

## ORIGINAL ARTICLES

# Reduction in the perinatal HIV transmission: the experience at the Maternal Infant Studies Center and Gamma Projects at the University of Puerto Rico School of Medicine

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**The AIDS pandemic had a significant impact in Puerto Rico, especially among the heterosexual populations, in particular women. Women are one of the fastest growing risk groups with HIV/AIDS in the USA and constitute about half of the AIDS cases in the world. During the past 10 years Puerto Rico has ranked among the top 5 jurisdictions in the United States in AIDS cases rates, among men, women and children. In 1987 a universal prenatal HIV screening program was implemented in the University Hospital catchment area consisting of approximately 5,000 deliveries per year. Because of the early identification of pregnant women living with HIV, access to lifesaving clinical research and the implementation of multiple strategies and comprehensive care, the perinatal HIV transmission has effectively reduced to zero since 1997, with a blip**

**of one case in 2002, and none since then. The availability and access to clinical and behavioral research has been one of the key elements for this success story. The programs involved and responsible for this spectacular outcome, namely the Maternal Infant Studies Center (CEMI-Spanish Acronym) and Gamma Projects at the University of Puerto Rico School of Medicine are described. The cost savings impact of stopping mother-infant perinatal HIV-1 transmission has been calculated to be approximately \$34 to \$58 million dollars in 10 years. The impact of the effectiveness of these programs in having healthy uninfected infants, prolonging and improving the quality of life of those living with HIV, and providing hope to families affected by this epidemic is incalculable.**

*Key words: Perinatal, Pediatric, HIV infection.*

**T**he HIV/AIDS epidemic has affected many individuals, particularly women. In 1985, 7% of the AIDS cases in the USA were reported in women, this proportion increased to 22% in 1997(1). For the same period, the AIDS cases in women in Puerto Rico increased from 11.3% to 24.7%. During the past 10 years Puerto Rico has ranked among the top 5 jurisdictions in the United States in AIDS cases rates, among men, women

and children. As of October, 2007, PR had 32,152 cumulative AIDS cases of which 7,566 were in adult/adolescent women and 24,116 in men. There were 470 pediatric AIDS cases (2). As we reflect on the 25 years of the HIV/AIDS epidemic, we have to acknowledge that there have been advances and successes, and that the impact of an HIV diagnosis is not as devastating today as it was 10 years ago, in particular to those who have access to antiretroviral medications. In those settings, HIV can be considered as a chronic disease with the particular needs of education, monitoring, support and management.

These advances in therapies and prevention strategies have been developed through clinical, biomedical and behavior research.

One of the most dramatic advances in the fight against the AIDS epidemic has been the success in the reduction of perinatal HIV transmission particularly in developed countries. Puerto Rico has been part of this history and has seen and benefited from these lifesaving interventions. The success of the reduction in the perinatal HIV transmission has involved many individuals and

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institutions. The collective efforts of the UPR School of Medicine through two of its programs (CEMI and GAMMA), the PR Health Department by instituting and implementing public health policies regarding testing and treatment availability, the Pediatric AIDS Demonstration Project (PR Health Department) and the dissemination and training provided by the PR AIDS Education and Training Center (AETC).

This has been the result multiple strategies that involve early and state-of-the-art research, dissemination of results, and implementation of public health policies and medical interventions such as: routine offering of HIV counseling and testing during prenatal care, access to comprehensive care that includes antiretroviral medications during pregnancy, labor, delivery and post partum, access to immunologic and virologic testing, opportunistic infection (OIs) prophylaxis, access to infant formula, access to elective cesarean deliveries when indicated, access to medical, psychological, social and educational interventions and support and many other strategies. The availability and access to clinical and behavioral research has been one of the key elements for this success story.

### **Description of the Programs**

Two programs will be described herein that have worked in close collaboration to provide integrated, multi and trans-disciplinary services to pregnant women living with HIV and their infants. These programs were instituted almost simultaneously and were in part the result of the University of Puerto Rico Medical Sciences Campus investments in the HIV/AIDS research infrastructure through institutional and external funds. A significant proportion of these funds were provided by the Research Centers for Minority Institutions (RCMI) from the National Center for Research Resources (NCRR) and the National Institutes of Health (NIH). Subsequently funding from the PR Health Department has kept some of the components of the programs for the past 10 years.

