

PREVENTION OF MOTHER TO CHILD TRANSMISSION OF HIV

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SUMMARY

AIDS is a chronic unpleasant fatal disease caused by infection with Human immune deficient virus (HIV1). It has reached endemic proportions and thereby caused wide spread alarm among public all over the world. HIV1 is highly mutable virus. This variability of HIV1 is believed to be due to error prone nature of enzyme reverse transcriptase. Latency and transactivation is characteristic of HIV1. HIV1 evades and undermines the immune system; hence vaccines are not effective against it. Highly active anti retroviral therapy (HAART) increases patient survival by 13.3 years on average. The perinatal transmission of HIV1 affects nearly seven lakh infants each year worldwide. Most of them born in developing countries. The prevalence rate of transmission is ante partum (25-35%), intrapartum (70-75%), breast feeding (14%). An attempt is made to give overall view of HIV1 infection, diagnosis and prevention of mother to child transmission (MCT) with anti retroviral therapeutic agents (ART).

Key words: - HIV1, AIDS, MTCT, HAART, Zidovudine, Nevirapine

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INTRODUCTION

In 1983-84 scientists established that HIV1 causes AIDS. In 2007 an estimated 33-34 million people worldwide were living with HIV1. Everyday some 6000 people die from HIV1 and another 6800 contract the virus. In children HIV1 is one of the top ten killers in the under developed world because of malnutrition, infection, lack of hygiene etc. It has reached endemic proportions and thereby caused wide spread alarm among public all over the world. Highly active anti retroviral therapy (HAART) increases patient survival by 13.3 years on average. AIDS is an unpleasant fatal disease caused by infection with Human immune virus (HIV1). Pediatric AIDS constitutes 2% in the western countries whereas in developing and under developed countries varies from 15-20% due to HIV1 infection is more in woman in the child bearing age group. HIV is member of lenti virus group belong to family retroviridae. HIV1 is Spherical icosohedral 80-120 nm in diameter containing single stranded RNA diploid with 4-9 kilo bases, reverse transcriptase enzyme containing virion, replicates with DNA intermediate and integrates into human host chromosomes. HIV1 is thermo labile easily destroyed at 60 °C in ten minutes and at 100 °C in two seconds and inactivated or killed by disinfectants like alcohol 50% , Lysol 0.5%, Formaldehyde 0.5%, Hypochloric acid 0.5% and Gluteraldehyde 2%. HIV1 is highly mutable virus in nucleotide sequence, cell tropism, growth characteristics and cytopathology. This variability of HIV1 is believed to be due to error prone nature of enzyme reverse transcriptase. HIV1 cellular targets are macrophages, dendritic cells in lymphoid tissue, antigen presenting langerhans cells in epidermis, neuroglia and other which express CD4+ molecule on their surface are major targets for infection. Homosexual and heterosexual mode of transmission accounts for the majority of people infected with HIV1. Intravenous drug users, Drug addicted mothers, infants with sexually promiscuous and Hemophiliacs receiving factor VIII derived from pooled plasma are at the risk of infection.¹

