CHARACTERISTICS OF CHILDREN STARTING ART

A literature review of 30 paediatric studies or treatment programmes found that children receiving ART ranged from infants aged 2 months to adolescents aged 15 years. 5 Of 26 studies that reported age at ART initiation, 19 (73%) showed a mean or median age at start of treatment of >5 years. Only two studies reported a median age at start of treatment of <2 years.

The majority of children assessed in this review had severe immunosuppression at initiation of ART. The proportion of children with a CD4 percentage <15% ranged from 56% to 96%.

Overall mortality during follow-up was mostly low, with a probability of survival at 1 year after initiation of ART of 84 - 97%. A study from Cote D’Ivoire reported over 3 years of follow-up, with 92 - 93% survival 6 months after initiation of ART, 91% at 12 months, 88% at 18 - 36 months and 86% at 42 months.

The majority of deaths occurred within 6 months of starting ART. The most commonly reported risk factor for death was low CD4 percentage at initiation of treatment. Age >12 - 18 months was among the other risk factors reported.

DATA FROM THE KIDS-ART-LINC COHORT COLLABORATION (AN INTERNATIONAL EPIDEMIOLOGICAL NETWORK IN SUB-SAHARAN AFRICA) CONCUR WITH THE ABOVE FINDINGS. 6 They report children starting ART at an average of 4.9 years, with only 12% starting at <12 months. Seventy per cent of children starting ART had severe immunodeficiency. The 2-year risk of death on ART was 6.9% (95% confidence interval (CI) 5.9 - 8.1%), and this was independently associated with immunodeficiency, adjusted hazard ratio (AHR) 2.95 (95% CI 1.49 - 5.83) and advanced clinical disease AHR 3.65 (95% CI 1.95 - 6.83).

KIDS-ART-LINC shows an increase in mortality risk in children starting ART when severely immunodeficient compared with children who were not immunodeficient, with the probability of death at 6 months rising from 1.8% to 7.8%. 9 Twelve months after starting ART the probabilities of death are 2.2% and 8.2% respectively.

Of note, where the entry point is reported, the majority of children are identified and enrolled into ART programmes through health facilities when they are treated when clinically indicated rather than as infants through PMTCT programmes.

Only two studies assessed in the literature review report how children were referred for ART. 5 In a Kenyan
69% of children were referred following admission to hospital and the remaining children were referred from other outpatient clinics. In Côte d’Ivoire, the paediatric department or other health care settings referred 64% of children, 24% were referred through people living with HIV/AIDS network and 12% through PMTCT programmes.

Programme data from Malawi show that only 1% of children starting treatment were identified through the programme. 63% of children were referred following hospital admission to hospital and the remaining children were referred from other outpatient clinics. In Côte d’Ivoire, the paediatric department or other health care settings referred 64% of children, 24% were referred through people living with HIV/AIDS network and 12% through PMTCT programmes.

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PMTCT follow-up, with the vast majority (80%) enrolled for ART through hospital wards.\textsuperscript{10}

The WHO reports that only 8\% of infants born to pregnant women with HIV in 2007 were tested for HIV before they were 2 months old.\textsuperscript{1}

**EVIDENCE FOR EARLY TREATMENT FROM THE CHER STUDY**

The Children with HIV Early Antiretroviral Therapy (CHER) study, conducted in South Africa, is looking at whether early limited ART until a child’s first or second birthday would have long-term benefit by delaying disease progression and/or delaying the time when long-term continuous ART needs to be initiated.\textsuperscript{3} In this study 377 young infants aged 6 - 12 weeks with a CD4 percentage >25\% were randomised to three arms:

- **Arm 1**: Deferred treatment – ART when the CD4 percentage declined to <20\% (25\% if <1 year; based on WHO guidelines).
- **Arm 2**: Short course (to first birthday) – ART with planned interruption at 1 year.
- **Arm 3**: Long course (to second birthday) – ART with planned interruption at 2 years.

ART was started or restarted in all arms when the CD4 percentage fell to <20\% (25\% in infants from August 2006) or the CD4 count fell to <1 000 cells/µl if age <12 months, or if indicated by a clinical event.

