REVIEW ARTICLE

Mother-to-Child HIV-1 Transmission: State of the Art and Implications for Public Policy

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ABSTRACT. During the past five years there have been significant advances in the knowledge of the factors that affect mother-to-infant HIV-1 transmission. Diverse interventions have been designed and proven effective in reducing the risk of such transmission. In reviewing the pivotal literature in such respect implications for public policy are also analyzed. Because of the constant evolution of the interventions, the public policies also need constant revisions. The impact of viral load assessment during pregnancy and its relationship to transmission risks is discussed, as well as the effectiveness of elective Caesarean delivery. The latter has both positive and negative aspects which merit consideration. Newer approaches, such as highly active anti retroviral therapies (HAART), which have shown to decrease the AIDS mortality, have also shown zero transmission in small cohorts. Shorter and cheaper interventions are also somewhat effective and are good alternatives to resource poor countries.
Key words: HIV/AIDS, Antiretrovirals, Gender.

During the last 5 years there have been remarkable improvements in both: the knowledge of factors that affect perinatal HIV transmission and the effectiveness of diverse interventions to reduce such transmission risk. This article will review the recent advances in mother-to-infant transmission and will analyze the impact of such knowledge in the public policies regarding interventions.

AIDS mortality trends. In 1996, a decrease in mortality due to AIDS was first reported in the US (1). This dramatic decline in mortality was directly associated to a decline in opportunistic infections (OI), which in turn was associated to the development and more generalized use of highly active anti retroviral therapies (HAART). The cornerstone of HAART was the use of a combination of drugs that included a new class known as protease inhibitors (PI). In the first report, mortality decreased disproportionaly among the ethnic groups and by gender. While non-Hispanic whites had the highest decrease in mortality (21%), African-Americans showed a decrease of 2% and women kept an increase of 3%. These differences were considered to "reflect reduced access to health care associated with disadvantaged socioeconomic status, cultural and language barriers that may limit access to prevention information, and differences in HIV/AIDS behavior". In recent years the mortality has been shown to decrease in all groups.

Recommendations for anti retroviral therapy. There is an international panel that periodically reviews the recommendations for initiation of therapy. Therapy is recommended when the viral load (HIV-RNA quantification) measurement is from 5,000 to 10,000 units/ml by the Roche Assay (2). The committee has addressed the issue of pregnant women who require therapy and has stated that therapy should not be withheld because of pregnancy. Another panel has stated as a principle of therapy that: "women should receive optimal therapy regardless of pregnancy status", so when HAART is indicated, it should be offered to pregnant women(3). Experience with the use of such medications for clinical care is constantly growing. In contrast, because of the relative novelty of such drugs, there are few studies published about the maternal or fetal short term effects during pregnancy. Information regarding the long-term effects of HAART to mothers and infants is scarce.

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Currently the AIDS Clinical Trials Group (ACTG) is carrying out four phase I/II trials, with each one of the PI in combination with zidovudine (ZDV) and 3TC. These trials will evaluate the pharmacokinetics and safety of such combinations during pregnancy, delivery and puerperium for the mothers and during the neonatal and early infancy periods for the infants.

HIV-RNA quantification and mother-to-infant transmission. Dickover and colleagues reported a relationship between maternal plasma HIV-RNA levels and transmission in a small group of women in 43 pregnancies and they concluded that maternal HIV-1RNA levels were highly predictive of perinatal transmission risk (4). The relationship between plasma HIV-RNA levels and transmission has not been clear and evident in all studies. For example, in the ACTG-076 a statistical relationship was found in the placebo group but no statistical significance was found in the ZDV treated group (5).

Two recent publications have shown statistical association between maternal plasma HIV-RNA levels and the risk of transmission. Mofenson and colleagues found that the maternal plasma HIV-RNA levels at baseline and at delivery were independtly associated to transmission (OR=2.4 per log increase in RNA at baseline, CI 1.2-4.7 and OR=3.4 for the delivery RNA, CI 1.7-6.8 p=0.001). They reported no perinatal transmission among 84 women with undetectable levels (<500 copies/ml) (6).

