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HIV IN PREGNANCY:

A REVIEW

WHO

UNAIDS

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TABLE OF CONTENTS

GLOSSARY OF ACRONYMS

3TC	Lamivudine
ADCC	Antibody-dependent cellular cytotoxicity
AIDS	Acquired Immune Deficiency Syndrome
ARV	Antiretroviral
AZT	Azidothymidine (zidovudine)
CD4+	Cluster designation 4 positive lymphocytes
CD8	Cluster designation 8 positive lymphocytes
DNA	Deoxyribonucleic acid
ECS	European Collaborative Study
ELISA	Enzyme-linked immunoabsorbent assay
FDA	Food and Drug Administration, United States of America
HBV	Hepatitis B virus
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus Type 1
HIV-2	Human Immunodeficiency Virus Type 2
HIVIG	Hyper-immune HIV immunoglobulin
HLA	Human leukocyte antigen
IgA	Immunoglobulin A
IgM	Immunoglobulin M
IVIG	Intravenous immunoglobulin
MTCT	Mother-to-child transmission
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NSI	Non-syncytium-inducing
PACTG	Pediatric AIDS Clinical Trials Group
PCP	*Pneumocystis carinii* pneumonia
PCR	Polymerase Chain Reaction
PETRA	Perinatal Transmission Study (UNAIDS)
RNA	Ribonucleic acid
SI	Syncytium-inducing
SLPI	Secretory leukocyte protease inhibitor
STI	Sexually transmitted infection
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children’s Fund
USA	United States of America
WHO	World Health Organization
WITS	Women and Infants Transmission Study
ZDV	Zidovudine

EXECUTIVE SUMMARY

Most of the thirty-three million people living with HIV (human immunodeficiency virus) are in the developing world, where HIV infection in pregnancy has become the most common complication of pregnancy in some countries. More than 70% of all HIV infections are a result of heterosexual transmission and over 90% of infections in children result from mother-to-child transmission (MTCT). Almost 600 000 children are infected by mother-to-child transmission of HIV annually, over 1600 each day. In parts of southern Africa, the prevalence of HIV in pregnant women is over 30%, while rates of new infections are rising in south-east Asia and the proportion of infections occurring in women is increasing in many developed countries. Women are particularly susceptible to HIV infection for both biological and socio-cultural reasons.

Pregnancy does not have a major adverse effect on the natural history of HIV infection in women in most studies, although AIDS (acquired immune deficiency syndrome) has become a leading cause of maternal mortality in some areas, as the epidemic progresses. Adverse pregnancy outcomes that have been reported in HIV positive women include increased rates of spontaneous early abortion, low birth weight babies, stillbirths, preterm labour, preterm rupture of membranes, other sexually transmitted infections, bacterial pneumonia, urinary tract infections and other infectious complications, although whether these are attributable to HIV infection is unknown.

Reported rates of transmission of HIV from mother to child range from 15% to over 40% in the absence of antiretroviral treatment and vary across countries. Transmission can occur in-utero, during labour and delivery or postpartum through breast milk. Most of the transmission is thought to occur in late pregnancy and during labour. Factors associated with an increase in the risk of transmission include viral factors, such as viral load, genotype and phenotype, strain diversity and viral resistance; maternal factors, including clinical and immunological status, nutritional status and behavioural factors such as drug use and sexual practice; obstetric factors such as duration of ruptured membranes, mode of delivery and intrapartum haemorrhage; and infant factors, predominantly related to the increased risk of transmission through breastfeeding.

The use of antiretroviral treatment in pregnancy in a long regimen (as used in the PACTG076 trial) reduces the risk of transmission by two-thirds. Where this has become standard treatment, transmission rates have dropped significantly. Short regimen of zidovudine which is started late in pregnancy and continues until delivery or into the postpartum period appears to decrease transmission risk by 40 to 50%. This relative decrease in risk has been seen in trial populations in which no breastfeeding took place as well as in populations where breastfeeding was practised by the majority of mothers. This observed effectiveness of zidovudine in breastfed infants has not yet been followed-up beyond six months of age. Several studies are in progress on alternative regimens and combination of antiretroviral therapy, which may prove more effective.

Elective Caesarean section also provides protection against mother-to-child transmission, although this is unlikely to be readily available in most developing country settings where HIV prevalence is high. Low serum vitamin A levels have been associated with increased rates of transmission and intervention studies are in progress to evaluate the protective effect of vitamin A and other microbutrients during pregnancy. Vaginal

cleansing with Chlorhexidine may be associated with a decreased risk of transmission, and more research is warranted in this field.

Breastfeeding contributes significantly to HIV transmission to children in developing countries. Adequate alternatives to breastfeeding should be provided for HIV-positive women wherever possible. Other possible modifications of infant feeding practices include early cessation of breastfeeding.

HIV testing in pregnancy has a number of benefits, but this must be balanced against the possible risks of stigmatization, discrimination and violence. Voluntary counselling and testing should be encouraged for couples. Post-test counselling is essential following a diagnosis of HIV and should include information about pregnancy-related issues and the risk of mother-to-child transmission. Counselling is also important for HIV-negative women as it provides an opportunity for risk-reduction information to be discussed.

The management of pregnancy in HIV-positive women should be seen as part of the holistic and long-term care of the woman. The medical care of HIV positive women should be tailored to the individual needs of the woman. Obstetric management will be similar to that for uninfected women in most instances, although invasive diagnostic procedures should be avoided, and iron, folate and other vitamin supplementation should be considered. The use of antiretroviral drugs in pregnancy for the prevention of mother-to-child transmission of HIV should be encouraged and provided as widely as possible. In settings where this cannot be implemented in the short-term, other interventions including modifications of obstetric practice should be considered. Postpartum care must include contraceptive advice and provision, infant feeding support and appropriate follow-up for the neonate and the mother.

Universal precautions against occupational exposure to HIV and other pathogens should be in place in maternity services. Basic precautions in obstetric practice include the use of impermeable gloves, the use of a needle holder for suturing episiotomies or vaginal tears and appropriate disposal of needles and blood or liquor contaminated dressings and linen. Where accidental exposure to HIV occurs, by needlestick or other injury, the use of antiretroviral drugs as post-exposure prophylaxis greatly reduces the risk of infection.

INTRODUCTION

At the end of 1998, more than thirty-three million people were living with HIV, almost half of whom were women in their reproductive years [1,2]. Over one million children are living with HIV, contracted predominantly through infection from their mothers. The majority of these women and children are in the developing world with two thirds of the infected adults and over 90% of the world's HIV-infected children in Africa. The face of the epidemic is changing as the increasing rate of infection in south-east Asia now accounts for an increasing proportion of new cases. In sub-Saharan Africa, HIV-1-related diseases may account for over 75% of annual deaths in the 15 to 60 age group within the next 15 to 20 years. Life expectancy at age 15 in countries severely affected by the AIDS epidemic could drop from 50 to below 30 years[3]. It is projected that by 2010, if the spread of HIV has not been contained, AIDS will increase infant mortality by 25 percent and under-five mortality by over 100 percent in the regions most affected by the disease. There have been 8.2 million children who have lost their mothers or both parents to AIDS to date in the epidemic[1], at least 95% of whom have been African.

HIV infection in pregnancy has become the most common complication of pregnancy in some developing countries. This has major implications for the management of pregnancy and birth. With an estimated one and a half million HIV-positive women becoming pregnant each year, almost 600 000 children will be infected by mother-to-child transmission annually: over 1600 each day[1,4]. Maternity services in areas of high HIV prevalence have several responsibilities. Firstly, to enable women to be tested and to use these results to maintain their health in an optimal manner; secondly to utilize appropriate interventions to reduce the rate of mother-to-child transmission of HIV; and thirdly to train staff and provide equipment to prevent nosocomial transmission of HIV and other pathogens[5].

There are two main types of HIV: type 1 (HIV-1) is the most common, with HIV type-2 (HIV-2) found predominantly in West Africa, with some pockets in Angola and Mozambique[6,7]. While HIV-1 prevalence is increasing in these areas, the prevalence of HIV-2 has remained fairly stable, and the clinical course of HIV-2 infection is slower than that of HIV-1. Dual infection with HIV-1 and HIV-2 is possible, although it has been suggested that HIV-2 infection may confer some protection against HIV-1 acquisition[7]. Although mother-to-child transmission of HIV-2 has been documented, this occurs less frequently than with HIV-1[8,9]. In view of the lesser prevalence of HIV-2 in pregnancy, this document will focus on HIV-1 infection.

The first section of the review consists of a summary of what is known about HIV in pregnancy, transmission of HIV from mother to child, and interventions to prevent transmission. The second part of the review provides some suggestions on the appropriate management of HIV-positive women during pregnancy, delivery and postpartum, and the third section lists guidelines for infection control and safe working conditions with regard to HIV in pregnancy.

SECTION A:

HIV IN PREGNANCY

Epidemiology of HIV

HIV is transmitted in only three ways: through unprotected sexual intercourse, heterosexual or homosexual; through blood or blood products, donated semen or organs; or from an infected mother to her child (vertical or mother-to-child transmission). More than 70% of infections are a result of heterosexual transmission and over 90% of infections in children result from mother-to-child transmission [4,10,11].

Although the HIV epidemic is centred in the developing world, AIDS has also become a leading cause of death for young women in the United States of America (USA)[12,13,14]. In developed countries, HIV seropositive women are more likely to be intravenous drug users, partners of drug users or bisexual men, or be involved in sex work [15,16,17]. In one American study, 47% of mothers of HIV-infected infants were intravenous drug users, and 22% reported sex with an intravenous drug user[18].

The situation is very different in developing countries, where heterosexual transmission is the predominant mode of spread. Southern Africa is the most affected region[1]. In Kenya, Malawi, Namibia, Rwanda, South Africa, the United Republic of Tanzania, Zambia and Zimbabwe, over 10% of women attending antenatal clinics in urban areas are HIV-positive, with rates of almost 60% in some sites[1,10,19,20,21]. To date, Africa has been the centre of the epidemic but a rapid rise in infection rates has been seen in south-east Asia. In Thailand, prevalence in women in antenatal clinics has climbed from 0% in 1989 to 2.3% in 1995 and continues to rise. Similar increases are reported from some Indian cities, Latin America and the Caribbean[10]. While prevalence rates in antenatal women have been taken as a good indication of the rate of infection in communities[22,23] sentinel surveillance at antenatal clinics may under-estimate the population prevalence, as shown in a study in the Mwanza district of the United Republic of Tanzania, where the prevalence in antenatal attenders was below that of the general population by a factor of 0.75[24]. A decrease in the fertility of HIV-infected women, both from subfertility and from increased early pregnancy loss, as reported from the Rakai district in Uganda, may exacerbate this underestimation[25].

In urban Uganda there has been a reported decrease in the prevalence of HIV infections in pregnant women over the past few years. The 20% drop in prevalence is thought to be due to behaviour change following aggressive AIDS education campaigns[26].

Susceptibility of women to HIV infection

Women in the developing world are at higher risk of HIV infection than their male counterparts for a number of reasons, biological and sociological.

Biological factors

The rate of transmission of HIV from male to female is two to three times higher than that from female to male[27,28]. The Langerhans' cells of the cervix may provide a portal of entry for HIV and it has been suggested that some HIV serotypes may have higher affinity for these, and therefore to be more efficient in heterosexual transmission[29].

Vulval and vaginal inflammation or ulceration may facilitate entry of the virus. Sexually transmitted infections (STI) are common in many African countries, where HIV prevalence is also high[30,31,32]. Inadequately treated or "silent" chlamydial and other sexually transmitted infections may act as co-factors for HIV infection and transmission[33,34,35,36,37,38]. Syphilis rates as high as 30% have been described in antenatal women[39,40] and 4.2% of women in a population based study in the United Republic of Tanzania reported a history of genital ulceration[41], which has been well established as a co-factor for HIV acquisition[42,43,44]. In Zimbabwe, women reporting a history of genital ulceration and pelvic inflammatory disease were six times more likely to be HIV-positive[45]. Improved STI treatment in a randomized controlled trial in the United Republic of Tanzania was shown to reduce the rate of new HIV infections[46]. Other non-sexually transmitted cervical lesions, such as schistosomiasis, may also facilitate HIV infection[47]. Although the evidence is still inconclusive, associations between oral and injectable contraceptive use and increased HIV risk have been reported[48,49].

Socio-cultural factors

Women are essentially at more risk in cultures and communities that remove their control over their own bodies. Women are often blamed incorrectly as the source of HIV infection and carry the dual burden of infection and of caring for infected family members. Gender inequalities, poverty, less access to education and lack of employment opportunities force many women into commercial sex work in order to survive, and this group of women are at very high risk of HIV infection[50,51]. Conversely, many more women are monogamous, but are at high risk due to the sexual behaviour of their male partner. Traditional practices and customs such as "dry sex" practices, vaginal douching with non antiseptic compounds, female circumcision and "widow cleansing" may all have an effect on increasing women's risk of HIV infection[51,52,53,54,55,56,57]. Despite their high risk of infection, cultural practices and pressures often prevent women from taking the necessary precautions to guard against infection. Use of male condoms is low in many developing countries. The desire and the societal pressure to reproduce make it difficult for women to practice protected sex. Young women are at highest risk of infections in developing countries, many of them at the beginning of their reproductive lives. Even after a diagnosis of HIV infection, most women will not change their reproductive choices[58,59]. There are no methods available for women to use to prevent HIV transmission, independent of the male partner, with the possible exception of the female condom[60,61]. Female barrier methods remain expensive or unavailable in most developing countries, where male resistance to condom use is common, although the recent introduction of social marketing of the female condom in some southern African countries has demonstrated that there is considerable demand.

Effect of pregnancy on the natural history of HIV infection

In pregnancy, immune function is suppressed in both HIV-infected and uninfected women[5,62,63]. There is a decrease in immunoglobulin, reduced complement levels in early

pregnancy and a more significant decrease in cell-mediated immunity during pregnancy. These normal changes during pregnancy have led to concern that the effect of pregnancy among HIV-infected women could be to accelerate the progression of the infection. Early reports of pregnancy in HIV-infected women seemed to support this[64,65]. Prospective follow-up studies have not confirmed these findings to date. One French study followed 57 HIV-infected women who completed a pregnancy and 114 who had never been pregnant, with a mean follow-up of 61 months. There was no difference in the rate of acceleration of disease between the groups[66]. An Edinburgh study showed no effect of pregnancy on marker paths of HIV infection in 145 women followed between 1985 and 1992[67]. A further study from Switzerland followed 32 HIV infected pregnant women who had preconception CD4 cell counts and compared their disease progression with 416 HIV infected women who did not have a pregnancy. Women were matched for age and CD4 cell count at entry. Mean follow-up time was 4.8 years for the pregnant women and 3.6 years for the controls. There was no overall difference in the rate of death between the two groups nor in the rate of progression to any AIDS defining event, except that HIV infected women with pregnancies were significantly more likely to develop bacterial pneumonia than their never-pregnant controls[68].

Several other studies have shown similar results[63,69,70,71,72,73]. Pregnancy had little effect on viral load in an American study[74]. Pregnancy appears to have little effect on the progress of infection in asymptomatic HIV-positive women or in those with early infection, although there may be more rapid progression in women with late stage HIV infection[75,76,77].

African women do not appear to experience more rapid progression of HIV infection during their pregnancies, despite the additional factors of repeated pregnancies, other infections and poor nutrition. African research does not support the existence of a short-term synergistic effect on the immune system between pregnancy and HIV infection. In a Kenyan study, the difference in the changes over pregnancy in CD4+ and CD8 cells and their ratio were not statistically significant between HIV-positive and negative women[78]. CD4+ and CD8 percentages were shown to be stable in HIV sero-positive women in late pregnancy and the postpartum period in a Malawi study, demonstrating little effect of pregnancy on immune status[79].

In some central African countries, AIDS has become a common cause of maternal mortality, as the epidemic has progressed[80,81]. This does not appear to be due to pregnancy-induced acceleration of the HIV-related conditions but to more women with advanced disease becoming pregnant, with resultant higher rates of HIV complications.

Effect of HIV infection on pregnancy

HIV infection has been reported to have little effect on pregnancy outcome or complications in the developed world[77,82,83,84]. It is often difficult to determine the relative contribution of HIV infection, drug use and inadequate antenatal care to adverse outcomes in these women[85,86]. Adverse pregnancy outcomes have, however, been reported more commonly in a number of African studies[87,88,89,90,91] including complications of both early and late pregnancy. HIV may be the direct cause or a marker of a complex interaction of related medical and social conditions that affect pregnancy. Other studies have demonstrated no association[84]. These complication rates vary across studies and may reflect the extent of the epidemic and the nature of HIV-related diseases in different communities.

Complications of early pregnancy have been associated with HIV infection in several studies[75,77, 79,92,93]. HIV-1 and HIV-2 infection in Africa have both been linked to a higher rate of spontaneous abortion[8]. HIV seropositive women were 1.47 times more likely to have had a previous spontaneous abortion, and this rose to 1.81 in women in Uganda who were seropositive for both HIV and syphilis[94]. An American study showed a three-fold increase in early spontaneous abortion in a prospective follow-up study[92,95]. More than half of these aborted fetuses had evidence of HIV infection, particularly with the thymus gland affected.

Higher rates of ectopic pregnancy have been reported in HIV-positive women than in uninfected women, which may be related to the effects of other concurrent sexually transmitted infections. Genital tract infections such as *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Candida albicans* and *Trichomonas vaginalis* infection have been reported to be more common in women with HIV[96,97]. Syphilis is more common in HIV-positive women in African studies. Concurrent infection with syphilis was shown in 33% of HIV-positive pregnant women in South Africa: three times higher than the rate in HIV seronegative women[96]. These high rates of syphilis may confound studies of pregnancy outcome unless the potential bias is taken into account in analysis. All HIV-positive pregnant women should be screened for syphilis, even in low prevalence areas[97].

Bacterial pneumonia, urinary tract infections and other infections are more common during pregnancy in HIV seropositive women[91,98,99]. In addition to these infections and parasitic infestations, any of the HIV-related opportunistic infections can be found during pregnancy. Tuberculosis is the commonest opportunistic infection associated with HIV in the developing world, and particular attention should be paid to its diagnosis in pregnant HIV-positive women. *Herpes zoster* is common in young HIV-positive women, although uncommon in this age group in the absence of HIV infection[100]. Kaposi's sarcoma has been reported during pregnancy in HIV-positive women[101].

Preterm labour may be more common in HIV-positive women, with rates as high as double those rates seen in uninfected women in some reports[79,90,102]. Preterm rupture of membranes may also be increased in HIV-positive women and *abruptio placentae* has been described as more common in HIV-positive women in Kenya and South Africa [88,103].

There is little difference in the birth weight of babies born to HIV-positive mothers in developed countries[104,105]. In Edinburgh, HIV seropositivity was associated with a decrease in birth weight, but this was less than the drop attributable to smoking[106]. Low birth weight has been reported in some studies in developing countries[100,107]. In a Nairobi study, HIV-positive women showed a threefold increase in the risk of delivering a low birth weight baby[103]. This risk was higher with symptomatic HIV infection. In Zambia, the birth weights of babies born to HIV-positive mothers were significantly lower than those of babies of seronegative women. In a prospective study in Rwanda, birth weight was significantly lower in singleton infants of asymptomatic women, although the difference in mean birth weight between the two groups was only 120 g[107]. Other studies in predominantly asymptomatic cohorts have shown no significant difference in birth weights[108].

Increased stillbirth rates have been reported, especially from areas where the epidemic has been present for a long time. The risk appears to be lower in asymptomatic women, although stillbirth rates more than double those in HIV sero-negative mothers have been shown in some African centres. However, some of the reported studies do not control for

the presence of syphilis or other factors associated with stillbirth. A large study in Nairobi showed an independent association between HIV infection and both intra-uterine and intra-partum death, after controlling for the presence of other STIs[90].

