HIV/AIDS Antiretroviral Newsletter

World Health Organization

Regional Office for the Western Pacific

AUGUST 1999
Issue No. 1

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.

New agents

Abacavir (Ziagen) - nucleoside reverse transcriptase inhibitor

The recommended dose of abacavir is 300 mg twice daily.

In key research studies, abacavir therapy has been evaluated in chronically HIV-infected patients as part of triple therapy with two other nucleosides (AZT and 3TC or Combivir®) and as part of dual therapy with a protease inhibitor (indinavir, saquinavir SGC, ritonavir, nelfinavir or amprenavir). In a study of the new protease inhibitor amprenavir with abacavir, 41 treatment-naive people took amprenavir (1 200 mg twice daily) and abacavir for 6 months. In an intention-to-treat analysis, 80% had HIV-RNA below 500 copies/ml and 68% were below 50 copies/ml. The mean increase in CD4+ lymphocytes was 100 cells/mm^3.

562 patients were enrolled into a randomized, double-blind study comparing abacavir/Combivir® with indinavir/Combivir® (CNA3005). Intent-to-treat analysis at week 24 showed 65% of both groups had viral loads below 400 copies/ml.

The incidence of hypersensitivity reaction in people taking abacavir is 3%. It is characterized by rash, fever, malaise, fatigue and gastrointestinal symptoms such as nausea, vomiting, and diarrhoea. It generally occurs within four weeks of starting abacavir, and usually resolves within one to two days after ceasing abacavir treatment. Abacavir should be stopped immediately and NOT resumed since rechallenge can produce a life-threatening anaphylactic reaction.

Cost per year in the USA: US$ 3 500.

Amprenavir - protease inhibitor

The recommended dose of amprenavir is 1 200 mg (eight 150 mg caps) twice daily with or without food. It is available as 50 mg and 150 mg soft gel capsules, and as 150 mg/ml oral solution.

In one of the two licensing studies, 221 treatment naive participants were randomized to AZT/3TC/amprenavir or AZT/3TC/placebo. Median baseline viral loads were 4.61 log and 4.74 log and CD4+ lymphocyte counts were 435 and 409 for the amprenavir and placebo groups, respectively. Intention-to-treat analysis at 16 weeks found that, in the amprenavir group, 60% of those on amprenavir treatment were below 50 copies/ml compared with 9% in the placebo group

Amprenavir (1 200 mg bid), abacavir (300 mg bid) and efavirenz (600 mg once daily) were given as salvage therapy to 99 people who had at least 20 weeks prior PI therapy and detectable plasma RNA following at least 12 weeks on their current PI containing regimen. Median baseline HIV-RNA was 5.06 log (100 000 copies) and median CD4 was 169. Participants with baseline viral load <40 000 copies/ml and those who were NNRTI-naive at baseline responded better to the salvage regimen. At week 16, 53% of those with the lower baseline viral load had HIV-RNA <400 copies, compared with 23% in the group with initial viral load > 40 000 copies/ml.

Combination protease inhibitor therapy was studied in 33 individuals who received amprenavir with one of three protease inhibitors or as a single protease inhibitor with AZT/3TC added after three weeks. All participants had baseline HIV-RNA of >10 000 copies/ml. The protease inhibitors used were saquinavir soft gel caps, indinavir and nelfinavir taken at standard doses and amprenavir, taken as 800 mg TID. At 24 weeks, reductions in viral load were 2.72 log in the saquinavir

IN THIS ISSUE:

arm, 2.25 log in the indinavir arm and 1.81 log in the nelfinavir arm. Ten out of 22 people remained below 50 copies/ml at week 24.

The safety profile of amprenavir in 606 subjects who had been exposed to amprenavir for at least 12 weeks, and 41 for at least 48 weeks was recently reviewed. The most frequently reported adverse events were nausea (51%), diarrhoea (37%), rash (28%), oral paraesthesia (25%), headache (24%), fatigue (23%) and vomiting (23%). The majority of adverse events were mild to moderate (grade 1 or 2), early onset (2-21 days after commencing therapy) and transient in nature (3-46 days duration). Laboratory abnormalities reported most frequently from the two phase III trials were increased transaminase levels (overall incidence ≤ 5%), and hypertriglyceridemia (3%).

The I50V mutation was observed in vitro to be a key amprenavir resistance mutation. In addition to this, the 154V, 154L, I84V, I50V, M46I and I47V mutations are associated with phenotypic resistance to amprenavir. Some of these are also associated with resistance to other PIs.

Cost per year in the USA: US$ 6 000.

