STARTING INFANTS ON ANTIRETROVIRAL THERAPY

Polly Clayden
HIV i-Base, London, UK

The most effective way to combat paediatric HIV infection is through good management of maternal health and prevention of mother-to-child transmission (PMTCT). However, by the end of 2007, of an estimated 33.2 million people living with HIV, 2.1 million were children. Of these 90% lived in sub-Saharan Africa and 420 000 were newly infected in that year.[1]

Although in recent years the number of children treated with antiretroviral therapy (ART) has increased from about 75 000 in 2005 to almost 200 000 in 2007, many children living with HIV are not receiving treatment. Without it approximately 35% will die before their first birthday and 53% by the time they reach the age of 2 years.[2] By age 5 years it is estimated that 62 - 89% of children will have died.[3,4]

Emerging data from sub-Saharan Africa show that most children starting ART are doing so at older ages, usually 5 years or more, that most start at a late stage of the disease, and that mortality in the first few months of treatment remains high.[5,6]

A recent study shows that starting treatment in early infancy can be lifesaving, and this has informed revisions in World Health Organization (WHO) guidelines[7,8] (see WHO 'Dear Health Care Provider' letter, Fig. 1). At present the majority of children who could benefit from these recommendations are not being diagnosed or treated.

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

programme 69% of children were referred following admission to hospital and the remaining children were from other outpatient clinics. In Cote D'Ivoire, the paediatric department or other health care settings referred 64% of children, 24% were referred through the 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

World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Tel. direct: +41 22 7911609
Fax direct: +41 22 791 4834
E-mail : crowleys@who.int

In reply please refer to: A21-370-31

Your reference:

Health Care Providers

03 November 2008

Dear Health Care Provider,

The World Health Organization (WHO) has recently revised the guidelines for diagnostic testing, initiation of treatment, and treatment regimens for HIV-exposed and infected infants **(children< 12 months of age)**. Currently very few infants are starting ART.

The new recommendations state that:

- all infants diagnosed with HIV need to immediately start ART and continue treatment for the rest of their lives;
- all HIV exposed infants need viral HIV testing at or around 4-6 weeks of age to detect HIV early;
- Infants with HIV who have NOT received nevirapine as prophylaxis at or around birth start on a nevirapine based first line regimen;
- Infants with HIV who have received nevirapine as prophylaxis should start ART with a lopinavir/ritonavir containing treatment regimen.

One of the key new recommendations is that all infants (children< 12 months of age) diagnosed with HIV should receive life-long therapy as soon as possible after diagnosis.

These recommendations have important implications for health care providers, which include the need to:

- perform early routine viral HIV testing for all HIV-exposed infants at 4-6 weeks or as early thereafter as possible;
- ensure viral HIV testing is performed for all infants suspected of having HIV;
- make sure recommendations for standard first-line antiretroviral treatment regimens for infants are followed;

.../2

- start ART even where the HIV infected infant is well, and prior to the development of signs and symptoms.

منظمة الصحة العالمية • 世界卫生组织
Organisation mondiale de la Santé • Всемирная организация здравоохранения • Organización Mundial de la Salud

Health Care Providers Page 2

- follow standardized appropriate dosing schedules for use of ART in infants;
- modify starting regimens for infants who have received nevirapine for prophylaxis wherever possible.

WHO has updated recommendations for dosing of ARVs in infants and children which is available at (http://www.who.int/hiv/paediatric/Sum_WHO_ARV_Ped_ARV_dosing.pdf)

It is hoped that these new recommendations will ensure that more infants are able to access life saving ART. Strenuous efforts should also be made to prevent new infections in infants.

It is also clear from published studies that children with HIV who survive infancy are also accessing ART very late, usually when they already very unwell. This makes ART more complicated to manage and worsens treatment outcomes. Earlier diagnostic testing for all sick children is also needed.

WHO is updating the full paediatric HIV treatment guidelines to make them available as soon as possible.

