



EDCTP

European & Developing Countries
Clinical Trials Partnership

FACT SHEET • FEBRUARY 2017

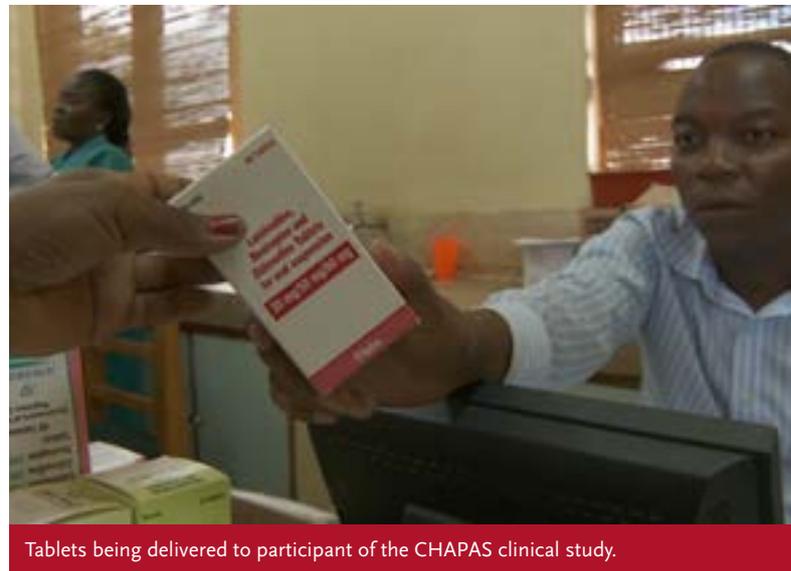
HIV treatment for children: the EDCTP-funded CHAPAS trials

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 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 under-dosing 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.

CHAPAS-1 AND CHAPAS-3: FIRST-LINE ANTIRETROVIRAL TREATMENT

Professor Chifumbe Chintu (University Teaching Hospital, Zambia) and his team in the **CHAPAS-1** trial studied the appropriate dosing of and adherence to Triomune Baby/Junior. This is a fixed-dose combination of stavudine (d4T), 3TC and NVP in a new formulation specifically developed for children. CHAPAS-1 specifically aimed to address the complete lack of appropriate first-line antiretroviral regimens available for children in developing countries.

The research team shared its preliminary pharmacokinetics data with the USA Food and Drug Authority (FDA) and the data contributed to the approval of Triomune Baby/Junior for use in HIV-infected children in 2007. This approval enabled many HIV-infected children to be placed on treatment in various developing countries. The drug was also made available under programmes such as the US President's Emergency Plan for HIV/AIDS Relief (PEPFAR) and the Clinton HIV/AIDS Initiative (CHAI). The study findings contributed to the WHO recommendations on the optimal drug ratios in fixed-drug combinations and on weight band dosage for antiretrovirals in children worldwide.



Tablets being delivered to participant of the CHAPAS clinical study.

The findings of CHAPAS-1 have 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.

However, the number of children on antiretroviral treatment still falls behind that of adults because of the lack of antiretroviral options. Moreover, the stavudine drug, contained in the Triomune fixed-dose combination, turned out to have cumulative toxicity side effects and was discontinued. Therefore, there was a need to increase options of first line fixed dose combination antiretroviral drugs for children.

The **CHAPAS-3** study, led by Dr Veronica Mulenga (University Teaching Hospital, Zambia), followed on CHAPAS-1 to contribute to addressing this gap. The study compared the

BRANING & BART TRIOMUNE JUNIOR	Number of tablets by weight band						
	3.0-3.9 kg	4.0-4.9 kg	5.0-5.9 kg	6.0-9.9 kg	10.0-13.9 kg	14.0-19.9 kg	20.0-24.9 kg
	1	1	1	1	1	1	1
	1	1	1	1	1	1	1

Card Triomune Baby/Junior fixed dose combination.

toxicity, pharmacokinetics, efficacy, adherence and acceptance of two newer fixed-dose combinations of ABC (abacavir) +3TC+NVP/EFZ (efavirenz) and AZT (zidovudine) +3TC+NVP/EFZ to the first fixed-dose drug Triomune.

The findings showed that the three regimens tested were well tolerated and that there was no difference in the primary toxicity end-point. These important results confirm that the anti-retroviral therapy given as WHO-recommended fixed-dose combinations is highly effective in children. The trial also included analyses of adherence/acceptability, cost-effectiveness and viral load suppression. The data on efavirenz have been shared with the USA FDA for preregistration of the new, scored 600mg efavirenz tablet, and the CHAPAS-3 trial results was shared with the WHO for prequalification of these fixed-dose combination drugs. The trial findings, which were published in *The Lancet Infectious Diseases* in 2015, indicate that priority must be given to early diagnosis and treatment in order to expand treatment to all HIV-infected children.



Participant of the CHAPAS trial takes the fixed dose combination.

CHAPAS-4: SECOND-LINE ANTIRETROVIRAL TREATMENT

Whilst HIV-infected children respond well to treatment, the number of children failing first-line treatment and needing to switch to second-line treatment will inevitably increase. Therefore, the CHAPAS-4 trial, funded under the second EDCTP programme, will evaluate new drug formulations to optimise second-line treatment in HIV-infected children. The project is coordinated by Dr Mutsa Bwakura-Dangarembizi (University of Zimbabwe College of Health Sciences, Zimbabwe).

PROJECTS AT A GLANCE

CHAPAS-1 Trial

Children with HIV in Africa-Pharmacokinetics and adherence of Simple Antiretroviral Regimens (CHAPAS 1 Trial)

University Teaching Hospital (UTH), Zambia with partners from Netherlands, United Kingdom, United States and Zambia

Starting date: 3 November 2005

Completion date: 28 February 2009

Grant budget: EUR 1,280,993.26

CHAPAS-3 Project

Expanding the availability of fixed dose combination antiretroviral formulations for first-line treatment of HIV-infected children - Children with HIV in Africa Pharmacokinetics and Acceptability/Adherence of Simple Antiretroviral Regimens

University Teaching Hospital (UTH), Zambia with partners from Ireland, Netherlands, Spain, Uganda and United Kingdom

Starting date: 9 December 2009

Completion date: 30 September 2014

Grant budget: EUR 4,580,943.69

CHAPAS-4

Children with HIV in Africa – Pharmacokinetics and Acceptability of Simple antiretroviral regimens

University of Zimbabwe College of Health Sciences, Zimbabwe with partners from Netherlands, South Africa, Uganda and United Kingdom

Starting date: 1 July 2017

Grant budget: EUR 7,556,256.20



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info@edctp.org



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