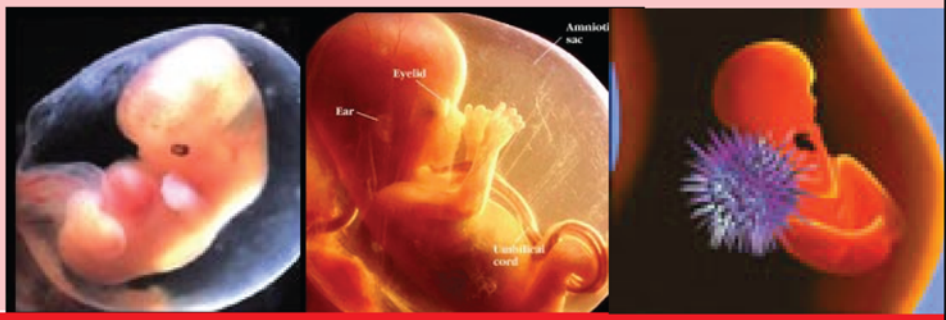
CLINICAL PRACTICE GUIDELINES

FEBRUARY 2008 MOH/P/PAK/ 156.08 (GU)

MANAGEMENT OF HIV INFECTION IN PREGNANT WOMEN



MINISTRY OF HEALTH MALAYSIA

ACADEMY OF MEDICINE OF MALAYSIA

This guideline is meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to this guideline may not necessarily guarantee the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

This guideline was issued in 2008 and will be reviewed in 2011or sooner if new evidence becomes available.

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GUIDELINES

DEVELOPMENT AND OBJECTIVE

The development group for this guideline comprised of Obstetricians and Gynaecologists, Consultant Physicians (Infectious Disease Specialist) and a Family Medicine Specialist from the Ministry of Health and the Ministry of Education, Malaysia. During the process of development of this guideline, there was active involvement of a review committee who consisted of healthcare professionals both from the public and private sector.

This document is the first Clinical Practice Guidelines (CPG) on The Management of HIV infection in Pregnant Women in Malaysia and has been developed in parallel with the CPG on Management of HIV Infection in Children.

Literature search was carried out at the following electronic databases, International Health Technology Assessment Website, PUBMED, Cochrane Database of Systemic Reviews (CDSR) Journal full text via the OVID search engine, Cochrane Controlled Trials Registered, CINAHL via EBSCO search engine. The search was limited to publications from 1985 – 2007 and for articles in the English language. Reference lists of all relevant articles retrieved were searched to identify further studies. The following free text terms or MeSH terms were used as the keywords: HIV infection AND pregnancy, screening, diagnostic test, confirmatory test, rapid test, Western Blot, immunoabsorbent assay, immunofluorescent assay, specificity, sensitivity, false positive, false negative AND accuracy; management and HIV and pregnancy; mother to child transmission and HIV; HIV and pregnancy; HIV and MTCT; HIV and membrane rupture; HIV and premature rupture of membrane; HIV and prom; HIV and preterm labour, 'HIV', 'pregnancy', 'CD4', 'viral load', 'monitoring', 'disease progression', 'vertical transmission'; HAART and pregnancy; zidovudine and pregnancy; efarvirenz and pregnancy; nevirapine and pregnancy; HIV and postpartum care; HIV and post natal care; HIV and nursing care; HIV and breastfeeding; HIV and formula feeding; HIV and complications; HIV/ AIDS and contraception. This guideline is based largely on the findings of systemic reviews and meta-analysis in the literature.

Reference was also made to other guidelines namely Management of HIV in Pregnancy by the Royal College Obstetricians Gynaecologists (2004), Public Health Service Task Force recommendations for Use of Antiretroviral Drugs in Pregnant HIV infected women (2006), DHSS Panel on Guidelines for the use of ARV agents in HIV-1-infected adults and adolescents (2006), Revised CDC guidelines for HIV on counselling, testing and referral (1999), World Health Organisation guidelines for antiretroviral drugs for treating pregnant women and preventing HIV infection in infants 2006, Centre for Disease Control and Prevention (CDC) revised recommendations for HIV testing of adults, adolescents and pregnant women in health care settings,

2001, CDC guidelines on introduction of routine HIV testing in prenatal care – Botswana, 2004 and British HIV Association guidelines for the management of HIV infection in pregnant women and the prevention of mother-to child transmission of HIV, March 2005.

The articles were graded using the modified version of those used by the Catalonian Agency for Health Technology Assessment and Research (CAHTAR) Spain, while the grading of recommendation in these guidelines was modified from the Scottish Intercollegiate guidelines Network (SIGN).

The clinical questions were divided into major subgroups and members of the development group were assigned individual topics within these subgroups. The group members met a total of twenty one times throughout the development of the guideline. All literature retrieved were appraised by individual members and presented and discussed during group meetings. All statements and recommendations formulated were agreed by both the development group and review committee. Where the evidence was insufficient the recommendations were derived by consensus of the development group and review committee.

The draft guideline was posted on both the Ministry of Health Malaysia and Academy of Medicine, Malaysia websites for comment and feedback. This guideline has also been presented to the Technical Advisory Committee for Clinical Practice Guidelines, and the Health Technology Assessment and Clinical Practice Guidelines Council, Ministry of Health Malaysia for review and approval.

OBJECTIVE

The aim of the guideline is to assist clinicians in making evidence based decisions about the appropriate management and treatment of HIV infection in pregnant women.

CLINICAL QUESTIONS

- How to screen and confirm HIV in pregnant women?
- What is the appropriate treatment for HIV in pregnant women?
- How to prevent mother-to-child transmission of HIV?

EXCLUSION

This guideline does not cover investigation and counselling during pre-pregnancy period.

TARGET POPULATION

This guideline is applicable to HIV positive pregnant women.

TARGET USER

This guideline is meant for all health care providers that are involved in the management of HIV positive pregnant women.

POSSIBLE CLINICAL INDICATORS FOR QUALITY MANAGEMENT

Indicator	Standard
Percentage of pregnant women screened for HIV infection during the first antenatal care visit in government facilities.	95%
Percentage of pregnant women detected HIV positive receiving antiretroviral therapy	100%

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REVIEW COMMITTEE

The draft guideline was reviewed by a panel of independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence supporting the recommendations in the guideline.

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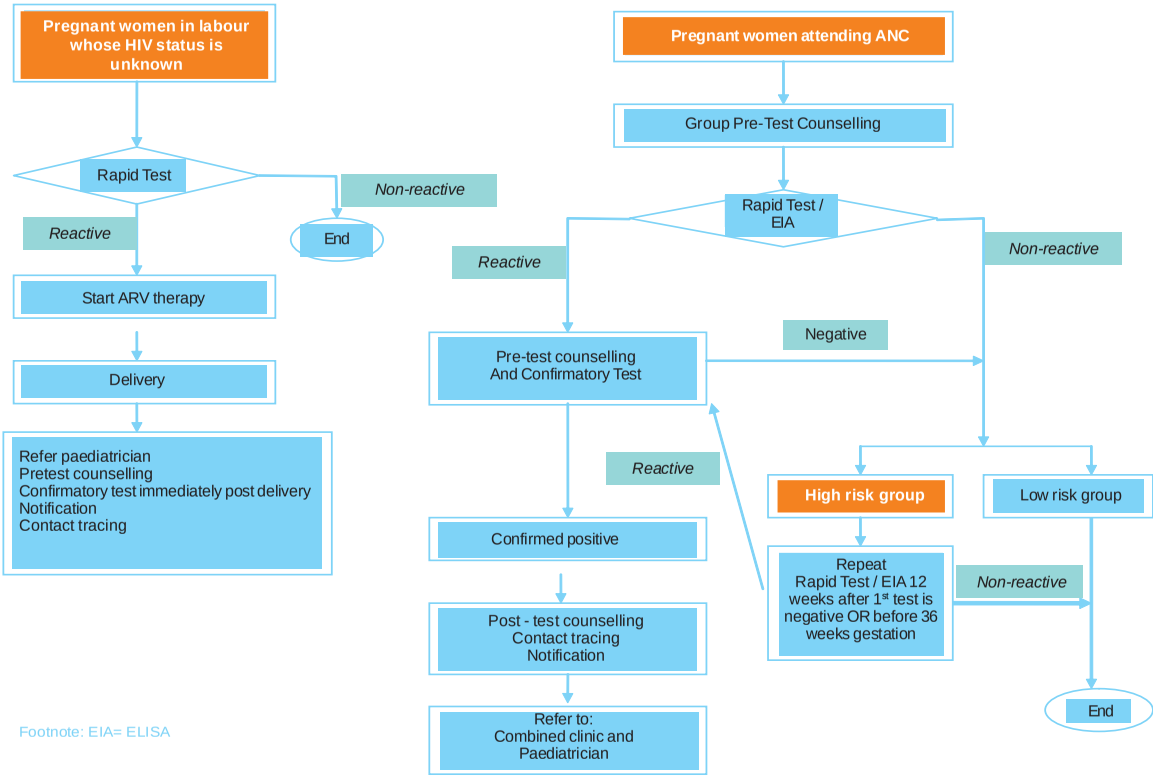
ALGORTHM 1- HIV SCREENING FOR PREGNANT WOMEN