PATHOPHYSIOLOGY OF HIV

HIV1 virion expresses 72 glycoprotein projections composed of gp 120 and gp 41.^{2, 3} HIV1 has special affinity for CD4 receptor bearing T lymphocytes. The envelope glycoprotein gp120 of HIV1 binds to CD 4 molecules but only initiates, gp 41 dependent fusion with the cell leading to infection.⁴ Early infections the virus utilizes the CCR-5 receptor for entry into many T cells and macrophages. These macrophage tropic strains which can infect resting T cells using CXCR-4 Co-receptor. CXCR-4 and CCR-5 are chemokine motif receptors involved in signaling mechanism. Mutant CCR-5 delta 32 is immune to HIV1. On gaining entry into a cell, HIV1 as an RNA retrovirus, utilizes a reverse transcriptase to convert its genetic RNA into corresponding DNA and it is integrated into the host genome where it can remain latent for long periods. Stimulation of latently infected T cells or macrophages activates HIV1 replication through an increase in intracellular nuclear transcription factor, which binds to consensus sequences in the HIV1 enhancer region. It is significantly that TNF which up regulates HIV1 replication through NFkB pathway; is present in elevated concentration in the plasma of HIV1 infected individuals, particularly in the advanced stage. Infectious viruses are finally released from the cell by budding and infect more helper cells eventually leading to their destruction. The cell infection by HIV1 turned to virus production cell and eventually be destroyed. The presence of HIV1 in some helper cells may also provoke and autoimmune response against non infected helper cells, causing further destruction of these important cells⁵. HIV1 infection also induces a premature programmed cell death i.e. apoptosis in infected CD4 T cells, which further deplete in their number⁷ Depletion of helper T cells leads to inefficient functioning of B lymphocytes as they require “help” of helper cells to produce specific antibodies. Cytotoxic CD8 T cells activity is also impaired,⁸ causing a decreased ability of immune system to destroy neoplastic and virus infected cells. Macrophages, having CD4 cell surface receptors, are also infected and destroyed⁹ leading to ‘diminished phagocytic response and decreased ability of the body to defend itself against extracellular pathogens. The infection of CD 4 cells result in a step by step depletion of these important cells and continually increasing the development of immune suppression¹⁰

This depletion of CD4 T cells is the fundamental abnormality in HIV1 infection. HIV1 is sufficient to cause AIDS, although cofactors, other microorganisms such as cytomegalovirus, mycoplasma penetrans etc., may impart adversely on the rate of progression to AIDS following infection and also exacerbate disease late in the course of infection.¹¹

MOTHER TO CHILD TRANSMISSION OF HIV1

Mother to child transmission of HIV1 is a major problem worldwide. Perinatal transmission of HIV1 affects nearly 5.00 lakh infants each year worldwide, most of them born in developing countries.¹² In India, 25 million births per year recorded. A seroprevalence amongst pregnant women of 1% and a vertical transmission rate from mother to child at around 30%¹³. We would expect to have 75,000 HIV1 infected neonates born every year. The burden of high infant and pediatric mortality from infection and malnutrition is today often associated with pediatric HIV1 disease as cofactor. Reducing this burden of pediatric morbidity from mother to child transmission of HIV1 is important. There is a clear need for strategies to prevent further MTCT in developing countries. Simple, low cost drug regimens are required that are suitable for use in countries where health care provision and newborns is limited.

Rates of transmission

Mother to child transmission rates have shown to have wide variations amongst different populations,¹⁴ transmission rates ranging from 14 to 33% have been reported in USA and western Europe¹⁵ In developing countries rates are as high as 43% have been reported¹⁶ this probably in due to the variations in the risk factors amongst different ethnic populations. Most babies with HIV1 infection (90%) are born in sub Saharan Africa. Comparing rates of vertical transmission between HIV1 and HIV-2, transmission of HIV-2 from mother to child appears to be low with very few reports of pediatric HIV1-2 infections from perinatal transmission^{17,18}. HIV1 transmission from mother to child can occur ante partum (in utero), intrapartum (during labour and delivery) or post partum (breast feeding).

Ante partum transmission

Most studies suggest that 25% to 35% of transmission occurs antepartum^{19, 20, 21}. Although transmission does take place even in early pregnancy²². Transmission is more frequent at term (late pregnancy), mostly at the time of labor or delivery²³ Evidence suggests that 70% to 75% of vertical transmission occur during labour and delivery. Increased transmission is noted with increased duration of rupture of membranes (greater than 4 hours) prior to delivery.²⁴ A higher risk of transmission is noted in the first born twin particularly when associated with prolonged labour,. The second of twins often gets spared²⁵, these evidences also support the view that intrapartum events play an important role in vertical transmission. The postulated mechanisms of intrapartum, transmission include transplacental micro transfusions from the constant massage the placental bed receives from uterine contractions or infection through mucocutaneous exposure to maternal blood or cervical secretions.

