Review Article

Human Immunodeficiency Virus (HIV) in Pregnancy: A Review of the Guidelines for Preventing Mother-to-Child Transmission in Malaysia

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Abstract

Mother-to-child transmission (MTCT) of human immunodeficiency virus (HIV) is a devastating consequence of HIV infection during pregnancy and is largely preventable. Evidence-based interventions such as universal antenatal screening, provision of antiretroviral therapy, delivery by elective caesarean section and avoidance of breastfeeding have ensured that the rates of MTCT remain low in Malaysia. This review discusses the most recent advances in the management of HIV infection in pregnancy with emphasis on antiretroviral treatment strategies and obstetric care in a middle income country.

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Introduction

Pregnancy, whether actual or anticipated, has been a critical driver for the diagnosis, treatment and care of women with human immunodeficiency virus (HIV). Unlike other viral infections during pregnancy, maternal HIV infection is not associated with congenital abnormalities, adverse effects on the miscarriage rate or pregnancy outcome. Transmission of HIV from mother to child is the main concern. This can occur in utero, during delivery, or postpartum through breastfeeding. Most mother-to-child transmissions (MTCT) occur during delivery or through breastfeeding. The risk of transmission to the infant is directly proportional to the maternal plasma HIV viral load, the risk being greatest with higher viral loads.[1,2] Without any intervention, up to 45% of children born to HIV positive mothers in lower income countries will become infected.[3] This can be reduced to less than 2% with strategies to reduce MTCT.[4-6]

This review discusses the current management strategies of HIV in pregnancy with emphasis on antiretroviral use during pregnancy and obstetric care in a middle income country such as Malaysia.

Epidemiology

The estimated prevalence of HIV in the general population in Malaysia is 0.5%. Malaysia has a concentrated epidemic in that the HIV epidemic has been mainly driven by injecting drug use.[7] However, recent years have shown a substantial increase in heterosexual transmission rising from 27% in 2009 to 45% in 2011. The proportion of women reported to have HIV has also increased significantly in the last decade, from 5% of new cases in 2000 to 21% in 2011.[8]

In 1998, the Malaysian Ministry of Health (MOH) implemented a nationwide Programme of Prevention of Mother to Child Transmission (PMTCT) of HIV to reduce the risk of vertical HIV transmission. This programme involving all government health clinics and hospitals includes an opt out approach for HIV screening, provision of antiretroviral therapy during pregnancy, safer modes of delivery and safer infant feeding practices.[7]

Approximately 75% of all pregnant mothers in Malaysia accessed public healthcare between 2007 and 2009. Of these, 98% were screened for HIV and 0.05% were found to be infected with HIV.[9] Amongst those who were screened

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positive for HIV in 2011, more than half were newly detected cases.[7] Women who presented late in pregnancy with unknown HIV status were more than 2 times (0.18%) likely to be HIV positive when compared to those who had antenatal screening (0.07%).[7] To further improve the coverage of HIV screening, the MOH in Malaysia has started using rapid tests kits for HIV screening in labour wards. Implementation of this extra layer of screening meant that 99% of children born to HIV positive mothers were not infected with HIV.[7]

Consideration should also be given to retest for HIV in high-risk groups later in pregnancy if initial tests were negative.[10] Awareness that false negatives can occur as a result of a delay in antibody detection after recent HIV infection during the seroconversion period is equally important.[11]

Prevention of mother to child transmission of HIV is a rapidly evolving practice. This has been particularly reflected in the recent 2012 programmatic update of the World Health Organization (WHO) guidelines[12] and the British HIV Association (BHIVA) guidelines[13] with the use of newer drugs in pregnancy,[13] earlier start of antiretroviral therapy after the first trimester[12,14,15] and a proposal to continue lifelong Highly Active Antiretroviral therapy (HAART) for all HIV infected women.[12]

Antiretroviral Therapy (ART)

Use of ART in pregnancy required in 2 settings:[13-16]

1. For PMTCT in women who do not require HIV treatment for their own health
2. To prevent maternal disease progression in women with CD4 counts <350 cells/mm^3

ART—Monotherapy

Zidovudine (AZT), a nucleoside reverse transcriptase inhibitor (NRTI) and the first antiretroviral drug to be approved by the US Food and Drug Administartion (FDA) in 1987 is the drug that has been used most extensively in pregnancy.

