

## WHEN TO START ANTIRETROVIRAL THERAPY IN HIV-INFECTED CHILDREN

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The right time to start antiretroviral therapy (ART) in adults and children is currently a topic of much discussion. Delaying the initiation of ART in children until absolutely necessary is of compelling importance for several reasons. Experience in the USA and Europe shows that achieving adequate long-term adherence in children remains a major challenge. Poor adherence is responsible for the emergence of resistant strains of HIV, resulting in treatment failures. Prolonged ART in children also exposes them to the increased risk of toxic side-effects. Metabolic complications (lactic acidosis, lipodystrophy) of ART have been well documented in adults and are now being described in children.<sup>1,2</sup> Importantly, in settings where resources are limited, delayed initiation of treatment could be a mechanism for reducing the cost of management.

category A, B, C) children and those with any immune suppression (immune category 2 or 3, CD4% < 25%).

The Pediatric European Network for the Treatment of AIDS (PENTA) group have updated treatment guidelines that adopt a less aggressive approach<sup>4</sup> (Table I).

Recently draft guidelines have also been published by the World Health Organisation (WHO).<sup>5</sup> The WHO recommends offering ART to HIV-infected infants with virologically proven infection and WHO paediatric stage III disease (AIDS) or WHO paediatric stage I and II HIV disease and a CD4% < 20%. For children >18 months who are HIV antibody-positive, the WHO recommends ART if they have

### GUIDELINES

Adult guidelines from both Europe and North America now advocate that therapy be initiated when the CD4 count is 200 - 350 cells/ $\mu$ l. Historically, ART has always been recommended for use in almost all children, regardless of the clinical staging of the disease. The recently updated guidelines from the Centers for Disease Control (CDC) still advocate initiation of ART for all infants less than 1 year of age.<sup>3</sup> The guidelines also continue to debate the initiation of ART in older, mildly affected children, but advocate early commencement of therapy for all symptomatic (clinical

### WHO paediatric classification of HIV/AIDS

#### Stage I

- Asymptomatic
- Generalised lymphadenopathy

#### Stage II

- Unexplained chronic diarrhoea
- Recurrent severe bacterial infection
- Oral candidiasis beyond neonatal period (severe persistent or recurrent)
- Persistent fever

#### Stage III

- AIDS opportunistic infection
- Severe failure to thrive
- Progressive encephalopathy
- Recurrent septicaemia
- Malignancy

TABLE I. RECOMMENDATION ON WHEN TO START ART

Infants	Children over 12 months of age
<p>1. <b>Always start</b> if any of:</p> <ul style="list-style-type: none"> <li>• clinical stage C</li> <li>• CD4 &lt; 20%</li> <li>• rapidly falling CD4% (irrespective of value), and /or</li> <li>• VL persistently &gt; 10<sup>6</sup> copies/ml</li> </ul> <p>2. <b>Consider</b> ART in any infant irrespective of clinical or immunological stage</p>	<p>1. <b>Always start</b> ART if:</p> <ul style="list-style-type: none"> <li>• clinical stage C or</li> <li>• CD4 &lt; 15%</li> </ul> <p>2. <b>Consider</b> ART if:</p> <ul style="list-style-type: none"> <li>• clinical stage B* or</li> <li>• CD4 &lt; 20% or</li> <li>• VL &gt; 5 log</li> </ul> <p>3. <b>Defer</b> ART if:</p> <ul style="list-style-type: none"> <li>• stage N or A disease, and</li> <li>• CD4 &gt; 20% and</li> <li>• low VL &lt; 5 log</li> </ul>
<p>* Some authors recommend starting if clinical stage B, but there is no consensus. VL = viral load.</p>	

WHO stage III HIV disease (AIDS) regardless of CD4 percentage. In children over 18 months of age with WHO stage I or II HIV disease, ART is recommended if the CD4 percentage is <15% (WHO clinical staging for children).

The South African Guidelines printed in this journal advocate initiation of treatment in the following situations:

- Clinical category B (except for a single episode of bacterial sepsis or a single episode of zoster) or C, or
- CD4% < 20%.

### WHICH GUIDELINES?

Deciding when to start therapy can become complex given all these different guidelines.

The rationale for the aggressive therapeutic approach in North America stems from the belief that initiating highly active antiretroviral therapy (HAART) may attenuate the severity of HIV infection and improve immune recovery. While there is some evidence that 'hitting hard' may be of benefit in early infection,<sup>8</sup> whether this is true once infection is established needs further investigation. There are no data at present showing that early initiation of therapy is associated with an improved long-term clinical outcome. The benefits of early therapy in infants also need to be weighed against the long-term exposure of the child to relatively toxic drugs.