Breast feeding

Prospective studies have suggested an increased risk of transmission associated with breast-feeding^{26, 27}. Dunn et al²⁸ in a meta-analysis have estimated that the proportion of transmission attributable to breast feeding worldwide from HIV1 is 14%. The risk of HIV1 transmission from breast milk is particularly high when maternal primary infection occurs in the first few months after delivery²⁹. For these reasons in developed countries standard recommendation is to avoid breast-feeding³⁰

FACTORS AFFECTING MOTHER TO CHILD TRANSMISSION

Multiple factors influence HIV1 perinatal transmission and these are often responsible for the observed variability in transmission rates.

Maternal viral load

Studies have shown that high maternal viral load increases the risk of perinatal HIV1 transmission³⁸,

Maternal Immune Status:

Maternal immune depletion appears to co-relate with vertical transmission. An increased risk of vertical transmission is noted with lowered CD4 T cell counts or maternal AIDS³⁹

A reduced risk of transmission is noted in women with high serum titers of antibodies capable of neutralizing their own viral strains suggesting that the mothers own specific immunity is important.

Background genital tract infections.

Presence of background sexually transmitted diseases leading to genital lesions increases the risk of vertical transmission.⁴⁰

Lifestyle and behavioral factors

Some studies have shown that transmission rates are higher when nutritional deficiencies coexist. This possibly is an important factor responsible for the geographical differences in transmission rates. Semba et al⁴¹ have show that when Vitamin A levels were less than 0.70 $\mu\text{mol/L}$ the transmission rate was 32.4%. When Vitamin A levels were greater than 1.40 $\mu\text{mol/L}$ the transmission rate was just 7.2%

Use of hard drugs

(Cocaine, heroin, opiates, methadone, injecting drugs) by HIV1 positive women in pregnancy has shown to increase perinatal transmission⁴². Increased transmission rates in this group in probably due to lowered immunity and increased incidence of preterm births in this group. There has been documented an association between cigarette smoking in pregnancy and an increased risk of mother to child transmission. Chronic exposure to nicotine in animal studies has shown that nicotine inhibits the T cell responsiveness and may account for the decreased antibody response to T dependent antigens. This increases the susceptibility to other infections

Obstetric factors

Duration of membrane rupture, preterm births, chorioamnionitis , invasive procedures during labour and delivery have all been associated with the increased risk of perinatal transmission.

DIAGNOSIS OF HIV1 IN INFANTS

Laboratory diagnosis of HIV1 infection in infants is complicated by the fact that all infants born to infected women are seropositive due to passively acquired maternal antibodies, irrespective of their infection status Sensitive dignostic tests, designed to pick up small amounts of HIV1 antibodies, give positive results in uninfected infants for 12 to

15 months , till they serorevert. The definitive diagnosis using traditional ELISA/ Western Blot can be made only after 18 months of age. Disease progression in infected infants is rather rapid with most affected infants developing AIDS by 4-5 years of age, with 10% to 20% mortality before 12 months of age. Several approaches have been used for early diagnosis of HIV1 infection in newborns. Some of them are classical while others are novel. They could be classified as virologic, molecular and immunologic depending upon the method used. These methods will remain the standards for diagnosis in infants. Use of dried blood spot specimens for PCR further increases practical utility of these methods.

Virus culture: - detection of culturable virus in infant is a definitive sign of infection. Separated blood lymphocytes are co-cultured with normal donor lymphocytes and monitored for virus over a period of 2-4 weeks. Reported sensitivity of virus culture has been variable in different studies. Thus, a negative culture may not rule out infection.

HIV1 -1 P24, antigen detection: - Major core protein of HIV1 constitutes almost 40% to 50% of viral protein. Commercial ELISA methods are available for detection of P 24 antigen. Specificity of the assay has been 90% to 100%, false positives usually occurring soon after birth. Maternal antibodies complexed with free P²⁴ may be passively transferred in some infants and could contribute to positivity in absence of infection.