Footnote: EIA= ELISA

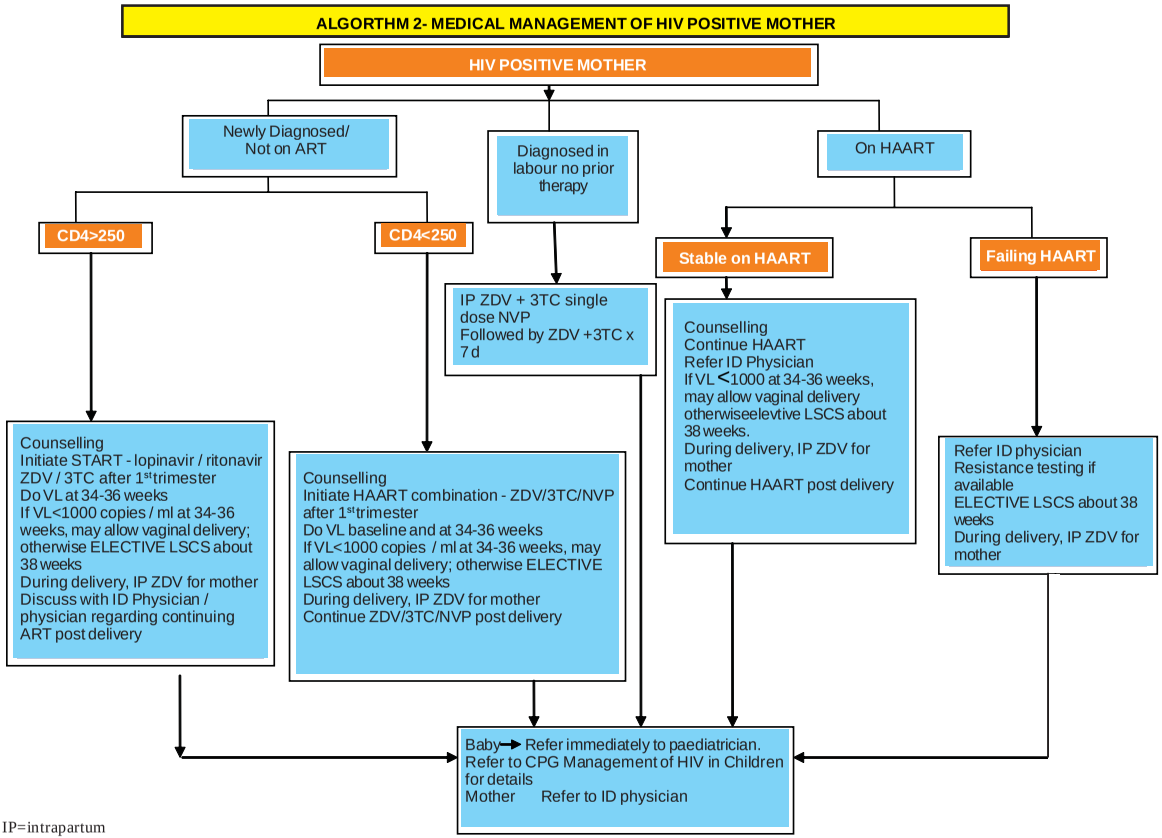


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TABLE OF CONTENTS

1.0 GENERAL INTRODUCTION

Mother-to-child transmission (MTCT) is the most common and important source of HIV infection in childhood. In the absence of any intervention, between 30% and 45% of children born to HIV positive mothers will become infected with HIV; the lower end of the range applies to higher income country settings, while the upper end of the range applies to lower income, higher prevalence settings[1]

Transmission is believed to be uncommon during early pregnancy, but the risk increases sharply in late pregnancy and during labour and delivery. Overall, about 15-20% of children who acquire HIV infection from their mothers are infected during the antenatal period, 50% during delivery and 33% through breast feeding.[2]

In June 2001, through its *Declaration of Commitment*, the United Nations General Assembly Special Session (UNGASS) on HIV/AIDS undertook to reduce the proportion of infants infected with HIV by 20% by 2005 and by 50% by 2010, through a four-pronged strategy:

- **I.** primary prevention of HIV infection in women of reproductive age;
- **II.** prevention of unintended pregnancy in HIV-positive women;
- **III**. prevention of mother-to-child transmission (PMTCT) of HIV by:
  - *a.* providing antiretroviral therapy (ART) during pregnancy,
  - *b.* implementing safer delivery practices,
  - *c.* providing counselling and support on infant feeding methods
- **IV.** provision of care, treatment and support to HIV-infected parents, infants and families.

From 1986 till December 2006, there have been 76, 389 cases of HIV reported by Ministry of Health (MOH) with 9,155 deaths.[3] Although males account for more than 93% of all the HIV infections reported in Malaysia to date, the proportion of new cases among females has increased sharply, from 1.4% in 2000 and 15% in 2006.

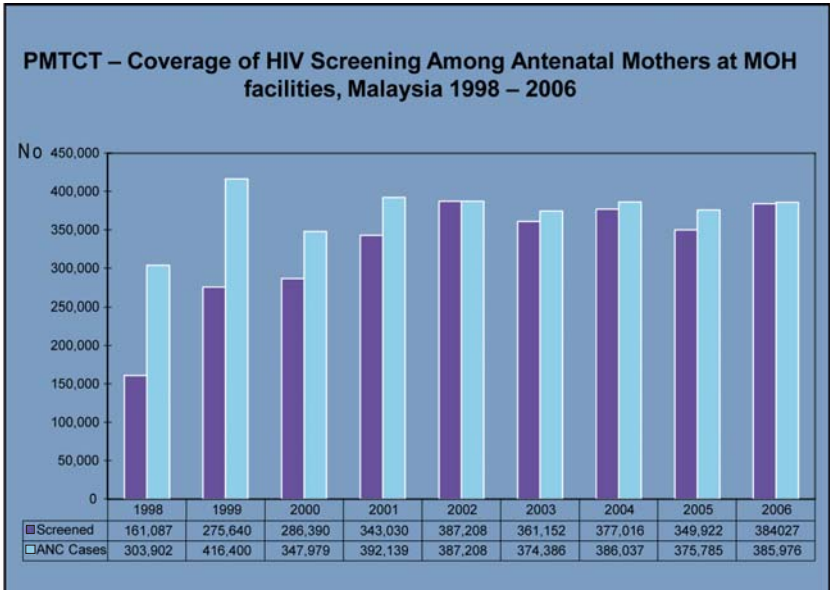
Determination of HIV status enables appropriate counselling, timely ARV therapy and management of HIV positive pregnant women to be provided to reduce the risk of vertical transmission.[4]

The Malaysian Ministry of Health (MOH) initiated a National Prevention of Mother-to-Child Transmission of HIV (PMTCT) Program in 1998. The Program is based partly on UNGASS “prong” 2 (i.e. detection of HIV infection during the antenatal period) and more strongly on UNGASS “prong” 3 (i.e. the provision of ARV therapy to mother and baby, safer modes of delivery and safer infant feeding practices for HIV positive mothers (through artificial feeding).

Since the introduction of the PMTCT program, a total of 2,925,472 mothers were screened for HIV during antenatal period from 1998 until the end of 2006 in government facilities. The coverage has been good and for the last five years, increased from 92.8% (2002) to 99.5% (2006). However the percentage of HIV positive pregnant women detected was maintained at below 0.04% (graph below). The vertical transmission rate of HIV from 1998 – 2006 was 3.8%. (* These data do not include the availability or result of testing in non-government facilities nor the outcomes in HIV infected pregnant women who do not seek antenatal testing or care).

In Malaysia, any woman in whom HIV infection is detected during pregnancy[5] is entitled to free ARV prophylaxis or, if indicated, highly active anti-retroviral therapy (HAART).The dual goals of antiretroviral (ARV) therapy in pregnant women are to provide treatment for the mother and to reduce the likelihood of transmission of the virus to the foetus or neonate.

In view of increasing numbers of HIV positive women and advancements in management, this guideline will facilitate the care of these women by disseminating relevant and contemporary information to all levels of health care workers in a systematic fashion.



*In 2006, the outcome of only 62 babies out of the 170 positive pregnant women is presently known.

In this guideline :

- Women' refers to pregnant women with HIV infection
- Combined clinic' refers to a clinic where both obstetrician and physician attend jointly to these women.
- START refers to short- term- antiretroviral therapy/ short term HAART for the purposes of PMTCT
- HAART- highly active antiretroviral therapy (long term)

2.0 RISK OF TRANSMISSION

The risk of transmission of HIV in pregnancy depends on maternal health status (WHO clinical stage of HIV –refer Appendix 3), viral load and a variety of obstetrical factors. In general the risk of transmission will be highest if the maternal viraemia is high and / or CD4 counts are low.[6,level 6;7,Level 6;8 Level 6] However, transmission has been reported in patients with low viral load of less than 1000 copies/ml. There is no evidence at which viral load transmission occurs.[9,Level 1]

Based on 13 cohort studies the risk of vertical transmission without ARV treatment was estimated to be about 15 to 30% worldwide.[4 Level 1] As maternal health plays an important role in reducing perinatal transmission, the strategy to improve HIV-related care for HIV-infected women is crucial to reduce HIV infection in children.

The most important obstetric factors that influence the transmission rate are duration of membrane rupture and mode of delivery. Invasive monitoring, instrumental delivery and prematurity have also been shown to increase the rate of perinatal transmission.[10, Level 9] Studies in twins suggest that the first born twin is at higher risk of transmission than the second born. This supports the evidence that the presence of virus in the genital tract influences vertical transmission.[11, Level 8]

Any invasive procedure (e.g. amniocentesis, chorionic villus sampling) for prenatal diagnosis is not recommended unless the potential benefits outweigh the risks.[10,Level 9;12 ,Level 9]

Recommendation for reducing risk of transmission

- **Invasive procedures (e.g. amniocentesis, chorionic villus sampling) in HIV pregnant women are not recommended (Grade C)**

3.0 SCREENING

3.1 Counselling

Group pre-test counselling has been advocated during booking to shorten counselling time.[1,Level 8] This is followed by individual pre-test counselling to screen-positive pregnant women to enable them to give informed consent for confirmatory testing.

Post-test counselling is provided to ensure these women receive appropriate treatment.[14, Level 8] The testing-result interval should be as short as possible.[15, Level 9]

There remains general consensus that HIV testing should be voluntary and performed after obtaining informed consent.[9,Level 1;16,Level 2.] Women are much more likely to get tested if they perceive their provider strongly recommends HIV testing.[17 ,Level 3]

A meta-analysis of 27 studies concluded that HIV counselling and testing was an effective intervention for HIV positive participants. These decreased their risk behaviours, however little effect was seen in HIV negative participants.[18, Level 1]

3.2 Recruitment strategy

In a systematic review carried out by The US Preventive Services Task Force it was noted that the acceptance rates for voluntary HIV testing among more than 174,000 pregnant women ranged from 23% to 100%. The HIV test rates during pregnancy appear to be higher using “opt-out” testing policies.[9,Level 1]

In order to ensure better coverage, intrapartum testing should be offered to women who have not been screened. [19,Level 8]

Opt-out screening is defined as performing a HIV test after notifying the patient that the test will be done; consent is inferred unless the patient declines.[20,Level 9]

3.3 Timing of Screening

Health care providers should perform a HIV test as early as possible during every pregnancy to ensure informed and timely management. [21,Level 9]

A repeat HIV test is necessary in high risk patients who were first screened negative. This is because some women seroconvert during pregnancy after first antenatal check-up. This test should be performed between 3 to 18 weeks after the initial test. [22, Level 9]

High risk factors include:

- Women whose past or present sexual partners were HIV infected, bisexual or IVDU [9, Level 1]
- Women seeking treatment for sexually transmitted disease (STD) [9,Level 1]
- Commercial sex worker[9,Level 1]
- Women with past or present history of intravenous drug use (IVDU)[9 ,Level 1]
- Women with history of blood transfusion before 1986
- Unprotected vaginal or anal intercourse with more than one sex partner[23,Level 9]

3.4 Methods of HIV testing

The standard diagnostic testing for HIV infection in adults also applies to HIV testing of pregnant women.

Enzyme immunoassay (EIA), in combination with a confirmatory Western Blot is considered the 'gold standard' for determining HIV infection. Together, these two tests have a sensitivity and specificity greater than 99%. [9 , Level 1]

However in the WHO HIV testing strategy, a reactive Enzyme Linked Immunosorbent Assay (ELISA) / Enzyme Immuno Assay (EIA) result is followed by Particle Agglutination (PA). A reactive PA test result will then require a confirmatory Western Blot test.[23 Level 9]

An alternative to the classic Western Blot confirmatory test is the Line Immunoassay (LIA). In this assay, recombinant or synthetic peptide antigens are applied on a nitrocellulose strip, rather than electrophoresed. Several studies have verified the accuracy of LIA is equivalent to the Western Blot test.[24,Level 4;25 Level 4]

Rapid HIV tests, using similar principles to ELISA / EIA, offer a quick, accurate and less resource-intensive alternative to traditional HIV testing methods.[26 ,Level 4; 9 Level 1] Therefore they can be used in remote areas where basic laboratory infrastructure is lacking.