Efavirenz

Efavirenz is the newest of the non-nucleoside reverse transcriptase inhibitors (NNRTI) and will be marketed under the tradename Sustiva in Europe and North America and as Stocrin in the rest of the world.

The recommended dose of efavirenz is 600 mg, taken as three 200 mg capsules once a day before bed, with or without food. Taking the drug with food may increase drug levels in some people by up to 50%.

Efavirenz is contra-indicated in pregnancy. Studies of animals treated with efavirenz showed high rates of birth defects. A pivotal study (DMP 266-006) enrolled 450 participants in an open-label, randomised comparison of efavirenz and AZT/3TC *versus* indinavir and AZT/3TC *versus* efavirenz and indinavir, all in standard doses. The participants were protease inhibitor, NNRTI and 3TC naive. At baseline, the mean CD4 count was 345 cells and mean viral load was 58 884 copies/ml. After 48 weeks, 71% of people on efavirenz/AZT/3TC had viral loads below 400 copies compared to 48% on indinavir/AZT/3TC and 54% on EFV/IDV by intent-to-treat analysis. For viral load below 50 copies, the figures are 65%, 43% and 48% respectively. Increase in CD4 count was approximately 175 cells in all three arms. There were more study medication related discontinuations in the indinavir/AZT/3TC arm (38%) compared to approximately 21% in the other arms.

CNS-related symptoms, mostly grade 1 in severity, were reported in 55% of efavirenz recipients. These were confusion, dizziness, agitation, amnesia, depersonalisation, euphoria, hallucinations, insomnia, somnolence, impaired concentration, abnormal dreaming and stupor. Approximately 30% of EFV recipients experienced rash resulting in four discontinuations.

Efavirenz was studied in 57 children, with an average age of 8 years, who took efavirenz/nelfinavir plus two NRTIs. Doses were adjusted based on drug levels at weeks two and six. Intent-to-treat analysis at week 20 found two-thirds of the children were below 400 copies/ml and median CD4 count rise was 106 cells.

K103N is the predominant resistance mutation observed in vivo among efavirenz treatment failures. In studies DMP 226-003 and DMP 266-004, treatment failure virus isolates carrying K103N, V108I and/or Y188L mutations showed a >20 fold increase in the in vitro IC50 for efavirenz compared to pre-therapy isolates. These isolates were also resistant to nevirapine and delavirdine.

Cost per year in the USA: US$ 4 700.

Treatment strategies

A three-year follow up study of 33 patients taking indinavir (800 mg TID) with AZT (200 mg TID) and 3TC (150 mg BID) was recently carried out. Participants in this study were AZT pre-treated, and protease inhibitor and 3TC naive. There were 11 withdrawals, 7 due to viral rebound. 39% had at least one episode of nephrolithiasis during the 36 months and 19% had lipodystrophy as assessed by the study investigators.

Results

% undetectable (Intent-to-treat analysis)			
Week	Week 100	Week 124	Week 148
<500 copies/ml	78% (25/32)	68% (21/31)	67% (20/30)
<50 copies/ml	66% (21/32)	55% (17/31)	67% (20/30)

Saquinavir SGC (Fortovase) taken twice daily is being compared to three times per day in the TID-BID study, with results at 32 weeks being reported.

840 treatment naive and experienced participants were randomized to one of three study arms.

ARM A: Fortovase 1 200 mg TID + 2 new nucleosides
ARM B: Fortovase 1 600 mg BID + 2 new nucleosides
ARM C: Fortovase 1 200 mg BID + nelfinavir 1 250 mg BID + 1 new nucleoside.

At 32 weeks, in 494 participants, there was no virological difference in outcome in the three treatment arms.

The 48-week data on the combination of efavirenz, AZT and 3TC showed superiority of this regimen over an indinavir (IDV)-based triple therapy regimen. Study 043 is an open-label multicenter trial in which d4T is substituted for AZT. Standard doses of efavirenz, d4T and 3TC were given to antiretroviral-naive subjects with an entry HIV-RNA level greater than 4 logs. The Study will follow 68 patients for 2 years. Data have been reported on the first 42 patients enrolled for 24 weeks. The proportion of patients with HIV-RNA <400 copies/ml at week 24 was 100% in the observed data (OD) analysis and 92% in the intent-to-treat (ITT) analysis. Using an ultrasensitive assay with a limit of

detection of 50 copies/ml, the proportions below detection were 97% and 89% in the OD and the ITT analyses, respectively. These data are comparable to those presented for the combination of efavirenz, AZT and 3TC.

