Evidence For Action on HIV treatment and care systems

arrow

Case Study
July 2010
No. 07

Use of scored tablets of first line antiretroviral drugs in HIV-infected children in resource limited settings:

Experiences from the ARROW Clinical trial

Summary

Liquid formulations of antiretroviral (ARV) drugs are usually given to young children but dispensing different volumes of multiple syrups which changes as the child grows is complex for caregivers, particularly older grand parents. As liquids are also proven to be bulky and problematic to store (Acceptability of Tablets Case Study), solid formulations may be preferable. However in resource limited settings, there is lack of appropriate low bulk, solid formulations which can be crushed, dissolved or swallowed whole by young children, and which are made in sizes that allow for the necessary incremental dose adjustments associated with a child's growth according to simple weight band tables. Scored tablets, with drug evenly distributed throughout enabling easy and accurate division in half, substantially increase accuracy of division compared with un-scored tablets. This improves dosing flexibility as the tablets are snapped in half by hand and are generally preferred. In addition, scored fixed dose combination tablets are easier for manufacturers as fewer tablets of different strengths are required for children. The children in the ARROW trial were the first worldwide to use scored tablets of Abacavir (ABC), Lamivudine (3TC) and Combivir (CBV).

Lamivudine Abacavir Combivir

Description of the ARROW study

Methods

ARROW (www.arrowtrial.org), which commenced in March 2007, is an ongoing 5 year open label randomised clinical trial in 1207 HIV infected children in Uganda and Zimbabwe, investigating monitoring practice and first line antiretroviral therapy strategies. Children aged 3 months to 17 years were randomised to regimens using scored tablets of ABC, 3TC and CBV dosed according to WHO weight bands (WHO 2007). A sub-study of the ARROW trial investigated the PK of these scored tablets, including the switch from once to twice daily dosing. The switch from liquids to scored tablets was also investigated among the younger children attaining a weight of 12kg (~3years) in this (PK) sub-study.

Findings

Scored tablets have been used successfully in HIV infected African children. The scored tablets had favourable pharmacokinetic (PK) profiles/ parameters (area under the curve and peak level). These PK parameters were higher than earlier reported in a similar European study where children mostly received syrups. There was high preference for the scored tablets to syrups among the caregivers and the children when the switch was made from syrups to tablets. Few problems were reported when the switch was made from syrups to scored tablets, and no child switched back to syrups.

> "The roll out of antiretroviral therapy to children in resource limited settings is limited by the lack of formulations, appropriate for children of different age groups."

MRC Clinical Trials Unit

funded by: DFID Department for International Development

What is the potential impact of this?

The children that have used and continue to use these scored tablets, as well as their caregivers have benefited from the ease of administration of the tablets. The successful use of the scored tablets in ARROW, within resource limited settings, with favourable pharmacokinetic profiles will be strong evidence for National ART programmes in Africa and other resource limited settings, to make scored tablets available to children enrolled in national programmes. The children in resource rich settings will also benefit from the ease of administration that these tablets provide. It is also strong evidence for drug manufacturers to adopt scored tablets as the formulation of choice for children of different ages and sizes.

How is this research novel?

Scored tablets of ABC, 3TC, and CBV were used for the first time worldwide among children in the ARROW trial. The sub-study investigating the PK of once versus twice daily 3TC and ABC in HIV infected children using these scored tablets, dosed according to WHO weight bands, was the first such study in resource limited settings.

What made the research successful?

ARROW is a multi-centre, three country (Uganda, Zimbabwe, and UK) trial and it is within strong collaborations. The institutions involved Joint Clinical Research Centre; Paediatric Infectious Disease Clinic; the Medical Research Council/ UVRI in Uganda; the University of Zimbabwe and the Medical Research Council, UK have a research track record. The scored tablets were provided by GlaxoSmithKline (GSK), who also provided funding for the PK sub-study. Other collaborators include DFID (co-funder of ARROW) and Radboud University Nijmegen Medical Centre in Netherlands (PK studies). These North to South and South to South collaborations ensured successful conduct of the evaluation.

Adherence to antiretroviral therapy (ART) is crucial to successful therapy. HIV infected children are very vulnerable in this regard as they depend on an adult care giver. To avoid both caregiver and child fatigue and stress regarding the child's ART, the ART regimen should be easy for the caregiver to follow and the formulations should be user friendly. Scored tablets go a long way in ensuring ease of administration of ARV drugs to young children. Coupled with the finding in the ARROW PK sub study that 3TC and ABC can be used once daily, these tablets will simplify ART in children thereby enhancing adherence to the medication.

Who has been involved?

The ARROW trial is collaboration between:

- Joint Clinical Research Centre (JCRC), Kampala, Uganda
- The Paediatric Infectious Diseases Clinic (PIDC), Kampala, Uganda
- Medical Research Council/ Uganda Virus Research Institute, Entebbe, Uganda
- University of Zimbabwe College of health sciences, Harare, Zimbabwe
- Medical Research Council Clinical Trials Unit (MRC CTU), UK
- Radboud University Nijmegen Medical Centre in Netherlands
- GlaxoSmithKline (GSK)

This case study was written by Dr Victor Musiime from the Joint Clinical Research Centre, Uganda in collaboration with the ARROW team at the MRC Clinical Trials Unit, London.

Evidence For Action on HIV treatment and care systems

About Evidence for Action

Evidence for Action is an international research consortium with partners in India, Malawi, Uganda, UK and Zambia, examining issues surrounding HIV treatment and care systems.

The research is organised in four key themes:

1. What "package" of HIV treatment and care services should be provided in different settings?
2. What delivery systems should be used in different contexts?
3. How best should HIV treatment and care be integrated into existing health and social systems?
4. How can new knowledge related to the first three questions be rapidly translated into improved policy and programming?

Partners:

International HIV/AIDS Alliance, UK

Lighthouse Trust, Malawi

London School of Hygiene and Tropical Medicine, UK

Medical Research Council Uganda Research Unit on AIDS, Uganda

Medical Research Council Clinical Trials Unit / University College London, UK

National AIDS Research Institute, India

ZAMBART, Zambia

This document is an output from a project funded by DFID for the benefit of developing countries. The views expressed are not necessarily those of DFID.