HIV/AIDS Antiretroviral Newsletter

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.

World Health Organization
Regional Office for the Western Pacific

December 2006
Issue No. 13

ANTIRETROVIRAL THERAPY IN RESOURCE LIMITED SETTINGS - 2006 UPDATE

INTRODUCTION

In 2006, WHO updated guidelines for antiretroviral therapy for adults (including pregnant women), adolescents and children and for the prevention of mother-to-child transmission (PMTCT) in resource-limited settings. Also published by WHO in 2006 are guidelines for the use of cotrimoxazole prophylaxis in resource-limited settings and revised HIV surveillance case definitions and clinical staging of HIV-related disease in adults and children.

The full set of guidelines is available at http://www.who.int/hiv/pub/guidelines/en/index.html

For the section on post-exposure prophylaxis, reference was made to:

Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Post-exposure Prophylaxis, Department of Health and Human Services (DHHS) (Morbidity and Mortality Weekly Report September 30, 2005); and

Antiretroviral Post-exposure Prophylaxis after Sexual, Injection-Drug Use, or other Nonoccupational Exposure to HIV in the United Sates; DHHS (Morbidity and Mortality Weekly Report, January 21, 2005).

This newsletter aims to summarize key recommendations for the use of Antiretroviral Therapy (ART) for the treatment and prevention of HIV infection in resource limited settings.

WHAT'S NEW IN PAEDIATRIC HIV CARE?

Antiretroviral therapy of HIV infection in infants and children in resource-limited settings, towards universal access: Recommendations for a public health approach (2006 revision) are stand-alone treatment guidelines which provide evidence-based recommendations for the selection of first- and second-line ART in resource-limited settings. They also provide new guidance on HIV diagnosis in infants and children, including the presumptive diagnosis of severe HIV disease in children less than 18 months of age. Immunological criteria for initiating ART in children are revised and recommendations provided on the management of children on ART with malnutrition, opportunistic infections (including tuberculosis) and those exposed to antiretroviral from prevention of PMTCT interventions or breastfeeding from an HIV-infected mother on ART. Specific issues of the care of adolescents on ART are outlined.

HIV DIAGNOSIS IN INFANTS AND CHILDREN

Maternal HIV antibodies persist in children up to 18 months of age. In children <18 months of age, definitive diagnosis of HIV infection requires virological testing with assays to detect plasma HIV RNA, (the most commonly used) HIV DNA or Immune Complex Dissociated (ICD) p24 antigen. Increased use of **dried blood spots** (DBS) for virological testing in resource-limited settings is recommended. Advantages of DBS are:

- venipuncture is not required;
- blood from a finger or heel-stick can be used;
- samples are stable at room temperature for prolonged periods; and
- samples are easy to ship facilitating centralized laboratory testing.[1, 2]

By age 4 weeks, virological testing approaches 98% sensitivity. However, performing initial virological testing at the time of the first postnatal visit is recommended, usually at age 6–8 weeks. A repeat confirmatory test on a separate specimen is recommended but may not be feasible if resources are limited.

The guidelines point out that it is often not understood that while HIV antibody testing cannot be used to diagnose HIV infection in infants under 18 months of age, it can be used to exclude HIV infection as early as 9 to 12 months of age in infants who are not breast-feeding or who have ceased breast-feeding 6 weeks or more prior to the antibody test, as most uninfected HIV-exposed infants will lose maternal antibodies by age 12 months.[3,4,5,6]

WHEN TO START ANTIRETROVIRAL THERAPY IN CHILDREN

To facilitate the scale up of universal access to ART, these guidelines place **new emphasis** on the importance of clinical indications of when to start ART. The new revised *WHO Paediatric Clinical Classification of HIV Related Disease* provides clinical indications on commencing ART in children with proven HIV infection. However, for children <18 months of age without confirmation of HIV diagnosis, ART should still be considered even if the diagnosis is presumptive based on clinical symptoms alone. Criteria suggestive of HIV infection are:

- The infant is HIV antibody positive and <18 months of age with any clinical stage 4 diagnosis.
- The infant is symptomatic with two or more of the following:
  - oral thrush; and
  - severe pneumonia or sepsis.
- Other factors that support the diagnosis of infection include recent HIV-related maternal death, advanced HIV disease in the mother or infant CD4 < 20%.