In another PI versus non-PI comparison, The Atlantic Study randomized 300 participants with baseline CD4+ count > 200 CD4 cells/mm and plasma HIV RNA > 500 copies/ml to d4T/ddI/3TC, d4T/ddI/nevirapine (NVP), or d4T/ddI/indinavir for 72 weeks. Preliminary 24-week data presented demonstrate equivalence of the three regimens.

An induction/maintenance strategy is being studied in an ongoing trial of AZT/3TC/abacavir following initial therapy with a PI-based combination. The study randomized people who maintain viral load less than 50 copies/ml for 6 months to continue their PI regimen or switch to AZT/3TC/abacavir. Preliminary data at 4-6 months of follow-up shows virologic failures in the two groups are equivalent.

Cost per year in the USA: US $ 6 800.

Average cost of ARV drugs (in USA)

ANTIRETROVIRAL	COST/ MONTH (US$)	COST/ YEAR (US$)
Zidovudine	280	3,360
Didanosine	202	2,424
Zalcitabine	210	2520
Stavudine	259	3,108
3TC	239	2,868
Combivir (AZT+3TC)	519	6,228
Abacavir	295	3,540
Delavirdine	223	2,676
Nevirapine	255	3,060
Efavirenz	389	4,668
Saquinavir (Invirase)	570	6,840
Saquinavir (Fortovase)	565	6,780
Indinavir	435	5,220
Ritonavir	612	7,344
Nelfinavir	563	6,756

Source: The 1999 HIV Drug Guide, Jan/Feb 1999.

Journal reviews

Antiviral effect and pharmacokinetic interaction between nevirapine and indinavir in persons infected with human immunodeficiency virus type 1

Murphy RL, Sommadossi J-P, Lamson M, et al. *J Infect Dis* 179(5):1116-1123, May 1999.

In a prospective study, 24 HIV-infected patients on stable nucleoside therapy or no therapy were given indinavir (800 mg q8h) for 7 days. Nevirapine was then added (200 mg/day for 7 days, then 200 mg BID). Pharmacokinetic parameters were assessed at day 7 and day 36. The addition of nevirapine resulted in an 11% reduction in median indinavir plasma Cmax, a 47.5% reduction in median indinavir plasma Cmin, and a 27.7% decrease in median indinavir plasma AUC. Indinavir did not affect nevirapine plasma clearance or steady-state trough concentrations. Ten of twelve patients treated with indinavir/nevirapine alone for at least 24 weeks had HIV RNA reductions to <20 copies/ml. The authors conclude that indinavir dose modifications may not be required when it is co-administered with nevirapine.

Outcome and predictors of failure of highly active antiretroviral therapy: one-year follow-up of a cohort of human immunodeficiency virus type 1-infected persons

Wit FWNM, van Leeuwen R, Weverling GJ, et al. *J Infect Dis* 179(4):790-798, April 1999 .

In a retrospective analysis, 271 protease inhibitor (PI)-naive patients taking antiretroviral regimens with at least one PI were studied. 78% had prior nucleoside exposure. After 48 weeks, in an intent-to-treat analysis, 75% had HIV RNA <1000 copies/ml, base on the PI initially given to the patient, the proportion <1000 copies/ml was 84% for indinavir, 89% for ritonavir, 59% for saquinavir (taken as Invirase), and 89% for ritonavir/saquinavir.

The proportion of patients with virological treatment failure (defined as those whose HIV RNA never declined below 1000 copies/ml, or rebounded above 1000 copies/ml) was 40% overall; 27% for indinavir, 30% for ritonavir, 59% for saquinavir, and 32% for ritonavir/saquinavir. In a multivariate analysis, factors associated with virological failure were baseline HIV RNA level, baseline CD4+ count and use of saquinavir as the only PI.

It was reported that 53% of patients modified their regimen during the first 48 weeks. Of these, 42% were because of toxicities, and 24% because of an increase in HIV RNA. Saquinavir regimens were changed most often due to rising viral load and ritonavir-containing regimens were most often changed because of intolerance. The overall proportion who changed therapy was 44% for those who originally received indinavir, 64% for ritonavir, 62% for saquinavir, and 30% for ritonavir/saquinavir.

HIV-1 rebound during interruption of highly active antiretroviral therapy has no deleterious effect on reinitiated therapy

Neumann AU, Tubiana R, Calvez V, et al. *AIDS* 13(6):677-83, April 1999.

