

# WHEN TO START ANTIRETROVIRAL THERAPY IN INFANTS AND CHILDREN

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We review the background and key studies that inform decisions on when to initiate antiretroviral therapy (ART) in infants and children. The World Health Organization staging system from 2006 was based on conditions commonly seen in Africa and provided an impetus for advancing ART in children. Because of poor predictive value of CD4 counts in infancy and inability to predict risk of death or disease progression, we recommend initiating ART in all infants under a year of age. CD4 thresholds for initiating therapy decline as children become older. WHO stage 3 and 4 should trigger ART regardless of CD4 count. Over 5 years of age, a CD4 count  $<350/\mu\text{l}$  requires ART.

When to initiate antiretroviral therapy (ART) in children and adults has been determined by disease stage and CD4 count or percentage. The starting criteria were based on cohort data and clinical experience. The main groups determining paediatric guidelines are from the USA, Europe (PENTA – Paediatric European Network for Treatment of AIDS) and the World Health Organization (WHO).<sup>1-3</sup> With the advent of effective triple therapy from 1995, guidelines have adapted to new data. Initial staging clinical and immunological criteria were those of the Centers for Diseases Control and Prevention (CDC).<sup>4</sup> The staging criteria were based on North American experience and were not always appropriate for Africa. For example, failure to thrive, bronchiectasis and pulmonary tuberculosis were not adequately addressed.

Although the CDC classification included CD4 depletion, it was only with the HIV Prognostic Markers Collaborative Study (HPMCS), representing the combined data of 3 941 HIV-infected infants and children from the USA and Europe in the pre-highly active antiretroviral therapy (HAART) era, that the relationship between age and CD4 percentage became clearer.<sup>5</sup> The study showed that the younger the infant, the higher the CD4 percentage or absolute count at which there was a high risk of disease progression or death within the next 12 months. As the CD4 count normally declines with age until 5 years of age and the CD4 percentage remains stable, the CD4 percentage is used as a guideline until then (in the absence of lymphopenia). However, the CD4 count is an extremely accurate predictor of outcome.<sup>6</sup> These findings were subsequently incorporated into all paediatric guidelines.

The establishment of a WHO classification system in 2006 helped to focus on conditions more frequently encountered in Africa.<sup>7</sup> The system has 4 stages, with ART recommended for stages 3 and 4. The special vulnerability of young infants to rapid disease progression and death was not fully appreciated at this time, although allowance was made for initiating ART in HIV antibody-positive infants with severe disease before confirmation by HIV DNA polymerase chain reaction (PCR).

The decision on when to initiate ART in infants and children has always been influenced by fears of long-term toxicity or antiretroviral (ARV) resistance if therapy is started too soon. Also, ARV choices for children are far more limited than for adults. Second-line therapy is especially unsatisfactory.

However, there is increasing realisation, especially from adult data, that delaying ART until the CD4 cell count falls below 350 cells/ $\mu\text{l}$  is associated with increased morbidity and mortality.<sup>8,9</sup> ART is therefore recommended at higher CD4 thresholds than previously.

## INFANTS BELOW 12 MONTHS OF AGE

Mortality in HIV-infected infants is exceedingly high. The first data came from a study of combined outcome in nine vertical transmission prevention (VTP) studies conducted in sub-Saharan Africa.<sup>10</sup> Thirty-five per cent of HIV-infected infants had died by 1 year of age and 52.5% by 2 years of age. The ZVITAMBO study in Zimbabwe showed a similar but slightly higher mortality in the first 2 years of life.<sup>11</sup> For both studies, co-tri-

moxazole prophylaxis for prevention of *Pneumocystis pneumonia* (PCP) was not given.

The Children with HIV Early Antiretroviral (CHER) trial is the first ARV trial to prospectively evaluate ART strategies to inform ARV guidelines.<sup>12</sup> Before this, limited cohort studies favoured early ART. For example, Faye *et al.* reported an improved outcome in 40 infants commencing ART before 6 months of age compared with 43 starting later. In the early group there was no disease progression versus 7 events, including 3 cases of encephalopathy, in those treated later.<sup>13</sup>

CHER commenced in July 2005 in two South African sites, the Perinatal HIV Research Unit (PHRU) in Soweto and the Children's Infectious Diseases Clinical Research Unit (KID-CRU) at Tygerberg in the Western Cape. The hypothesis of the study is that early ART will have long-term benefit by delaying the need for continuous therapy. At the time of planning and initiation, the standard practice in infants was to initiate ART for a low CD4 percentage (<20% until August 2006 and 25% thereafter, in the first year of life) or evidence of severe clinical disease.<sup>3,14</sup> In the first part of the study, infants with baseline CD4  $\geq$ 25% were randomised to deferred ART (arm 1), where ART was initiated once treatment criteria were reached (CD4 <20% until August 2006 and <25% thereafter or severe HIV disease), or early ART commencing before 12 weeks of age until either the first (arm 2) or second (arm 3) birthdays, with interruption of ART until indicated through CD4 depletion (<20% after the first birthday) or clinical disease progression. For the first year of the study, deferred ART (arm 1) was compared with early ART (arms 2 and 3).