All infants were drug-naïve except for PMTCT prophylaxis (either nevirapine (NVP) single dose to mother and baby - 68\% arm 1; 64.3\% arms 2/3, or NVP plus short-course zidovudine (AZT) - 21\% arm 1; 20.2\% arms 2/3). The infants’ ART regimen was AZT + lamivudine (3TC) + lopinavir/ritonavir (LPV/r).

Following a data safety monitoring board (DSMB) review on 20 June 2007, after the trial was fully recruited and on 20 June 2007, the DSMB recommended modification to the study and the release of the results of arm 1 vs. arms 2/3 combined. They recommended that infants in arm 1 should be recalled urgently and assessed for ART initiation and that the trial follow-up should continue.

At the time of the review, 10 (4\%) infants in arms 2/3 and 4 (3.2\%) in arm 1 were lost to follow-up. By the end of April 2007, 61 (59\%) infants had initiated ART in arm 1. A total of 30 infants had died: 10 (4\%) in arms 2/3 and 20 (16\%) in arm 1 (hazard ratio (HR) 0.24 (95\% CI 0.11 – 0.52); p=0.0002).

Of the infants who died, 12 died at home from unknown causes. Causes of death in the 18 infants who died in hospital were gastroenteritis (4, arm 1; 4 arms 2/3), sepsis/pneumonia (5 arm 1; 0 arms 2/3), Pneumocystis jiroveci pneumonia/cytomegalovirus infection (3 arm 1; 0 arms 2/3), sudden infant death syndrome (0 arm 1; 1 arms 2/3), liver failure (0 arm 1, 1 arms 2/3).

The investigators noted that the deaths in this study were not always from AIDS-defining causes and were often sudden.

The CHER study found that starting ART before 12 weeks of age reduced early mortality by a highly significant 75\% compared with starting at CD4 percentages <25\% or guided by clinical symptoms.

**NEW WHO RECOMMENDATIONS**

On 13 June 2008, following a technical review of these data and another small study conducted in South Africa that supports the CHER findings, the WHO revised their guidelines to recommend universal treatment of all HIV-infected infants <12 months of age.\textsuperscript{7,11} The WHO strongly recommends that ‘All infants under 12 months of age with confirmed HIV infection should be started on ART, irrespective of clinical or immunological stage.’

In order to benefit from early treatment and to reduce their risk of disease and death, infants will need to be tested at the earliest opportunity.

For diagnosing infants the WHO strongly recommends that:

- Infants known to be HIV exposed, i.e. born to mothers in PMTCT programmes, have a virological test (HIV nucleic acid test) at 4 - 6 weeks of age.
- Any infant presenting at a health facility with signs or symptoms that may be an indication for HIV, should initially be tested using an HIV antibody test with a positive test confirmed by virological testing if possible.
- All infants should have their HIV status established at their first contact with the health system, preferably before 6 weeks of age (in most cases this will be established by asking the mother and checking her history of HIV testing).
- They also conditionally recommend that infants <6 weeks of age in settings of high antenatal HIV prevalence (i.e. >1\%) should be offered maternal or infant HIV antibody testing.

The WHO recommends that infants are diagnosed using virological tests (HIV DNA polymerase chain reaction (PCR), HIV RNA PCR or bDNA or NASBA; or ultrasensitive p24 antigen). The HIV DNA PCR is the only test that can be performed using dried blood spot samples and is the most useful for early diagnosis in PMTCT follow-up.

They also recommend that testing is performed around 4 - 6 weeks for PMTCT follow-up, and whenever an infant
is sick or HIV is suspected in those known to be exposed. Testing at 4 weeks instead of at 6 weeks provides an additional 2 weeks to start treatment at a time when the infant is very vulnerable.

If virological testing is not available, the WHO recommends presumptive diagnosis in accordance with nationally defined algorithms. Based on data from the CHER study, they are refining an algorithm based on symptoms and signs of HIV at 6 weeks of age. Although lacking sensitivity, suggestive signs include oral thrush, hepatomegaly, splenomegaly, lymphadenopathy, diaper dermatitis, and clinical gastro-oesophageal disease (cough and/or vomiting during feeds).