Confirmation of the diagnosis of HIV infection should be sought as soon as possible.

WHAT TO START

Recommendations for first line ART are **unchanged** from previous guidelines.

2 nucleoside reverse transcriptase inhibitors (NRTIs) plus 1 non-nucleoside reverse transcriptase inhibitors (NNRTI)

- AZT + 3TC + NVP/ EFV
- d4T + 3TC + NVP/ EFV
- ABC +3TC + NVP/ EFV

A recommended alternative regimen is:

- AZT/ d4T + 3TC + ABC

ANTIRETROVIRAL THERAPY IN INFANTS PREVIOUSLY EXPOSED TO ANTIRETROVIRAL

It is not known whether ART regimens should be modified for infants who have been exposed to ARVs used for PMTCT. Studies are urgently needed. Until further data are available, children who require ART should receive the standard recommended first-line regimen (2 NRTIs plus 1 NNRTI).

TREATMENT FAILURE IN CHILDREN

The revised WHO Paediatric Clinical Staging System is also recommended to guide decision-making in suspected treatment failure. A new clinical staging for children on treatment has been introduced and is designated T1-T4. A child with WHO stage 3 disease on ART is designated as having stage T3. Treatment failure should be considered when symptoms suggestive of a more severe clinical stage develop in a child on ART. The main clinical indication to switch therapy is the development of new or recurrent stage 3 or 4 events (WHO clinical stage T3 or T4) at least 24 weeks after starting therapy with a first-line regimen. See table 2 for more information on T staging in adults and children.

Table 1. Recommendations for initiating ART in HIV-infected infants and children according to clinical stage and availability of immunological markers

WHO paediatric stage	Availability of CD4 cell measurements	<12 months	≥12 months
4[a]	CD4	Treat all	
	No CD4		
3[a]	CD4	Treat all	Treat all, CD4 guided in those children with TB,[b] LIP, OHL, thrombocytopenia
	No CD4		Treat all [b]
2	CD4	CD4-guided	
	No CD4	TLC-guided	
1	CD4	CD4-guided	
	No CD4	Do not treat	

LIP - lymphocytic interstitial pneumonia; OHL- Oral hairy leukoplakia; TB – tuberculosis

a. Stabilize any opportunistic infection prior to initiation of ARV therapy

b. In children with pulmonary tuberculosis, the CD4 level and clinical status should be used to determine the need for and timing of initiation of ART in relation to tuberculosis treatment

Table 2. T staging

New or recurrent event after at least 6 months on ART	Recommendations[2]
Asymptomatic (T1)	Do not switch
Stage 2 event (T2)	Do not switch
Stage 3 event (T3)	Consider switching
Stage 4 event (T4)	Switch

Note: This table is the same for adults and children[1]

Table 3. CD4 and total lymphocyte count (TLC) criteria for initiation of ART in children

Immunological marker	Age-specific recommendation to initiate ART			
	≤ 11 months	12-35 months	36-59 months	≥ 5 years
CD4 %	<25%	<20%	<15%	<15%
CD4 count	<1500	<750	<350	<200
TLC	<4000	<3000	<2500	<2000
% CD4 is preferred for children <5 years of age. TLC should only be used in children with clinical stage 2 and where no CD4 is available. TLC is **not** useful monitoring response to ART or in defining ART failure.				

Unlike staging of HIV disease, in which a patient diagnosed as WHO stage 4 is always WHO stage 4, in T staging, patients who improve on ART can move from T4 to T3 to T2 to T1 and subsequently move back if they are failing ART.

Additional management:

- Treat and manage staging event.
- Assess response to treatment. Consider not switching ART if response to treatment is good, especially in the case of WHO stage 3 events, including pulmonary TB.
- Assess and support adherence.
- Check if on treatment at least 6 months.
- Check CD4 cell count (if available).

WHAT'S NEW IN ADULT HIV CARE?

Recommendations for first- and second-line therapies have changed. Three new drugs are now recommended for consideration in first-line treatment of adults with HIV infection. These are tenofovir (TDF), emtricitabine (FTC) and abacavir (ABC).

