

Abacavir/Lamivudine STADA 600 mg/300 mg kalvopäällysteiset tabletit

(abakaviiri/lamivudiini)

Tämä dokumentti on lyhyt tiivistelmä abakaviirin riskinhallintasuunnitelmaan sisällytetystä abakaviirin (ABC) aiheuttamaa yliherkkyysoireita koskevasta koulutusmateriaalista. Koko koulutusmateriaali englanninkielisenä on liitetty tähän yhteenvedon.

Koulutusmateriaalin keskeiset elementit, joiden tarkoitus on lisätä ymmärrystä ja tietoisuutta ABC-yliherkkyysoireista sekä käsitellä laajemmin tietoja, jotka sisältyvät EU:n alueella hyväksytyyn valmisteyhteenvedon:

1. **Merkittävimmät abakaviiriyliherkkyysoireet** ovat kuume (~ 80 %), ihottuma (~ 70 %), ruoansulatuskanavan oireet (> 50 %) kuten pahoinvointi, vatsakipu, oksentelu ja ripuli, yleinen huonovointisuus, väsymys ja päänsärky (~ 50 %) ja muut oireet (~ 30 %), kuten hengitystie-, limakalvo- ja lihas/luusto-oireet.

Yllä mainitun perusteella potilaita on neuvottava ottamaan välittömästi yhteyttä lääkäriin, joka päättää, onko heidän lopetettava abakaviirin ottaminen:

- jos heillä on ihottumaa TAI
- jos heille kehittyy 1 tai useampi oire vähintään kahdesta seuraavista ryhmistä:
 - kuume
 - hengenahdistus, kurkkukipu tai yskä
 - pahoinvointi tai oksentelu tai ripuli tai vatsakipu
 - äärimmäinen väsymys tai kipuilu tai yleinen huonovointisuus.

2. Abakaviirin aiheuttaman yliherkkyysoireiden riskitekijät

HLA-B*5701 on ainoa tunnistettu farmakogeeninen markkeri, joka johdonmukaisesti liittyy ABC-yliherkkyysoireiden kliiniseen diagnoosiin. On kuitenkin potilaita, joilla epäillään ABC-yliherkkyysoireita, vaikka heillä ei välttämättä ole HLA-B*5701-alleelia.

3. Suositukset HLA-B*5701-alleelin testaamiseksi

Ennen abakaviirihoitoa aloittamista kliinikon tulee seuloa HLA-B*5701 (paikoissa, joissa validoituja testausmenetelmiä on saatavilla). Kliinisen päätöksenteon tulee perustua epäiltyä abakaviiriyliherkkyyttä koskevaan kliiniseen diagnoosiin. HLA-B*5701-testaus abakaviiriyliherkkyyden toteamiseksi ei voi koskaan korvata asianmukaista kliinistä valppautta ja potilaan hoitoa niiden henkilöiden kohdalla, jotka saavat abakaviiria. Jos ABC-yliherkkyyttä ei voida sulkea pois kliinisin perustein, abakaviirin käyttö on keskeytettävä pysyvästi eikä sitä saa aloittaa uudelleen huolimatta HLA-B*5701-testin tuloksesta. Seulontaa suositellaan myös ennen abakaviirihoitoa uudelleen aloittamista potilaille, joiden HLA-B*5701-status on tuntematon ja jotka ovat aiemmin sietäneet abakaviiria.

4. Tietoa HLA-B*5701-testauksesta

HLA-B*5701-kertatestillä tunnistetaan ihmiset, joilla on suuri vakavan allergisen reaktion riski. HLA-B*5701:n seulonnan parhaat mahdolliset arviointimenetelmät ovat genotyypitys sekvenssien perusteella ja spesifisten oligonukleotidikoettimien sekvensointi polymeraasiketjureaktiomenetelmällä. Kerätyistä veri- tai sylkinäytteistä tutkitaan HLA-B*5701-alleelia koodaavat geenisekvenssit. PREDICT-1- ja SHAPE-tutkimusten tulokset osoittavat, että

HLA-B*5701-alleelin läsnäoloon liittyy abakaviiriyliherkkyyden suurentunut riski rodusta riippumatta. HLA-B*5701:n seulonnalla ennen abakaviirihoidon aloitusta voidaan tunnistaa henkilöt, joilla on suurentunut yliherkkyyden riski. Kun HLA-B*5701-alleelia kantavia potilaita ei hoidettu abakaviirilla, kliinisesti todettujen yliherkkyydystapausten osoitettiin vähenevän merkittävästi. Näistä tutkimuksista saadut tulokset eivät tue laastaritestin käyttöä tavanomaisessa käytännön hoitotyössä. Abakaviirihoito voidaan aloittaa ainoastaan potilaille, joilla ei ole HLA-B*5701-alleelia.

