ABACAVIR: ITS USE AND HYPERSENSITIVITY

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Abacavir, a nucleoside reverse transcriptase inhibitor, is useful in first- and second-line HIV therapy and as a substitute for stavudine and zidovudine when toxicity is a problem. Although it is safe and well tolerated, a life-threatening hypersensitivity reaction can occur. The risk for developing this reaction relates to the presence of specific genotypes, especially HLA-B*5701.

Abacavir (ABC), a nucleoside reverse transcriptase inhibitor (NRTI), combined with lamivudine (3TC), has a better short- and long-term outcome than 3TC combined with zidovudine (ZDV) as first-line HIV therapy.[1,2] In addition, children failing ABC/3TC-based first-line therapy do not select thymidine NRTI-related mutations, allowing for better choice in second-line therapy.[2] With current first-line options, both first-line (stavudine (d4T)) and second-line therapy (ZDV) include a thymidine-based NRTI, thus compromising second-line regimens.[3-5] In well-selected children, ABC is also an important drug in second-line and salvage therapy.[6]

Of all the NRTIs, ABC is associated with the lowest rate of mitochondrial dysfunction. Types of dysfunction include lactic acidosis, peripheral neuropathy and lipo-atrophy. Substitution of d4T for ABC improves mitochondrial indices and reduces adipocyte apoptosis.[7] In adults, switching from d4T to ABC was superior to switching from d4T to ZDV.[8] In older children, once-daily use of ABC has also been shown to be effective, thereby facilitating adherence and improving patient satisfaction, particularly when all drugs are given once daily.[9,10]

Despite these advantages, ABC is rarely used as part of first-line therapy in South Africa owing to cost. Tenofovir, commonly used in adults experiencing NRTI adverse events, is not licensed for children. With large cohorts of children now on antiretroviral therapy for long periods of time, increased use of ABC is likely as NRTI adverse events become apparent. Currently, the National Department of Health permits using ABC when there have been adverse events related to other NRTIs.

Of concern is the severe and life-threatening hypersensitivity reaction (HSR) that occasionally occurs, necessitating permanent discontinuation of ABC.

EPIDEMIOLOGY AND ESTIMATION OF RISK FOR HSR

ABC HSR has been reported in adults and children. The prevalence in clinical trials varies.[11] In a European trial of first-line therapy, where 92 children were initiated on ABC, 4 (4.3%) terminated ABC for adverse reactions, 1 case (1%) being considered an HSR. There is clear heterogeneity in risk according to ethnic groups, with Caucasians at higher risk and a 40% reduction in risk for African Americans. In the ARROW study of >1 200 HIV-infected children in Uganda and Zimbabwe, HSR was reported in 0.2% of the children.[12]

Other factors that may be protective are male sex and more advanced disease. However, this assessment was performed before identification of the genetic link to HSR.[13]

HLA-B*5701 AND HSR

An association with ABC HSR was described with HLA-B*5701, HLA-DR7 and HLA-DQ3. If all three markers are present, the positive predictive value for HSR is 100% with a negative predictive value of 97%. HLA-B*5701 alone is highly predictive.[14]

It is clear that the varied distribution of the HLA-B*5701 genotype is responsible for variability of the risk of ABC HSR between races and studies.[15] Studies from the USA indicated that this mutation is more prevalent among white and Hispanic persons than African Americans.[16] In Korea the HLA-B*5701 genotype and ABC HSR are rare.[17]

In the PREDICT-1 study, where patients with HLA-B*5701 did not receive ABC, 3.4% of patients given ABC were diagnosed with HSR but no cases could be confirmed with patch testing (a research tool only).[18] Prospective screening for HLA-B*5701 in patients and

avoidance of ABC in positive patients is effective in reducing HSR, and this is now the standard of care in the First World. Over-diagnosis of HSR is well documented in the absence of testing.[19] A reduction in confirmed cases occurs when routine testing is performed.[18]

Despite the availability of testing and the recommendation to test, there is a debate as to the cost effectiveness and cost benefit of testing in ethnic groups where HLA-B*5701 is not prevalent.[17]

There are no data on the prevalence of HLA-B*5701 in the various South African ethnic groups. Full genetic screening for HLA-B*5701 is very costly. Cheaper methods involving PCR for small sequences of the gene are currently under review. Although full testing is available in South Africa, patients in the public sector do not have access. We recommend that testing be offered to all patients where affordable, regardless of ethnic group, until more information is available. However, it is reasonable to use ABC without prior screening if there is no alternative.

