



## HIV and Preconception - a review

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### Abstract

*In the recent past there has been a significant improvement in the quality of life and vast reduction in Human Immunodeficiency Virus- related mortality rates. The advent of antiretroviral therapy has largely contributed to this drastic increase in the life expectancy of Human Immunodeficiency Virus -infected individuals. In this review we have discussed about fertility issues in -infected people, preconception, fertility desires, effect of Human Immunodeficiency Virus on pregnancy, factors affecting mother to child transmission, diet and advice in pre-conception, behavioural and psychological support, impact of preconception services and areas of future researches. Method- A internet based PUBMED, MD CONSULT, Science direct and African journals online search of all the articles dating from 1998 to 2012 available under the heading of Human Immunodeficiency Virus and preconception was carried out and a detailed review was presented.*

**Key Words:** Preconception, pregnancy, HIV, nutrition, fertility

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## **Introduction**

According to the UNAIDS 2010 report, more than 50% of people living with Human Immunodeficiency Virus (HIV) are women and girls, with the highest burden of disease in sub-Saharan Africa. Though there has been a decline in incidence of new HIV infections worldwide, Asia is showing a resurgence of the epidemic. In 2005, around 35% of HIV infections occurred in women, a significant increase from 21% in 1990. On the positive side, 53% of women in low and middle income countries in 2009 received antiretroviral therapy to prevent mother to infant transmission (MTCT) of HIV 2009 and this is a significant improvement over 15% in 2005 [1]. There has been marked improvement in health of HIV infected persons with the advent of antiretroviral therapy (ART) over the last 15 years, thereby leading to dramatic reductions in HIV-related morbidity and mortality and improvements in quality of life. There has been a reduction in death rates from 7 deaths per 100 person years in 1996 to 1.3 deaths per 100 person years in 2004 with use of effective antiretroviral therapy [2]. HIV has now been transformed into a treatable condition and antiretroviral therapy has lead to increase in life expectancy from 10.5 years in 1996 to 22.5 years in 2005 and now approaches that of uninfected people [3]. The risk of vertical transmission has now been reduced to 1% with timely ART during pregnancy, achieving optimal viral suppression, delivery by caesarean-section when appropriate, and avoidance of breastfeeding [4]. With the improved life expectancy and quality of life, HIV infected women desire to have children just like any other healthy women [5]. We have presented a detailed review of PUBMED, MD consult and Science Direct articles available in the internet from the year 1998 to 2012 under the title HIV and preconception. The aim of this review is present the readers with a concise review about preconception in HIV.

## **Effect of HIV on fertility**

It has been noted in various studies that fertility is lower in HIV infected women as compared to uninfected women except among the youngest age group. Factors causing infertility include co-infection with Sexually Transmitted Infections (STI) and social factors like widowhood and divorce, reduced sexual activity also contribute [6].

Other factors like chronic anovulation, premature ovarian failure have been implicated but there is no clear evidence [7].

HIV infection is also known to adversely affect male reproductive system with orchitis, leukospermia and hypogonadism being more common. Semen parameters like semen volume, morphology, concentration and motility are significantly impaired [7]. Prior to investigating an HIV infected couple for infertility it is recommended that both male and female partners undergo a thorough sexual health examination and screening for concurrent STI. It is done with the intention of preventing pelvic inflammatory disease prior to HSG in a female and to improve semen parameters in a male with undetected genital tract infection [8].

### **HIV discordant couples**

The needs of HIV positive and discordant couples are different and require different approach. Hence it is of paramount importance that these couples receive the necessary information and guidance to plan a pregnancy with minimal adverse effects on them, their partners and children.

### **Male positive**

If only the male partner is suffering from HIV, then donor insemination from a screened donor is recommended by NICE to reduce transmission during conception.

However for couples who wish to preserve their genetic link, other option is sperm washing. Following sperm washing, intrauterine insemination, in-vitro fertilisation or intracytoplasmic sperm injection can be used to achieve pregnancy. Timed ovulatory intercourse where in unprotected intercourse is restricted only during ovulation period is another method to be used in resource poor settings [8]. It is recommended to do HIV-1 and HIV-2 testing of both the female recipient and her male partner to address potential medical/legal complications that could arise if the recipient seroconverts following donor insemination [9].