Infectious complications are also more common during the postpartum period in HIV-positive women[88,102,109]. Caesarean section is particularly associated with higher infectious morbidity in some reports, especially in women with low CD4+ counts, with an increased mortality in one Rwandan study[109,110].

Mother-to-child transmission

Reported rates of transmission of HIV from mother to child range from around 15%-25% in Europe and the USA to 25% to 40% in some African and Asian studies[111,112]. With the advent of routine antiretroviral [ARV] therapy in many developed countries, much lower transmission rates are now being described[113,114]. The estimated annual incidence of perinatal infections declined by 27% in the USA between 1992 and 1995 after the widespread implementation of antiretroviral therapy in pregnancy[18].

Transmission of HIV-1 can occur in-utero, at the time of labour and delivery, or postnatally through breastfeeding. Knowledge about the likely timing of transmission is important for the design of possible interventions. Evidence for in utero transmission (as early as 8 weeks gestation) comes from: the detection of HIV-1 and viral antigens (p24) in fetal specimens and placental tissue, viral isolation from some infected infants at the time of birth which implies that transmission occurred before birth; in addition, the observation that some infants get sick very early in life whilst others have a prognosis similar to adults suggests that the first ones (rapid progressors) have acquired infection in utero[92,115,116,117]. The evidence for intrapartum transmission came first from observations from a register of twins[118], which found that the first born twin had a two-fold higher risk of contracting HIV-1 than the second born twin. It is thought that vaginal delivery of the first twin reduces exposure of the second twin to the virus in cervico-vaginal secretions although the same phenomenon is observed for twins delivered by Caesarean section. In addition, recent reports have indicated that mode of delivery may affect the transmission rate. Caesarean section whether elective or emergency has been shown to decrease transmission in some studies[119] and prolonged rupture of membranes [more than four hours] to increase the risk of transmission[120]. Around half of the infected infants will have negative viral studies at the time of birth[116] indicating that transmission occurred during labour/delivery at the soonest (it takes some days after infection for viral studies to become positive). The evidence for post-partum transmission came from recovery of HIV in both the cell-free and cellular portions of breast milk. In addition, postnatal transmission through breastfeeding is generally assumed to explain most of the differences in transmission rates between developed countries (no or short breastfeeding) and developing countries (prolonged breastfeeding).

The contribution of each of these routes to overall transmission has not been quantified exactly but it appears that in-utero transmission is less frequent and that a substantial proportion of infection occurs at the time of delivery or late in pregnancy[121,122,123]. This conclusion is based on the absence of an HIV-1 dysmorphic syndrome, the lack of manifestations of HIV-1 infection at birth and the finding that HIV-1 is detected in the first week of life in only about 50% of children later proven to be infected[111,113,122,123,124,125,126]. A working definition for the classification of the timing of transmission has been proposed, based on the time of detection of HIV in the infant.

Where virus is detectable within 48 hours of birth, an infant is considered to have been infected in utero, while intrapartum infection is assumed if viral studies are negative during the first week of life, but become positive between 7 and 90 days[127]. A Markov model of the time to p24 antigenaemia based on results from the French Collaborative Study group suggested that 65% of infants were infected around the time of labour and 35% in utero[128]. A probability of 27% for in utero transmission was obtained in the Women and Infants Transmission Study (WITS) in the USA[129], while in Kinshasa, 23% of infants were thought to be infected in utero, 65% intrapartum or early postpartum and 12% in late postpartum[130].

Factors affecting mother-to-child transmission of HIV-1

Transmission from mother to child of HIV is affected by a number of factors, not all of which have been fully elucidated. These can be divided into viral, maternal, obstetrical, fetal and infant factors as demonstrated in Table 1.

Table 1
Factors affecting mother-to-child transmission of HIV-1
131,132,133,134,135,136,137,138,139,140,141

VIRAL	Viral load Viral genotype and phenotype Viral resistance
MATERNAL	Maternal immunological status Maternal nutritional status Maternal clinical status Behavioural factors Antiretroviral treatment
OBSTETRICAL	Prolonged rupture of membranes (> 4 hours) Mode of delivery Intrapartum haemorrhage Obstetrical procedures Invasive fetal monitoring
FETAL	Prematurity Genetic Multiple pregnancy
INFANT	Breastfeeding Gastrointestinal tract factors Immature immune system

Viral factors

Viral load

Transmission is increased in the presence of high levels of maternal viraemia. Clinical observations of increased transmission in these situations, such as in advanced disease and at the time of seroconversion, are supported by the presence of high levels of p24 antigenaemia[142,143]. With the development of new techniques for the measurement of the virus, such as quantitative Polymerase Chain Reaction (PCR) DNA and RNA, an association has been shown between the maternal viral load and the risk of transmission from mother to child[144,145,146,147,148,149,150,151,152,153]. More than half of the women with viral loads of >50 000 RNA copies per ml at the time of delivery have been shown to transmit

the virus[145,154]. A New York study showed a mean viral load of 16 000 RNA copies/ml in transmitters and 6600 RNA copies/ml in non-transmitters[145]. Women in this study with measurable viral loads were almost six times more likely to transmit than those in whom the virus was undetectable, after controlling for the CD4+ count. In a French study, transmission rates increased with increasing viral load: 12% in those with less than 1000 copies/ml compared with 29% in those with more than 10 000 copies/ml[144]. Few studies have shown a threshold viral load for transmission and it appears that it can occur at low viral levels, for reasons which are not well understood, but which probably reflect the multiple influences acting on mother-to-child transmission[145,154,155].

The local viral load in cervico-vaginal secretions and in breast milk may also be an important determinant of transmission risk intrapartum and through breastfeeding[156,157,158]. HIV-1 levels in these fluids have been shown in most studies to be correlated with CD4+ count and plasma viral load[156,159,160,161]. The presence of sexually transmitted infections or other causes of inflammation, vitamin A deficiency and local immune response may affect viral shedding[162]. In Rwanda, postnatal transmission was associated with the presence of HIV-1 infected cells in breast milk[161].

Maternal antiretroviral therapy during pregnancy is thought to reduce transmission partly through the reduction of viral load, although the mechanism may also include post-exposure prophylaxis in the child after birth, as the use of zidovudine has been shown to reduce transmission at all levels of maternal viral load[111,146,163]. Combination antiretroviral therapy may be more effective in preventing transmission due to the greater reductions in viral load, but no large-scale study results are available yet on this[164].

Viral genotype and phenotype

A number of HIV-1 sub-types or clade groups have been identified, with differing geographical distributions[165]. There is little evidence on the effect of sub-type on infection or transmission, although some studies have shown an increased in-vitro ability of sub-type E to infect epithelial cells from the vagina and cervix[156,166]. The subtype may affect the cell tropism of the virus, and in turn the infectivity, in-utero, through genital infection or in breast milk.

Most studies on viral variants in mothers and children have demonstrated that the strains in the infant are a distinct subset of maternal virus, although the major maternal variant has also been shown to be transmitted[149,156,131,167,168,169,170,171]. Different viral phenotypes show differing tissue tropism. Macrophage-tropic non-syncytium-inducing (NSI) viral isolates appear to be preferentially transmitted to children even when the dominant maternal strains are syncytium inducing (SI)[149,156,131,172,173,174]. There may be a difference in disease progression for the child related to the viral strain. Rapid/high virus isolates have been associated with transmitting mothers whereas slow/low virus isolates were associated with non-transmitting mothers[175,176].

Increased strain diversity in the mother may theoretically influence the rate of transmission. Repeated exposure to different viral strains through pregnancy, occurring through unprotected intercourse may be the mechanism responsible for the observed increase in transmission in these cases[177]. The development of resistance to zidovudine during pregnancy has been shown to be infrequent, but concern has been expressed that the possible development of resistant strains of HIV-1 in women receiving zidovudine monotherapy during pregnancy may result in higher transmission rates in subsequent pregnancies[178,179]. Since the risk of resistance emergence increases with the duration of treatment and since resistance to AZT usually emerges after 3-4 months of treatment, the

emergence of resistance with short-regimen of zidovudine (1 month) is very low and less likely compared to long regimen of zidovudine.

Maternal factors

Maternal immunological status

Transmission from mother to child is more likely with decreased maternal immune status, reflected by low CD4+ counts, low CD4+ percentages or high CD4+/CD8 ratios[5,180]. These in turn may be markers for higher viral loads, as opposed to risk factors in themselves, although an interaction between viral load and immune response may be present. In the European Collaborative Study (ECS), there was an increased risk of mother-to-child transmission where maternal CD4+ counts were below 700/cubic mm[142]. Transmission increased almost linearly in this study with decreasing CD4+ counts[181]. Several other studies have noted similar associations[181, 182,183,184]. In the WITS study, the association between low CD4+ percentages and transmission was only seen in women without persistently positive viral cultures. Where there was at least one negative culture and high CD4+ cell percentages, transmission rates were in the range of 1-4%[182].

There have been conflicting results about the role of neutralizing antibodies in preventing transmission. Some studies have shown that high levels of maternal neutralizing antibody are associated with lower rates of transmission, while in others no association was observed[185,186,187,188]. Women who transmit in-utero may have lower levels of autologous neutralizing antibody than those who do not transmit, or those women where transmission occurs intrapartum[131]. Antibody to the V3 loop of HIV-1 envelope gp120 has not been shown to be protective, neither do antibody-dependent cellular cytotoxicity (ADCC) antibodies appear to be protective[189,190,191]. One report has correlated maternal antibodies to the carboxy region of the gp41 envelope glycoprotein with lack of vertical transmission[192]. The involvement of specific T-cell immunity in the pathogenesis of mother-to-child transmission has yet to be determined.

Little is known about the role of mucosal HIV-1 antibodies and viral shedding in the genital tract which may affect intrapartum transmission rates[156,160]. Infection through breastfeeding has been associated with a lack of IgM and IgA in breast milk[193,194].

Maternal nutritional factors

Serum vitamin A levels in HIV-1 positive mothers have been correlated with the risk of transmission in a Malawi study. The mean vitamin A level in those mothers who transmitted the virus to their children was significantly lower than in those who did not transmit. Women with vitamin A levels below 1.4 umol/l had a 4.4-fold increased risk of transmission, which dropped with increasing vitamin A levels[195]. One US study showed no relationship between low vitamin A levels and transmission[196], while another cohort study did show a correlation[197]. The mechanism of vitamin A effect is uncertain, but the influence of vitamin A on the integrity of the vaginal mucosa or placenta and the immune stimulatory properties of the vitamin have been suggested [162,198]. Alternatively, low vitamin A levels may be a marker for other deficiencies or behavioural factors, which influence transmission. Other micronutrients, including zinc and selenium, have been suggested as having a possible role .

Behavioural factors

Several behavioural factors have been associated with an increased rate of transmission from mother to child. These include cigarette smoking[199,200] and maternal hard drug use[119,201,202].

Unprotected sexual intercourse during pregnancy has been linked to an increased risk of mother-to-child transmission. A transmission rate of 30% was shown in women who had more than 80 episodes of unprotected sex during pregnancy compared with 9.1% in those with no unprotected intercourse[203]. A similar association is suggested in two African studies[204,205]. This may be due to an increased concentration or strain diversity of HIV-1, or the effect of cervical or vaginal inflammation or abrasions. An increase in chorioamnionitis has previously been reported linked to sexual activity in pregnancy[206], and this may be an alternative mechanism. The presence of sexually transmitted infection during pregnancy has been correlated with increased risk of transmission[207], and STIs have been shown to increase viral shedding in cervico-vaginal secretions[32].

Placental factors

Placental factors have been implicated in transmission of the virus from mother to child[116, 208,209,210,211]. Placental infection with HIV-1 has been reported and Hofbauer cells and possibly trophoblasts express CD4+ and are thus susceptible to infection[212]. An association between increased transmission and the presence of chorioamnionitis was described early in the epidemic. Other placental infections and non-infectious conditions such as abruptio placentae have also been implicated[162,213,214]. Breaks in the placental surface can occur at any stage of pregnancy and may be related to transmission, although the significance of these may, in turn, depend upon the maternal viral load[215]. Smoking and drug use, both associated with increased transmission, may exert this effect through placental disruption[116]. In areas of high malaria prevalence, infection of the placenta is common in pregnancy. Placental *P. falciparum* infestation has been associated with poorer survival in infants born to HIV-1 positive mothers in Malawi, which may represent increased transmission rates[216] and with higher rates of transmission from mother to child in Kenya[217].

Obstetric factors

With the majority of mother-to-child transmission occurring at the time of labour and delivery, obstetric factors are important determinants of transmission. Suggested mechanisms for intrapartum transmission of HIV-1 include direct skin and mucous membrane contact between the infant and maternal cervico-vaginal secretions during labour, ingestion of virus from these secretions, and ascending infection to the amniotic fluid[113,207]. HIV-1 in cervico-vaginal secretions may be raised four-fold during pregnancy[218]. The higher rate of infection in first-born twins may be due to longer exposure of the infants to infected secretions[219].

Several obstetric factors have been implicated, although results are not consistent across studies with regard to the relative importance of different obstetric factors. In the French perinatal cohort study, preterm delivery, intrapartum haemorrhage and obstetric procedures were related to transmission risk[207]. Other factors such as the use of fetal scalp electrodes, episiotomy, vaginal tears and operative delivery have been implicated in some studies but not in others[113,120,181,214,220].

The duration of labour does not appear to be as important as the duration of rupture of membranes[182,221]. Prolonged rupture of membranes has been associated with increased

risk of transmission in a number of studies and is an important risk factor[119,207,222]. In an American study, duration of ruptured membranes of over four hours nearly doubled the risk of infection, regardless of the eventual mode of delivery[119].

Delivery by Caesarean section has been shown to be protective in some prospective follow-up studies, but not in all[181,119,223,224,225]. This has now been confirmed in a randomized controlled trial in Europe[226]. A Swiss study showed an additive protective effect of elective Caesarean section for women receiving antiretroviral treatment[227]. In France, women who received long-course antiretroviral treatment in pregnancy and had an elective Caesarean section had a transmission rate of less than 1%[228].

Fetal factors

Fetal genetic factors may play a part in transmission. Little is known yet about the role of genetic factors such as the CCR-5 delta32 deletion and human leukocyte antigen (HLA) compatibility of mother and infant in the determination of transmission risk[229,230,231]. Concordance between infant and maternal HLA has been associated with increased risk of transmission[232].

Preterm infants have higher reported rates of transmission of HIV-1 in several studies[111,181,220,233]. Women with low CD4+ counts are more likely to have preterm deliveries, which may influence this finding. The higher rates of infection seen in first-born twins have been widely reported and have formed part of the evidence for the role of intrapartum transmission[234,235]. This effect is more pronounced in vaginally delivered twins, where a two fold increase in infection is seen in first born twins over second born, but is also present in twins delivered by Caesarean section[219].

Other fetal factors may include co-infection with other pathogens, fetal nutrition and fetal immune status[132].

Infant factors

Breastfeeding is responsible for a high proportion of mother-to-child transmission in developing countries, where 30% or more of perinatal HIV infections will occur through breast milk. This is less common in the developed world, where most HIV-positive women will not breastfeed. Breast milk contains both cell associated and free virus, the amount of which may be related to the immune suppression of the mother and vitamin A levels[159,236]. Other protective factors are also present in breast milk, including mucins, HIV antibodies, lactoferrin, and secretory leukocyte protease inhibitor (SLPI)[111,161,234,132].

A meta-analysis of studies of transmission through breastfeeding showed the additional risk of transmission through breastfeeding to be between 7 and 22%, equivalent to a doubling of transmission rates [237]. That is to say that, in breastfeeding populations, between one third and one half of mother-to-child transmission occurs during breastfeeding. A Soweto study has shown transmission rates of 18% in formula fed infants compared with 42% in breastfed[238]. Rates are higher when the mother sero-converts during breastfeeding, where the estimated additional risk is around 30%[237,239]. The risk of breast milk transmission may also depend upon other factors, such as maternal disease stage, breast abscesses, mastitis, nipple cracks, patterns of breastfeeding (i.e. exclusive or mixed), maternal vitamin A and oral thrush in the child[111,193]. A Zimbabwe study showed that 31% of breastfeeding mothers of HIV-1 infected children had active nipple disease[240].

Late postnatal transmission, after the age of six months, has been described in a number of studies[111,220,130,241]. In Abidjan, 12% of infants born to HIV-1 positive mothers were diagnosed as HIV-infected after the age of six months but may have been infected earlier[242].

The risks of postnatal transmission may also be related to other factors in the newborn. HIV entry may occur through the gastro-intestinal tract following ingestion of virus in utero or at birth[83,132]. There is decreased acidity, decreased mucus, lower IgA activity and thinned mucosa in the newborn gastro-intestinal tract, which may facilitate transmission[111,234,132]. The newborn immune system may also be deficient in macrophage and T cell immune response[132], increasing the susceptibility to infection. At least part of the effect of antiretroviral drugs in pregnancy appears to be due to a post exposure prophylaxis effect after birth[113].

Further information on HIV transmission and breastfeeding can be found in the joint UNAIDS, UNICEF and WHO publication *A review of HIV transmission through breastfeeding* (WHO/FRH/NUT/CHD/98.3 / UNAIDS 98.5) / UNICEF/PD/NUT/(J)98.1.

Interventions to prevent mother-to-child transmission of HIV

With increasing knowledge about the underlying mechanisms of mother-to-child transmission of HIV-1 has come an increased emphasis on the search for interventions to prevent or reduce the risk of transmission[111,113,243,244]. The successful use of antiretroviral therapy and replacement feeding in developed countries has lead to suggestions that it may eventually be possible to reduce perinatal transmission rates to less than 2%[131]. A number of possible intervention strategies have been proposed or are under investigation. These are shown in Table 2.

Table 2
Possible strategies known or under investigation for the prevention of mother-to-child transmission of HIV

TERMINATION OF PREGNANCY
BEHAVIOURAL INTERVENTIONS Reduction in the frequency of unprotected sexual intercourse during pregnancy Reduction in the number of sexual partners during pregnancy Lifestyle changes, including avoidance of drug use and smoking in pregnancy
THERAPEUTIC INTERVENTIONS Antiretroviral therapy: zidovudine alone or combination, long- or short-regimen Vitamin A and other micronutrients Immunotherapy Treatment of STI
OBSTETRIC INTERVENTIONS Avoidance of invasive tests Birth canal cleansing Caesarean section delivery
MODIFICATION OF INFANT FEEDING PRACTICE Avoidance of breastfeeding Early cessation of breastfeeding Heat treatment of expressed breast milk

The prevention of new infections in women of reproductive age remains an important component[245]. This includes the reduction of women's vulnerability to HIV-1 infection through the improvement of women's status in society, the provision of information about HIV/AIDS and its prevention, the promotion of safer sex including the use of barrier methods, and the adequate treatment of sexually transmitted infections[246,247]. Women known to be HIV positive should have access to appropriate contraception and information to help them determine their future fertility. Access to termination of pregnancy for HIV positive women can also reduce the burden of paediatric AIDS cases, but should be viewed as an option for individual women, rather than a public health intervention for the prevention of transmission. Most women living with HIV will decide to continue with pregnancy, even where termination is offered[248,249].