There are a few types of Rapid tests used in the United States. The sensitivity ranges from 95.8% to 100%, specificity from 98% to 100% with a positive predictive value of 33% to 100%.[9 Level 1]

In the Ministry of Health Malaysia (MOH), the Rapid test has been selected as a screening test. The MOH bases the selection of the Rapid test on the evaluation by IMR that it has a 99.9% sensitivity and 99.8% specificity.

Despite the high sensitivity and specificity of rapid tests, the issue of indeterminate or false-positive results in pregnant women is not resolved. A negative test result effectively rules out HIV except in the case of recent infection in which antibodies have not yet developed. A positive HIV rapid test result still requires a confirmatory test. [27,Level 9]

Some studies have shown that the Rapid test followed by the PA test constitutes a reasonable alternative to the standard ELISA / Western Blot combination.[28, Level 4;29, Level 4]

3.5 Screening during Labour

Rapid HIV testing using a highly sensitive test is feasible and delivers accurate and quick results for women in labour who have not been previously screened. This strategy provides HIV-positive women prompt access to intrapartum and neonatal ARV prophylaxis. Median time from blood collection to patient notification of result is faster than compared to EIA.[30 ,Level 8]

Recommendations for antenatal HIV counselling and screening

- HIV testing should be offered to all pregnant women as part of routine antenatal care using the opt-out strategy. **(Grade A)**
- Screening should be voluntarily undertaken with the patient's knowledge and consent. **(Grade A)**
- Screening should be done as early as possible during every pregnancy. **(Grade A)**
- Group pre test of counselling is an acceptable method**. (Grade C)**
- If the rapid/ screening test is positive, individual pre- and post-test counselling are essential elements to enable women to give informed consent**. (Grade C)**
- In high risk patients, a repeat test should be done preferably after 12 weeks of the first test if the initial test is negative **(Grade C)**

  OR

  before 36 weeks of gestation if the initial test is negative. **(Grade C)**
- 3 test strategies are required for diagnosis of HIV **(Grade C)**
  - For screening, Rapid test/ Enzyme immunoassay (EIA) / Enzyme linked immunosorbent immunoassay (ELISA) is recommended**. (Grade A)**
  - A positive screening test should be followed by a Particle Agglutination (PA).(**Grade B)**
  - Final confirmation with LIA / Western Blot is required.**(Grade B)**
- Screening during labour
  - Rapid test is to be done in patients who have not been screened. (**Grade C)**
  - All positive tests should be verified with standard confirmatory tests. **(Grade A)**

For details, please refer to algorithm on HIV screening for pregnant women (pg viii)

3.6 Notification and contact tracing

Under the Infectious Disease Act 342 (1988), health care providers are legally bound to notify the local health authority about anyone found to be HIV positive.[31] Providers should recommend that their partners receive HIV testing. Health departments can assist patients by notifying, counselling and providing HIV testing for partners without disclosing the patient's identity.[32, Level 9; 33, Level 9]

Under the Infectious Disease Act 342 (1988), health care providers are legally bound to notify the local health authority anyone found to be HIV positive.

4.0 INVESTIGATIONS AND MONITORING

HIV is known to cause progressive impairment of the immune system that will put the patient at risk of opportunistic infection and tumours. In pregnancy, the progression of the disease will further increase the risk of perinatal transmission.

There are several markers that have been looked into as the best monitoring tool, such as plasma viral load (HIV- RNA), CD4 count, â2-microglobulin and HIV-1 p24 antigen. [34, level 9; 35, Level 2] Plasma viral load is the best marker as it correlates well with disease progression and predicts the risk of perinatal transmission.[34,Level 2; 36, Level 4; 37, Level 4]

Plasma viral load should be monitored in patients with HIV especially those who receive HAART and the test should be done at 36 weeks gestation.[38, Level 9] The plasma viral load at 36 weeks gestation is the best predictor of perinatal transmission and it can also be used to determine mode of delivery.

As HIV increases the risk of opportunistic infection, all patients with HIV should be screened for Hepatitis B & C, syphilis, gonorrhoea, toxoplasmosis and Chlamydia.[39, Level 9; 40, Level 8]

The relationship of bacterial vaginosis and maternal to child transmission (MTCT) of HIV is still controversial.[41,Level 9;42, Level 8;43,Level 8]

Recommendations for investigations and monitoring
• Plasma HIV-1 RNA levels should be monitored in all women on HAART and START. (**Grade A)**
• CD4 counts should be monitored in all women on HAART and START. **(Grade C)**
• All HIV positive women should be examined for genital infections and treated appropriately. If negative, the examination should be repeated at 28 weeks.**(Grade C)**
• Co-infections (Hepatitis B, Hepatitis C, syphilis, gonorrhoea, toxoplasmosis and chlamydia) should also be screened in these women. **(Grade C)**

5.0 MANAGEMENT OF HIV PREGNANT WOMEN

There should be a proper referral pathway for these patients to the combined clinic. The availability of an ID physician is an additional option.[10, Level 9] Public health nurses play a pivotal role in ensuring that these women are compliant to their Anti Retroviral Therapy (ART) and antenatal follow-up.

It is important that all healthcare professionals involved in the management of a HIV positive pregnant woman are aware of the diagnosis and the plan of her care. Confidentiality must be respected and ensured. Health professionals should not presume that the woman's partner or her relatives are aware of her illness even though they may attend clinics as well as the delivery. [10, Level 9]

Interventions to reduce the risk of HIV transmission should be discussed with the women. These measures would include the use of ARV therapy, elective caesarean delivery and avoidance of breastfeeding. The implementation of these 3 interventions will reduce the vertical transmission risk to below 2%. [44, Level 2;45 Level 8; 46,Level 9;10, Level 9]

Multidisciplinary team should comprise of an obstetrician, physician, family medicine specialist and paediatrician. Optional members in the team would include the ID physician, specialist midwives, social workers, psychiatrist, clinical psychologist, counsellors and relevant non government organisation (NGO's).

Modified from 10, Level 9

Recommendations for management of HIV pregnant women
• Women with HIV positive in pregnancy should be managed by a multidisciplinary team including community healthcare personnel. **(Grade C)**
• Women diagnosed as HIV positive after 28 weeks gestation should be referred to hospital **URGENTLY** for initiation of antiretroviral therapy. **(Grade C)**
• Women should be informed that use of antiretroviral therapy, elective caesarean delivery and avoidance of breastfeeding can reduce the mother to child transmission rates to <2%. (**Grade A)**
• After delivery, the patient should be followed up by the physician. **(Grade C)**
• The baby will be followed up by a paediatrician*. **(Grade C)**

***** *Please refer to the MOH CPG on Management of HIV Infection in Children (2008) for further details*

6.0 MEDICAL TREATMENT

Introduction

ARV therapy is given for two reasons during pregnancy; first for the prevention of MTCT and secondly for the treatment of mother to prevent maternal disease progression (therapy continued indefinitely after delivery). [10, Level 9;47,Level 9;38, Level 9]

The current treatment of pregnant women infected with HIV has evolved from monotherapy to Highly Active Anti-Retroviral Therapy (HAART). Zidovudine (ZDV) has been the most extensively studied ARV in pregnant women and forms a component of treatment in most trials.

PACTG 076[44,Level 2] was the first major study that demonstrated the effectiveness of a 3-part regimen (antepartum, intrapartum and postpartum) in reducing MTCT from 22.6% to 7.6%. The vertical transmission rate was further reduced to < 2 % when elective Caesarean Section was performed and breastfeeding was not permitted.[48,Level 6; 49,Level 6]

In a systematic review of 4 RCTs comparing ZDV with placebo, it was demonstrated that ZDV significantly reduced MTCT. [50,Level 1] There is also

no evidence ZDV influences the incidence of premature delivery or low birth weight.

Development of ZDV drug resistance with PACTG 076 ZDV regimen alone appears uncommon in women with higher CD4 count and low viral load. [51,Level 8; 52, Level 9] It has been demonstrated to be more common in women who have more advanced disease and lower CD4 count. [53, Level 6]

In the North American Women and Infant Transmission study (WITS) cohort there was reduction in transmission from 7.8% in mother-infants pairs receiving ZDV monotherapy to 1.1% in mother exposed to triple therapy. [53, Level 6] In PACTG 367, the transmission rate among 3081 women in N. America fell from 4.2% in 1998 to 0.5% in 2002. Among women who did not receive any ARV therapy, transmission was 18.5% falling to 5.1% with ZDV monotherapy, 1.4% with dual NRTIs and 1.3% with three or more drugs. [54 ,Level 2]

Combination antiretroviral therapy of three or more ARVs or HAART (usually from ⩾" 2 classes), is the recommended standard treatment for HIV-1 infected adults who are not pregnant. [55,Level 9]

Pregnancy should not preclude the use of optimal therapeutic regimens. However, recommendations regarding the choice of antiretroviral drugs for treatment of infected pregnant women are subject to unique considerations, including

I. the potential effects of antiretroviral drugs on the pregnant woman, and
II. the potential short- and long-term effects of the antiretroviral drug on the fetus and newborn. [56, Level 9; 38,Level 9;10,Level,9]

Avoid the combination of Stavudine plus Didanosine as part of the triple therapy whenever possible, due to case reports of fatal lactic acidosis in pregnancy.[57, Level 6]

The decision to use any antiretroviral drug during pregnancy should be made by the woman after discussing with her health-care provider the known and unknown benefits and risks to her and her foetus.[38,Level 9; 56 ,Level 9] ARV should be initiated by Physician/ ID Physician and /or Obstetrician. The patients will be monitored in the combined clinic.

