Antenatal prevention of mother to child transmission of HIV

Theron GB, MMed(O&G), MCOG(SA), Hons BSc, MD
Department of Obstetrics and Gynaecology, Faculty of Health Sciences,
Stellenbosch University and Tygerberg Hospital.

Correspondence to: Prof GB Theron, e-mail: gbth@sun.ac.za

Abstract

An effective perinatal mother to child transmission (PMTCT) programme will reduce perinatal acquired HIV infections. This goal is within reach of the South African public health sector. Early antenatal attendance and knowledge of HIV status allows sufficient time to implement highly active antiretroviral therapy (HAART) or ART intervention. Both measures have been proved to be efficient to reduce MTCT of HIV. A transmission rate of 2% can be achieved with a dual therapy regimen in non-breast-feeding women. Mono therapy with single dose nevirapine (sd NVP) often fails due to the once off nature of the intervention as opposed to ample opportunity to administer zudovudine (AZT) antenatally with dual therapy. A higher CD_4 threshold to initiate HAART increases the window of opportunity while women are reasonably healthy. Irrespective of the maternal disease the newborn babies receive the same ART regimen. Women requiring HAART following pregnancy with an interval of 6 months or longer since NVP exposure had the same virological response as compared to NVP naïve women. Dual or mono therapy for a second time will be as effective as with NVP naïve women. The present day routine use of ART will reduce the risk of obstetric interventions.

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HIV positive children

During 2005 the global prevalence of HIV among children (less than 15 years) was 2.3 million; of these 1.8 million (80%) were in Sub-Saharan Africa. In 2006 there were 580,000 children newly infected and 370,000 children died due to HIV. The vast majority of children acquired HIV through vertical transmission from mother to child.[1]

During 2006 the sero-positive HIV prevalence amongst women attending antenatal clinics in the public health sector within South Africa was 29.1%.[2] The province with the lowest prevalence was the Western Cape (15.2%) and the highest prevalence occurred in KwaZulu Natal (39.1%). During 2006 the National Department of Health estimated that in South Africa only 47% of pregnant women in the public health sector were tested for HIV with an estimated range between the 9 provinces a mere 24 to close to 100%.[3]

The third South African AIDS Conference

At the third South African AIDS Conference it was clear that huge progress has been made towards increasing awareness of HIV/AIDS among the public at large,[4] inthat there is agreement amongst public, private and non-governmental organisations representing all walks of life, about the disease and, in general, what measures are required to combat the pandemic. Huge progress has also been made in treating AIDS by commencing highly active antiretroviral therapy (HAART) when required for stages 3 and 4 disease. The number of people on HAART within the public health sector is ever increasing. The 230,000 people on HAART are globally the largest programme.

However, the number of new infections is increasing. The horizontally acquired infection is difficult to curtail. The strong driving forces of sexual behaviour do require a comprehensive approach. This will have to include every organisation and group, with health care workers being one of the many role players involved.

During 2006 only 14.6% of HIV positive mothers within the public health sector in South Africa received some form of antiretroviral therapy (ART) to prevent perinatal mother to child transmission (PMTCT) during labour, delivery and the postpartum period. An effective PMTCT programme will impact hugely on the number of perinatal acquired HIV infections. This is a goal within reach of the South African public health sector. Key Priority Area 1 (Prevention) number 3.2 of the HIV/AIDS and STI National Strategic Plan for 2007 to 2011 compiled by the South African National AIDS Council (SANAC) states[5]: Scale up coverage and improve quality of PMTCT to reduce MTCT to less than 5%.

Perinatal mother to child transmission of HIV

Without any intervention the vertical HIV transmission from mother to child will be 14 to 50%. The transmission rate can be vastly reduced by an effective PMTCT programme. An effective PMTCT is a most worthwhile and cost effective intervention and must receive high priority in Sub-Saharan Africa. The programme should begin with pre-pregnancy counselling and voluntary testing for HIV. Knowledge of HIV status prior to pregnancy allows a large widow of opportunity during which HIV positive women requiring HAART could commence treatment. This measure will improve their health and immunity and reduce their viral loads to undetectable levels. Women not requiring HAART will commence with ART during the antenatal period. HIV discordant couples should be referred to infertility clinics for artificial insemination.

Presently, pre-pregnancy counselling is an ideal not within our short and medium term grasp. Therefore the antenatal period remains the most important time for universal counselling and voluntary testing for HIV. All women must be en-

couraged to have early confirmation of pregnancy. With pregnancy confirmed, health care providers must continue straight away with the first antenatal or booking visit. Women attending antenatal care from early in pregnancy tend to have the least pregnancy complications. Gestational age is established accurately with ultrasound, medical problems and pregnancy complications are detected early and appropriate measures can be instituted timeously. In addition, early antenatal attendance and knowledge of HIV status also allows women and health care providers a sufficient time window to implement HAART or for ART intervention. Both measures have been proved to be highly efficient in reducing MTCT of HIV.[1]

AN EFFECTIVE PMTCT PROGRAMME CONSISTS OF:

Measures taken during the first antenatal visit

Counsel all antenatal women about HIV and the PMTCT programme. This must be done individually in a room where privacy is assured. Thereafter each woman choosing to take part in the programme must receive individual pre-test counselling. Written consent must be obtained from women who want to be tested for HIV.

