



Successful management of suspected Abacavir hypersensitivity reactions among African children in the ARROW (AntiRetroviral Research fOR Watoto) trial



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BACKGROUND

- The World Health Organization (WHO) recommends abacavir (ABC) for first-line paediatric anti-retroviral therapy (ART)
- Hypersensitivity Reactions (HSRs) are reported in 2-5% individuals receiving ABC in clinical studies
- Testing for HLAB*5701 prior to treatment with ABC is often recommended, but availability of this test is limited in low resource countries
- Diagnosis and management of abacavir hypersensitivity (ABC-HSR) in children in resource limited settings may be further complicated by febrile infectious diseases, and by overlapping toxicity due to concurrent use of nevirapine (NVP) and cotrimoxazole
- Children in the ARROW trial receive cotrimoxazole prophylaxis and are treated with ABC, 3TC, and Nevirapine (NVP) or Efavirenz (EFV). Children in the induction-maintenance arm of the trial also receive Zidovudine (ZDV)
- This represents the first use in African children of ABC dosed according to WHO weight band recommendations, and utilising scored tablets of ABC and the fixed dose combination 3TC+ABC (*Kivexa*®)

Scored tablets of Abacavir



- We describe the presentation and management of suspected AB-HSR in children in the ARROW trial

METHODS

- Clinical staff and carers were trained in management of ABC-HSR:
 - Recognition of suspicious signs and symptoms
 - Discontinuation of ABC only for suspected HSR
 - Avoidance of ABC re-challenge
- Carers were given an ABC-HSR warning card
- Expedited reporting of all HSRs as serious adverse events (SAEs)
- All suspected HSRs underwent independent clinical review

RESULTS

- 1,207 ART-naïve children aged 3 months to 17 years were recruited to ARROW in Uganda and Zimbabwe; median age 6 years at ART initiation
- 52 expedited SAE/HSR reports were received from the 1,207 participants
 - 90% (47/52) were within 4 weeks of ART initiation
 - The majority of reports occurred early on in the trial (75% of reports were on the first 50% of enrolled children)
 - ABC was NOT discontinued in 45/52 cases
- ABC (± NNRTI & cotrimoxazole) were stopped in 7/52 children
 - 4/7 cases were found NOT to be ABC-HSR at independent review.
 - Alternative diagnoses assigned: pneumonia, staphylococcal impetigo, URTI, isosporiasis
 - In 2 cases the drugs had been stopped by the carer; in the other 2 by study clinicians
 - 3/7 cases were judged possible/probable ABC-HSR at independent review
 - Median time from onset of symptoms to stopping drugs was 1 day (range 0-26)
 - Symptoms resolved upon stopping ARVs in all surviving cases (1 child with isosporiasis died)
 - NVP and cotrimoxazole reintroduced in all surviving cases with no recurrence of symptoms
 - ABC was permanently discontinued in all 7 cases

CLINICAL FEATURES IN 3 CASES of ABC-HSR

- 3/7 cases were considered possible/probable ABC-HSR
 - Incidence 0.2% (3/1207, 95% CI 0.05-0.7)
- Clinical symptoms (fever, rash) occurred 9 to 13 days after ART initiation:
- 2/3 cases had additional gastrointestinal and respiratory symptoms and were hospitalized
- Liver function: AST mildly elevated in 1 case

Symptoms/ labs	7 yr old	8 yr old	10 yr old
Generalised Rash (maculopapular)	X	X	
Generalised Rash (erythematous)	X		X
Generalised Rash (pruritic)	X		X
Mucous membrane involvement	X	X	
Fever	X	X	X
Fatigue	X		
Myalgia	X		
Dysphagia		X	
Pharyngitis	X		
Cough	X	X	
Vomiting	X		X
Abdominal pain	X		
Hospitalised	X	X	
AST	52	28	84
ALT	44	20	28
Bilirubin	Normal	Normal	Normal

Generalised erythematous maculopapular rash



CONCLUSIONS

- Suspected ABC-HSR was rare: 3/1207 (0.2%), consistent with reports of lower prevalence of HLAB*5701 in African populations
 - [Hughes et al: Pharmacogenomics 2004; 5: 203-112]
- ABC-HSR was successfully managed despite co-administration of cotrimoxazole and NVP
 - This illustrates the importance of clear communication with health-workers and carers on diagnosis and clinical management
- ABC can be safely used in resource limited countries
 - Erroneous discontinuation of ABC can occur and should be avoided

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