### **Artificial reproductive techniques**

A retrospective study done in Colombia University on 181 HIV-serodiscordant infertile couples over 10 years demonstrated that IVF-ICSI was a safe option and no cases of transmission of virus to either the mother or child occurred. The authors were of the opinion that IVF-ICSI further reduced transmission of virus by minimising oocyte contact with seminal plasma and other cells. There also would be no exposure of mother to the man's

biological material. However costs, nonavailability and increased complications when compared to IUI remain major deterrents for the widespread use of this method [10].

### **HIV discordant couples with female positive**

In HIV discordant couples with female being HIV positive, either intrauterine insemination or self insemination of partner's semen at the time of ovulation is advised. Safe sexual practises are recommended to prevent acquisition of STI's and transmission of virus to uninfected partner [11]. One strategy to prevent HIV acquisition in serodiscordant couples with female positive is male circumcision. Several observational studies and few RCTs have noted that male circumcision reduced acquisition of HIV by 60% in heterosexual relationships and it has been recommended by WHO and Joint United Nations Programme on HIV/AIDS as a male HIV preventive tool [12].

A RCT done in Uganda failed to show that circumcision of infected men resulted in a reduction of HIV transmission to their partners. WHO is of the opinion that male circumcision should not be refused to HIV infected men to avoid stigmatisation [13].

### **Serocordant couples**

Sperm washing and intrauterine insemination is recommended even in serocordant couples who wish to conceive to prevent the risk of superinfection with drug resistant viruses and other sexually transmitted diseases through unprotected intercourse [11].

### **Preconception**

Providers have to be aware of the unique challenges in HIV infected women which are achieving optimal health before conception, identification of risk factors for adverse maternal or fetal outcomes and intervening to optimize outcomes. It is important to counsel these women to adopt safe sexual practises to prevent acquisition of STI's and additional strains of HIV which are virulent or resistant to therapy. It is advisable to use effective contraception and defer pregnancy until low or undetectable viral load and good immune function is achieved [14, 15].

## **Fertility Desires**

In a cross – sectional study done by Kessler et al , 181 HIV infected women of reproductive age group who received HIV clinical care in 2 urban clinics in Africa were interviewed. Among this study population, 38% had at least one child since their HIV diagnosis, 59% wanted to have a child in the future. When they were asked regarding communication with their provider, 67% of the women reported a general discussion about pregnancy and HIV while 31% had a personalized discussion about future childbearing plans. Of the personalized discussions, 64% were patient initiated and such women were 3 times more likely to have more accurate information regarding MTCT of HIV. In this study, it was noted that general discussions and personalised were more likely to occur in women less than 30 years. There was a group of women who were ambivalent regarding their reproductive intention and hence did not receive counselling. Hence it was recommended by this study that providers initiate discussions regarding fertility plans with all women of reproductive age [15].

## **Effect of HIV on pregnancy**

A prospective observational study done on 266 HIV positive pregnant women of Swiss mother and child HIV cohort, there was an increase preterm delivery rate of 27%. Around 7 % of these women delivered at less than 34 weeks .All the women were on antiretroviral therapy and women who had a preterm delivery had lower CD4 cell count. The diagnosis of HIV infection was made in 25% of the study population during pregnancy and this makes it important to offer HIV test to all women of reproductive age and as early in pregnancy. However no other adverse pregnancy outcome attributable to the disease or treatment was noted although the study was underpowered to address these concerns effectively [5]. In developed countries, most reports do not suggest significant increase in low birth weight babies, intrauterine growth retardation and stillbirths in comparison with similar groups of HIV non-infected women. This is not true of developing countries wherein higher rates of perinatal mortality are reported [16].

Many studies have been done to evaluate the relationship between HIV infection and preeclampsia and the results have been conflicting. A case control study was undertaken in a high risk obstetrical unit on 81 HIV positive and 170 HIV negative women. In this study, only 8.6% of HIV positive women received antiretroviral therapy during labor. An increased

