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

AUTHORS: P. Nahirya-Ntege*[1], B. Naidoo[2], K.J. Nathoo[3], P. Mugyenyi[4], A. Kekitiinwa[5], R. Katuramu[1], M. Spyer[2], M.F. Bwakura-Dangarembizi[3], V. Musiime[4], P. Kasirye[5], T. Vhembo[3], S. Mubokyi[4], S. Bakeera-Kitaka[5], J. Crawley[2], P. Munderi[1], on behalf of the ARROW trial team

[1]MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda, [2]Medical Research Council Clinical Trials Unit, London, United Kingdom, [3]University of Zimbabwe Medical School, Department of Paediatrics and Child Health, Harare, Zimbabwe, [4]Joint Clinical Research Centre, Kampala, Uganda, [5]Paediatric Infectious Disease Clinic, Mulago (Baylor-Uganda), Kampala, Uganda

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

COLLABORATORS and ACKNOWLEDGEMENTS

Contact details: MRC/UVRI Uganda Research Unit on AIDS, Uganda Virus Research Institute, P.O. Box 49 , Entebbe, Uganda
Tel: + 256- 417- 704 000 / 704 157 *Email*: Patricia.nahirya@mrcuganda.org

We thank all the patients and staff from all the centres participating in the ARROW trial. Trial Steering Committee: I Weller (Chair), E Luyirika, H Lyall, E Malianga, C Mwansambo, M Nyathi, A Wapakhabulo, DM Gibb, A Kekitiinwa, P Mugyenyi, P Munderi, KJ Nathoo Data and Safety Monitoring Committee: A Breckenridge (Chair), C Giaquinto, C Hill, J Matenga, J Tumwine Endpoint Review Committee: G Tudor-Williams (Chair), H Barigye, HA Mujuru, G Ndeezi, MF Bwakura-Dangarembizi, V Musiime, P Musoke, P Nahirya-Ntege, JM Crawley, DM Gibb Joint Clinical Research Centre, Kampala, Uganda: P Mugyenyi, V Musiime, V D Afayo, E Bagurukira, J Bwomezi, J Byaruhanga, P Erimu, C Karungi, H Kizito, S Mubokyi, WS Namala, J Namusanje, R Nandugwa, D Nanyumba, TK Najjuko, E Natukunda, M Ndigendawani, F Nghania, SO Nsiyona, F Odongo, K Robinah, M Ssenyonga, D Sseremba, J Tezikyabbiri, CS Tumusiime University of Zimbabwe, Harare, Zimbabwe: KJ Nathoo, MF Bwakura-Dangarembizi, MM Chipiti, R Dzapasi, J Gumbo, C Katanda, R Mandidewa, F Mapinge, C Marozva, T Mhute, D Muchabaiwa, S Mudzingwa, D Nyoni, M Phiri, J Steamer, T Vhembo MRC/UVRI Uganda Research Unit on AIDS, Uganda Virus Research Institute, Entebbe, Uganda: P Munderi, P Nahirya-Ntege, M Aber, FN Kaggwa, P Kaleebu,R Katuramu, JH Kyarimpa, J Lutaakome, L Matama, M Musinguzi, G Nabulime, A Ruberantwari, R Sebukyu, IM Ssekamatte, G Tushabe, D Wangi Baylor-Uganda, Paediatric Infectious Disease Centre, Mulago Hospital, Uganda: A Kekitiinwa, P Musoke, S Bakeera-Kitaka, J Asello, JK Balungi, G Kaps, JN Kairu, P Kasirye, B Mugisa, C Mukasa, G Musoba, SJ Mutebi, J Nakafeero, S Nakyanzi, R Namuddu, C Semambo, Victoria Ssebudde, S Ssenyonjo, A Wanyoto MRC Clinical Trials Unit, London, UK: DM Gibb, MJ Thomason, AD Cook, JM Crawley, AA Ferrier, B Naidoo, MJ Spyer, AS Walker Funding: ARROW is funded by the UK Medical Research Council and the UK and Department for International Development (DfID). Drugs are provided by GlaxoSmithKline