It is important to remember that HSR has been reported in patients negative for HLA-B*5701.[20] In patients in whom HSR reaction was diagnosed and who subsequently tested negative for HLA-B*5701, ABC remains contraindicated.

CLINICAL FEATURES AND DIAGNOSIS OF ABC HSR

Diagnosis of ABC HSR is complicated by its subtle initial features. Also, other drugs such as trimethoprim-sulfamethoxazole, nevirapine and efavirenz are known to cause hypersensitivity and should be recognised. Distinguishing the ABC HSR from other drug-related adverse events, intercurrent infections and even immune reconstitution inflammatory syndrome may be particularly difficult when ABC is used as first-line therapy, as all drugs are initiated simultaneously. In addition, ABC initiation may lead to symptoms that are similar but not related to HSR, including nausea and vomiting, fever and rash. These reactions are usually mild.

Ninety-four per cent of patients who experience HSR do so within 6 weeks after initiation of therapy. The median time to onset is 11 days, but symptoms can start on the first day and have been reported up to 318 days later. ABC HSR has occurred in patients who interrupted therapy without having had hypersensitivity and subsequently restart, but this is believed to be rare.[11,21] A single case of ABC HSR after switching from twice daily to once daily administration has also been reported.[22] Vigilance for the duration of ABC exposure is required.

The ABC HSR is a multi-organ process manifesting signs or symptoms from at least two of the following groups:

- **Fever** is the most common manifestation of ABC HSR, occurring in 80% of cases. Chills have been reported to accompany fever.
- **Rash** is experienced by 70% of cases, and pruritus can also occur. In contrast to the rash caused by non-NRTIs and sulphonamides, it is often mild and may go unnoticed by patients. When rash occurs in the absence of other features of HSR, ABC should not be discontinued.
- **Gastro-intestinal symptoms** such as nausea, vomiting, diarrhoea and abdominal pain are all features of HSR but may also occur in the absence of HSR, particularly when ABC is used with ZDV. Therefore, as with rash, patients with isolated gastro-intestinal symptoms should not discontinue ABC but should be followed up closely.
- **Constitutional symptoms** include fatigue, myalgias and generalised malaise.
- **Respiratory symptoms** occur in 18% of cases and include dyspnoea, cough and pharyngitis. Symptoms may be difficult to distinguish from those caused by influenza and other respiratory viruses. Respiratory symptoms together with abdominal symptoms suggest HSR rather than influenza or other respiratory illness.[23]

Clusters and combinations of symptoms are important in the diagnosis of ABC HSR. Table I illustrates the frequency of some combinations.[11,24]

TABLE I. FREQUENCY OF SYMPTOM COMBINATIONS IN ABACAVIR HYPERSENSITIVITY (ADAPTED FROM CLAY[24])

Systems and combinations	%
3 or 4 organ systems	49
Fever and rash	20
Fever and GIT	8
Skin and GIT	3
Skin and constitutional	3
Other combinations	17

GIT = gastro-intestinal.

With ABC HSR, there is an accentuation of symptoms in the hours immediately after the dose and worsening of symptoms with each subsequent dose. A number of case reports illustrate the varied clinical presentation, with Kawasaki-like illness, prominent exanthema and even disseminated intravascular coagulation being seen.[25-29]

If ABC is not terminated, or if it is re-initiated after temporary cessation, the HSR will progress to hypotension, renal dysfunction, bronchospasm and ultimately death.[11]

Abnormal laboratory findings may include leucopenia, anaemia and thrombocytopenia, as well as elevations

in transaminases, urea, creatinine and lactate dehydrogenase (LDH). Eosinophilia is usually absent.[11] Patch testing is currently only a research tool.

Termination of therapy is followed by rapid improvement in the symptoms.

