



The aim of this biannual newsletter is to provide health workers in the Region with a brief, up-to-date summary of the latest developments in antiretroviral therapies.

SPECIAL FOCUS: PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV (In collaboration with UNICEF/EAPRO)

Introduction

In 1998, it was estimated that 2.4 million HIV-infected women delivered babies each year, resulting in 600 000 infants being infected with HIV annually. With 1 600 infants becoming infected with HIV each day, HIV/AIDS is now one of the world's leading causes of death among children.

In Africa, HIV infection has increased infant mortality by 75% and childhood mortality by 100%.

Of the HIV-infected children who survive infancy, 34% die in the first year of life, 66% die within 3 years of birth and 75% die by the age of 5 years. Mother-to-child transmission (MTCT) accounts for over 90% of childhood HIV infections. Most infants acquire HIV infection soon after to delivery or by breastfeeding, with a minority becoming infected in utero.

Table 1: Antiretroviral interventions to reduce HIV perinatal transmission

Study	Drug	Antiretroviral regimen				Relative efficacy	Cost ³ (U.S.)	Cost ³ developing Country
		Antenatal	Intrapartum	Postpartum mother	Postpartum infant			
USA/France PACT 076	ZDV	100 mg orally five times daily from 14-34 weeks gestation	2 mg/kg IV infusion over 1 hour, followed by continuous infusion of 1 mg/kg/hr	No	2mg/kg orally 6 ^h hourly for 6 weeks	68% (infection status at age 18 months)	\$800 to \$1000	\$200 to \$400
Thailand CT: Mod 07	ZI	300 mg orally twice daily from 36 weeks gestation	300 mg orally every 3 hours	No	No	50% (infection status at age 6 months)	\$200 to \$300	\$50 to \$100
Ivory Coast	ZDV	300 mg orally twice daily from 36 weeks gestation	300 mg orally every 3 hours	No	No	37% (infection status at age 3 months)	\$200 to \$400	\$50 to \$100
Ivory Coast/Burkina Faso	ZI	300 mg orally twice daily from 36-38 weeks gestation	600 mg oral at onset of labor	No	No	38% (infection status at age 3 months)	\$210 to \$300	\$70 to \$210
Africa PETRA Arm 1	ZDV/3TC	ZDV 300 mg + 3TC 150 mg orally twice daily from 36 weeks gestation	ZDV 300 mg orally every 3 hours + 3TC 150 mg orally 12 ^h hrly	ZDV 300 mg + 3TC 150 mg orally twice daily for 1 week	ZDV 4mg/kg + 3TC 2mg/kg orally twice daily for 1 week	50% (infection status at age 6 weeks)	\$500 to \$600	\$130 to \$175
Africa PETRA Arm 2	ZI/3TC	No	ZDV 300 mg orally every 3 hours + 3TC 150 mg orally 12 ^h hrly	ZDV 300 mg + 3TC 150 mg orally twice daily for 1 week	ZDV 4mg/kg + 3TC 2mg/kg orally twice daily for 1 week	37% (infection status at age 6 weeks)	\$85	\$20 to \$30
Uganda HIVNET 012 Arm 1	Nevirapine	Single 200mg dose orally at the onset of labor	No	No	Single dose of 2mg/kg within 72 hours of birth	83% ⁴ (infection status at age 14-16 weeks)	Approx. \$4	Approx. \$4
Uganda HIVNET 012 Arm 2	ZI	No	600mg oral at onset of labor then 300 mg orally every 3 hours	No	ZDV 4mg/kg orally twice daily for 1 week	43% ⁴ (infection status at age 14-16 weeks)	not stated	not stated

ZDV = Zidovudine

1. If no antenatal drug is administered in the 12 hours prior to the commencement of labour, loading dose of 600mg ZDV administered followed by 300mg orally every 3 hours.
2. Relative efficacy is the transmission rate with an intervention compared to that observed without intervention – the higher the efficacy rate, the more effective the intervention.
3. Cost of antiretroviral agent(s) only.
4. Based on 30% transmission rate with no intervention

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The efficacy of zidovudine prophylaxis on preventing MTCT is now clearly established and strategies to reduce MTCT in developed countries are focused on antiretroviral intervention regimens. The results of pivotal MTCT intervention trials to date are summarized in Table 1.

