MATERNAL AND FETAL OUTCOMES OF PREGNANT WOMEN ON ANTIRETROVIRAL (AVR) THERAPY AT DR GEORGE MUKHARI HOSPITAL:

[A CASE-CONTROLLED CLINICAL STUDY]

DR M.P. MAVUKANI

NOVEMBER 2009

OBSTETRICS AND GYNAECOLOGY

DISSERTATION

DR M.P. MAVUKANI
(MBCHB)

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY
FACULTY OF MEDICINE
SCHOOL OF HEALTH SCIENCES
UNIVERSITY OF LIMPOPO [MEDUNSA CAMPUS]

2009

MATERNAL AND FETAL OUTCOMES OF PREGNANT WOMEN ON ANTIRETROVIRAL (ARV) THERAPY AT DR GEORGE MUKHARI HOSPITAL: A CASE-CONTROLLED CLINICAL STUDY

BY

M.P. MAVUKANI

RESEARCH DISSERTATION

Submitted in fulfillment of the requirements for the degree of

MASTER OF MEDICINE [MMed]

in

OBSTETRICS & GYNAECOLOGY

in the

FACULTY OF HEALTH SCIENCES

(School of Medicine)

at the

UNIVERSITY OF LIMPOPO

SUPERVISOR: DR L. MATSELA

CO-SUPERVISOR: PROF O.A. TOWOBOLA

2009

DECLARATION

I declare that the dissertation hereby submitted to the University of Limpopo, for the degree of MMed (Obstetrics & Gynaecology) has not previously been submitted by me for a degree at this or any other University; that it is my work in design and execution, and that all materials contained herein has been duly acknowledged.

M.P. MAVUKANI (DR) — Initials & Surname (Title)

NOVEMBER 2009 — Date

Student Number: **8715505**

DEDICATION

The work of this study is dedicated first and foremost to the Almighty God, for providing me the strength and fortitude to go through this study. I also dedicate the work to the entire staff of Obstetrics and Gynaecology of Dr George Mukhari Hospital [DGMH] for their enormous support during this study. I give special thanks and dedication to my family for their constant encouragement during the study.

The work of this study is also dedicated to the patients who made themselves and their babies available, from whom the entire information in this dissertation had been compiled.

TABLE OF CONTENT

LIST OF TABLES

FIGURE

LIST OF ABBREVIATIONS

ABC	**Abicar**
ALT	**Alanine aminotransferase**
ALP	**Alkaline phosphate**
AST	**Aspartate aminotransferase**
ART	**Antiretroviral therapy**
ARV	**Antiretroviral**
ACOG	**American College of Obstetrics & Gynecology**
CDC	**Center for Disease Control and Prevention**
d4T	**Stavudine**
ddi	**Didanosine**
ddc	**Zalcitabine**
C/S	**Caesarean Section**
DGMH	**Dr George Mukhari Hospital**
FBC	**Full Blood Count**
FTC	**Emtricitabine**
EFV	**Efavirenz**
LDH	**Lactate dehydrogenase**
LFT	**Liver Function Test**
HIV	**Human Immunodeficiency Virus**
3TC	**Lamivudine**
MAC	**Mycobacterium avium complex**
NVP	**Nevirapine**
PIS	**Protease Inhibitors**
MTCT	**Mother-to-child Transmission**
PMTCT	**Prevention of mother-to-child Transmission**
PCP	**Pneumocystic Carini**
PACTG	**Paediatric AIDS Clinical Trial Group**
SAINT	**South African Intrapartum Nevirapine Trial**
TFV	**Tenofovir**
VCT	**Voluntary Counseling and Testing**
ZDV	**Zidovudine**
HAART	**Highly Active Antiretroviral Therapy**

ABSTRACT

MATERNAL AND FETAL OUTCOMES OF PREGNANT WOMEN ON ANTIRETROVIRAL (ARV) THERAPY AT DR GEORGE MUKHARI HOSPITAL: A CASE-CONTROLLED CLINICAL STUDY.

OBJECTIVE:

The objectives of the study were:

1) To determine the pattern of toxicity/side-effects among women using Highly Active Antiretroviral Therapy (HAART) in the perinatal period in comparison with women who were treated with intra-partum prophylaxis of nevirapine at the time of delivery.
2) To evaluate the effects of either approach of therapy on maternal and fetal outcomes.

METHODOLOGY:

STUDY DESIGN

The department of Obstetrics and Gynaecology has begun to administer HAART to pregnant women identified for ARV programme. These women were counseled and recruited prospectively for the study. The study involved comparison of pregnancy outcomes between women identified for HAART and those who were HIV infected but who only required intra-partum prophylaxis in labour to prevent mother-to-child transmission of HIV with nevirapine.

INCLUSION/EXCLUSION CRITERIA

For inclusion to the study a pregnant woman would have undergone voluntary counseling and testing and would have been identified to be HIV positive. The woman must have booked and accepted to attend antenatal clinic at Dr George Mukhari hospital (DGMH). She would also have indicated willingness to deliver her baby at this hospital. Any woman diagnosed with multiple pregnancy and any pregnant woman who had started (ARV) prior to her first visit to DGMH, was excluded from the study. Mothers younger than 18 years of age and those who did not give consent to participate in the study were also excluded.

SETTING

This study was conducted initially at the antenatal clinic of Dr Gorge Mukhari hospital, where the pregnant HIV positive women were identified and subsequently at the labour ward of the hospital when the women reported for delivery.

SAMPLE SIZE

HIV-infected pregnant women were classified into two groups: those with $CD4^+$ cell counts greater than 200 cells/mm^3 and who did not require ARV drugs and women with $CD4^+$ cell counts less than 200 cells/mm^3.

Two hundred patients were enrolled for the study. Thirty-nine (39) patients were lost to follow-up, leaving 161 patients who successfully completed the study.

PROCEDURE

Gestational age was confirmed by dates and by sonar. Laboratory evaluation included: Full Blood Counts (FBC), Liver Function Tests (LFT), $CD4^+$ Count, Viral Load at the time of recruitment and at the time of delivery. Any pregnant woman who presented with Stage IV (WHO Staging) or $CD4^+$ cell count < 200 cells/mm3 placed on therapy of:

i) Stavudine (d4T) – 400 mg every 12hours (30 mg every 12 hours if 60kg).

ii) Lamivudine (3TC) – 150 mg every 12 hours.

iii) Nevirapine (NVP) – 200 mg daily for 2 weeks followed by 200 mg every 12 hours.

Women with early stage of HIV infection and with $CD4^+$ cell count > 200 cells/mm^3 were given Nevirapine 200 mg per os, were required to take the tablets at the onset of labour and nevirapine syrup (2 ml/kg) was given to the baby within 72 hours after delivery.

All mothers were counseled about the risks of breastfeeding. Mothers whose $CD4^+$ cell counts dropped below 200 cells/mm^3 after having been recruited for the study, were counseled about starting HAART.

RESULTS

Out of the 200 women enrolled in the study, 39 patients were lost to follow-up while 161 women completed the study. Ninety-five women received nevirapine and 66 received HAART. Nine women (13.6%) on HAART developed abnormalities in liver function test. Five patients (7.6%) of those on HAART also tested positive for syphilis whereas all those who received nevirapine alone tested negative for syphilis. Two patients on HAART developed puerperal sepsis as compared with 3 patients in the nevirapine only group. There was one early neonatal death among the group that received HAART. Four babies (6.1%) who were delivered by mothers on HAART were HIV positive by PCR analysis. This is in comparison with 11 babies (11.6%) who were HIV positive and who were delivered by mothers who received prophylactic nevirapine alone [Relative Risk: 1.9; 95% CI = 1.25 – 2.72].

CONCLUSION

The obstetric outcomes were not adversely affected when women who were on HAART treatment were compared with those who received only intra-partum nevirapine in respect of preterm delivery, haematological indices and mode of delivery. Liver function tests were negatively affected among pregnant women who were being treated with HAART in contrast to women who did not receive HAART medication. More importantly, this study demonstrates and emphasizes

the usefulness of HAART in reducing the rate of mother-to-child transmission of HIV infection.

INTRODUCTION

Human Immunodeficiency virus (HIV) infection has compounded the obstetric problems of many overstretched and under resourced health facilities such as the situation at Dr George Mukhari hospital (DGMH). In sub-Saharan Africa many pregnant women with unknown HIV status, present late in gestation for antenatal care. This obstetric scenario possibly accounts for the increasing burden of maternal as well as fetal morbidity, especially among those who could have benefitted from perinatal prophylaxis or treatment with antiretroviral drugs.

Among those that present early in pregnancy, voluntary counseling and testing for HIV infection have become part of the routine services at the antenatal clinic of this hospital. Once the women have been tested and found to be positive for HIV, they become eligible for possible use of highly active antiretroviral therapy (HAART), depending on the level of their $CD4^+$ cells count as well as their viral load. Those who qualify for immediate antiretroviral therapy, often have to take a cocktail of antiretroviral drugs over several weeks before they go into labour. Pregnant women whose $CD4^+$ cells count were more than 200 cells/mm3 and with viral load less than 1000 copies were excluded from immediate antiretroviral therapy with HAART but were given nevirapine as an intra-partum

prophylaxis for the prevention of mother-to-child transmission during delivery.

The concern of many obstetricians is the need to establish the effects of HAART which is often taken over several weeks before delivery and nevirapine which is given as an intra-partum prophylaxis, on the eventual outcome of pregnancy. The low compliance rate among those women who are taking HAART during pregnancy is an indication of adverse effects on the women. It becomes ethically and professionally important to evaluate the effects of these drugs on both the pregnant mothers and their babies.

It is against this background that I have decided to evaluate the use of HAART during pregnancy, on the eventual effects on both the mothers and the fetuses.

LITERATURE REVIEW

By the end of 2003, a World Health Organization (WHO) report on the state of the HIV pandemic around the world estimated that 40 million people world-wide, most of whom were reported to be in sub-Saharan Africa **(1)** were living with HIV infection. In South Africa alone, more than 5 million people are estimated to be infected with HIV and about half of this number are women of child-bearing age **(2).**

The implications of this infection among pregnant women are enormous, with higher maternal morbidity and mortality and the possibility of transmitting the infection to the newborn baby. Observational studies have shown that HIV infection is associated with varying rates of adverse pregnancy outcomes, such as increased spontaneous abortions, stillbirths, perinatal and infant mortality, intrauterine growth restriction, low birth weight and chorioamnionitis **(3)**. HIV infection also reduces fertility, irrespective of the stage of the infection. In Uganda, HIV infected women have lower pregnancy rate and more pregnancy losses than uninfected women **(3)**.

The possibility of adverse effects associated with exposure to short term HAART for HIV infected mother during pregnancy calls for special concern. It has been shown that the rate of premature delivery is increased where combination therapy with protease inhibitors was received in early pregnancy **[4, 5]**. Protease inhibitors have also been associated with an increased risk of maternal glucose intolerance and pre-eclampsia **[6]**.

Enhanced toxicity of nevirapine has been noted among women with $CD4^+$ lymphocyte counts >250 cells/μl at treatment initiation and among pregnant women on long term didanosine and stavudine. These drugs should be avoided in such situations if alternatives are available. Efavirenz has been associated

with birth defects in monkeys and several cases of neural tube defects have been reported in humans after first trimester exposure and should therefore, be avoided during the first trimester [6].

Mortality among children born to HIV infected mothers in Sub-Saharan Africa is substantially higher than among children born to HIV un-infected mothers [7]. While adverse effects of therapy have been highlighted in many reports, the pattern and severity of adverse effects are reported to be dependent on the class of antiretroviral agents used in the treatment of HIV/AIDS patients. Neither the use of monotherapy regimen such as nevirapine (a non-nucleoside reverse transcriptase inhibitor) nor the use of a cocktail (Triple regimen: Nevirapine, Lamivudine and Stavudine) is free from adverse effects. Some of these adverse effects can be life-threatening such as drug eruptions with Nevirapine and Abicar, pancreatitis with Didanosine or lactic acidosis with the nucleoside analogues –Lamivudine and Stavudine [8]. Other side effects often reported are liver and haematological abnormalities.

Although antiretroviral medications have the potential to improve health and extend the life of HIV-infected women, they may also result in unwanted adverse effects that may also compromise successful pregnancy and delivery.

HIV INFECTION IN PREGNANCY

HIV replicates in most individual cells at high rates from the time of acquisition. The virus which must transcribe its genomic RNA into DNA in order to integrate into the host $CD4^+$ and lymphocyte is prone to transcriptional errors. Some mutations are deleterious, whereas others may confer advantage to the progeny virus under certain selective conditions, such as the presence of antiretroviral drugs. Spontaneous development of mutations in wild-type HIV may produce a viral strain with resistance to any one or two antiretroviral agents. Some individual acquire infection with drug-resistant HIV, which may be overgrown over time by wild-type virus. However, these individuals may retain a sub-population of drug-resistant virus that could rapidly reemerge under selective drug pressure.

The concern about HIV in pregnancy is about the progression of maternal disease and mother-to-child-transmission. Pregnancy does not adversely affect HIV progression or survival. Dual infection with HIV and malaria has been associated with increased risk of maternal, perinatal and early infant deaths. Although HIV RNA levels seem to remain stable during pregnancy, some studies have shown increased viral load in the post-partum period [3].

In developed countries, with easy access to specialist care, HIV is a rare cause of maternal mortality. In contrast to this, HIV infection is an important contributing cause of maternal mortality in Africa. In areas of high HIV prevalence, the infection has become a leading cause of maternal mortality. Several reports from Southern African countries have shown this trend, including maternal mortality rates that are five-fold higher in HIV infected women compared with uninfected women. In South Africa's report on Confidential Enquiries into Maternal Deaths [2002 – 2004], HIV/AIDS was reported to be the leading cause of maternal deaths and was responsible for 20.1% of all deaths – higher than any other direct obstetric cause. In the absence of treatment 15 – 45% of HIV infected pregnant women will pass the infection to their infants. Five to ten percent of these infants would have been infected across the placenta, 10 – 20% infected from exposure at or around the time of delivery and 5 – 20% being infected through breast feeding. The later mode of transmission is thought to be responsible for up to 50% of HIV-infected children in Africa **[9]**.

The table below shows the risk factors for increased perinatal HIV transmission/vertical transmission.

Table 1: Risk factors for increased perinatal HIV transmission.

Type of Risk	Examples
VIROLOGIC/IMMUNOLOGIC	- Maternal plasma HIV-1 viral load - Maternal cervico-vaginal HIV-1 levels - HIV co-receptor mutation - Multi-Drug resistant HIV genotype - Maternal $CD4^+$ T-Lymphocyte
MATERNAL	- Breastfeeding - Illicit drug use - Increased base-line weight - Cigarettes smoking - Vitamin A deficiency - Malnutrition
OBSTETRIC	- Vaginal delivery - Prolonged membrane rupture (>4 hrs) - Fetal scalp electrode use - Episiotomy - Vaginal laceration - Chorioamnionitis - Active genital ulcer disease - Amniocentesis

MATERNAL HIV – PLASMA VIRAL LOAD (PVL)

A report by Garcia and Co-workers [10] had stated that the most predictive risk factor for vertical transmission of HIV was the plasma viral load. In their study of 552 HIV infected pregnant women, 321 used ART. They reported that perinatal transmission rates were 0% when HIV-1 RNA was less than 1000

copies/ml, and transmission rates increased stepwise as maternal viral load increased: 20% rate with viral load of 1,000 – 10,000 copies/ml, 24.1% with 10,001 – 50,000 copies/ml, 31.6% with 50,001 – 100,000 copies/ml and 63.3% with > 100,000 copies/ml.