5. Abakaviiriyliherkkyyden hoito

Oireet voivat ilmaantua milloin tahansa abakaviirihoidon aikana, mutta tavallisesti ne ilmenevät 6 ensimmäisen hoitoviikon aikana. Oireet ovat aluksi lieviä ja kehittyvät muutamien päivien kuluessa vaikeammiksi abakaviirihoidon jatkuessa. Oireet lieviytyvät, kun abakaviirihoito keskeytetään. Uudelleenaltistaminen voi aiheuttaa nopeamman ja vaikeamman reaktion, joka voi olla hengenvaarallinen, minkä vuoksi uudelleenaltistaminen on vasta-aiheinen.

6. Yliherkkyydystapausselostukset

Koulutusmateriaali sisältää kolme tapauselostusta, joissa havainnollistetaan erilaisia kliinisiä skenaarioita ja niiden hoitoa.

Epäillyistä haittavaikutuksista ilmoittaminen

On tärkeää ilmoittaa myyntiluvan myöntämisen jälkeisistä lääkevalmisteen epäillyistä haittavaikutuksista. Se mahdollistaa lääkevalmisteen hyöty-haittasapainon jatkuvan arvioinnin. Terveystieteiden ammattilaisia pyydetään ilmoittamaan kaikista epäillyistä haittavaikutuksista seuraaville tahoille:

STADA Nordic ApS, Suomen sivuliike PL 1310 00101 Helsinki stada@stada.fi	www-sivusto: www.fimea.fi Lääkealan turvallisuus- ja kehittämiskeskus Fimea Lääkkeiden haittavaikutusrekisteri PL 55 00034 FIMEA
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Educational material for Healthcare Professionals

ABACAVIR HYPERSENSITIVITY REACTION

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AIM OF ABACAVIR HYPERSENSITIVITY REACTION PROGRAMME

The Abacavir Hypersensitivity Reaction (ABC HSR) educational programme is a global risk minimisation measure that has the following aims:

- Maintaining 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.

KEY RISK MINIMISATION POINTS: Abacavir Hypersensitivity Reaction (HSR)

- Abacavir is associated with a risk for hypersensitivity reactions (HSR) characterized by fever and/or rash with other symptoms indicating multiorgan involvement.
 - o 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.

**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
 - o 1% in trials that excluded subjects testing positive for the HLA-B*5701 allele¹
 - o 5% in trials where HLA B*5701 screening was not performed²
- Clinically well characterised³
 - o Most HSR include fever and/or rash
 - o Other symptoms include respiratory, gastrointestinal and constitutional symptoms such as lethargy and malaise.
 - o Multiple symptoms are typical in most cases of hypersensitivity.
- Symptoms usually appear within first 6 weeks of starting abacavir⁴
 - o Median time to onset of 11 days
 - o However, reactions can occur at any time during therapy
- Diagnosis is complicated by
 - o Variable presentation with nonspecific symptoms
 - o Concomitant use of other antiretroviral medications with overlapping adverse event profiles
- Symptoms improve on cessation of abacavir

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

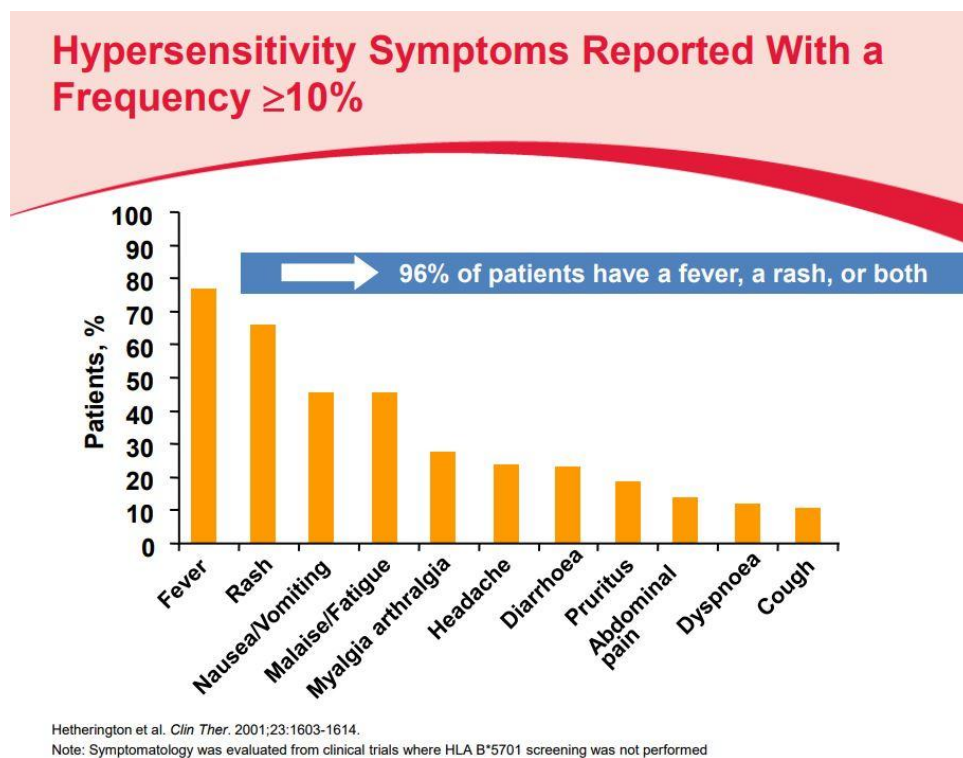
2. Cutrell et al. *Ann Pharmacother*. 2004;38:2171-217

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.