There is also clear evidence that elective Caesarean section and avoidance of breast-feeding independently reduce the risk of MTCT of HIV.

Prevention strategies, in addition to antiretroviral agents, include improving maternal and child health care infrastructure, antenatal counselling and HIV testing, appropriate antenatal and intrapartum care and tactics to reduce the substantial risk of transmission by breast milk.

Nevirapine

Results from a recently published pivotal study (HIVNET 012) indicate the value of single-dose nevirapine in the prevention of MTCT.

Nevirapine is a potent non-nucleoside reverse transcriptase inhibitor, which is rapidly absorbed following oral administration and readily crosses the placenta. It has a long plasma half-life, 45 hours following a single dose, falling to 20-30 hours after multiple dosing due to autoinduction of hepatic cytochrome p450 enzymes. Median cord blood concentrations reach 83% and median breast milk concentrations 60% of maternal serum concentrations. In vitro studies of nevirapine indicate inhibition of viral replication by 50% (IC₅₀) at a concentration of 0.01µg/ml.

Phase I/II studies have shown that a single oral dose of 200mg given to the mother at the onset of labour and a single oral dose of 2mg/kg given to the infant at age 24-72 hours produce serum concentrations in excess of 0.1µ/ml (10 times higher than the IC₅₀) throughout the first week of life.

HIVNET 012 compared nevirapine given in the above regime to the mother and infant with zidovudine given to the mother at the onset of labour as a single oral dose of 600mg followed by 300mg every 3 hours until delivery. The infant received zidovudine 4mg/kg twice daily for 7 days after birth. All women were infected with HIV-1. Nevirapine does not inhibit replication of HIV-2, which is prevalent in both West Africa and India.

In the study, 645 pregnant women were randomly selected to receive nevirapine, zidovudine or a placebo. The placebo group was dropped (19 women received the placebo) following the results of the CDC Thai short-course zidovudine trial. 302 first-born evaluable infants received nevirapine and 307 received zidovudine. 98.8% of the infants were breast-fed from birth and 95.6% were still being breast-fed at 14-16 weeks of life.

Table 2: HIV vertical transmission rate with ZDV and Niverapine

Estimated risk of transmission	ZIDOVDINE	NEVIRAPINE	p-value
At birth	10.4%	8.2%	0.34
Weeks 6-8	21.3%	11.9%	0.0027
Weeks 14- 6	25.1%	13.1%	0.0016

The transmission rates were 47% lower in the nevirapine group compared to the zidovudine group (95% confidence interval 20%-64%) up to the age of 14-16 weeks. The control group was too small to act as a valid comparison but 6 of the 19 infants (37%) in the placebo group were infected at 14-16 weeks. The two regimens were well tolerated and adverse events were similar in the two groups. 18 infants (9 from each group) developed maculopapular rash, none of which was considered serious.

In ongoing studies, ACTG 316 (USA, Europe and Brazil) is comparing the combination of zidovudine and nevirapine with zidovudine alone. The SAINT (South Africa Intrapartum Nevirapine Trial) is comparing the HIVNET 012 nevirapine regimen with the B regimen of the PETRA study (zidovudine + lamivudine).

An article accompanying the HIVNET 012 report assessed the cost-effectiveness of this intervention. The drug cost of the two dose nevirapine regimen is US\$4 per mother-infant pair. However, when calculating the real cost of the intervention, associated costs such as HIV testing of pregnant women, counselling and care services should also be considered.

Caesarean section

The protective effect of Caesarean section has been variably reported in studies of MTCT.