These are in addition to the previously recommended five drug formulary of stavudine (D4T), zidovudine (AZT, ZDV), lamivudine (3TC), nevirapine (NVP) and efavirenz (EFV). TDF and AZT are the preferred first-line NRTIs. As in the case of children, the preferred first-line ART for adults and adolescents remains 2 NRTIs + 1 NNRTI. In situations where these regimens may be problematic, such as pregnancy, HIV/TB coinfection, or treatment of HIV-2 (naturally resistant to the NNRTIs), triple non-nucleoside regimens (e.g. AZT+3TC+ABC, AZT+3TC+TDF) are recommended as the alternative strategy.

There is a new guideline for *WHO clinical staging of HIV/AIDS for adults and adolescents with confirmed HIV infection* and a new table for the presumptive and definitive diagnosis of HIV related conditions.

WHY ADD NEW DRUGS

Reasons to include these three new drugs include:

- D4T-related side effects (lipoatrophy, lactic acidosis, peripheral neuropathy) remain a concern;
- FTC and TDF are active against hepatitis B;
- FTC and TDF are available as a coformulation;
- Generic formulations of TDF will become available; and
- Triple NRTIs may be an option on some situations and preserve NNRTIs and protease inhibitors for the second-line regimen.

TRIPLE NRTIS AS FIRST-LINE THERAPY

While this new option has advantages in special situations as described above and facilitates more choice of second-line regimen, there are concerns about the potency of three NRTIs. The AACTG 5095 study compared AZT+3TC+ABC to AZT+3TC+EFV and AZT+3TC+ABC+EFV. After 48 weeks, 61% of the triple nucleoside group had a viral load <50 copies compared to 83% in the other two groups, both of which contained efavirenz. In the DART study in South Africa, 61% of 300 adults had virological suppression (<50 copies/ml) after 48 weeks of AZT/3TC/TDF.

WHEN TO START ART IN ADULTS

In the case of children, emphasis is given to clinical criteria for in deciding when to initiate ART and to monitor adults on ART. Increased access to affordable CD4 testing is encouraged.

The main change to this recommendation is to consider initiating ART if patients have a CD4 count <350 and to start ART **before CD4 cell count drops below 200**. If no CD4 count is available, all patients with WHO clinical stage 3 or 4 should receive ART. Patients with WHO clinical stage 2 and TLC < 1200 should also start ART.

TLC is not used in most ART programmes and it is recommended that the use of TLC in deciding when to start ART gradually be phased out on adult ART guidelines. There is better evidence for the use of TLC in the paediatric setting and it is retained in the new paediatric guidelines.

Table 4. Starting ART by clinical staging

WHO clinical stage	Recommendation
1	Do not treat
2*	Do not treat
3	Treat
4	Treat

*Consider treatment in WHO stage II disease and total lymphocyte count < 1200 cells/mm^3

Table5. Starting ART by CD4 count

WHO clinical staging	CD4 testing available
1	Treat if CD4 cell count < 200 cells/mm^3
2	
3	Consider treatment if CD4 cell count < 350 cells/mm^3 **Start ART before CD4 cell count drops below 200 cells/mm^3**
4	Treat irrespective of CD4 count

WHEN TO START ART IN PREGNANT WOMEN

The only new recommendation is to commence ART in pregnant women at WHO clinical stage 3 and with a CD4 count <350. This is because some will need ART soon after delivery and a lower rate of viral suppression has been demonstrated if ART is started less than six months after single dose nevirapine (SD-NVP) exposure.[7]

Table 6. When to start ART in pregnant woman

WHO clinical stage	CD4 testing not available	CD4 testing available
1	Do not treat	Treat if CD4 count < 200 cells/mm^3
2*	Do not treat	
3	Treat	Treat if CD4 count < 350 cells/mm^3
4	Treat	Treat irrespective of CD4 cell count

*Consider treatment in WHO stage II disease and total lymphocyte count < 1200 cells/mm^3

WHAT NOT TO USE AS INITIAL THERAPY

The combination of any NNRTI with **ddI and tenofovir** is not recommended due to reports of early virological failure and rapid emergence of resistant mutations. Not new, but still not recommended, are the combinations of AZT and D4T (common metabolic pathways) or DDI and D4T (toxicity).

TREATMENT FAILURE IN ADULTS

Second-line regimens should contain three different drugs, at least one from a different class. Ritonavir boosted protease inhibitors (PI/r) are the backbone for all second-line regimens to which is added two new nucleosides/nucleotides or a nucleoside plus non-nucleoside combination depending if triple NNRTIs were used in the first-line therapy. Nelfinavir is an alternative but is inferior to PI/r.