AIDS was described in 1981 and shortly thereafter symptomatic patients (cases) were seen at the diverse hospitals in the island. It was difficult to identify or confirm cases until a laboratory test was available. After the discovery of the human immunodeficiency virus type 1 (HIV-1) in 1983, two tests became available and (with some modifications) they are still in use. The ELISA (enzyme-linked immunosorbent assay) which is an antibody screening test and the Western Blot which is a confirmatory test of specific antibodies to the various elements or gene products of the HIV are used to identify individuals infected with HIV.

With the advent of the tests it was possible to identify

asymptomatic individuals (such as pregnant women) and offer whatever services were available then. The identification of pregnant women living with HIV could allow for interventions during the pregnancy and postpartum and for the coordination of needed services for mother and infants. The identification of asymptomatic individuals also provides an opportunity for secondary prevention and early management of the condition. As stated in the Adult guidelines: "the ultimate goals are to prevent further immune deterioration and to avoid HIV-associated morbidity and mortality" (3).

### **Universal HIV Prenatal Screening**

In 1986 an anonymous survey of pregnant women admitted in labor at the University Hospital, showed that one of every 71 samples to be positive (1.8%) for HIV antibodies by ELISA and Western Blot. Because of this, a universal HIV prenatal testing program was implemented in 1987 in the University Hospital catchment area, possibly making this the first within the US jurisdiction. All women attending prenatal care were offered the HIV test after a written consent. The acceptance rate was 97%. The seroprevalence rate was 1.4% in 1987-88. For comparison, the seroprevalence for Hispanic pregnant women in NY was 1.3% during the same time period. From July 1, 1990 to June 26, 1991 a total of 4,700 tests were performed. Because of the fear of discrimination, the results to the pregnant women were given at the PR Medical Center. The women who tested positive were given an appointment to the PR Medical Center's High Risk Clinic, results were provided, and obstetrical services provided at this High Risk Ob Clinic. Counseling included information about pregnancy outcomes, perinatal transmission risks, pregnancy options, lifestyle changes and disclosure. Socio-demographic data, lifestyles and sexual practice information was obtained to help guide the management and policies then. Information was scarce then and the data obtained from the follow up of the initial group of women provided for several abstracts and scientific presentations. The seroprevalence rate in our region showed a decreasing trend from the initial 1.7% in 1986, 1.4% in 1987 to 0.9% in 1992. This decreasing trend was in part due to the reduction in subsequent pregnancies in the population of women identified by the screening program. Out of 100 women followed during pregnancy only 2 had a subsequent pregnancy in the following 2 years after delivery (4). The overall seroprevalence for pregnant women in PR during the years 1993 and 1994 was 0.54% (5). So, a higher prevalence was seen (as expected) in major metropolitan areas such as San Juan.

The Maternal Infant Studies Center (CEMI-Spanish Acronym).

Because other providers refused to follow them, all of the women identified through the prenatal testing program were followed initially at the Gynecology clinic and then at the Longitudinal Women's Clinic sponsored by the RCMI Program. It became the Maternal Infant Studies Center (CEMI-Spanish Acronym) because all of the perinatal programs and the longitudinal clinic were integrated. From 1996 to 1993 we had evaluated more than 400 women at the center. Up to October 2007 we have seen more than 1,541 women. We continue to evaluate between 40-45 new pregnant women per year. So early in the epidemic we were able to establish a screening program and a longitudinal clinic. The concept of long term follow up was necessary due to the particular needs of the population and the nature of the HIV diagnosis.

The early policy of universal offering of the HIV test during pregnancy was later endorsed by the Centers for Disease Control (CDC) and as of September 2006 the recommendations were revised to offer screening to all patients in all health care facilities, and to every pregnant women in care as part of the routine testing. These revised CDC recommendations advocate routine voluntary HIV screening as a normal part of medical practice, similar to screening for other treatable conditions (6).

As we will describe later, all of the services to women living with HIV (pregnant and non-pregnant) are offered at CEMI with the integration of clinical and behavior research activities.