Another study by Sperling et al [11] showed that perinatal transmission, albeit at an extremely low rate, did occur in mothers in the lowest quartile and even if viral load was below the quantitative limit of the assay used. Because no upper or lower threshold can be described, viral load data, although useful in assessing the risk, it cannot definitively predict whether transmission will or will not occur. Low maternal $CD4^+$ cell counts at the time of delivery have been associated with increased risk of transmission [12]. However, this association was established before the availability of viral load measurements. A low $CD4^+$ cell counts may be a surrogate marker of high maternal viral burden.

DELIVERY RELATED FACTORS

Prolonged rupture of fetal membrane (≥ 4 hrs.), which increases newborn exposure to maternal blood/body fluids, has been shown to increase the risk of vertical transmission. Other delivery related factors such as placental abruption, use of fetal scalp electrode, performing an episiotomy, labour induced vaginal

lacerations, chorioamnionitis and presence of ulcerative sexually transmitted diseases in the maternal genital tract may similarly expose the newborn to maternal blood and secretions.

High levels of HIV in the cervico-vaginal fluid have also been shown to increase the risk of vertical HIV transmission. Elective caesarean section (C/S) performed before rupture of membranes decreases the risk of vertical transmission of HIV. A meta-analysis by the International Perinatal HIV Group **(13)** of 15 prospective cohort studies examined mode of delivery and the risk of vertical HIV transmission in approximately 8,000 HIV–infected pregnant women. The results showed a significantly lower risk of vertical transmission after an elective C/S compared with either vaginal delivery or C/S performed after membranes had ruptured. ART reduced transmission rates to 7.3% in HIV-infected mothers who did not undergo elective C/S **(13)**.

Mothers who had an elective C/S and took ART had a rate of transmission of only 2.0% **[13]**. The benefits of elective C/S may be lost if maternal viral load are substantially suppressed at the time of delivery. HIV-infected pregnant women have higher rates of post-operative complications and infections, especially when such procedures are performed in resource poor countries. The usefulness

of elective C/S in countries where potent ART options are available may be reserved for those HIV-infected pregnant women who have uncontrolled viral loads at the time of delivery.

BREASTFEEDING

Breastfeeding is a major post-partum risk of HIV transmission. It is responsible for up to 50% of HIV infections in children in Africa **(14)**. It has been found that the risk of HIV transmission from breast feeding is 14% from mothers with established HIV infection and 29% from mothers who acquire HIV after birth **(15)**. Viral loads in breast milk correlate with plasma viral loads and are at their peak during and just after seroconversion. Most HIV infections of infants from breast feeding occur during the first 6 weeks of life, with a lower risk thereafter. Transmission of HIV by breast feeding is increased in the setting of low maternal $CD4^+$ cell counts, mastitis and prolonged exposure. Antibodies to HIV in breast milk are not protective.

T-Helper cell responses to HIV-specific antigen in newborns may also play an important role in determining whether infants exposed to HIV in all stages of pregnancy and via breast feeding will become infected. A recent study in Africa found no HIV transmission to infants in whom there was early development of

T-Helper cell responses to HIV envelope peptides, whereas there was 17% transmission in those infants without such a response [16]. Vitamin A deficiency and malnutrition can cause an immune deficiency and disruption of mucosal integrity and are associated with increased vertical transmission of HIV.

HOW DOES HIV AFFECT PREGNANCY AND PREGNANCY OUTCOMES?

Observational studies [3, 5] have shown that HIV infection is associated with varying rates of adverse pregnancy outcomes, such as increased spontaneous abortions, stillbirths, perinatal and infant mortality, intrauterine growth restriction, low birth weights and chorioamnionitis. HIV infection may also reduce fertility at any stage of the infection.

PRECONCEPTION COUNSELLING AND CARE FOR HIV-INFECTED WOMEN OF CHILD-BEARING AGE

The Center for Disease Control and Prevention (CDC), the American College of Obstetrics and Gynecology (ACOG) and other national organizations recommend offering all women of child bearing age the opportunity to receive counseling and care as a component of routine primary medical care [17, 18]. The purpose of preconception care is to improve the health of the woman prior to

conception and to identify the risk factors for adverse maternal and fetal outcomes. Preconception counseling and education should be targeted to the patients' individual needs and treating or stabilizing medical conditions to optimize fetal and maternal outcomes.

It should not be a single visit but an ongoing process of care and intervention integrated into primary health care, to address the needs of women during the different stages of reproductive life. It is important that preconception care is integrated into routine health visits because most of the pregnancies are not planned. HIV healthcare professionals who routinely care for women of reproductive age, play an important role in promoting preconception health care. HIV infected women have specific needs over and above those of the general reproductive age women who seek preconception care.

THE FOLLOWING COMPONENTS OF COUNSELING AND CARE ARE SPECIFICALLY RECOMMENDED FOR HIV INFECTED WOMEN [19]

a) Select effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy. Providers should be aware of potential interactions of antiretroviral drugs with hormonal contraceptives that could lower contraceptive efficacy.

b) Give counseling on safe sexual practices that prevent HIV transmission to sexual partners and protect women from acquiring sexually transmitted infections (STI) and the potential to acquire more virulent or resistant HIV strains.

c) Counsel on eliminating alcohol, illicit drug use and cigarette smoking.

d) Educate and counsel women about risk factors for perinatal HIV transmission, strategies to reduce those risks and the potential effects of HIV or its treatment on pregnancy course or outcomes.

e) When prescribing antiretroviral treatment to women of child-bearing potential, considerations should include the regimen's effectiveness for treatment of HIV disease and the drug's potential for teratogenicity should pregnancy occur. Women who are planning to get pregnant should strongly consider the use of antiretroviral regimens that do not contain efavirenz (EFV) or other drugs with teratogenic potential. In addition, the effectiveness of a regimen in preventing mother to child transmission should be considered.

f) Attain stable, maximally suppressed maternal viral load prior to conception in women who are on antiretroviral therapy and want to get pregnant.

g) Evaluate and control therapy-associated side-effects that may adversely impact maternal and fetal outcomes (e.g. hyperglycaemia, anaemia and hepatic toxicity).

h) Evaluate for appropriate prophylaxis for opportunistic infections and administration of medical immunizations (e.g. Influenza, pneumococci or hepatitis-B vaccines) as indicated.

i) Encourage sexual partners to receive HIV testing and counseling and appropriate HIV care if infected.

j) Counsel regarding available reproductive options such as intrauterine or intra-vaginal insemination that prevent HIV exposure to an uninfected partner, expert consultation is recommended.

k) Although the benefit of breast feeding is well recognized, this must be balanced against risk of HIV transmission to the baby.

ANTEPARTUM CARE

Medical care of an HIV-infected woman requires co-ordination and communication between HIV-Specialists and obstetric care providers. Several counseling sessions should include current knowledge regarding risk factors for perinatal transmission. Cigarette smoking, illicit drug use, genital tract infections and unprotected sexual intercourse with multiple partners during pregnancy have been associated risk for perinatal HIV transmission **(19)**. Discontinuation of cigarette smoking and drug use, treatment of genital tract infections and use of condoms

with sexual intercourse during pregnancy may also reduce the risk of perinatal transmission. HIV-infected mothers should refrain from breast-feeding as it causes postnatal transmission of HIV. The initial assessment of an HIV-infected pregnant woman should include the assessment of HIV disease status and recommendations regarding antiretroviral treatment or alterations of her current antiretroviral regimen.

THE INITIAL ASSESSMENT SHOULD INCLUDE THE FOLLOWING:

1) Evaluation of the degree of existing immunodeficiency as determined by past and current $CD4^+$ cell counts.
2) Evaluation of the risk for disease progression and perinatal HIV transmission as determined by current plasma HIV RNA copy number.
3) Assessment of the need for prophylaxis against opportunistic infections such as pneumocystic carinii pneumonia (PCP) or mycobacterium avium complex (MAC).
4) Baseline evaluation with complete blood count, as well as renal and liver function testing.
5) History of prior and current antiretroviral therapy.
6) History of prior antiretroviral drug use for prevention of perinatal HIV transmission.
7) Results of prior and current HIV antiretroviral drug resistance studies.

8) Assessment of supportive care needs.

WHO STAGING SYSTEM FOR HIV INFECTION AND DISEASE IN ADULTS AND ADOLESCENTS [20]

CLINICAL STAGE 1

1 Asymptomatic

2 Generalized lymphadenopathy

Performance scale 1: Asymptomatic, Normal activity.

CLINICAL STAGE 2

1 Weight loss: < 10% of body weight.

2 Minor mucocutaneous manifestations (Seborrhoeic dermatitis, purigo, fungal nail manifestations, recurrent oral ulcerations and angular cheilitis).

3 Herpes zoster within the last 5 years.

4 Recurrent upper respiratory tract infections (i.e. Bacterial sinusitis).

And/or performance scale 2: Symptomatic, Normal activity.

CLINCAL STAGE 3

1 Weight loss > 10% of body weight.

2 Unexplained chronic diarrhea, > 1 month.

3 Unexplained prolonged fever (intermittent/constant) > 1 month.

4 Oral candidiasis (Thrush).

5 Oral hairy leukoplakia.

6 Pulmonary tuberculosis.

7 Severe bacterial infections (i.e. pneumonia, pyomyositis).

And/or performance scale 3: Bedridden <50% of the day in the last month.

CLINICAL STAGE 4

1 HIV wasting syndrome.

2 Pneumocystic carinii pneumonia

3 Toxoplasmosis of the brain.

4 Cryptosporidiosis with diarrhea: > 1 month.

5 Cryptococcosis, extrapulmonary.

6 Cytomegalovirus disease of an organ other than the liver, spleen or lymph node (e.g. retinitis).

7 Herpes simplex virus infection, mucocutaneous (> 1 month) or visceral.

8 Progressive multifocal leucoencephalopathy.

9 Any disseminated endemic mycosis.

10 Candidiasis of oesophagus, trachea and the bronchi.

11 Atypical mycobacteriosis, disseminated or pulmonary.

12 Non-typhoid salmonella septicaemia.

13 Extra-pulmonary tuberculosis.

14 Lymphoma

15 Kaposi's sarcoma.

16 HIV encephalopathy.

And/or performance scale 4: Bedridden >50% of the day during the last one month.

General guidelines for the use of antiretroviral drugs [19].

Treatment in pregnancy for the benefit of maternal health is the same as for women who are not pregnant. There are also recommendations for the use of antiretroviral drugs for prophylaxis to prevent perinatal HIV transmission, even in women for whom therapy would not be indicated. If plasma HIV RNA is detectable, antiretroviral drug resistance studies should be performed before starting antiretroviral therapy or prophylaxis. If HIV is diagnosed late in pregnancy, therapy should be initiated while awaiting results of resistance testing. Maternal toxicities and risks of therapy must be considered, together with additional considerations of the potential impact of such therapy on the outcome of pregnancy and on the fetus and infant.

Decisions regarding the use and choice of antiretroviral regimen should be individualized based on the following factors:

a) Gestational age of the pregnancy.

b) Antiretroviral treatment recommendations for the health of the HIV-infected woman.

c) The efficacy of the antiretroviral regimens for prevention of perinatal HIV transmission.

d) Known, suspected or unknown effects of particular drugs or regimens on the fetus and the newborn, on the outcome of the pregnancy and for the women.

e) HIV antiretroviral drug resistance studies.

The clinician must discuss the treatment options with the pregnant woman. The final decision regarding the use of antiretroviral drugs is the responsibility of the woman. Results from pre-clinical animal studies and available clinical information about the use of various antiretroviral agents during pregnancy should be discussed with the woman **(19)**. Risks and benefits of antiretroviral therapy should be discussed with the pregnant woman. HIV RNA levels should not be the determining factor when deciding whether to use antiretroviral drugs for the prevention of perinatal transmission.

DISCUSSION WITH THE WOMAN ABOUT INITIATION OF ARV THERAPY SHOULD INCLUDE THE FOLLOWING [19]

(a) Maternal risk for disease progression and the benefits and risks of initiation of therapy for her own health.

(b) Benefit of lowering HIV viral load to reduce the risk of perinatal transmission.

(c) Benefits of antiretroviral prophylaxis, independent of the effect on viral load as well as additive benefit of combination antiretroviral regimens for preventing perinatal transmission.

(d) The possibility of drug resistance, including the need for strict adherence to the prescribed drug schedule to avoid its development, as well as the increased likelihood of development of resistance in the setting of high viral loads with use of non-suppressive therapy.

(e) The limited long-term data for both infant with in utero antiretroviral exposure and for women who temporarily use antiretroviral drugs for prophylaxis against transmission.

Coordination of services among prenatal care providers, primary health care and HIV specialty care providers, mental health services and drug abuse treatment services and public assistance programmes, is essential to ensure adherence of the infected woman to antiretroviral treatment regimens.

EVOLUTION OF ANTIRETROVIRAL TREATMENT & PROPHYLACTIC ANTIRETROVIRAL THERAPY IN PREVENTION OF MOTHER TO CHILD TRANSMISSION

In 1994, the PACTG 076 trial demonstrated that administration of a zidovudine regimen comprised of oral dosing initiated at 14 – 34 weeks of gestation, continuous intravenous infusion during labour and 6 weeks oral dosing to the newborn, reduced mother to child transmission by 67% [21].

Shortened zidovudine regimens that start at 36-38 weeks of gestation (alone or in combination with lamivudine), used oral rather than intravenous dosing during labour, decreased or eliminated postnatal infant dosing have been shown to reduce transmission by 38 – 50%. The Thailand study gave AZT 300 mg orally twice daily starting at 36 weeks gestation. AZT 300 mg p.o. every 3 hours was given intra-partum. No antiretroviral drugs including AZT were given to the mother or infant postpartum. Mother-to-child transmission was reduced by 50% at 6 months. Infants were given formula feeding. Vertical transmission rate was 9.4% with zidovudine versus 18.9% in placebo at 6 months [25].

In Ivory Coast CDC trial – AZT 300 mg p.o. twice daily starting at 36 weeks of gestation was given to the pregnant mothers. AZT 300 mg every 3 hours was given orally. No antiretroviral drugs were given to the infants post-natally. The

infants were breastfed and the vertical transmission rate was 15.7% with zidovudine versus 24.9% in placebo at 3 months. The overall efficacy was 37% **[23, 24]**.

The Ditrame trial **[25]** which was conducted in Ivory Coast and Burkina Faso gave AZT 300 mg p.o. twice daily starting at 36 – 38 weeks of gestation to the pregnant mothers. AZT 600 mg orally was again given at the onset of labour and an additional (AZT) 300 mg p.o. bd. was given during labour. Antiretroviral drugs were given to the infant postnatally for 1 week. Infants were breastfed. Vertical transmission rate was 22.5% in the zidovudine group versus 30.2% in the placebo group. There was a 26% efficacy at 24 months.