The International Perinatal HIV Group has published results of a meta-analysis of 15 prospective North American and European studies to examine the impact of mode of delivery on MTCT. (N Engl J Med 340:April 1 1999)

8533 mother-child pairs were included in the analysis of whom 4675 mother-child pairs did not receive antiretroviral therapy. Breast-feeding women were excluded. Four methods of delivery were compared:

- Elective Caesarean section prior to labour and membrane rupture
- Non-elective Caesarean section after membrane rupture/onset of labor
- Instrumental vaginal delivery
- Non-instrumental vaginal delivery

Other variables studied were use of zidovudine by mother and child and HIV disease status as measured by presence of an AIDS defining illness and/or CD4 count <200 cells/mm³ or <14%. Viral load data were not available. Results are summarized in Table 3.

Table 3: Results of US/European study on HIV vertical transmission prevention: rates of HIV transmission		
	Vaginal delivery	Elective Caesarian section
No antiretroviral therapy	19%	10.4%
Antiretroviral therapy	7.3%	2%

Longer duration of rupture of membranes prior to delivery also increased the rate of MTCT (11.7% with rupture less than one hour and 13.5% with rupture less than 4 hours).

Antiretroviral use and elective Caesarian section were independent, additive variables in reducing vertical transmission of HIV-1. Elective Caesarian section reduced MTCT of HIV-1 by approximately 50% and, in conjunction with zidovudine, by approximately 87%.

Infant feeding and mother-to-child transmission of HIV

Current estimates are that a child breast-feeding from an HIV-positive mother has a 15% risk of infection by this route, with transmission of HIV occurring at a rate of approximately 0.5% per month that the infant is breast-fed. The studies on which this estimate is based do not distinguish between infants who are exclusively breast-fed and those who receive breast milk and other foods and drinks. A recently published early report (Coutsoudis et al., Lancet 1999; 354; 471-76) suggests that exclusive breast-feeding may be less likely to transmit infection. It is postulated that this may be due to other foods damaging the mucosal lining of the infant's gut allowing HIV to cross more readily.

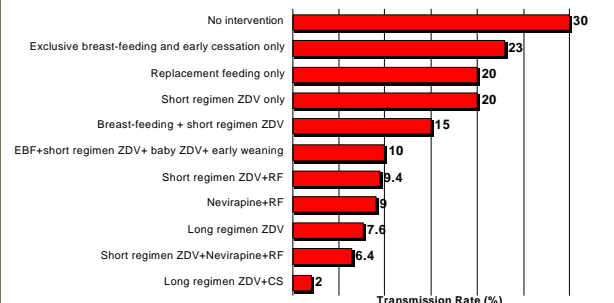
In August 1999, the World Health Organization published an update of the WHO/UNAIDS/UNICEF guidelines for infant feeding. These guidelines call for a strengthening of initiatives to promote and support breast-feeding in women who are HIV negative or of unknown HIV status. Infant feeding options for consideration by HIV-positive women include:

- Replacement feeding with commercial formula or home prepared formula
- Breast-feeding and timely supplementary feeding as normally recommended
- Exclusive breast-feeding and stopping early (3-6 months)
- Use of heat-treated expressed breast milk
- Wet nursing

There is no attempt to favour any one of these options and the guiding principle is for women to receive counselling that will enable them to make an informed decision appropriate to their situation. Where resources

permit, most HIV-positive mothers now choose to avoid breast-feeding completely. In resource limited settings, the availability, risks and cost of artificial feeding make decision making for mothers and policy-makers more difficult.

Figure 1: Estimated Rates of Mother-Infant HIV Transmission by Intervention



EBF = Exclusive Breast-feeding

RF = Replacement Feeding

CS = Caesarian section

(Sources: UNAIDS Asia Pacific Inter-country Team in Bangkok; UNICEF East Asia Pacific Regional Office and WHO Thailand)

Long-term effects of in utero Zidovudine exposure

The significant reduction in MTCT with the use of zidovudine has led to its widespread use by pregnant women and newborn infants. Its potential to affect rapidly dividing cells is demonstrated by the macrocytosis routinely observed in patients on zidovudine therapy. The potential exists for zidovudine to effect organ and growth development. Vaginal epithelial tumors have been observed in zidovudine animal studies.

The Pediatric AIDS Clinical Trials Group (PACTG) conducted a study in the US to ascertain the effects of in utero and perinatal exposure to zidovudine among children who were enrolled in the PACTG 076 trial.