incidence of eclampsia was noted in HIV negative group (17.1%) when compared to HIV positive group (4.7%). The authors noted that their study findings supported the hypothesis of ‘protection’ afforded to HIV infected patients for eclampsia and preeclampsia [17]. With the advent of ART, there seems to have been an increase in preeclampsia in women with HIV to the level of HIV uninfected women. A prospective study was done in Spain over a period of 2 years by Suy et al on 8768 pregnant women, of whom 82 were HIV infected. All the pregnant infected women received highly active antiretroviral therapy (HAART). There were significantly higher rates of preeclampsia in HIV infected women when compared to uninfected women. [109.8/1000 versus 28.6/1000; crude odds ratio (OR), 4.3; 95% CI, 1.9–9.0;  $P < 0.001$ ]. They analysed another database in use since 1985 and they noted that with the increase in proportion of coverage of infected pregnant women with HAART, there was an increase in cases of pre-eclampsia and eclampsia.<sup>[18]</sup> In the European Collaborative Study, a postal questionnaire was sent to clinicians in 36 centres in 11 European countries. The researchers noted that preeclampsia was the most important adverse event noted in women with ART [19]. However several case control studies done have shown no significant risk of pre-eclampsia and eclampsia in women on HAART [20, 21, 22]. Due to the conflicting evidence, it would be prudent to monitor HIV infected women carefully for the appearance of pre-eclampsia.

### **Effect of pregnancy on HIV**

There is no evidence that pregnancy accelerates immunologic decline or affects disease progression and survival among HIV infected women [23].

### **Factors affecting Mother to child transmission**

There are numerous variables which exert an influence on mother to child transmission of HIV. Garcia et al demonstrated the importance of maternal plasma HIV-1 RNA measurements in predicting the risk of perinatal transmission of the infection. In the Women and Infants transmission study done on 552 women with HIV1 infection, the rates of HIV transmission increased with the increase in mean HIV1 RNA loads. In this study, there was no transmission of HIV in 57 women with RNA levels below 1000 copies per millilitre [24]. Other factors implicated are low CD4 count, poor maternal nutrition, concomitant sexually

transmitted diseases, prolonged rupture of membranes, invasive fetal monitoring, vaginal delivery, chorioamnionitis, and prematurity [25].

### **Antiretroviral therapy**

Significant progress has been made since 1994 when initial US Paediatric AIDS Clinical Trial Protocol 076 demonstrated that zidovudine given to 477 HIV infected pregnant women from 14 weeks orally, intravenously during pregnancy and labour and followed by 6 weeks of zidovudine prophylaxis to neonate reduced transmission by two thirds. It was a multicenter double blinded placebo controlled randomised controlled trial which initially had a target of 636 accessible mother infant pairs. At the interim data analysis in view of the efficacy of the drug in reducing transmission, additional recruiting of mothers was stopped and all women be offered zidovudine treatment [26]. The placenta affords partial protection to HIV transmission with only 15- 20% of infants in nonbreast feeding mothers and 25-40% infants in breastfeeding mothers becoming positive in the absence of interventions [16,27]. In infants with positive PCR in the first few weeks of life, in utero transmissions occur in 20-25% and 35-50% occurred intrapartum. Breastfeeding is responsible for 25-30% cases of transmission of HIV in infants negative at birth and in first 6 weeks [27].

Most developed countries have now nearly eliminated MTCT of HIV with the use of combination antiretroviral, scheduled caesarean delivery and avoiding breastfeeding [27]. The three important mechanisms by which antiretroviral drugs prevent mother to HIV transmission is reducing viral loads in maternal blood and genital secretions, infant pre-exposure prophylaxis and infant post-exposure prophylaxis [28].

The choice of antiretrovirals depend on numerous factors like viral loads, whether previously received antiretrovirals, whether criteria for antiretroviral therapy has been met, drug resistance and resources available. It is recommended to continue HAART for those women who conceive while on treatment if the regimen is successful in maintaining viral loads. A change in treatment may be necessitated if the mother is intolerant to a particular drug or if the drug is known to be teratogenic. Zidovudine is an essential component of all regimens [29].

Several trials which employed simple, short course ART like the PETRA trial, HIVNET012 trial in developing countries demonstrated efficacy in reducing MTCT though not to the

extent seen with HAART. There is still no universal implementation of these simpler regimens in developing countries due to lack of funding, ignorance, socio cultural factors and reduced number of institutional deliveries [30]. A detailed review regarding choice of antiretroviral treatment, indications and adverse effects would be beyond the scope of this article.

### **Mode of delivery**

Exposure of fetus to infected maternal blood and cervicovaginal secretion during labour is one of the mechanisms of vertical transmission of HIV. There is increased incidence of transmission following rupture of membranes and with the increase in duration of rupture. Another mechanism of transmission is through microtransfusion of maternal blood which occurs during every contraction [31].