In the PETRA study involving South Africa, Tanzania and Uganda – Zidovudine + Lamivudine were given to the mothers from 36 weeks of gestation. The same drugs were given for 7 days post-delivery to the mother and the infant and the infants were breastfed. Vertical transmission rate 14.9% for antenatal/intrapartum/neonatal zidovudine + lamivudine compared with 18.1% for intrapartum/neonatal zidovudine + lamivudine **[26]**.

In another trial in Thailand (ZDV +3TC) – Zidovudine + Lamivudine were given to the mothers from 34 weeks of gestation. Zidovudine was given to the infant for 4 weeks post-delivery. The infant received formula-feeding and the vertical transmission rate was 2.8% at 18 months [27].

$HIVNET_{(012)}$ trial conducted in Uganda used a single dose of nevirapine (NVP), administered to the mother during labour and to the infant 24 hours later in one arm. In the other arm, AZT 600 mg was given orally to the mother at the onset of labour and then AZT 300 mg every 3 hours during labour. The mother received no antiretroviral drugs postpartum. Postpartum, the infant received nevirapine 2 mg/kg doses in 72 hours on the nevirapine arm versus oral AZT 4 mg/kg orally twice daily for 1 week on the zidovudine arm. The infants received breast feeding post-delivery. Vertical transmission rate was 15.7% in the nevirapine arm in comparison with 25.8% in the zidovudine arm. The efficacy was 47% (for infection at 14 to 16 weeks) in the nevirapine treated group and 41% in the zidovudine treated group at 18 months [28, 29].

The SAINT trial (South African Intrapartum Nevirapine Trial) carried out at 11 maternity health institutions in South Africa. Enrollment was either to give single dose nevirapine to the mother intrapartum or zidovudine + lamivudine

intrapartum. The infant received single nevirapine dose of 2mg/kg less than 48 hours postpartum versus zidovudine + lamivudineto both the mother and the infant for 7 days postpartum. The infant was breastfed and others formula-fed. Women who chose to breastfeed, were advised to exclusively breastfeed and were informed of the dangers of mixed feeding. Vertical transmission rate was 12.3% in the nevirapine arm versus 9.3% in the zidovudine + lamivudine arm 8 weeks post-delivery [2].

Currently at our institution (Dr George Mukhari hospital) the policy for the prevention of mother–to-child transmission has changed from when we used to give the mother nevirapine 200 mg at the onset of labour and nevirapine syrup 2 mg/kg body weight to the infant within 72 hours post-delivery to dual therapy. With the dual therapy protocol, the mother receives zidovudine 300 mg p.o. twice daily from 28 weeks gestation and zidovudine 600 mg p.o. stat at the onset of labour plus nevirapine 200 mg also at the onset of labour. The mother continues with zidovudine orally during labour. The infant receives zidovudine syrup twice daily for 7 days post-delivery.

In 2001, the United Nations General Assembly (Special Session) on HIV/AIDS committed countries to reduce the proportion of infants infected with HIV by

20% by 2005 and by 50% by 2010. Achieving this target urgently requires an increase in access to integrated and comprehensive programmes to prevent HIV infection in infants and young children. Such a programme should include:

a) Interventions focusing on prevention of HIV infection among women and their partners.

b) Preventing un-intended pregnancies among HIV infected women.

c) Prevention of HIV transmission from HIV infected women to their children.

d) The provision of treatment, care and support for women living with HIV/AIDS, their children and families.

WHO convened a technical consultation on antiretroviral drugs and the prevention of mother-to-child transmission of HIV infection in resource limited settings in Geneva, Switzerland [5 – 6 February 2004] **(30)**. Information was reviewed in the context of the rapid expansion of ARV treatment in resource-constrained settings using standardized and simplified drug regimens. Women may receive ARV drugs during pregnancy as part of combination regimens for their own health or as prophylaxis to prevent mother-to-child transmission of HIV. ARV treatment for women benefits their own health but at the same time can prevent/reduce mother-to-child transmission of HIV.

Therapeutic decisions relating to ARV treatment for women should be based on their need and eligibility for such treatment. ARV regimens for women of child bearing age should be selected considering the possibility of planned or unplanned pregnancy and considering that ARV drugs may be taken in the first trimester of pregnancy, particularly in the first 10 weeks of pregnancy during which organogenesis may be taking place and hence predispose the fetus to teratogenic effects of the ARV drugs.

Short courses of ARV drugs started late in pregnancy or during labour reduce the risk of vertical transmission of HIV two to three-folds and in 2000, WHO recommended that they should also be included in programmes to prevent mother-to-child transmission [30]. The simplest regimen consisted of single dose nevirapine at the onset of labour plus a single dose for the infant soon after birth. Programmes for preventing mother-to-child transmission using this regimen have been found to be feasible and acceptable. Other programmes used a regimen of zidovudine alone or in combination with lamivudine.

The efficacy of zidovudine plus single dose maternal and infant nevirapine has also been examined and is more efficacious than single drug regimens. Longer drug regimens are more efficacious than shorter regimens. Triple combination

regimens are widely used in industrialized countries for preventing mother-to-child transmission in women who do not yet require ARV treatment for their own health, but their safety and effectiveness have not been assessed in resource limited settings. Treatment of this nature requires monitoring for toxicity to the mother as the mother does not require them for her own health. Short-course regimens are well tolerated with few mild and transient side-effects for the woman and her infant. Additional concern has been raised about the safety of ARV drugs taken by the pregnant women for extended periods especially when they do not require ARV treatment for their own health **(30)**. Among women who require triple-combination regimens for treatment of their HIV disease, the benefits for the woman's health outweigh the adverse effects. Drug resistance occurs if short regimens are used to prevent mother-to-child transmission and they do not fully suppress the virus **(30)**. Viral resistance has been detected in HIV infected infants exposed to short course ARV regimens. Resistance to nevirapine develops rapidly and has been found following single doses of nevirapine **(30)**. Zidovudine resistance usually only emerges after several months of suppressive therapy.

The concerns about resistance should be balanced with the simplicity of the programme and practicality of single dose nevirapine regimen

compared with other regimens and the urgent need to expand programmes to prevent mother-to-child transmission. The primary aim being to achieve the WHO goal of reducing the proportion of infants infected with HIV to 50% by 2010.

ARV regimens constitute one of the components of successful programmes to prevent mother-to-child transmission. Regimens using zidovudine plus single dose of nevirapine are highly efficacious, but providing twice daily ARV prophylaxis to the pregnant woman from 28 weeks of gestation increases the burden on the programmes and on the women who participate. Single dose maternal and infant nevirapine is a practical alternative to the above mentioned regimen.

The Technical Consultation recommended specific ARV regimens according to different clinical situations **(30)**. These guidelines are based on those recommendations and on expert opinion where evidence was lacking. The key recommendations in the guidelines are as follows:

1. Women who need ARV treatment for their own health should receive it in accordance with the WHO guidelines on ARV treatment. The use of ARV

treatment, when indicated during pregnancy substantially benefits the health of the woman and decreases the risk of HIV transmission to the infant.

2. HIV infected pregnant women who do not have the indications for ARV treatment, or do not have access to treatment should be offered ARV prophylaxis to prevent mother-to-child transmission using one of several ARV regimens known to be safe and effective:

   - AZT from 28 weeks of pregnancy plus single dose nevirapine during labour and single dose nevirapine and one week zidovudine for the infant. This regimen is more efficacious than starting zidovudine later in pregnancy.

   - Alternative regimens based on zidovudine alone, short-course zidovudine + lamivudine or single dose nevirapine alone are also recommended.

3. Although expanding access to programmes to prevent mother-to-child transmission presents many challenges and single dose maternal and infant nevirapine is the simplest regimen to deliver, programmes should consider introducing more complex ARV regimens where possible. The expansion of programmes to prevent PMTCT using single dose nevirapine should not be hindered while necessary improvements in the health systems are taking place to enable more complex ARV regimens to be delivered.

CURRENT GUIDELINES FOR TREATMENT OF HIV-INFECTED PATIENTS IN RESOURCE CONSTRAINED SETTINGS [31]

- Treatment should be offered to women with WHO stage IV disease regardless of their $CD4^+$ cell counts or total lymphocyte counts
- To women with WHO stage III disease who have $CD4^+$ cell counts <350 cells/μl or all women with stage III disease if $CD4^+$ cell counts results are not available.
- To women with stage I or II disease who have $CD4^+$ cell counts <200 cells/μl, with consideration for treatment for women with $CD4^+$ cell counts between 200 and 350 cells/μl, or stage II disease with total lymphocyte count < 1200 cells/μl if $CD4^+$ cell counts results are not available.

Of the regimens for first line treatment available using the WHO recommended five-drug formulary, the regimens of zidovudine plus lamivudine and nevirapine or stavudine plus lamivudine plus nevirapine should be used in pregnant women or women of child-bearing potential [31]. The therapy generally consists of two nucleoside reverse transcriptase inhibitors (NRTI) plus a non-nucleoside reverse transcriptase inhibitor or protease inhibitor, with continuation of therapy postpartum. For women who require immediate initiation of therapy for their own health, treatment should be started as soon as possible, including in the first trimester, as the potential benefit of treatment for the mother outweighs the risks.

The regimen should be chosen from those recommended for non-pregnant adults, while trying to avoid those drugs that are teratogenic to the fetus.

PHARMACOLOGY OF ANTIRETROVIRAL DRUGS DURING PREGNANCY

There are many classes of antiretroviral drugs:

a) Nucleoside/Nucleotide reverse transcriptase inhibitors

- Abicar (ABC)
- Didanosine (ddi)
- Emtricitabine (FTC)
- Lamivudine (3TC)
- Tenofovir (TFV)
- Zalcitabine (ddc)
- Zidovudine (ZDV)

b) Non-nucleoside reverse transcriptase inhibitors

- Nevirapine
- Efavirenz
- Delavirdine

c) Protease inhibitor

- Amprenavir
- Atazanavir
- Indanavir

- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir

d) Viral entry inhibitors

- Enfuvirtide (T-20)

e) Miscellaneous products: Hydroxyurea

EFFECT OF PREGNANCY ON DRUG DISPOSITION [9]

Pregnancy affects all four components of drug disposition; i.e. absorption distribution, metabolism and excretion. Alteration of gastrointestinal function during pregnancy may impair drug absorption. Increased plasma progesterone is associated with 30 – 50% decrease in intestinal motility, resulting in increased gastric emptying time and intestinal transit time. Gastric acid secretion is reduced by 40% and gastric pH increases affecting the ionization and absorption of weak acids and bases. Nausea and vomiting which occur more frequently in early pregnancy may decrease drug absorption.

Changes in body composition and protein binding during pregnancy have significant effect on volume of distribution. During an average pregnancy, total body water increases by 8 liters, plasma volume enlarges by 50% and body fat stores increase, changing the distribution of both hydrophilic and lipophilic

drugs. There is a dilutional decrease in serum albumin leading to decreased protein binding of drugs and hence increasing the free fraction of the drug unbound in plasma. The volume of distribution increases and C_{max} decreases during pregnancy.

The effect of pregnancy on drug elimination is variable. Hepatic drug metabolic pathways may be induced by progesterone. There is suggestive evidence that the activity of the CYP2c, 2D6 and 3A enzymes is increased whereas CYP 1A2 is reduced [32]. Renal functions increase in pregnancy with 25 – 50% increases in the renal plasma flow and glomerular filtration rate, resulting in an increased clearance of renally excreted drugs.

The need for dosing adjustments will depend on the severity of the above changes. Pharmacokinetic studies are difficult to perform in pregnancy and published studies of pharmacokinetics in pregnancy are limited and often contradictory and almost always fail to provide clinical guidelines.

NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside reverse transcriptase inhibitors are inactive until metabolized within the cell to tri-phosphorylated forms. The resulting nucleotides compete with

endogenous nucleotides to inhibit HIV reverse transcriptase and viral replication. The half-life of nucleoside reverse transcriptase inhibitor tri-

phosphorylated forms generally exceed that of the parent drug in the plasma, allowing once or twice daily dosing. Prolonged treatment of HIV-infected individuals with either single agent in this class (mono-therapy) or two agents (dual therapy) generally results in only a transient suppression of HIV replication, as resistant mutations develop in the HIV gene that encodes for reverse transcriptase **(28)**. It is therefore recommended that nucleoside reverse transcriptase inhibitors be used only as part of combination regimen of at least three drugs – most commonly two nucleoside reverse transcriptase inhibitors with either a protease inhibitor or non-nucleoside reverse transcriptase inhibitor. The use of less intensive regimens such as monotherapy or dual therapy in pregnant women should not be used for the pregnant woman's own health but to prevent mother-to-child HIV transmission.

ZIDOVUDINE **(9)**:

This is the most widely used nucleoside reverse transcriptase inhibitor to prevent mother-to-child transmission. It is rapidly and completely absorbed after oral administration. Its protein binding is less than 25%. Zidovudine is rapidly metabolized by the liver via glucuronidation with lesser portion being excreted

unchanged in urine. It undergoes extensive first-pass metabolism with a bioavailability of approximately 63% despite complete absorption. Zidovudine is eliminated by the kidneys, primarily as zidovudine glucuronide. Zidovudine C_{max}, T_{max}, bioavailability and T_{max} do not appear to differ during pregnancy when compared with historical values for non-pregnant adults. All nucleoside reverse transcriptase inhibitors are pro-drugs that require intracellular metabolism by cellular enzymes to their active forms of tri-phosphorylated nucleotides. Zidovudine plasma half-life (t½) averages around 1.1 hours and apparent clearance (Ct/f) of 1.3L/h/kg in non-pregnant adults. The current standard adult zidovudine regimens of either 200mg (three times a day) or 300 mg (twice a day) are generally used in pregnant women. Zidovudine crosses the placenta well with roughly equivalent concentrations in maternal plasma, amniotic fluid and cord blood plasma. Protocols to prevent mother-to-child transmission of HIV generally incorporate antiretroviral dose administration during labour to ensure that suppression of HIV viral replication continues throughout labour and that protective plasma antiretroviral concentrations are present in the infant at the time of birth. A 2 mg/kg intravenous loading dose followed by continuous infusion at 1 mg/kg/hour was studied during labour. While using this regimen, the average zidovudine plasma concentration at the time of birth was 0.82 μg/ml in the mother and 0.75 μg/ml in the newborn. The median levels of zidovudine tri-phosphate following intravenous administration

were similar between maternal and cord blood in various studies and were 2 – 3 times higher than in those reported in HIV infected adults on oral therapy. Less intensive zidovudine regimens are utilized in resource poor settings. In these regimens, zidovudine is started later in gestation and oral rather than intravenous administration during labour is used and short or no postpartum newborn dosing is administered. These regimens have been shown to reduce mother-to-child transmission, but not to the full levels seen with the full PACTG 076 study regimen. Newborns have immature glucuronidation activity and renal function resulting in prolonged elimination of transplacentally acquired zidovudine with t½ averaging 13 hours. Zidovudine clearance is reduced in premature infants compared to term infants, particularly those infants born before 30 weeks.