In the Comet Study, 10 antiretroviral-naive patients initiated therapy with zidovudine, lamivudine, and indinavir for 28 days, followed by interruption of all drugs for 28 days and then reintroduction of the same regimen. The rate of viral decline was measured during each period of therapy, and was found not to differ significantly. The mean $T_{1/2}$ of viral decay during the rapid initial phase was 1.48 days during the first

treatment period and 1.62 days during the second period. During the slower second phase of viral decay, the mean $T_{1/2}$ was 8.93 days during the first treatment period and 7.97 days during the second period. No new resistance mutations developed during the study. The authors conclude that a 1-month interruption of all drugs in a HAART regimen does not adversely affect the virologic efficacy of the same regimen once reinitiated.

Abnormal body-fat distribution in HIV-1-infected children on antiretrovirals

Babi FE, Regan AM, Pelton SI *Lancet* 353(9160):1243-1244, April 1999.

The authors conducted a questionnaire survey of 1 644 children receiving combination therapy that included a PI and 1069 children on a non-PI-containing regimen. Twenty-eight cases of body fat redistribution were reported from a total of 16 investigator sites. 24 of these children were receiving a PI and 4 were not. The duration of PI therapy ranged from 1 to 14 months, with a gradually increasing prevalence over time. Sites of abnormal body fat distribution were the abdomen (17 cases), upper back (12 cases), and face (10 cases).

Drugs in development

T20, a fusion inhibitor, inhibits HIV replication by blocking virus entry into CD4 lymphocytes. Early studies used T20 intravenously but new research suggests that it is also effective when given subcutaneously. A small dose-ranging study demonstrated viral load reduction of 1.5 $\log_{10}$ after one month at the highest dose studied. Resistance to this compound developed reasonably quickly and further studies are planned using it in combination with other antiretrovirals, initially in salvage regimens.

ABT-378, is a second-generation protease inhibitor currently in phase II studies. In vitro studies have shown ABT-378 is ten times more potent than ritonavir. In combination with small doses of ritonavir, drug levels of ABT 378 are sustained such that once daily dosing may be possible. The most common side effect is loose stools or diarrhoea, which occurred in approximately one-third of phase II study participants.

In vitro studies suggest that ABT-378 is cross-resistant with other protease inhibitors. Initial mutations can be at codons 50 and 46, or at codons 84, 46 and 10. Both mutation patterns produce 7-10 fold resistance and are followed by mutations common to other protease inhibitors.

An access scheme is likely during 2000, with licensing predicted for the same year.

AG 1549 is a new non-nucleoside reverse transcriptase inhibitor.

Phase 1 trials suggest that AG 1549 is ten times more potent than current NNRTIs. This drug is active against HIV variants with single mutations at codons K103N or V106A or L100I, which confer resistance to other NNRTIs.

In vitro studies show that BMS 232632 is a highly potent protease inhibitor. Studies in HIV-negative volunteers found good bioavailability of 57% to 80% which may allow for once daily dosing. BMS expects the daily dose to fit into a single tablet.

Tipranavir is a new protease inhibitor. There are phase II studies in planning in the USA and Europe. A pediatric formulation of the drug is also being developed. Tipranavir reduces delavirdine levels by 95% and studies so far suggest a TID dosing schedule.

The resistance pattern of tipranavir is still the subject of study.

New treatment guidelines

6 May 1999: The Panel on Clinical Practices for the Treatment of HIV Infection, convened by the Department of Health and Human Resources in the USA, has just updated its guidelines. The full text is available at www.hivatis.org/guidelines/AA

May 1999: The British HIV Association has published a discussion draft of its 1999 guidelines. The full document is available from the joint BHIVA/National AIDS Manual website at www.aidsmap.com

Key points are:

- therapy is recommended at CD4 count <350cells/mm^3 or viral load >55 000 copies/ml;
- treatment of acute HIV infection is recommended;
- a regimen including a non-nucleoside RTI may have advantages as first line therapy but there is insufficient data as to which NNRTI is best.