HIV1 DNA detection: With the advent of polymerase chain reaction, HIV1 proviral DNA could be detected to low levels of few molecules. A method was developed to detect HIV1 DNA in cells and was applied to early diagnosis in infants. This direct detection of HIV1 DNA has high sensitivity and specificity when done appropriately and has been found to be very useful. Pro viral DNA in infant blood could be detected in about 30% to 35% of infected infants within one week after birth. Sensitivity of detection increased with age and after one month almost all infected infants could be diagnosed (90%-100%).^{31, 32} this technique has also been applied to dried blood spot specimens with considerable success³³. High sensitivity, specificity and convenience of this approach could be particularly useful for early diagnosis in infants.

HIV1 RNA detection: Virus RNA quantitation methods are designed for prognosis and monitoring effectiveness of antiviral therapy in HIV1 infected patients. The methods have been utilized to examine viral load dynamics in infants. Incidentally its use as a method to diagnose HIV1 infection is very promising. Comparative analysis of DNA and RNA detection has indicated that viral RNA detection is somewhat more sensitive than DNA detection, especially during early periods after birth^{32, 34}. High sensitivity of RNA detection is apparently due to significantly high viral load observed in infants soon after birth.

Enzyme linked immunospot assay (ELISPOT) and In vitro antibody production (IVAP): - ELISPOT and IVAP both directly or indirectly detect either antibody secreting B cells or soluble HIV1 –antibody produced by cells during incubation of infant peripheral mononuclear cells (PBMCs). They are based on the knowledge that of all infants born to seropositive mothers, only infected infants have HIV1 – antibody secreting B cells.

Ig G capture EIA: - A simple EIA could distinguish infected and seroreverting infants at or after 6 months of age. The sensitivity of the method was >90% and specificity was 100%. This assay has great potential to be used as a diagnostic tool in infants 6 months of age or older in areas of the world where RNA/DNA based diagnostic tests may not be available due to cost and complexity.

HIV1 –specific Ig A: - It was recognized that although Ig G crosses placenta, Ig A is not transferred from mother to infants during gestation. Therefore, detection of HIV1 – specific Ig A in infants may be suggestive of HIV1 infection.³⁶ highly sensitive nucleic acid amplification methodology, in particular DNA and RNA PCR, has allowed to diagnose all infected infants within 2-3 months after birth.

**GLOBAL VIEW OF PREVENTION OF MOTHER TO CHILD
TRANSMISSION³⁷**

According Dr. Marc Lallemand a global overview of HIV1 perinatal prevention touching upon the knowledge available on the timing of and the factors associated with transmission. This knowledge provides clues to determine the target window of time and types of interventions.

Anti retrovirals

Various studies were undertaken to identify and establish prevention of Mother to child transmission of HIV1 using anti retroviral agents like Nevirapine and Zidovudine/Lamivudine. Preclinical study in adult chimpanzees showed Nevirapine prevents MTCT. The cohort study in Durban, South Africa, and randomized clinical trials in Kenya have shown that Infants born to HIV1 positive mothers and breast fed for 3 months have shown 44% MTCT of HIV1. It was conducted to establish MTCT through breast milk. The ACTG 076 trial in USA categorically demonstrated the usefulness of antiretroviral drug Zidovudine (ZDV) in preventing vertical transmission MTCT in developed countries. ACTG 076 study was the first demonstration that it is possible to reduce MTCT with antiretroviral drugs in Non-breast feeding population. ACTG 250 trials in USA and Puerto Rico and HIV1NET006 trials in Uganda showed Nevirapine has properties that suggest that it could be useful in preventing MTCT of HIV1. Nevirapine is rapidly absorbed and has long half life. A single oral dose of Nevirapine to women during labour and to their infants shortly after birth maintains the neonate's serum levels of Nevirapine above 100ng/mL (10XIC50) for seven days.