4. 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



ADDITIONAL PHYSICAL AND LABORATORY FINDINGS

Physical findings	Possible laboratory abnormalities
Lymphadenopathy	Haematological: lymphopaenia and thrombocytopenia
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

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

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

HYPERSENSITIVITY REACTION WARNING 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

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
 - o Therefore, clinical diagnosis of suspected HSR to abacavir remains the basis for clinical decision making.
 - o 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.

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 subjects randomised 1:1 in a double blinded fashion to:
 - o Arm A) Retrospective HLA B*5701 testing after starting ABC therapy (Controls)
 - o 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)	<0.0001	0.40 (0.25–0.62)
Immunologically (EPT) Confirmed	2.7% (23/842)	0.0% (0/802)	<0.0001	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.

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 subjects with and without suspected ABC HSR, using EPT to supplement clinical diagnosis of abacavir hypersensitivity¹

Conclusions

- 100% sensitivity of HLA-B*5701 in white and black subjects 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 subjects had a positive EPT test result
- Prospective HLA-B*5701 screening may reduce ABC HSR rates in white and black subjects
- The presence of the HLA-B*5701 allele is associated with increased risk of ABC HSR, regardless of race

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

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

A limitation from PREDICT-1: Investigators were blinded to subject's 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 subjects 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 (4/491)
ASSURE (EPZ113734) ³	ABC/3TC + ATV	<1 (1/199)
SINGLE (ING114467) ⁴	ABC/3TC + DTG	<1 (1/414)
Total		1 (12/1320)

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.
 - o 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.
 - o 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
 - o 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.**
 - o 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

- Before prescribing abacavir-containing medicines, please refer to the local country label.
- Reporting of suspected adverse reactions
 - o Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to:

STADA Nordic ApS, Finland P.O.Box 1310 FI-00101 Helsinki, FINLAND stada@stada.fi	webpage: www.fimea.fi Finnish Medicines Agency (FIMEA) Adverse Reaction Register P.O.Box 55 FI-00034 FIMEA, FINLAND
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MODEL CASE STUDIES ON HYPERSENSITIVITY

CASE PRESENTATION #1

- A 46-year-old woman, newly diagnosed with HIV infection, initiated therapy with abacavir, lamivudine, and efavirenz
 - o HLA-B*5701 status unknown
- On day 8 of therapy, her physician noted a mild pruritic rash on her neck and trunk
 - o The patient was afebrile, had no gastrointestinal symptoms, and felt well
 - o She did not have any muscle or joint aches, respiratory symptoms, or tenderness or swelling of the lymph nodes
 - o She had not taken any other medications
- Differential diagnoses include
 - o A reaction to efavirenz
 - o Abacavir hypersensitivity
 - o Immune reconstitution syndrome
- Course of action
- Patient has a single mild symptom, so closely monitor for resolution or progression before making a decision
 - o Review symptoms of hypersensitivity
 - o Instruct patient to continue all medications and immediately contact physician if other symptoms develop
 - o Re-evaluate patient after 24 hours
- Follow-up
 - o Patient continued all medications
 - o Rash improved over the next 4 days with no further symptoms
- Conclusion
 - o 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
 - o 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
 - o **Drug interruption after a single symptom should be avoided**
 - Resolution of symptom off-drug makes a differential diagnosis impossible
 - o 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/mm³), and high viral load
- Negative screening result for HLA-B*5701
- Initiated abacavir, lamivudine, and lopinavir/r
- Concomitant medications
 - o Valacyclovir (chronic medication) initiated before antiretroviral therapy
 - o 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
 - o Temperature 37°C
 - o Generalised fine urticarial rash
 - o Asymptomatic
- Course of action
 - o Symptoms appear to have been resolving each day despite continued abacavir dosing over several days
 - o Symptom resolution and the patient's negative HLA-B*5701 screening status suggest another aetiology
 - o Continue abacavir dosing with close monitoring and discontinue co-trimoxazole
- Follow-up
 - o 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
 - o Patient is given topical steroids and antihistamines for the rash
 - o By day 15, rash and myalgias have resolved and patient remains afebrile on abacavir, lamivudine, and lopinavir/r
- Conclusion
 - o 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
 - o 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
 - o 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
 - o 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
 - o Permanently discontinue abacavir
 - Cumulative, multiorgan symptomatic onset indicates a high probability of a developing abacavir hypersensitivity reaction
- Follow-up
 - o Within 24 hours of abacavir discontinuation, patient is afebrile and gastrointestinal symptoms are resolving
- Conclusion
 - o 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
 - o 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

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