Many experts recommend the inclusion of 3TC in all second-line regimens despite its use in the first-line regimen. This is because, even in the presence of 3TC resistance, 3TC maintains the M184V which reduces viral fitness as well as inducing some degree of resensitization to AZT or TDF. Some experts recommend adding AZT (if not used first-line) or retaining AZT (if used in the first-line) prevent or delay the emergence of the K65R mutation.

Table 7. First and second line regimens in adults

1st Line	2nd Line	
(3TC or FTC) In every regimen +		
TDF + (NVP or EFV)	ddI+ ABC ± 3TC or ddI+ AZT ± 3TC	PI/r
(AZT or d4T) + (NVP or EFV)	ddI+ ABC ± 3TC or TDF+ ABC ± 3TC or TDF+ZDV± 3TC	
ABC + (NVP or EFV)	ddI+ ZDV ± 3TC or TDF+ ZDV ± 3TC	
ZDV or d4T + TDF or ABC	EFV or NVP ± ddI or EFV or NVP ± 3TC	

WHAT'S NEW IN PMTCT GUIDELINES?

There are four components to the WHO strategy for prevention of HIV infection in infants and young children:[8]

- primary prevention of HIV infection;
- prevention of unintended pregnancies among women living with HIV;
- prevention of HIV transmission from mothers living with HIV to their infants; and
- care, treatment and support for mothers living with HIV, their children and families.

KEY RECOMMENDATIONS

(1) Programmes are strongly encouraged to implement the recommended PMCT regimen for women who do not have indications for ART.

(2) One of the recommended options is AZT starting from 28 weeks of pregnancy (or as soon as possible thereafter); AZT and 3TC + SD-NVP intrapartum; and AZT and 3TC postpartum for seven days for women, and for infants SD-NVP and AZT for one week.

(3) Omission of the NVP dose for the mother may be considered for women who receive at least four weeks of AZT before delivery.

(4) The NVP dose can be given to an infant up to 72 hours after childbirth but preferably as soon as possible after delivery.

(5) If the mother receives less than four weeks of AZT before delivery, the AZT dose for the infant is extended to four weeks.

(6) When SD-NVP is used to prevent MTCT, either alone or in combination with AZT, women are given AZT and 3TC intrapartum and for seven days postpartum to prevent resistance to NVP.

(7) When delivery occurs within two hours of a woman taking SD-NVP, the infant receives SD-NVP immediately after delivery and AZT for four weeks.

(8) SD-NVP as the only PMCT intervention is only recommended in situations where health care systems cannot support the delivery of other antiretroviral.

For women who need ART for their own health, the preferred regimen is AZT + 3TC+ NVP. Use NVP with careful clinical and liver enzyme monitoring in women with CD4 count 250-350. EFV may be considered as an alternative to NVP after the first trimester. If a PI containing regimen is used, (e.g. women who are intolerant to NNRTIs) the preferred PIs are SQV/r or nelfinavir.

Table 8. Recommended firt-line ARV regimen for pregnant women who need ART for their own health and prophylactic regimen for children

Mother	
Antepartum	AZT + 3TC + NVP twice daily
Intrapartum	
Postpartum	
Infant	
AZT 7 days (4 weeks if the mother received <4 weeks AZT)	

Table 9. ART recommendations for PMCT

Preferred regimen	**Antepartum**	
	AZT from 28 weeks	
	Intrapartum	
	Mother SD-NVP[1] + AZT/3TC during deliver	Infant SD-NVP as soon as possible and within 72 hours
	Post partum	
	Mother: AZT/3TC for 7 days	Infant SD-NVP + AZT for 7 days[2]
	Mother SD-NVP	Infant SD-NVP + AZT for 7days[2]
Special situations	**Recommendations**	
Women who have not received any ART	**Mother:** SD-NVP + AZT and 3TC during labour and for 7 days **Infant:** SD-NVP immediately after delivery and AZT for 4 weeks	
If delivery is imminent	**Mother:** Omit NVP **Infant**: SD-NVP immediately after delivery and AZT for 4 weeks	

(1) Maternal AZT > 4 weeks.