### **The UPR School of Medicine Pediatric HIV/AIDS Unit (GAMMA Project).**

The Pediatric program was created to provide services to children who were diagnosed with AIDS because they became symptomatic and were admitted to the University Pediatric Hospital. Dr. Clemente Diaz started the unit in 1986 and directed it until 2000 when Dr. Irma Febo assumed its direction. Since there were no treatments for AIDS, research was an essential component of the care of patients with HIV/AIDS. It was only through research that people living with HIV would have access to a potentially lifesaving drug or therapy. One of the first protocols carried out at the pediatric unit utilized gamma-globulin infusions to try to prevent bacterial infections. The unit was referred to as the GAMMA Project and it is still known this way by the community. So we will refer to the UPR School of Medicine Pediatric HIV/AIDS Unit for services and research as the GAMMA project from now on.

This unit provides comprehensive longitudinal services to HIV infected, affected or exposed children and adolescents. Services include: medical, nutritional, psychological evaluations and interventions. Attention is given to the family with social work interventions, access

to free vaccinations, specialized laboratories, referral to diverse sub-specialties, referrals to other services including family planning, support groups and access to clinical trials and research interventions. Services and care are provided by a multi- and inter-disciplinary team that includes pediatricians, nurses, pharmacists, psychologists, infectious disease specialists and other sub-specialists.

### **Integration of research, service and training.**

The UPR GAMMA project site was selected as one of the first pilot sites for the PACTG 076 study. This particular study utilizing the drug zidovudine (AZT) during pregnancy, labor and to the infants immediately after birth changed forever the history of AIDS in the USA and in the world. The concept was to give the drug to pregnant women in order to potentially prevent the infant from infection. At that time one of every 4 (25%) babies of women living with HIV were infected, but we could not predict which babies were to be infected. So, all infants had to receive the drug AZT in order for the 1 out 4 not to be infected. The ethical dilemma included treating infants in-utero with a drug that could be life-saving to some and potentially toxic to others. The drug proved to be so successful that the trial had to be stopped in February 1994 for ethical reasons (it was not justified to give placebo when the study drug was so effective (7)). In March 1994, the PR Health Department announced its public policy of offering the drug AZT to every pregnant woman identified with HIV during prenatal care. Through this and other experiences, the investigators from Puerto Rico, particularly at the UPR School of Medicine became pioneers in the management of pregnant women and children living with HIV. Puerto Rico was again one of the first jurisdictions to implement a public policy of providing free AZT to every pregnant women living with HIV. The PR Health Department, through the pediatric AIDS program coordinated this task island wide. This required the training of Obstetricians, Pediatricians and nurses in most of the island hospitals.

Shortly thereafter the UPR participated in the Women and Infants Transmission Study (WITS) which was a natural history study but provided the infrastructure for state-of-the-art laboratory evaluations and a multiplicity of assessments both for mothers and infants including neuro-developmental testing of infants. The PR Site recruited 600 pairs of mothers and infants into this landmark study whose information has provided for a large number of scientific publications.

Since then, the clinic has provided with cutting edge therapies and interventions during pregnancy and the transmission rate has been essentially zero since 1996-2006 with the exception of one case in 2002. This is a success story that is not unique to our clinic in Puerto

Rico but is the general expectation of pregnant women living with HIV in the USA. Still, not every pregnant woman is tested and there are still women who do not know their HIV status in pregnancy, and therefore cannot benefit from the interventions.

Both programs have provided access to clinical trials of new drugs to women and children living with HIV and they had access to new drugs throughout their participation in sponsored research.

### **The UPR Clinical Trials Unit (UPR-CTU)**

The pediatric unit became a site for the Pediatric AIDS Clinical Trials Group (PACTG) in 1992 funded by the National Institute of Allergy and Infectious Diseases (NIAID) and the Longitudinal Women's Clinic continued its research funding through the RCMi Program and also became part of the HIV Vaccine Trials Network (HVTN).