Adherence to ARV therapy is of vital importance for the success of treatment and pregnant women may need extra support and planning in this area, especially if there are practical or psychosocial issues that may impact adversely on adherence. [38,Level 9]

In utero exposure

Most studies looking at the safety of ARV therapy are based on animal studies.[58, Level 9] One meta-analysis of 5 prospective cohort studies carried out in the USA and one large European prospective cohort study found no significant difference in the rates of congenital anomalies, neonatal conditions or low birth weight between infants exposed to combination ARV therapy and unexposed infants. [59,Level 9; 60 ,Level 6]

Data on the association between combination of ARV regimens and increased rates of premature delivery are mixed.[9, Level 1] Although molecular and biochemical evidence of mitochondrial dysfunction have been reported in infants exposed to in utero to ARV agents,[61,Level 6;62 Level 7;63,Level 8] the clinical impact of such dysfunction was unclear.[64, Level 8; 65, Level 8]

However there were significant malformations (anencephaly, anophthalmia, cleft palate) observed in 3 (15%) of 20 infants born to cynomolgus monkeys receiving efavirenz during the first trimester at a dose giving plasma levels comparable to systemic human therapeutic exposure.There are three case reports of neural tube defects in humans after first trimester exposure however the relative risk was unclear.[38, Level 9]

Recommendations to start antiretroviral therapy
• Women require antiretroviral therapy to prevent mother-to-child transmission of HIV. **(Grade A)**
• Women should be advised to take antiretroviral therapy during pregnancy and during delivery. **(Grade A)**
• Combination of more than three or more antiretroviral drugs is recommended for all HIV pregnant mothers to reduce mother-to-child transmission of HIV. **(Grade B)**
• Antiretroviral therapy should be started as early as possible in pregnancy after the first trimester. **(Grade B)**
• Adherence to antiretroviral therapy is of utmost importance in the success of treatment. **(Grade C)**
• A detailed anomaly ultrasound should be performed for all foetus exposed to HAART during the first trimester**. (Grade C)**

6.1 CLINICAL SCENARIOS AND RECOMMENDATIONS FOR THE USE OF ARV PROPHYLAXIS

Women with advanced HIV (refer Appendix 3) or those women with CD4 T cell count < 250 cells/uL (Scenario A1), should commence treatment with a combination of three or more drugs (i.e. HAART). The treatment which should be continued indefinitely after delivery. [10, Level 9;56 Level 9; 38, Level 9]

Where ARV therapy is not required during pregnancy for maternal health (Scenario A2), a combination of three drugs to suppress HIV viral replication may be prescribed for the duration of pregnancy and after delivery to reduce transmission: administered correctly, this will preserve future maternal therapeutic options. In this scenario, ARV therapy is usually discontinued at, or soon after delivery. [10, Level 9;38 Level 9; 56, Level 9]

For women whose CD4 T cell count is > 250 cells/uL**,** a short term antiretroviral therapy (i.e. START) combination of 2 (nucleoside reverse transcriptase inhibitor ARVs (NRTIs) and a protease inhibitors (PI) should be prescribed. The non-nucleoside reverse transcriptase inhibitor (NNRTI), nevirapine(NVP), has been shown to have an increased incidence of hepatotoxicity if initiated in women with pre-treatment CD4 > 250 cells/µl, [66,Level 3; 67,Level 9] hence, a PI based regimen needs to be used in such women to prevent this occurrence (refer Appendix 1).

In most circumstances initiation of ARV therapy should be delayed until after the first trimester unless early initiation is judged important for maternal health. Delaying the initiation of HAART after the first trimester minimises the risk of drug related teratogenecity and usually results in better adherence as the nausea associated with pregnancy has usually diminished by this time.[68, Level 9; 38, Level 9; 56 Level, 9]

In women who are newly diagnosed as HIV infected, clinical staging according to symptoms and CD4 count is recommended (refer Appendix 3)

In pregnant women who refuse HAART/ START or if there is a reasonable doubt on compliance, ZDV monotherapy is an alternative but an inferior option.[38, Level 9; 56, Level, 9]

The following recommendations for the use of ARV therapy to reduce MTCT are based on scenarios that may commonly present in clinical practice.

A. Newly diagnosed HIV pregnant women not on ARV

A.1 HIV women with CD4 T cell count < 250 cells/uL

Most guidelines recommend that the initiation of HAART should be between 14-28 weeks of gestation.[68, Level 9; 38, Level 9;56 Level, 9]

Based on the PACTG 076, PHPT 2 and HIVNET 012 protocols, a safe and efficacious three-drug combination would be Zidovudine (ZDV), Lamivudine (3TC) and Nevirapine (NVP). In the intrapartum period regardless of mode of delivery, intravenous ZDV should be given to the patient. [38, Level 9;69, Level 2; 70, Level 2;71, Level 2;72, Level 2]

After initiating HAART the following should be looked for and monitored:

- NVP should be stopped immediately in all women who develop signs and symptoms of hepatitis or severe rash. [38, Level 9]

- Full Blood Count to monitor haemoglobin (ZDV is known to cause anaemia) if women developed anaemia they need to be investigated and treated. If anaemia occurs with ZDV therapy (600mg o.d.), consider dosage reduction to 500mg daily, i.e. 300mg followed by 200mg twelve hours later or substitute with another NRTI drug. Please refer to Infectious Diseases Physician for further information.

- Liver Function Test to monitor Aspartate Aminotransferase (AST) and Alkaline Phosphotase (ALP) (NVP is known to cause hepatitis) particularly during the first 18 weeks of treatment.[38, Level 9]

Monitoring should be carried out 2 weekly for the first month after initiating HAART and then monthly till delivery.CD4 count should be monitored at 4 monthly interval.[73, Level 9]

HIV RNA viral load should be taken at baseline before initiation of therapy and at 34-36 week of gestation to help in decision on the mode of delivery. If HIV viral load at 34-36 week <1000 copies/ml, vaginal delivery may be allowed.[10,Level 9]

During the intrapartum period, it is recommended to give i.v. ZDV with elective Caesarean section.[74, Level 1,50, Level 1,75, Level 1]

Post partum, HAART should be continued for the mother and the baby will be followed up by the paediatrician. The mother should be on regular follow up with physician.

Pneumocyitis (carinii) jiroveci Pneumonia Prophylaxis

Prophylaxis against Pneumocystis (carinii) jiroveci Pneumonia (PCP) is an important component of HIV related clinical care. There is mixed evidence linking ingestion of Trimethoprim-Sulfamethoxazole (TMP/SMX: co- trimxazole) and other sulfonamides in early pregnancy to increase risk of oral clefts, neural tube defects, and cardiovascular and urinary tract abnormalities. [76, Level 7]

It is recommended that HIV-infected pregnant women with a CD4+ T-lymphocyte count of < 200/µl receive PCP prophylaxis with TMP / SMX. [77, Level 9;78, Level 9;79 Level 8] Use of TMP / SMX in the first trimester should target women at highest risk for HIV-related illness (those with clinical evidence of advanced disease, or those who have been previously diagnosed with PCP). The benefit of improved morbidity and mortality with TMP / SMX prophylaxis among these high-risk women may outweigh the small risk to the foetus.[77, Level 9]

Recommendations for HIV pregnant women with CD4 T cell count < 250 cells/uL
• The preferred first line for HAART regime is zidovudine (ZDV)*, lamivudine (3TC)* and nevirapine (NVP)* **(Grade C)**
• For women who have NVP intolerance or allergy, please refer to infectious disease physician **(Grade C)**
• Full Blood Count and Liver Function Test should be monitored two weekly for the first month after initiating HAART and then monthly. **(Grade C)**
• CD4 counts should be monitored 4 monthly in women on HAART. **(Grade C)**
• Plasma HIV-1 RNA levels should be monitored in all women on HAART at baseline and at 34-36 weeks gestation. (**Grade A)**
• Intrapartum zidovudine (ZDV)* should be given to women. **(Grade A)**
• Zidovudine (ZDV)*, lamivudine (3TC)* and nevirapine (NVP)/ combination therapy should be continued post delivery and for life for the mother. **(Grade A**)
• Women with a CD4 + T-lymphocyte count of < 200/µl should receive PCP prophylaxis with TMP/SMX. **(Grade C)**

** Refer to Appendix 1 and 2 for dosage and side effects*

A.2 HIV pregnant women with CD4 T cell count > 250 cells/uL

Initiate combination of Short Term Antiretroviral Therapy (START) as soon as possible after 14 weeks' gestation (and, in any case, before 28 weeks' gestation), to avoid the organogenesis period and to allow adequate time interval to achieve viral suppression by delivery. [38, Level 9; 56 ,Level 9] The decision to continue or stop ARV therapy post partum depends on the initial CD4 count. This should be discussed with the ID specialist / physician before delivery.

The guideline development group recommends a PI based ARV combination with 2 NRTI. The recommended drug combination is *AZT + 3TC + Lopinavir / Ritonavir* with the intention to achieve undetectable viral loads of <50 copies per ml prior to delivery. [80, Level 6; 81, Level 6]

If the patient presents late in pregnancy i.e. > 28 weeks of gestation, START should be initiated immediately with AZT/3TC and lopinavir / ritonavir (even before any CD4 results are available) in the hospital. During follow-up, if the CD4+ T-lymphocyte count of < 250 cells/uL**,** consider switching to the Nevirapine based regimen (i.e. two NRTI drugs + NVP).

Full Blood Count should be done 2 weekly for the first month and then monthly till delivery for detecting possible anemia due to ZDV.

Hyperglycemia, new-onset diabetes mellitus, exacerbation of existing diabetes mellitus, and diabetic ketoacidosis have been reported for women who have been treated with protease inhibitor antiretroviral drugs like lopinavir /ritonavir. [82, level 9, 83, Level 9] In a Spanish cohort of 609 pregnant women with HIV infection, the incidence of gestational diabetes was 7% higher than the expected for the general population. [84, Level 6]

Therefore clinicians caring for these women should be aware of the risk of this complication. Symptoms of hyperglycemia should be discussed with pregnant women who are receiving protease inhibitors. HIV pregnant women receiving START should be screened for glucose intolerance [38, Level 9]

Plasma viral load should be taken at 36 weeks gestation for women on START, in order to make informed decisions on the mode of delivery. If HIV is viral load <1000 copies/ml, allow for vaginal delivery.[10, Level 9] During intrapartum, it is recommended to give i.v. ZDV. [38, Level 9; 50 Level 1; 75, Level 1; 86, Level 8]

Postpartum, START will either be discontinued immediately after delivery[10, Level 9] or continued indefinitely in the mother, depending on the nadir CD4 on presentation. This decision has to be discussed with the ID physician/ physician prior to delivery.

The mother should be on regular follow up with the physician whereas the baby will be followed up by the paediatrician.