Consider omitting SD-NVP dose for mothers. In this case give SD-NVP to the infant immediately after birth and AZT for four weeks instead. The mother will not require 3TC during labour and not AZT and 3TC postpartum.

(2) AZT for four weeks instead if maternal AZT<4 weeks.

HIV-infected women should use replacement feeding if it is acceptable, feasible, affordable, sustainable and safe. Exclusive breastfeeding is otherwise advised including those on ART. Mixed feeding with a combination of bottle-feeding, water or formula feeding is not recommended.

CO-TRIMOXAZOLE PROPHYLAXIS FOR ADULTS WITH HIV INFECTION AND CHILDREN EXPOSED TO HIV OR WITH CONFIRMED HIV INFECTION

Co-trimoxazole has proven efficacy in preventing infection with *Pneumocystis jiroveci* pneumonia (PCP), formerly *Pneumocystis carinii* pneumonia, and toxoplasmosis in both children [9, 10] and adults[11,12] with HIV infection.

In children, co-trimoxazole prophylaxis also is associated with a reduction of mortality and hospital admissions due to pneumonia[9] and malaria.[13] Similar benefit has been demonstrated in the reduction in rates of malaria, diarrhoea, hospital admission and death in adults.[14,15,16]

INITIATING CO-TRIMOXAZOLE PROPHYLAXIS

Co-trimoxazole prophylaxis may be initiated in two different contexts. "Classic" prophylaxis, where the target is the prevention of PCP and toxoplasmosis, is recommended for all HIV-infected adults with WHO stages 2, 3 and 4 HIV disease or with a CD4 count<200 cells/mm^3 (if available). If the targets of prophylaxis are the reduction in morbidity and mortality associated with bacterial infections and malaria, in addition to the prevention of PCP and toxoplasmosis, co-trimoxazole is recommended for HIV-infected adult with a CD4 count <350 cells/mm^3 or with WHO stages 2, 3 or 4 disease.

In children, co-trimoxazole prophylaxis is recommended for all **HIV exposed infants** (those born to HIV-infected mothers) until HIV infection is excluded in the infant. Exclusion is by HIV antibody testing at 18 months or by virological testing (HIV DNA HIV RNA or ICD p24Ag) any time after six weeks of age. Before negative HIV status can be confirmed, the infant must be no longer at risk of acquiring HIV infection and have ceased all breastfeeding for at least six weeks.

For children with **confirmed HIV infection**, co-trimoxazole prophylaxis is recommended for those with WHO stages 2, 3 and 4 disease or a CD% of <25%.

STOPPING CO-TRIMOXAZOLE PROPHYLAXIS

Co-trimoxazole prophylaxis may be ceased in adults with a CD4 count greater than the starting threshold (200 or 350 cells) for at least 6 months on ART. In the absence of CD4 testing, discontinuation of prophylaxis may be considered in those on ART and without WHO clinical stage 2, 3 or 4 events for 12 months, good adherence and secure access to ART.

For HIV-infected children, continued prophylaxis is recommended irrespective of clinical and immunologic response. Children over 5 years of age can be reassessed and managed according to adults recommendations.

ANTIRETROVIRAL FOR POST-EXPOSURE PROPHYLAXIS (PEP)

There are no recently updated guidelines for post-exposure prophylaxis in resource limited settings. WHO is finalizing a guideline in this topic that will be available in November 2006. The following material is adapted from the United States of America DHHS guidelines.[18,22]

This newsletter provides an overview of the current thinking on the principles of PEP. It does not attempt to provide prescriptive details on the provision of PEP. A decision to initiate PEP should be always based on counselling and discussion between the exposed person and the treating clinician regarding the risks versus benefits of PEP. Readers should refer to the recommendations, including the importance of counselling, contained in the source documents [18,**22**] and in their own national guidelines before prescribing PEP.

There are two situations in which PEP may be needed. One is occupational exposure of health care workers, laboratory staff and others involved in the care of patients with HIV infection (child day care centre staff, family members caring for patients). The other situation is non-occupational exposures, i.e. sexual, injection-drug use.

