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Human Immune Deficiency Virus positivity and Pregnancy – an evidence based review

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Introduction

Human immunodeficiency virus (HIV) infection, 'the disease of the millennium' has affected people of all age groups and of all socio economic strata in the society. This disease has had a major impact on the socio-economic resources in the developing countries. In this chapter, the focus would be on (a) risk factors which facilitate the perinatal transmission of the virus from mother to the child (b) interventions needed to prevent the perinatal transmission of the virus (c) role of breast feeding in the resource poor setting.

Magnitude of the disease

The HIV epidemic has shown an increasing trend among women and the young. Women of child bearing age constitute nearly 30 million adults currently living with HIV/AIDS[1]. In India, 39% of adults living with HIV/AIDS are women[2].This increase in the prevalence of the disease among

women, is reflected in increased transmission of the virus from mother to the fetus, i.e. vertical transmission.

Until 2002, over 4.3 million children have succumbed to the AIDS epidemic worldwide and in 2003 about 700,000 children under the age of 15 years became infected with HIV[3].The developing countries, those with the least available resources, have been the most severely affected by the burden of the HIV pandemic. The increasing number of HIV infected adults, particularly women, makes the prevention of mother-to-child transmission of HIV a public health priority in many developing countries[4]. Currently, more than 95% of children with HIV live in developing countries.

Testing for HIV

Among pregnant women, knowing one's HIV status is the cornerstone to the prevention of mother to child transmission of the disease. Centers for Voluntary Counseling and Testing (VCT) established in some of the countries like in India, combine services of confidential provision of information on serostatus, counseling for seropositive individuals and education on reducing the risks of transmission. In centers, where facilities for antiretroviral therapy exist, VCT can also identify candidates for prevention of mother to child transmission or AIDS treatment[5].

Risk factors involved in the transmission of the virus from the mother to child

Transmission from mother to child of HIV is affected by number of factors (Table 1), though not all of which have been fully elucidated. Their influence varies depending on whether she is still antenatal, in labor or has delivered and lactating.

Table 1: Risk factors for mother to child transmission of HIV

Period	Risk factor
Antepartum	• Maternal plasma viral load • Lack of antiretroviral therapy • vitamin A deficiency • Malnutrition • Maternal CD4+ T-Lymphocyte count • cigarette smoking • illicit drug use • multiple sexual partners • amniocentesis
Intrapartum	• vaginal delivery • prolonged rupture of membranes • premature delivery • chorioamnionitis • fetal scalp electrode use • genital infections • episiotomy • vaginal lacerations
Post partum	• breast feeding • mastitis

Source: Rongkavilit C, Asmar BI[4]

Interventions to reduce the mother to child transmission of HIV

With increasing knowledge about the underlying mechanisms of mother to child transmission of HIV has come an increased emphasis on the search for interventions to prevent or reduce the risk of transmission. With different intervention strategies, differing and startling rates of perinatal transmission are noted (Fig1), from rates of about 2% in those receiving antiretroviral therapy, having elective cesarean delivery and not breast feeding to 25 to 40% among groups without any intervention[6].