In 1994, the landmark Paediatric Aids Clinical Trial Group (PACTG) Protocol 076 demonstrated that zidovudine monotherapy given to HIV infected women during the second and third trimester of pregnancy, administered intravenously during delivery and given to infants for 6 weeks reduced the risk of HIV infection in non breastfeeding infants by 67%.[17] This intervention was quickly adopted as standard of care in most developed countries and had a significant impact on MTCT in countries where its use was adopted. With zidovudine monotherapy, the transmission rate was reduced from 8% to 6%. When combined with pre-labour Caesarean section (PLCS), irrespective of viral load, the transmission was further reduced to less than 2%.[18] Development of resistance mutations following zidovudine monotherapy is a concern but is uncommon with a tendency to occur more frequently in women with higher plasma viral loads and longer duration of therapy.[19,20]

Nevirapine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), which has a long half-life is rapidly transferred across the placenta. Use of single dose (sd) nevirapine as prophylaxis given to both mother and infant during the onset of labour has been adopted by WHO in many resource limited settings. Its long half-life contributes to the development of resistance seen after nevirapine monotherapy which can impact on the response of subsequent NNRTI containing HAART.[21,22] Adding zidovudine (AZT) and lamivudine (3TC) for 1 week after single dose nevirapine reduces the rate of development of nevirapine resistance.[23] This current strategy is not recommended in Malaysia but may be useful in certain situations where the mother presents as an emergency in labour.

The use of HIV treatment during pregnancy has evolved over the years from zidovudine monotherapy to HAART.

Combination Antiretroviral Therapy

Combination therapy using at least 3 antiretroviral drugs or Highly Active Antiretroviral Therapy (HAART) is now the standard of care for the treatment of the adult HIV-infected population.[24] Treatment naïve HIV-positive pregnant mothers in Malaysia are usually started on a combination comprising 2 NRTIs and an NNRTI or a protease inhibitor (PI).[16] The use of HAART is now recommended as it is more likely to suppress viral loads to undetectable levels with lower risk of development of resistance.

The impact of combination therapy on MTCT was demonstrated by the North American Women and Infants Transmission study (WITS) which showed that the use of combination therapy that included a protease inhibitor was associated with a reduction in MTCT from 7.8% to 1.1% compared with the zidovudine monotherapy.[25]

Recommendations regarding the choice of antiretroviral drugs to use during pregnancy should be based on the mother's own health needs, potential short- and long-term toxicities to the foetus and the need to reduce vertical transmission.[10]

Maternal Drug Toxicity

NRTIs (Table 1)

The NRTI backbone with the most experience in pregnancy is with zidovudine (AZT) and lamivudine (3TC), available in a fixed dose combination called combivir.

The major toxicity of AZT is haematological, including the risk of anaemia and neutropaenia. There have been theoretical concerns of adverse effects of tenofovir on foetal growth and bone mineralisation which have not been substantiated in clinical trials.[26] The use of NRTIs has also been associated with mitochondrial dysfunction. Case reports of fatal lactic acidosis in pregnant women receiving didanosine and stavudine in combination prompted a clinical alert recommending the avoidance of this combination in pregnancy.[27]

NNRTIs (Table 2)

Nevirapine is associated with a serious skin rash and hepatotoxicity. This risk is increased in those who initiate