The recommended dose of zidovudine in infants from birth to 3 months of age is 2 mg/kg orally or 1.5 mg/kg intravenously four times a day **(29)**. In order to facilitate adherence, 4 mg/kg orally twice a day is being used more frequently. Infants born before 35 weeks of gestation should receive initial doses of 2 mg/kg orally or 1.5 mg/kg iv. Every 12 hours. Zidovudine dosing frequency should increase to every 8 hours at 2 weeks of age if gestational age at birth is 30 -35 weeks or 4 weeks of age if gestational age at birth is less than 30 weeks.

Zidovudine has the best safety profiles in pregnancy. Bone marrow depression is a common toxicity of zidovudine and mild, transient depression of haematologic parameters has been observed in the newborns after exposure to a full PACTG 076 regimen and to less intensive regimens [21].

LAMIVUDINE (9)

Lamivudine is the second most commonly used nucleoside reverse transcriptase inhibitor in pregnancy. In non-pregnant adults lamivudine is rapidly absorbed with bioavailability averaging 85%. It is rapidly eliminated via renal excretion as unchanged drug. Its protein binding is low (10 – 50%) and its volume of distribution is large. The overall plasma CL/F is 0.3 L/hour/kg and its half-life is around 6 hours.

The intracellular half-life of lamivudine tri-phosphate is longer than that of zidovudine or stavudine with a median of 15 hours. Lamivudine crosses the placenta by simple diffuision and the ratio of lamivudine concentration in maternal plasma at the time of delivery and cord blood is around 1. Lamivudine accumulates in amniotic fluid where the concentration at the time of delivery averages around 5-fold more than maternal plasma concentration. Pregnant

women should receive the usual adult dose of lamivudine which is 150 mg per os twice daily.

Lamivudine clearance is prolonged in neonates at birth, with the elimination half-life in neonates of transplacentally acquired drug averaging around 14 hours. The recommended lamivudine dose for neonates less than 1 month old is 2 mg/kg twice a day. Lamivudine is known to depress bone marrow function which is the most common toxicity reported with perinatal exposure. Because lamivudine is almost always given in combination with zidovudine, its contribution to anaemia and neutropenia is difficult to determine.

STAVUDINE [9]

Stavudine is a deoxythymidine analog also used as an alternative nucleoside reverse transcriptase inhibitor. Stavudine has rapid absorption and good bioavailability, approaching 100%. It is eliminated through metabolic and renal routes. It has a serum half-life of 1 hour and an intracellular half-life of 3.5 – 7 hours. Placental transfer of stavudine is good and in a study of 14 pregnant women cord blood stavudine concentration was averaging 130% that of maternal serum concentration at the time of delivery.

The combination of didanosine and stavudine should be avoided during pregnancy as several cases of fatal lactic acidosis have been reported in pregnant women treated with these two drugs. Standard adult dosing of 40 mg twice daily (30 mg if weight less than 60 kg) should be used during pregnancy.

DIDANOSINE [9]

Didanosine is a deoxyadenosine analog often used as an alternative nucleoside reverse transcriptase inhibitor in women intolerant or resistant to zidovudine and/or lamivudine. In non-pregnant adults, didanosine bioavailability is poor, averaging around 40 – 45%. It is degraded by stomach acid and must be administered with antacid. Its clearance is rapid and occurs through both renal elimination of unchanged drug and metabolism by purine nucleoside phosphorylase and xanthine oxidase. While the plasma half-life of didanosine is short (1.5 hours), the half-life of the intracellular phosphorylated derivative is 12 – 40 hours and once daily administration with enteric coated didanosine capsules has been approved, bioavailability of buffered capsules averaged 50%. Primate studies suggest that didanosine crosses the placenta by passive diffusion with fetal plasma concentrations averaging about 50% of maternal plasma concentrations. The enteric coated capsule provides more constant exposure and is better tolerated, thus making it the preferred formulation.

Adult dosing of didanosine is weight based: Adults weighing > 60 kg receive 200 mg twice daily or 400 mg once daily and those weighing < 60 mg receive 125 mg twice daily or 250 mg once a day. The recommended dose for didanosine in newborns is 50 mg/m^2 twice a day.

OTHER NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS [9]

No pharmacokinetic data are available for zalcitabine, abacavir, entricitabine or tenofovir during human pregnancy. Animal and ex-vivo human placenta studies suggest that zalcitabine and abacavir are transported across the placenta by simple diffusion. There are no human perinatal safety data for abacavir, entricitabine or zalcitabine.

Tenofovir is the first nucleoside reverse transcriptase inhibitor for use against HIV. It requires phosphorylation with addition of tri-phosphate for activity. Tenofovir therapy with 1 – 2 doses has been shown to protect newborn macaques against infection following exposure to simian immunodeficiency virus. A previous study in primates [9] has demonstrated osteomalacia and renal toxicity with prolonged high tenofovir exposure to adult animals and fetal growth retardation and reduction in bone porosity after prolonged in utero

exposure. Although tenofovir holds promise as an agent for prevention of mother-to-child transmission of HIV, clinical studies are needed to define its pharmacokinetic safety and efficacy in the perinatal setting.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS [9]

Non-nucleoside reverse transcriptase inhibitors non-competitively bind to HIV reverse transcriptase, inhibiting its activity. Unlike nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors do not require intracellular phosphorylation for activation. They are highly potent against wild type virus. High level resistance can develop from single point mutation.

NEVIRAPINE [9]

Nevirapine is a potent non-nucleoside inhibitor of reverse transcriptase with desirable pharmacokinetics for use in perinatal settings. Nevirapine absorption is complete with oral bioavailability exceeding 90%. The protein-bound fraction of nevirapine in plasma is approximately 60%. The main route of elimination of nevirapine is hepatic metabolism by enzymes of the CyP-450 family – primarily CyP-3A4 and 2B6. Elimination following initial doses is slow, with mean

elimination half-life of 40 hours (Ranging: 22 – 84 hours). With chronic therapy there is auto-induction of metabolism. After 2 weeks of treatment, nevirapine

clearance increases 1.5 – 2 fold and the mean elimination half-life decreases to 20 – 30 hours. The recommended dosing schedule for nevirapine in HIV-infected adults is 200 mg once daily for the first 2 weeks followed by 200 mg twice daily. Nevirapine pharmacokinetics in pregnant women are similar to those of non-pregnant women. Nevirapine crosses the placenta rapidly. Cord blood concentrations average around 1000 ng/ml after administration of single doses to the mother during labour and the ratio of the nevirapine concentrations in cord blood and maternal blood at the time of delivery averages approximately 80%. Average cord blood concentration doubles to over 2000 ng/ml with chronic maternal dosing during the last trimester of pregnancy.

In newborns, washout elimination from maternal nevirapine dosing is prolonged and variable, with a median half-life of 65 hours (Ranging: 35 – 331 hours). Elimination accelerates during the first days of life. Taking advantage of the good placental passage and slow elimination in the neonate, a two-dose intrapartum – postnatal nevirapine regimen was developed. The regimen consists of a single oral 200 mg dose to the mother during labour and a single oral 2 mg/kg dose to the infant postpartum. It was designed to maintain newborn

plasma nevirapine concentrations greater than 100 ng/ml from birth, through to the end of the first week of life. This two-dose intra-partum-postnatal nevirapine regimen reduced mother-to-child HIV transmission by 41% compared to an equivalently abbreviated zidovudine regimen in randomized control trial in Uganda, and by 49% compared to untreated population in a prospective cohort in Zambia.

Infants delivered within 2 hours of maternal nevirapine dosing can have low cord blood nevirapine concentrations. These infants should receive an extra dose of nevirapine immediately after birth in addition to the standard infant dose at 48 – 72 hours. Pregnant women receiving chronic nevirapine during pregnancy achieve maternal and cord blood nevirapine concentrations that are 2 – 5 times those following single dose nevirapine during labour. Chronic maternal nevirapine dosing appears to induce infant nevirapine metabolism in utero and increases newborn nevirapine elimination. If an infant's mother receives prolonged nevirapine therapy prior to delivery, then an additional newborn nevirapine dose is needed around day 5 of life to maintain infant nevirapine concentrations above 1000 ng/ml throughout the first week of life.

The two-dose intra-partum-postnatal nevirapine regimen is well tolerated. No

adverse effects of this short course regimen were seen when compared to placebo in Ugandan infants exposed to no other antiretroviral agents and infants from the US, Europe, Brazil and the Bahamas exposed to standard perinatal antiretroviral regimens.

The development of nevirapine resistance is common after maternal exposure to single intra-partum nevirapine dose. Nevirapine-resistant viral clones were found in 19% of women using no antiretrovirals and in 15% of women receiving standard perinatal antiretroviral regimens. These resistant clones appear to fade in the absence of continued nevirapine exposure.

EFAVIRENZ AND DELAVIRDINE [(9)]

Efavirenz and delavirdine have been found to be teratogenic in laboratory animals. Administration of efavirenz to 20 pregnant cynomolgus monkeys resulted in three monkeys with severe malformations, including anencephaly, anophthalmia, microphthalmia and cleft palate. A neural tube defect has been reported in an infant exposed to efavirenz in-utero. The use of efavirenz should be avoided in pregnancy and no human pharmacokinetic data are available. Administration of delavirdine to pregnant rats at doses that produced systemic exposures, equal to or lower than typical human exposures, caused ventricular

septal defects and increased infant mortality. There are no human data describing delavirdine pharmacokinetics during pregnancy.

PROTEASE INHIBITORS (PI) [9]

Protease inhibitors are potent antiretrovirals used as components of combination antiretroviral regimens. Inhibition of HIV protease, the enzyme responsible for cleavage of large polypeptides into smaller proteins needed for production of functional HIV virions, leads to release of structurally disorganized and non-infectious viral particles. Protease inhibitors when used as part of the combination regimens can provide a sustained suppression of HIV replication and are considered first line therapies in HIV infected individuals. Protease inhibitors are metabolized by the enzymes of the CyP-450 system, especially those of the 3A family, with lesser contributions by CyP-2C9, CyP-2C19and CyP-2D6 isoforms. The interaction of protease inhibitors with the CyP-450 system is complex and besides being substrates, PIs can induce or inhibit CyP-450 activity. Ritonavir is a potent CyP-450 inhibitor and is used in combination with other PIs to pharmacologically boost PI exposure. Currently available PIs are substrates of P-glycoprotein an active transporter that is expressed in various tissues including the gastrointestinal tract and the placenta. P-glycoprotein is thought to limit the absorption of drugs and reduce fetal drug exposure.

Plasma protein binding is > 85% for the available protease inhibitors with the exception of indinavir. Protease inhibitors are lipophilic, tend to be difficult to formulate into convenient and palatable dosage forms and generally have poor absorption. These factors result in variable bioavailability of these agents. PIs cross the placenta poorly and most infants born to mothers receiving PIs have low or undetectable PI concentrations in cord blood, suggesting that the primary mechanism of action of protease inhibitor in preventing mother-to-child HIV transmission is by decreasing maternal viral load rather than by direct protection of the fetus. Limited placental transfer of protease inhibitors may protect the fetus against potential toxic or teratogenic effects of these agents and also that maternal protease inhibitor therapy during labour will not provide post-exposure prophylaxis of the newborn at the time of birth, in contrast to nucleoside and no-nucleoside reverse transcriptase inhibitors. Frequently encountered adverse effects of the PIs might limit their tolerability in pregnant women. Gastrointestinal adverse effects such as nausea, vomiting and diarrhea are common with all agents in this class. There are numerous PI pharmacokinetic drug interactions with other medications used in pregnant women.

NELFINAVIR [(9)]

Nelfinavir pharmacokinetics in non-pregnant adults is characterized by erratic and variable absorption, which increases 2 – 3 times when administered with a

meal of high fat content. Nelfinavir is highly protein bound (> 98%) and is extensively metabolized by the CyP-450 system. Its active metabolite, M8 is produced by CyP-2C19 metabolism and both nelfinavir and M8 are eliminated via metabolism by the CyP-3A family. Nelfinavir's half-life is 3 – 5 hours in non-pregnant adults.

The pharmacokinetics of nelfinavir had been studied in pregnant women receiving 750 mg three times a day and 1250 mg twice daily dosing. In a group of 9 pregnant women receiving 750 mg three times daily, median nelfinavir AUC during a dose interval was 8.2 μg/hour/ml, about half AUC in non-pregnant adults receiving this dose. Pregnant women receiving the 1250 mg dose had a median AUC of 28.3 μg/hour/ml. Lower nelfinavir exposure with 750 mg three times daily risks development of viral resistance and should be avoided during pregnancy. Nelfinavir pharmacokinetics have been described in infants during the first month of life. These studies suggest that higher doses are needed in infants than in older paediatric populations.

INDINAVIR [(9)]

Published data describing indinavir pharmacokinetic parameters in pregnant women are limited. In a study of nine women receiving 800 mg three times/day,

C_{max} and AUC were lower during pregnancy than at postpartum. The ratio of 6β-hydroxy- cortisol to cortisol in urine was associated with the decrease in indinavir exposure during pregnancy, suggesting enhanced CyP-3A activity is responsible for lower indinavir concentrations during pregnancy. These studies suggest "unboosted" indinavir should be avoided in pregnant women and the pharmacokinetics of indinavir in combination with low-dose ritonavir should be investigated.

Indinavir inhibits liver glucoronidation, resulting in increased bilirubin concentrations. This effect along with lack of a liquid formulation makes indinavir use unsuitable in newborn infants.

SAQUINAVIR [9]

Saquinavir has the lowest bioavailability of all PIs. It is available as both hard and soft-gelatin capsule formulations but no liquid formulation for the infants. Bioavailability averages only 4% with the hard gelatin capsules and is approximately three times better with soft-gelatin capsules. Saquinavir use in pregnancy should include boosting with ritonavir.

RITONAVIR [9]

Ritonavir is the most difficult PI to tolerate in pregnancy due to its frequent and severe gastrointestinal side-effects.

SIDE-EFFECTS OF ARVs [6]

MATERNAL TOXICITY: The most common toxicity of zidovudine is bone marrow suppression, resulting in anaemia or neutropenia. During pregnancy there is 50% increase in plasma volume and only a 30% increase in red cell mass. Because of this marked increase in plasma volume compared to red cell mass, pregnancy may increase the risk of anaemia. Pregnant women receiving zidovudine should be monitored regularly for anaemia and neutropenia. Women with significant anaemia while receiving zidovudine may have the dose reduced or have stavudine substituted for zidovudine.

A more serious but less frequent side-effect with the use of nucleoside agents is the development of mitochondrial dysfunction. Nucleoside agents bind to mitochondrial DNA polymerase and interfere with mitochondrial replication, leading to depletion and dysfunction. In-vitro, the relative potencies of antiretrovirals for inhibition of mitochondrial DNA polymerase are Zalcitabine

(Highest), Didanosine, Stavudine, Lamivudine, Zidovudine and Abacavir (lowest).