Recommendations for HIV pregnant women with CD4 T cell count > 250 cells/uL
• Short term antiretroviral therapy (START) should be initiated after the first trimester **(Grade C)**
• The preferred first line regime is zidovudine (ZDV)*, lamivudine (3TC)* and lopinavir/ritonavir * **(Grade C)**
• Full Blood Count should be done 2 weekly for the first month and then monthly. **(Grade C)**
• Modified glucose tolerance test (MGTT) should be done after initiating START. **(Grade C)**
• CD4 count should be monitored 4 monthly**. (Grade C)**
• Plasma HIV viral load should be done at 34-36 weeks of gestation**. (Grade C)**
• Intrapartum intravenous zidovudine (ZDV**)*** should be given**. (Grade A)**
• The decision to stop or continue START (zidovudine+lamivudine+ lopinavir/ritonavir) *post delivery should be individualized after discussion with the ID physician/physician **(Grade C)**

** Refer to Appendix 1 for dosage and side effects*

A.3. Women diagnosed in labour without prior therapy

In the HIVNET 012 protocol, a single dose of NVP given to mothers at the onset of labour and to their babies soon after birth was compared to a suboptimal course of ZDV given to mothers only during labour and to their babies for the first week of life. In this trial, the NVP arm had a reduction in MTCT at 4 to 8 weeks by about 40% with the benefit persisting at 18 months of life.[88, Level 2]

If Caesarean section cannot be preformed in time, combination ART is then indicated to reduce MTCT. The regimen is intrapartum ZDV by intravenous infusion + Single Dose NVP + 3TC during delivery. To reduce the development of NVP resistance, continue twice - daily oral ZDV and 3TC for one week post delivery for the mother.[38, Level 9]

Recommendations for women diagnosed in labour without prior therapy

- Regardless of the mode of delivery, provide prophylactic ARVs as follows:
  - Intrapartum intravenous zidovudine (ZDV)* + oral lamivudine (3TC)* + Single Dose oral nevirapine (sdNVP)* during delivery

AND

  - Continue oral zidovudine (ZDV)* and 3TC* for one week post delivery for the mother. **(Grade C)**

** Refer to Appendix 1 for dosage and side effects*

B. HIV positive women who are already on a HAART regime

B.1 Women stable on HAART

The data provide conflicting advice as to whether continuation of combination ARV therapy during pregnancy is associated with adverse pregnancy outcomes such as preterm labour and delivery. Furthermore if HAART is interrupted during the first trimester, this may cause immunological deterioration and rebound HIV viraemia with possible development of ARV drug resistant strains in a HIV infected pregnant woman who is already stable on HAART.[89,Level 8; 90, Level 3]

For patients presenting in first trimester while on potentially teratogenic drugs like efavirenz, the pros and cons of continuing this regimen should be discussed with her.[56,Level 9; 38, Level 9]

Women on HAART should be monitored closely for possible toxicities and complications due to HAART. HIV RNA viral load should be done at 36 weeks of gestation to determine the mode of delivery for the mother. HAART should be continued after delivery and the mother will be reviewed by the ID or physician in their subsequent follow-up.

Recommendations for women stable on HAART
• Women should **continue** their HAART regime (unless they present in the first trimester on efavirenz). **(Grade C)**
• Plasma HIV-1 RNA levels and CD4 should be monitored 4 monthly. **(Grade C)**
• They should receive careful, regular monitoring for potential toxicities*. **(Grade C)**
• Intrapartum zidovudine (ZDV)* should be given to women. **(Grade A)**

** Refer to Appendix 1 for dosage and side effects*

B.2 Women failing HAART

Failing HAART therapy (detectable HIV RNA, declining CD4 T cell count or clinical failure) is an indication to change regime. HIV viral resistant testing should be done if available to choose the best optimum regime for the patient [73, Level 9]

Recommendation for women failing HAART
• Women failing HAART should be referred to the Infectious Disease Physician. **(Grade C)**

7.0 OBSTETRIC MANAGEMENT

7.1 Vaginal Disinfection to reduce MTCT

A systematic review of randomised trials has shown that there is no difference in outcomes of MTCT when vaginal disinfections have been used[91, Level 1]

Recommendation for vaginal disinfection to reduce mother-to-child transmission of HIV
• There is no evidence to support vaginal disinfection in preventing mother-to-child transmission of HIV. **(Grade A)**

7.2 Management of ruptured membranes

A cohort of 525 women infected with HIV-1 demonstrated that ruptured membranes for > 4 hours and mean $CD4^+$ count < 29% (CD4 count < 500 cells/uL) were significantly associated with higher risk of MTCT.[92, Level 6]

In a metanalysis of 15 prospective cohort studies, the risk of vertical transmission increases approximately 2% with an increase of every hour in duration of ruptured membranes. The estimated probability of transmission increased from 8% to 31% with duration of ruptured membranes of 2 and 24 hours respectively.[93, Level 1]

To reduce the risk of MTCT, caesarean section should be performed within 4 hours of membrane rupture (with the exception of women stable on HAART with viral load <1000 at 34-36 weeks'). [94 Level 9; 10,Level 9]

Recommendation for management of ruptured membranes

- The duration of ruptured membranes increases the risk of perinatal transmission **(Grade A)** therefore Caesarean section is of doubtful benefit after 4 hours of membrane rupture. **(Grade C)**

7.3 Mode of delivery and viral load

Several systematic reviews showed that elective caesarean section reduces MTCT. This benefit appears additive with prophylactic ZDV monotherapy and the likelihood of transmission was reduced by approximately 87% with both elective caesarean section and full-course ZDV compared to other modes of delivery.[38,Level 9; 50, Level 1; 75, Level 1]

In a meta-analysis of 7 prospective studies of women with viral loads < 1000 copies /mL at delivery or at the measurement closest to delivery, there was a 1% risk of transmission rate for those on ARV, compared with 9.8% for untreated mothers. Elective LSCS has been shown to further reduce transmission rates. [86 ,Level 1]

Women who have a detectable viral load and / or who are not taking HAART should be offered an elective caesarean section as it reduces MTCT. It is recommended that delivery by elective caesarean section should take place after 38 weeks of gestation. [10, Level 9]

Increasing geometric levels of plasma HIV-1 RNA were associated with increasing rates of transmission. The highest transmission rate was among women whose plasma HIV-1 RNA levels exceeded 100,000 copies who had

not received ZDV (63.3%). The level of plasma HIV-1 RNA predicts the risk but not the timing of transmission of HIV-1 to their infants. [96, Level 1]

In women who have been treated with START/HAART with a viral load of less than 1000 copies/ml may opt for a vaginal delivery.[10, Level 9]

Women who opt for a planned vaginal delivery should have their membranes intact as long as possible. Women should continue their HAART throughout labour and be given intravenous ZDV till the cord is clamped as soon as possible after delivery.[10, Level 9]

Recommendations for mode of delivery and viral load
• Elective caesarean section is recommended about 38 weeks for those not on treatment, those who are on zidovudine monotherapy, or those with START/ HAART but with a viral load of more than 1000 copies/ ml. **(Grade A)**
• Those who are treated with START/ HAART with a viral load of less than 1000 copies / ml may opt for a vaginal delivery**. (Grade B)**

7.4 Safety Issues

Higher maternal HIV-1 RNA level at or close to delivery significantly increased disease progression risk with a borderline effect on mortality. Effects were independent of maternal and infant treatment. [95,Level 1] Post partum morbidity is generally higher among women who undergo caesarean as compared to vaginal delivery. There are more minor morbidities (fever, urinary tract infection, anaemia) than major events (pneumonia, pulmonary embolism, sepsis). [75, Level 1; 97, Level 4; 38,Level 9]

Please refer to Ministry of Health Standard Precaution Guidelines [98,Level 9] with regards on standard precaution and disposal of waste hazards in HIV infected patients.

8.0 BREASTFEEDING

The risk of vertical transmission is significantly higher (14-16%) with breastfeeding despite receiving ARV [9, Level 1;99,Level 2;100, Level 6;10, Level 9] Strategies should be made to ensure babies of HIV mothers are formula fed and their care givers educated on proper hygiene. [68,Level 9]

A cohort study of 549 children born to HIV women in Africa demonstrated that mixed feeding carried a higher risk of HIV transmission to the baby compared to exclusive breastfeeding in their babies less than 3 months of age or those babies that who were artificially fed.[100, Level 6]

A Ministry of Health Malaysia circular provides for free infant formula for the first six months for perinatally exposed babies from low income families (RM <1200) in the first instance and case to case basis for such infants whose families income is more then RM1200.[87]

Recommendations for breastfeeding
• All HIV infected mothers should be advised not to breastfeed their infants as it is associated with a higher risk of vertical transmission. **(Grade A)**
• Families should be counselled against mixed feeding at any time, as it has carries a higher risk of mother-to-child transmission than exclusive breastfeeding or formula milk feeding **(Grade B)**

9.0 POST NATAL CARE

Basic postnatal care of the mother and her infant is no different from routine postnatal care. Multidisciplinary support from the obstetrician, paediatrician, infectious disease physician and primary care doctors and nurses for the mother and her family is essential to ensure adequate care.[101, Level 9]

The community clinic staff should be informed about the mode of delivery, potential complications to expect and advice about the therapy that the patient may be on. They can assist in monitoring and managing the patient adequately. The issue of confidentiality for these patients is of utmost importance, and health care workers must be reminded to maintain this.

Concerns have been raised about adherence to ARV regimens during the postpartum period. Studies have shown that adherence is extremely low during late pregnancy and declines significantly postpartum.[102, Level 6; 103, Level 9]

The puerperium is a period at risk of postnatal depression, and women with HIV may require additional support especially while there is uncertainty regarding the status of their infants.[101 ,Level 9; 38,Level 9]

Breast feeding is not recommended for mothers with HIV. Some women may require medication to suppress lactation and carbegolin may be prescribed.

Recommendations for post natal care
• Confidentiality should be maintained at all times regarding the patient's diagnosis. **(Grade C)**
• Community health care personnel i.e. public health nurses should be informed when a mother is discharged to their area and the potential complications. **(Grade C)**
• Community health care personnel should provide support and counselling to help the mother to adhere to her antiretroviral regime. **(Grade C)**
• Community health care personnel must help to ensure the mother and her baby attend their follow up visits to the Infectious Diseases Clinic and Paediatric Clinic. **(Grade C)**
• The health care provider should be vigilant for signs of depression. **(Grade C)**
• Breast feeding should be avoided and lactation suppression provided when necessary. **(Grade C)**

10. CONTRACEPTION

Contraception not only prevents unwanted pregnancies, but also plays a role in prevention of sexual transmission of HIV including HIV super-infection. The issues related to contraception and HIV are more complex than for uninfected women.

Consistent, correct condom use has been shown to provide a high degree of protection against sexual transmission of HIV.[104, Level 1; 105,Level 4;106, Level 6] Use of condoms result in pregnancy rates of 3%,[107,Level 8; 108 ,Level 9] and also protects against other sexually transmissible infections (STIs). This is known as "Dual protection".

There is an increase in genital shedding in HIV-1 infected women after starting combined hormonal contraception.[109 ,Level 6] This raises the possibility that use of hormonal contraception may increase the infectivity of HIV-1 infected women to uninfected partners. Therefore partner protection with the use of condoms is recommended.

There are drug interactions between ARV therapy and hormonal contraceptives with an increased risk of failure of the contraceptive. [110, Level 8;111, Level 6;112,Level 6.]

The insertion of an Intra Uterine Contraceptive Device (IUD) did not significantly alter the prevalence of cervical shedding of HIV-1 infected cells. [113, Level 4] Therefore IUD use seems safe from the standpoint of infectivity to a sexual partner. There are low rates of overall and infection-related complications among HIV-1 infected women after IUD insertion.[114, Level 9; 115,Level 9]

Spermicides offer very limited protection from pregnancy and may increase risk of HIV transmission[116, Level 1]

Ethically, there is no medical reason to deny or force sterilization to patients with HIV. [117,Level 6;118,Level 6]

Recommendations for contraception
• The condom is the only contraceptive method proven to prevent both pregnancy and sexual transmission of HIV. (**Grade A)**
• If an intra uterine device or hormonal contraception is to be considered, they must be used together with the condom. **(Grade B)**
• There is no medical indication for permanent sterilization of HIV-infected individuals. **(Grade B)**

REFERENCES

1 De Cock KM, Foweler MG, Mercier E, et al. Prevention of mother-to-child HIV transmission in resource–poor countries- Translating research into policy and practice. *JAMA* 2000;283(9); 1175-1182

2 Rashid H. Merchant & Mamatha M. Lala. Prevention of mother-to child transmission of *HIV. Indian .J Med Res 121*; April 2005: pp 489-501.