Table 3
Some research projects in progress on the prevention of mother-to-child transmission of HIV (1998)

STRATEGY	RESEARCH PROJECTS
A: ANTIRETROVIRAL THERAPY	Phase III: 1. PETRA: ZDV & 3TC 2. ZDV alone in short-reginmen in breastfeeding women 3. Nevirapine (HIVNET 012 & PACTG 316) Phase I/II: Drugs under investigation include: ddi, d4T, Nevirapine, Melfinavir, Ritonavir, Indinavir, Saquinavir, PMPA, MKC-442
B: ACTIVE IMMUNIZATION	1. Recombinant Gp120 vaccine to pregnant women (PACTG 235). 2. Recombinant Gp 120 to newborns; phase I/II (PACTG 230) 3. Canary pox vaccine to newborns (PACTG 327)
C: PASSIVE IMMUNIZATION	1. HIVIG (Uganda) 2. Phase I Katinger antibody
D: MICRONUTRIENTS	1. Vitamin A (Malawi: 10 000IU) 2. Vitamin A (South Africa: 5000 IU + B Carotene 30 mg) 3. 13 Vitamin A 10 000 IU and 12 other vitamins and minerals (Zimbabwe) 4. Factorial design Vitamin A & B Carotene (United Republic of Tanzania) 5. Vitamin A (Zvitambo) (Zimbabwe) postpartum and to children
E: VAGINAL CLEANSING	Chlorhexidine (Kenya)
F: INFANT FEEDING	Randomized trial of breast vs formula feeding (Kenya)

The only interventions proven to be effective in reducing mother-to-child transmission of HIV at present are the use of zidovudine (either as long-course through pregnancy, labour and for six weeks to the infant, or as short-regimen), Caesarean section and the avoidance of breastfeeding[250,251,226]. Research continues into a number of other alternatives, with a major focus on interventions active at the time of labour and delivery, when much of the transmission is believed to occur. Studies that are completed and in the analysis stage include a vitamin A study in Malawi, a randomized formula feeding study conducted in Nairobi and a self-selection study looking at the effects of breastfeeding on transmission in Soweto. Other studies on the effect of vitamin A administration (South Africa, the United Republic of Tanzania and Zimbabwe), vaginal disinfection (Kenya), and short-regimen antiretrovirals are ongoing. Postpartum interventions besides the use of formula feeding have not been studied. These trials are summarized in Table 3.

Appropriate interventions to reduce mother-to-child transmission

The ideal intervention for the reduction of mother-to-child transmission would be one that is widely applicable in resource poor settings[252]. Vaginal disinfection and vitamin A administration would not require identification of HIV positive women, but would be applicable to all pregnant women. The minimum requirements for the implementation of other interventions in health services include[253]:

- access to and use of appropriate antenatal, intrapartum and postpartum care with adequately trained health workers
- adequate pre and post test counselling services
- ability to afford the cost of reliable HIV testing
- appropriate laboratory facilities to monitor blood parameters during long regimen
- delivery units with access to disinfectants, gloves and clean needles
- acceptance and uptake of the intervention by HIV-infected women
- a regimen that is logistically possible to implement in terms of dosing times and routes, drug storage and distribution
- a regimen which is affordable for the health service.

The widespread implementation of strategies to prevent mother-to-child transmission of HIV presents a number of challenges to the existing antenatal and obstetric services. The need for such strategies is greatest in the most resource constrained settings. The provision of interventions to prevent mother-to-child transmission of HIV should not further overburden existing services. In many areas, antenatal care services are not sufficiently available, accessible or utilized and they may not be of adequate quality to take on these interventions. These services will need to be strengthened in the years ahead in order to deliver mother-to-child transmission prevention strategies effectively.

In addition if interventions are introduced into clinical practice to decrease the risk of mother-to-child transmission their effectiveness outside of the context of a randomized controlled trial should be monitored. Careful follow-up of the mothers and infants of such programmes will be essential to determine the generalisability of clinical trial results to the practical setting.

The management of HIV infection and AIDS is changing rapidly. New drugs become available and are rapidly adopted into clinical practice with little rigorous evaluation of their effectiveness. In pregnancy the situation is little different. Within one month in 1999, four substantial randomized trials of interventions aimed at decreasing the risk of mother-

to-child transmission of HIV infection were published. Many more trials are on-going and can be expected to report in the next two years. The following section, therefore, represents the evidence that was available at the end of May 1999. As new randomized trials are published they will be incorporated into an ongoing systematic review and meta-analysis of interventions aimed at decreasing the risk of mother-to-child transmission of HIV infection published in the Cochrane Library[254].

Antiretroviral therapy

Long-course zidovudine treatment

The success of the Paediatric AIDS Clinical Trials Group (PACTG) trial PACTG076 of the use of zidovudine (ZDV) in pregnancy in asymptomatic women has been a major advance in the prevention of mother-to-child transmission of HIV-1[255]. Zidovudine given orally after 14 weeks of pregnancy, intravenously during labour and for six weeks to the neonate in a non-breastfed population has been shown to reduce mother-to-child transmission of HIV-1 significantly. This has become the standard of care during pregnancy in many developed countries, with a concomitant decrease in reported transmission rates[111,113].

In this randomized placebo-controlled trial conducted in France and the USA, in a non-breastfeeding population, treatment with ZDV [100 mg 5 times daily] or placebo was started between 14-34 weeks of pregnancy [median 26 weeks]. Women also received intravenous ZDV or placebo during labour and the infants received oral ZDV [2 mg/kg 4 times daily] or placebo for six weeks. All women had CD4+ counts >200 per cubic mm, were symptom free and had not previously received ZDV. The first interim analysis on 356 mother-infant pairs demonstrated a rate of mother-to-child transmission of 25.5% in the placebo group, and 8.3% in the ZDV group. Treatment with ZDV achieved a 67.5% reduction in transmission risk. The drug was well tolerated in the short-term in the pregnant women and the neonates.

The effect of ZDV in reducing transmission appears to be partly through the reduction of maternal viral load, although transmission occurred at a wide range of viral loads in the PACTG076 study[163,256]. An additional level of protection through post exposure prophylaxis in the infant is also hypothesized, as ZDV readily crosses the placenta[111].

Further evidence for a post-exposure effect comes from a retrospective New York State study of the efficacy of abbreviated zidovudine regimens. Women who received ZDV from the prenatal period had a transmission rate of 6.1%. When treatment was commenced intrapartum, transmission was 10%, when started within 48 hours of birth 9.3% and when started on day 3 or later, transmission was 18.4%[257,258].

Reassurance that in-utero exposure to zidovudine does not appear to produce any unexpected long-term effects has been supported by a follow-up study among the uninfected children born to women participating in ACTG076[259]. This study reported follow-up information from 122 uninfected children in the zidovudine group and 112 uninfected children in the placebo group. Median age of the children at time of last follow-up was 4.2 years with a range of 3.2-5.6 years. No differences could be detected in any parameters of growth, cognitive and developmental function assessed by the Bailey Scales of Infant Development, immunologic function, cardiac function or ophthalmologic function. In addition there were no late deaths and no malignancies detected in this group.

The use of long-course ZDV in pregnancy is recommended as the standard of care in Europe, the USA and in some other countries, including Brazil and Thailand[260,261,262,263,264]. The introduction of this policy has led to a dramatic reduction in the reported transmission rates in France and the USA[18,265,70]. In France, a two-thirds reduction in transmission [from 14% to 5%] has been reported[265]. Transmission rates in Los Angeles have dropped from 30% to 10%, in North Carolina from 21% to 8.5%[131,266]. However, the success of the intervention depends upon the access of HIV positive women to therapy. In areas where utilization of antenatal care is low, and thus access to counselling, testing and drug provision is reduced, the efficacy will be lower. This has been shown in the Bronx, New York, where only 40% of HIV-infected women were identified before birth and less than half of these received ZDV[267].

The use of ZDV in this regimen is not directly applicable to most women in the developing world where the majority of mother-to-child transmission occurs. This is because of the high cost of the intervention (in the USA the regimen costs over US$ 1000 per mother-child pair); the logistics of monitoring of blood parameters, drug reactions; intravenous infusions during delivery and treatment to the newborn for six weeks. In addition, the intervention needs to be introduced early on in pregnancy, when most women in resource-poor settings only attend antenatal care late in pregnancy. Lack of access to counselling and testing in these settings limits the use of antiretrovirals in pregnancy. Women in developing countries have higher rates of anaemia, which may be exacerbated by antiretroviral treatment, and may differ in disease status from those in developed countries.

The PACTG076 trial was conducted in a non-breastfeeding population, and the efficacy of the regimen in a breastfeeding population needs to be determined, as any reduction in transmission prior to or during labour may be negated by an increased transmission from breast milk[264,268]. The acceptability of these interventions in developing countries will require further study[111,252,269,270].

Some resistant strains of virus have been reported after ZDV treatment to prevent transmission[178, 179,271]. Although resistance appears to be uncommon, there has been concern about the use of ZDV monotherapy in the management in any subsequent pregnancy[179,271].

The results from the PACTG076 trial and the ZDV in Pregnancy Register show as yet no evidence of teratogenicity or short-term adverse effects in the fetus or newborn. In addition follow-up to age four of uninfected children who were exposed to in-utero zidovudine has also revealed no medium term adverse effects[259]. However, longer term follow-up is still required and larger groups of children need to be followed to determine whether rare but serious adverse effects may occur[131,272,273]. However, recent reports of ZDV toxicity in mice[274,275] have renewed concern about the long-term effects of the drug. A consensus panel convened by the National Institutes for Health in early 1997 advised that the evidence was not sufficient to alter the recommendations for the use of ZDV in pregnancy. Children exposed to ZDV in pregnancy should be monitored for long-term toxicity effects.

It has been suggested that ZDV use in pregnancy would be a cost effective intervention in both developed and developing countries if implementation problems can be overcome[276,277,278,279]. The use of shorter regimens or other antiretroviral drugs provides a feasible alternative.

Short-regimen of zidovudine therapy

Shorter drug regimens in pregnancy would be more feasible in resource-poor settings. Results from some developed country studies suggest that antenatal oral ZDV alone may be as effective as antenatal, intrapartum and postpartum regimens[280,281]. To date three randomized trials of short-regimen have been published from resource-poor settings.

A trial of short-regimen zidovudine treatment in Thailand has shown a significant effect in preventing transmission[251].

The Bangkok Perinatal AZT Study, was a randomized placebo-controlled trial to evaluate the safety and efficacy of a short-regimen of oral zidovudine [ZDV] administered during late pregnancy and labour to reduce the risk for perinatal HIV transmission. The regimen was 300 mg ZDV orally twice daily from 36 weeks gestation until the onset of labour and 300 mg every three hours from the onset of labour until delivery. All women were advised not to breastfeed and were provided with infant formula, and it is important to bear in mind that these results are directly applicable only to formula-fed infants[251].

Transmission in the treatment group was 9.4% [95% confidence interval, 5.2%-13.5%] and 18.9% [95% confidence interval, 13.2%-24.2%] in the placebo group, representing a 50% reduction in transmission risk [95% confidence interval, 15.4%-70.6%].

A further trial of short-regimen in over 350 women conducted in Burkina Faso and Côte d'Ivoire compared placebo with oral zidovudine, started between 36 and 38 weeks gestation at 300mg twice daily, followed by a single loading dose of 600mg at the onset of labour followed by oral zidovudine 300mg twice a day to the mother continued until seven days after delivery[282]. In this trial over 85% of infants were breastfed for longer than three months. By six months of age, HIV transmission was diagnosed in 33 children born to 180 women in the zidovudine group and 52 born to 175 women in the placebo group. The efficacy of zidovudine was thus estimated at 38% (95% confidence intervals 5% - 60%). There was no evidence of 'catch up' by the treated group during the period of breastfeeding up to 180 days. Data for children older (and breastfed for more) than six months are not yet available.

A further trial conducted in 260 women in Côte d'Ivoire randomized women to receive either oral zidovudine 300mg twice a day from 36 weeks until the onset of labour or matching placebo[283]. At the onset of labour zidovudine 300mg was given every three hours until delivery versus placebo. In this trial population, over 95% of the infants were breastfed by their mothers and by three months of age 19 out of 115 babies in the zidovudine group were HIV infected compared with 30 out of 115 in the placebo group. This represents a relative risk of transmission of 0.63 (95% confidence intervals 0.38 - 1.06). The transmission risk at three months was similar to the transmission risk seen at four weeks also suggesting that breastfeeding had not produced a substantial narrowing of the difference between the two groups.

These results demonstrate that short-regimen of oral zidovudine appears to be safe and effective at reducing the risk of mother-to-infant HIV transmission. Of importance for many developing countries is that whether women do or do not breastfeed does not appear to make a substantial difference to the effectiveness of treatment. Other trials of reduced courses of ZDV alone are underway in Africa, and Haiti (see Table 3).

A reduction in the cost of zidovudine for developing countries has been announced by the manufacturers after negotiation with UNAIDS and in response to the results of the Thailand study[284]. This will assist in the implementation of these strategies. The World Health Organization has prepared guidelines for the use of antiretroviral drugs in developing countries[285].

Combination therapy and other antiretroviral drugs

The UNAIDS co-ordinated PETRA trial uses a combination of ZDV and 3TC (lamivudine), and has been undertaken in predominantly breastfeeding populations in five sites in South Africa, the United Republic of Tanzania and Uganda. Long-term follow-up of the children is in progress but interim early efficacy results at six weeks of age of the infant have been reported. This trial compared the effectiveness of three different drug regimens with placebo. Arm A received zidovudine and 3TC from 36 weeks gestation, during labour and for one week postpartum to mother and child. Arm B received zidovudine and 3TC from the onset of labour and for one week postpartum to mother and child. Arm C received zidovudine and 3TC during labour only. Over 1790 women were recruited in all. The risk of transmission by six weeks of age in Arm A was 8.6%, in Arm B 10.8%, Arm C 17.7% and in the placebo group 17.2%. The study population continues to be followed up and the majority of women are breastfeeding[254].

A recent French study, presented in abstract only, reported the use of 3TC (lamivudine) commencing at 32 weeks gestation in addition to the standard ACTG 076 zidovudine regimen[286]. Babies were treated with both drugs until six weeks of age. Two hundred women receiving this combination were compared with a cohort of 899 women receiving zidovudine alone. The rate of transmission in the combination group was 2.6% compared with 6.5% in the zidovudine group. This study was not a randomized trial and other factors may explain the decrease in transmission risk. One finding, however, was that two uninfected babies having received ZDV+3TC died of a neurological disorder due to a mitochondrial myopathy. This condition is rare and two neonatal deaths in 200 women suggest that 3TC or the drug combination may be responsible.

The use of non-nucleoside reverse transcriptase inhibitors (NNRTI) for the prevention of perinatal transmission is another possible approach. Nevirapine is a NNRTI with potent antiretroviral activity and a favourable safety profile but in which there is rapid development of drug resistance limiting the duration of its effect. Of particular interest is that the drug achieves high circulating levels which are long-lasting, raising the possibility of a one dose treatment in labour. Efficacy studies have commenced in South Africa and Uganda.

The use of combination antiretroviral therapy is becoming more common, with greater reductions in viral load. Recent recommendations for drug therapy for HIV advise the use of at least two agents, with the possible addition of a protease inhibitor[287,288,289] although rapid advances in the therapy of HIV infection means that such recommendations change frequently. Patients receiving this level of treatment may have undetectable viral loads. There has been little experience to date with the use of most of these drugs in pregnancy and many of the newer antiretroviral (ARV) drugs have not been fully evaluated for long-term effects on the infants. Table 4 shows the status of the USA's Food and Drug Administration (FDA) classification of the available antiretroviral drugs, while long-term animal toxicity studies and more experience in pregnant women are awaited. Phase I trials are completed or in progress for nevirapine, stavudine, didanosine, lamivudine, MKC-442 and the protease inhibitors[111]. DMP-266 (Efavirenz, Sustiva) was shown to

cause moderate to serious birth defects in monkeys, and may not be suitable for use in early pregnancy.

Table 4
FDA classifications of antiretroviral drugs for use in pregnancy[290,291]

DRUG	FDA CATEGORY
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS	
Zidovudine (ZDV, AZT)	C
Zalcitabine (ddC)	C
Didanosine (ddI)	B
Stavudine (d4T)	C
Lamivudine (3TC)	C
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS	
Nevirapine	C
Delavirdene	C
PROTEASE INHIBITORS	
Indinavir	C
Ritonavir	B
Saquinavir	B
Nelfinavir	B

Classification:

A: Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters)

B: Animal reproduction studies fail to demonstrate a risk to the fetus but well controlled studies of pregnant women have not been conducted

C: Safety in human pregnancy has not been determined, animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus

D: Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks

X: Studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit

Assuming favourable safety profiles, the use of combination therapy may be more effective in reducing mother-to-child transmission, by the greater reduction of viral load, and may be the most appropriate course in those countries where this is possible. However, cost and supply considerations will limit the availability of these drugs, and the issue of resistance development and the desirability of continuing therapy after pregnancy will have to be considered[179].

Immune therapy

Both passive immunization with hyper-immune HIV immunoglobulin (HIVIG) and active immunization with HIV vaccines have been proposed as alternative mechanisms to prevent mother-to-child transmission[111,113,292].

Passive immunization with intravenous HIV immunoglobulin has been investigated. A trial [ACTG185] of the use of HIVIG, in a cohort of women, who all received ZDV, was stopped after an interim analysis showed low transmission rates in both the study and control group. The transmission risk for the HIVIG Group was 4.1% (95% confidence interval 1.5%-6.7%) and the transmission risk for IVIG was 6.0% (95% confidence interval 2.8%-9.1%)[293]. Very large numbers would have been required to show any significant reduction in these rates attributable to the HIVIG use. Another study is ongoing in Uganda in ZDV naïve patients. Concerns remain about the costs and the donor sources for these products, standardized preparations and optimal delivery time.

Active immunization could possibly induce immunity in the mother and in the fetus by passive transfer of antibodies[111,294]. Effective vaccines have not yet been identified, although several Phase I/II trials are in progress[113].

Nutritional interventions

Following the finding that mothers with low serum levels of vitamin A were more likely to transmit HIV to their children[195], supplementation of vitamin A has been suggested as a preventive treatment. Several randomized controlled trials of vitamin A and other micronutrients are in progress (Table 3). The potential advantages of micronutrient supplementation would be the low price, possible other nutritional and health benefits for the mother and the fact that the intervention could be implemented simply without the need for HIV testing. Vitamin A deficiency has also been associated with increased viral loads in breast milk, and any reduction following supplementation would also be of benefit in breastfeeding women[159]. Other micronutrients such as Zinc and Selenium have also been suggested as possible preventive agents.

A randomized controlled trial in the United Republic of Tanzania showed that multivitamin supplementation in HIV positive pregnant women decreased the risk of low birth weight by 44%, severe preterm birth (under 34 weeks gestation) by 39% and small size for gestational age at birth by 43%. Vitamin A supplementation had no effect on these variables. The multivitamin supplementation, but not vitamin A, resulted in significant increases in CD4+, CD8 and CD3 counts. The effect on mother-to-child transmission in this study has yet to be determined[295]. Preliminary reports from other vitamin A intervention trials suggest little benefit on transmission from vitamin A supplementation alone.

Mode of delivery

Caesarean section delivery has been associated with a reduction in transmission in a number of studies, although not in all[119,181,207,223,296]. In some centres, Caesarean section has become a common mode of delivery for HIV positive women, despite the lack of conclusive evidence at the time. In 1995 in the United Kingdom, 44% of HIV positive mothers were delivered by Caesarean section[262].

A 1994 meta-analysis of prospective follow-up studies showed a small reduction in transmission with Caesarean section[224]. A more recent meta-analysis included five European and ten North American prospective studies totalling over 8500 mother-infant pairs. Elective Caesarean section reduced the risk of mother-to-child transmission by more than 50%, after adjusting for antiretroviral therapy, birth weight and maternal infection stage[297].

A French study showed a transmission rate of 0.8% in women who had received long-course antiretroviral treatment and had an elective Caesarean section, compared to 6.6% with vaginal delivery[228]. A study in Switzerland reported no transmission in 45 women who received long-course ZDV and an elective Caesarean section[227].

A randomized controlled trial of mode of delivery has been undertaken in Europe[226]. This trial randomized in excess of 400 women to elective Caesarean section delivery or expectation of vaginal delivery. Three out of 170 infants (1.8%) born to women in the Caesarean section group were HIV infected compared with 21 out of 200 (10.5%) born to women in the vaginal delivery group. A treatment effect odds ratio of 0.2 (95% confidence intervals 0.1-0.6).

