Dear Sirs

We are writing to restate PENTA's position on recommended thresholds for initiating antiretroviral therapy in children, following the recent publication of updated WHO guidance (1). PENTA continues to recommend that paediatricians in Europe use the thresholds in the 2009 PENTA guideline for use of ART in children (2), and sees no conflict between this and the updated WHO guidance. The PENTA guideline thresholds may also be appropriate for middle-income countries outside Europe.

Both the PENTA 2009 and WHO 2010 guidelines recommend starting ART in all infants below 12 months, all children with significant symptoms (WHO stage 3 or 4), and in asymptomatic children from age 5 years onwards at the same CD4 thresholds as adults, ie 350 cells/mm^3.

For asymptomatic children between ages 1 and 5 years, PENTA 2009 and previous WHO 2008 guidance recommended starting ART according to CD4 count in 2 identical age bands (12 to 36 and 36 to 59 months), albeit at different CD4 levels. The new WHO guidance extends the recommendation for universal treatment from 12 months to 24 months, as well as using lower CD4 thresholds from age 2 to 5 years in a single age band (see table 1 below).

Both PENTA 2009 and WHO 2010 guidelines considered the same body of evidence, and several experts took part in the drafting of both sets of recommendations. The universal treatment of infants is based on evidence from the CHER study (3), children over 5 are treated at adult thresholds in both guidelines, based on comparisons between the HPPMCS child cohort and CASCADE adult seroconverter cohort. The recommendations for children aged between 2 and 5 are based on cohort data, largely from the HPPMCS study (4, 5).

The new recommendations in the WHO guidance for children between age 1 and 5 are based on programmatic considerations, in particular the ability to closely monitor a child clinically and by repeat CD4 count measurement if they are not started on ART. Such monitoring is available in Europe, and in many settings outside Europe. It is also noted that the evidence basis for these recommendations is weak or very weak, and that studies expected to publish results soon may shed more light on the subject. We endorse WHO's recommendation to treat early where the ability to provide monitoring is limited, as well as the call for more research to provide RCT evidence for treatment initiation thresholds after infancy. We continue to recommend PENTA 2009 guidance as appropriate for European and other settings with the facility to monitor closely children in whom treatment is deferred.

References:

1. WHO: Guideline Antiretroviral therapy for HIV infection in infants and children. Recommendations for a public health approach (2010 revision) http://whqlibdoc.who.int/publications/2010/9789241599801_eng.pdf (Date accessed: 21st July 2010)
2. PENTA Steering Committee: PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. *HIV Medicine, 2009, 10,* 591-613.

3. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, Jean-Philippe P, McIntyre JA; CHER Study Team: Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med. 2008 Nov 20;359(21):2233-44. PMID: 19020325*

4. Dunn D, Woodburn P, Duong T, Peto J, Phillips A, Gibb DM, et al. Current CD4 cell count and the short-term risk of AIDS and death before the availability of effective antiretroviral therapy in HIV-infected children and adults. *The Journal of infectious diseases. 2008 Feb 1;197(3):* 398-404.

5. HIV Paediatric Prognostic Markers Collaborative Study Group: Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. *Lancet. 2003 Nov 15;362(9396):*1605-1611.

Table 1.

	PENTA 2009		WHO 2010	
Clinical **Immunological** **Virological**	0 -11 months	Treat all	Treat all	0-23 months
Clinical **Immunological** **Virological**	12 – 35 months	Treat if CDC Stage B or C/WHO Stage 3 or 4 Treat < 25% or < 1000 cells/µl Consider treatment if viral load >10^5 copies/mL	Treat if WHO Stage 3 or 4 Treat <25% or <750 cells/µl No virological threshold	24-59 months
Clinical **Immunological** **Virological**	36 – 59 months	Treat if CDC Stage B or C/WHO Stage 3 or 4 Treat < 20% oder < 500 cells/µl Consider treatment if viral load >10^5 copies/mL		
Clinical **Immunological** **Virological**	5 years +	Treat CDC Stage B or C/WHO Stage 3 or 4 Treat < 350 cells/µl Consider treatment if viral load >10^5 copies/mL	Treat WHO Stage 3 or 4 Treat < 350 cells/µl	5 years +

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