Table 1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Drug	Side effects	Significant Drug interactions	Consideration of Use
Zidovudine (AZT)	Nausea, vomiting, bone marrow suppression (anaemia, neutropaenia), headache, malaise, myalgia, myopathy, mitochondrial toxicity (lactic acidosis, lipodysrotphy), skin hyperpigmentation	Additive toxicity with other drugs causing myelosuppression e.g. ganciclovir and co-trimoxazole	NRTI of choice in pregnancy. Available as a fixed dose combination with lamivudine in the form of Combivir
Lamivudine (3TC)	Very few side effects	No significant drug interactions	Active against hepatitis B virus
Emtricitabine (FTC)	Headache, nausea, insomnia, hyperpigmentation of palms and soles	No significant drug interactions	Active against hepatitis B virus
Didanosine (DDI)	Mitochondrial toxicity, peripheral neuropathy, pancreatitis	Increased risk of lactic acidosis when combined with stavudine in pregnancy	Avoid in pregnancy
Stavudine (D4T)	Greatest risk of mitochondrial toxicity, peripheral neuropathy, pancreatitis, dyslipidaemia	Additive toxicity with other drugs that cause peripheral neuropathy e.g. isoniazid	Avoid in pregnancy
Tenofovir	Gastrointestional (nausea, diarrhoea), renal impairment, loss of bone mineral density	Potential additive toxicity with nephrotoxic drugs e.g. IV amphotericin	Available in fixed dose combination with emtricitabine as Truvada. Avoid in women with renal impairment or those on nephrotoxic drugs. Active against hepatitis B virus.
Abacavir	Hypersensitivity reaction (fever, rash, respiratory symptoms, nausea, vomiting, abdominal pain)	No significant drug interactions	Available in a fixed dose combination with lamivudine as Kivexa. Must not be used in women who are HLA B5701 positive. Should not be used in those with significant cardiovascular disease and with viral loads > 10^5 copies/mL

Table 2. Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Drug	Side Effects	Significant Drug Interactions	Consideration of Use
Efavirenz (EFV)	Central nervous system side effects e.g dizziness, vivid dreams, sleep disturbance, hallucinations, depression, rash, hepatitis, hyperlipidaemia. Teratogenic in animal studies.	Efavirenz is a mixed enzyme inducer/inhibitor. Expect altered levels of co-administered drugs metabolized by cytochrome P_{450}. Anticonvulsants – carbamazepine/phenytion – contraindicated Methadone – EFV reduces serum levels Rifampicin – reduces EFV levels Rifabutin – EFV reduces rifabutin levels Taking Efavirenz with fatty food increases efavirenz concentrations and may increase the frequency of adverse events	No increased risk of teratogenic effects compared to that of other antiretrovirals. Recent guidelines now allow use of Efavirenz in all stages of pregnancy.
Nevirapine (NVP)	Rash including Stevens Johnson Syndrome and rarely toxic epidermal necrosis, hepatitis	Nevirapine is an enzyme inducer. Expect lower drug levels of co-administered drugs metabolized by cytochrome P_{450} Anticonvulsants – carbamazepine/phenytoin – Contraindicated Methadone – NVP reduces serum levels Rifampicin – reduces NVP levels significantly – Contraindicated	Avoid in women with pre-treatment CD4 counts > 250 cells/mm^3. 2 week dose escalation of NVP reduces risk of rash

Table 3. Protease Inhibitors (PIs)

Drug	Side Effects	Significant Drug Interactions	Consideration of Use
Lopinavir/ ritonavir (Kaletra)	Gastrointestinal (diarrhoea, nausea, vomiting), hyperlipidaemia, hyperglycaemia, insulin resistance, hepatitis, lipohypertrophy	Kaletra is an enzyme inhibitor. Anticonvulsants – carbamazepine/phenytion – Contraindicated Simvastatin – increased levels significantly – Contraindicated Rifampicin – significant reduction in levels of kaletra – Contraindicated Rifabutin – Increased levels of rifabutin, therefore reduce dose.	Used in women who present late in pregnancy (with unknown CD4 counts) or in women with CD4 counts > 250 cells/mm^3.

nevirapine with pre-treatment CD4 counts >250 cells/mm^3.[28]

Protease Inhibitors (PIs) (Table 3)

Boosted PI antiretroviral based regimens such as ritonavir/lopinavir are second line regimens in Malaysia in the non pregnant population and are available free from the MOH for pregnant women. The main side effects are gastrointestinal disturbance. Use of PIs in pregnancy has been associated with increased risk of impaired glucose tolerance and pre-eclampsia although their associations have remained inconclusive.[10,29-31] The associations between PIs and increased risk of pre-term delivery have been conflicting.[14, 32-34] PIs have a greater barrier to resistance development than NNRTIs and can be stopped concurrently with the NRTI backbone after delivery.