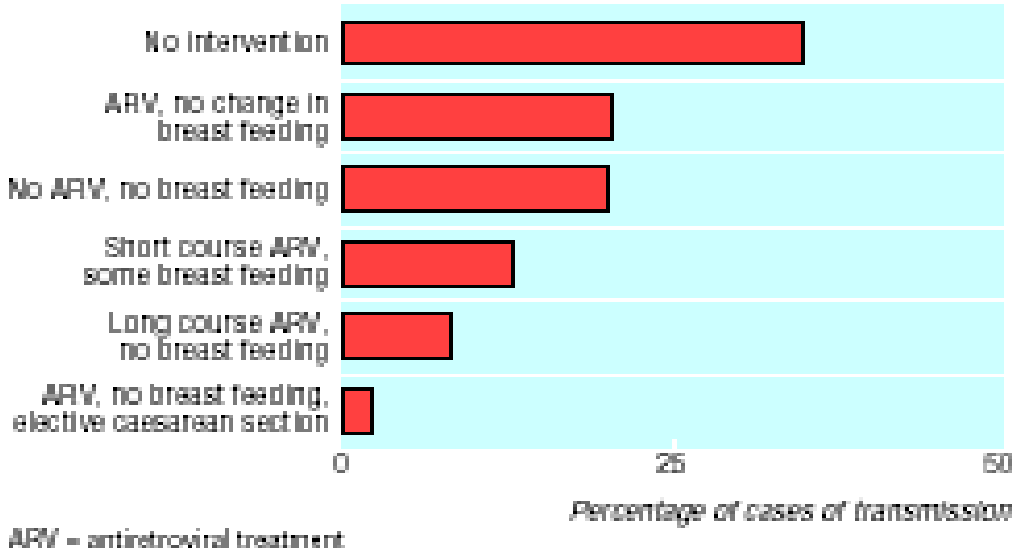

Fig.1 Effect of interventions on rates of mother to child transmission of HIV (Source: McIntyre and Gray[6])

To reduce mother to child transmission of the virus, World Health Organization has suggested prevention of new infections in parents-to-be, unwanted pregnancies in HIV infected women and transmission from an infected mother to her infant[6] as the effective strategies.

(a) Prevention of new infections in, parents-to-be

The parents-to-be should be counseled about the safe sexual practices and the various aspects of HIV. The various contraceptive options need to be given to the couple. The WHO medical eligibility criteria cautions against the use of intrauterine devices (IUD) and LNG –IUS by women at risk of HIV, HIV positive women and women with AIDS. There are number of concerns about IUD use in women with HIV infection relating to contraceptive efficacy, risk of sexual transmission and acute pelvic inflammatory disease[8]. Caution may be required in prescribing hormonal contraceptives in women taking enzyme inducing drugs including some Highly Active Antiretroviral Therapy (HAART) and anti-

tuberculosis drugs, since some of the antiretroviral drugs may reduce the efficacy of oral hormonal contraceptives (Box 1).[9]

Box 1

Anti retroviral enzyme inducers that may reduce the efficacy of oral hormonal contraceptive	
Protease inhibitors	Non nucleoside reverse transcriptase inhibitors
Ritanavir Nelfinavir Lopinavir with Ritonavir	Nevirapine Efavirenz

Source: Mitchell and Stephen[9]

(b) Prevention of unwanted pregnancies in HIV infected women

The option of termination of pregnancy needs to be given to the antenatal patient in early pregnancy, especially in resource limited settings. The decision taken by the couple/mother should be given due consideration.

(c) Interventions to prevent the transmission of HIV during pregnancy, labor and in the postpartum period

i) During pregnancy: Pregnant women should be offered screening for HIV early in pregnancy because appropriate antenatal interventions can reduce mother to child transmission of HIV infection[10] (*grade* **A**). Screening early in pregnancy can help in assessing future risks, reinforcing risk reducing behaviors, making early diagnosis and start treatment early and thus facilitate preventing and or reducing perinatal transmission (Box 2).

Box 2

Reasons to screen pregnant patients for HIV

(i) Assessing future risks
(ii) Reinforcing HIV risk-reducing behavior
(iii) Allowing referrals to prevention services
(iv) Making an early diagnosis
(v) Starting early treatment
(vi) Informing patients about reproductive decisions
(vii) Preventing transmission to others
(viii) Obtaining psychologic and social support services
(ix) Reducing perinatal transmission

Source: information from center for disease control and prevention. U.S. Public health service recommendations for Human Immunodeficiency Virus counseling and voluntary testing for pregnant women. MMWR Morb Mort Wkly Rep1995; 44(RR-7):1-15.

Counseling pregnant HIV women

Counseling is an important component in the management of HIV in pregnancy. As discussed earlier, termination of pregnancy remains an option for patients in resource poor or resource limited conditions. The chance of vertical transmission with and without interventions (with antiretroviral drugs) needs to be discussed with the couple. The patient also needs to be told about personal prognosis based on the CD4 count and the viral load. The decision of whether to breast feed or not is to be made by the patient after being counseled about the advantages and disadvantages of breast feeding and the decision must be respected. The data currently available on the pharmacokinetics and safety of

Box 3 Points for counseling

- Personal prognosis based on lymphocytic subset and HIV viral load
- Illicit drug use (whether relevant)
- Vertical transmission rates
- No method of prenatal diagnosis
- Option of pregnancy termination
- Breast feeding options
- Neonatal prognosis
- Death of HIV –infected parent(s)

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Source: Olaitan A, Johnson MA[12]

antiretroviral drugs in pregnancy are minimal, and therefore all treatment decisions during pregnancy require full discussion between the physician and the patient with regard to the known potential benefits and the risks[13]. The patient also need to be told about the various tests that she needs to undergo to note the progress of the disease and also to detect the side effects of antiretroviral therapy at the earliest (Table 2).

