

- Conclusions
  - 100% sensitivity of HLA-B*5701 in white and black participants with EPT– confirmed ABC HSR
  - Lower sensitivity of HLA-B*5701 screening observed when ABC HSR was defined by clinical diagnosis alone
  - Not all HLA-B*5701–positive participants had a positive EPT test result
  - Prospective HLA-B*5701 screening may reduce ABC HSR rates in white and black participants
  - The presence of the HLA-B*5701 allele is associated with increased risk of ABC HSR, regardless of race

Data from PREDICT-1 and SHAPE do not support the use of skin patch testing in routine clinical practice

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

Supporting study data for HLA-B*5701 screening

- A limitation from PREDICT-1: Investigators were blinded to participants HLA-B*5701 status during the study, which would not be the case in clinical practice
- Recent marketing authorisation holder (MAH) trials, which prospectively screened for the HLA-B*5701 allele and excluded participants testing positive, more accurately reflect experience and reporting rates in clinical practice

MAH Sponsored Clinical Trials with prospective HLA-B*5701 screening	ABC- containing treatment group	HSR Reporting Rate % (n/N)
ASSERT (CNA109586)[1]	ABC/3TC + EFV	3.1 (6/192)
ARIES (EPZ108859)[2]	ABC/3TC + ATV+ RTV	1 (4/517)
ASSURE (EPZ113734)[3]	ABC/3TC + ATV	<1 (1/199)
SINGLE (ING114467)[4]	ABC/3TC + DTG	<1 (1/414)
Total		1 (12/1322)

ABC/3TC = KIVEXA; ATV = atazanvir; DTG = dolutegravir; EFV = efavirenz; RTV = ritonavir.

1. Post F et al. JAIDS. 2010;55 (1):9-57 2. Young B et al. AIDS. 2008;22(13):1673-1675. 3. Wohl DA et al. *PLoS One*. 2014;9(5):e96187
4. Walmsley SL et al. *N Engl J Med.* 2013; 369(19):1807-18

MANAGEMENT OF ABACAVIR HYPERSENSITIVITY REACTION

Counseling the Patient

- Patients must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life-threatening reaction or death, and that the risk of a hypersensitivity reaction is increased if they are HLA-B*5701 positive.

- Each patient should be reminded to read the Package Leaflet included in the abacavir pack. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.

- In order to avoid restarting abacavir, patients who have experienced a hypersensitivity reaction should be asked to return the remaining abacavir tablets or oral solution to the pharmacy.

Clinical Management of Abacavir Hypersensitivity

- Regardless of HLA-B*5701 status, patients who are diagnosed with a hypersensitivity reaction MUST discontinue abacavir immediately.
  - Abacavir must be permanently discontinued if hypersensitivity cannot be ruled out.
- Delay in stopping treatment with abacavir after the onset of hypersensitivity may result in an immediate and life-threatening reaction.
- Regardless of HLA-B*5701 status, abacavir or any medicinal product containing abacavir, MUST NEVER be restarted in patients who have stopped therapy due to a hypersensitivity reaction.
- Following discontinuation of abacavir, the symptoms of the reaction should be treated according to local standard of care

Clinical Management of Abacavir HSR – Restarting Abacavir

- Abacavir or any medicinal product containing abacavir, MUST NEVER be restarted in patients who have stopped therapy due to HSR.
  - Restarting abacavir following HSR results in a prompt return of symptoms within hours and this recurrence is usually more severe than on initial presentation, and may include life-threatening hypotension and death.
- If abacavir therapy is stopped for reasons other than suspected HSR
  - Screening for carriage of the HLA-B*5701 allele is recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. **Re-initiation of abacavir in such patients who test positive for the HLA-B*5701 allele is contraindicated.**
  - Rarely, patients who have stopped abacavir for reasons other than symptoms of HSR have also experienced life-threatening reactions within hours of re- initiating abacavir therapy. Restarting abacavir in such patients must be done in a setting where medical assistance is readily available.