Mitochondrial toxicity has been associated with long term use of nucleoside agents and generally resolves when the drugs are stopped. Conditions which have been associated with mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis and lactic acidosis **(6)**. Pregnancy may increase the susceptibility to mitochondrial dysfunction, based on evidence from studies in mice showing significant reductions in fatty acid oxidation in late gestation and after exogenous administration of oestradiol and progesterone, mimicking levels in pregnancy. Several cases of severe lactic acidosis have been reported in pregnant women receiving stavudine with didanosine. Stavudine and didanosine have increased affinity for mitochondrial DNA polymerase and the combination of stavudine and didanosine should be avoided in pregnancy unless no other alternative nucleoside agents are available. Pregnant women on antiretrovirals should be educated about the symptoms of mitochondrial dysfunction and should have levels of hepatic transaminases and electrolytes assessed frequently during the third trimester. The most common toxicities of non-nucleoside reverse transcriptase inhibitors are hepatotoxicity, rash and potential for drug interaction with agents such as PIs, anti-tuberculous drugs and other commonly used agents. These interactions lead to sub-therapeutic levels of

antiretrovirals or other agents, or to higher levels with enhanced toxicity.

Rash is common among patients initiating nevirapine or efavirenz and mild rashes may resolve with continued treatment. Steven-Johnson syndrome has been reported with both nevirapine and efavirenz. If rash associated with blistering, desquamation, mucosal involvement or fever, non-nucleoside reverse transcriptase inhibitors should be stopped immediately and not re-instituted. The rate of occurrence of rash may be decreased with nevirapine by starting with a dose of 200 mg daily for 2 weeks and then increasing the dosage to 200 mg twice daily. Significant psychiatric symptoms such as severe depression and suicidal tendencies may occur rarely with the use of efavirenz, but other CNS effects such as somnolence and unusual dreams occur more frequently and usually resolve over time. Delavirdine is rarely used and not recommended for use in pregnancy because of malformations in animal studies. The two-dose intra-partum- postpartum nevirapine regimen is 200 mg intra-partum dose to the mother and 2 mg/kg dose to the neonate within 48 – 72 hours post-delivery, has not been associated with significant toxicity. There is significantly high rate of asymptomatic hepatotoxicity among nevirapine exposed patients than among controls. Nevirapine containing treatment regimens are associated with a higher incidence of symptomatic hepatic events. The risk of severe hepatic toxicity and skin rash with nevirapine based treatment varies according to the $CD4^+$ cell

count at the time treatment is initiated. Women with $CD4^+$ cell count greater than 250 x 10^6 cells/L when nevirapine-based ARV treatment starts, including pregnant women initiating ARV treatment, have about a 10-fold higher risk of severe symptomatic hepatotoxicity than women with lower $CD4^+$ cell counts [6].

Long term use of protease inhibitors can be associated with a variety of metabolic disorders, including lipodystrophy, hyperglycaemia, onset or exacerbation of diabetes mellitus and diabetic ketoacidosis because of production of hormones such as human placenta lactogen, cortisol and progesterone. Pregnancy is diabetogenic, hence using PIs during pregnancy could increase the risk for pregnancy-associated hyperglycaemia. Because of the diabetogenic effect of corticosteroids, pregnant women on PI therapy who require corticosteroids (e.g. for fetal lung maturity), should be monitored closely. Other common toxicities seen with PI drugs are nausea, vomiting, diarrhea and increased bleeding in haemophiliacs.

LONGTERM TOXICITY

Most of the toxicities, such as laboratory parameter abnormalities, seen with the use of antiretrovirals in pregnancy are reversible upon discontinuation of therapy. Use of short course therapy to prevent perinatal transmission can result

in development of a treatment-resistant virus which may have implications for future treatment responses. There may be detection of resistant HIV in up to 67% of women receiving short course nevirapine for prophylaxis of perinatal transmission, depending on the timing of testing, number of doses received, concomitant therapy and viral load.

Concentrations of nevirapine remain detectable (above 50 ng) in up to 50% of women at 2 weeks after a single intra-partum dose of 200 mg. These persistent low levels allow selection of resistant mutants that occur because of error-prone process of HIV replication. Only a single mutation is required for development of nevirapine resistance such that among women with detectable HIV RNA, resistance is detectable in 20% of women at 2 weeks after a delivery dose, in 15 – 67% at 4 – 6 weeks and 25 – 40% at 7 – 8 weeks. If the infant is infected despite prophylaxis, resistance may be detected in up to 52% of such children. Factors associated with an increased rate of detection of nevirapine resistance include receiving more than one dose of peripartum nevirapine, higher HIV RNA level or lower $CD4^+$ cell count, viral grade C, time of sampling and the assay used for detection. In the absence of continued nevirapine therapy, the frequency of nevirapine resistance mutations using standard consensus techniques declines over time, but using more sensitive techniques such as

polymerase chain reaction assays, mutations can be detected among 40 – 88% of treated women.

The most important issue regarding the detection of resistant mutations after single dose, short-course monotherapy regimens is how it will affect the woman's response to subsequent antiretroviral therapy, especially since such therapy is likely to include non-nucleoside reverse transcriptase inhibitor such as nevirapine or efavirenz.

ANTIRETROVIRAL DRUG RESISTANCE AND RESISTANCE TESTING IN PREGNANCY [19]

- HIV drug resistance testing is recommended for:

1. All pregnant women not currently receiving antiretrovirals, before starting treatment or prophylaxis.

2. All pregnant women receiving antenatal antiretroviral therapy who have virological failure with persistently detectable HIV RNA levels or who have sub-optimal viral suppression after initiation of antiretroviral therapy under an ideal situation.

This testing will be done at a pre-conception visit to allow receipt of results and selection of an antiretroviral drug regimen to be used during pregnancy or started before pregnancy if maternal therapy is indicated. There is accumulating evidence that transmitted resistant mutants may persist for indefinite period after initial infection that these viral variant may be detectable by standard assays used in clinical practice, that the prevalence of resistance in antiretroviral naïve patients is increasing and that baseline resistance may be associated with adverse virological outcomes. Baseline HIV resistance testing is now recommended for all patients with established infection, including pregnant women, prior to initiating treatment. Resistance testing should be performed before initiation of therapy or prophylaxis in pregnant women who received prophylaxis in previous pregnancy and are now restarting antiretroviral drugs for prevention of perinatal transmission. The identification of baseline resistant mutations may allow selection of more effective and more durable antiretroviral regimens in women needing treatment and greater preservation of future treatment options in women receiving antiretroviral therapy only for perinatal prophylaxis. There is no evidence that baseline resistance testing in pregnancy is associated with a reduction in perinatal transmission rates.

For pregnant women who are already receiving antiretroviral therapy at the time they are seen, resistance testing is indicated if there is sub-optimal initial viral

suppression following initiation of antiretroviral therapy or if there is persistently detectable HIV RNA levels indicative of virologic failure on the current regimen.

In most settings, the results of resistance testing are used to guide selection of the initial regimen, but in some clinical situations the clinician may choose to initiate empiric antiretroviral therapy or prophylaxis before results of resistance testing are available, in order to maximize prevention of perinatal transmission. The antiretroviral drug regimen may be modified if necessary once resistance test results become available. This type of approach may be applied if women have initial resistance testing in the third trimester and test results may not be back in time to allow effective reduction of viral load before delivery. If resistance testing is done in the latter half of the second trimester, experts differ as to whether the benefit of immediate initiation of antiretroviral drugs and more rapid reduction of viral load outweighed the possible risk of initiating a regimen that could be sub-optimal due to pre-existing resistance [19].

SIGNIFICANCE OF ANTIRETROVIRAL DRUG RESISTANCE IN PREGNANCY [19]

The development of antiretroviral drug resistance is one of the major factors leading to therapy failure in HIV infected persons. Resistant viral variants

emerge if there is normal suppression of viral replication, because of the mutation-prone process of reverse transcription in viral replication. The administration of combination antiretroviral therapy with maximal suppression of viral replication to undetectable levels limits the development of antiretroviral resistance in both pregnant and non-pregnant persons. Over and above the development of drug resistance in the general population, pregnancy presents some special concerns related to the development of drug resistance.

If there is pre-existing resistance to a drug used for antiretroviral prophylaxis, it may reduce the efficacy of such a drug or regimen in preventing perinatal transmission. Again if drugs are used during pregnancy for prophylaxis of perinatal transmission, development of resistance to such drugs may limit future maternal treatment options when the woman later needs treatment with ARVs for her own health or also decrease the effectiveness of prophylactic regimens in the current pregnancy or in future pregnancies. Additionally, if maternal resistance is present or develops and resistant virus is transmitted to the fetus, the infant treatment options may be limited.

Several factors unique to pregnancy may increase the chance of development of resistance. Antiretroviral drugs used for prophylaxis of perinatal transmission are usually stopped post delivery in women who do not need them for their own

health. If regimens used for prophylaxis contain drugs with different half-lives, such as nevirapine combined with two nucleoside analog drugs, discontinuation of all regimen drugs simultaneously postpartum may result in functional monotherapy and increase the risk of development of resistance. In early pregnancy nausea and vomiting may compromise adherence to the regimen and increase the risk of resistance in women receiving antiretroviral treatment.

PREVALENCE OF ANTIRETROVIRAL DRUG RESISTANCE [19]

1. General Population

Prevalence of antiretroviral drug resistance varies depending on several factors such as population studied, prior to and current exposure to antiretroviral drugs and the type of regimen (HAART versus non-HAART), geographical area and type of resistance assay used (genotypic versus phenotypic).

More recently, studies have examined antiretroviral drug resistance in drug naïve persons with newly diagnosed HIV infection or unknown duration, which is a more typical picture of patients who present for initial evaluation and care, 8.3% to 10.8% of patients had HIV with genotypic mutations associated with reduced antiretroviral susceptibility. The highest rates of antiretroviral drug resistance have been reported in antiretroviral treatment-experienced individuals, with

resistance rates as high as 88% reported in viraemic individuals currently receiving therapy and in 30% in individuals with past history of treatment [33].

2. Pregnancy

The rates of antiretroviral drug resistance are similar in pregnant women and in non-pregnant individuals with antiretroviral drug resistance more frequent among antiretroviral experienced women. Among 220 pregnant antiretroviral experienced women in the perinatal AIDS Collaborative Transmission study, all of whom had prior zidovudine exposure in pregnancy from 1991 to 1997, 17.3% had zidovudine-associated mutations [34]. In a sub-study of the PACTG 316 protocol, an International, multi-center clinical trial comparing single dose nevirapine with placebo in HIV-infected pregnant women receiving standard antiretroviral therapy, 3.2% of 217 women with detectable HIV RNA had mutations associated with nevirapine resistance at 6 weeks postpartum, despite no history of prior exposure to non-nucleoside drugs or receipt of nevirapine at delivery. Additionally, more than 60% of women receiving combination therapy (either dual nucleoside or combinations containing a protease inhibitor) had the M184V mutation conferring resistance to 3TC, and 11% of 217 women had primary or secondary protease mutations [35].

Despite the increasing prevalence of drug resistance in treatment-naïve and

treatment experienced individuals, there is currently no evidence to indicate on a population basis that antiretroviral drug resistance in HIV-infected pregnant women is compromising the efficacy of perinatal HIV prevention efforts in Europe or North America, where mother-to-child transmission rates remain less than 2%.

INCIDENCE OF ANTIRETROVIRAL RESISTANCE WITH PERINATAL PROPHYLACTIC REGIMEN

The presence of mutations conferring resistance to nucleoside analogue drugs appears to be correlated with more advanced maternal disease and duration of prior or current exposure to these drugs. Development of zidovudine resistance with the PACTG 076 ZDV (zidovudine) regimen alone appears to be uncommon in women with higher $CD4^+$ cell counts and low viral load, but is more of a concern in women who have more advanced disease and lower $CD4^+$ cell count **[21]**.

Development of resistance to 3TC (lamivudine), which requires one point mutation for high-level resistance, was reported in 52 (39%) of 132 women with viral RNA samples amplified using standard genotypic assays at 6 weeks postpartum in a French cohort in which 3TC was added at 32 weeks gestation to the PACTG 076 zidovudine regimen **[36]**. When women received 3TC for more

than 2 months, resistance was identified in 50%, as compared to more of 12 women receiving it for less than 1 month. In the PETRA study, 12% of women who received 1 month ante-partum, intra-partum and 1 week post-partum combination of zidovudine/3TC developed 3TC resistance, while none of the women who received only intra-partum and 1 week post-partum zidovudine (2DV)/3TC developed resistance, none of the women in the other arm developed resistance [26]. Nevirapine resistance only requires 1 point mutation to develop. The long half-life of nevirapine (NVP) with blood levels detectable up to 21 days after a single dose in labour increases selection pressure and risk of resistance. Factors associated with increased risk of resistance following single dose NVP exposure include high baseline viral load, low baseline $CD4^+$ cell count, viral sub-type and number of doses. The rate of genotypic resistance after exposure to single dose NVP has varied in studies, ranging from 15% to 75%. Studies using more sensitive real-time polymerase chain reaction (PCR) techniques suggest that up to one-half of resistance that develops is not detectable by conventional sequence analysis.

Studies demonstrate that while resistance occurs in the first few weeks of post-exposure in the majority of women exposed to single-dose NVP, the prevalence of resistance declines rapidly over time. The proportion of resistant virus in those with detectable resistance 12 months after exposure is reported to be low.

In a study of 67 South African women, using a sensitive allele-specific resistance assay, K103N mutation was seen in 87% of women at 6 weeks, but in only 11% at 12 months after single-dose NVP exposure [37]. Addition of single-dose NVP to other background regimens still resulted in NVP resistance in 15% of 95 women in the PACTG 316 study. Because PACTG 316 demonstrated that the addition of single-dose NVP in situation where combination antiretroviral therapy is being received did not provide any additional efficacy in preventing mother-to-child transmission and because there is a risk of NVP resistance, this approach is not recommended [35].

MANAGEMENT OF ANTIRETROVIRAL DRUG RESISTANCE DURING PREGNANCY

In an ideal situation, antiretroviral regimens used during pregnancy for treatment or for prophylaxis should be chosen based on the results of antiretroviral resistance testing. Although most of mother-to-child transmission of HIV occurs during the intra-partum period, as much as 30% to 35% of transmission may occur in utero, majority of in utero infection is thought to occur later in pregnancy and may be more likely in women with advanced HIV disease and/or high viral load. Therefore, delay in initiation of antiretroviral drug regimen to await results of resistance testing could result in in-utero infection of the infant, particularly in women at high risk of transmission or who are late in pregnancy at the time the drugs are initiated. In such circumstances, empiric initiation of

antiretroviral prophylaxis may be warranted to maximize prevention of perinatal transmission, with the regimen being modified if needed once resistance testing results become available.