HIV1NET 012 (USA) it was a comparative study showed a simple Nevirapine regimen significantly reduce the MTCT of HIV1 compared with a short course Zidovudine regimen. The reduction in the risk of HIV1 transmission was maintained for 12-18 months in a breast feeding population. HIV1NET 023 (South Africa and Zimbabwe) aimed at to study the role of Nevirapine in preventing HIV1 transmission via breast milk. SAINT (South Africa) showed a simple Nevirapine regimen was as effective as a more complex Zidovudine/ Lamivudine regimen during the first eight weeks of life. PACTG 316 (USA and Europe)– It is follow up of ACTG 250 trial showed

The MTCT rates with simple Nevirapine regimens are reproducible. The benefits of Nevirapine regimens greatly outweigh any theoretical concerns related to the development of drug resistance. Nevirapine was added to WHO Model List of Essential drugs for MTCT in 1999.

Nevirapine regimen is superior in lowering transmission risk by decreasing plasma HIV1 RNA concentration after single dose.⁵⁰ It is active immediately against intracellular and extracellular virus.⁵¹ And does not have to be taken up by the cell and metabolized to its active form. Therefore Nevirapine could be more effective than Zidovudine when given close to the time of exposure and may have had more striking effects in decreasing viral load in colostrums and early breast milk samples. Nevirapine also has a long life compared with Zidovudine and needs to be administered to the babies only once to maintain a plasma drug concentration more than 10 times the IC₅₀ for seven days. Further, the variability of drug concentrations during the first week of life would be expected to be much less than that seen with Zidovudine,⁵² which has a short half-life and requires multiple dosing to maintain virucidal concentrations. Therefore, maintenance of an effective prophylactic drug concentration during the first week of life, when additional HIV1 exposure may occur through breast milk, may be important in explaining relative efficacy of Nevirapine compared with Zidovudine in breast feeding population. Single dose Nevirapine given to the mother and the baby is likely to be one of the few deliverable and sustainable strategies for prevention of perinatal HIV1 transmission in resource poor settings. HIV1 has so far defeated the best efforts of vaccine scientists because the virus evades and undermines the immune system. If HIV1 infection cannot currently be prevented, the aim should be to reduce the virus spread and the severity of illness it causes. The current drug regimens can dramatically suppress HIV1 in patients, but none of these agents can completely eliminate the virus. Even after therapy forces HIV1 in the blood down to undetectable levels, the virus still lurks elsewhere ready to storm back if given chance. Drugs already on the market take aim at the virus's envelope protein and the T cells chemokine motif receptors to block viral entry into the cells, and try to inhibit HIV1's reverse transcriptase to halt replication, integrase to prevent integration into cell genome, protease to maturation of viral proteins.⁴⁴

The scientists all over the world are trying to eradicate HIV by considering various intracellular targets to hit. At a minimum, erasing HIV1 from the body would require inducing infected dormant T cells to make new virus or viral proteins –actions that would invite attract by the drug or immune system. Such treatments should be given together with standard drugs that block cell-to- cell spread of the virus.

SOME POTENTIAL THERAPEUTIC TARGETS IN FUTURE

Viral infectivity factor (VIF):- A cellular protein called A3G responsible for mutations in genes. Inhibition of VIF inhibits mutations.

Lense epithelium derived growth Factor (LEDGF):- It helps in integrase to splice HIV1 DNA into the cell genome. Inhibition of LEDGF reduces HIV1 replication.