Two thirds of the women taking part in this trial were exposed to zidovudine during pregnancy. In this sub-group 0.8% of babies born to the women allocated to Caesarean section were HIV infected compared with 4.3% of those born to women allocated vaginal delivery. This gives an odds ratio of 0.2 with 95% confidence intervals of 0-1.7. For women not exposed to zidovudine during pregnancy the odds ratio for transmission was also 0.2 suggesting that the protective effect of Caesarean section persists whether women were or were not prescribed zidovudine during pregnancy.

In addition there were no serious adverse complications in either group. Postpartum fever was reported more commonly in women delivered by Caesarean section although the overall incidence was low.

The use of Caesarean section must take into account the possibility of maternal morbidity and mortality[109,110,298], the availability of safe operating facilities, the potential increased service commitments and the accessibility of maternity services for women in future pregnancies.

Vaginal cleansing

The use of antiseptic or antiviral agents to cleanse the birth canal during labour and delivery has been hypothesized as a possible approach to reducing intrapartum transmission of HIV-1. The use of chlorhexidine lavage to reduce the transmission of group B streptococci was demonstrated in Scandinavian studies[299]. The concept is attractive for HIV prevention, as it would be an inexpensive intervention, readily achievable in most health care settings, would not require identification of HIV-infected women prior to the intervention and could have other health benefits.

A Malawian quasi-randomized study compared four-hourly aqueous chlorhexidine 0.25% solution by vaginal swabbing after vaginal examinations and a chlorhexidine wash for the baby, with a control group receiving no wash. No overall reduction was shown in the rate of HIV transmission in the study group, however, only 60% of infants were followed up. There was a significant reduction in transmission in mothers who had ruptured membranes for more than four hours[222]. Most deliveries in this trial occurred within a

short time of the vaginal swabbing procedure. Significant reductions in neonatal and puerperal sepsis were also seen following this intervention[300] and use of this procedure may be advantageous for these other health benefits, in addition to any possible role in prevention of mother-to-child transmission of HIV[301].

Benzalkonium Chloride has been suggested as an alternative antiseptic agent for vaginal lavage, utilizing the antiseptic from 36 weeks gestation in an attempt to maximize the possible benefit (Table 3). The intervention of vaginal cleansing remains a feasible option for resource poor settings and further research work should be undertaken on different concentrations or formulations of agents and methods of application to determine whether the efficacy can be improved.

Modification of infant feeding practice

The increased risk of HIV transmission through breastfeeding is well documented[237,238,302,303]. Breastfeeding is responsible for a high proportion of mother-to-child transmission in developing countries, where 1 in 7 children born to HIV-positive mother will be infected through breast milk[247]. Breastfeeding may double the transmission rate[111,238,304] and may be the major determinant for the difference in transmission rates between developed and developing countries. A meta-analysis of studies of transmission through breastfeeding showed the additional risk of transmission through breastfeeding to be between 7 and 22%, and close to 30% for women who are infected during the breastfeeding period[237]. Potential modifications of infant feeding practices include complete avoidance of breastfeeding, early cessation, pasteurisation of breast milk, and avoiding breastfeeding in the presence of breast abscesses or cracked nipples[111,305].

The debate on appropriate infant feeding has focused almost exclusively on the risks and benefits of breastfeeding for the infant. Maternal considerations should also be taken into account, although there is a need for further research into the relationship between HIV infection, nutritional status and immune function in breastfeeding mothers. The concerns about the effect of breastfeeding on maternal health in HIV positive women include the potential effects of breastfeeding and resultant weight loss on the immunity and long-term prognosis of the mother. The effects of advanced disease or nutritional deficiencies on the risk of transmission in breast milk and the function of immunologically active components of breast milk from severely immune suppressed or malnourished mothers also need to be considered[306]. Breast milk could have advantages for those infants already infected with HIV by the time of birth, if there was a way to identify these children.

In developed countries, few HIV positive women will breastfeed[307]. In resource poor settings, alternatives to breastfeeding may not be feasible for financial, logistical and cultural reasons[126,308,309]. Mothers should be given the information on the advantages and disadvantages of breastfeeding and replacement feeding with regard to HIV infection, and encouraged to make a fully informed decision about infant feeding. They should be supported in their decision[247].

Voluntary HIV counselling and testing in pregnancy

Testing of antenatal women

Pregnant women have been the target of many seroprevalence studies, as they provide an accessible cohort for HIV testing and a stable sampling frame[19,23,22,310,311]. While valuable information has been obtained on trends in the epidemic, the practice of testing in pregnancy has been criticized in the past, as one which stigmatizes women and which has not led to implementation of appropriate health strategies[312,313].

With increasing knowledge about HIV and about mother-to-child transmission in particular, the focus has moved from the possible public health benefits of testing in pregnancy to the potential benefits for the individual woman[314,315]. This has re-emphasized the need for the provision of appropriate facilities for testing and counselling[126,277,316,317,318,319,320,321,322,323,324]. Voluntary testing of pregnant women is recommended and offered in many countries[17,325,326,327]. The introduction of testing programmes has increased the number of identified HIV positive women in many centres[328]. Despite this, identification of infected women may not be optimal if women do not access antenatal care, or where counselling and testing services are inadequate[262,327,329,330,331,332,333].

Wherever possible, voluntary counselling and testing should be available to any pregnant woman who requests it and offered to all in areas of moderate or high prevalence. Routine testing of pregnant women without consent or without access to counselling is, however, an unacceptable practice and the disadvantages may negate any benefit obtained from knowing the HIV status of the women. These include a reluctance to utilize maternity services through fear of discrimination, denial of a positive diagnosis and stigmatization. Recent discussion about, and recommendations for mandatory testing of pregnant women or newborns have led to concern about the autonomy and rights of women[315,329].

There are, however, a number of potential benefits to women of voluntary HIV testing prior to or during pregnancy. This is the case even in the absence of expensive interventions such as long-course antiretroviral therapy. These benefits include:

1 Where a woman is found to be infected, this knowledge can facilitate early counselling and treatment.
2 A diagnosis in the mother allows appropriate treatment and follow-up of her child.
3 Knowledge of her HIV status enables the woman to take decisions on continuation of the pregnancy and on future fertility.
4 Testing allows an opportunity to implement strategies to attempt to prevent transmission to the child.
5 Knowledge of HIV status enables the woman to take precautions to help prevent transmission to sexual partners.
6 Women diagnosed as HIV positive can tell their sexual partners and enable partners to be counselled and tested.
7 If the test result is negative, women can be guided in appropriate HIV prevention measures and risk reduction behaviour.

Balanced against these advantages are the possible disadvantages of HIV testing in pregnancy. These will vary from community to community, but reports have described an increase in the risk of violence against women; the possibility that the woman may be stigmatized within her community and by health workers; higher levels of anxiety and psychological sequelae; and concerns about the additional work load for maternity services[334,335,336,337]. Several studies have described the reluctance of some women to return for their test results[337,338,339]. In Nairobi, 5.9% of HIV-positive women reported

violence related to the HIV test result. After changing to a policy of giving results out only on request, only 35% of women who had agreed to testing returned to ask for results[337]. In Kigali, 63.9% of positive women and 71.3% of HIV-negative women returned for test results and the only variable found to be associated with failure to return for counselling was a positive HIV test[338].

Women should be encouraged to bring their sexual partner(s) for counselling and testing wherever possible. However, very few testing services have managed to achieve much success in this regard[336,338]. The best predictor of return for counselling by women in one US study was the time spent in counselling women and the counsellor's skills[339]. Voluntary counselling and testing (VCT) services for couples, preconceptual counselling and testing services not linked to antenatal care may increase testing uptake. However, it must be emphasized that, unless people have real choices for action once they have their test results (i.e. access to affordable services such as mother-to-child transmission preventive interventions, and care and support services), there is no good reason to take a test (see: *Counselling and voluntary HIV testing for pregnant women in high HIV prevalence countries: Guidance for service providers* (UNAIDS, May 1999))

A qualified person should take the blood specimen for an HIV test, using "universal precautions" against accidental transmission in all cases. These must include the safe disposal of needles and syringes. The type of tests used will depend upon local seroprevalence, policy and available facilities. In most cases blood specimens will be sent to the appropriate laboratory, but in some areas, dry blood spot testing may be an acceptable alternative. The first line test for HIV-antibodies is an enzyme-linked immuno-absorbent assay (ELISA) test, or a rapid test algorithm. Depending on local conditions, a confirmatory test with a second ELISA or rapid test using a different test kit, or a Western Blot should be performed. Any testing strategy must be undertaken with appropriate laboratory quality assessment[340,341].

With increasingly sensitive and specific simple and "rapid" tests becoming available, on-site testing may become more feasible (see The importance of simple/rapid assays in HIV testing. WHO/UNAIDS recommendations; WER 1998, 73, 321-328). Recent reports of the use of "same-day" rapid test results in a rural hospital in a resource-poor setting and in an urban STI clinic have suggested that this is an acceptable and appropriate intervention[342,343]. Preliminary reports of the use of dual rapid tests for same day diagnosis in antenatal clinics suggest that this is an appropriate and acceptable way to provide testing in this setting. The major advantage is that early results enable more women to access antenatal strategies for the prevention of mother-to-child transmission.

Counselling before and after HIV testing in pregnancy

Pre- and post-test counselling are essential elements of the management of HIV in pregnancy. Pre-test counselling enables women and men to make informed decisions about an HIV test. Post-test counselling is an integral part of the management of the HIV-positive person, and provides an important opportunity for risk-reduction messages for those found to be HIV-negative.

Pre-test counselling

HIV testing should be accompanied by the provision of pre-test information and by informed consent to the test by the woman (see Table 5). Pre-test counselling implies explanation of both the test and the illness to the woman in a non-directive manner, and

answering any questions prior to the performance of the test. The woman should be given time to decide on the test and, if unsure, should be counselled to take more time to think about the test and return at a later stage. Information about HIV testing can be incorporated into the health education and promotion activities of antenatal clinics and need not be too time consuming within maternity services[319]. Various models have been tried, including group counselling, video education, incorporating information on HIV into the first visit interview by midwives and the use of lay counsellors[344,345]. An appropriate model should be developed for the circumstances of each service, based on the prevalence and the level of prior awareness of the women in the community.

Table 5
Pre-test counselling
[Based on guidelines from the Johannesburg Community AIDS Centre]

Take client to private setting for counselling
Assure the client of confidentiality
Explain or determine the reasons for HIV testing
Elicit information about the person's current and previous risk behaviour in a sensitive manner
Provide information about HIV and AIDS
Provide information about the HIV antibody test, including information about the "window period" of infection
Review the implications of a positive test result for the client
Discuss the person's possible responses to a positive test result
Discuss the implications of a negative test result
Provide information about test procedures
Obtain informed consent

Post-test counselling

The essential elements of post test counselling for HIV positive women are illustrated in Table 6. Counselling implies more than merely giving a positive result, and continued care and advice will be necessary as part of the management throughout the pregnancy and beyond[344,346,347]. The choice of appropriate counsellor will depend upon the circumstance of the practice or health service: counsellors ideally should have personal qualities, which equip them for the job, but many of the skills can be acquired during training. Wherever possible, counselling should be provided in the woman's home language and within the same cultural background. The involvement of peer counsellors – women who are themselves HIV-infected, who are able to counsel and to share their own experiences, fears and successes may be very valuable and should be encouraged. The integration of peer counsellors and support groups into the work of health services can be a very valuable addition to the available services.

Table 6
Post-test counselling
[Based on guidelines from the Johannesburg Community AIDS Centre]

See the client personally to give result – no telephonic results, preferably not before a weekend
Give the result as soon as possible after the test is done
Inform the client of the test result
Deal with the feelings arising from a negative result and explore prevention of infection and the window period
Deal with the feelings arising from a positive result
Identify the person's immediate concerns
Discuss how the client plans to spend the next few hours and days
Identify what support the client has
Discuss who the client may want to tell about the result and risks to sexual partners
Identify what difficulties or problems the client foresees and how to deal with them
Encourage the client to ask questions
Provide information on a healthy lifestyle, medical follow-up, local support systems
Refer for follow-up care and counselling

The delay between taking the test and giving the result should be as short as possible, as the woman may be very concerned about the test and the implications of the result. Women who test positive should be encouraged to bring their male partner(s) for counselling and testing wherever possible.

Post-test counselling should also be provided for HIV-negative women, with a focus on providing information to enable them to avoid infection. This could be provided on a group basis, or by individual health workers, depending on the circumstances.

Counselling about pregnancy-related issues

There are several issues to be addressed when counselling HIV positive pregnant women, in addition to the general issues related to HIV infection. These include information about the interactions of HIV and pregnancy, options of termination of pregnancy, discussion about disclosure to the male partner, the risk of mother-to-child transmission and possible interventions to prevent this, other treatment options, infant feeding and HIV and future fertility. Some of these pregnancy-related issues are detailed in Table 7.

Table 7
Issues in counselling HIV-positive pregnant women

The effect of pregnancy on HIV infection
The effect of HIV infection on pregnancy outcome: risks of adverse pregnancy events
The risk of transmission to the fetus during pregnancy, delivery and breastfeeding
Termination of pregnancy options
Treatment options during pregnancy
Interventions available to attempt to prevent mother-to-child transmission
Infant feeding options: the advantages and disadvantages of breastfeeding
Disclosure of results to male partners and/or to other significant family or community members: advantages and risks
The need for follow-up of both mother and child
Future fertility and contraceptive options

HIV-infected women should be given appropriate information to make informed decisions about the continuation of their pregnancy and future fertility[348]. Termination of pregnancy should be offered to HIV positive women, where this is legal. It should be clear to health care workers that offering termination should never be coercive and that all women, irrespective of their HIV status, have the right to determine the course of their reproductive life. Although there are some reports of increased rates of termination in HIV positive women, the majority of women will elect to continue with the pregnancy[249,349,350,351]. Knowledge of HIV infection had little effect on reproductive trends and the decision on future children in a number of studies[248,352,353,354] although this has been seen more in developing countries than developed countries. However, a family planning intervention in Rwanda, providing access to and information about contraceptives, showed a reduction in subsequent pregnancies which was greater than in HIV-negative women[355], and other studies have shown a reduction in the number of pregnancies in HIV positive women[349,356,357,358].

SECTION B:

MANAGEMENT OF HIV-POSITIVE PREGNANT WOMEN

The management of HIV positive women during pregnancy is multifaceted, combining medical and obstetrical management with counselling and social support. The woman's social and psychological concerns may be as important as her need for medical care. Ideally, a team approach with health workers, counsellors and support groups should be used[358,359,360,361,362].

In all cases, the management in pregnancy, including antiretroviral treatment, should be seen as only a part of the continuum of care for the mother and child[360,363,364,290]. Ongoing care may be undertaken at home, within the primary health care services, at hospitals, or at specialist clinics, depending upon the individual needs and available facilities[365]. The following discussion highlights some of the management issues for HIV positive pregnant women, and does not provide detailed guidelines. Diagnostic procedures and medical management will be dependent upon the available resources and each country should develop appropriate recommendations for their own situation.

Antenatal care

Most HIV positive women will be asymptomatic and have no major obstetrical problems during their pregnancies[99,366,367,368,369]. They should receive similar obstetric antenatal care to that given to HIV-negative women, unless indicated by the need to provide specific HIV-related treatment. There is no evidence that there is a need to increase the number of antenatal visits, provided there are no complications of the HIV infection, although additional counselling time may be required. The care of the HIV positive woman during pregnancy should include ongoing counselling and support as an integral part of the management. Advice on the possible risks of unprotected intercourse during pregnancy should be provided.

Obstetrical management

Antenatal care of the HIV positive pregnant woman will depend on the woman's risk of experiencing an adverse perinatal outcome. To an extent this will be mediated by other obstetric risk factors and antenatal care will need to be tailored to the individual woman. Consideration can be given to the assessment of fetal growth, whether by regular uterine fundal height measurements or, where available, by serial ultrasound assessments.

Invasive diagnostic procedures, such as chorion villus sampling, amniocentesis or cordocentesis should be avoided where possible, due to a possible risk of infection of the fetus[302]. External cephalic version of a breech fetus may be associated with potential maternal-fetal circulation leaks and the advantages and disadvantages of the procedure should be very carefully considered.

Examination and investigations

HIV positive women should have a full physical examination at the first visit. Particular attention should be paid to any signs of HIV-related infections [particularly tuberculosis], oral or vaginal thrush, or lymphadenopathy. *Herpes zoster* [shingles] in a young woman is often an early sign of HIV infection and current herpes lesions or the scars from previous infection may be found. Other co-existent sexually transmitted infections, especially syphilis, are common in HIV positive women[96,97,370,371] and may increase the risk of transmission and the level of virus in vaginal and cervical secretions. Clinical diagnosis and treatment of vaginal or cervical inflammation, abnormal discharge or STI should be a priority. The pregnant woman should be monitored for any signs of HIV-related opportunistic infections and for any other intercurrent infections, such as urinary or respiratory infection. Maternal weight should be monitored and nutritional supplementation advised where necessary. The oro-pharynx should be examined at each visit, for the presence of thrush.

Laboratory investigations will depend upon the available resources of the health service. Syphilis testing should be undertaken, and repeat testing in late pregnancy may be advisable[40]. A haemoglobin estimation is mandatory and a complete blood count should be performed and T cell subset investigations undertaken where possible. Anaemia is more common in HIV-infected women and repeated haemoglobin tests may be helpful. Viral load estimation may provide a valuable prognostic indicator, where available. A cervical smear should be performed if this has not been undertaken within the recent past. Colposcopy should be reserved for women who have an abnormal cervical smear result.

Medical treatment during pregnancy

The medical care of HIV positive women should be tailored to the individual needs of the woman. In general, pregnancy is not a contraindication for the most appropriate antiretroviral therapy for a woman or for most of the medical management of HIV-related conditions, but the risk to the fetus should always be considered, and treatment modified if necessary [290].

The value of vitamin A supplementation in reducing transmission has not been proven, but multivitamins may provide cost effective nutritional support[372,373,374]. Mebendazole should be given at the first visit in areas of high hookworm prevalence.

Malaria in pregnancy causes high maternal and infant morbidity and mortality, and may be associated with increased risk of mother-to-child transmission of HIV[216,217]. Current recommendations are that intermittent treatment with an effective, preferably one-dose antimalarial drug should be made available to all primigravidae and secundigravidae in highly endemic areas. This should be started from the second trimester and given at intervals of not more than one month apart.

Prophylaxis for opportunistic infections should be given in pregnancy, as indicated by the clinical stage of the HIV infection, and according to local policy. Prophylaxis and treatment for tuberculosis should be given where indicated, although streptomycin and pyrazinamide are not recommended during pregnancy. *Pneumocystis carinii* pneumonia (PCP) prophylaxis should continue through pregnancy: sulfamethoxazole/trimethoprim (Bactrim/Septran) or pentamidine can be used. The risk to the fetus of maternal sulphonamide administration in the third trimester is outweighed by the risk to maternal health of PCP and kernicterus has not been reported where the drug was not also used in

the neonatal period[5]. Consideration should be given to pneumococcal and Hepatitis B vaccination.

Treatment for opportunistic infections during pregnancy depends on the clinical stage of the patient. Treatment regimens should follow local policy guidelines. Where a variety of treatment options are available, those with the lowest risk to the fetus should be used. Dermatological conditions are common in HIV positive women and men, and treatment may be required for prolonged periods. Acyclovir can be used safely after the first trimester. Topical imidazole antifungals or topical gentian violet can be used throughout pregnancy and oral fluconazole can be used after the first trimester, if required.