García and colleagues reported a statistical association between HIV-RNA levels and transmission for the women in the WITS (Women-Infant Transmission Study). No transmission was seen with HIV-RNA levels below 1,000 copies/ml, 16.6% among women with 1,000-10,000 copies, 21.3% among women with 10,001 to 50,000 copies, 30.9% among women with 50,001 to 100,000 copies and 40.6% among women with >100,000 copies (p<0.001) (7). An intervention study in Thailand that used a short course of ZDV concluded that as much as two thirds (2/3) of the risk of transmission was attributable to maternal high plasma RNA levels (8).

The data strongly suggests that although maternal plasma HIV viral load is a strong predictor of the risk for transmission, other factors are also contributing. Some transmission occurred even at low maternal viral RNA levels and no upper threshold is always associated to transmission; other studies have reported transmission in women with undetectable levels.

Rasheed and co-workers have showed that HIV viral load may be compartamentalized, and even with undetectable plasma HIV, virus can still be identified in the genital tract and viceversa (9). In a group of 46 non-pregnant women, HIV was identified in cell-free cervico-vaginal secretions of all women with undetectable plasma HIV (12/46). In contrast, 17% (8/46) women with significant quantity of HIV in plasma had negative results in the cervico-vaginal secretion. They concluded that the replication kinetics of HIV-1 in blood and cervico-vaginal cells are unrelated, suggesting that unsupressed genital tract viremia might be responsible for transmission even in the absence of quantifiable maternal plasma viremia. Ongoing studies are assessing the genital tract viral load and transmission and this information should be available in the near future.

Highly active anti retroviral therapy (HAART) and pregnancy. The use of HAART has shown a beneficial effect in reducing both the incidence of OI's and AIDS mortality. Pregnant women living with HIV are increasingly offered this therapy, according to the current trends. Among 1,201 pregnant women in the WITS study, the transmission rate decreased from 18% in 1990 to 3.9%. (Cooper E, Personal communication. 1998). The use of anti retrovirals in this population has increased throughout the years. During 1998 one third of the women were receving ZDV monotherapy, another third were receiving dual therapy with ZDV and 3TC, and the remaining third were receiving HAART.

Although ZDV monotherapy is still the official recommendation (10), both dual therapy (ZDV/3TC) and HAART are increasingly used in clinical settings. The use of HAART is clearly indicated when maternal viral load is high or reaches the treatment guidelines threshold, but there is no current indication for the use of HAART to prevent mother-to-infant HIV-1 transmission. Some centers continue to offer ZDV monotherapy to women with "lower" viral loads in order to prevent transmission, although the use of dual therapy (ZDV/3TC) has become popular both in Europe and North America. Several studies have reported the use of HAART during pregnancy. Morris and colleagues reported on the use of PI in 89 pregnancies in which the transmission rate was zero (11).

The data on HAART during pregnancy has been generated in small retrospective studies, therefore, making it difficult to generalize to the rest of the cohorts. There are many unanswered questions regarding this issue:

- Should HAART be offered to pregnant women to prevent mother-to-infant HIV-1 transmission?
- If the plasma HIV level is used as a threshold for initiating HAART, should it be lowered to 1,000 copies per ml?
- If all women are offered HAART irrespective of plasma viral load, should it be discontinued post partum in those women with baseline lower viral load?

This questions might be answered within the near future because the Public Health Service Task Force

Recommendations for the use of antiretroviral group in pregnant women infected with HIV-1 for maternal health and for reducing perinatal HIV-1 transmission in the US will be updated within the next months.

One of the concerns related to initiating HAART in pregnant women with "lower" viral loads is the possible development of resistance mutations. Another concern is the difficulty in achieving adherence to complex regimens during the post partum period. It has been shown that adherence is related to viral replication control (maintaining undetectable levels). It has also been shown that lack of adherence may lead to increased replication and the development of resistance mutations (12). The risks and benefits of initiating HAART at a lower viral threshold to reduce the risk of mother-to-infant transmission have to be considered before public policy recommendations are generated.