A rapid HIV test can be performed with one of the many reliable rapid tests presently available (Determine®, Oraquick®, First Response®, etc). A negative result indicates that the patient is HIV negative and post test counselling will focus on safe sexual practices in order to remain negative. A second test 6 weeks later is advisable if a woman is considered to be at risk of being in the window period, due to recent sero-conversion.

If the rapid test is positive, the patient is informed thereof and the importance of a second test explained. In circumstances where a laboratory is available to provide the result of an ELISA test within 2 hours, this is the preferred test. However, if this is not possible the confirmatory test can be done with a rapid test from another manufacturer. If this test is also positive, the HIV status is regarded as positive and post-test counselling is performed. The result is then noted on the antenatal record.

Patients that are found to be HIV positive must have a CD_4 lymphocyte count performed. This can be done on the same blood specimen sent for RPR testing, blood group and haemoglobin determination at National Health Laboratory Services (NHLS) laboratories.

The first antenatal visit includes taking a thorough history. The medical history taken from women that tested HIV positive must include questions aimed at an initial decision regarding the World Health Organisation (WHO) stage of the disease:

- persistent painful lymph nodes
- weight loss
- skin rashes and a chronic itchy skin
- recurrent sinusitis
- fever and rigors extending over a period of more than four weeks
- painful or difficult swallowing
- chronic coughing for more than two weeks
- TB treatment within the past year
- severe headache

A thorough clinical examination is also part of the first antenatal visit. Women that tested HIV positive must be carefully examined for:

- enlarged lymph nodes of more than 2 cm
- skin rashes
- signs of weight loss
- oral ulcers and oral or pharyngeal thrush
- abnormal physical finding of the respiratory system

If the history and physical examination indicates WHO stage 3 or 4 disease, the patient must be referred to an antiretroviral (ARV) or infectious diseases clinic for assessment and further management. Waiting for the CD_4 result will cause an unnecessary delay with potentially disastrous consequences. Early adherence counselling and commencement with HAART will be life saving.

The second antenatal visit and subsequent management

The second visit is usually 2 weeks later. At this visit the result of the CD_4 count is checked. A second assessment is required to finally stage the patient according to the WHO clinical staging. In addition, counselling regarding infant feeding options is given. The CD_4 count must be noted on the antenatal record. Subsequent management is as follows:

CD_4 count 250 cells/mm^3 or more and WHO stage one or two

These patients have a reasonably intact immune system and are generally healthy. They should receive **dual therapy**:

- Oral zidovudine (AZT) 300 mg twice daily from 28 weeks and 300 mg 3 hourly during labour
- Oral nevirapine (NVP) 200 mg to be administered once labour is confirmed

Laboratory haemoglobin (Hb) at 26 weeks is done if a recent laboratory Hb is not available. The ward Hb needs to be repeated 2 weeks following commencement of AZT and then with 4 weekly intervals. An Hb concentration of less that 8g% is a contra-indication for the use of AZT. HIV positive women with low Hb concentrations and a normochromic normocytic anaemia need NOT be investigated for micronutrient deficiency. The anaemia invariably will be caused by the viral infection. Often the anaemia will also be due to iron deficiency. These women will have a hypochromic microcytic anaemia. “Double iron” therapy (2 ferrosulphate tablets 3 times a day) and folic acid 5 mg per day will result in a rise in the Hb concentration, allowing AZT to be commenced.

A transmission rate of 2% can be achieved with this regimen in non-breastfeeding women.[6] A transmission rate of 1.9% was achieved in Thailand irrespective of the obstetric management. This regimen will greatly improve the estimated 6 to 8% transmission rate presently achieved with a dual therapy protocol that commences with AZT at 34 weeks.

CD_4 count less than 250 cells/mm^3 and WHO stage three or four

These patients do not have an intact immune system and need to be carefully evaluated for opportunistic infections. They will receive:

- Co-trimoxazole two tablets per day.
- HAART if the gestational age is more than 12 weeks and less than 34 weeks.
  - o When <12 weeks with a CD4 count less than 50 cells/mm3 or severe HIV illness, commence HAART as soon as treatment ready.
  - o When >34 weeks dual therapy is provided as it will not be possible to assess treatment readiness and initiate HAART prior to delivery. However, if the CD4 count is less than 50 cells/mm3 or with severe HIV illness, commence HAART as soon as treatment ready.