A cohort of 234 HIV-uninfected children born to 230 HIV-infected women during this study were followed for 3-5 years. 122 received zidovudine (see Table 1) and 112 received a placebo. Twenty six children were lost to follow-up. The children had six monthly assessments until 24 months followed by annual review. Parameters studied were growth, immunological status, cognitive/developmental milestones, cardiac ECHO, fundoscopy, visual acuity, development of neoplasm and mortality.

No deaths or malignancies occurred and there were no statistically significant differences between the two groups in assessment of growth, cognitive/

developmental function and fundoscopy. Cardiac ECHO was abnormal in 16% of the zidovudine treated group and 15% of the children who received placebo. One of these abnormalities was considered significant. A four-year-old child who received 6 weeks of zidovudine following 20 weeks antepartum zidovudine administration to the mother had a cardiomyopathy of unknown origin. Two children exposed to zidovudine had abnormal fundoscopy, one reported as insignificant and the other to be followed up.

It should be noted that this study has several weaknesses including the short follow-up time, the lack of blinding and a true prospective study design. The sample size also has insufficient power to detect rare effects and malignancies.

There is increasing evidence that nucleoside reverse transcriptase inhibitors as a class cause mitochondrial toxicity resulting in multiple metabolic abnormalities. There has been a recent report of the deaths in two children participating in a Zidovudine/3TC study. Neither child had evidence of HIV infection and both died from a suspected mitochondrial disorder.

Summary of guidelines for the use of antiretroviral agents in paediatric HIV infection

While the general principles underlying the use of antiretroviral therapy (ARV) are similar for all HIV-infected persons, there are unique considerations in the management of HIV-infected infants, children and adolescents.

- Differences in diagnostic evaluation in perinatally infected children
- Differences in immunological markers in young children
- Changing pharmacokinetic parameters as organ systems involved in drug metabolism and clearance develop and mature with age
- The effect on viral dynamics of primary infection occurring in immunologically immature persons
- In utero exposure to zidovudine and other antiretroviral agents in perinatally infected children

- Special considerations related to adherence in this group of patients

Identification of infants at risk of perinatal exposure is best accomplished by the identification of HIV-infected women before or during pregnancy. If this is not possible, counselling and testing should be provided during the immediate post-natal period.

Diagnosis of HIV infection in infant

For neonates at risk, diagnostic testing for HIV (HIV antibody and/or HIV RNA assay) is recommended during the first 48 hours of life, at age 1-2 months and at 3-6 months. Using virological diagnostic assays, most infected infants can be definitively diagnosed by age one month and virtually all by age 6 months. Two negative HIV antibody tests at least one month apart performed after age 6 months can reasonably exclude HIV infection in children with no clinical evidence of infection. However, antibody tests can remain positive for 12 months in children who are not HIV-infected.

Monitoring of paediatric HIV infection

CD4+ lymphocyte (absolute count and percentage) is considerably higher in healthy HIV-uninfected infants compared to adults and declines to adult levels by age 6 years. While the CD4+ absolute count used to stage the level immune suppression is age dependent, the CD4% is not and may be a better marker of disease progression in children.

High HIV RNA copy numbers persist in perinatally infected children for prolonged periods. In one prospective study (Shearer et al., N Engl. J Med 1997; 336:1337-42), mean HIV RNA level in the first year of life was 185,000 copies. In contrast to the adult pattern HIV RNA levels decline over the next few years of life. This pattern reflects the reduced efficiency of the immature but developing immune system in containing viral replication. Studies have shown that HIV RNA levels in children with rapidly progressive disease and those who are clinically stable overlap considerably. Given this and the difficulty of interpreting viral load results in the first year of life, the predictive value of specific HIV RNA levels for disease progression and death is moderate.