Antiretroviral therapy

The use of antiretroviral drugs in pregnancy should be considered for two indications: the health of the mother and prevention of transmission[364,290,291]. Pregnancy should not be a contra-indication for antiretroviral therapy in the mother, if indicated. The use of ZDV in the prevention of transmission to the fetus has been discussed above[375,376,377]. Current recommendations for adult antiretroviral therapy are that monotherapy with ZDV is sub-optimal treatment and that two antiretrovirals with the possible addition of a protease inhibitor is preferable[288,289,378,379]. Although there is a theoretical risk to the fetus from combination therapy, there is limited experience with the use of other antiretrovirals such as lamivudine, stavudine, and protease inhibitors in pregnancy. Some have recommended stopping these therapies during the first trimester and restarting the combinations, but this also carries a risk of developing resistance. Detailed recommendations have been released in the USA on combination therapy in pregnancy[291]. As many of the newer compounds do not have long-term safety data following use in pregnancy, this should be discussed with the patients. The use of any antiretroviral drugs should be accompanied by an explanation of the available knowledge to the women and advice that there should be long-term follow-up of the child[272].

Care during labour and delivery

Care during labour for HIV positive women should follow routine practice in most respects. Prolonged rupture of membranes should be avoided, as mother-to-child transmission is increased where membranes are ruptured for more than four hours[119]. Artificial rupture of membranes should not be undertaken if progress of labour is adequate. Given these advantages, this may be introduced as a routine part of the management of labour for all women in high prevalence areas.

There are conflicting reports of the importance of obstetric interventions in the facilitation of transmission[111,113]. As a general rule, any procedure which breaks the baby's skin or increases the baby's contact with the mother's blood – such as scalp electrodes or scalp blood sampling – should be avoided unless absolutely necessary, due to the unconfirmed magnitude of the risk of these for HIV transmission. Universal precautions should be applied in managing labouring women in all cases. Episiotomy should not be performed routinely, but reserved for those cases with an obstetrical indication.

If an assisted delivery is required, forceps may be preferable to vacuum extraction, given the risk of micro-lacerations of the scalp from the vacuum cup. There is increasing evidence that elective Caesarean section may help prevent transmission of HIV to the baby[225]. The operation carries risks of maternal complications and is associated with

higher post operative morbidity in HIV positive women[110]. The decision on Caesarean section delivery should be made on an individual basis, taking into account the available facilities, and will not be possible in most developing countries with high HIV prevalence. Prophylactic antibiotics should be given for both elective and emergency Caesarean sections.

Postpartum care

The postpartum care of HIV positive women should be similar to that for uninfected patients. They do not require separate nursing facilities. Women may, however, require private facilities to lessen the social stigma associated with not breastfeeding if this is the choice they make in a culture which is likely to condemn such behaviour.

HIV positive women are more prone to postpartum infectious complications – including urinary tract, chest, episiotomy and Caesarean section wound infections. Health workers should be aware of this and observe for signs of infection. Mothers should be given information on the early symptoms of infection at the time of discharge, especially where the postpartum hospital stay is short. All mothers should be given instructions on perineal care and the safe handling of lochia and blood stained sanitary pads or materials.

Mothers should be given information on how to care for their babies without the risk of exposure to infection, and full discussion on the risks and benefits of infant feeding choices. If, after counselling, the mother chooses not to breastfeed, she should receive full information on adequate replacement feeding up to two years of age, and guidance on breast care, until lactation stops. Mothers who choose to breastfeed should be advised of the possible increased transmission risk in the presence of cracked nipples, mastitis, breast abscess or of oral lesions in the child and should be taught how to prevent such problems through adequate breastfeeding techniques. Reduced duration of breastfeeding and early cessation may be encouraged to reduce the risk of transmission where this can be achieved safely. The mother should be counselled on the need for follow-up care for her and her child, and the available options for testing of the child. She should be given information about and referred to local HIV support groups. Contraceptive advice should be given and early arrangements made to start with an appropriate method. Contraceptive advice is particularly important when a mother does not breastfeed because of the loss of the contraceptive properties of breastfeeding[380,381].

Care of neonates

Babies of HIV positive mothers should be handled with gloves until maternal blood and secretions are washed off, after which time they can be handled safely by mothers and health workers. Anaemia has been the most common complication seen in the neonate with the long-course treatment of six weeks ZDV to the child. Haemoglobin should be measured at baseline and after six weeks and 12 weeks if this regimen is used. The anaemia risk is much less with the short-regimen. Infants receiving long-course antiretrovirals may experience a transient elevation of hepatic transaminases. There is less experience with the use of combination therapy in the pregnant mother and the risk of toxicity to these infants, and more intensive haematological monitoring would be advised.

Mothers should decide on infant feeding practice before delivery and be supported in their choice. Children should be referred for long-term follow-up and for repeat testing for

diagnosis of HIV infection, either by early PCR if available, or by ELISA at 15 to 18 months.

SECTION C:

INFECTION CONTROL MEASURES

(See Guidance Module on Antiretroviral Treatments, Module 7. Treatments following exposure to HIV)

Exposure to blood and other body fluids is common in obstetric practice[382,383,384,385,386] and staff should receive information, training and access to equipment in order to protect themselves[387]. In areas of highest HIV prevalence, tests may not be available and many women will also be in the "window period" before seroconversion, and may not be identified by routine HIV-antibody tests. Lack of access to nosocomial infection prevention measures may unfortunately be common in these countries[388,389,390]. A study of occupational exposure in the United Republic of Tanzania showed that health workers were exposed on average to five sharp injuries and nine splashed exposures each year, with a higher risk in surgeons[391]. In Rwanda, no evidence was found for any HIV infection caused by occupational blood contact in 215 traditional birth attendants, exposed to an estimated 2234 potentially infectious blood-skin contacts over five years[392].

All patients should be regarded as potentially infectious, not only for HIV, but also for Hepatitis and other pathogens[393,394]. Health care workers must ensure that they use universal precautions against accidental infection at all times. These require the provision within health services of protective devices and clothing and access to safe containers for sharp instruments[395].

Universal precautions

The best protection against occupational exposure to pathogens is the use of universal (or standard) precautions in all cases.

Important precautions in obstetrics include:

1 Reducing needlestick injuries by handling used needles as little as possible, using a needle holder during episiotomy, avoiding recapping disposable needles and taking great care in recapping blood sampling barrel system needles or non disposable syringes, placing needles and other sharps in the appropriate containers
2 Washing hands with soap and water immediately after contact with blood or body fluids
3 Wearing suitable gloves when expecting exposure to blood or body fluids
4 Covering broken skin or open wounds with watertight dressings
5 Wearing an impermeable plastic apron for delivery
6 Wearing eye shield for operating or assisting at Caesarean Section, and for suturing episiotomies
7 Wearing double gloves, if possible, for all operations, which reduce considerably the amount of blood carried through if a glove is punctured
8 Using an appropriate sized needle (21 gauge, 4 cm, curved) for the repair of episiotomy, together with a technique using a needle holder
9 Passing all sharp instruments onto a receiver, rather than hand-to-hand at Caesarean section and modifying surgical practice to use needle holders and to avoid using fingers in needle placement

10 Using long-cuffed gloves for manual removal of a placenta
11 Wherever possible, avoiding the need for suction of newborns and using wall suction or a suction machine when suction is required. Suction pressure should be less than 140 mm Hg to avoid damage to the neonate. If no other suction is available, ensuring that the trap in the mouth operated De Lee suction apparatus is functional
12 Disposing of solid waste such as blood soaked dressings or placentas safely

Risks of needlestick injuries

Needlestick injuries occur relatively commonly in obstetric practice and health workers should know their local policy for the appropriate management of injury. The most common form of injury occurs when re-sheathing needles. Injuries from hollow needles are more dangerous than those from solid surgical needles, as they are more likely to transfer blood.

Any such injury carries a risk of exposure to HIV, Hepatitis virus, and other pathogens. For Hepatitis B the risk of infection is between 5% (HBV-e Ag negative source patient) and 43% (HBV-e Ag positive source patient). The amount of blood required to transmit Hepatitis B is only 0.00004 ml, while a minimum of 0.1 ml is required for HIV transmission. All health care workers should have Hepatitis B vaccinations, in view of the high risk of accidental transmission, and high prevalence in many developing countries.

Estimates of the risk of HIV transmission from patient to health care worker vary from 0.23% to 0.5% per exposure[384,396,397,398,399]. The type of exposure and the stage of the HIV positive source patient affect the risk, since the viral load will be greater in the recently infected patient and in late stages of the disease. The estimated risk of transmission of HIV from a deep needlestick injury from an HIV-positive patient is 0.4%, and the estimated risk of transmission from a trans-cutaneous exposure is 0.05%.

Management of needlestick injuries and other accidental blood exposure

There is evidence that the risk of infection is reduced by the use of post exposure prophylaxis with anti-retroviral drugs, by as much as 79%[400]. The management of needlestick injuries should be according to local guidelines and antiretroviral drugs should be used for significant injury, if available in the country. Recent guidelines have set out recommendations for the use of antiretrovirals in these cases[379,401,402,403,404,405].

First aid treatment

First aid measures should be undertaken as soon as possible after injury. These should include decontamination of the exposure site as soon as possible, allowing a needlestick injury or cut to bleed, washing the area with chlorhexidine or other antiseptic and decontaminating exposed mucosa or conjunctivae by vigorous flushing with water.

Assessment of risk following exposure

A clinical assessment should be made about the level of risk following exposure. This is based upon the following factors:

A. THE NATURE OF THE INJURY:

Puncture:	*type of needle [hollow or solid]*
	depth of penetration
	volume of blood thought to have been injected
Laceration	
Mucosal contamination	
Contamination of non intact skin	
Bite	

B. THE SOURCE OF EXPOSURE:

Blood, blood products, body fluids, amniotic fluid, semen and vaginal secretions are associated with transmission of HIV, while stool and urine are not

C. THE SOURCE PATIENT:

Clinical condition or available laboratory results such as viral load

Counselling and testing of the source patient

HIV testing should be offered to all source patients, with their informed consent. Where such consent is not available (for example in a comatose or anaesthetized patient), this consent should be obtained from a relative or senior medical staff member. Where the source patient does not wish to know the HIV result, it may be acceptable to offer to take blood for the test (for the protection of the health care worker), without disclosing the result to the source patient. In practice, very few patients refuse consent and most are extremely concerned about health worker risk.

Counselling and testing of the health worker

A baseline HIV test is required for the management of the health worker and in case of a later claim for compensation. If the health worker has not been immunized for Hepatitis B, a test for HBV should also be undertaken at this time.

Follow-up tests should be done at six weeks, three months and six months. PCR testing may provide an earlier result, if available, which can reduce the stress of waiting for many months for a test result for seroconversion.

The injured staff member should receive follow-up counselling at any stage during the six months that this is required. Counselling should include advice to practise safe sex, to avoid blood donation and to consider delaying pregnancy for six months, if this had been planned.

Post exposure prophylaxis

Post-exposure drug prophylaxis should take into account the type and source of the injury and is not recommended for superficial needlestick injuries or cutaneous exposure. For deeper injuries or lacerations, the use of post exposure prophylaxis should be considered, and treatment started as soon as possible after the injury, with the first dose of ZDV ideally taken within two hours[402].

Combination therapy, such as ZDV and 3TC (lamivudine), is currently recommended[402,403,404]. The addition of a protease inhibitor is recommended for deep exposures in the guidelines of Canada and the USA[402,403]. Where viral drug resistance is less common, this may not be as necessary. The decision to use post exposure prophylaxis must be taken by the injured party, after discussion of the benefits and risks.

REFERENCES

1. *Report on the Global HIV/AIDS epidemic*. Geneva, Joint United Nations Programme on HIV/AIDS, 1997:1-13.
2. *AIDS epidemic update: December 1998.*Geneva, Joint United Nations Programme on HIV/AIDS, 1998.
3. Gregson S, Garnett GP, Anderson RM. Is HIV-1 likely to become a leading cause of adult mortality in subSaharan Africa? *J Acquir Immune Defic Syndr*, 1994, 7(8):839-852.
4. World AIDS day 1996. *One world one hope*. Geneva, Joint United Nations Programme on HIV/AIDS, 1996.
5. Minkoff H. Pregnancy and HIV infection. In: *HIV infection in women*, Minkoff H, DeHovitzJA, Duerr A (eds). New York, Raven Press, 1995:173-188.
6. Miyazaki M. Epidemiological characteristics of human immunodeficiency virus type-2 infection in Africa. *Int J STD AIDS*, 1995, 6(2):75-80.
7. Kanki P et al. *HIV-2 provides natural protection against HIV-1 infection*. IX International conference on AIDS and STD in Africa, Kampala, 1995, Abstract MoA026.
8. Gnaore E et al. Prevalence and mortality from HIV Type 2 in Guinea Bissau, West Africa. *Lancet*, 1989, 334 (ii):513.
9. Matheron S et al. Vertical transmission of HIV-2. *Lancet*, 1990, 335:1103-1104.
10. *HIV/AIDS: the global epidemic*. Geneva, Joint United Nations Programme on HIV/AIDS, 1996 (fact sheet).
11. Fowler MG, Melnick SL, Mathieson BJ. Women and HIV. Epidemiology and global overview. *Obstet Gynecol Clin North Am*, 1997, 24(4):705-729.
12. Gregson S et al. Recent upturn in mortality in rural Zimbabwe: evidence for an early demographic effect of HIV-1 infection. *AIDS*, 1997, 11(10):1269-1280.
13. Selik R, Chu S. HIV infection as a leading cause of death among young adults in US cities and states. *JAMA*, 1991, 271:903.
14. Rogers MF. Epidemiology of HIV/AIDS in women and children in the USA. *Acta Pediatr*, 1997, Suppl 421:15-16.
15. Brotman R et al. Childbearing women at risk for HIV infection in New York City. *AIDS & Public Policy J*, 1993, 8(4):186-193.
16. European Collaborative Study. Characteristics of pregnant HIV-1 infected women in Europe. *AIDS Care*, 1996, 8(1):33-42.
17. Newell ML, Thorne C. Pregnancy and HIV infection in Europe. *Acta Pediatr*, 1997, Suppl 421:10-14.
18. Centers for Disease Control and Prevention. AIDS among children - United States 1996. *MMWR*, 1996, 45:1005-1010.
19. Department of Health, South Africa. Sixth National HIV survey of women attending antenatal clinics of the public health services in the Republic of South Africa, October/November 1995. *Epidemiological Comments*, 1996, 23(1):3-17.

20. Namibia updates its figures - what more should it do as a response? *AIDS Analysis Africa*, 1997, 7(3):1.

21. Taha TE et al. Trends of HIV-1 and sexually transmitted diseases among pregnant and postpartum women in urban Malawi. *AIDS*, 1998, 12(2):197-203.

22. Boisson E et al. Interpreting HIV seroprevalence data from pregnant women. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1996, 13:434-439.

23. Dondero TJ, Gill ON. Large scale HIV serologic surveys: what has been learned? *AIDS*, 1991, 5(Suppl 1):S63-S69.

24. Borgdorff M et al. Sentinel surveillance for HIV-1 infection: how representative are blood donors, outpatients with fever, anaemia or sexually transmitted diseases, and antenatal clinic attenders in Mwanza Region, Tanzania. *AIDS*, 1993, 7:567-572.

25. Gray RH et al. Population-based study of fertility in women with HIV-1 infection in Uganda. *Lancet*, 1998, 351:98-103.

26. Asiimwe-Okiror G et al. Change in sexual behaviour and decline in HIV infection among young pregnant women in urban Uganda. *AIDS*, 1997, 11(14):1757-1763.

27. Downs AM, De Vincenzi I, for the European Study Group in Heterosexual Transmission of HIV. Probability of heterosexual transmission of HIV: relationship to number of unprotected sexual contacts. *J Acquir Immune Defic Syndr*, 1996, 11:388-395.

28. Royce RA et al. Sexual transmission of HIV. *N Engl J Med*, 1997, 15:1072-1078.

29. Soto-Ramirez LE et al. HIV-1 Langerhans' cell tropism associated with heterosexual transmission of HIV. *Science*, 1996, 271:1291-1293.

30. Klouman E et al. HIV and reproductive tract infections in a total village population in rural Kilimanjaro, Tanzania: women at increased risk. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1997, 14:163-168.

31. Laga M, Nzila N, Goeman J. The interrelationship of sexually transmitted diseases and HIV infection: implications for the control of both epidemics in Africa. *AIDS*, 1991, 5(Suppl 1):55-63.

32. Ghys PD et al. The associations between cervicovaginal HIV shedding, sexually transmitted diseases and immunosuppression in female sex workers in Abidjan, Cote d'Ivoire. *AIDS*, 1997, 11(12):F85-F93.

33. Dallabetta G. HIV and STDs: how are they linked? *Africa Health*, 1994, November:19-20.

34. Hoegsberg B et al. Sexually transmitted diseases and human immunodeficiency virus among women with pelvic inflammatory disease. *Am J Obstet Gynecol*, 1990, 163:1135-1139.

35. Irwin L, Ellerbrock T. Does pelvic inflammatory disease increase the risk for acquisition of human immunodeficiency virus type 1? (letter). *J Infect Dis*, 1995, 172:898-899.

36. Mayaud P. Tackling bacterial vaginosis and HIV in developing countries. *Lancet*, 1997, 350:530-531.

37. Sewankambo N et al. HIV-1 infection associated with abnormal vaginal flora morphology and bacterial vaginosis. *Lancet*, 1997, 350:546-550.

38. Laga M et al. Nonulcerative sexually transmitted diseases on HIV as risk factors for HIV-1 transmission in women: results from a cohort study. *AIDS*, 1993, 7:95-102.

39. Mlisana KP et al. Syphilis in the "unbooked" pregnant woman. *S Afr Med J*, 1992, 82:18-20.

40. Qolohle DC et al. Serological screening for sexually transmitted infections in pregnancy: is there any value in re-screening for HIV and syphilis at the time of delivery. *Genitourin Med*, 1995, 71:65-67.

41. Mosha F et al. A population based study of syphilis and sexually transmitted disease syndromes in northwestern Tanzania. I. Prevalence and incidence. *Genitourin Med*, 1993, 69:415-420.

42. Latif AS et al. Genital ulcers and transmission of HIV among couples in Zimbabwe. *AIDS*, 1989, 3:519-523.

43. Johnson MA et al. Transmission of HIV to sexual partners of infected men and women. *AIDS*, 1989, 3:367-372.

44. Plourde PJ et al. Human immunodeficiency virus type-1 seroconversion in women with genital ulcers. *J Infect Dis*, 1994, 170:313-317.

45. Mbizvo M et al. Trends in HIV-1 and HIV-2 prevalence and risk factors in pregnant women in Harare, Zimbabwe. *Cent Afr J Med*, 1996, 42(1):14-21.

46. Grosskurth H et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in northern Tanzania: randomised controlled trial. *Lancet*, 1995, 346:530-536.

47. Feldmeier H, Krantz I, Poggensee G. Female genital schistosomiasis as a risk factor for the transmission of HIV. *Int J STD AIDS*, 1994, 5(5):368-372.

48. Plummer FA et al. Co-factors in male-female sexual transmission of human immunodeficiency virus type -1. *J Infect Dis*, 1991, 163:233-239.

49. Daly CC et al. Contraceptive methods and the transmission of HIV: implications for family planning. *Genitourin Med*, 1994, 70(2):110-117.

50. Lamptey P, Potts M. Targeting of prevention programs in Africa. In: Lamptey P, Piot P (eds). *AIDS Prevention Handbook*. Durham, Family Health International, 1990.

51. Campbell T, Kelly M. Women and AIDS in Zambia: a review of the psychosocial factors implicated in the transmission of HIV. *AIDS Care*, 1995, 7(3):365-373.

52. Runyanga A. Pitts M, McMaster J. The use of herbal and other agents to enhance sexual experience. *Soc Sci Med*, 1992, 35(8):1037-1042.

53. Runyanga A, Kasule J. The vaginal use of herbs/substances: an HIV transmission factor? *AIDS Care*, 1995, 7(5):639-645.