The guidelines provided by the National and Provincial Departments of Health in

South Africa recommend a CD_4 count of 200 cells/mm^3 or more for either single dose NVP or dual therapy with NVP and AZT as recommended above.[7,8] A higher CD_4 threshold increases the window of opportunity to initiate HAART while the patient is reasonably healthy. In addition, the problem of NVP resistance will be solved, as the interval between delivery and the need for HAART will be 6 months or more in most cases as explained later.[9] The use of NVP as part of HAART will not be associated with hepatitis as this complication has only been described in cases with a CD_4 count of above 250 cells/mm.[3,10]

HAART during pregnancy

Treatment readiness must be assessed. Pre-treatment counselling includes:

- Ensuring a clear understanding of the disease progression and benefit of AVR drugs. Pamphlets are of great help.
- Stressing the importance of adherence (compliance).
- Encouraging disclosure of status to a treatment support person and sexual partner.
- Encouraging participation in a support group.

Baseline full blood count with a differential white cell count and alanine aminotransferase (ALT) is done. Patients with AIDS will often be anaemic and AZT and 3TC can cause anaemia. NVP can cause hepatitis.

To assess compliance patients are supplied with 7 days of co-trimoxazole 2 tablets per day (the packet must to be brought back at the next visit) and an appointment is given one week later.

HAART is initiated 1 week later if patients kept their appointments, complied with co-trimoxazole therapy, disclosed their status at least to support persons and whose baseline blood results are normal. This indicates treatment readiness. Further pre-treatment counselling includes:

- Drug specific side effects (nausea and diarrhoea occur commonly)
- Re-emphasise adherence
- Drug dosing specifics

HAART is then initiated:

- Stavudine (d4T) 40 mg (30 mg if weight less than 60 Kg) every 12 hours
- Lamivudine (3TC) 150 mg every 12 hours
- NVP 200 mg per day for 2 weeks

After 2 weeks the ALT is determined and if it is not elevated, NVP is increased to 200 mg every 12 hours. The ALT levels must be checked every 4 weeks.

Women on HAART stay on the twice a day regimen throughout pregnancy, labour and delivery. These women will have non-detectable or very low viral loads that depend on adherence. The PMTCT of HIV will be very low.

Important side effects of ARV that require discussion with an ARV specialist:

- NVP – a skin rash and hepatitis
- d4T – peripheral neuropathy, lactic acidosis and lipo-atrophy
- AZT – bone marrow suppression (anaemia, neutropenia), myopathy and lactic acidosis
- 3TC – diarrhoea, pancreatitis and anaemia

Neonatal antiretroviral therapy

Irrespective of the maternal disease, the newborn babies receive the same ART regimen:

- NVP syrup more than 4 hours post delivery and more than one hours prior to discharge. NVP must be given within 72 hours postpartum. The dose with a birth weight equal or more than 2 Kg is 0.6 ml and with a weight less than 2 Kg 0.2 ml per Kg.
  If maternal NVP was taken less than 2 hours before delivery, NVP must be administered to the neonate within 60 minutes of delivery and AZT following the first feed.
- AZT syrup with the first dose of NVP and thereafter 12 hourly for 7 days. The dose with a weight equal or more than 2 Kg is 1.2 ml and if the weight is less than 2 Kg 0.4 ml per Kg 12 hourly.
  The mother must feed the infant according to the decision reached following counselling during the antenatal period. The choice of the mother must be respected and reinforced to prevent mixed feeding.

Logic behind dual therapy

Mono therapy with sd NVP often fails due to the once off nature of the intervention as opposed to ample opportunity to administer AZT antenatally. In addition:

- 20% of transmission occurs antenatally, that is not addressed with sd NVP.
- The viral load is reduced at time of onset of labour, contributing to a lower intrapartum transmission rate and reducing the risk of NVP resistance.

Safety of ART during pregnancy

Efavirenz (EFV) presently is the only ARV drug known to be teratogenic and causes neural tube defects if used during the first trimester of pregnancy. This drug is one of the first line HAART drugs. Women on this drug must use reliable contraception. Women desiring to fall pregnant must have the EFV replaced with NVP. If on EFV and found to be pregnant, women less than 14 weeks must be changed to NVP. However, with a gestational age of 14 weeks or beyond, EFV can be continued. All women exposed to EFV during the first trimester must have a detail ultrasound scan between 18 and 22 weeks of pregnancy to rule out neural tube defects.