Drug Toxicity to the Foetus

Efavirenz

Efavirenz, the preferred NNRTI in first-line regimens in the non-pregnant population in Malaysia has been, until recently, discouraged from being used in the first trimester of pregnancy or for women contemplating pregnancy due to concerns of risk of teratogenicity. This was based on reports of neural tube defects in animal studies and retrospective human case reports in offspring born to women exposed to first trimester efavirenz.[35]

There is now accumulating evidence from surveillance data from established pregnancy registries and clinical experience reporting no increased risk of overall birth defects in women exposed to first trimester efavirenz compared with other antiretrovirals or the background population.[36-38] WHO recently updated a review on the use of efavirenz in early pregnancy providing further reassurance.[39] The 2012 BHIVA pregnancy guidelines also recommend the use of efavirenz in pregnancy without considerations over and above those of other antiretrovirals.[14]

Recommendations for Prescribing Antiretroviral Therapy in Pregnancy:[13-16]

1. Women with an AIDS defining illness or CD4 counts <350 cells/mm^3 or requiring treatment for their own heath

HAART is started as soon as possible in accordance with the adult treatment guidelines. In the absence of an opportunistic infection, HAART can be deferred till after the first trimester. A regimen consisting of combivir and nevirapine should be commenced if the CD4 count is <250 cells/mm^3. Efavirenz is now a permissible alternative to nevirapine across any CD4 count range. An alternative is to use ritonavir/lopinavir and switch back to efavirenz after delivery. Treatment is continued indefinitely after delivery.

2. Women with CD4 counts >350/mm^3 and who do not require treatment for their own health

Short-term HAART (START) is started at 14 weeks gestation at the beginning of the second trimester. A PI-based regimen consisting of combivir and ritonavir/lopinavir is recommended. If efavirenz is used instead of a PI, it is important to continue the combivir for a further 1 week after stopping efavirenz. Treatment is stopped after delivery. Use of AZT monotherapy as an alternative to START in these circumstances remains an option for women with low viral loads. It however needs to be combined with PLCS and intrapartum intravenous AZT.

3. Women who present late in pregnancy

HAART should be started immediately before CD4 count and viral load results are available. A PI-based regimen consisting of combivir and ritonavir/lopinavir is recommended. For women diagnosed in labour without prior therapy, it is recommended to give single dose nevirapine to the mother at the onset of labour. Intrapartum AZT should be administered intravenously and AZT and 3TC continued for 1 week after delivery

Women who present in labour without a prior documented HIV test must be recommended to have a rapid HIV Point of Care test

4. Women who conceive on HAART

It is advisable to continue the same HAART regimen even if this contains efavirenz.

The PMCT programme in Malaysia incorporates the use

of triple ARVs for both prophylaxis and treatment of HIV infection in pregnancy and continued for the duration of pregnancy.[16] In circumstances where ARV was used as prophylaxis, this is stopped after the delivery. The option of continuing ARVs for life in all HIV positive pregnant women irrespective of CD4 count has recently been proposed by WHO as a move towards simplification of regimens and service delivery, protection of MTCT in future pregnancies, and avoiding stopping and restarting ART.[12]

Antenatal Management

All pregnant women should be encouraged to be screened for infections such as HIV, syphilis, hepatitis B and C in early stage of pregnancy. Appropriate treatment can also be administered.[10,11] Screening for genital infections such as Chlamydia and bacterial vaginosis should be performed at the first consultation with consideration given to re-screening at around 28 weeks.[10,11]

All HIV-positive pregnant women should be managed by a multidisciplinary team consisting of an HIV physician, obstetrician, specialist midwife and paediatrician.[10,11,16] It is important to maintain confidentiality of the patient's diagnosis at all times. Continuity of care with the same healthcare team may encourage a good patient-doctor relationship, enabling the physical, social and psychological needs of these high risk patients to be met.

