



Development of simple and appropriate formulations for scale-up of HIV treatment for children: an example from the CHAPAS-1 trial

Summary

Whilst there has been considerable progress in antiretroviral (ARV) drug options for adults, the development of affordable drugs in appropriate formulations for children has lagged behind. Where liquids are available they are costly, have short shelf-lives, and are difficult to transport and store. As a result divided adult fixed-dose combination (FDC) tablets (combining 2 or 3 drugs into 1 pill) have been frequently given to children in resource-limited settings. Parts of adult tablets, although acceptable for older children, prevent reliable and easy adjustment of dose as a child grows and often contain suboptimal ratios of drugs for young children, risking either toxicity or underdosing and the development of drug resistance. This is a particular concern given that many children face a lifetime requirement of ARVs and key first line drugs like nevirapine (NVP) and lamivudine (3TC) are highly susceptible to resistance.

The CHAPAS-1 trial investigated the appropriate dosing of, and adherence to, a new FDC specifically for children, Triomune Baby (50mg NVP; 6mg stavudine (d4T); 30mg 3TC) and Triomune Junior (double Baby dose). Pharmacokinetic (dosing) data from a subset of children in CHAPAS-1 showed the ratio of drugs contained

within Triomune Baby/Junior to be appropriate for African children. Data were submitted to the US Food and Drug Administration (FDA) as part of the approval process for use of the tablets in Africa. These combination tablets are the first licensed specifically for children under 12 years and are now widely available throughout Africa. They are dosed according to simple weightband tables, now endorsed and standardised across different ARV regimens by World Health Organisation.

Background

CHAPAS-1 was a trial in 211 HIV-infected Zambian children (3 months to 14 years) initiating ART with scored dispersible tablets of stavudine/lamivudine/nevirapine (Triomune Baby/Junior). A subset of 65 children took part in a pharmacokinetic study to investigate the appropriate dosing of these drugs. The need for the recommended dose escalation of nevirapine (half dose for 14 days), to minimise side effects requires the use of a 2-drug combination pill or separate tablet/syrup formulations and has never been assessed in children. Children were randomised to start ART using the full dose of the 3-drug combination (Triomune Baby/Junior) or with nevirapine dose escalation



using the 3-drug combination in the morning and a 2-drug combination pill in the evening. All doses followed WHO weightband tables.

Findings and Interpretation

The ratio of drugs within Triomune Baby/Junior is appropriate for children, indicating their suitability for the treatment of HIV infected children. Although skin rashes were more frequently found among children starting nevirapine at full-dose (12 children) than when dose escalating (2 children), 88% of children starting at full dose had no clinical side effects. Wherever possible, 2-drug paediatric stavudine/lamivudine dispersible mini-tablets, which are more cost effective than syrups, should be made available for safe and simple dose escalation. If 2-drug adult or paediatric solid formulations are not available and full-dose Triomune Baby/Junior is used, caregivers need to be aware of the timing of rash, which occurs within the first month of starting ART. For children developing rash, options are to 'treat through' with careful clinical observation or to reduce to half-dose Triomune during re-escalation, as we

“The availability of fixed dose combination products, like Triomune Baby and Junior, has had a significant impact on the scale up of ART for children. Costing just \$55 per child for 1 year’s treatment they have become widely available in treatment programmes across Africa.”

Adherence to antiretroviral therapy is crucial for successful treatment of HIV infected children. Treatment with liquids requires caregivers to administer three syrups, twice a day, every day.

Now with three-in-one fixed dose combination tablets, like Triomune Baby/Junior, a month's drug supply can be supplied in just a single bottle. It contains the correct ratio of drugs for children, is generic and represents an entire HIV regimen in one pill. This has made

it manageable for caregivers to administer the correct dosage and easy for children to take. Being scored and layered these tablets can easily be snapped in half allowing use within a simple weight band dosing table that ensures children receive the correct dose for their weight. The tablets have the added advantage of being crushable and dispersible in water, making them accessible for the treatment of infants as young as 3 months.

observed few recurrences of rash with dose escalation in children who had initial rash with full-dose nevirapine. These recommendations are being incorporated into updated paediatric WHO 2010 guidelines.

What is the potential impact of this?

Simplification and standardisation of ART is an essential feature of HIV treatment scale up but a lack of affordable and appropriate paediatric formulations has restricted this in resource-limited settings. FDA approval of Triomune Baby/Junior has allowed its distribution widely in sub-Saharan Africa through treatment programmes including those provided by the Clinton Foundation (introducing them into 26 countries in 2007) and PEPFAR. Furthermore, as Triomune Baby/Junior contains the same drugs as adult Triomune its use should aid a family approach to HIV care helping to prevent sharing of medication and encouraging adherence.

ART coverage levels have risen greatly, yet in 2008 still only 42% of adults and 38% of children in need of ART received it. WHO, national regulators and funding bodies are continuing to encourage and prioritise the availability and development of fixed dose combination products.

How to initiate nevirapine containing FDCs is important to paediatricians, healthcare workers and planners in resource-limited settings because

a lack of formulations (either liquids or 2-drug tablets) to dose escalate nevirapine can be an important barrier to ART initiation in children who urgently need to start.

Who has been involved?

The CHAPAS-1 trial is a collaboration between:

- University Teaching Hospital (UTH), Lusaka, Zambia
- Medical Research Council Clinical Trials Unit (MRC CTU), London, UK
- Radboud University Nijmegen Medical Center (RUNMC), Nijmegen, Netherlands

The lead researchers on this trial are Prof. Chifumbe Chintu, Dr Veronica Mulenga, Prof. Diana Gibb and Dr David Burger.

DFID contributes funding to the next trial (CHAPAS-3), through EDCTP. CHAPAS-3 is evaluating alternative fixed dose combination pills for children, which don't contain stavudine.

References

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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

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