Women who have documented zidovudine resistance and are on regimens that do not include zidovudine for their own health should receive intravenous zidovudine during labour, along with their established antiretroviral regimens and oral zidovudine for their infants according to the PACTG 076 protocol. For women who are receiving stavudine (d4T)-containing regimen, d4T should be discontinued during labour while intravenous zidovudine is being administered, this should be restarted after delivery. Other antiretrovirals should be continued orally during labour. Oral zidovudine should be administered to the infant for 6 weeks. Data have suggested that when mothers have mixed populations of wild-type virus and virus with low-level resistance to zidovudine, only the wild-type virus is found in the infant. Another study has suggested that drug resistance mutations may diminish viral fitness and possibly diminish transmissibility **(38)**. Zidovudine crosses the placenta rapidly and has one of the highest maternal: cord blood ratios among the nucleoside analogue agents. Zidovudine is metabolized to the active triphosphate within the placenta, which may provide additional protection against transmission. The above reasons provide the

rationale for including zidovudine intra-partum and to the infant when a woman is known to habour virus with zidovudine resistance.

The optimal prophylactic regimen for newborns of women with ARV resistance is unknown. Therefore, ARV prophylaxis for an infant born to a woman with known or suspected drug resistance should be determined in consultation with a paediatric HIV specialist, preferably before delivery.

PREVENTION OF ANTIRETROVIRAL DRUG RESISTANCE

- The use of HAART to maximally suppress viral replication during pregnancy is the most effective strategy to prevent the development of resistance and to minimize the risk of perinatal transmission.
- All pregnant women should be counseled about the importance of adherence to prescribed antiretroviral medications, to reduce the potential for the development of resistance.

EFFECTS ON PREGNANCY OUTCOME

Early studies of women in developed countries **(39)** that included appropriate control groups did not suggest an adverse effect of HIV infection itself on

pregnancy outcome. Although rates of complications were high due to maternal drug use and other risk factors. Studies from resource-limited settings have been more suggestive of a negative impact of HIV on pregnancy outcome, with rates of low birth weight increasing with more advanced disease. Studies evaluating the effects of zidovudine monotherapy on pregnancy outcome have found either similar or improved pregnancy outcomes among women receiving zidovudine compared with those not receiving antiretroviral agents. Risk factors for preterm delivery among HIV infected women are similar to those women without HIV infection.

The effects of HAART on pregnancy have been less clear. Several studies from Europe such as European Collaborative study (ECS) have demonstrated an increased risk of preterm delivery as the number of antiretroviral agents increased, with the highest risk occurring among pregnant women receiving combination therapy that included a PI [40]. Recently, a 4.4-fold increased risk of preterm birth before 34 weeks was documented among women who became pregnant while on HAART and continued treatment throughout pregnancy [5].

Contrary to the above findings, a combined analysis from several studies in the US did not find a difference in the rate of preterm birth between HIV-infected

women who were not receiving antiretroviral, those receiving zidovudine, those receiving combination therapy that did not include a PI and those receiving combination regimens that included a PI. Currently, the benefits of HAART regimens, including those with a PI component, on reduction of perinatal transmission appear to outweigh the potential risk of preterm birth, but continued surveillance of the effects of antiretrovirals on pregnancy outcome is needed, and women receiving therapy should be educated about the symptoms of preterm labour.

Another concern that has been raised regarding the use of HAART in pregnancy is that multi-agent therapy may increase the risk of other pregnancy complications, including pre-eclampsia and stillbirths. Any change in the risk of pre-eclampsia associated with HIV infection or HAART has not been confirmed, but continued evaluation is indicated. Another concern related to antiretroviral drug exposure in pregnancy is the potential for teratogenesis, especially as an increasing proportion of women enter pregnancy already on antiretroviral therapy. Commonly used nucleoside agents have not been associated with an increased risk of birth defects in animals when administered at doses similar to those used in humans. Among non-nucleoside reverse transcriptase inhibitors, both efavirenz and delavirdine have been associated with birth defects in

animals. Exposure to efavirenz in the first trimester in cynomulgus monkeys resulted in anencephaly, or midline facial defects including anopthalmia and cleft palate in 3 (20%) of 15 monkeys **(41)**. Data in humans are available from pregnancy registries, cohort studies and case reports. Currently > 5000 prospective exposures have been reported to the registry. The rate of birth defects detected among infants born to women with first trimester exposure to any antiretroviral agent is 54 (2.9%) of 1,835 and among those with later exposures during pregnancy, it is 63 (2.1%) of 2,956, these rates are not significantly different. While no signal of concern for efavirenz has been detected among a relatively small number of prospective cases in which there was first trimester exposure, three cases of neural tube defects and a case of Dandy-Walker malformations have been reported after first trimester efavirenz exposure.

A retrospective review of outcomes among 195 infants found an increased rate of birth defects among infants exposed to the combination of first trimester antiretroviral drugs and folate antagonists.

INFANT TOXICITY

(1) SHORT-TERM TOXICITY

The most well studied prophylactic regimens have been zidovudine monotherapy and single-dose nevirapine. When comparing toxicity in infants between zidovudine and placebo groups in several trials, with regards to laboratory parameters, the only difference noted after maternal zidovudine regimens of 4 – 26 weeks during pregnancy and 1 – 6 weeks in the infant, was mild, transient anaemia. No difference occurred with regard to liver enzyme abnormalities or toxicity requiring treatment discontinuation. In the European Collaborative study, anaemia was noticed in infants exposed to antiretroviral therapy but resolved once therapy was discontinued [42]. In a study with zidovudine and lamivudine at 32 weeks of gestation in the mother and for 6 weeks in the newborn performed in France, higher rates of anaemia and neutropenia were seen compared with historical controls receiving zidovudine alone [36]. In a follow-up study of 2,745 antiretroviral-exposed and 1,504 unexposed, all uninfected infants born to HIV-infected women in the French perinatal cohort, haemoglobin levels were noted to be transiently decreased among antiretroviral exposed infants [42]. Neutrophil, lymphocyte and platelet counts were slightly but significantly lower until the age of 18 months after antiretroviral exposure and combination therapy was associated with larger decreases than monotherapy. In the HIVNET 012 trial, rates of adverse events

were similar among 320 infants who received nevirapine and 30% who received zidovudine [28, 29]. Among more than 4,000 infants evaluated after receiving single-dose nevirapine prophylaxis in the studies other than the HIVNET 012, no significant differences in clinical or laboratory toxicities were seen compared with those receiving placebo, zidovudine or zidovudine/lamivudine. In the short term, haematological and hepatic toxicity in infants exposed to maternal antiretroviral therapy and short term neonatal therapy is minimal and transient. Infants should be monitored for anaemia if they receive neonatal therapy for more than 1 week.

Because of known effects of nucleoside agents on mitochondrial functions and the frequent use of these agents for treatment and prophylaxis during pregnancy and neonatal periods, several studies have evaluated lactic acid levels in infants exposed to nucleosides. In normal infants, mild elevations in lactate levels may be seen after delivery but rarely exceeds 5mmol/L and decreasing to adult levels of less than 2.0 mmol/L by 1 week of age. In a study of 127 antiretroviral exposed infants, 63 (50%) had at least one elevated lactate level [44]. Three of the infants with elevated levels had neurological symptoms, which resolved over time as lactate levels decreased. Elevated lactate levels are seen commonly among infants with antepartum and neonatal antiretroviral exposure. Most elevations are transient and not associated with symptoms.

Routine evaluation of lactate levels is not recommended, but may be helpful to rule out lactic acidosis in symptomatic infants.

LONG-TERM TOXICITIES

Long-term follow-up data from cohort studies of uninfected children born to HIV-infected women have been re-assuring. In the European Collaborative study of 2,414 children, including 1,008 with antiretroviral exposure, there was no difference in the rate of severe or moderate symptomatic events related to antiretroviral exposure [42]. In another European Collaborative study focusing on growth in HIV-exposed children, the height, weight and body mass index were normal for children who were not infected with HIV but lagged over time among those who were infected with HIV [45]. In a follow-up study of children born to women enrolled into the PACTG 076 study, which had placebo and zidovudine treatment arms, no differences were seen between placebo and zidovudine-exposed children in growth, cognitive and motor development, and lymphocyte sub-set results [46]. A specific concern raised for infants exposed to antiretroviral therapy, especially combination regimens, is that of mitochondrial toxicity which may persist after discontinuation of therapy. The symptoms and laboratory abnormalities suggestive of mitochondrial dysfunction were first detected in eight of 1,754 uninfected infants in the perinatal cohort study in

France [47]. Two infants had progressive neurological symptoms and died at 11 and 13 months of age respectively. Three additional infants had neurological symptoms and one of these also had a transient cardiomyopathy. Two infants had mild transient metabolic abnormalities but were asymptomatic.

Subsequently, four additional cases of suspected mitochondrial dysfunction were identified among a combined cohort of 2,644 children, for an 18-month incidence of 0.26% and an 18-month mortality rate of 0.007% [48]. In a separate report from the same cohort, investigators evaluated the rate of seizures among antiretroviral-exposed and unexposed children. The rate of neonatal or a febrile seizure did not differ between the two groups, but the rate of febrile seizures among those exposed to antiretrovirals was 11.0 per 1000 compared to 4.1 per 1000 among the exposed individuals.

In a study of HIV-exposed children who were exposed to zidovudine compared with children who were not exposed to HIV, mitochondrial DNA levels were lower among infants born to HIV-infected women even without antiretroviral exposure and lowest among infants born to women who received zidovudine [49]. Differences in mitochondrial DNA levels persisted through to 2 years of age, but

correlations between mitochondrial DNA levels and clinical outcomes were not provided. These findings on mitochondrial dysfunction have not been replicated in other cohorts.

In the European Collaborative study which included follow-up of 1,008 antiretroviral-exposed children, no symptoms consistent with moderate or severe mitochondrial dysfunction were detected among antiretroviral-exposed infants and all seizures occurred among infants with no antiretroviral exposure [30]. In another review of data from five US cohorts totaling > 16,000 children born to HIV-infected women during 1985 – 1999, no deaths attributable to or associated with symptoms, signs or laboratory abnormalities that indicated mitochondrial dysfunction were detected [50]. In a follow-up of 1,798 children born to women enrolled into an African trial that compared placebo with three different durations of zidovudine and lamivudine therapy during pregnancy and in the neonates, no difference in the rate of neurological events was observed among children exposed to zidovudine and lamivudine compared with those exposed to placebo [26].

The development of severe or fatal disease related to mitochondrial dysfunction after in utero and neonatal antiretroviral exposure appears to be extremely rare

and does not outweigh the benefits of antiretroviral therapy in the prevention of perinatal transmission of HIV infection.

Animal studies have also raised concern about the potential for carcinogenicity of antiretrovirals after in-utero exposure. An increased risk of benign vaginal tumours in rodents was likely related to reflux of urine containing high concentrations of un-metabolized zidovudine onto the vaginal mucosa of rats, conditions that are not present in humans. Studies in humans have thus far not detected an increase in the risk of cancers in children born to women receiving antiretroviral therapy during pregnancy. Since the lag time from exposure to tumour development may be many years, continued surveillance of antiretroviral-exposed children into adulthood is indicated.

OBJECTIVES OF THE STUDY

The study has been designed to:

1) Determine the pattern of toxicity, side-effects among women using HAART in the perinatal period as opposed to those who were given single-dose intra-partum nevirapine prophylaxis.

2) Evaluate the effects of either therapy on maternal and fetal outcomes.

STUDY DESIGN

The study was conducted prospectively with strict adherence to inclusion and exclusion criteria. The selection of patients for the study was random as it was impractical to include all consecutive patients.

SETTING

The study was conducted at Dr George Mukhari hospital, which is a level 3 hospital. It was conducted initially at the antenatal clinic of the same hospital where the HIV-infected pregnant women were indentified and subsequently at the labour ward of the hospital when the women reported for delivery.

METHODOLOGY

Blood sample was taken from each patient and subjected to rapid HIV test (ELISA), and when tested positive a confirmatory test (Western blot) was done. HIV-infected pregnant mothers with $CD4^+$ counts less than 200 cells/mm3) were prospectively recruited and counseled to start HAART and those with $CD4^+$ counts $\geq$ 200 cells/mm3 were informed of the need to have a single-dose intra-partum nevirapine prophylaxis and nevirapine syrup 2mg/kg given to the baby within 72 hours post-delivery. The mothers on HAART continued with HAART

intra-partum and nevirapine syrup 2mg/kg was given to the baby within 72 hours post-delivery.

The study involved comparison of pregnancy outcomes between women who were identified for HAART and those who were HIV-infected but only required intra-partum nevirapine prophylaxis to prevent mother-to-child transmission of HIV. Samples from the babies were examined by PCR 6 weeks post-delivery to assess the rate of vertical transmission of HIV.

INCLUSION/EXCLUSION CRITERIA

- Pregnant women who had undergone voluntary counseling and testing (VCT) and were identified to be HIV-infected were included.
- Each woman recruited for the study would have booked, had accepted to attend antenatal care at Dr George Mukhari hospital and indicated willingness to deliver her baby at this hospital.
- Pregnant women with multiple pregnancies were excluded.
- Women who had started antiretroviral therapy (ARVs) and those who were less than 18 years of age were also excluded.
- Pregnant women who had declined consent for HIV testing were also excluded.

SAMPLE SIZE

For the purpose of this study, pregnant women who were HIV positive were classified into two groups: those with $CD4^+$ counts greater than 200 cells/mm3 who did not require antiretroviral drugs for their own health but needed a single-dose of intra-partum nevirapine to prevent mother-to-child transmission. The second group consisted of pregnant women with $CD4^+$ counts less than 200 cells/mm^3 who needed HAART for their own health. Two hundred women were enrolled for the study, out of this number 39 patients were lost to follow-up while the remaining 161 women were successfully followed up to delivery and six weeks post-delivery assessment.

PROCEDURE

Gestational age was confirmed by dates and by sonography. Laboratory evaluation included: FBC, LFT, $CD4^+$ cell counts and viral load at the time of recruitment and at the time of delivery. $CD4^+$ count at entry was determined but $CD4^+$ count and viral load at delivery were not investigated because not all patients on HAART had those samples collected at delivery. The information that was routinely gathered from patients is reflected on the Data collection form (a copy is attached to this thesis).

Pregnant women who presented with stage IV HIV infection (WHO Staging) or with $CD4^+$ counts less than 200 cells/mm3 were given:

1. Stavudine (d4T) 40 mg p.o. every 12 hours (30 mg every 12 hours if weighing < 60 kg).
2. Lamivudine (3TC) 150 mg every 12 hours.
3. Nevirapine (NVP) 200 mg p.o. daily for 2 weeks, followed by 200 mg every 12 hours.

Women who were diagnosed with early stage HIV infection, with $CD4^+$ counts ≥ 200 cells/mm3 were given nevirapine 200 mg per os at the onset of labour. Nevirapine syrup (2 mg/kg), was given to the baby within 72 hours post-delivery. All mothers were counseled about the risk of breastfeeding. Those mothers whose $CD4^+$ cell counts dropped below 200 cells/mm3 after having been enrolled for the study, were counseled about starting HAART.

DATA ANALYSIS

Data from the study were subjected to descriptive statistics with most variables being reported as ranges as well as mean or median values. Statistically significant differences in values between the two groups were calculated for p-value and significant differences were noted if the p-value was ≤ 0.05 Whenever

it was necessary to demonstrate comparative level of risk for a variable an Odds Ratio and its 95% Confidence Interval were calculated.