3 AIDS/STD Section, Disease Control Division, Ministry of Health, Malaysia. Summary of HIV/ AIDS cases,2006

4 Volmink J, Siegfried NL, Van der Merwe L, Brocklehurst P. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. *Cochrane Database Syst Rev*. 2007 Jan 24;(1).

5 Ministry of Health Malaysia. Criteria For Commencing Highly Active Antiretroviral Therapy (HAART) In Women detected to be HIV Positive during Antenatal Screening. HIV Bil 1/ 2001.

6 Cooper ER, Charurat M, Mofenson LM, et al.Combination antiretroviral strategies for the treatment of pregnant HIV-1 infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr Hum Retrovirol*, 2002.29(5):484-494.

7 European Collaborative study, Risk factors for mother-to-child transmission of HIV-1. European Collaborative. *Lancet*. 1992 Aug 15; 340(8816):435.

8 Mayaux MJ, Blanche S, Rouzioux C, et al. Maternal factors associated with perinatal HIV-1 transmission: the French Cohort Study: 7 years of follow-up observation. The French Pediatric HIV Infection Study Group. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1995 Feb 1;8(2):188-194.

9 Chou R, Smits AK, Huffman LH, et al,. Prenatal screening for HIV: A review of the evidence for the U.S.Preventive Services Task Force. *Ann Intern Med*. 2005 Jul 5;143(1):38-54

10 Royal College of Obstetricians and Gynaecologists (RCOG). Management of HIV in pregnancy. London (UK): *Royal College of Obstetricians and Gynaecologists (RCOG*); 2004 Apr. 12 p. (Guideline; no. 39).

11 Goedert JJ. "Prevalence of conditions associated with human immunodeficiency and hepatitis virus infections among persons with haemophilia, 2001-2003." *Haemophilia.* 2005; 11:516-528

12 Burdge DR, Money DM, Forbes JC, et al. The Canadian HIV Trials Network Working Group on Vertical HIV Transmission, Canadian consensus guidelines for the management of pregnancy, labour and delivery and for postpartum care in HIV-positive pregnant women and their offspring (summary of 2002 guidelines). *CMAJ.* 2003;168(13):1671-1674.

13 Ngidi AC, Myeni ZE, Bland RM, et al; International Conference on AIDS. Acceptability and limitations of HIV group pre-test counselling for pregnant women in rural KwaZulu Natal, South Africa. *Int Conf AIDS*. 2002 Jul 7-12; 14: abstract no. TuPeF5414.

14 Delva W, Mutunga L, Quaghebeur A, et al. Quality and quantity of antenatal HIV counselling in a PMTCT programme in Mombasa, Kenya. *AIDS Care*. 2006 Apr;18(3): 189-193.

15 Obuekwe I.F HIV in pregnancy: the risk of mother-to-child transmission and possible interventions. Available at: http://mwia.regional.org.au/papers/full/33_flossy.htm and http://www.regional.org.au

16 Grinstead OA, Gregorich SE, Choi KH, et al. Voluntary HIV-1 Counselling and Testing Efficacy Study Group. Positive and negative life events after counselling and testing: the Voluntary HIV-1 Counselling and Testing Efficacy Study. *AIDS*. 2001 May 25;15(8):1045-1052.

17 Kellock DJ, Rogstad KE. Attitudes to HIV testing in general practice. *Int J STD AIDS*. 1998 May;9(5):263-267.

18 Weinhardt LS, Carey MP, Johnson BT, et al. Effects of HIV counseling and testing on sexual risk behaviour: a meta-analytic review of published research, 1985-1997. *Am J Public Health*. 1999 Sep;89(9):1397-1405.

19 Homsy J, Kalamya JN, Obonyo J, et al. Routine intrapartum HIV counseling and testing for prevention of mother-to-child transmission of HIV in a rural Ugandan hospital. *J Acquir Immune Defic Syndr*. 2006 Jun;42(2):149-154.

20 Centers for Disease Control and Prevention (CDC). Revised guidelines for HIV counseling, testing, and referral. *MMWR Recomm Rep* 2001 Nov 9;50(RR-19):1-58.

21 Morbidity and Mortality Weekly Report (CDC). Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings Recommendations and Reports September 22, 2006: Vol. 55 ; No.RR-14.

22 Soorapanth S, Sansom S, Bulterys M, et al. Cost - effectiveness of HIV rescreening during late pregnancy to prevent mother-to-child HIV transmission in South Africa and other resource-limited settings. *J Acquir Immune Defic Syndr.* 2006 Jun;42(2):213-221.

23 World Health Organization. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants in resource limited settings. Towards universal access. Recommendations for a public health approach. 2006 version. *http://www.who.int/3by5/ PMTCTreport_June2006.pdf. Accessed on 23 September 2007*

24 Pollet DE, Saman E, Van der Borght B, et al. *Int Conf AIDS* Line immunoassay for the simultaneous detection ofantibodies to HIV-1 and HIV-2 in human sera. 1989 Jun 4-9; 5: 369.

25 Fransen K, Pollet DE, Peeters M, et al. Evaluation of a line immunoassay for simultaneous confirmation of antibodies to HIV-1 and HIV-2. *Eur J Clin Microbiol Infect Dis.*1991 Nov;10(11):939-946.

26 Orlando M, Tucker JS, Sherbourne CD, et al. A cross-lagged model of psychiatric problems and health-related quality of life among a national sample of HIV positive adults. *Med Care*. 2005 Jan; 43(1):21-7

27 Doran TI, Parra E. False-positive and indeterminate human immunodeficiency virus test results in pregnant women. *Arch Fam Med. 2*000 Sep-Oct;9(9):924-929.

28 Mitchell SW, Mboup S, Mingle J, et al. Field evaluation of alternative HIV testing strategy with a rapid immunobinding assay and an agglutination assay. *Lancet.* 1991 Jun 1;337(8753):1328-1331

29 Urassa WK, Bredberg-Rådén U, Mbena E, et al. Alternative confirmatory strategies in HIV-1 antibody testing. *J Acquir Immune Defic Syndr.*1992;5(2):170-176.

30 Bulterys M, Jamieson DJ, O'Sullivan MJ, et al. Mother-Infant Rapid Intervention At Delivery (MIRIAD) Study Group. Rapid HIV-1 testing during labor: a multicenter study. *JAMA*. 2004 Jul 14;292(2):219-223

31 Laws Of Malaysia Act 342. Prevention And Control Of Infectious Disease Act 1988. Avaiable from http://www.dph.gov.my/survelans/Guidelines%202006/LAWS%20OF%20MALAYSIA.pdf

32. MMWR (CDC) Revised Guidelines for HIV Counseling, Testing, and Referral Technical Expert Panel Review of CDC HIV Counseling, Testing, and Referral Guidelines November 9, 2001 / 50(RR19);1-58

33. AIDS/STD Section, Disease Control Division, Department of Public Health, Malaysia National Strategic Plan: Prevention and Control of HIV Infection, Malaysia *In print* Ministry of Health, Malaysia, 30 June 1998, 26 pp

34. Churchill DR. Prognostic markers and surrogate markers of clinical progression in HIV infection. *Int J STD AIDS*. 1997 Sep;8(9):552-556

35 Mofenson LM, Fowler MG. Interruption of materno-fetal transmission. *AIDS*. 1999;13 Suppl A:S205-214.

36 Iuliano R, Forastieri G, Brizzi M, et al. Correlation between plasma HIV-1 RNA levels and the rate of immunologic decline. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1997 Apr 15;14(5):408-414.

37 Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and Infants Transmission Study Group. *N Engl J Med*. 1999 Aug 5;341(6):394-402.

38 Public Health Task Force .Perinatal HIV Guidelines Working Group. Public Health Service Task Force recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. Rockville (MD): U.S. Public Health Service; 2007 Nov 2. 96 p.

39. Katz, M, Martin J, Roland M, et al. The San Francisco postexposure prevention program: Lessons and future challenges. Programs and abstracts of the 7th Conference on Retroviruses and Opportunistic Infections, January 30-February 2, 2000; San Francisco.

40 Chaisilwattana P, Chuachoowong R, Siriwasin W, et al. Chlamydial and gonococcal cervicitis in HIV-seropositive and HIV-seronegative pregnant women in Bangkok: prevalence, risk factors, and relation to perinatal HIV transmission. *Sex Transm Dis.* 1997 Oct;24(9):495-502

41 Hashemi FB, Ghassemi M, Roebuck KA, et al. Activation of human immunodeficiency virus type 1 expression by Gardnerella vaginalis. *J Infect Dis*. 1999 Apr;179(4): 924-930

42 Cohen CR, Duerr A, Pruithithada N, et al. Bacterial vaginosis and HIV seroprevalence among female commercial sex workers in Chiang Mai, Thailand. *AIDS.* 1995 Sep;9(9):1093 -1097.

43 Mwanyumba F, Gaillard P, Inion I, et al. Placental inflammation and perinatal transmission of HIV-1. *J Acquir Immune Defic Syndr.* 2002 Mar 1;29(3):262-269

44 Connor EM, Sperling RS, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N *Engl J Med. 1994 Nov* 3;331(18):1173-1180

45 Cooper ER, Charurat M, Mofenson LM, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1 infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr Hum Retrovirol*, 2002.29(5):484-494.

46 European Collaborative study. Risk factors for mother-to-child transmission of HIV-1. European Collaborative. *Lancet. 1992* Aug 15;340(8816):435.

47 Gazzard B; BHIVA Writing Committee. British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2005). *HIV Med*. 2005 Jul;6 Suppl 2:1-61.

48 Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, et al. Lamivudine-Zidovudine combination for the prevention of maternal Infection transmission of HIV-1. *JAMA,*2001;285(160):2083 - 2093.

49 Kind C, Rudin C, Siegrist CA, et al. Prevention of vertical HIV transmission: additive protective effect of elective Cesarean section and zidovudine prophylaxis. Swiss Neonatal HIV Study Group. *AIDS.* 1998 Jan 22;12(2):205-210.

50 Volmink J, Siegfried NL, van der Merwe L, et al. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. *Cochrane Database Syst Rev.* 2007 Jan 24; (1) : CD003510.

51 Eastman PS, Mittler J, Kelso R, et al. Genotypic changes in human immunodeficiency virus type 1 associated with loss of suppression of plasma viral RNA levels in subjects treated with ritonavir (Norvir) monotherapy. *J Virol.* 1998 Jun;72(6):5154-5164

52 Larbalestier N, Mullen J, O'Shea S, et al .Drug resistance is uncommon in pregnant women with low viral loads taking zidovudine monotherapy to prevent perinatal HIV transmission. *AIDS.* 2003 Dec 5;17(18):2665-2667.