Table 4: Levels of immunodeficiency in children from 12 months to 12 years

Immune category	<12 months		1-5 years		6-12 years	
	CD4 count	CD4 %	CD4 count	CD4 %	CD4 count	CD4 %
Category 1 no suppression	≥1,500	≥25	≥1,000	≥25	≥500	≥25
Category 2 moderate suppression	750-1,499	15-24	500-999	15-24	200-499	15-24
Category 3 severe suppression	<750	<15	<500	<15	<200	<15

When to initiate therapy

Antiretroviral therapy is recommended for children with symptomatic HIV-infection and those with evidence of immunodeficiency (Table 4: categories 2 & 3) regardless of age or viral load.

Children over one year of age with HIV RNA levels >100,000 copies/mL have a high mortality risk and ARV should be initiated regardless of clinical or immune status. In the same age group, two approaches exist for children with low viral loads (<100,000 copies/mL). Treat all patients before immunological and clinical deterioration occurs or defer therapy until there is evidence of declining CD4+ count and/or rising HIV RNA. These recommendations are based on limited data and may require revision as more information becomes available.

The high risk of disease progression in the first year of life and the limited predictive value of virological and immunological markers argues for the initiation of ARV therapy in all infants less than 12 months of age. However, there are no clinical trial data to substantiate this approach. Further, issues of adherence, drug resistance, cost and limited data on dosing schedules in neonates make definitive guidelines for the age group difficult.

Choice of antiretroviral therapy

Combination ARV is recommended for all infants, children and adolescents based on similar principles to those guiding adult therapy. A highly active combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and one protease inhibitor (PI) capable of inducing maximum suppression of viral replication offers the best chance of long term durability and immune preservation.

The preferred PIs for children who cannot swallow pills or capsules are nelfinavir and ritonavir, both of which are available in liquid formulation. Indinavir is an alternative for children who can swallow capsules.

Based on limited clinical trial evidence, alternative regimes are nevirapine plus two NRTIs, abacavir in combination with zidovudine 3TC and efavirenz plus two NRTIs. A liquid formulation of efavirenz is currently being evaluated.

Current data do not suggest that the antiretroviral regimen for infected infants should be chosen on the basis of prior maternal ARV use. However, as maternal therapy with multiple ARV agents becomes more common, the frequency of perinatal transmission of ARV-resistant isolates may increase.

Table 5: Neonatal and paediatric antiretroviral dosing schedules

	Neonatal dose	Usual paediatric dose
Zidovudin	Oral: 2mg/kg 6 th hourly Intravenously: 1.5mg/kg 6 th hourly	Oral: 160mg per m ² of body surface area 8 th hourly IV: (intermittent) 120mg per m ² of body surface area 8 th hourly IV: (continuous infusion) 20mg per m ² of body surface area hourly
Lamivudin	2mg/kg twice daily	4mg/kg twice daily
Stavudine	Under evaluation	1mg/kg 12 th hourly
Didanosir	50mg per m ² of body surface area 12 th hourly	90mg per m ² of body surface area 12 th hourly
Zalcitabine	Unknown	0.01 mg/kg 8 th hourly
Abacavir	Under evaluation	8mg/kg 12 th hourly (max 30mg twice daily)
Nevirapine	Under evaluation	120 mg per m ² of body surface area 12 th hourly for 14 days then 200mg per m ² of body surface area 12 th hourly (if no rash)
Efavirenz	Unknown	200mg-600mg once daily (10-40kg)
Delavirdine	Unknown	Unknown
Indinavir	Unknown	Under evaluation
Nelfinavir	Under evaluation	20-30 mg/kg 8 th hourly
Ritonavir	Under evaluation	Initially, 250 mg per m ² of body surface area 12 th hourly increasing step-wise to 400mg per m ² of body surface area 12 th hourly over 5 days
Saquinavir	Unknown	Unknown

Further reading

1. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children convened by the National Pediatric and Family HIV Resource Center (NPHRC), the Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH) International Association of Physicians in AIDS Care
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**Sexually Transmitted Infections
and AIDS Focus
WHO Regional Office for
the Western Pacific**

**United Nations Avenue, (P.O. Box 2932),
1000 Manila, Philippines
Fax no. (632)521-1036, 526-0279, 526-0362
Tel. No.: (632)528-8001
Email: sti@who.org.ph
Website: www.who.org.ph**