Clearly, where resources are limited it is almost impossible to adopt such an aggressive approach if we are to treat thousands of HIV-infected children. Delaying ART for a few years would certainly be one way of sparing some of the expense of treatment. There is evidence that delaying initiation of ART is a reasonable approach in some children. It has been reported that 40 - 50% of vertically HIV-infected children survived to around 10 years of age without ART.<sup>7-9</sup> Mortality in a cohort of HIV-infected children in Malawi demonstrated 55% survival to 3 years of age.<sup>10</sup> In the PENTA 1 trial, no added benefit was demonstrated for starting zidovudine early over deferring until the development of symptoms.<sup>11</sup> In adults, immune recovery appears to be independent of the baseline CD4 count as long as ART is started before the CD4 count falls below 200.<sup>12</sup> In addition, although ART can markedly reduce viral replication, it has become clear that it does not eliminate the virus.

### WHAT CRITERIA FOR TREATMENT DEFERRAL ARE SAFE FOR CHILDREN?

A cohort of 51 HIV-infected children at Chris Hani Baragwanath Hospital has been followed up over 3 years. Children selected were age-matched according to clinically defined mild ( $N = 26$ ) or severe ( $N = 25$ ) disease (median age 4 years). These children have been followed up

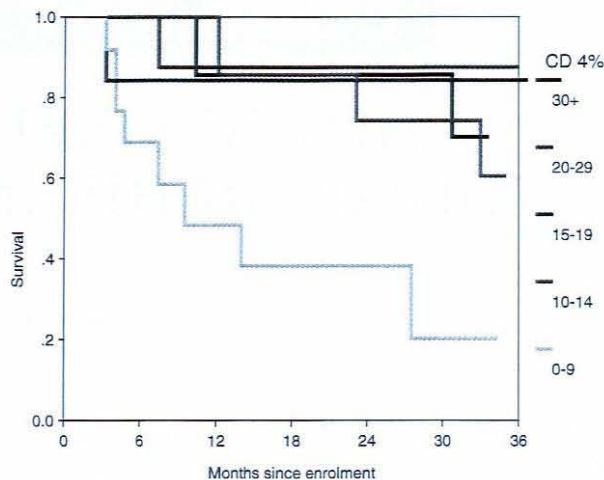


Fig. 1. Survival by CD4% at baseline.

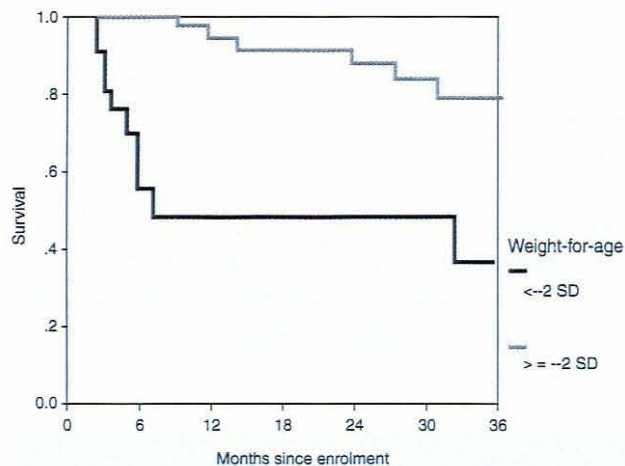


Fig. 2. Survival by weight-for-age z-score at baseline.

clinically and have annual tests for virological and immunological deterioration. Survival to 3 years by Kaplan-Meier methods was significantly associated with higher CD4% and higher weight-for-age at enrolment (Figs 1 and 2).<sup>13</sup> Children with CD4% < 10% had the worst outcomes, with no significant difference between the groups at higher levels. Those with weight-for-age z-scores less than -2 SD also had a significantly poorer outcome than the others. Viral load at baseline was not a useful predictor of outcome over the 3 years. Clinical status at enrolment predicted 88% of the deaths. Data from a North American study of 254 untreated children with mild to moderate symptoms of HIV show similar outcomes. Mean CD4% was 25% and there was a mean observation period on study of 5.1 years. Survival statistics demonstrated dramatic thresholds at a CD4% of > 15% (Table II).<sup>14</sup>

TABLE II. CORRELATION OF CD4 CELL% WITH MORTALITY

CD4%	Deaths	No. of children	% mortality
> 25	31	130	23.8
15-25	16	62	25.8
< 15	44	60	73.3

It is hoped that the guidelines presented in this journal will provide a wide safety net for the initiation of therapy. In the South African context, where facilities are available for those who are on medical aid or who are able to pay for medication, it seems prudent to offer this wide safety margin. If ART becomes more widely accessible in the public sector, implementation of the WHO guidelines may be a more affordable option. Deferring treatment should not, however, preclude continued and regular monitoring. If it is decided that a child does not require therapy at the initial visit, the patient should be monitored at regular intervals (3 - 6-monthly) for clinical and immunological deterioration so that treatment can be started timeously. Continued monitoring ensures that the risks of delaying therapy are minimised as much as possible. The concern remains whether delaying therapy will ultimately affect immune recovery, thereby compromising the long-term outcome, and this needs further research.

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