Further resources and adverse event reporting

- Before prescribing abacavir-containing medicines (Ziagen, Kivexa, Trizivir or Triumeq), please refer to local respective product labelling

- If you are in the UK, adverse events can be reported directly via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow card in the Google Play or Apple App store

- If you are outside the UK, you can report adverse events to GSK/ViiV by selecting your region and market, here.

Summary

- In the majority of abacavir HSR cases, patients experience fever and/or rash, with other symptoms indicating multi-organ involvement.
- Risk of abacavir HSR is higher for HLA-B*5701 positive patients and abacavir should never be initiated in these patients.
- Abacavir HSRs have been reported in HLA-B*5701 negative patients. Therefore, clinical diagnosis of suspected HSR to abacavir remains the basis for clinical decision making.
- Abacavir should never be initiated in patients who had a suspected abacavir HSR on a previous abacavir-containing regimen.
- Regardless of HLA-B*5701 status, patients who are diagnosed with a HSR must discontinue abacavir immediately.
- Rechallenge can result in a more rapid and severe reaction, which can be fatal.
- Patients must be made aware of the possibility of Abacavir HSRs, reminded to read the Package Leaflet and reminded of the importance the Alert Card.

MODEL CASE STUDIES ON HYPERSENSITIVITY

Note: The model case studies are fictional examples.

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
    - Re-evaluate 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 (i.e. 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 as they may mask the development of additional symptoms
- Antihistamines may be used, 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
  - Hypersensitivity to Co-trimoxazole

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 darunavir
  - 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

Case Presentation #4

- A 40-year-old woman, initiated abacavir, lamivudine, dolutegravir,. The therapy was started before the HLA-B*5701 result was received.
- Within a few days of starting therapy, the patient experienced dyspnoea, vomiting and rash.
- The patient was identified as being HLA-B*5701 positive in medical records (2010 HLA-B*5701 assay result) but it had remained unnoticed by the physician when prescribing the therapy.
- Treatment with abacavir, lamivudine, dolutegravir was discontinued and the events resolved.
- Previously administered products included abacavir, lamivudine which had been discontinued due to suspected HSR.

Conclusion: Patient experienced abacavir hypersensitivity

Case Presentation #4 Summary

- The abacavir containing product should not have been started prior to receiving the test result. In this example a previous test result was not noticed either, which would have alerted the prescriber to the previous HLA-B*5701 positive status.

- Abacavir should never be initiated in patients with a positive HLA-B*5701 status.

- After stopping abacavir for a suspected HSR, any product containing abacavir must never be re-initiated.

- Restarting abacavir following a suspected HSR can result in a return of symptoms within hours which is more severe than on initial presentation and may include life-threatening hypotension and death.

Case Presentation #5

- A 50 year old male who was HLA-B*5701 negative, initiated abacavir, lamivudine and efavirenz.
- Less than a day after starting abacavir, lamivudine, the patient experienced hypotension, rash and vomiting.
- The treating physician considered that the rash on initial exposure could be due to co-suspect product efavirenz. All medications (efavirenz, abacavir, lamivudine) were interrupted.
- The patient was rechallenged with abacavir, lamivudine and within hours experienced vomiting and severe hypotension, which was considered life threatening and resulted in hospitalisation.
- Treatment with abacavir, lamivudine was permanently discontinued and the patient recovered.

Conclusion: The patient experienced abacavir hypersensitivity

Case Presentation #5 Summary

- HLA-B*5701 is not always present in people who have a suspected abacavir HSR. Clinical diagnosis of suspected HSR to abacavir remains the basis for clinical decision making.

- HLA-B*5701 testing should never be a substituted for clinical vigilance/ judgement and patient management.

- Restarting abacavir following a suspected HSR, even in the absence of the HLA-B*5701 allele, can result in a return of symptoms within hours which is more severe than on initial presentation and may include life-threatening hypotension and death.