RESULTS

The study was conducted from 1st March 2007 to 31st January 2008. Two hundred patients (200) were enrolled into the study of which 66 were on HAART, 95 patients were on single dose intra-partum nevirapine prophylaxis and 39 patients were lost to follow-up. Out of 39 women who were lost to follow-up, 23 were to receive single dose intra-partum nevirapine prophylaxis and 16 were on therapy with HAART.

Patients who were on HAART were enrolled into the study from 1st March 2007 to 31st January 2008 but those on single dose intrapartum nevirapine were enrolled for the study from 1st March 2007 till 31st July 2007. The study continued till 31st January 2008 to allow for sufficient patients on HAART to be enrolled for comparison with those in the single dose intrapartum nevirapine arm. Patients on HAART were not reclassified according to their viral load and $CD4^+$ count at delivery because not all the patients had those tests done at the time of delivery (this is reflected in Table 1).

Table 1 below shows maternal characteristics such as, maternal age, parity, gestational age at booking and gestational age at delivery. Although the range of maternal age was similar for the two groups (20 – 38 yrs; HAART treated group compared with 18 – 39yrs non-HAART group), there was statistically significant ($p < 0.02$) older women among those who were on HAART compared with those given intra-partum nevirapine. There were no significant differences in the range of parity of women in the two groups and in both groups more than

Table 1: Comparison of maternal characteristics between HAART-treated and nevirapine prophylacticly treated groups.

Patients	**HAART Treated [N = 66]**	**Nevirapine Treated Patients [N = 95]**
AGE (yrs): Range	20 – 38	18 - 39
Median	30	27
Mean (± SD)	30.0 (± 5.8)	27.9 (± 5.3) ∗**[p < 0.02]**
PARITY: 0	12 (18.2%)	27 (28.4%)
1 – 2	43 (65.2%)	58 (61.1%)
3 – 4	9 (13.6%)	10 (10.5%)
≥ 5	2 (3.0%)	Nil
GESTATION @ ENROLLMENT		
Range	8 – 28 weeks	9 – 37 weeks
Mean (± SD)	18.7 (± 5.0)	22.2 (± 5.8) ∗**[p < 0.001]**
GESTATION @ DELIVERY		
Range	30 - 42 weeks	33 – 44 weeks
Mean (± SD)	38.0 (± 1.9)	38.6 (± 2.3 ∗**[p = NS]**
PRETERM DELIVERY	9 (13.6%)	18 (18.9%) ∗**[p = NS]**
DELIVERY AT TERM	57 (86.4%)	77 (81.1%)

∗ p = level of significant difference; ∗ NS = Not statistically significant

60% of the women were of 1 – 2 parity. There were more nulliparous women among the nevirapine treated group (28.4%) as compared with the HAART treated women (18.2%).

The mean (± SD) of gestational age at enrollment was significantly lower [$p < 0.001$] among women who were on HAART therapy (18.7 wks ± 5.0) as compared with 22.2 wks ± 5.8 for women treated with nevirapine. There were no statistically significant differences in the gestational age at delivery with both groups of patients having delivered between 30 – 42 weeks (HAART treated) and 33 – 44 weeks (nevirapine treated group). Although there were more cases of preterm delivery among women treated with nevirapine alone (18.9%) as compared with 13.6% for women on HAART therapy, the difference was not statistically significant.

Table 2 shows the results of the laboratory tests performed for the pregnant women in this study. As was anticipated, the $CD4^+$ cell counts for women on HAART therapy (129 ± 49; mean ± SD) were significantly lower ($p < 0.001$) than for women who were not treated with HAART (483 ± 220; mean ± SD). This was a selection criterion as it provided justification for treatment with HAART.

However, FBC (Haemoglobin and Platelets) did not show any statistically significant difference between the two groups of patients. All the women not treated with HAART had normal LFT results but there were 9 women (13.6%) among those on HAART therapy, who had abnormally high LFT results. Table 2 also shows that whereas no case of positive serological test for RPR was found among women who did not receive HAART therapy, there were 5 (7.6%) positive cases among women who were treated with HAART.

Table 2: Laboratory findings for the two groups of women in this study [HAART treated versus Nevirapine treated women]

	HAART therapy group	**Nevirapine group**
$CD4^+$ Counts: Range **Median** **Mean (± SD)** **[p < 0.001]**	**18 – 198 cells** **135** **129 (± 49)**	**210 – 1234 cells** **447** **483 (± 220)**
FBC: Hb (Range) (Mean ± SD)	**8.6 – 15.4 g/dL** **11.5 (± 1.3) g/dl**	**7.0 – 15.4 g/dL** **11.7 (± 1.6)**
Platelets (Range) (Mean ± SD)	**64 – 504 x 10^9** **251 (± 86)**	**141 -440 x 10^9** **247 (± 70)**
LFT: - AST **- ALT** **- ALP** **- LDH** **- gamaGT**	**9 elevated values for AST, ALT, ALP & LDH (13.6%)**	**All results were normal (100%)**
RPR Results: Positive Negative	**5 (7.6%)** **61 (92.4%)**	**NONE** **95 (100%)**

Table 3 provides a comparison of the obstetric performance between women treated with HAART and those who only received intra-partum prophylaxis of

nevirapine. Women on HAART treatment had duration of therapy ranging from 1 to 38 weeks (Median treatment – 10 weeks). No statistically significant differences were found between the two groups for duration of labour (12.4 hours ± 7.0 for HAART group; 11.8 ± 5.9 nevirapine group) and mode of delivery. The group on HAART therapy delivered vaginally (71.2%) or by C/S (28.8%) as compared with the second group whose delivery was per vaginal (75.8%) or by C/S (24.2%). The figures show no statistically significant differences in the mode of delivery by both groups of women.

Table 3: Comparison of the obstetric outcomes between pregnant women on HAART and women treated with intra-partum nevirapine

	HAART Therapy Group	Nevirapine Treated Group
DURATION OF LABOUR - **Range** - **Mean ± SD**	**3 – 30 hours** **12.4 ± 7.0**	**3 – 29 hours** **11.8 ± 5.9** **[p = 0.59]**
MODE OF DELIVERY - **NVD** - **C/S** - **ELECTIVE C/S**	**47 (71.2%)** **19 (28.8%)** **5 (7.6%)**	**72 (75.8%) [p = 0.64]** **23 (24.2%) [p = 0.72]** **6 (6.3%) [p = 0.51]**
COMPLICATIONS - **Pueperal Sepsis** - **Wound Sepsis**	**2 (3.0%)** **2 (3.0%)**	**3 (3.2%) [p = 0.84]** **1 (1.1%)**

Very few complications were recorded for the two groups of pregnant women.

Pueperal sepsis occurred in 2 cases of women treated with HAART and in 3 cases among women treated with nevirapine. Similarly, 2 cases of wound sepsis

were treated among women on HAART whereas only one case of wound sepsis was noted among women who had intra-partum nevirapine. There were no complications encountered for vaginal deliveries among all the women in the two groups.

Table 4 and Figure 1 illustrate the fetal outcomes for women treated with HAART compared with those who were given intra-partum nevirapine.

Table 4: Fetal outcomes for women treated with HAART [N = 66] compared with the Nevirapine group [N = 95].

	HAART Treated Patients	**Nevirapine Treated Patients**
STILLBIRTHS	**NONE**	**NONE**
ENND	**1 BABY**	**NONE**
LNND	**NONE**	**NONE**
NEONATAL INFECTION	**I BABY**	**NONE**

There were no recorded cases of stillbirths among both groups of patients. The only case of early neonatal death occurred among women who were treated with HAART and there was one case of neonatal infection in the same group of patients.

Figure1: The rate of vertical transmission of HIV infection – HAART treated group versus Intra-partum nevirapine treated group [PCR TEST].

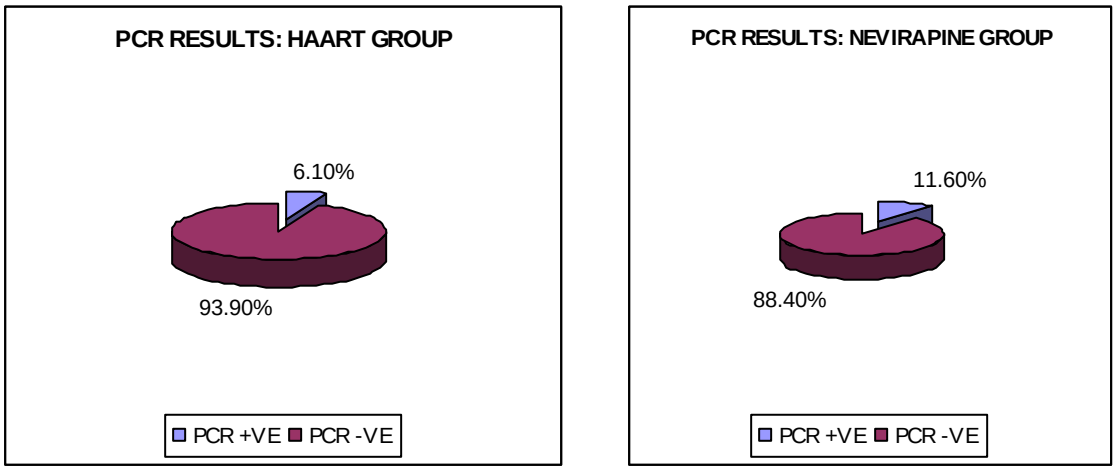

Figure 1 shown above illustrates the rate of mother-to-child transmission of HIV infection in which the group treated with HAART had lower (6.1%) transmission rate compared with the group of women who received intra-partum nevirapine (11.6%). The Odds Ratio between the two groups regarding possibility of mother-to-child transmission of HIV is 1.9 (95% Confidence Interval = 0.88 – 2.92). This means that there is approximately a two-fold possibility of transmission of HIV infection among women who had not received HAART during pregnancy compared with those who were on HAART therapy during pregnancy.

DISCUSSION

This study has proved the effectiveness of a two-dose intra-partum-postnatal nevirapine in preventing mother-to-child transmission (MTCT) of HIV in a population where either formula feeding or breastfeeding was offered to the infants. In the group of HIV infected mothers where the mother received nevirapine 200 mg orally at the onset of labour and the infant received nevirapine syrup 2 mg/kg body weight within 72 hours post delivery, the vertical transmission rate was 11.6%. These findings were comparable to the SAINT trial [2]. The SAINT trial had two arms where in one arm the mother received nevirapine 200 mg at the onset of labour and the infant received nevirapine

syrup 2 mg/kg body weight within 48 hours post delivery. The vertical transmission rate on this arm was 12.3%, which was comparable to the present study. On the other arm of the SAINT trial the mother received zidovudine and lamivudine intra-partum and zidovudine plus lamivudine for 7 days post partum and the infant received zidovudine plus lamivudine syrup for 7 days post delivery. The vertical transmission rate in this arm was 9.3% at 8 weeks compared to 12.3% in the nevirapine arm of the same study.

The findings of this study were also comparable to the findings of the HIV-NET 012 study conducted in Uganda [28, 29]. In the HIV-NET 012 study HIV infected

mothers were given nevirapine 200 mg orally at the onset of labour and the infant was given nevirapine syrup 2 mg/kg within 72 hours post delivery in one arm and on the other arm i.e. the zidovudine arm the mother received zidovudine 600 mg orally at the onset of labour and zidovudine 300 mg per os 3 hourly until delivery and the infant received zidovudine syrup 4 mg/kg orally twice daily for 7 days after birth. The vertical transmission rate was 21.3% at 6 – 8 weeks for the zidovudine arm and 11.9% at 6 – 8 weeks for the nevirapine arm. The vertical transmission rate was 25.1% for the zidovudine arm and 13.1% for the nevirapine arm at 14 – 16 weeks post delivery. The vertical transmission rate of 11.0% for the nevirapine arm at 6 – 8 weeks post delivery was comparable to this study. In the HIV-NET trial, 98% of mothers were noted to have breast-fed their babies.

In the Malawian study of 1,119 babies of HIV-infected women were given either nevirapine syrup 2 mg/kg single dose or nevirapine plus zidovudine immediately after birth **[51]**. Zidovudine syrup 4 mg/kg was given twice daily for one week. The mother received no intra-partum antiretroviral drugs as the mother presented late to the hospital i.e. within 2 hours prior to delivery. The vertical transmission rate at 6 – 8 weeks was 15.3% in 484 babies who received nevirapine and zidovudine and 20.9% in 468 babies who received nevirapine only.

Among the patients who received HAART, 4 (6.0%) of the babies were PCR positive at 6 weeks post delivery which is a very high percentage considering that the vertical transmission rate for patients on HAART should be between 1.2% and 1.5% in non-breastfeeding populations.

In the European Collaborative study done in 29 centers in 10 European countries, 1,147 women who received HAART during pregnancy, 654 (57%) started receiving HAART for the first time during pregnancy, 50 (4.0%) had been receiving monotherapy or dual therapy before their pregnancies and the

remaining 443 (39.0%) were already receiving HAART when they fell pregnant [52]. The vertical transmission rate was 2.87% which was by far lower compared to the present study which reported 6.0% vertical transmission rate at 6 weeks. In another study of combination antiretroviral therapy by McGowan et al. involving 30 patients – none of the 26 infants who were followed up for at least 4 months had HIV infection. Although these number of study patients were lower than in my study [53].

In the Women and Infants Transmission Study by Cooper et al. the vertical transmission rate was 1.2% for 250 mothers who were on highly active

antiretroviral therapy (HAART) which was very low compared to the rate reported in the present study [54].

The main reason for the difference in transmission rate in my study compared to the above cited studies is that in my study patients were not given intravenous intra-partum zidovudine during labour and instead continued with stavudine, lamivudine and nevirapine during labour. The other reason is that the infant only received nevirapine syrup within 72 hours post delivery instead of zidovudine syrup 2 mg/kg body weight 6 hourly for 6 weeks post delivery. In addition, those other studies were conducted in non-breastfeeding populations

Nine patients (13.6%) of the mothers on HAART had liver enzyme derangements. These findings are comparable to the findings by Martinez et al [55], carried out in non-pregnant patients who received nevirapine-containing HAART regimens. There was 12.5% incidence of hepatotoxicity in the same report by Martinez et al. Sulkowski et al found 30% incidence of hepatotoxicity in ritonavir containing regimens in non-pregnant patients but only found 5.9% incidence of hepatotoxicity in nelfinavir containing regimens [56]. In another study, van Schalkwyk et al found 12.5% incidence of hepatotoxicity among pregnant mothers who received nevirapine-containing regimens [57]. In contrast to all these reports Joao et al [8] found 1.5% incidence of toxicity among

pregnant mothers who received nevirapine-based regimens – an incidence which is far lower than in my study. All these findings, both from my study and from the literature emphasize the need for continued surveillance of mothers on HAART in order to detect and determine the severity of the toxicities.

Among the HIV infected mothers who received a two-dose intra-partum-postnatal nevirapine who delivered infants who were PCR positive at 6 weeks post delivery, 4 of the mothers delivered by caesarean section. These four mothers had other risk factors for vertical transmission of HIV such as premature rupture of membranes and prolonged labour. Three of these babies were formula-fed and only one baby was breast-fed.