Newly diagnosed HIV patients should be encouraged to disclose their status to their partners[40,41] so that the latter as well as any children[42] can be screened. The process of disclosure may take time and should never be rushed. Detailed and consistent advice from the team may encourage drug compliance and regular attendance for follow-up at the antenatal clinic.

All women diagnosed during pregnancy should have a baseline CD4 count and viral load. After commencement of HAART, a repeat CD4 count and viral load should be performed 2 to 4 weeks after, at least once every trimester, at 36 weeks and at delivery.[10,16] The plasma viral load at 36 weeks is the best predictor of perinatal transmission and allows to decide on mode of delivery.[10,16]

Measurement of Full Blood Count, Renal Function Test and Liver Function Tests should also be performed. HIV resistance testing is not routinely available in Malaysia. The decision to continue HAART post delivery will depend on the baseline CD4 count.[10,16]

An early pregnancy scan to confirm viability, numbers of foetuses and gestation and an anomaly scan should be carried out at around 20 weeks' gestation.[10,11] Serial growth scans can be considered if there were concerns regarding fetal well-being. Down's screening in the form of nuchal translucency with serum screening between 11 and 14 weeks gestation would be the most appropriate as it is a non-invasive test and it would reduce the need for subsequent invasive prenatal diagnostic testing. For those women who undergo procedures such as amniocentesis, it is best to avoid needling the placenta, to delay the tests until the viral load is undetectable if possible and to cover the procedure with antiretrovirals.[10]

Intrapartum Management

Before the introduction of antiretrovirals, elective Caesarean sections alone have been found to reduce the risk of HIV transmission from mother to child by 50% to 70%.[43,44] In developed countries where facilities for elective surgery are safe and available, planned Caesarean sections at 39 weeks' gestation has become routine practice. More recent studies have shown that for women on HAART with plasma viral loads at delivery of less than 50 copies/mL, the rate MTCT of HIV with both elective caesarean section and vaginal delivery was similar.[43,44] Vaginal delivery is therefore an option for women with no detectable viraemia on HAART.[45,46]

Women on zidovudine monotherapy and those on HAART (or START) with a detectable viral load at 36 weeks are recommended to have elective caesarean section at 38 weeks.[10] Counselling should balance the operative risks associated with Caesarean section as well as its implications to future pregnancies with the foetal risks of vertical HIV transmission associated with vaginal delivery. Decision on the mode of delivery should be made by 36 weeks' gestation with clear documentation in the medical notes.[11] During labour, invasive procedures such as foetal blood sampling, foetal electrode application and artificial rupture of membranes should be avoided.[10,11]

Special situations which warrant further discussion include:

1. Preterm premature rupture of membranes (PROM) ± preterm labour

Women presenting with confirmed preterm rupture of membranes should have a vaginal swab taken for microscopy, culture and sensitivity and started immediately on prophylactic antibiotics. If gestation is before 34 weeks, 2 doses of intramuscular corticosteroids 12 hours apart should be given to promote fetal lung maturity. In general, an emergency Caesarean section should be performed without any delay if gestation is 34 weeks or more.[10,11] For foetuses at less than 34 weeks' gestation, the decision to manage conservatively or to expedite delivery depends on the gestation of the pregnancy, foetal and maternal conditions as well as the availability of neonatal care facilities. The risks of foetal prematurity must be weighed against the risk of HIV transmission from mother to foetus.[11]

2. Term pre-labour rupture of membranes (PROM) ± labour

The transmission risk for women with term PROM taking HAART who have undetectable plasma viraemia is unknown. A meta-analysis of studies conducted before the use of HAART in pregnancy demonstrated a 2% incremental increase in transmission risk for every hour of ruptured membranes up to 24 hours.[47] If the mother is already on HAART with a negligible viral load, the options would be induction of labour or emergency Caesarean section.[10]