Internet web sites

www.natap.org Site of National AIDS Treatment Advocacy Project (NY). Free e-mail and paper-based monthly reports. This site was used in part as a reference source for the preparation of this newsletter

www.aidsmap.com Monthly online treatment updates and fact sheets

www.medscape.com Extensive, well-arranged site. Includes drug interaction "calculator".

www.infoweb.com Links to many HIV sites

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

HIV/AIDS Antiretroviral Newsletter

World Health Organizatic n

Regional Office for the Western Pacific

November
Issue No. 2

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[2]	Cost[3] (U.S.)	Cost[3] developing Country)
		Antepartum	Intrapartum[1]	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 6th hourly for 6 weeks	68 % (infection status at age 18 months)	$800 to $1000	$200 to $400
Thailand CDC Modified 07	ZDV	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 $400	$50 to $10
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	ZDV	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 $21
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 12th 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	ZDV/ 3TC	No	ZDV 300 mg orally every 3 hours + 3TC 150 mg orally 12th 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	ZDV	No	600mg orally 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 the12 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

IN THIS ISSUE:

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% (IC_{50}) 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 IC_{50}) 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	ZIDOVUDINE	NEVIRAPINE	p-value
At birth	10.4%	8.2%	0.3 4
Weeks 6-8	21.3%	11.9%	0.0027
Weeks 14- 6	25.1%	13.1%	0.0( )6

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/mm^3 or <14%. Viral load data were not available. Results are summarized in Table 3.

Table 3: Results of US/European study on HIV vertica 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 Caesarean section were independent, additive variables in reducing vertical transmission of HIV-1. Elective Caesarean 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

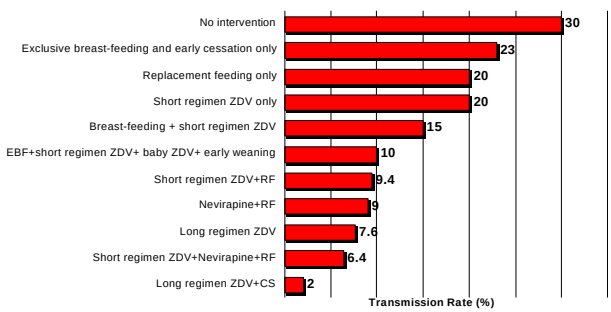
Current estimates are that a child breast-feeding from an HIV-positive mother has a 15% risk of infection by this route, with transmission of HIV occurring at a rate of approximately 0.5% per month that the infant is breast-fed. The studies on which this estimate is based do not distinguish between infants 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 = Cesarian 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	750-1499	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 6th hourly Intravenously: 1.5mg/kg 6th hourly	Oral: 160mg per m^2 of body surface area 8th hourly IV: (intermittent) 120mg per m^2 of body surface area 6th hourly IV: (continuous infusion) 20mg per m^2 of body surfac area hourly
Lamivudi e	2mg/kg twice daily	4mg/kg twice daily
Stavudine	Under evaluation	1mg/kg 12th hourly
Didanosir	50mg per m^2 of body surface area 12th hourly	90mg per m^2 of body surface area 12th hourly
Zalcitabine	Unknown	0.01 mg/kg 8th hourly
Abacavir	Under evaluation	8mg/kg 12th hourly (max 30mg twice daily)
Nevirapine	Under evaluation	120 mg per m^2 of body surface area 12th hourly for 14 days then 200mg per m^2 of body surface area 12th 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 8th hourly
Ritonavir	Under evaluation	Initially, 250 mg per m^2 of body surface area 12th ho rly increasing step-wise to 400mg per m^2 of body surfac area 12th 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 website:http://www.iapac.org/guidelinesped/index.html
2. Mother to Child Transmission of HIV: UNAIDS Technical Update. UNAIDS Best Practice Collection Geneva Oct. 1998 WC 503.71
3. HIV and Infant Feeding. Guidelines for decision-makers. WHO/FRH/NUT/CHD/98.1;UNAIDS/98.3; UNICEF/PD/NUT/(J) 98-1
4. HIV and Infant Feeding. A guide for health care managers and supervisors. WHO/FRH/NUT/CHD/98.2; UNICEF/PD/NUT/(J) 98.2
5. Influence of infant feeding patterns on early mother to child transmission of HIV-1 in Durban, South Africa: a prospective cohort study. *Lancet* 1999; **354:471**-76
6. European mode of delivery collaboration: Elective caesarean section versus vaginal delivery in prevention of vertical transmission: a randomised trial. *Lancet* 1999 April 17;**353**:1035-9
7. The International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1. *N Eng J Med* **340**:977-78 Editorial 1032-33 April 1999
8. Short course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. *Lancet*; March 1999 **353**:773-80
9. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Connor EM, Sperling RS, Gelber R et al. Paediatric AIDS Clinical Trials Group Protocol 076 study. *N Eng L Med* 1994, **333**(18):1173-80
10. Interim analysis of early efficacy of three short ZDV/3TC combination regimens to prevent mother to child transmission of HIV-1. The PETRA trial. Sixth conference on retroviruses and opportunistic infections, Chicago, Jan. 1999.

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