Yours sincerely,

Dr Kevin M. De Cock
Director
Department of HIV/AIDS

For further details please contact:

Dr Siobhan Crowley
Paediatric & Family HIV Care
Department of HIV/AIDS
World Heath Organization,
20 Avenue Apia,
1211 Geneva 27 - Switzerland.
Tel +41 (0)22 791 1609
E-mail: crowleys@who.int

منظمة الصحة العالمية • 世界卫生组织
Organisation mondiale de la Santé • Всемирная организация здравоохранения • Organización Mundial de la Salud

Fig. 1. WHO 'Dear Health Care Provider' letter.

PMTCT follow-up, with the vast majority (80%) enrolled for ART through hospital wards.[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.[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.[7] 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 at a median follow-up of 32 (range 20 - 48) weeks, 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.[7,8,11] 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.[12] 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 challenge 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.'[13]

More recently manufacturers have developed more convenient crushable mini-pills or dispersable formulations and fixed-dose combinations, which can be used by very young children.[14-16] 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/m^2
- 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

Drug	Strength of tab (mg) or liquid mg/ml	Number of tablets or ml by weight band (twice daily)												Strength of adult tab (mg)	Number of tablets by weight band (twice daily)	
		Children 6 weeks of age and above (0.75 BD is delivered as 1 tablet AM and 0.5 tablets PM and 1.5 BD is delivered as 2 tablets AM and 1 tablet PM)														
		3-3.9 kg	4-4.9 kg	5-5.9 kg	6-6.9 kg	7-7.9 kg	8-8.9 kg	9-9.9 kg	10-10.9 kg	11-11.9 kg	12-13.9 kg	14-16.9 kg	17-19.9 kg	20-24.9 kg		25-29.9 kg	30-34.9 kg
AZT	60	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300	1	1
AZT (new annex E)	300; 10 mg/ml	6 ml	6 ml	6 ml	9 ml	9 ml	9 ml	9 ml	12 ml	12 ml	12 ml	0.5	0.5	0.75	300	1	1
AZT/3TC	60/30	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300/150	1	1
AZT/3TC/NVP	60/30/50	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300/150/200	1	1
ABC	60	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300	1	1
ABC (new annex E)	300; 20 mg/ml	3 ml	3 ml	3 ml	4 ml	4 ml	4 ml	4 ml	6 ml	6 ml	6 ml	0.5	0.5	0.75	300	1	1
ABC/3TC	60/30	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300/150	1	1
ABC/3TC/NVP	60/30/50	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300/150/200	1	1
ABC/AZT/3TC	60/60/30	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300/300/150	1	1
3TC	30	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	150	1	1
3TC (new annex E)	150; 10 mg/ml	3 ml	3 ml	3 ml	4 ml	4 ml	4 ml	4 ml	6 ml	6 ml	6 ml	0.5	0.5	0.75	150	1	1
d4T	6	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	30	1	1
d4T (new annex E)	various; 1 mg/ml	6 ml	6 ml	6 ml	9 ml	9 ml	9 ml	9 ml	1x15 mg	1x15 mg	1x15 mg	1x20 mg	1x20 mg	1x20 mg	30	1	1
d4T/3TC	6/30	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	30/150	1	1
d4T/3TC/NVP	6/30/50	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	30/150/200	1	1
NVP	50	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	200	1	1
NVP (new annex E)	200; 10 mg/ml	5 ml	5 ml	5 ml	8 ml	8 ml	8 ml	8 ml	10 ml	10ml	10 ml	0.75	0.75	0.75	200	1	1
Lopinavir/ritonavir	100/25	n/r	n/r	n/r	n/r	n/r	n/r	n/r	1.5	1.5	1.5	2	2	2.5	100/25 * (paed)	3	3
Lop/rit (new annex E)	80/20 mg/ml	1 ml	1.5 ml	1.5 ml	1.5 ml	1.5 ml	1.5 ml	1.5 ml	2 ml	2 ml	2 ml	2.5 ml	2.5 ml	3 ml	80/20 mg/ml	3.5 ml	4 ml

* 3 tablets BD of 100/25 may be substituted with 2 tablets am and 1 tablet pm of 200/50
Note: higher doses of Lop/rit may be required when co-administered with enzyme-inducing drugs such as NVP, EFV; fosamprenavir, rifampicin.