ACOG recommends that HIV infected women with viral loads more than 1000 copies per millilitre should be offered elective scheduled caesarean delivery at 38 weeks prior to onset of labor to reduce the chances of MTCT. In women with viral loads less than 1000 copies per millilitre even without the use of elective caesarean delivery, the risk of vertical transmission remains unchanged at less than 2%. Antiretrovirals have to be continued during pregnancy, labor and caesarean delivery. Prophylactic antibiotics are recommended for all caesarean deliveries. Clinical estimates have to be used to calculate gestation age and invasive procedures like amniocentesis are not recommended [32].

Some authors recommend elective Caesarean section even for women with detectable viral load (>50 copies /ml) to prevent vertical transmission of HIV [29]. A Spanish study evaluated the feasibility in the application of vaginal delivery for selected cases of HIV infected women with gestational age more than 36 weeks without preterm labour or PROM, on HAART and with viral load <1000copies/ml. It was a prospective observational study where 47 women out of 91 pregnant HIV infected women met the criteria for vaginal delivery. Though the sample size of women (21) who achieved vaginal delivery was small, no cases of HIV vertical transmission occurred [33].

If vaginal delivery is attempted, all measures like avoiding episiotomies, instrumental delivery, invasive fetal monitoring and keeping membranes intact for as long as possible to minimise vertical transmission [16].

### **Preconception work up**

In resource abundant settings CD4 count, HIV viral load, syphilis serology and investigations for sexually transmitted infections is recommended as part of preconception workup for HIV infected couples. In addition, the female partner also needs hepatitis serology, CMV, rubella, HSV, toxoplasmosis and Pap smear. For resource poor settings it has been recommended to do at the minimum CD 4, syphilis serology and clinical assessment for other sexually transmitted infections. In addition haemoglobin and visual inspection of the cervix is done for the female partner [34]. The WHO recommends cotrimoxazole prophylaxis if required, screening for, prevention and treatment of TB, liver diseases, STI's and intravenous drug use in HIV infected women during pregnancy. In areas with stable malaria, it is advisable for pregnant women to use insecticide treated nets. WHO also recommends intermittent preventive treatment with at least 3 doses of sulfadoxine –pyrimethamine or daily cotrimoxazole prophylaxis [35].

### **Diet and advice**

All women planning a pregnancy are recommended to consume a well-balanced diet including fruits and vegetables, calcium rich foods, and protein-containing foods daily. They need to increase their consumption of iron-rich or iron-fortified food along with vitamin C-rich foods to enhance iron absorption. Women should consume folate-rich foods and also take 400 microgram of folic acid daily [36]. A randomised controlled trial of antepartum and peripartum antibiotics to prevent chorioamnionitis associated MTCT and preterm birth on 2126 pregnant HIV infected women was done by Mehta et al. It was noted that severe anaemia was a significant risk factor for fetal loss or stillbirth (OR: 3.67; 95% CI: 1.16, 11.66), preterm birth (OR: 2.08; 95% CI: 1.39, 3.10), low birth weight (OR: 1.76; 95% CI: 1.07, 2.90). Severe anaemia was associated with increased MTCT of HIV at birth (OR: 2.26; 95%CI: 1.18, 4.34) and at 4–6 weeks among those negative at birth (OR: 2.33; 95% CI: 1.15, 4.73). So the investigators suggested that protein-energy and micronutrient supplementation and treatment of malaria, intestinal parasitic infestation and other opportunistic infections could help in reducing MTCT [37]. The strength of this study was antibiotic prophylaxis for the prevention of chorioamnionitis which excluded the effect of chorioamnionitis on MTCT of HIV and the large number of study subjects. The main limitations are its observational design and its antiretroviral policy of nevirapine being given only at the onset of labour. It is

not known whether severe anaemia is an independent risk factor for increased MTCT of HIV. Severe anaemia is a marker of advanced HIV disease and increased MTCT of HIV could be explained by this [37]. However severe anaemia by itself is associated with other adverse effects like preterm birth, low birth weight and fetal growth restriction. Hence it would be prudent to make sure that nutrition of these high risk women is not compromised. Women have to be counselled about the importance of eliminating alcohol and substance use and about smoking cessation during preconception [38]. Smoking has been associated with increased rates of vertical transmission due to alterations in maternal immunity [29]. These women have to be administered vaccines for influenza, pneumococcal infections, and hepatitis A and B viruses before pregnancy if antibody titres indicate need for immunisation [38, 39].