Anti retroviral pregnancy registry. An antiretroviral pregnancy registry was established in January 1989 to monitor zidovudine use and was modified in 1993 to include all available agents. The purpose is to detect the major teratogenic effects of all available retroviral agents when administered to pregnant women. They encourage reporting such events to the following address:

The Antiretroviral Pregnancy Registry
115 N 3rd Street, Suite 306
Wilmington NC 28401
Tel. (800) 258-4263

The Registry provides periodic reports on the experience with such medications. The most recent antiretroviral registry report states that: "The observed proportion of live births exhibiting birth defects (n=18) for total live births with any trimester of exposure (n=706) is 2.5% and does not differ from the expected proportion in the general population".

Long-term outcomes from intrauterine exposure to antiretrovirals. In February 1999, Dr. S Blanche presented data from the French prospective perinatal cohort. He described two cases of fatal mitochondrial toxicity syndrome in HIV-exposed neonates who were uninfected and had been exposed to ZDV and 3TC in utero. Another group of six children with diverse clinical findings was added to the series. Five patients had neurologic abnormalities and persistent lactic acidosis (13,14). In response to this report the US analyzed the databases of several National Institutes of Health (NIH) sponsored trials as well as Centers for Disease Control (CDC) sponsored studies. A total of 15,229 children participated in these studies. No evidence for fatal mitochondrial toxicity in children exposed to nucleoside analogues was found (15).

Recent data on 234 infants exposed to intrauterine ZDV in ACTG Protocol 076 was published by Culnane and co-workers (16). After 4.2 years of follow up, no deaths or cancers were noted and no adverse effects on growth or cognitive development were reported.

Because of potential unknown long-term effects, the children born to women living with HIV should be followed longitudinally, infants exposed to antiretroviral therapy in utero should be followed whether they are HIV infected or not. The benefits of antenatal therapy far outweighs the potential long-term risks. Public policy still should offer and make available therapies that have been proven to reduce the risk of mother-to-infant transmission, while facilitating the long-term follow up of such infants.

Additional maternal risk factors. Known factors associated to mother-to-infant HIV-1 transmission are: maternal virus load, mode of delivery, prolongued rupture of membranes, the presence of histopathological chorioamnionitis, the use of illicit drugs during pregnancy, low birth weight, and pre-term delivery. Among biologic factors are: decreased maternal CD4 lymphocyte count, higher concordance in class I HLA types between mother and child, and viral syncytia formation. Genetic polymorphisms in the regulatory region of CCR5 (the secondary HIV co-receptors) may also influence transmission.

Although genetic factors cannot be altered in specific populations, the behavioral and some of the immune responses may be altered by diverse interventions. Facilitating the access of pregnant women and women of reproductive potential for drug rehabilitation programs may change the behavioral factors that increase the risk of transmission in women who are drug users. This is an area where public policy might facilitate the access to drug-rehabilitation treatments and mental health services to pregnant women living with HIV and thus, decrease the risk of perinatal transmission.

Mode of delivery and transmission. A recently published meta-analysis in the mode of delivery and perinatal HIV-1 transmission found a reduced risk with the use of elective Caesarean section (C-section). The primary analysis included data on 8,533 mother-infant pairs (17). The likelihood of transmission was decreased by 50% with elective C-section as compared with other modes of delivery. The transmission rate with elective C-section in women without antiretroviral therapy was 10.4% as compared to other modes of delivery 19%. The transmission rate for those who received ZDV and underwent elective C-section was 2% compared to 7.3% in those with other modes of delivery receiving ZDV. Thus, in both groups, those who received ZDV and those not treated, the C-section had a protective effect.

Shortly afterwards, in August 1999, the American College

of Obstetrics and Gynecology (ACOG) published a Committee Opinion based on the review of published literature including the meta-analysis (18). Their consensus recommendations are summarized in Table 1.