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

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.

The author would like to thank Siobhan Crowley, Mark Cotton and Di Gibb for discussion of these data and recommendations.

REFERENCES

1. *Towards Universal Access: Scaling Up Priority HIV/AIDS Interventions in the Health Sector.* WHO/UNAIDS/UNICEF 2008. http://www.who.int/hiv/pub/towards_universal_access_report_2008.pdf (accessed 27 November 2008).
2. Newell ML, Coovadia H, Cortina-Borja M, *et al.* Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. *Lancet* 2004; 364: 1236–1243.
3. Spira R, Lepage P, Msellati P, *et al.* Natural history of human immunodeficiency virus type 1 infection in children: a five-year prospective study in Rwanda. *Pediatrics* 1999; 104: e56.
4. Taha TE, Graham SM, Kumwenda NI, *et al.* Morbidity among human immunodeficiency virus-1-infected and uninfected African children. *Pediatrics* 2000; 106: E77.
5. Sutcliffe CG, van Dijk JH, Bolton C, *et al.* Effectiveness of antiretroviral therapy among HIV-infected children in sub-Saharan Africa. *Lancet Infect Dis* 2008; 8: 477–489.
6. Arrive E, Kyabayinze DJ, Marquis B, *et al.* Cohort profile: The Paediatric Antiretroviral Treatment Programmes in Lower-Income Countries (KIDS-ART-LINC) Collaboration. *Int J Epidemiol* 2007; 37(3): 474-480.
7. Violari A, Cotton M, Gibb D, *et al.* Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med* 2008; 359: 2233-2244.
8. World Health Organization. Antiretroviral therapy of HIV infection in infants and children: towards universal access. http://www.who.int/hiv/pub/guidelines/art/en/index.html (accessed 27 November 2008).
9. Arrivé E, Marquis B, Tumwesiye N, *et al.* Response to ART in children in sub-Saharan Africa: A pooled analysis of clinical databases, the KIDS-ART-LINC Collaboration. 14th Conference on Retroviruses and Opportunistic Infections, 25 – 28 February 2008, Los Angeles. Abstract 727.
10. World Health Organization. http://www.who.int/hiv/topics/paediatric/en/index.html (accessed 27 November 2008).
11. Prendergast A, Chonco F, Tudor-Williams G, *et al.* Randomised, controlled trial of 3 approaches to management of HIV-infected infants. 15th Conference on Retroviruses and Opportunistic Infections, 3 – 6 February 2008, Boston, USA. Oral abstract 77LB.
12. Jaspan HJ, Myer L, Violari A, *et al.* Clinical and immunological characteristics of very young infants with HIV infection: Children with HIV Early Antiretroviral Study. In: 15th Conference on Retroviruses and Opportunistic Infections, 3 – 6 February 2008, Boston, USA.
13. American Academy of Paediatrics. Increasing antiretroviral drug access for children with HIV infection. *Paediatrics* 2007; 119(4): 838-844.
14. L'homme R, Dijkema T, Warris A, *et al.* Pharmacokinetics of two generic fixed dose combinations for HIV-infected children (Pedimune Baby & Pedimune Junior) are comparable to the branded products. 7th International Workshop on Clinical Pharmacology of HIV Therapy, 20 - 22 April 2006, Lisbon. Abstract 23.
15. Pharmacokinetics for generic fixed dose combinations for children are comparable to the branded products. *HIV Treatment Bulletin* 2006; 7(6). http://www.i-base.info/htb/v7/htb7-6/Pharmacokinetics.html (accessed 27 November 2008).
16. Singla A, Rampal A, Garg M. *et al.* Formulation development of novel fixed dose combination (FDC) of lamivudine, stavudine and nevirapine for paediatrics. XVI International AIDS Conference, Toronto, Canada, 13 - 18 August 2006. Poster abstract MOPE0252.