Rechallenging with ABC leads to anaphylaxis and should be avoided even in cases where there was diagnostic uncertainty.

In Table II we set out the features of the first 3 cases of suspected HSR seen at the Tygerberg Children's Hospital Family Clinic for HIV. Of note is that HSR was documented in children across the racial spectrum. In all patients there was progression of symptoms over time and in 1 case there was a clear increase in severity associated with dosing. All children had abdominal symptoms and nonspecific rash. In these cases, children were stable on other ART drugs as they had all switched to ABC because of d4T toxicity.

MANAGEMENT OF PATIENTS INITIATING ABC

On commencement of ABC, patients should be counselled in detail about the possible signs of HSR and be advised to contact their care provider should any occur. To avoid confusion, therapy should not be initiated in patients with intercurrent symptoms.
It is advisable for patients to discuss symptoms early with the clinician rather than terminating therapy without consultation. Where termination without consultation occurs, ABC cannot be reinitiated. Patients should also be made aware of the special 'patient alert card' that comes in the packaging. This card should be presented to any health care provider who sees the child, especially when care is not given by the usual provider. Providers at emergency facilities may be less familiar with this condition, and where possible contact information for the usual care provider should be supplied as well.

Deciding whether to terminate therapy in a patient with suggestive symptoms can be difficult given the very nonspecific nature of the presentation. A detailed medical history should be obtained. The following should be considered:

- When was ABC initiated? In the case of ABC HSR, usually within the past 6 weeks.
- Are two or more systems involved?
- Do the symptoms increase with each dose?
- Are the symptoms exacerbated just after the dose?
- Do the symptoms fit into the well-recognised clusters?
- What other medications/medication is the patient taking, and what was the timing of their initiation related to the ABC?

If patients present with mild symptoms and it is not clear whether symptoms are due to HSR, the clinician may consider allowing an additional dose. The patient should be able to report back, or hospitalisation may be required for observation. If symptoms worsen, ABC should be terminated immediately and permanently. If symptoms do not worsen, ABC can be carefully con-

TABLE II. CLINICAL FEATURES IN 3 CHILDREN DIAGNOSED WITH ABC HSR AT TYGERBERG CHILDREN'S HOSPITAL AFTER A SINGLE DRUG SUBSTITUTION OF STAVUDINE FOR LIPO-ATROPHY

	Case 1	Case 2	Case 3
Race	White	Coloured	Black
Age (years)	9	5	10
Gender	Female	Male	Male
Time to onset of symptoms	<1 day	9 days	2 months
Accentuation with dose	Yes	Uncertain	Uncertain
Increasing severity	Yes	Yes	Yes
Time after onset to presentation to TCH (days)	1	5	3
Fever	No	Yes	No
Rash	Blotchy, erythematous on neck and hands Papules on the trunk and left arm	Extensive maculopapular on trunk, arms and legs Exanthema in mouth Non-purulent conjunctivitis	Fine papular rash on the chest
Gastrointestinal	Loss of appetite Epigastric and right upper quadrant tenderness	Nausea Loose stools	Abdominal pain and tenderness Vomiting Loss of appetite
Constitutional	Myalgias Malaise	Lethargy	Weight loss (1 kg)
Respiratory	No	No	Cough Red throat
Number of systems affected	3	4	4
Time to resolution	48 hours	5 days	2 - 3 days
HLA-B*5701	Negative – tested after the HSR	Positive – tested after the HSR	Negative – tested after the HSR

tinued while other possible reasons for the patient's symptoms are investigated. When the diagnosis is thought to be clear or there is sufficient concern, ABC should be terminated immediately and permanently.

Hospitalisation and special investigations will depend on the severity of symptoms. Corticosteroids do not prevent or alter the natural history of ABC HSR.[30] The reaction usually improves within 48 hours.

CONCLUSION

Clinicians treating children need to be very aware of the usefulness of ABC. Although there is no information on the prevalence of either ABC hypersensitivity or HLA-B*5701 in South African children, available data suggest that black children are at lower risk than Caucasian children, with no data on children of mixed race. Although screening for HLA-B*5701 is recommended and will prevent cases, research is needed to assess its cost effectiveness in the South African public health setting.

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