OCCUPATIONAL POST-EXPOSURE PROPHYLAXIS

The risk of occupational transmission of HIV varies with the type and severity of exposure.[17]

It is estimated that the transmission rate of HIV from an infected patient to a health worker through significant needle stick accidents is approximately 0.3% (3 per 1000) and approximately 0.09% in the case of mucous membrane exposure.[18]

COMPONENTS OF POST-EXPOSURE PROPHYLAXIS

- Treatment of exposure site
- Assessment of risk
- Provision of ARV if needed
- Documentation of the incident

Table 10. Treatment of exposure site

Skin	Wash skin with soap and water
Eyes	Rinse eyes immediately with eye wash fluid
Oral exposure	Spit out immediately Rinse mouth immediately several times

High risk exposure is characterized by a deep penetrating injury with a hollow needle containing blood (other high risk body fluids are semen, vaginal secretions, cerebrospinal fluid, synovial, pleural, peritoneal pericardial amniotic fluids) from a known HIV-positive source or a cut or other injury (which penetrates the skin) from a sharp instrument contaminated with HIV-infected material.

Intermediate risk exposure is characterized by contact with mucous membrane or non-intact skin by a major splash exposure with a large volume and long duration of exposure (>1 minute) with known HIV-infected material. Other intermediate risk exposures include superficial scratches with instruments contaminated with HIV-infected material.

Low risk exposure includes small volume, short duration (<1 minute) exposure of mucous membrane or non-intact skin to HIV-contaminated material. **No risk** is exposure of **intact skin** to HIV contaminated material or exposure to material from a source patient known to be HIV negative. Saliva and urine are low risk fluids. For **human bites**, the clinical evaluation must include the possibility that both the person bitten and the person who inflicted the bite were exposed to bloodborne pathogens. Transmission of Hepatitis B Virus or HIV infection only rarely has been reported by this route.[19,20,21] In the clinical evaluation for human bites, possible exposure of both the person bitten and the person who inflicted the bite must be considered. If a bite results in HIV-infected blood exposure to either person involved, post-exposure prophylaxis should be considered.

Table 11. ARV regimens for PEP

Starting PEP	As soon as possible after exposure and within one hour if possible Not > than 72 hours if possible Consider PEP > 72 hours after a high risk exposure	
Duration	One month	
Which regimen to choose	**Basic regimen**	**Expanded regimen**
	Intermediate risk exposure 2 ARVs	High risk exposure 3 ARVs
Preferred ARVs	Basic regimen AZT + 3TC Expanded regimen AZT+3TC + PI or efavirenz	
PEP in pregnant women	PEP should be provided if clinically indicated. Pregnant women should not receive efavirenz, tenofovir or the combination of d4T + ddI Preferred PIs in pregnancy are saquinavir/r or nelfinavir	

NON-OCCUPATIONAL POST-EXPOSURE PROPHYLAXIS

The principles of management are the similar to those of occupational exposure.[22] Assessment of risk exposure is performed in counselling with the exposed person and a decision made on whether the exposure was **substantial or negligible** in the view of the exposed person and the health care provider.

If non-occupational post-exposure prophylaxis are required, expanded three drug regimens for one month are recommended. If three drugs are not available, the basic two drug regimen is an alternative (Table 11). Provision of emergency contraception ("morning after pill") is a key component of sexual non-occupational post-exposure prophylaxis.

Table 12. Estimated risk for acquisition of HIV by exposure route[22]

Exposure type (Sexual exposure assumes no condom use)	Risk per 10 000 exposures
Blood transfusion	9 000
Needle-sharing injection-drug use	67
Receptive anal intercourse	50
Percutaneous needle stick	30
Receptive penile-vaginal intercourse	10
Insertive anal intercourse	6.5
Insertive vaginal intercourse	5
Receptive oral intercourse	1

REFERENCES

[1] Sherman GG *et al*. Dried blood spots improve access to HIV diagnosis and care for infants in low-resource settings. *Journal of Acquired Immune Deficiency Syndromes*, 2005, 38(5):615-7.

[2] Patton JC *et al*. Ultra sensitive human immunodeficiency virus type 1 p24 antigen assay modified for use on dried whole-blood spots as a reliable, affordable test for infant diagnosis. *Clinical Vaccine Immunology*, 2006, 13(1):152-5.

[3] *Antiretroviral therapy of HIV infection in infants and children in resource-limited settings, towards universal access: Recommendations for a public health approach (2006 revision*), Geneva, World Health Organization, 2006.