Table 2 Tests for monitoring antiretroviral treatment

Test	Frequency	Changes with HIV disease
Full blood count	3 monthly	Anaemia,lymphocytopenia, thrombocytopenia
Liver function tests	3 monthly	Concurrent hepatitis or drug treatment may affect
Hepatitis B and C markers	Baseline	May be acquired via same route as HIV
Toxoplasma serology	Baseline	Seropositive are at a risk of reactivation if immunosupressed
Syphilis serology	Baseline	High endemicity may correspond with high HIV prevalence
Cervical cytology	Baseline	Higher rate of abnormality and faster progression in HIV positive women
T cells	3 monthly	CD4 cells fall with increasing immune suppression
P24 antigen	3 monthly	Rises with disease progression
HIV viral load	4-6 weekly	Predicts vertical transmission

Source : Olaitan A, Johnson MA[12]

Screening for genital tract infections

All pregnant women need to be screened for genital tract infections, in view of the fact that increased HIV genital tract replication may occur due to other local infection. Viral load in the cervicovaginal secretions has been correlated with mother to child transmission[14].

Anti retroviral therapy

In women of child bearing age, antiretroviral choices should be made such that the agent with the potential side effects in pregnancy or for the developing fetus are avoided and agents known to be effective in preventing the perinatal transmission are used wherever possible[13]. CD4 counts and viral loads need to

be monitored at the time of diagnosis, during each trimester and towards term. The optimal interval is about 4-6 weeks[13]. In pregnancy, the woman should be offered combination antiretroviral therapy regardless of their viral load and CD4 count. The objective of managing pregnant women infected with HIV is to treat maternal HIV disease and to prevent transmission to the fetus. Antiretroviral agents decrease the mother to child transmission either by reducing the viral load and/or by preventing the virus from fixing itself in the infant. There are trials of various regimens of antiretroviral therapy used in the prevention of mother to child transmission of HIV designed to take into account of various variables such as drug availability, affordability and service utilization (Table 3). There is no one standard of care because of the same reasons.

Table 3

Regimen	Schedule-mother			Schedule infant	Breast feeding	Efficiency
	antepartum	intrapartum	postpartum			
ACTG trial Azidothymidine **(AZT**)	from 14 weeks, 100mg, 5 times a day.	2mg/kg iv stat , then 1mg/kg/hour until delivery	no drugs	2mg/kg 6 hourly for 6 weeks (to be initiated within 6 -12 hours of birth)	no	68%
Thai regimen (short course AZT)	from 36 weeks,300mg twice a day	300mg every 3 hours until delivery		no drug given to the baby	no	50%
PETRA-A AZT/Lamivudine (3TC)	from 36 weeks, AZT(300mg)+3TC(150mg) twice a day.	600mg at the onset of labour, then 300mg every 3 hourly until delivery. 3TC 150 mg orally at the onset of labour and then 150 mg every 12 hourly orally until delivery.	AZT (300mg) and 3TC (150mg) twice a day for a week	AZT (4mg/kg)+ 3TC (2mg/kg) 12 hourly for 7 days	allowed	54%
PETRA-B	no drugs	AZT 600mg at the onset of labour, then 300mg every 3 hourly until delivery. 3TC 150 mg orally at the onset of labour and then 150 mg every 12 hourly orally until delivery.	AZT (300mg) and 3TC (150mg) twice a day for a week	AZT (4mg/kg)+ 3TC (2mg/kg) 12 hourly for 7 days	allowed	39%
HIVNET-012 (NVP)	no drugs	200mg of Nevirapine once in first stage of labor.	no drugs	Nevirapine (NVP) 2mg/kg stat, within 72 hours of life	allowed	47%

The ACTG-076 trial demonstrated the effectiveness of ART in the prevention of perinatal transmission of HIV. Zidovudine (AZT) was given after 14 weeks at a dose of 100mg, 5 times a day daily. During labour, after the bolus of 2mg/kg given intravenously over 1 hour was followed by 1 mg/kg/hour of continuous infusion until delivery. The infants received oral AZT 2mg/kg four times a day for 6 weeks, beginning 8-12 hours after birth. Mother to child transmission rates dropped from 22.6% to 7.6%. In a study in Thailand, Zidovudine 300mg, twice a day from 36 weeks onwards and then 300mg every 3 hourly during labour reduced the transmission risk by 50% if the mother did not breastfeed the baby. This regimen has been recommended for the developing countries that can adopt it. Although Zidovudine monotherapy has substantially reduced the risk of perinatal transmission, is now considered to be suboptimal treatment. Combination therapy is considered the standard care[13].