Table 1. Summary of ACOG Recommendations on the Mode of Delivery

1. HIV infected women should be offered scheduled cesarean delivery to further reduce the risk of transmission.
2. Neonates of women at highest risk for transmission, with high plasma viral load benefit most. The decision regarding the mode of delivery should be individualized.
3. Patients should be counseled about the transmission risk with absence of ZDV and with the use of ZDV. No combination of therapies can guarantee zero transmission.
4. The patient's autonomy must be respected. A patient's decision for a vaginal delivery must be honored as well as the decision for C-section.
5. Patients should receive antiretroviral therapy during pregnancy according to currently accepted guidelines for adults.
6. The use of prophylactic antibiotics should be considered because of the potential morbidity.
7. The scheduled C-section should be performed at 38 completed weeks instead of 39 weeks to reduce the risk of premature rupture of membranes.
8. Gestational age should be estimated with the best clinical criteria. Amniocenthesis for lung maturity determination should be avoided.
9. Plasma viral load should be monitored during pregnancy as well. Non-pregnant adults have a baseline and then every three months or following changes of therapy.

The use of an elective Caesarean section remains highly controversial among the providers of pregnant women living with HIV and among policy-makers. In a recently published opinion, Stringer and colleagues argue in favor of restraint and wait for more evidence to be accumulated on both the post partum morbidity risks, and the potential beneficial effects of HAART during pregnancy (19). They argue that if the effect of the elective C-section is to reduce by 50% the current transmission risk, women with much lower risk of transmission (such as those receiving HAART) might not benefit from it. They still agree that the usefulness of the C-section would be greater in those patients without the benefit of antiretrovirals or in those with adherence problems. Given the current public policy of recommending ZDV monotherapy, an elective C-section might further reduce the transmission risk of HIV-1 in Puerto Rico.

The concerns for post partum morbidity has been addressed in two studies: limited post partum morbidity among 435 women participating in a randomized trial of elective C-sections was evidenced. As preliminary analysis of 265 mother-infant pairs was presented in Geneva in 1998. The incidence of post partum fever was 6.7% among the C-section group and 1.1% among the vaginal delivery group. No differences among groups were found for bleeding or anemia (20, 21). The second analysis involved the women enrolled in the WITS study, where elective C-section was associated with fever without infection (OR 3.96, CI 1.41, 9.63). It was concluded that "the elective Caesarean section is associated with an increased risk of post partum fever. The risk of post partum morbidity according to mode of delivery appears similar to, and probably not greater than, that observed in the general obstetrical population" (J. Read, Personal communication, 1999). While acknow-ledging that post partum morbidity is higher in any patient undergoing Caesarean section (even among the HIV seronegative), this risk is acceptable and should not be the major reason to withhold an elective Caesarean section in a woman living with HIV.

Given limited knowledge in the use of HAART during pregnancy, and its association to lack of transmission, the benefit of the elective Caesarean section might be limited in this group of patients. On the other hand, and elective Caesarean section might be indicated in the following situations: antiretroviral naïve, ZDV monotherapy or dual therapy with ZDV/3TC, other maternal risk such as illicit drug use, pre-term delivery, premature rupture of membranes, and concerns with the maternal adherence to antiretrovirals. Other indications are rising maternal HIV titers or persistently high (over 1,000) viral titers during pregnancy.

Short course antiretroviral regimens. Since the ACTG 076 trial was first published, many other trials have been developed in an attempt to decrease the cost and simplify the intervention. The original study used ZDV in three ways: as an oral form during pregnancy, intravenously during labor and delivery and for 6 weeks to the infants. A recent Thailand trial sponsored by the CDC, demonstrated a 51% reduction of transmission from 18.9% in the placebo group to 9.4% in the ZDV group when this drug was started at about 36 weeks gestational age and given orally every 3 hours during labor. There was no breastfeeding in this population (22).

The PETRA trial, carried out in Africa (Uganda, Tanzania and South Africa) compared the use of ZDV in

combination with 3TC in four different regimens including a placebo arm that was eliminated after the Thai study results were made public. The first arm (A) consisted of ZDV/3TC started at 36 weeks, given orally, intrapartum and post partum for one week. The infants in this arm also received ZDV/3TC for one week. The second arm (B) consisted of intrapartum ZDV/3TC and post partum to mother and infant for one week. The third arm (C) consisted only of intrapartum oral ZDV/3TC. The overall rate of breastfeeding was 69% for the whole cohort (23).