The problem of NVP resistance

A single gene mutation of HIV is required to develop resistance against NVP. This is a problem of mono therapy with NVP. In the HIVNET 012 study in Uganda (subtype A and D HIV) with single dose (sd) NVP, 25% of women had resistant strains at 4 to 6 weeks postpartum.[11] However, all viruses reverted back to the wild type by 12 months. In the SAINT study in South Africa (subtype C HIV) where the women received two doses of NVP, 67% of women had resistant strains at 4 to 6 weeks postpartum. By 12 months 20% of women remained with resistant strains.[12] Only sd NVP must be used with mono or dual NVP based regimens. The long half-life (60 hours) of NVP is an ideal property that obviates the administration of a second dose of NVP if inadvertently given to a woman in false labour. Measurable levels of NVP can be found in the serum of women 21 days following sd NVP.[13]

The relevant question is whether women requiring non neocleoside reverse transcriptase inhibitor (EFV) based HAART following sd NVP exposure are at a disadvantage? Jourdain ***et al*** compared NVP naïve and previous sd NVP exposed women and found that the clinical and immunological responses did not differ.[9] However, the virologic response of women with sd NVP exposure was significantly less likely to maximally suppress after 6 months on HAART (RNA viral load less than 50 copies per ml) than those without exposure (68% vs 38%).This is a cause of concern. However, if this group was divided in groups with intervals shorter than 6 months and 6 months or longer since sd NVP exposure, the virological response in the NVP exposed group did not differ from the NVP naïve group.

Women requiring PMTCT for a second time

Due to the national antenatal HIV prevalence of more than 20% since 1998, it is common to have women pregnant for a second time.[2] The question then arises about the effectiveness of sd NVP to prevent transmission a second time. This is a pertinent question taking into account the problem of NVP resistance following sd NVP exposure. A prospective cohort study in Uganda provided valuable insight about the effectiveness of single dose NVP with a second pregnancy.[14] In the sd NVP naïve group, the HIV transmission rate was 17.5% and in the previous sd NVP exposed group 18.4% (p=0.92). In women who do not require HAART, sd NVP can be used with confidence as a component of dual or mono therapy for PMTCT. Women on HAART with a second pregnancy require routine follow-up with viral load estimation to assess the efficiency of their treatment.

Obstetric interventions that may influence PMTCT

The knowledge of the transmission risks of obstetric interventions mostly dates back to the era prior to the routine use of ART during pregnancy.[15] The present day routine use of ART will reduce the risk of interventions as illustrated by a transmission rate of 1.9% that was achieved in a non-breastfeeding study population in Thailand with dual therapy irrespective of the obstetric management.[6]

Amniocentesis

Presently this procedure is performed under ultrasound guidance with a thin needle containing a stilet. Avoid inserting the needle through the placenta.[16] The risk of transmission could be lower than with a needle stick injury. If the woman is on HAART with a non detectable viral load, the risk will be very small.[17] As amniocentesis will be performed early in the second trimester, women that will be using dual therapy should be covered with AZT and 3TC for 28 days. However, the procedure should only be performed if there is a definite indication that outweighs possible risks.

External cephalic version (ECV)

The knowledge that a foetal-maternal bleed could occur in 2 to 3% of cases during external ECV done on Rhesus negative women, does raise concern regarding transmission with ECV performed on HIV positive women. However, the pressure gradient across the placental barrier does favour a foetal-maternal bleed.[18] Therefore, knowledge gained from Rhesus negative women cannot be extrapolated to HIV transmission. Until more knowledge is available, ECV for HIV positive women should be limited to women who may not have medical care readily available when labour commences.

Rupture of membranes during labour

The transmission rates are increased with ruptured membranes and the risk increases the longer labour continues with ruptured membranes. If the duration of ruptured membranes continues beyond four hours, the risk of transmission increases significantly.[19] When transferring the progress of labour of HIV positive women with intact membranes from the latent phase of labour to the active phase on the partogram, their membranes must not be ruptured. However, progress of labour must be reassessed after two hours and if normal the membranes must be kept intact. If progress is slow, the membranes could be ruptured and progress again assessed after two hours. This measure will allow timeous delivery within the first four hours of ruptured membranes.

Intrapartum interventions

Transmission rates were reported to be higher with forceps and vacuum deliveries as well as when episiotomies were preformed.[15] However, when ARV's are used, the risk will be reduced. If a policy of vaginal deliveries for HIV positive women is followed, these procedures could be preformed when indicated, with a provision that a more conservative approach should always be favoured.

Caesarean sections (CS)

Elective CS sections have been reported to reduce transmission by more than 50%.[20] The most recent meta-analysis resulted in an even more pronounced beneficial effect. Women enrolled between 34 and 36 weeks that were delivered by elective caesarean section before labour and rupture of membranes, had a 66% reduction (odds ratio 0.34 and 95% CI 0.14 – 0.8) in transmission rates.[21] This information raised the question as to whether transmission rates of women on HAART with a non-detectable viral load delivered by elective CS may be less than following vaginal birth.

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