[4] Sherman GG, Matsebula TC, Jones SA. Is early HIV testing of infants in poorly resourced prevention of mother to child transmission programmes unaffordable? *Tropical Medicine International Health*, 2005, 10(11):1108-13.

[5] Moodley D *et al*. Predicting perinatal human immunodeficiency virus infection by antibody patterns. *Paediatric Infectious Diseases Journal*, 1995, 14(10):850-2.

[6] Sherman GG, Jones SA. Oral fluid human immunodeficiency virus tests: improved access to diagnosis for infants in poorly resourced prevention of mother to child transmission programs. *Paediatric Infectious Diseases Journal*, 2005, 24(3):253-6.

[7] Lockman S *et al.* Maternal and infant response to nevirapine (NVP)-based antiretroviral treatment (ART) following peripartum single-dose NVP or placebo (Plc). *Infectious Disease Society of America*, San Francisco, 2005 (in press).

[8] *Strategic Approaches to the Prevention of HIV Infection in Infants. A report of a WHO meeting*. Geneva, World Health Organization, 2003 http://www.who.int/hiv/pub/mtct/en/StrategicApproachesE.pdf

[9] Chintu C *et al.* Co-trimoxazole as prophylaxis against opportunistic infections as HIV infected Zambian children (CHAP): a double-blind randomized placebo-controlled trial. *Lancet*, 2004, 364:1865–1871.

[10] Graham SM *et al*. Clinical presentation and outcome of *Pneumocystis carinii* pneumonia in Malawian children. *Lancet*, 2000, 355:369–373.

[11] Wiktor SZ *et al*. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Côte d'Ivoire: a randomised controlled trial. *Lancet*, 1999, 353:1469–1475.

[12] Kaplan JE *et al*. Guidelines for preventing opportunistic infections among HIV-infected persons. *Recommendations of the U.S. Public Health Service and the Infectious Morbidity and Mortality Weekly Report*, 2002, 51(RR08):1–46.

[13] Thera MA *et al.* Impact of trimethoprim-sulfamethoxazole prophylaxis on falciparum malaria infection and disease. *Journal of Infectious Diseases*, 2005, 192:1823–1829.

[14] Anglaret X *et al*. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1 infected adults in Abidjan, Côte d'Ivoire: a randomized trial. *Lancet*, 1999, 353:1463–1468.

[15] Grimwade K *et al.* Effectiveness of co-trimoxazole prophylaxis on mortality in adults with tuberculosis in rural South Africa. *AIDS*, 2005, 19:163–168.

[16] Mermin J *et al*. Effect of co-trimoxazole prophylaxis on morbidity, mortality, CD4-cell count, and viral load in HIV infection in rural Uganda. *Lancet*, 2004, 364:1428–1434.

[17] Bell DM. Occupational risk of human immunodeficiency virus infection in health-care workers: an overview. *American Journal of Medicine*, 1997, 102(5B):9–15.

[18] *Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Post exposure Prophylaxis.* Department of Health and Human Services (DHHS)

Morbidity and Mortality Weekly Report, 2005, Volume 54/No. RR-9

[19] Shapiro CN *et al*. Hepatitis B virus transmission between children in day care. *Paediatric Infectious Diseases Journal*, 1989, 8:870–5. 34, *Morbidity and Mortality Weekly Report*, 2001

[20] Richman KM, Rickman LS. The potential for transmission of human immunodeficiency virus through human bites. *Journal of Acquired Immune Deficiency Syndrome*, 1993, 6:402–6.

[21] Vidmar L *et al*. Transmission of HIV-1 by human bite [Letter]. *Lancet*, 1996, 347:1762

[22] *Antiretroviral Post-exposure Prophylaxis after Sexual, Injection-Drug Use or other Non-occupational Exposure to HIV in the United States.* Department of Health and Human Services (DHHS) Morbidity and Mortality Weekly Report, January, 2005/Volume 54/No. RR-2.

HIV/AIDS and STI
World Health Organization
Regional Office for the Western Pacific

WHO/WPRO, (P.O. Box 2932),
1000 Manila, Philippines

Fax no. (632) 521-1036, (632) 526-0279
Tel. No.: (632) 528-8001; (632) 303 1000

Email: hiv.in.wp@wpro.who.int.
Website: http://www.wpro.who.int