In the PETRA study conducted in Uganda, Tanzania and South Africa, a combination of Zidovudine and Lamivudine were tried. The rate of transmission at 6 weeks for cohorts using the combination from 36 weeks onwards including labour with neonatal component was 5.7%, in those who were on intrapartum and neonatal component was 8.9%, and for those using only the intrapartum component of the regime was 14.2% in comparison to 15.3% among those not on any ART. The reduction in rates of transmission was 50% in children of women receiving antiretroviral drugs from 36 weeks and 37% for those on intrapartum therapy only when compared to placebo group.

The HIVNET012 trial conducted in Uganda which compared short course of Zidovudine and Nevirapine showed that efficacy of the latter was 47% greater probably related to the long half life of the drug and its ability to achieve high concentrations in the circulation.

The SAINT trial that compared Nevirapine with Zidovudine and Lamivudine combination documented the perinatal transmission rates of 12.3% and 9.3%, respectively for them, at the end of 8 weeks.

Safety of antiretroviral drugs in pregnancy

Nucleoside analogues such as Zidovudine, Didanosine are known to potentially induce mitochondrial dysfunction[16]. Clinical disorders linked to mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis, and lactic acidosis. Protease inhibitors have been associated with increased incidence of glucose intolerance and in some cases, overt diabetes[17]. Though the concern about the association of protease inhibitors with prematurity is expressed, not all studies have found such relationship[18]. The European Collaborative Study found similar prevalence and the pattern of congenital abnormalities among infants exposed to antenatal ART and those who were not and this was true for the highly active antiretroviral therapy (HAART). There was no evidence to suggest that exposure to first trimester antiretroviral therapy increases the risk of congenital abnormalities[19]. Various categories of antiretroviral drugs, some of the significant side effects and recommended monitoring while on those drugs is abridged in table 4 below.

Table 4 Antiretroviral drugs used in pregnancy

Drug Category	Drug names	Selected adverse effects in pregnancy	Recommended monitoring
Nucleoside or nucleotide reverse transcriptase inhibitors	Zidovudine Lamivudine Stavudine Didanosine Abacavir Tenofovir	Anemia; mitochondrial toxic effects (lactic acidosis, pancreatitis, hepatosteatosis) in the mother and possibly fetus; neuropathy; hypersensitivity Possible effects on fetal bone metabolism	Complete blood count and Hemoglobin levels; monitoring for mitochondrial toxic effects(measurements of electrolytes and liver enzymes)
Nonnucleoside reverse transcriptase inhibitors	Efavirenz Nevirapine	Neural malformations Hepatotoxic effects (especially with CD4 T cells >250/mm^3)	Avoid in pregnancy Aminotransferase levels (every two weeks initially, then monthly)
Protease inhibitors	Amprenavir Atazanavir Indinavir Lopinavir Nelfinavir Ritonavir Saquinavir	Hyperglycemia, gestational diabetes, possible increase in preterm birth, hepatitis.	Glucose levels (Standard Glucose loading test early in pregnancy and repeated in third trimester)

Source: Lorenzi et al [15]

Mode of delivery

As labor and delivery have been suggested as times of high risk for vertical transmission of HIV from mother to the child, much attention has focused on the mode of delivery as being an important time of intervention. A meta-analysis summarizing data from 15 prospective cohort studies found that elective caesarean delivery, before rupture of membranes or the onset of labor, was associated with a decreased risk of perinatal transmission compared with other

modes of delivery[20]. The European Collaborative study suggested that offering an elective caesarean section delivery to all HIV-infected women, even in areas where HAART is available, is appropriate clinical management, especially for persons with detectable viral loads. In the presence of HAART, the absolute rate of mother to child transmission was likely to be low (in the region of 1-2%); the study suggested that elective caesarean section would further reduce the risk to less than 0.5%[21]. On an individual level, the decision regarding mode of delivery rests with the woman and her clinician, who should inform her of the potential risks and benefits. Women receiving optimal antiretroviral therapy with complete suppression of the plasma viral load (less than 50 copies/ml) may deliver vaginally (in the absence of other obstetric indications for caesarean delivery) [13]. Women who opt for a planned vaginal delivery should have their membranes left intact for as long as possible. Fetal scalp electrodes and fetal blood sampling should be avoided. Scalp laceration has been reported with the use of ventouse and therefore forceps should be the instrument of choice for assisted delivery. Routine precautions for blood and body fluid infection control should be taken[13].