53 Welles SL, Pitt J, Colgrove R, et al. HIV-1 genotypic zidovudine drug resistance and the risk of maternal-infant-transmission in the women and infants transmission study. The Women and Infants Transmission Study Group. *AIDS*. 2000 Feb 18;14(3):263-271.

54 Dorenbaum A, Cunningham CK, Gelber RD, et al. International PACTG 316 Team. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. *JAMA.* 2002Jul 10;288(2):189-198.

55 Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Jan 28, 2000. [AIDS Treatment Information Service: Current Treatment] Available at: http://www.hivatis.org/trtgdlns.html. Accessed April 26, 2006

56 British HIV Association (BHIVA) Guidelines for the Management of HIV infection in Pregnant Women and the Prevention of Mother-to-Child Transmission of HIV Publication history information: Originally published 2001, updated March 2005

57 Claas GJ, Julg B, Goebel FD, et al. Metabolic and anthropometric changes one year after switching from didanosine/stavudine to tenofovir in HIV-infected patients. *Eur J Med Res*, 2007 Feb 26;12(2): 54-60.

58 Taylor GP, Low-Beer N. Antiretroviral therapy in pregnancy: a focus on safety. *Drug Saf.* 2001;24(9):683-702.

59 No authors. Immunological markers in HIV-infected pregnant women. The European Collaborative Study and the Swiss HIV Pregnancy Cohort. *AIDS*. 1997 Dec;11(15):1859-1865.

60 Tuomala RE, Shapiro DE, Mofenson LM, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. *N Engl J Med*. 2002 Jun 13;346(24):1863-1870

61 Alimenti A, Burdge DR, Ogilvie GS, et al. Lactic acidemia in human immunodeficiency virus-uninfected infants exposed to perinatal antiretroviral therapy. *Pediatr Infect Dis J.* 2003 Sep;22(9):782-789

62 Poirier MC, Divi RL, Al-Harthi L, et al. Women and Infants Transmission Study (WITS) Group.Long-term mitochondrial toxicity in HIV-uninfected infants born to HIV-infected mothers. *J Acquir Immune Defic Syndr.* 2003 Jun 1;33(2):175-183

63 Divi RL, Walker VE, Wade NA, et al. Mitochondrial damage and DNA depletion in cord blood and umbilical cord from infants exposed in utero to combivir. *AIDS.* 2004 Apr30; 18(7):1013-1021

64 Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet.* 1999 Sep 25;354(9184):1084-1089

65 Barret B, Tardieu M, Rustin P. Mitochondrial dysfunction in HIV uninfected children**.** *AIDS* 2003;17:1769–1785.

66 Hitti J, Frenkel LM, Stek AM, et al. Maternal toxicity with continuous nevirapine in pregnancy: results from PACTG 1022. *J Acquir Immune Defic Syndr.* 2004 Jul 1;36(3):772-776.

67 Watts DH. Treating HIV during pregnancy: an update on safety issues. *Drug Saf*.2006; 29(6):467-490.

68 Burdge DR, Money DM, Forbes JC, et al. Canadian consensus guidelines for the management of pregnant HIV-positive women and their offspring on behalf of the Canadian HIV Trials Network Working Group on Vertical HIV Transmission. This article appears online only and is an appendix to *CMAJ* 2003;168(13):1683-1688

69 Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Eng J Med*. 1994 Nov 3;331(18):1173-1180

70 Lallemant M, Jourdain G, Le Coeur S, et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodefi ciency virus type 1.Perinatal HIV Prevention Trial (Thailand) Investigators. *N Eng J Med*. 2000 Oct 5;343(14):982-991.

71 Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda*: Lancet*. 1999 Sep 4;354(9181):795-802.

72 Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind,placebo-controlled trial. *Lancet.* 2002 Apr 6;359(9313):1168-1169.

73 DHSS Panel on Guidelines for the use of ARV agents in HIV-1-infected adults and adolescents 2006

74 Suksomboon N, Poolsup N, Ket-Aim S. Systematic review of the efficacy of antiretroviral therapies for reducing the risk of mother-to-child transmission of HIV infection. *J Clin Pharm Ther*. 2007 Jun; 32(3):293-311

75 Read JS, Newell MK. Efficacy and safety of cesarean delivery for prevention of mother-to-child transmission of HIV-1. *Cochrane Database Syst Rev.* 2005 Oct 19;(4)

76 Hernandez-Diaz S, Werler MM, Walker AM et al. Folic acid antagonists during pregnancy and the risk of birth defects. *N Eng J Med* 2000; 343: 1608-1614

77 No authors. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. U.S. Public Health Services (USPHS) and Infectious Diseases Society of America (ISAA), *Infect Dis Object Gynecol* 2008;8 (1):5-74

78 Centers for Disease Control and Prevention, National Institutes of Health, HIV Medicine Association/Infectious Diseases Society of America. Treating Opportunistic Infections among HIV-Infected Adults and Adolescents. *MMWR Recomm Rep*. 2004 Dec 17; 53(RR15);111-112.

79 Walter J, Mwiya M, Scott N et al. Reduction in preterm delivery and neonatal mortality after the introduction of antenatal cotrimoxazole prophylaxis among HIV-infected women with low CD4 cell counts. *J Infect Dis*. 2006 Dec 1;194(11):1510-1518

80 Stek AM, Mirochnick M, Capparelli E, et al. Reduced lopinavir exposure during pregnancy. *AIDS*, 2006.20(15):1931-1939

81 Tuboi SH, Harrison LH, Spinz E, *et al.* Predictors of Virologic Failure in HIV-1- Infected Patients Starting Highly Active Antiretroviral Therapy in Porto Alegre, Brazil. *J Acquir Immune Defic Syndr* 2005;40:324-328.

82 Dube MP, Sattler FR. Metabolic complications of antiretroviral therapies. *AIDS Clin Care.*1998 Jun;10(6):41-44

83 Khilnani P, Rajdev SK, Uttam R. Characteristics of available antiretroviral drugs - Part 2. *Indian J Crit Care Med* 2003;7:273-282

84 Justman JE, Benning L, Danoff A, et al. Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women. *J Acquir Immune Defic Syndr*. 2003 Mar 1;32(3):298-302

85 U.S .Public Health Service Task Force recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States (revised November 3, 2000).

86 Ioannidis JP, Abrams EJ, Ammann A, et al. Perinatal transmission of human immuno deficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/ml. *J Infect Dis. 2001 Feb* 15;183(4):539-545

87 Ministry of Health Malaysia. *Pekeliling Ketua Pengarah Kesihatan Bil. 5/200; Polisi Penyusuan Susu Ibu bagi bayi-bayi yang dilahirkan oleh ibu-ibu yang HIV positif.*

88 Eshleman SH, Hoover DR, Hudelson SE, et al. Development of nevirapine resistance in infants is reduced by use of infant-only single-dose nevirapine plus zidovudine postexposure prophylaxis for the prevention of mother-to-child transmission of HIV-1. *J Infect Dis*. 2006 Feb 15;193(4):479-781

89 Bucceri A.M, Somigliana E, Matrone R, et al. Discontinuing combination antiretroviral therapy during the first trimester of pregnancy: Insights from plasma human immunodeficiency virus-1 RNA viral load and CD4 count. *American journal of obstetries and gynecology.* 2003;189:545-551

90 Achenbach CJ, Till M, Palella FJ, et al. Extended antiretroviral treatment interruption in HIV-infected patients with long-term suppression of plasma HIV RNA. *HIV Med.* 2005 Jan;6(1):7-12.

91 Wiysonge CS, Shey MS, Shang JD, et al. Vaginal disinfection for preventing mother-to-child transmission of HIV infection. *Cochrane Database Syst Rev. 2005* Oct 19;(4)

92 Landesman SH, Kalish LA, Burns DN, et al. Obstetrical factors and the transmission of human immunodeficiency virus type 1 from mother to child. The Women and Infants Transmission Study. *N Engl J Med.* 1996; 334(25):1617-1623.

93 International Perinatal HIV Group . Duration of ruptured membranes and vertical transmission of HIV-1: a meta-analysis from 15 prospective cohort studies. *AIDS*. 2001 Feb 16;15(3):357-368.

94 Davies, Jill K. Management of HIV in Pregnancy Part II. *Contempory Ophthalmology*. 26(3): 1-5, February 15, 2006.

95 Ioannidis JP, Tatsioni A, Abrams EJ, et al. Maternal viral load and rate of disease progression among vertically HIV-1-Infected children : an International meta-analysis. *AIDS*. 2004 Jan 2;18(1):99-108.

96 Garcia, JA, Harrich D, Soultanakis E. et al. Human immunodeficiency virus type 1 LTR TATA and TAR region sequences required for transcriptional regulation. *EMBO J*. 1989;8:765-778

97 Navas-Nacher EL, Read JS, Leighty RM, et al. Women and Infants Transmission Study Group. Mode of delivery and postpartum HIV-1 disease progression: the Women and Infants Transmission Study. *AIDS*. 2006 Feb 14;20(3):429-436

98 Ministry of Health Malaysia. KKM/3,000/2004: Ministry of Health Standard Precaution Guidelines"AIDS / STI section.

99 Nduati R, John G, Mbori-Ngacha D et al. Effect of Breastfeeding and Formula Feeding on Transmission of HIV-1: a randomized clinical trial. *JAMA.* 2000;283:1167-1174.

100 Coutsoudis A, Pillay K, Kuhn L, Spooner E, Tsai WY, Coovadia HM. South African Vitamin A Study Group. Method of feeding and transmission of HIV-1 from mothers to children by 15 months of age: prospective cohort study from Durban, South Africa. *AIDS*. 2001 Feb 16;15(3):379-387

101 Mandelbro Coll O, Fiore S, Floridia M, et al. Pregnancy and HIV infection:An European consensus on management. *AIDS*. 2002 Jun;16 *Supp l* 2:S1-18

102 Ickovics JR, Wilson TE, Royce RA, et al. Perinatal Guidelines Evaluation Group.Prenatal and postpartum zidovudine adherence among pregnant women with HIV:results of a MEMS substudy from the Perinatal Guidelines Evaluation Project. *J Acquir Immune Defic Syndr*. 2002 Jul 1;30(3):311-315.