54. Civic D, Wilson D. Dry sex in Zimbabwe and implications for condom use. *Soc Sci Med*, 1996, 42:91-98.

55. Gresenguet G et al. HIV infection and vaginal douching in Central Africa. *AIDS*, 1997, 11:101-106.

56. Dallabetta GA et al. Traditional vaginal agents: use and association with HIV infection in Malawian women. *AIDS*, 1995, 9:193-297.

57. Sandala L et al. "Dry Sex" and HIV infection among women attending a sexually transmitted diseases clinic in Lusaka, Zambia. *AIDS*, 1995, 9(Suppl 1):S61-S68.

58. Taha TE et al. *Knowledge of HIV status and its influence on Reproductive intentions of women in Blantyre, Malawi*. Xth International Conference on AIDS and STD in Africa, Abidjan, Côte d'Ivoire, 7-11 December 1997, Abstract.

59. Ahluwalia IB, De Villis RF, Thomas JC. Reproductive decisions of women at risk for acquiring HIV infection. *AIDS Educ Prev*, 1998, 10(1):90-97.

60. Feldblum PJ et al. The effectiveness of barrier methods in preventing the spread of HIV. *AIDS*, 1995, 9(Suppl A):585-593.

61. Drew WL et al. Evaluation of the virus permeability of a new condom for women. *Sexually Transmitted Diseases*, 1990, 17:110-112.

62. Lindgren S et al. A Pattern of HIV viraemia and CD4 levels in relation to pregnancy in HIV 1 infected women. *Scan J Infect Dis*, 1996, 28:425-433.

63. Rich KC et al. CD4+ lymphocytes in perinatal human immunodeficiency virus (HIV) infection: evidence for pregnancy-induced immune depression in uninfected and HIV-infected women. *J Infect Dis*, 1995, 172:1221-1227.

64. Jensen LP et al. Acquired immune deficiency syndrome in pregnancy. *Am J Obstet Gynecol*, 1984, 148(8):1145-6.

65. Minkoff H et al. Pregnancies resulting in infants with acquired immune deficiency syndrome or AIDS related complex. *Obstet Gynecol*, 1987, 69:285.

66. Hocke C et al and the Groupe d'épidémiologie clinique du SIDA en Aquitaine. Prospective cohort study of the effect of pregnancy in the progression of human immunodeficiency virus infection. *Obstet Gynecol*, 1995, 86(6):886-891.

67. Brettle RP et al. HIV infection in women: immunological markers and the influence of pregnancy. *AIDS*, 1995, 9:1177-1184.

68. Weisser M et al. The Swiss HIV Cohort Study (SHCS), and the Swiss Collaborative HIV and Pregnancy Study (SCHPS). Does pregnancy influence the course of HIV infection? Evidence from two large Swiss cohort studies. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1998, 17(5):404-410.

69. Schaefer A et al. *The effect of pregnancy on the natural course of HIV infection.* IV International Conference on AIDS, Stockholm, 1988, Abstract 4039.

70. Bessinger R et al. Pregnancy is not associated with the progression of HIV disease in women attending an HIV outpatient program. *Am J Epidemiol*, 1998 147(5):434-440.

71. Landers DV, Martinez de Tejada B, Coyne BA. Immunology of HIV and pregnancy. The effects of each on the other. *Obstet Gynecol Clin North Am*, 1997, 24(4):821-831.

72. Biggar RJ et al. *Helper and suppresser lymphocyte changes in HIV-infected mothers and their infants.* IV International Conference on AIDS, Stockholm, 1988, Abstract 4032.

73. French R, Brocklehurst P. The effect of pregnancy on survival in women infected with HIV: a systematic review of literature and meta-analysis. *Br J Obstet Gynaecol*, 1998, 105:827-835.

74. Burns DN et al. The influence of pregnancy on human immunodeficiency virus type 1 infection: antepartum and postpartum changes in human immunodeficiency virus type 1 viral load. *Am J Obstet Gynecol*, 1998, 178(2):355-359.

75. Temmerman M. Human immunodeficiency virus and women. *J Obstet Gynecol*, 1994, 14(Suppl 2):S70-S75.

76. Ryder RW, Temmerman M. The effects of HIV-1 infection during pregnancy and the perinatal period on maternal and child health in Africa. *AIDS*, 1991, 5(Suppl 1):S75-S85.

77. Johnstone FD. Pregnancy outcome and pregnancy management in HIV-infected women. In: Johnson MA, Johnstone FD (eds). *HIV Infection in women*. Edinburgh, Churchill Livingstone, 1993:187-198.

78. Temmerman M et al. HIV-1 and immunological changes during pregnancy: a comparison between HIV-1 seropositive and HIV-1 seronegative women in Nairobi, Kenya. *AIDS*, 1995, 9:1057-1060.

79. Miotti PG, Chiphangwi JD, Dallabetta G. The situation in Africa. *Ballieres Clinical Obstet Gynecol*, 1992, 6(1):165-185.

80. Taha TET et al. HIV, maternal death and child survival in Africa. *AIDS*, 1996, 10(1):111-112.

81. Ryder RW et al. Mortality in HIV-1 seropositive women, their spouse and their newly born children during 36 months of follow up in Kinshasa, Zaire. *AIDS*, 1994, 8:667-672.

82. Bakas C, Zarou DM, de Caprariis PJ. First-trimester spontaneous abortions and the incidence of human immunodeficiency virus seropositivity. *J Reprod Med*, 1996, 41(1):15-18.

83. Johnstone FD. HIV and pregnancy. *Br J Obstet Gynaecol*, 1996, 103:1184-1190.

84. Brocklehurst P, French R. The association between maternal HIV infection and perinatal outcome: a systematic review of the literature and meta-analysis. *British Journal of Obstetrics and Gynaecology*, 1998, 105:839-848.

85. Turner BJ et al. Prenatal care and birth outcomes of a cohort of HIV-infected women. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1996, 12:259-267.

86. Turner NJ et al. Prenatal care of HIV-infected women: analysis of a large New York State cohort. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1995, 9:371-378.

87. Hira SK et al. Apparent vertical transmission of HIV-1 by breastfeeding in Zambia. *J Paediatr*, 1990, 117:421-424.

88. McIntyre JA. *Pregnancy and HIV infection at Baragwanath Hospital, 1987-1993*. Eighth International Conference on AIDS and STD in Africa, Marrakesh, 1993, Abstract ThOP13.

89. Ryder RW et al. Perinatal transmission of the human immunodeficiency virus type-1 to infants of seropositive women in Zaire. *N Engl J Med*, 1989, 320:1637-1642.

90. Temmerman M et al. Infection with HIV as a risk factor for adverse pregnancy outcome. *AIDS*, 1990, 4:139-144.

91. Minkoff HL et al. Serious infections during pregnancy among women with advanced human immunodeficiency virus infection. *Am J Obstet Gynecol*, 1990,

162:30-34.

92. Langston C et al. Excess intrauterine fetal demise associated with maternal human immunodeficiency virus infection. *J Infect Dis*, 1995, 172:1451-1460.

93. D'Ubaldo C et al. Association between HIV-1 infection and miscarriage: a retrospective study. *AIDS*, 1998, 12(9):1087-93.

94. Byabamazina CR et al. *HIV/Syphilis serology as an indicator of past pregnancy outcomes among antenatal attendees in Kampala*. IXth International Conference on AIDS and STD in Africa, Kampala, 1995, Abstract TuC108.

95. Shearer WT et al. Early spontaneous abortion and fetal thymic abnormalities in maternal-to-fetal HIV infection. *Acta Pediatr*, 1997, Suppl 421:60-64.

96. Klugman KP et al. Serological markers of sexually transmitted diseases associated with HIV-1 infection in pregnant black women. *S Afr Med J*, 1991, 80:243-244.

97. Leroy V et al. Should screening of genital infections be part of antenatal care in areas of high HIV prevalence? *Genitourin Med*, 1995, 71(4):207-211.

98. Johnstone FD et al. Does infection with HIV affect the outcome of pregnancy? *Br Med J*, 1988, 296:487.

99. Mauri A et al. Obstetric and perinatal outcome in human immunodeficiency virus-infected pregnant women with and without opiate addiction. *Euro J Obstet Gynecol*, 1995, 58:135-140.

100. Taha TET et al. The effect of human immunodeficiency virus infection on birthweight, and infant and child survival in urban Malawi. *Int J epidemiol*, 1995, 24:1022-1028.

101. Rabkin CS et al. Kaposi's sarcoma in pregnant women. *Nature*, 1995, 377:21-22.

102. Bergstrom S et al. HIV infection and maternal outcome of pregnancy in Mozambican women: a case control study. *Genitourin Med*, 1995, 71:323-324.

103. Braddick MR et al. Impact of maternal HIV infection on obstetrical and early pregnancy outcome. *AIDS*, 1990, 4:1001-1005.

104. Spinello A et al. The effect of fetal infection with human immunodeficiency virus type 1 on birthweight and length of gestation. *Euro J Obstet Gynecol*, 1994, 57:13-17.

105. Markson LE et al. Association of maternal HIV infection with low birth weight. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1996, 13(3):227-234.

106. Johnstone FD, Raab GM, Hamilton BA. The effect of human immunodeficiency virus infection and drug use on birth characteristics. *Obstet Gynecol*, 1996, 88(3):321-326.

107. Leroy V et al. Effect of HIV-1 infection on pregnancy outcome in women in Kigali, Rwanda, 1992-1994. *AIDS*, 1998, 12(6):643-650.

108. Gray G, McIntyre JA, Pettifor J. *Difference in growth and illness between breastfed and formula fed infants born to HIV positive women in Soweto.* IXth International Conference on AIDS and STD in Africa, Kampala, 1995, Abstract ThB280.

109. Bulterys M et al. Fatal complications after Caesarian section in HIV-infected women. *AIDS*, 1996, 10(8):923-924.

110. Semprini AE et al. The incidence of complications after caesarean section in 156 HIV-positive women. *AIDS*, 1995, 9:913-917.

111. Newell M-L, Gray G, Bryson YJ. Prevention of mother-to child transmission of HIV-1 transmission. *AIDS*, 1997, 11(Suppl A):S165-S172.

112. Working Group on mother-to-child transmission of HIV. Rates of mother-to-child transmission of HIV-1 in Africa, America and Europe: results from 13 perinatal studies. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1995, 8:506-510.

113. Reggy A, Simonds RJ, Rogers M. Preventing perinatal HIV transmission. *AIDS*, 1997, 11(Suppl A):S61-S67.

114. Simonds RJ et al. Impact of zidovudine use on risk and risk factors for perinatal transmission of HIV. Perinatal AIDS Collaborative Transmission Studies. *AIDS*, 1998, 12(3):301-308.

115. Backe E et al. Fetal organs infected by HIV-1. *AIDS*, 1993, 7:896-897.

116. Mofenson LM. Interaction between the timing of perinatal human immunodeficiency virus infection and the design of preventive and therapeutic interventions. *Acta Pediatr*, 1997, Suppl 421:1-9.

117. Viscarello RR et al. Fetal blood sampling in HIV- seropositive women before elective midtrimester termination of pregnancy. *Am J Obstet Gynecol*, 1992, 167:1075-1079.

118. Goedert JJ et al. International Registry of HIV-exposed twins. High risk of HIV-1 infection for first born twins. *Lancet*, 1991, 338:1471-1475.

119. European Collaborative Study. Caesarean section and the risk of vertical transmission of HIV-1 infection. *Lancet*, 1994, 343:1464-1467.

120. Landesman SH et al for the Women and Infants Transmission Study. Obstetrical factors and the transmission of human immunodeficiency virus type 1 from mother to child. *N Engl J Med*, 1996, 334:1617-1623.

121. Brossard Y et al. Frequency of early in-utero HIV-1 infection: a blind DNA polymerase chain reaction study on 100 fetal thymuses. *AIDS*, 1995, 9(4):359-366.

122. Mofenson LM. Mother-child HIV-1 transmission: timing and determinants. *Obstetr Gynecol Clin North Am*, 1997, 24(4):759-784.

123. Fowler MG. Update: transmission of HIV-1 from mother to child. *Curr Opin Obstet Gynecol*, 1997, 9(6):343-348.

124. Kuhn L et al. Timing of maternal-infant HIV transmission: associations between intrapartum factors and early polymerase chain reaction results. *AIDS*, 1997, 11:429-435.

125. Choquet C et al. Timing of mother-to-child transmission and diagnosis of infection based on polymerase chain reaction in the neonatal period by a non-parametric methods. *AIDS*, 1997, 11:1183-1199.

126. Vials JM. A review of the literature on prevention of early vertical transmission of the HIV virus. *Midwifery*, 1997, 13(4):216-220.

127. Bryson YJ et al. Proposed definition for in-utero versus intrapartum transmission of HIV-1. *N Engl J Med*, 1992, 327:1246-1247.

128. Rouzioux C et al and the HIV infection in newborns French Collaborative Study Group. Estimated timing of mother-to-child human immunodeficiency virus type 1 (HIV-1) transmission by use of a Marcov model. *Am J Epidemiol*, 1995, 142(12):1330-1337.

129. Kalish LA et al. Defining the time of fetal or perinatal acquisition of human immunodeficiency virus type 1 on the basis of age at first positive culture. *J Infect Dis*, 1997, 175:712-715.

130. Bertolli J et al. Estimating the timing of mother-to-child transmission of human immunodeficiency virus in a breastfeeding cohort in Kinshasa, Zaire. *J Infect Dis*, 1996, 174:722-726.

131. Bryson Y. Perinatal HIV-1 transmission: recent advances and therapeutic interventions. *AIDS*, 1996, 10(Suppl 3):S33-S42.

132. Steihm ER. Newborn factors in maternal-infant transmission of pediatric HIV infection. *J Nutr*, 1996, 126:2632S-2636S.

133. Goedert JJ et al. Mother-to-infant transmission of human immunodeficiency virus type 1: association with prematurity or low anti gp-120. *Lancet*, 1989, 2:1351-1354.

134. Shearer WT, Kalish LA, Zimmerman PA. CCR5 HIV-1 vertical transmission. Women and Infants Transmission Study Group. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1998, 17(2):180-181.

135. Mtimavalye L et al. Maternal-infant transmission of HIV-1. *N Engl J Med*, 1995, 332:890-891.

136. Ryder RW, Behets F. Reasons for the wide variation in reported rates of mother-to-child transmission of HIV-1. *AIDS*, 1994, 8:1495-1497.

137. Nieburg P et al. Contribution of breastfeeding to the reported variation in rates of mother-to-child HIV transmission. *AIDS*, 1995, 9(4):396-397.

138. Hengel RL et al. Neutralizing antibody and perinatal transmission of human immunodeficiency virus type 1. New York City Perinatal HIV Transmission Collaborative Study Group. *AIDS Res Hum Retroviruses*, 1998, 14(6):475-481.

139. Cohen M et al. Prophylactic cesarean section and HIV seropositive patients. *J Gynecol Obstet Biol Reprod*, 1996, 25(8):846-850.

140. Newell ML. Mechanisms and timing of mother-to-child transmission of HIV-1. *AIDS*, 1997, 12:831-837.

141. Butlerys M, Lepage P. Mother-to-child transmission of HIV. *Curr Opin Ped*, 1998, 10:143-150.

142. European Collaborative Study. Risk factors for mother-to-child transmission of HIV-1. *Lancet*, 1992, 339:1007-1012.

143. Mayaux MJ et al. Maternal factors associated with perinatal HIV-1 transmission: the French cohort study: 7 years of follow up observation. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1995, 8:188-194.

144. Mayaux MJ et al. Maternal viral load during pregnancy and mother-to child transmission of human immunodeficiency virus type 1: the French Perinatal Cohort Studies. *J Infect Dis*, 1997, 175:172-175.

145. Thea DM et al and the New York City Perinatal HIV Transmission Collaborative Group. The effect of maternal viral load on the risk of perinatal transmission of HIV-1. *AIDS*, 1997, 11:437-444.

146. Sperling R et al. *Maternal plasma HIV-1 RNA and the success of zidovudine (ZDV) in the prevention of mother-to-child transmission*. Third International Conference on Retroviruses and Opportunistic Infections, Washington DC, 1996, Abstract LB1.

147. Burchett S et al. *Assessment of maternal plasma viral load as a correlate of vertical transmission*. Third International Conference on Retroviruses and Opportunistic Infections, Washington DC, 1996, Abstract LB3.

148. Coll O et al. Vertical HIV-1 transmission correlated with a high maternal viral load at delivery. *J Acquir Immune Defic Hum Retrovirol*, 1997, 14:26-30.

149. Scarlatti G et al. Transmission of human immunodeficiency virus type 1 (HIV-1) from mother to child correlates with viral phenotype. *Virology*, 1993, 197:624-629.

150. Thea DM et al. The effect of maternal viral load on the risk of perinatal transmission of HIV-1. *J Infect Dis*, 1997 175:707-711.

151. Cao Y et al. Maternal HIV-1 viral load and vertical transmission of infection: The Ariel Project for the prevention of HIV transmission from mother to infant. *Nature Medicine*, 1997, 3:549-552.

152. O'Shea S et al. Maternal viral load, CD4 cell count and vertical transmission of HIV-1. *J Med Virol*, 1998, 54(2):113-117.

153. Shaffer N et al. *High maternal viral load predicts perinatal HIV-1 transmission and early infant progression*. Third International Conference on Retroviruses and Opportunistic Infections, Washington DC, 1996, Abstract 30.

154. Fang G et al. Maternal plasma human immunodeficiency virus type 1 RNA level: a determinant and projected threshold for mother-to-child transmission. *Proc Natl Acad Sci USA*, 1995, 92:12100-12104.

155. Koup R et al. *Lack of maternal viral threshold for vertical transmission of HIV-1*. Third International Conference on Retroviruses and Opportunistic Infections, Washington DC, 1996, Abstract LB2.

156. John GC, Kreiss J. Mother-to child transmission of human immunodeficiency virus type 1. *Epidemiol Rev*, 1996, 18(2):149-157.

157. Clemetson DBA et al. Detection of HIV DNA in cervical and vaginal secretions. *JAMA*, 1993, 269:2860-2864.

158. Loussert-Ajaka I et al. HIV-1 detection in cervicovaginal secretions during pregnancy. *AIDS*, 1997, 11(13):1575-1581.

159. Nduati R et al. Human immunodeficiency virus type 1-infected cells in breast milk: association with immunosuppression and vitamin A deficiency. *J Infect Dis*, 1995, 172:1461-1468.

160. John GC et al. Genital shedding of human immunodeficiency virus type-1 DNA during pregnancy: association with immunosuppression, abnormal cervical and vaginal discharge and severe vitamin A deficiency. *J Infect Dis*, 1997, 175(1):57-62.

161. Van de Perre P et al. Infective and anti-infective properties of breast milk from HIV-1 infected women. *Lancet*, 1993, 341(8850):914-8.

162. Landers DV. Nutrition and immune function II: maternal factors influencing transmission. *J Nutr*, 1996, 126:S2637-2640.

163. Dickover RE et al. Identification of levels of maternal HIV-1 RNA associated with risk of perinatal transmission: effect of maternal zidovudine treatment on viral load. *JAMA*, 1996, 275:599-605.

164. Bulterys M, Lepage P. Mother-to-child transmission of HIV. *Curr Opin Pediatr*, 1998, 10(2):143-150.

165. Boswell et al. *The distribution of HIV-1 serotypes in Africa.* IX International Conference on AIDS and STD in Africa, Kampala, 1995, Abstract MoA041.

166. Kunanusont C et al. HIV-1 subtypes and male to female transmission in Thailand. *Lancet*, 1995, 345:1078-1083.

167. Cavaco-Silva P et al. Virological and molecular demonstration of human immunodeficiency virus type 2 vertical transmission. *J Virol*, 1998, 72(4):3418-3422.

168. Lamers SL et al. Persistence of multiple maternal genotypes of human immunodeficiency virus type 1 in infants infected by vertical transmission. *J Clin Invest*, 1994, 93:380-390.