On 20 June 2007, after the study had been open for 2 years, the Data Safety Monitoring Board for CHER, noting significantly improved survival in subjects in the early ART arms, recommended that no infants be randomised to deferred ART and that data until this time point be released.<sup>12</sup> The difference in mortality and disease progression is shown in Fig. 1.

A key finding in CHER was high early mortality, mainly in the deferred arm, which diminished as the infants became older (Table I). Also of note, however, is that mortality was also higher early on in the early ART group, diminishing over time in the first year of the study.

Subsequently, ARV guidelines for children throughout the world incorporated the findings of CHER and recommended that all HIV-infected children below 12 months of age start ART irrespective of CD4 status or disease progression.<sup>1, 2, 15</sup>

More recently, a study by Bourne and colleagues, using birth and death data from Statistics South Africa between 1997 and 2002, showed a peak in post-neonatal

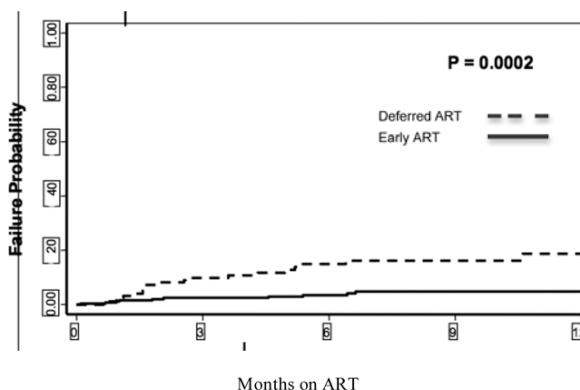


Fig. 1. Deferred ART is associated with a) a higher probability of death or b) first HIV event in the CHER trial.

TABLE I. HIGH EARLY MORTALITY RATE IN THE CHER STUDY		
Weeks on study*	Death rate per 100 person-years (95% CI)	
	Early ART	Deferred ART
0 - 13	9.8 (3.6 - 21.4)	40.6 (21 - 71)
>13 - 26	3.7 (0.4 - 13.2)	19.7 (6.4 - 45.9)
>26 - 52	3.1 (0.4 - 11.2)	6.8 (0.8 - 24.7)

\*Infants were  $\leq$ 12 weeks of age at study entry.<sup>12</sup>

mortality, rising each year directly proportional to the rising HIV antenatal seroprevalence.<sup>16</sup> These data are shown in Fig. 2. Also of note is that neonatal deaths are not addressed. It is possible that HIV may contribute significantly to neonatal deaths as well.

These data, together with CHER, illustrate the enormous dilemma and problems for child health programmes. In CHER the diagnostic HIV DNA PCR was done from 4 weeks of age with a 7-day turnaround time. In the public sector, the PCR is done at 6 weeks of age, to coincide with the 6-week immunisation visit. Turnaround time for the test results and then communication to the caregiver all take time during a period of great vulnerability.

One of the main problems is identifying HIV-infected children early and getting them into care. Because of

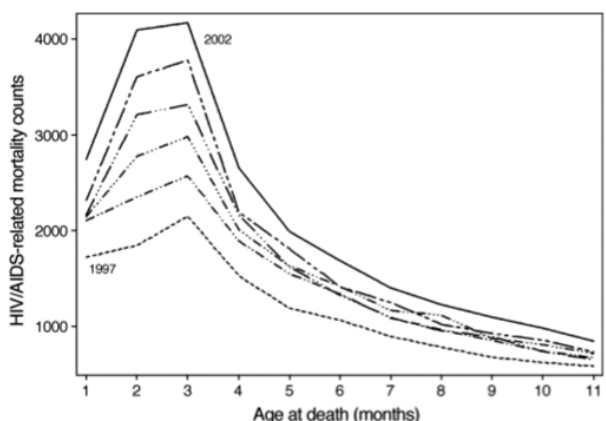


Fig. 2. Early peak in infant mortality proportional to rising antenatal HIV seroprevalence, 1997 - 2002 (reproduced with permission from AIDS<sup>16</sup>).



the importance of the caregiver in giving ARVs, previous guidelines emphasised adequate preparation and training over a number of weeks. Because of the new recognition of early infancy as a period of high mortality, there is a need to 'fast-track' preparation and also to continue training and support after having initiated ARVs.