The transmission rates were 8.6% for arm A, 10.8% for B, and 17.7% for C; the limited placebo group had a 17.2% transmission rate. A multivariate logistic repression analysis demonstrated that the C-section had a protective effect in the first and second arms (A + B), but not protective effect in arm 3 or the placebo group (24).

Another recently published trial compared a single intrapartum dose of nevirapine (NVP) and a single neonatal NVP dose to oral ZDV during labor and for one week to the neonates. This study: the HIVNET 012 trial found that NVP was more effective than ZDV in this extremely shortened dosing scheme. The transmission rates at birth were equivalent for ZDV and NVP (10.4% and 8.2%) while at 6-8 weeks of age were 21.3% and 11.9% respectively. The efficacy of NVP was 47% when compared to ZDV (25). The ZDV regimen in this trial was equivalent to arm C in the PETRA trial which was found equal to the placebo arm. Therefore, in essence, NVP was compared with an intervention that was no different than placebo. The benefit of NVP consists of its simplicity to administer (single oral dose) and lower cost as compared to ZDV.

At the proceedings of the Global Strategies for the Prevention of HIV Transmission from Mothers-to-Infants held in Montreal last September, a cost-effectiveness analysis was presented by E. Marseille in which NVP would be given to all pregnant women without offering HIV testing (26). Given a prevalence of 15%, universal treatment would be cheaper than targeting testing and then treating. Transmission rates would also be lower, since all HIV positive women would have received treatment. This could be subject to debate, given the ethical issues of foregoing testing and the other benefits of knowing the HIV serostatus.

It is clear that transmission still occurs with these shortened antiretroviral interventions as compared to the strategies available for developed countries. In resource-poor nations, shorter, simpler and cheaper interventions might benefit a proportion of the infants even if this proportion is lower than what our experience has been. For developing countries a public policy that encompasses any of these regimens might still be beneficial and ethical.

Conclusions

Significant progress has been made in the prevention of mother-to-infant HIV transmission. The widespread use of potent antiretroviral therapy such as HAART has been associated with zero transmission in small cohorts. The strong association between maternal plasma HIV-viral load and transmission might help in the decision-making and management of pregnant women living with HIV. Although transmission has been reported with undetectable maternal HIV viral load, the risks are lower for such transmission. The use of elective C-section has clear indications in specific situations such as: high or rising maternal viral load, lack of exposure to antiretrovirals or use of monotherapy, concerns with maternal lack of adherence to HAART and other risk behaviors such as preterm delivery, maternal illicit drug use, advanced maternal HIV stage with uncontrolled replication, and evidence or suspicion of viral ressistance mutations to the antiretroviral drugs.

The public policy towards the risk-reduction in mother-to-infant transmission should reflect the newer interventions such as C-sections, HAART and viral load monitoring during pregnancy. This public policy should also consider the referral of pregnant women living with HIV to centers experienced in managing HIV infection. This will ensure a higher quality of services and the initiation of therapies for the long-term supression of viral replication in women.

The survival of both, women and children is at stake. The revision of public policies and standards of care is urgently needed. The benefits will outweight our efforts to provide better options to pregnant women living with HIV.

Resumen

Durante los últimos cinco años han ocurrido avances significativos en el conocimiento de los factores que afectan la transmisión materno-infantil de VIH-1. Se han diseñado diversas intervenciones que han demostrado su efectividad en reducir el riesgo de esta forma de transmisión. Al revisar la literatura relacionada se analizan además las implicaciones para la política pública. Debido a la evolución constante de estas intervenciones las políticas públicas también requieren ser revisadas. Se discute también el impacto de la evaluación de la carga viral durante el embarazo y su relación con el riesgo de transmisión, además de la efectividad de la cesárea electiva. Esto último, tiene tanto aspectos positivos como negativos que merecen consideración. Los nuevos acercamientos, como las terapias antiretrovirales

(HAART), que han logrado un descenso en la mortalidad por SIDA, también han demostrado evitar la transmisión en cohortes pequeños. Las intervenciones cortas y baratas son también efectivas y pueden ser alternativas adecuadas para los países de bajos recursos económicos.

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