Chromatin: - .It is a complex DNA and protein that compasses chromosomes. It activates synthesis of HIV1 proteins and mask HIV1 susceptible to attack

Viral protein U (VPU):- HIV1 infected cells tether newly made virus to surface but VPU sets it free. A VPU inhibitor should keep the virus from spreading to other cells.⁴⁵

CONCLUSION

AIDS is a chronic disease caused by infection with Human immune deficient virus (HIV1). HIV1 is highly mutable virus hence vaccines are not effective against it. It is one of the most dreadful disease in the world. New evidence suggests that intensifying control of HIV1 replication by hitting new viral or cellular targets could be helpful. Prevention of HIV infection from mother to fetus is the major challenge in the field of pharmacy and medicine. Survey suggests that there is a wide scope for drug design for antiretroviral drugs for prevention of HIV infection from mother to fetus

Categories	Factors	Interventions
Mother	-advanced stage of disease -impaired immunity -micronutrient deficiencies e.g. Vit A	-decrease viral replication with antiretrovirals e.g. AZT -boost maternal immune response to HIV1 by giving antibodies or a vaccine -give Vitamin A supplement ,which could be efficacious
Placenta	- Transmission unclear, but could occur through initial infection of the trophoblast, then endothelial Cells, allowing virus to enter fetal blood stream.	-Preventing and treating STDs- avoid causes of chorioaminonitis such as smoking or drug use.
Fetus	-little clarity re fetal cell HIV1 susceptibility which is speculated to vary during gestation.	- could give antiretrovirals or ant HIV1 antibodies which cross the placenta easily to mother
Labor and birth process	-exposure of infant's skin and mucosal surfaces to mother's blood and secretions, the risk of which related to cervico-vaginal viral load -membrane rupture several hours before delivery	-reduce viral load in genital tract with antiretroviral or use of local virucides -give local immunization, active or passive -decrease transmission with C-section
New born	-----	-prevent viral replication with pre/ post exposure prophylaxis with antiretrovirals and immunization
Breast feeding	-possible relation to duration of breastfeeding , time of exposure, infectious of the milk, presence of HIV1 antibodies in the milk	-avoid breastfeeding

Table 1: Factors Responsible For Mother to Child Transmission

**Prevention of mother to child transmission of HIV
Regimens for Prevention of Perinatal Transmission**

Trial	Regimen	Transmission	Efficacy
ACTG 076 ⁴³	Antenatal:ZDV 100mg 5times/day, starting 14-34wk Labour : ZDV IV loading 2mg/kg/ followed by 1mg/kg/hr. Infant :ZDV Syrup 2mg/kg qid X 6weeks No breast feeding	ZDV --8% Placebo-26%	68% - -
Thai ⁴⁶	Antenatal: ZDV 300mgbid, starting 36wk. Labour : ZDV 300mg 3hourly Infant : None. No breast feeding	ZDV --9% Placebo-19%	51% - -
Ivory Coast ⁴⁷	Antenatal: ZDV 300mgbid, starting 36wk. Labour : ZDV 300mg 3hourly Infant : breast feeding allowed	ZDV --16% Placebo-25%	37% -
PETRA ⁴⁸	Gr 1- Antepartum :ZDV+ 3TC start 36 wk Post partum+Infant :ZDV +3TC X 1 wk Gr 2- Labour : ZDV +3TC Post partum+Infant :ZDV +3TC X 1 wk Gr 3- Labour : ZDV +3TC Gr 4- Placebo Breast feeding allowed in all groups.	Gr 1- 25% Gr 2- 11% Gr 3- 18% Gr 4- 17%	42% 37% - -
DITRAME ⁴⁹ .	Antenatal : ZDV 300mg bid, starting 36-38wk. Labour : ZDV 600mg 3hourly Post partum: ZDV 300mg bid X 1 wk. Infant : breast feeding allowed	ZDV -18% Placebo-26%	38% - -
HIV1NET012 ⁴⁸ .	Gr 1- Labour :Nevirapine +200mg at onset Infant :Breast fed, Nevirapine 2mg/kg Single dose Gr 2- Labour :ZDV600mg at onset later 300mg 3 hourly till delivery Infant :Breast fed, ZDV 4mg/kg bidX1 wk	Gr 1- 13% Gr 2- 25%	47% -

Table 2: Regimens for Prevention of Perinatal Transmission

ZDV- Zidovudine

3TC- Lamivudine

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