Practical difficulties are illustrated by experience in the Tshwane district. In 2009, 82% of children newly referred to the Kalafong ART site had stage 3 or 4 disease, the majority being referred from the in- and out-patient service. Of the 14 000 - 22 000 HIV-infected children thought to be in Tshwane, only between 3 000 and 4 000 are receiving ART or are in care.

### CHILDREN >12 MONTHS OF AGE

In this group there is less certainty on when to initiate ART. Ideally, decisions must be based on randomised studies. The PREDICT is underway in Thailand and Cambodia and will assess the CD4 thresholds for therapy in children between 1 and 12 years of age.

All guidelines recommend using absolute CD4 counts from 5 years of age. For simplicity, the WHO regards 1 - 5 years of age as a single group, while the PENTA guidelines have 1 - 3 and 3 - 5 years of age. This group of children also represents a wide age spectrum. Clinical disease stage is extremely important and the majority of children are symptomatic. The dissociation of CD4 from disease severity has been well documented in South African children.<sup>17</sup> The HPMCS data, although showing a low risk of disease progression for higher CD4 percentages, still showed notable death and disease progression with CD4 >30% up to 6 years of age.<sup>5,6</sup>

Initial data suggested that young children show excellent immune restoration once ART is initiated, but more recent studies suggest a poorer response if therapy is delayed to CD4 <15%. Initial reports also suggested that viral suppression was difficult to achieve, especially in younger infants with extremely high viral loads. However, potent regimens and a better understanding of pharmacokinetics have improved outcomes.

Importantly, health care providers caring for children often do not fully appreciate the extent of end-organ damage. Mild cognitive and behavioural changes, milder forms of chronic lung disease, renal and hepatic disease and poor growth may easily be overlooked, leading to irreversible organ damage, growth failure and delayed puberty.

In the 3C4KIDS, 2 510 children over a year of age from Africa and Brazil contributed 357 deaths and 3 769 child-years at risk.<sup>18</sup> None had access to ART, with 81%

follow-up occurring on co-trimoxazole. The 12-month risk of death was higher than in the HPMCS for CD4 count and percentage. Most importantly, when anaemia and failure to thrive were included, the CD4 thresholds for predicting death or severe disease were much higher (Fig. 3). Both of these conditions are markers for advanced HIV disease. Most importantly, there was a real risk of death at high CD4 counts and percentages. For these reasons, our guidelines favour earlier ART between 1 and 5 years of age, in keeping with current US recommendations.<sup>2</sup>

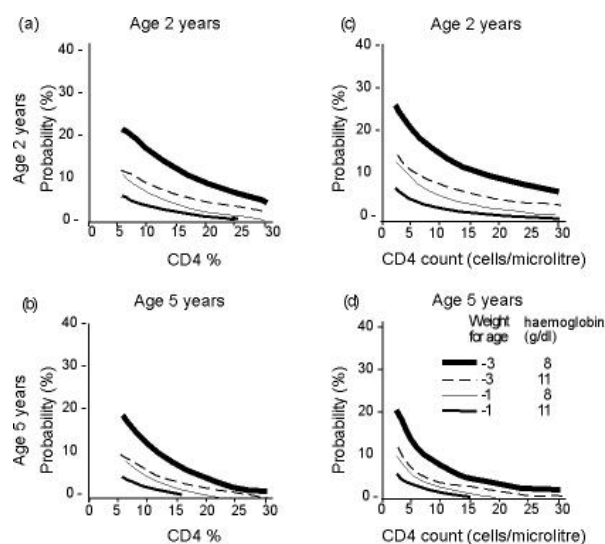


Fig. 3. Estimated risk of death within 12 months for a child on co-trimoxazole prophylaxis by age, weight-for-age z-score and haemoglobin and CD4 percentage or count. (a) CD4% at 2 years of age; (b) CD4% at 5 years of age; (c) CD4 count at 2 years of age; and (d) CD4 count at 5 years of age (reproduced with permission from AIDS<sup>18</sup>).

### CONCLUSION

There has been much progress in refining and improving ARV guidelines for children. More changes can be expected as knowledge advances. Most important, however, is the realisation that each child is unique and his or her individual and family circumstances need to be considered for maximum benefit.

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