### STARTING TREATMENT

The guidelines recommend ART regimens as follows:

- No maternal or infant antiretroviral exposure; exposure to antiretrovirals other than non-nucleoside reverse inhibitors; unknown exposure – NVP-containing triple ART.

- Maternal or infant single-dose NVP or maternal NNRTI-containing ART – PI-containing triple ART (usually LPV/r).

Paediatric formulations for children too young to swallow tablets have traditionally been liquids or syrups. These formulations are expensive and not easy to store or transport. Cost and logistical issues have prohibited their widespread use. This example illustrates the challenges faced by the caregiver: ‘A 10 kg child being treated with standard doses of stavudine, lamivudine, and nevirapine, for whom a 3-month supply of drugs is dispensed at a clinic visit, would require 18 bottles of liquid weighing almost half as much as the child (4.3 kg). For a rural family who may have walked a long distance to reach the clinical centre, this is a significant issue’.

More recently manufacturers have developed more convenient crushable mini-pills or dispersible formulations and fixed-dose combinations, which can be used by very young children. Many programmes are now using these formulations and the WHO recommends dosing according to its simplified weight band tables (see Fig. 2).

The WHO have also identified data and formulations that need to be provided as a matter of urgency in order to support the revised recommendations:

- Additional data on dosing of efavirenz (EFV) for young children and infants
- Dosing for LPV/r for the group under 6 months and 5 kg based on a target dose of 300 mg/m²
- LPV/r sprinkles (50/12.5 mg)
- Atazanavir/ritonavir (ATV/r) (heat stable)
- Ritonavir (RTV) (solid, heat-stable forms).

### COMMENT

These recommendations from the WHO are welcome, and having a single ‘one size fits all’ policy that can be implemented without waiting for CD4 results will make

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**Fig. 2. Summary of simplified dosage of antiretrovirals for infants and children.**

**Table: Summary of simplified dosage of antiretrovirals for infants and children.**

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<thead>
<tr>
<th>Drug</th>
<th>Number of tablets or ml by weight band (twice daily)</th>
<th>Strength of adult tab (twice daily)</th>
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<td>Children 6 weeks of age and above</td>
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*Note: higher doses of Lop/rit may be substituted with 2 tablets am and 1 tablet pm of 200/50 mg. Note: higher doses of Lop/rit may be substituted with 2 tablets am and 1 tablet pm of 200/50 mg. Note: higher doses of Lop/rit may be substituted with 2 tablets am and 1 tablet pm of 200/50 mg.
starting paediatric ART more feasible. Nevertheless, implementing universal treatment for HIV-positive infants will be no small matter. Data show that currently only a few young infants are being identified and enrolled in treatment programmes in sub-Saharan Africa. The majority of children who receive ART are being diagnosed and start at about 5 years old, by which time many who needed it will have died.

The CHER investigators wrote that their results ‘... support the need for enhanced PMTCT programmes, early infant diagnosis and effective transition to care.’

Firstly, then, the focus on PMTCT deserves emphasis. Identifying and treating an HIV-positive pregnant woman who meets the eligibility criteria for ART or ensuring that a healthier HIV-positive woman receives an effective prophylaxis regimen (some would say ART for all) – and in turn avoiding the majority of paediatric infections – surely must be a massive priority. Taking appropriate care of an easier-to-manage adult patient can avoid an additional, more complicated paediatric case, and where this has not been possible, the goal of universal ART for HIV-positive infants will be far easier to achieve with lower mother-to-child transmission rates.

Secondly, running DNA PCR tests in order to diagnose infants early enough to benefit from these recommendations is not going to be feasible in many places. Low-cost, simple diagnostic assays are urgently needed. In the meantime improved clinical and laboratory-based algorithms are expected to refine the specificity of presumptive diagnosis. Clear recommendations are needed for repeat testing in breastfeeding populations.

Thirdly, better links between PMTCT and treatment programmes for those children who are infected are important and will reduce delays in starting infants on ART.

Finally, we need good data to give guidance as to whether, once started, ART can be safely stopped in children after early initiation, and if it can, when the best time will be to resume therapy.

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REFERENCES