### **Behavioural and psychological support**

A subset of Women's Interagency HIV Study cohort which included 1288 HIV infected women and 357 uninfected women at risk for acquisition of infection were interviewed regarding domestic violence and childhood sexual abuse. It was noted that the lifetime prevalence of domestic violence was as high as 66% in women with HIV and childhood sexual abuse was reported in 31% of such women. A similar percentage of HIV negative women reported domestic violence and childhood sexual abuse. This has important policy implications since such women in abusive relationships may not be able to adhere to comply with medication regimens and providers have to extend special care for such women [40]. A study done in Rwanda by Ntaganira et al among 300 HIV positive and 300 HIV women wherein HIV infected pregnant women had almost 2 fold increase in rates of all forms of intimate partner violence compared to seronegative pregnant women and they recommended screening of intimate partner violence as part of prenatal care. There may be under reporting of the violence since most abused women may not have prenatal care and information was obtained by questionnaire from these women. These women suffer from societal stigma, concerns regarding disclosure, worry about their health and anxiety regarding the possibility of transmission of HIV to their child [41].

## **Perinatally acquired HIV**

Due to effective treatment, there is now a group of women who acquired HIV perinatally and now as adults are ready to embrace parenthood. There is limited information regarding health issues and other challenges faced by these women. In a study done on children enrolled in the Paediatric AIDS Clinical Trials Group (PACTG) protocol 219C, the investigators sought to describe the reproductive health of 638 adolescent girls perinatally infected with HIV. The girls reported to be sexually active were 174(27.3%). There were 38 first pregnancies, 6 girls had a second pregnancy and one girl had a third pregnancy. The rate of perinatal HIV transmission among infants was 3.3% in this study which is comparable to rates achieved in Woman and Infants Transmission Study. There was increased incidence of sexually transmitted diseases (12%) abnormal pap smear (47.5%) and lower CD4 cell counts in the sexually active adolescents [42]. Another small retrospective study done in Bronx, USA found increased viral loads, lower CD4 counts among women with perinatally acquired HIV when compared to women with behaviourally acquired HIV. 3 of 11 women in their perinatally acquired HIV died within 5 years following delivery [43]. These women have more complicated treatment history, presence of multi drug resistance and other medical co morbid factors. It is not known whether there would be any change in course of perinatally acquired HIV based on exposure to antiretroviral therapy in utero. This group presents a unique challenge to health care providers due to psychosocial issues, treatment issues, anxiety regarding disclosure, discrimination and stigma in addition to concerns faced by uninfected teenagers. Most of these perinatally infected teenagers are engaging in risky sexual behaviours, are not compliant with their treatment schedule and also are desirous of producing children. There are not enough adolescent friendly centres to deal with this group and this requires a major change in policy. The policy should aim at providing contraception services to these adolescents to prevent unwanted pregnancies and sexually transmitted infection and for those who intend to conceive information regarding measures to prevent mother to infant transmission and institution of such measures [44].

## **Areas for research**

In an article published in 2010, Mathews et al opined that pre-conception pre-exposure prophylaxis with tenofovir has a potential role in reducing sexual and vertical transmission in HIV discordant couples having unprotected intercourse with intent to conceive. However

questions regarding feasibility, acceptability, adherence, resistance, cost, long term effects on conceptus and pregnancy have to be addressed before implementation of this method [45]. Other potential areas of research are methods to inactivate the HIV virus in breast milk and if proved to be feasible and efficacious would be more acceptable especially in developing countries. Several methods have been proposed like chemical treatment with sodium dodecyl sulphate, chloroquine and heat based treatments [46]. There have been attempts to develop a vaccine to control the HIV pandemic and trials have been done in both adults and children. A variety of approaches like T cell inducing vaccines, mucosal vaccines and use of HIV immune globulin have been used with mixed results [47, 48]. Though most of the vaccine trials have resulted in disappointing results some researchers are of the opinion that ultimately HIV control will be achieved with the use of a safe and effective vaccine [49]. The best treatment would be a permanent cure for HIV/AIDS. A HIV infected man with stable disease had undetectable disease following stem cell transplantation from a donor with CCR5 delta32 deletion for acute myeloid leukaemia. There are many obstacles to overcome before stem cell therapy or even CCR5 targeted gene therapy will become a reality if ever it does [50,51].

## **Conclusion**

We are now in the era where young women who acquire HIV through heterosexual contact are the new wave of the epidemic and advances in antiretroviral treatment allow them to lead near normal lives. So it is of paramount importance that these women are counselled regarding preconception services and optimise their health. They should be able to embrace motherhood at their chosen time without endangering their, their sexual partner's and their unborn child's health.

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