Postpartum Management

Infant Post Exposure Prophylaxis

In Malaysia, all infants born to HIV positive mothers are treated from birth with twice daily zidovudine monotherapy for 6 weeks.[15,48] For HIV exposed infants whose mothers have detectable viraemia at delivery or those that did not receive antepartum or intrapartum ART, single dose nevirapine is given to the neonate in addition to 6 weeks of AZT.[48] In these situations, continued combination therapy with a 2- or 3-drug regimen is likely to further reduce intrapartum HIV transmission as shown recently in the HPTN 040/ PACTG 1043 study.[49]

HIV infection in infancy is diagnosed using PCR detection of HIV DNA or RNA. HIV PCR DNA is the preferred diagnostic test. HIV PCR DNA testing is performed at 14 to 21 days, 1 to 2 months and 4 to 6 months of age.[15,48] A negative test at 4 months or older indicate that the child has not been infected. Final confirmation of absence of HIV infection is a negative HIV antibody test at 18 months.

Breastfeeding

Breastfeeding accounts for about 16% of HIV transmission from mother to child.[50] In Malaysia where formula feeding is safe, affordable and feasible, HIV infected mothers are advised not to breastfeed their infants.[16,48] Exclusive feeding with infant formula milk is recommended. In settings where exclusive formula milk feeding is not an option such as in Africa, ART has been shown to significantly reduce the risk of HIV transmission through breastfeeding.[51-55] The risk of MTCT from a woman on HAART with an undetectable viral load whilst breastfeeding is likely to be very low. WHO recommends that in settings where mortality from formula feeding outweighs the additional mortality from HIV transmission from breastfeeding, mothers should exclusively breastfeed for 6 months provided that the mother or baby is taking combination therapy throughout this period.[56]

Conclusion

Management of HIV in pregnancy is a rapidly evolving field. There is a wealth of comprehensive guidelines which are constantly being updated to guide both the HIV physician and obstetrician. Most data are derived from observational cohort studies, retrospective studies and from clinical experience of experts in the field. There is a need for more randomised controlled clinical trials.

Early detection of HIV by an opt-out screening policy is important so that interventions can be implemented to reduce MTCT. Coverage of testing within government hospitals and clinics has thus far been good but this could be further improved by extending the opt-out HIV screening policy to the private sector. Stigma and discrimination act as barriers to prevent women from testing and accessing care, and efforts need to be scaled up to normalise HIV testing.

A multidisciplinary approach to provision of antenatal care in HIV positive women is crucial. Greater empowerment of HIV positive women in decisions around treatment, mode of delivery and use of pre- and post-conceptual contraception should be encouraged. There should be a shift towards allowing more planned vaginal deliveries in women with undetectable HIV viral loads at 36 weeks in keeping with evidence-based medicine as there has been in resource unlimited countries.

Ongoing surveillance of mothers and infants exposed to established and newer antiretroviral drugs is important to provide long-term safety and toxicity data to guide physicians on the use of antiretrovirals in pregnancy.

A detailed discussion around the reproductive health options and fertility management of HIV serodiscordant couples is of utmost importance to minimise sexual transmission to uninfected partners, the discussion of which is beyond the scope of this review.

Areas of future research that need to be addressed include the use of newer drugs in pregnancy, the safety of treatment interruption of ART prophylaxis in pregnant women and assessment of feasibility, cost, safety and prevention benefit of provision of lifelong ART to all HIV-infected pregnant women. Use of combination ART in HIV exposed infants in mothers who did not receive antepartum ART need to be further explored. Finally, newer strategies to prevent HIV transmission in serodiscordant couples such as timed unprotected intercourse with use of HIV pre-exposure prophylaxis in the uninfected partner, a very topical area in HIV medicine need to be studied to ensure conception with minimal risk to uninfected partners.

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