103 Minkoff H, Ahdieh L, Watts H, et al. The relationship of pregnancy to the use of highly active antiretroviral therapy *Am J Obstet Gynecol*. 2001 May;184(6):1221-1227

104 Weller S, Davis K. Condom effectiveness in reducing heterosexual HIV transmission. *Cochrane Database Syst Rev. 2002*

105 de Vincenzi I. A longitudinal study of human immunodeficiency virus transmission by heterosexual partners. European Study Group on Hetero sexual Transmission of HIV. *N Engl J Med.* 1994 Aug 11;331(6):341-346

106 Deschamps MM, Pape JW, Hafner A, et al. Heterosexual transmission of HIV in Haiti. *Ann Intern Med*. 1996; 125(4):324-330

107 Trussell J. Contraceptive efficacy of the personal hormone monitoring system Persona. *Br J Fam Plann*. 1999 Jul;25(2):34-35

108 Kubba A, Guillebaud J, Anderson RA, et al. Contraception. *Lancet.* 2000 Dec 2;356(9245):1913-1919.

109 Wang CC, McClelland RS, Overbaugh J, et al. The effect of hormonal contraception on genital tract shedding of HIV-1. *AIDS.* 2004 Jan 23;18(2):205-209.

110 Ouellet D, Hsu A, Qian Jet al. Effect of fluoxetine on pharmacokinetics of ritonavir. *Antimicrob Agents Chemother*. 1998 Dec;42(12):3107-3112.

111 Mildvan D, Yarrish R, Marshak A, et al. Pharmacokinetic interaction between nevirapine and ethinyl estradiol/norethindrone when administered concurrently to HIV-infected women. *J Acquir Immune Defic Syndr.* 2002 Apr 15;29(5):471-477

112 Clark RA, Theall KP. Trends and correlates of hormonal contraception use among HIV-infected women. *J Acquir Immune Defic Syndr.* 2004 Aug 1;36(4):986-988.

113 Richardson BA, Morrison CS, Sekadde-Kigondu C, et al. Effect of intrauterine device use on cervical shedding of HIV-1 DNA. *AIDS*. 1999 Oct 22;13(15):2091-2097.

114 Sinei SK, M'riara G, Schulz KF, et al. The prevalence of Neisseria gonorrhoea and Chlamydia trachomatis in intra-uterine contraceptive acceptors in Kenya. *J Obstet Gynaecol East Cent Africa.* 1988;7(2):71-73.

115 World health Organization (WHO). Department of Reproductive Health And Research. Selected practice recommendations for contraceptive use. 2nd ed. Geneva, WHO, 2004. 170 p

116 Wilkinson D, Tholandi M, Ramjee G, et al. Nonoxynol-9 spermicide for prevention of vaginally acquired HIV and other sexually transmitted infections: systematic review and meta-analysis of randomised controlled trials including more than 5000 women. *Lancet Infect Dis*. 2002 Oct;2(10):613-617

117 Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Out patient Study Investigators. *N Engl J Med.* 1998 Mar 26;338(13):853-860.

118 Schwarcz SK, Hsu LC, Vittinghoff E, et al. Impact of protease inhibitors and other antiretroviral treatments on acquired immunodeficiency syndrome survival in San Francisco, California, 1987-1996. *Am J Epidemio*l. 2000; 152(2):178-185

ANTIRETROVIRAL DRUGS
Nucleoside Analogue Reverse Transcriptase Inhibitors

DRUG	DOSAGE	ADVERSE REACTIONS	DRUG INTERACTIONS	SPECIAL INSTRUCTIONS
Zidovudine (ZDV) RETROVIR <u>Preparations:</u> Capsules: 100mg Concentrate for i.v. infusion/ injection: 10mg/ml in 20ml vial	300 mg bid i.v. dosage for intrapartum usage 2mg /kg loading dose , then followed by 1mg/kg per hour infusion until third stage of labour oral dosage for intrapartum usage - 300mg 3 hourly and to be given during first stage of labour	More common: Hematologic toxicity, including granulocytopenia and anemia (which may require transfusions), headache Less common (more severe): myopathy, myositis and liver toxicity. Rare: Lactic acidosis, severe hepatomegaly with steatosis (fatal cases)	Avoid combination with stavudine (antagonism).	Best on an empty stomach. Can take with a non-fatty meal to minimize nausea. Fatty food result in a 57% decrease in AZT concentrations Decrease dosage in severe renal impairment and significant hepatic dysfunction. Significant neutropenia or anemia may necessitate interruption of therapy until marrow recovery is observed; use of erythropoietin, filgrastim, or reduced ZDV dosage may be necessary.
Lamivudine (3TC) EPIVIR Tablet: 150mg	150mg q12H or 300mg once daily	More common: Headache, fatigue, decreased appetite nausea, vomiting, diarrhea, skin rash and upper abdominal pain, Less common (more severe): Pancreatitis peripheral neuropathy, anemia, decreased neutrophil count, increased liver enzymes and lipodystrophy syndrome. Lactic acidosis and severe hepatomegaly with steatosis (fatal cases have been reported)	When used with ZDV may prevent emergence of resistance.	Can be given with or without food. Decreased dosage in patients with impaired renal function. Patients should be screened for HBV infection before starting therapy; exacerbation of hepatitis has been reported after discontinuation of 3TC

Non-Nucleoside Reverse Transcriptase Inhibitors

DRUG	DOSAGE	ADVERSE REACTIONS	DRUG INTERACTIONS	SPECIAL INSTRUCTIONS
Nevirapine (NVP) VIRAMUNE Preparations: Tablets: 200 mg	200 mg q12H initiate therapy at half dose for the first 14 days. Increase to full dose if no rash or other untoward effects.	More common: Skin rash, Steven-Johnson syndrome, toxic epidermal necrolysis (some severe), fever, headache, nausea and abnormal liver function tests. Less common (more severe): Severe, life-threatening and rare cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure (less common in children)	Induces hepatic cytochrome PH50 3A (CYP3A); auto-induction of metabolism occurs in 2-4 weeks with a 1.5-2 times increase in clearance. Potential for multiple drug interactions. Before administration, the patient s medication profile should be carefully reviewed for potential drug interactions.	Can be given without regard to food. Patients experiencing rash during the 2-week lead in period should not have their NVP dose increased until the rash has resolved. If NVP dosing is interrupted for more than 7 days, NVP dosing should be restarted with once daily dosing for 14 days, followed by escalation to the full twice daily regimen.
Efavirenz STOCRIN Preparations: Tablets: 200mg and 600mg	600mg o.d.	More comon: skin rash, increased transaminase levels, nausea, dizziness, diarrhea, headache, psychiatric symptons (hallucinations, confusion), agitation, vivid dreams.	Inducer of CYP3A4 Concentration of Efavirenz will be decreased with co administration of rifampicin	To improve tolerability of central nervous system side effects, bedtimedosing recommended during the first 2-4 weeks. May be taken with or without food. Pregnancy should be avoided in woman.
PROTEASE INHIBITOR				
Lopinavir/Ritonavir (LPV/r) Preparations: Soft gelatin capsule: Each contain Lopinavir 133.3 mg Ritonavir 33.3mg	3 capsule twice daily during pregnancy	More common: Diarrhea, headache, asthenia, nausea and vomiting and rash , lipid abnormalities Less common (more common): lipodystrophy syndrome Rare: New onset of diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, hemolytic anemia, pancreatitis, elevation in serum transaminases and hepatitis	Contraindicated with amiodarone, piroxicam, astemizole/terfinadine, cisapride, alprazolam, midazolam,zolpidem	LPV/RTV tablets can be administered without regard to food LPV/RTV oral solution should be administered with food. A high fat meal increases absorption, especially of the liquid preparation. Should be refrigerated and if kept at room temperature up to 25^{o}C , used within 2 months If coadministered with ddI, ddI should be given 1 hour before or 2 hours after LPV/r

PNEUMOCYSTIS (CARINII) JIROVECI PNEUMONIA (PCP) PROPHYLAXIS

DRUG	DOSAGE	ADVERSE REACTIONS	DRUG INTERACTIONS	SPECIAL INSTRUCTIONS
Trimethoprim-Sulfamethoxazole (TMP/SMX) Preparations: Tablets 400mg SMX and 80 mg TMP OR 800mg SMX and 160 mg TMP (double strength tablet)	1-2 tablets of 400mg SMX and 80mg TMP to be taken daily OR 1 tablet of 800mg SMX and 160mg TMP to be taken once daily.	SMX is associated with jaundice and haemolytic anaemia		Used after 1st trimester because of potential teratogenicity of TMP If have to be prescribed in the first trimester then folic acid supplement should be given

WHO CLINICAL STAGING / AIDS FOR ADULTS AND ADOLESCENTS WITH CONFIRMED HIV INFECTION[i]

Source : World Health Organisation, WHO Definations of HIV Surveillance and Revised Clinical Staging and Immunological Classification of HIV related disease in Adults and Children 2007

Clinical stage 1
Asymptomatic Persistent generalized lymphadenophathy
Clinical stage 2
Moderate unexplained weight loss (<10% of presumed or measured body weight)[i] Recurrent respiratory tract infections sinusitis, tonsillitis, otitis media and pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrhoeic dermatitis Fungal nail infections
Clinical stage 3
Unexplained[ii] severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhoea for longer than one month Unexplained persistent fever (above 37.6°C intermittent or constant,for longer than one month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis (current) Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 109 per litre)or chronic thrombocytopaenia (<50 × 109 per litre)

i. Asessment of body weight in pregnant woman needs to consider the expected weight gain of pregnancy.

ii. Unexplained refers to where the condition is not explained by other causes.

WHO CLINICAL STAGING /AIDS FOR ADULTS AND ADOLESCENTS WITH CONFIRMED HIV INFECTION

Clinical stage 4[iii]
HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi's sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacterial infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis (with diarrhea)
Chronic isosporiasis
Disseminated mycosis (coccidiomycosis or histoplasmosis)
Recurrent non-typhoidal Salmonella bacteraemia
Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumours
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

iii Some additional specific conditions can also be included in regional classification (Such as reactivation of American trypanosomiasis [meningoencephalitis and / or myocarditis] in the WHO Region of America and disseminated penicilliosis in Asia.

LIST OF ABBREVIATIONS

Abbreviations	Generic name
3TC	Lamivudine
ZDV	Zidovudine
EFV	Efavirenz
NVP	Nevirapine
TMP/SMX	Trimethoprim-Sulfamethoxazole
AZT + 3TC	Zidovudine + Lamivudine

MISCELLANEOUS ABBREVIATION

AIDS	Acquired immunodeficiency syndrome
ARV	Antiretroviral
HIV	Human immunodeficiency virus
HAART	Highly Active Anti-Retroviral Therapy
MTCT	Mother-to-child transmission of HIV
PMTCT	Prevention of mother-to-child transmission of HIV
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitors
PI	Protease inhibitor
PCP	Pneumocyitis (carinii) jiroveci Pneumonia
STD	Sexually Transmitted Diseases

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LEVELS OF EVIDENCE SCALE

Level	Strength of Evidence	Study Design
1	Good	Meta-analysis of RCT, Systematic review
2	Good	Large sample RCT
3	Good to Fair	Small sample RCT
4	Good to Fair	Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled prospective trial with historical control
6	Fair	Cohort studies
7	Poor	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case reports anecdotes

SOURCE : ADAPTED FROM THE CATALONIAN AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT & RESEARCH, (CAHTAR) SPAIN

GRADES OF RECOMMENDATIONS

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and / or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SOURCE : MODIFIED FROM THE SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)