Role of breast feeding

Breast feeding by HIV infected women is not recommended because it is associated with an additional 15% to 25% increase in transmission rate. The UNAIDS guidelines suggest that “when children born to HIV-1 infected women can be assured of uninterrupted access to nutritionally adequate breast milk substitutes that are prepared and fed to them they are at less risk of illness and death”[22]. In resource-poor settings, transmission of HIV from mother to child by breast feeding remains responsible for a significant proportion of infections. The WHO guidelines (2004) estimate that up to half of infections in children will be a result of breast feeding transmission[23]. In affluent societies an HIV positive mother is encouraged to feed her infant with formula to prevent HIV transmission from breast milk. It is assumed that she has access to a continuous source of formula, clean water and facilities for washing the bottle. In resource poor

countries these assumptions cannot be made and in addition formula feeds may identify the woman as HIV positive when she has not disclosed this fact[24]. In a study of infants born to HIV-infected women in South Africa, Coutsoudis and colleagues found that HIV infection was detected at 6 months in identical population of exclusively breastfed infants (19%) and never breast fed infants (19%) and that infants who received mixed breast feeding had a higher rate of infection (26%). But by 15 months, the infection rate was higher in exclusively breast fed children than in never-breastfed children, and the rate remained highest in children who received mixed feeding[25]. The explanation for this finding may be the infant's immune response to novel foods, which results in the recruitment of white blood cells into the gastrointestinal tract, providing additional targets for HIV infection. It is also possible that delicate mucosal lining of infant gastrointestinal tract gets abraded by relatively granular formula milk, and such breaches provide portal for transmission of virus when breast feeding follows.

The World Health Organisation currently makes recommendations regarding breast feeding that include the following**.**

- Promotion of exclusive breast feeding for at least 6 months of life among women uninfected with HIV or with unknown status;
- Avoidance of breastfeeding by mothers with HIV infection, wherever "acceptable, feasible, affordable, sustainable and safe replacement feeding" is available;
- Exclusive breast feeding by mothers with HIV infection when no safe alternatives are available;
- Discontinuation of breastfeeding by mothers with infection when safe and acceptable alternatives become available;
- Provision of information and clinical care to mothers with HIV infection including contraception and nutrition.

Clinical recommendations and practice points (with levels of evidence)

- **It is particularly important to monitor for toxic effects related to a particular antiretroviral therapy being used (e.g., hematologic, hepatic, renal, pancreatic or metabolic effects.) Such monitoring should be performed 2 weeks after initiation of antiretroviral therapy and monthly thereafter[13].** (III A)
- **In addition to usual pregnancy management, monitor CD4 cell count and viral load at diagnosis, during each trimester and towards term. The optimal interval is every 4-6 weeks[13].** (III A)
- **Screen all women appropriately for other sexually transmitted infections and for cervical cytologic abnormalities.** (III A)
- **Option of termination of pregnancy needs to be given to the mother in the first trimester after counseling her about the need of antiretroviral drugs.**
- **Consider a detailed anomaly ultrasound at 21 weeks for all fetuses exposed to ART during the first trimester**
- **In the antenatal period, Zidovudine orally 100mg 3-5 times a day reduces the perinatal transmission.** (Ia-A)
- **For women who are immunocompromised, with CD4 counts of $0.20X10^6$/L (200/µL) or below, prophylaxis against Pneumocystis carinii pneumonia (PCP), Mycobacterium avium complex infection and other prophylactic therapies, according to the usual adult guidelines.** (IIIA)
- **Elective caesarean section reduces the vertical transmission.** (Ia-A)
- **Oral Zidovudine for the newborn for 6 weeks is recommended.** (Ib-A)

References:

1. UNAIDS. AIDS epidemic update. December 1998. Available from :URL.http://www.unaids.org/unaids/document/epidemio/wadr98e.pdf
2. USAID. 'HIV/AIDS country profile India', March 2003. Available from:http://www.avert.org/aidsindia.htm. Accessed on Oct19,2004

3. UNAIDS. WHO. AIDS Epidemic update, December 2003. Available from: http://www.who.int/hiv/. Accessed on Oct19, 2004.
4. Rongkavilit C, Asmar BI. Advances in prevention of mother-to-child HIV transmission. Indian J Paediatr 2004;71(1):69-71.
5. Hogan DR, Salomon JA. Prevention and treatment of human immunodeficiency virus/acquired immunodeficiency syndrome in resource limited settings. Bulletin of the World Health Organization. 2005; 83:135-43.
6. McIntyre J, Gray G. what can we do to reduce mother to child transmission of HIV? Br Med J 2002; 324:218-21.
7. WHO medical eligibility criteria for contraceptive use,2nd ed available for download on internet at www.who.int/reproductive-health/publications/RHR
8. Carlin EM, Baag FC. Women, contraception and STDs including HIV. Int. J STD AIDS. 1995; 6:373-86.
9. Mitchell HS, Stephens E. Contraception choice for HIV positive women. Sex Transm Infect 2004; 80:167-73.
10. RCOG guidelines. Management of HIV in pregnancy. NO.39 April 2004.
11. Centers for disease control and prevention. U.S. Public health service recommendations for human immunodeficiency virus counseling and voluntary testing for pregnant women. MMWR Morb Mortal Wkly Rep 1995; 44(RR-7):1-15.
12. Olaitan A, Johnson MA. Human immunodeficiency virus in obstetrics. In "Progress in Obstetrics and Gynaecology" John Studd Vol 13. Churchill Livingstone publication 1998.
13. Burge DR, Money DM, Forbes JC, Walmsley SL, Small FM et al. Canadian consensus guidelines for the management of pregnancy, labor and delivery and postpartum care in HIV positive women and their offspring (summary of 2002 guidelines). Canad Med Assos J 2003; 168; 1671-74.
14. Chuachoowong R, Shaffer N, Siriwasin W et al. short-course antenatal Zidovudine reduces both cervico-vaginal HIV1RNA levels and risk of perinatal transmission. Bangkok Collaborative perinatal HIV transmission study group. J. Infect Dis 2000; 181:99-106.
15. Lorenzi P, Spicher VM, Laubereau B, and et al. Antiretroviral therapies in pregnancy: maternal, fetal and neonatal effects: Swiss HIV cohort study, the Swiss collaborative HIV and pregnancy study, and the Swiss neonatal HIV study. AIDS 1998; 12:F241-F247.

16. Brinkman K, Hofstede HJ, Burger DM, Smeitink JA, Koopmans PP. adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as a common pathway. AIDS 1998; 12:1735-44.
17. Visnergarwala F, Krause KL, Musher DM. Severe diabetes associated with protease inhibitor therapy: Ann Intern Med 1997; 127:947.
18. Morris AB, Dobles AR, Uvin SC, Zorilla C et al. Protease inhibitor use in 233 pregnancies. J Acquir Immune Defic Syndr 2005; 40:30-33.
19. Patel D, Thorne C, Fiore S, Newell ML. European Collaborative Study. J Acquir Immune Defic Syndr 2005; 40:116-18.
20. The international perinatal HIV group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type1- A meta-analysis of 15 prospective studies. N Engl J Med 1999; 340:977-87.
21. Mother to child transmission of HIV infection in the era of Highly Active Antiretroviral therapy. European Collaborative study. Clin.infect Dis2005; 40:458-65.
22. WHO/UNAIDS/UNICEF. HIV and infant feeding guidelines for decision-makers. Geneva: WHO, 1998.
23. Newell ML. HIV transmission through breast feeding. A review of available evidence. Geneva: World Health Organisation. 2004
24. Moodley J, Wennberg JL. HIV in pregnancy. Curr Opin Obstet Gynecol 2005; 17:117-121.
25. Coutsoudis A. Promotion of exclusive breast feeding in the face of HIV pandemic. Lancet 2000; 356:1620-21.
26. World Health Organisation. Effect of breastfeeding on mortality among HIV infected women. www.who.int/HIV_AIDS/MTCT/