169. Wolinsky SM et al. Selective transmission of human immunodeficiency virus type-1 variants from mothers to children. *Science*, 1992, 225:1134-1137.

170. Scarlatti G et al. Comparison of variable region 3 sequences of human immunodeficiency virus type 1 from infected children with the RNA and DNA sequences of the virus populations of their mothers. *Proc Natl Acad Sci USA*, 1993, 90:1721-1725.

171. Ometto L et al. Viral phenotype and host cell susceptibility to HIV-1 infection as risk factors for mother-to-child HIV-1 transmission. *AIDS*, 1996, 9:427-434.

172. Spencer TL, Danker OM, Spector SA. Clinical significance of HIV-1 phenotype in infected children. *J Infect Dis*, 1994, 169:491-495.

173. Reinhardt PP et al. Human cord blood mononuclear cells are preferentially infected by non syncitium-inducing, macrophage-tropic human immunodeficiency type 1 isolates. *J Clin Microbiol*, 1995, 33:292-297.

174. van't Wout AB et al. Macrophage-tropic variants initiate human immunodeficiency virus type-1 infection after sexual, parenteral, and vertical transmission. *J Clin Invest*, 1994, 94(5):2060-2067.

175. Colognesi C et al. The role of virologic and immunologic factors in mother-to-child transmission of HIV-1. *Am J Reprod Immunol*, 1997, 38(3):197-200.

176. De Rossi A et al. Viral phenotype in mother-to-child HIV-1 transmission and disease progression of vertically acquired HIV-1 infection. *Acta Pediatr*, 1997 Suppl 421:22-28.

177. Bulterys M, Goedert JJ. From biology to sexual behaviour - towards the prevention of mother to child transmission of HIV. *AIDS*, 1995, 10:1287-1289.

178. Eastman PS et al. Maternal viral genotypic zidovudine resistance and infrequent failure of zidovudine therapy to prevent perinatal transmission of human immunodeficiency virus type 1 in pediatric AIDS Clinical Trials Group Protocol

076. *J Infect Dis*, 1998, 177(3):557-564.

179. McIntosh K. Antiretroviral resistance and HIV vertical transmission. *Acta Pediatr*, 1997, Suppl 421:29-32.

180. Fowler MG, Rogers MF. Overview of perinatal infection. *J Nutr*, 1996, 126:2602S-2607S.

181. European Collaborative Study. Vertical transmission of HIV-1: maternal immune status and obstetric factors. *AIDS*, 1996, 10:1675-1681.

182. Pitt J et al. Maternal immunologic and virologic risk factors for infant human immunodeficiency virus type 1 infection: findings from the Women and Infants Transmission Study. *J Infect Dis*, 1997, 175:567-575.

183. Lallemant M, Lallemant-Le Coeur S, Nzingoula S. Perinatal transmission of HIV in Africa. In: Essex M et al (eds). *AIDS in Africa.* New York, Raven Press, 1994:211-235.

184. Wood L. Perinatal Transmission of HIV-1 (letter). *JAMA*, 1996, 276(16):1300.

185. Scarlatti G et al. Mother to child transmission of human immunodeficiency virus type 1: correlation with neutralizing antibodies against primary isolates. *J Infect Dis*, 1993, 168:207-210.

186. Kliks SC et al. Features of HIV-1 that could influence maternal-child transmission. *JAMA*, 1994, 272:467-474.

187. Husson RN et al. Vertical transmission of human immunodeficiency virus type 1: autologous neutralizing antibody, virus load and virus phenotype. *J Pediatr*, 1995, 126:865-871.

188. Bryson YJ et al. The role of maternal autologous neutralizing antibody in prevention of maternal fetal HIV-1 transmission. *J Cell Biochem,* 1993, Suppl 17E:95.

189. Halsey NA et al. Lack of association between maternal antibodies to V3 loop peptides and maternal-infant transmission. *J Acquir Immune Defic Syndr,* 1992, 5:153-157.

190. Robertson CA et al. Maternal antibodies to gp120 V3 sequence do not correlate with protection against vertical transmission of human immunodeficiency virus. *J Infect Dis*, 1992, 166:704-709.

191. Jenkins M et al. Association between anti-human immunodeficiency virus type-1 (HIV-1) antibody-dependent cellular cytotoxicity antibody titres at birth and vertical transmission of HIV-1. *J Infect Dis*, 1994, 170:308-312.

192. Ugen KE et al. Vertical transmission of Human immunodeficiency virus type 1: seroreactivity by maternal antibodies to the carboxy region of the gp41 envelope glycoprotein. *J Infect Dis*, 1997, 175:63-69.

193. Van de Perre P et al. Postnatal transmission of HIV-1 associated with breast abscess. *Lancet*, 1992, 339:1490-1491.

194. Nduati RW et al. Human immunodeficiency virus type 1-infected cells in breast milk: association with immunosuppression and vitamin A deficiency. *J Infect Dis*, 1995, 172(6):1461-1468.

195. Semba RD et al. Maternal vitamin A deficiency and mother to child transmission of HIV-1. *Lancet*, 1994, 343:1593-1597.

196. Burger H et al. Maternal serum vitamin A levels are not associated with mother-to-child transmission in the United States. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1997, 14(4):321-326.

197. Greenberg BL et al. Vitamin A deficiency and maternal-infant transmission of HIV in two metropolitan areas in the United States. *AIDS*, 1997, 11:325-332.

198. Semba RD. Vitamin A, immunity and infection. *Clin Infect Dis*, 1994, 19:489-499.

199. Burns DN et al. Cigarette smoking, premature rupture of membranes, and vertical transmission of HIV-1 among women with low CD4+ levels. *J Acquir Immune Defic Syndr*, 1994, 7:718-726.

200. Turner BJ et al. Cigarette smoking and maternal-child HIV transmission. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1997, 14:327-337.

201. Matheson PB et al and the New York City Perinatal HIV transmission Collaborative Study. Association of maternal drug use during pregnancy with mother-to-child transmission. *AIDS*, 1997, 11(7):941-942.

202. Rodriguez EM et al. Association of maternal drug use during pregnancy with maternal HIV culture positivity and perinatal transmission. *AIDS*, 1996, 10(3):273-282.

203. Matheson PB et al. Heterosexual behaviour during pregnancy and perinatal transmission of HIV-1. *AIDS*, 1996, 10:1249-1256.

204. Lallemant M et al. Mother to child transmission of HIV-1 in Congo, central Africa. *AIDS*, 1994, 8(10):1451-1456.

205. Bulterys M et al. Multiple sexual partners and mother-to-child transmission of HIV-1. *AIDS*, 1993, 7:1639-1645.

206. Naeye RL, Ross S. Coitus and chorioamnionitis: a prospective study. *Hum Devel*, 1983, 6:91-94.

207. Mandelbrot L et al. Obstetric factors and mother-to-child transmission of human immunodeficiency virus type 1: the French perinatal cohorts. *Am J Obstet Gynecol*, 1996, 175:661-667.

208. Temmerman M et al. Risk factors for mother-to-child transmission of human immunodeficiency virus-1 infection. *Am J Obstet Gynecol*, 1995, 172:700-705.

209. Wabire-Mangen F et al. *Placental risk factors for the vertical transmission of HIV-1 in Uganda*. XI International Conference on AIDS, Vancouver, 1996, Abstract TuC341.

210. Shearer WT et al. Role of placental cytokines and inflammation in vertical transmission of HIV infection. *Acta Pediatr*, 1997, Suppl 421:33-38.

211. Anderson VM. The placental barrier to maternal HIV infection. *Obstet Gynecol Clin North Am*, 1997, 24(4):797-820.

212. Douglas GC, King BF. Maternal-fetal transmission of human immunodeficiency virus: a review of possible routes and cellular mechanisms of infection. *Clin Infect Dis*, 1992, 15:678-691.

213. St Louis ME et al. Risk for perinatal HIV-1 transmission according to maternal immunologic, virologic and placental factors. *JAMA*, 1993, 169:2853-2859.

214. Boyer PJ et al. Factors predictive of maternal-fetal transmission of HIV-1. *JAMA*, 1994, 217:1925-1930.

215. Burton GJ et al. Physical breaks in the placental trophoblastic surface: significance in vertical transmission of HIV. *AIDS*, 1996, 10(11):1294-1295.

216. Bloland PB et al. Maternal HIV infection and infant mortality in Malawi: evidence for increased mortality due to placental malaria infection. *AIDS*, 1995, 9:721-726.

217. Nahlen B et al. *Association between placental malarial infection and increased risk of mother to infant transmission of HIV-1 in western Kenya*. 12th World AIDS Conference, Geneva, 28 June - 3 July 1998, Abstract 23268.

218. Henin Y et al. Virus excretion in the cervicovaginal secretions of pregnant and nonpregnant HIV-infected women. *J Acquir Immune Defic Syndr*, 1993, 6:72-75.

219. Duliege AM et al. Birth order, delivery route and concordance in the transmission of human immunodeficiency virus type 1 from mothers to twins. *J Pediatr*, 1995, 126:625-632.

220. Datta P et al. Mother-to child transmission of Human Immunodeficiency Virus Type 1: Report from the Nairobi study. *J Infect Dis*, 1994, 170:1134-1140.

221. Minkoff H et al. The relationship of the duration of ruptured membranes to vertical transmission of human immunodeficiency virus. *Am J Obstet Gynecol*, 1995, 173:585-589.

222. Biggar RJ et al. Perinatal intervention trial in Africa: effect of birth canal cleansing intervention to prevent HIV transmission. *Lancet*, 1996, 347:1647-1650.

223. Kuhn L et al. Cesarean deliveries and maternal-infant HIV transmission: results from a prospective study in South Africa. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1996, 11:478-483.

224. Dunn DT et al. Mode of delivery and vertical transmission of HIV-1: a review of prospective studies. *J Acquir Immune Defic Syndr*, 1994, 7:1064-1066.

225. Peckham C. Human immunodeficiency virus and mode of delivery. *Acta Pediatr*, 1997, Suppl 421:104-106.

226. The European Mode of Delivery Collaboration. Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. *Lancet*, 1999, 353:1035-1039.

227. Kind C et al. Prevention of vertical HIV transmission: additive protective effect of elective Cesarean section and zidovudine prophylaxis. Swiss Neonatal HIV Study Group. *AIDS*, 1998, 12(2):205-210.

228. Mandelbrot L et al. Perinatal HIV-1 transmission: interaction between zidovudine prophylaxis and mode of delivery in the French Perinatal Cohort. *JAMA*, 1 July 1998, 280(1):55-60.

229. Luscher MA et al. Anti-HLA alloantibody is found in children but does not correlate with a lack of HIV type 1 transmission from infected mothers. *AIDS Res Hum Retroviruses*, 1998, 4(2):99-107.

230. Misrahi M et al. CCR5 chemokine receptor variant in HIV-1 mother-to-child transmission and disease progression in children. French Pediatric HIV Infection Study Group. *JAMA*, 1998, 279(4):277-280.

231. Mangano A et al. Distribution of the CCR-5 delta32 allele in Argentinian children at risk of HIV-1 infection: its role on vertical transmission. *AIDS*, 1998, 12(1):109-110.

232. MacDonald KS et al. Mother-child class I HLA concordance increases perinatal human immunodeficiency virus type 1 transmission. *J Infect Dis*, 1998, 177(3):551-556.

233. Tovo P et al. Mode of delivery and gestational age influence perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1996, 343:390-391.

234. Mofenson L, Wolinsky SM. Current insights regarding vertical transmission. In: Pizzo PA, Wilfert CM (eds.) *Paediatric AIDS,* Edition 4. Baltimore, Williams and Wilkins, 1995:179-203.

235. Goedert JJ. Vertical transmission of human immunodeficiency virus type 1: insights from studies of multiple pregnancies. *Acta Pediatr*, 1997, Suppl 421:56-59.

236. Lewis P et al. Cell-free human immunodeficiency virus type 1 in breast milk. *J Infect Dis*, 1998, 177(1):34-39.

237. Dunn DT et al. Risk of human immunodeficiency virus type 1 transmission through breastfeeding. *Lancet*, 1992, 340:585-588.

238. Gray GE, McIntyre JA, Lyons SF. The effect of breastfeeding on vertical transmission of HIV-1 in Soweto, South Africa. XI International Conference on AIDS, Vancouver, 1997, Abstract ThC415.

239. Van de Perre P et al. Postnatal transmission of human immunodeficiency virus type 1 from mother to child: a prospective study in Kigali, Rwanda. *N Engl J Med*, 1991, 325:585-588.

240. Kambarami RA, Kowo H. The prevalence of nipple disease among breast feeding mothers of HIV seropositive infants. *Cent Afr J Med*, 1997, 43(1):20-22.

241. Bulterys M et al. HIV-1 seroconversion after 20 months of age in a cohort of breastfed children born to HIV-1 infected women in Rwanda. *AIDS*, 1995, 9(1):93-94.

242. Ekpini ER et al. Late postnatal mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire. *Lancet*, 1997, 349:1054-1059.

243. Newell ML, Peckham C. Vertical transmission of HIV infection. *Acta Paediatr*, 1994, Suppl 400:43-45.

244. Newell ML. Vertical transmission of HIV-1: risks and prevention. *J Hosp Infect*, 1995, 30(Supp l):191-196.

245. Kuhn L, Stein Z. Mother to infant HIV transmission. *Paediatr Perinat Epidemiol*, 1995, 9(1):1-29.

246. *Reducing women's vulnerability to HIV infection*. Geneva, Joint United Nations Programme on HIV/AIDS, 1997:1-6.

247. *HIV and infant feeding*. Geneva, Joint United Nations Programme on HIV/AIDS, 1997:1-2.

248. Kline A, Strickler J, Kempf J. Factors associated with pregnancy and pregnancy resolution in HIV seropositive women. *Soc Sci Med*, 1995, 40(11):1539-1547.

249. Thackway SV et al. Fertility and reproductive choice in women with HIV-1 infection. *AIDS*, 1997, 11:663-667.

250. McIntyre JA. Transmission of HIV from mother to child: strategies for prevention. *Maternal & Child Health*, 1996, 21(5):116-118.

251. Shaffer N et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. *Lancet*, 1999, 353:773-780.

252. Wiktor SZ, Ekpini E, Nduati RW. Prevention of mother-to-child transmission of HIV-1 in Africa. *AIDS*, 1997, 11(Suppl B):S79-S87.

253. Gray GE. Antiretrovirals and their role in preventing mother-to-child transmission of HIV-1 infection. In: Van Praag E, Fernyak S, Katz AM (eds.) *The implications of antiretroviral treatments*. Informal Consultation April 1997, Geneva, World Health Organization, 1997 (WHO/ASD/97.2).

254. Brocklehurst P. Interventions for reducing mother-to-child transmission of HIV infection (Cochrane Review). In: *The Cochrane Library*. Oxford: Update Software.

255. Connor EM et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Engl J Med*, 1994, 331(18):1173-1180.

256. Sperling RS et al. Maternal, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. Pediatric AIDS Clinical Trial Group Protocol 076 Study Group. *N Engl J Med*, 1996, 335(22):1621-1629.

257. Wade NA et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med*, 1998, 339:1409-14.

258. McIntosh K. Short (and shorter) courses of zidovudine. *N Engl J Med*, 1998, 339:1487-1468.

259. Culnane M et al for the Pediatric AIDS Clinical Trials Group Protocol 219/076 Teams. Lack of long-term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women. *JAMA*, 1999, 281(2):151-157.

260. Centers for Disease Control and Prevention. Recommendations of the US Public Health Service Task Force on the use of zidovudine to reduce perinatal transmission of human immunodeficiency virus. *MMWR*, 1994, 43:RR-11.

261. Simonds RJ, Rogers M. Preventing perinatal HIV infection: how far have we come? *JAMA*, 1996, 275:1514-1515.

262. Gibb DM et al. Uptake of interventions to reduce mother-to-child transmission of HIV in the United Kingdom and Ireland. *AIDS*, 1997, 11:F53-F58.

263. Landers DV, Sweet RL. Reducing mother-to-infant transmission of HIV - the door remains open. *N Engl J Med*, 1996, 334:1664-1665.

264. Van de Perre P et al. Zidovudine and breast-feeding. *AIDS Patient Care and STDs*, 1997, 11(1):4-5.

265. Mayaux MJ et al. Acceptability and impact of zidovudine for prevention of mother-to-child human immunodeficiency virus-1 transmission in France. *J Pediatr*, 1997, 131(6):857-862.

266. Fiscus SA et al. Perinatal HIV infection and the effect of zidovudine therapy on transmission in rural and urban counties. *JAMA*, 1996, 275(19):1483-1488.

267. Wiznia A. Zidovudine use to reduce perinatal HIV type 1 transmission in an urban medical center. *JAMA*, 1996, 275:1504-1506.

268. Dabis F et al. Zidovudine to decrease mother-to-child transmission of HIV-1: is it good for developing countries. *AIDS*, 1995, 9(2):204-206.

269. Cartoux M et al. Acceptability of interventions to reduce mother-to-child transmission of HIV-1 in West Africa. *J Acquir Immune Syndr Hum Retrovirol*, 1996, 12:290-292.

270. Meda N et al. The reduction of mother-child transmission of HIV infection in developing countries: potential intervention strategies, obstacles to implementation and perspectives. *Santé*, 1997, 7(2):115-125.

271. Srinivas RV et al. Development of zidovudine-resistant HIV genotypes following postnatal prophylaxis in a perinatally infected infant. *AIDS*, 1996, 10(7):795-796.

272. White A, Eldridge R, Andrews E and the Antiretroviral Pregnancy Registry Advisory Committee. Birth outcomes following zidovudine exposure in pregnant women: the Antiretroviral Pregnancy Registry. *Acta Pediatr*, 1997, Suppl 421:86-88.

273. Connor E et al and Protocol 076 and 219 study groups. *Long term effect of ZDV exposure among uninfected infants born to HIV infected mothers in PACTG Protocol 076.* 36th Interscience Conference on antimicrobial agents and chemotherapy, New Orleans, 1996, Abstract 111.

274. Ayers KM et al. Nonclinical toxicology studies with zidovudine: genetic toxicity tests and carcinogenicity bioassays in mice and rats. *Fundam Appl Toxicol*, 1996, 32:148-158.

275. Olivero OA et al. AZT is a genotoxic transplacental carcinogen in animal models. *JAIDS*, 1997, 14:A29 Abstract 52.

276. Mansergh G et al. Cost-effectiveness of short-course zidovudine to prevent perinatal HIV type 1 infection in a sub-Saharan African developing country setting. *JAMA*, 1996, 276:139-145.

277. Bueckert H. Costs and benefits of screening pregnant women for HIV (letter). *Can Med Assoc J*, 1996, 155(10):1387.

278. Ecker JL. The cost-effectiveness of human immunodeficiency virus screening in pregnancy. *Am J Obstet Gynecol*, 1996, 174(2):716-721.

279. Mauskopf J et al. Economic impact of treatment of HIV-positive pregnant women and their newborns with zidovudine. *JAMA*, 1996, 276:132-138.

280. Frenkel LM et al. Analysis of the maternal components of the AIDS Clinical Trial Group 076 zidovudine regimen in the prevention of mother-to infant transmission of human immunodeficiency virus type 1. *J Infect Dis*, 1997,175:971-974.

281. Simpson BJ, Shapiro ED, Andiman WA. Reduction in the risk of vertical transmission of HIV-1 associated with treatment of pregnant women with orally administered zidovudine alone. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1997, 14:145-152.

282. Dabis F et al for the DITRAME Study Group. 6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Côte d'Ivoire and Burkina Faso: a double-blind placebo-controlled multicentre trial. *Lancet*, 1999, 353:786-92.

283. Wiktor S et al. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Côte d'Ivoire: a randomised trial. *Lancet*, 1999, 353:781-785.

284. Glaxo cuts HIV drug cost for developing world. *Nature*, 1998, 392:118.

285. Van Praag E, Fernyak S, Katz AM (eds.) *The implications of antiretroviral treatments.* Informal Consultation April 1997, Geneva, World Health Organization, 1997 (WHO/ASD/97.2).