STUDY LIMITATIONS

Limitations of this study were that the investigator was not blinded to the treatment status or outcome of the study. The other limitation was that it was difficult to compare the outcome of the nevirapine regimen with placebo and also the outcome of those who were receiving HAART with a placebo as those mothers needed HAART to improve their health. I also did not compare this study with the full PACTG 076 trial where the mother received antiretroviral,

intra-partum zidovudine and the infant received zidovudine syrup for 6 weeks [21].

The advantage of using intra-partum-postnatal nevirapine is that nevirapine has several characteristics that distinguish it from zidovudine which may explain why its use as an intra-partum post-partum regimen is superior in lowering transmission risk. Unlike zidovudine, nevirapine can decrease plasma HIV RNA concentration by at least 1.3 log after a single dose, is active immediately against intracellular and extracellular virus and does not have to be taken up by the cell and metabolized to its active form. Nevirapine could be more effective than zidovudine when given close to the time of exposure and may have more striking effect in decreasing viral load in the colostrums and early breast milk samples.

The advantage of HAART is that it suppresses viral replication and achieves maximal viral suppression and hence lowers viral load to undetectable level. In a patient who receives HAART addition of intra-partum-postnatal nevirapine does not further decrease the transmission rate. In a patient who receives intra-partum intravenous zidovudine and zidovudine syrup given to the infant for 6 weeks post-partum as proven by the PACTG 316 study [35].

This study highlights the effectiveness of a two-dose intra-partum-postnatal nevirapine in preventing mother-to-child transmission of HIV and also the need to give intravenous intra-partum zidovudine for patients on HAART and to give zidovudine syrup for 6 weeks post delivery to the infant.

CONCLUSION

This study highlights the following findings:

1. A two-dose intra-partum-postnatal nevirapine is effective in preventing mother-to-child transmission of HIV.
2. The use of HAART without adding intravenous intra-partum zidovidine syrup to the mother and 6 weeks zidovudine syrup to the infant did not lower the vertical transmission rate to the required level of between 1.2% and 1.5%.
3. Emergency caesarean section was not associated with decreased vertical transmission in patients who received a two-dose intra-partum-postnatal nevirapine.

ACKNOWLEDGEMENTS

I am immensely grateful and indebted to my two supervisors Dr L. Matsela and Professor O.A. Towobola whose encouragements have led me to the proverbial 'end-of the road' in the pursuit of extra knowledge. I wish to express my sincere thanks to my colleagues in the Department of Obstetrics & Gynaecology (Dr George Mukhari Hospital) for providing me the conducive environment within which I was able to complete this study.

REFERENCES

1. WHO – Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: Guidelines for care, treatment and support for women living with HIV/AIDS and their children in resource constrained settings. World Health Organization; 2004, Geneva.

2. Moodley D.; Moodley J.; Coovadia H. et al – The South African intra-partum nevirapine trial (SAINT). A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intra-partum and early post-partum mother-to-child transmission of human immunodeficiency virus type I. Journal of Infectious Diseases; 2003, vol. 187: 725 – 735.

3. Gray G.E. & McIntyre J. – Pregnancy plus HIV and pregnancy. British Medical Journal; 5 May 2007, vol. 334: 950 – 953.

4. Thorne C. and Newell M.L. – Prevention of mother-to-child transmission of HIV infection. Current Opinion in Infectious Diseases; 2004, vol. 17: 247 – 252.

5. Thorne C.; Patel D. and Newell M.L. – Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. AIDS; 2004, vol.18: 2337 – 2339.

6. Watts D.H. – Treating HIV during pregnancy – an up-date on Safety Issues. Drug Safety; 2006, vol. 29(6): 467 – 490.

7. Newell M.L.; Coovadia H.M.; Corina-Borja M. et al. – For the Ghent IAS Working Group on HIV in women and children. Mortality among infected and uninfected infants born to HIV-infected mothers in Africa: A pooled analysis. Lancet; 2004, vol. 364: 1236 – 1243.

8. Joao E.C.; Calvert G.A.; Meneze J.A. et al. – Nevirapine toxicity in a cohort of HIV-infected pregnant women. American Journal of Obstetrics & Gynecology; 2006, vol. 194(1): 199 – 202.

9. Capparelli E.; Rakhmanina M. & Mirochnick M. – Pharmacotherapy of perinatal HIV. Seminars in Fetal and Neonatal Medicine; 2005, vol. 10: 161 – 175.

10. Garcia P.M.; Kalish L.A.; Pitt J. et al. – Maternal levels of plasma human immunodeficiency virus Type I RNA and the risk of perinatal transmission. New England Journal of Medicine; 1999, vol. 341: 394 – 402.

11. Sperling R.S.; Shapiro D.E.; Coombs R.W. et al. – Maternal viral load, zidovudine treatment and the risk of transmission of human immunodeficiency virus Type I from mother to infant. New England Journal of Medicine; 1996, vol. 335: 1621 – 1629.

12. Mofenson L.M.; Lambert J.S.; Stiehm E.R. et al. – Risk factors for perinatal transmission of human immunodeficiency virus Type I in women treated with zidovudine. New England Journal of Medicine; 1999, vol. 341: 385 – 393.

13. The International Perinatal HIV Group – The mode of delivery and the risk of vertical transmission of human immunodeficiency virus Type I. New England Journal of Medicine; 1999, vol. 340: 977 – 987.

14. De Cock RM.; Fowler MG.; Mecier E.; De Vincenzil L.; Saba J.; Hoff E. et al. - Prevention of mother-to-child HIV transmission in resource poor countries: Translating research into policy and practice. Journal of American Medical Association; 2000, vol. 283: 1175 – 1182.

15. The International Perinatal Group: The mode of delivery and the risk of vertical transmission of human immunodeficiency virus Type 1. New England Journal of Medicine; 199, vol. 340: 977 – 987.

16. Kuan L. et al. – **In**: Programme and Abstracts of the Seventh Conference on retroviruses and opportunistic infections. San Fransisco; 2000.

17. Johnson K.; Posner S.F.; Biermann J. et al. – Recommendations to improve pre-conception health and health care in the Unites States. A report of the CDC/ATSDR preconception care work Group and the select panel on preconception care: MMWR Recommendations. REP; 2006, 55 (RR-6): 1 – 23.

18. American College of Obstetricians and Gynecologists. ACOG Committee Opinion, Number 313; September 2005, The importance preconception care in the continuum of women's health care. Obstetrics Gynecology; 2005, vol. 106 (3): 665 – 666.

19. Public Health Task Force: Recommendations for use of antiretroviral drugs in pregnant HIV-Infected women for maternal health and intervention to reduce perinatal HIV transmission in the United States. HIV Info: July 8; 2008, (http://www.AIDS info.nih.gov): 1 – 98.

20. WHO Staging system for HIV infection and disease in adults and adolescents: Scaling up antiretroviral therapy in resource – limited settings. Treatment guidelines for a public approach – 2003 Revision. http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en/pdf: pages 4-66. World Health Organization, Geneva 2004:

21. Connor E.M.; Sperling R.S.; Gelber R.; Kiselev P.; Scott G.; O'Sullivan M.J. et al. – Reduction of maternal infant transmission of human immunodeficiency virus Type I with zidovudine treatment. Paediatric AIDS Clinical Trial Group Protocol 076 Study Group. New England Journal of Medicine; 1994, vol. 331: 1173 – 1180.

22. Shaffer N. et al. – Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: A randomized controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. Lancet; 1999, vol. 353(1955): 773 – 780.

23. Leroy V. et al. – Twenty-four month efficacy of a maternal short-course zidovudine regimen to prevent mother-to-child transmission of HIV-1 in West Africa. AIDS; 2002, vol. 6(4): 631 – 641.

24. Wiktor S.Z. et al. – Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abijan, Ivory Cote d'Ivoire: A randomized trial. Lancet; 1999, vol. 353 (9155): 781 – 785.

25. Dabis F. et al. – 6-month efficacy, tolerance and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Cote d'Ivoire and Burkina Faso: A double-blind placebo-controlled multi-center trial. – DTRAME Study Group – Diminution de la transmission mere – enfant. Lancet; 1999, vol. 353 (9155): 786 – 792.

26. The PETRA Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa and Uganda (PETRA STUDY): a randomized, double-blind, placebo-controlled trial. Lancet; 2002, vol. 359 (9313): 1178 – 1186.

27. Chaisilwattana P. et al. – Short-course therapy with zidovudine plus lamivudine for prevention of mother-to-child transmission of human immunodeficiency virus Type I in Thailand. Clinical & Infectious Diseases; 2002, vol. 35(11): 1405 – 1413.

28. Jackson J.B. et al. – Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kanpala, Uganda: 18-month follow-up of the HIV-NET 012 randomized trial. Lancet; 2003, vol. 362(9387): 859 – 868.

29. Guay L.A. et al. – Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1, Kanpala, Uganda: HIV-NET 012 randomized trial. Lancet; 1999, vol. 354 (9181): 795 – 802.

30. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: Guidelines on care, treatment and support for women living with HIV/AIDS and their children in resource-constrained settings; World Health Organization, Geneva. Accessed April 2009, http://www.who.int/hiv/pub/mtct/guidelines/en, pages 1 – 50.

31. World Health Organization – Antiretroviral drugs for treating HIV infection in resource-limited settings, 2005 Revisions. Available on-line from: URL: http://www.int/3by5/medicentre/news51/en

32. Wadellius M.;Darj E.; Frenne G.; Rame A. – Induction of CYP 206 in pregnancy. Clinical Pharmacology & Therapeutics; 1997, vol. 62: 400 – 407.

33. Richman D.D.; Morton S.C.; Wrin T. et al. – The prevalence of antiretroviral drug resistance in the United States. AIDS; 2004, vol. 18(10): 1393 – 1401.

34. Palumbo P.; Holland B.; Dobbs T. et al. – Antiretroviral resistance mutations among pregnant human immunodeficiency virus Type-1 infected women and their newborns in the United States: vertical transmission and Clades. Journal of Infectious Diseases; 2001, vol. 184(9): 1120 – 1126.

35. Cunningham C.K.; Chaix M.L.; Rekacewicz C. et al. – Development of resistance mutations in women receiving standard antiretroviral therapy who received intrapartum nevirapine to prevent perinatal human immunodeficiency virus Type 1 transmission: A sub-study of Paediatric AIDS Clinical Trials Group, Protocol 316. Journal of Infectious Diseases; 2002, vol. 186(2): 181 – 188.

36. Mandelbrot L.; Landreau M.A.; Rekawitz C. et al. – Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. Journal of American Medical Association; 2001, vol. 285(16): 2083 – 2093.

37. Loubser S.; Balfe P.; Sherman G. et al. – Decay of K-103N mutants in cellular DNA and plasma RNA after single-dose nevirapine to reduce mother-to-child HIV transmission. AIDS; 2006, vol. 20(7): 995 – 1002.

38. Nijhuis M.; Deeks S. and Boucher C. – Implications of antiretroviral resistance: Viral fitness. Current Opinion in Infectious Diseases; 2001, vol. 14(1): 23 – 28.

39. Watts D.H. – Management of the HIV-infected pregnancy. New England Journal of Medicine; 2002, vol. 346: 1879 – 1891.

40. The European Collaborative Study and the Swiss mother-to-child HIV Cohort Study. Combination antiretroviral therapy and duration of Pregnancy. AIDS; 2000, vol. 14: 2913 – 2920.

41. Nightingale S.L. – From the Food and Drugs Administration. Journal of American Medical Association; 1998, vol. 280: 1472 – 1474.

42. European Collaborative Study. Exposure to antiretroviral therapy in utero or early life: The health of uninfected children born to HIV-infected women. Journal of AIDS; 2003, vol. 32: 380 – 387.

43. Le Chenadec J.; Mayaux M.J.; Guihenneuc-Jouyaux C. et al. – For the enquete perinatale francaise Study Group. Perinatal antiretroviral treatment and hematopoiesis in HIV-uninfected infants. AIDS; 2003, vol.17: 2053 – 2061.

44. Noguera A.; Fortuny C.; Munoz-Almagro C. et al. – Hyperlactatemia in human immunodeficiency virus-uninfected infants who are exposed to antiretrovirals. Paediatrics; 2004, vol.114: 598 – 603.

45. Newell M.L.; Borja M.C.; Peckham C. et al. – Height, weight and growth in children born to mothers with HIV-1 infection in Europe. Paediatrics; 2003, vol.111: 52 – 60.

46. Culnane M.; Fowler M.G.; Lee S.S. et al. – Lack of long-term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women. Journal of American Medical Association; 1999, vol. 281: 151 – 157.

47. Blanche S.;Tardieu M.; Rustin P. et al. – Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. Lancet; 1999, vol. 354: 1084 – 1089.

48. Barret B.; Tardieu M.; Rustin P. et al. – For the French Perinatal Cohort Study Group. Persistent mitochondrial dysfunction in HIV-exposed but uninfected infants: Clinical screening in a large prospective cohort. AIDS; 2003, vol.17: 1769 – 1785.

49. Poirier M.C.; Divi R.L. Al-Harthi L. et al. – The women and infants transmission study. Long-term mitochondrial toxicity in HIV-uninfected infants born to HIV-infected mothers. Journal of Acquired Immune Deficiency Syndrome; 2003, vol.33: 175 – 183.

50. The Perinatal Safety Review Working Group. Nucleoside exposure in the children of HIV-infected women receiving antiretroviral drugs: Absence of clear evidence for mitochondrial disease in children who died before 5 years of age in 5 United States cohorts. Journal of Acquired Immune Deficiency Syndrome; 2000, vol. 25: 261 – 268.

51. Taha E.T.; Kamwenda N.; Gibbons A. et al. – Short post-exposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1, NVA2: Randomized clinical trial. Lancet; 2003, vol.362: 1171 –1177.

52. The European Collaborative Study – Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. Clinical Infectious Diseases; 2005, vol. 40: 458 – 465.

53. McGowan J.P.; Crane M.; Andrew A. et al. – Combination antiretroviral therapy in human immunodeficiency virus infected pregnant woman. Obstetrics & Gynaecology; 1999 (Nov.), vol. 94 (5): 641 – 646.

54. Cooper E.R.; Charurat M.; Mofenson L.M. et al. – Combination antiretroviral strategies for the treatment of pregnant HIV1-infected women and prevention of perinatal HIV1 transmission. Journal of Acquired Immune Deficiency Syndrome & Human Retrovirology; 2002, vol. 29(5): 484 – 494.

55. Esteban M.; Blanco J.L.; Arnaiz J.A. et al. – Hepatotoxicity in HIV-1 infected patients receiving nevirapine-containing antiretroviral therapy. AIDS; 2001, vol. 15: 1261 – 1268.

56. Sulkowski M.S.; Thomas D.L.; Chaisson R.E. et al. – Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. Journal of American Medical Association; 2000, vol. 283(1): 74 – 80.

57. van Schalkwyk J.E.; Alimenti A.; Khoo D. et al. – Serious toxicity associated with continuous nevirapine-based HAART in pregnancy. British Journal of Obstetrics & Gynaecology; 2008, vol. 115: 1297 – 1302.