

ABACAVIR HYPERSENSITIVITY REACTION

Key Risk Minimisation Points:

Abacavir Hypersensitivity Reaction (HSR)

- Abacavir is associated with a risk for hypersensitivity reactions (HSR) characterised by fever and/or rash with other symptoms indicating multiorgan 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 HLAB* 5701 allele. However, abacavir HSRs have been reported at a lower frequency in patients who do not carry this allele.
- 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.
- Abacavir must be stopped without delay, even in the absence of the HLAB*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 is more severe than on initial presentation and may include life-threatening hypotension and death.

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

Diagnosis of Abacavir Hypersensitivity

- Symptoms usually appear within the first 6 weeks of starting abacavir
 - 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 antiretroviral medications with overlapping adverse event profiles
- Symptoms improve on cessation of abacavir

Hypersensitivity Symptoms Reported with a Frequency ≥ 10

Fever	Rash	Nausea/ Vomiting	
Malaise/ fatigue	Myalgia/ arthralgia	Headache	Diarrhoea
Pruritus	Abdominal pain	Dyspnoea	Cough

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

<i>Physical findings</i>	<i>Possible laboratory abnormalities</i>
Lymphadenopathy	Haematological: lymphopaenia 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 creatinine phosphokinase

Pharmacogenetic Testing

- 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

- Before initiating treatment with abacavir, screening for HLA-B*5701 should be performed.
- 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

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 product 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.

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 which 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.
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Further resources

- Before prescribing abacavir-containing medicines, please refer to the respective Summary of Product Characteristics.
- Healthcare providers are asked to report any suspected adverse reactions. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.

Case Studies On Hypersensitivity

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

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 Studies On Hypersensitivity

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

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 necessary for the patient's comfort**

Case Studies On Hypersensitivity

Case Presentation #2

29-year-old male with a history of HSV and syphilis

Newly diagnosed with HIV, low CD4 (<200 cells/mm³), 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

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

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 Studies On Hypersensitivity

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

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 Studies On Hypersensitivity

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
- 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

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