286. Blanche et al. Zidovudine-lamivudine for prevention of mother to child HIV-1 transmission. Sixth Conference on Retroviruses and Opportunistic Infections, Chicago. Abstract 267, 1999.

287. BHIVA Guidelines Co-ordinating Committee. British HIV Association guidelines for antiretroviral treatment of HIV seropositive individuals. *Lancet*, 1997, 349:1086-1092.

288. Carpenter CCJ et al. Antiretroviral therapy for HIV infection in 1997. *JAMA*, 1997, 277:1962-1969.

289. De Cock K. Guidelines for managing HIV infection (editorial). *Br Med J*, 1997, 315:1-2.

290. Augenbaum M, Minkoff HL. Antiretroviral therapy in the pregnant woman. *Obstet Gynecol Clin North Am*, 1997, 24(4):833-854.

291. Centers for Disease Control and Prevention. Public Health Service Task Force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and for reducing perinatal HIV-1 transmission in the United States. *MMWR*, 1998, 47(Rr-2):1-30.

292. Lambert IS. The prevention of maternal-fetal HIV-1 infection through passive antibody products (HIVIG) and active immunisation (AIDS vaccines). *Pediatr AIDS HIV Infect Fetus Adolesc*, 1995, 6:300-302.

293. Stiehm R et al. for the Pediatric AIDS Clinical Trials Group Protocol 185 Team. Efficacy of zidovudine and human immunodeficiency virus (HIV) hyperimmune immunoglobulin for reducing perinatal HIV transmission from HIV-infected women with advanced disease: results of Pediatric AIDS Clinical Trials Group Protocol 185. *JID*, 1999, 179:567-575.

294. Fast P, Newell M, Mofenson P. Strategies for prevention of perinatal transmission of HIV infection. Report of a consensus workshop (II) Sienna Italy, June 3-6, 1993. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1993, 8:161-175.

295. Fawzi WW et al for the Tanzania Vitamin and HIV Infection Trial Team. Randomised trial of effects of vitamin supplements on pregnancy outcomes and T cell counts in HIV-1 infected women in Tanzania. *Lancet*, 1998, 351:1477-1478.

296. Moodley D, Bobat RA, Cousidis A, Coovadia HM. Caesarean section and vertical transmission of HIV-1. *Lancet*, 1994, 34:338.

297. Read J. *Mode of delivery and vertical transmission of HIV-1: a meta analysis from fifteen prospective cohort studies* (The International Perinatal HIV Group). 12th World AIDS Conference, Geneva, 28 June - 3 July 1998, Abstract 23603.

298. Fowler MG, Mofenson L. Progress in the prevention of perinatal HIV-1. *Acta Pediatr*, 1997, Suppl 421:97-103.

299. Burman LG et al. Prevention of excess neonatal morbidity associated with group B streptococci by vaginal chlorhexidine disinfection during labour. *Lancet*, 1992, 340:65-69.

300. Taha TE et al. The effect of cleansing the birth canal with antiseptic solution on maternal, and newborn morbidity and mortality in Malawi: clinical trial. *Br Med J*, 1997, 315:216-219.

301. Hofmeyr GJ, McIntyre JA. Preventing perinatal infections (editorial). *Br Med J*, 1997, 315(7102):199-200.

302. Tess BH et al. Breastfeeding, genetic, obstetric and other risk factors associated with mother-to-child transmission of HIV-1 in Sao Paulo State, Brazil. *AIDS*, 1998, 12(5):513-520.

303. Bobat R et al. Breastfeeding by HIV-1 infected women and outcome in their infants: a cohort study from Durban, South Africa. *AIDS*, 1997, 11(13):1627-1633.

304. Kreiss J. Breastfeeding and vertical transmission of HIV-1. *Acta Pediatr* 1997, Suppl 421:113-117.

305. Kuhn L, Stein Z. Infant survival, HIV infection and feeding alternatives in less-developed countries. *Am J Public Health*, 1997, 87(6):926-931.

306. Zimmer P, Garza C. Maternal considerations in formulating HIV-related breast-feeding recommendations (editorial). *Am J Public Health*, 1997, 87(6):904-906.

307. The Italian Register for HIV Infection in Children. Human immunodeficiency virus type 1 infection and breast milk. *Acta Paediatr*, 1994, Suppl 400:51-58.

308. Kennedy KA, Visness CM, Rogan WJ. Breastfeeding and AIDS: a health policy analysis. *AIDS & Public Policy J*, 1992, Spring:18-27.

309. Nicoll A et al. Infant feeding policy and practice in the presence of HIV-1 infection. *AIDS*, 1995, 9:107-109.

310. Brookmeyer R et al. Estimating the rate of occurrence of new HIV infections using serial prevalence surveys: the epidemic in India. *AIDS*, 1996, 19(8):924-925.

311. *Recent HIV seroprevalence levels by country*. Washington, DC, United States Bureau of the Censuses, Health Studies Branch, 1993.

312. Sherr L. HIV testing in pregnancy. In: Squire C (ed.) *Women and AIDS: psychological perspectives*. London, Sage Publications, 1993:42-68.

313. Meadows J, Catalan J. Comment on "Is HIV testing in antenatal clinics worthwhile? Can we afford it?" *AIDS Care*, 1995, 7(2):143-145.

314. Saba J. Identification of HIV infection in pregnancy: another era. *Acta Pediatr*, 1997, Suppl 421:65-66.

315. Minkoff H, Willoughby A. The future of prenatal HIV testing. *Acta Pediatr*, 1997, Suppl 421:72-77.

316. American Medical Association. Provisional Committee on Pediatric AIDS Perinatal Human Immunodeficiency Virus Testing. *Pediatrics*, 1995, 95(2):303-307.

317. Grady GF. HIV mass screening of infants and mothers: historical, technical and practical issues. *Acta Paediatr Suppl*, 1994, 40:39-42.

318. Brenner B. Testing for HIV in pregnancy: some ethical considerations. *N Z Med J*, 1996, 109(1032):409-410.

319. Chrystie IL et al. Is HIV testing in antenatal clinics worthwhile? Can we afford it? *AIDS Care*, 1995, 7(2):135-1142.

320. Phillips KA et al. HIV counseling and testing of pregnant women and women of childbearing age by primary care providers: self reported beliefs and practices. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1997, 14:174-178.

321. Houshyar A. Screening pregnant women for HIV antibody: cost-benefit analysis. *AIDS & Public Policy J*, 1991, 6(2):98-103.

322. Fischer CT. Prenatal and neonatal HIV testing (letter). *JAMA*, 1996, 275(5):357.

323. The status and trends of the global HIV/AIDS pandemic. Satellite symposium, July 5-6 1996. Geneva, Joint United Nations Programme on HIV/AIDS, 1996.

324. Bergsjo P. African strategy. How to fight the human immunodeficiency virus. *Acta Obstet Gynecol Scand*, 1995, 74:325-329.

325. Centers for Disease Control and Prevention. US Public Health Service recommendations for human immunodeficiency virus counseling and voluntary testing for HIV of pregnant women. *MMWR*, 1995, 44:1-15.

326. Department of Health. *Guidelines for offering voluntary named HIV antibody testing to women receiving antenatal care.* London, Department of Health, 1994.

327. Noone A, Goldberg D. Antenatal testing: what now? *Br Med J*, 1997, 314:1429-1430.

328. Lewis R et al. The impact of initiating a human immunodeficiency virus screening program in an urban obstetric population. *Am J Obstetr Gynecol*, 1995, 173(4):1329-1333.

329. Minkoff H, Willoughby A. Pediatric HIV disease, zidovudine in pregnancy and unblinding heelstick surveys. *JAMA*, 1995, 274(14):1165-1168.

330. Macdonagh SE et al. Descriptive survey of antenatal HIV testing in London: policy, uptake and detection. *Br Med J*, 1996, 313:532-533.

331. Phillips KA et al. HIV counselling and testing of pregnant women (letter). *JAMA*, 1996, 276(4):283-284.

332. Centers for Disease Control and Prevention. HIV testing among women aged 18-44 years - United States 1991 and 1993. *Morb Mortal Wkly Rep*, 1996, 45(34):733-737.

333. Rey D et al. Knowledge and behaviour of pregnant women towards HIV infection and screening. *J Gynecol Obstet Biol Reprod* (Paris), 1997, 26(1):57-63.

334. Adu-Sarkodie Y. Why Abena is not having an HIV test. *Br Med J* (SA edition), 1996, 4:725.

335. Rothenberg KH, Paskey SJ. The risk of domestic violence and women with HIV infection: implications for partner notification, public policy and the law. *Am J Public Health*, 1995, 85:1569-1576.

336. Lester P et al. The consequences of a positive prenatal HIV antibody test for women. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1995, 10:341-349.

337. Temmerman M et al. The right not to know HIV-test results. *Lancet*, 1995, 345:969-970.

338. Ladner J et al. A cohort study of factors associated with failure to return for HIV post test counselling in pregnant women: Kigali, Rwanda, 1992-1993. *AIDS*, 1996, 10:69-75.

339. Sorin MD, Tesoriero JM, LaChance-McCullough ML. Correlates of acceptance of HIV testing and post-test counselling in the obstetrical setting. *AIDS Educ Prev*, 1996, 8(1):71-85.

340. World Health Organization. The importance of simple/rapid assays in HIV testing: WHO recommendations. *Weekly Epidemiological Record*, October 1998.

341. World Health Organization. Revised recommendations for the selection and cure of HIV antibody tests. *Weekly Epidemiological Record*, 1997, 72:81-83.

342. Wilkinson D et al. On site HIV testing in resource poor settings: is one rapid test enough? *AIDS*, 1997, 11:377-381.

343. Kassler WJ et al. On-site, rapid HIV testing with same day results and counselling. *AIDS*, 1997, 11:1045-1051.

344. Sherr L. Psychosocial aspects of providing care for women with HIV infection. In: Minkoff H, DeHovitz JA, Duerr A (eds.), *HIV infection in women*, New York, Raven Press, 1995:107-123.

345. Sherr L. Pregnancy and childbirth. *AIDS Care*, 1997, 9:69-77.

346. Levine C, Allen MH. Social interventions in the care of human immunodeficiency virus (HIV)-infected pregnant women. *Semin Perinatol*, 1995, 19(4):232-329.

347. *Provision of HIV/AIDS care in resource-strained settings.* Geneva, World Health Organization, 1995 (WHO/GPA/TCO/HCS/95.14).

348. Kass NE. Policy, ethics and reproductive choice: pregnancy and childbearing among HIV infected women. *Acta Paediatr Suppl*, 1994, 400:95-98.

349. De Vincenzi I et al and the SEROCO Study Group. Pregnancy and contraception in a French cohort of HIV-infected women. *AIDS*, 1997, 11:333-338.

350. Johnstone FD et al. Women's knowledge of their HIV state: its effect on their decision whether to continue the pregnancy. *Br Med J*, 1990, 300:23-24.

351. Selwyn P et al. Prospective study of human immunodeficiency virus infection and pregnancy outcome in intravenous drug users. *JAMA*, 1989, 261:1289-1294.

352. Allen S et al. Pregnancy and contraception use among Rwandan women after HIV testing and counselling. *Am J Public Health*, 1993, 83(5):705-710.

353. Lindsay MK et al. The impact of knowledge of Human Immunodeficiency Virus Serostatus on contraceptive choice and repeat pregnancy. *Obstet Gynecol*, 1995, 85:675-679.

354. Amaro H. Reproductive choice in the age of AIDS: policy and counselling issues. In: Squire C (ed.) *Women and AIDS: psychological perspectives*. London, SAGE Publications, 1993:21-41.

355. King R et al. A family planning intervention to reduce vertical transmission of HIV in Rwanda. *AIDS*, 1995, 9(Suppl 1):S45-S51.

356. Stephenson JM, Griffioen A and the study group for the Medical Research Council. Collaborative Study of Women with HIV. The effect of HIV diagnosis on reproductive experience. *AIDS*, 1996, 10:1683-1687.

357. Allen S et al. Confidential HIV testing and condom promotion in Africa. *JAMA*, 1992, 268:3338-3343.

358. Baker DA. Management of the female HIV-infected patient. *AIDS Research and Human Retroviruses*, 1994, 10:935-938.

359. McIntyre JA. Management of HIV positive pregnant women. *Cont Med Educ*, 1996, 14(6):781-788.

360. McIntyre JA. HIV/AIDS. In: *Topics in Obstetrics & Gynaecology*, Bassin J (ed.) Johannesburg, Julmar Communications, 1994:72-77.

361. Silebi MI. Case management of the perinatal patient with HIV infection. *AIDS Patient Care*, 1995:82-85.

362. Scaravelli G, Thorne C, Newell ML. The management of pregnancy and delivery in HIV-infected women in Europe. *Euro J Obstet Gynecol*, 1995, 62:7-13.

363. Cooper ER et al. After AIDS Clinical Trial 076: the changing pattern of zidovudine use in pregnancy and the subsequent reduction in the vertical transmission of human immunodeficiency virus in a cohort of infected women and their infants. *J Infect Dis*, 1996, 174:1207-1211.

364. Tuomala RE. Prevention of transmission Pharmaceutical and obstetric approaches. *Obstet Gynecol Clin North Am*, 1997, 24(4):785-795.

365. Campbell ID, Williams G. *AIDS management: an integrated approach*. Strategies for Hope No 3. London, Actionaid, 1990.

366. Urassa EJN et al. The role of HIV infection in pregnancy wastage in Dar es Salaam, Tanzania. *J Obstet Gynaecol Central Af*, 1992, 10:70-72.

367. Sukwa TY, Bakketeig L, Kanyama I, Samdal HH. Maternal Human Immunodeficiency Virus infection and pregnancy outcome. *Cent Afr J Med*, 1996, 42(8):233-235.

368. Newell M-L et al. Immunological markers in HIV-infected pregnant women. *AIDS*, 1997 11(15):1859-1865.

369. Lepage P et al. Perinatal transmission of HIV-1: lack of impact of maternal HIV infection on characteristics of live births and neonatal mortality in Kigali, Rwanda. *AIDS*, 1990, 5:295-300.

370. Mwakagile D et al. High frequency of sexually transmitted diseases among pregnant women in Dar es Salaam, Tanzania: need for intervention. *East Afr Med J*, 1996, 73(10):675-678.

371. Govender L et al. Bacterial vaginosis and associated infections in pregnancy. *Int J Gynecol Obstet*, 1996, 55(1):23-28.

372. Semba R. Overview of the potential role of vitamin A in mother-to-child transmission of HIV-1. *Acta Pediatr*, 1997, Suppl 421:107-112.

373. Semba RD et al. Maternal vitamin A deficiency and child growth failure during human immunodeficiency virus infection. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1997, 14:219-222.

374. Semba RD et al. Infant mortality and maternal vitamin A deficiency during human immunodeficiency virus infection. *Clin Infect Dis*, 1995, 21:966-972.

375. Hoffman CA, Munson R. Ethical issues in the use of zidovudine to reduce perinatal transmission of HIV. *N Engl J Med*, 1995, 332:891.

376. Melvin AJ et al. Effect of pregnancy and zidovudine therapy on in HIV-1 infected women. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1997, 14:232-236.

377. Carmichael C. Preventing perinatal HIV transmission: zidovudine use during pregnancy. *Am Fam Phys*, 1997, 55(1):171-174.

378. Montaner JSG, Hogg RS, O'Shaughnessy MV. Emerging international consensus for use of antiretroviral therapy. *Lancet*, 1997, 349:1042.

379. Antiretroviral therapy for HIV infection in 1996. Recommendations of an International Panel. *JAMA*, 1996, 276:146-154.

380. *HIV and infant feeding: Guidelines for decision makers*. Geneva, 1998 (UNAIDS/98.3, WHO/FRH/NUT/CHD/98.1, UNICEF/PD/NUT(J)98.1).

381. *HIV and infant feeding: A guide for health care managers and supervisors*. Geneva, 1998 (UNAIDS/98.4, WHO/FRH/NUT/CHD/98.2, UNICEF/PD/NUT(J)98.2).

382. Royal College of Pathologists. *HIV infection: hazards of transmission to patients and health care workers during invasive procedures*. London, Royal College of Pathologists, 1992.

383. Verkuyl DA. Practising obstetrics and gynaecology in areas with a high prevalence of HIV infection. *Lancet*, 1995, 346:293-296.

384. Veeken H et al. Occupational HIV infection and health care workers in the tropics. *Trop Doctor*, 1991, 21:28-31.

385. Smith JR, Grant JM. The incidence of glove puncture during caesarean section. *J Obstet Gynecol*, 1990, 10:317-318.

386. Smith JR, Kitchen VS. Reducing the risk of infection for obstetricians. *Br J Obstet Gynecol*, 1991, 98:124-126.

387. *HIV prevention and care: teaching modules for nurses and midwives.* Geneva, World Health Organization, 1993 (WHO/GPA/CNP/TMD/93).

388. Kasongo Z. Zambia: impact of HIV on surgical practice. *Lancet*, 1997, 349(Suppl III):19.

389. Haran D. Africa: do health reforms recognise the challenge of HIV. *Lancet*, 1997, 349(Suppl III):19.

390. Gilks C. Tropical medicine in the HIV/AIDS era. *Lancet*, 1997, 349(Suppl III):17-19.

391. Gumodoka B et al.. Occupational exposure to the risk of HIV infection among health workers in Mwanza Region, United Republic of Tanzania. *Bull WHO*,

1997, 75:133-140.

392. Habimana P et al. A survey of occupational blood contact and HIV infection among traditional birth attendants in Rwanda. *AIDS*, 1994, 8:701-704.

393. Centers for Disease Control and Prevention. Update universal precautions of prevention of transmission of human immunodeficiency virus, hepatitis B virus and other bloodborne pathogens in health care settings. *MMWR*, 1988, 37:377-388.

394. *Preventing HIV transmission in health facilities.* Geneva, World Health Organization, 1995 (GPA/TCO/HCS/95.16).

395. *Infection control.* HIV/AIDS Reference Library for Nurses 3, Geneva, World Health Organization, 1995.

396. Fitch K et al. *HIV seroconversions following occupational exposure in European health care workers: the EC multicentre study of occupational exposure to HIV.* IXth International Conference on AIDS, Berlin, 1993, Abstract POC183040.

397. Henderson DK et al. Risk for occupational exposure of HIV-1 associated with clinical exposures. *Arch Intern Med*, 1990, 113:740-746.

398. Hu DJ, Kane MA, Heymann DI. Transmission of HIV, hepatitis B virus and other blood borne pathogens in health care settings: a review of risk factors and guidelines for prevention. *Bull WHO*, 1991, 69:623-630.

399. Easterbrook P, Ippolito G. Prophylaxis after occupational exposure to HIV. *Br Med J*, 1997, 315:557-558.

400. Centers for Disease Control and Prevention. Case control study of HIV seroconversion in health-care workers after percutaneous exposure to HIV-infected blood - France, United Kingdom and United States, January 1988 - August 1994. *MMWR*, 1995, 44:929-933.

401. Centers for Disease Control and Prevention. Update: provisional public health service recommendations for chemoprophylaxis after occupational exposure to HIV. *MMWR*, 1996, 45:468-472.

402. Patrick DM. HIV postexposure prophylaxis: new recommendations. *Can Med Assoc J*, 1997, 156(2):233.

403. Perlmutter BL, Harris BR. New recommendations for prophylaxis after HIV exposure. *Am Fam Phys*, 1997, 55(2):507-517.

404. Expert Advisory Group on AIDS. Post exposure prophylaxis for health care workers exposed occupationally to HIV. London, Department of Health, 1997.

405. *Treatment following exposure to HIV (module 7). Nine guidance modules on antiretroviral treatments*. Geneva, 1998 (UNAIDS/98.7, WHO/ASD/98.1).