In 2006 both units merged with the adult unit and the UPR Clinical Trials Unit (UPR-CTU) was established. The pediatric program became part of the newly formed International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT), and it was integrated with the HIV Vaccine Trials Network (HVTN) and the Adult AIDS Clinical Trials Group (ACTG). This merger (UPR-CTU) will facilitate the comprehensive and collaborative research both among people living with HIV as well as among those at risk. It integrated and enhanced the existing infrastructure (Research Pharmacy, Community Education and Mobilization and professional training).

### **Care of Women Living with HIV**

We specify women and not just pregnant women because some of the preventive and medical services that have impacted the outcome of the pregnancies are provided out of the pregnancy window in many instances. Because of the multi- and trans-disciplinary approach to the longitudinal care of the women, the clinic is able to provide not just medical care but a holistic view of health. For the past 10 years we have carried out Empowerment interventions initially aimed at survival and safer sexual practices, now with a more intense focus on adherence, disclosure and quality of life. (8) A series of full day workshops allow the women to learn and explore concepts of HIV infection and therapies, self image, alternative and complementary medicine, nutrition, exercise, lifestyle changes, sexual negotiation, disclosure, adherence, beauty and other topics during group activities. This has allowed our clinic to become a "safe space" with an open-door policy. To the extent that the patient-provider relationship is respectful, professional but sensitive to the client's needs, it also serves as an example and practice for other relationships.

Women living with HIV are more at risk for developing uterine cervical abnormalities and cervical cancer, and depending on the immune status they need closer surveillance of the genital tract. In addition the management of these genital premalignant lesions requires more aggressive approaches and closer follow-up due to a high rate of recurrence. Knowledge of the drug interactions, side effects, co-morbidities and diversity of opportunistic infections is needed in order to provide good care and to prevent additional morbidity in this population. The care of women living with HIV needs specialized knowledge and expertise that a dedicated center can provide.

### **Management During Pregnancy.**

Because transmission occurs mostly during labor and delivery, we have been able to identify women during pregnancy and offer treatment during pregnancy, delivery and post-natal to the infant (9).

Currently the Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women recommends more aggressive combination antiretroviral therapy (10). They specify that the "use of antiretroviral drugs in pregnancy requires unique considerations, including the possible need to alter dosage as a result of physiologic changes associated with pregnancy, the potential for adverse short- or long term effects on the fetus and newborn, and the effectiveness of the drugs in reducing the risk for perinatal transmission."

We have used Highly Active Antiretroviral Therapy (HAART) for the past 13 years with good maternal and infant outcomes (11-13). This, in conjunction with the use of elective Cesarean Sections (C/S) and the use of infant formula and antiretroviral prophylaxis during the first 6 weeks of life has been the key to our success in the reduction of the perinatal transmission. While acknowledging that an elective Cesarean Section might carry increased postpartum morbidity as compared with a vaginal delivery, we continue to offer the C/S and most if not all of our patients opt for it. The Guidelines call for the elective C/S to be beneficial when the mother has more than a 1,000 RNA viral copies/ml in plasma. The immunologic status is ascertained by the CD4 lymphocyte count, the virologic status is evaluated by the HIV-RNA viral count on every trimester or after the initiation of HAART. All of the routine pregnancy tests are continued as well as any other medical evaluation required by the patient. This comprehensive management is needed due to the complexity of the antiretroviral regimens and the potential drug interactions with other therapies. The toxicity of some of the antiretrovirals could be more severe during pregnancy and deaths due to hepatic failure have

been reported in pregnant women receiving nevirapine as part of their regimen (14). In addition, pregnancy is an excellent opportunity to provide counseling and prevention to partners and to provide evaluation and screening to other members of the family. Confidentiality has always been one of our main concerns since not every patient is ready to disclose their diagnosis. Disclosure is a personal issue and we work with our patients to prepare them for such goal. There are many issues that surround disclosure perhaps being the more salient the fear of discrimination and stigma, the concerns with violence and concerns with loss of services, jobs or school services. The overall environment of the center provides for a safe space, comprehensive services of high quality, access to research and close communication with the pediatric program with the subsequent longitudinal management of the infants.

### Care of Children exposed or living with HIV

Most of the children followed at the GAMMA Project are from the San Juan Metropolitan Area although services can be provided to children from all over the island. At present 82 children living with HIV/AIDS are being followed in addition to the close to 40 infants evaluated on an annual basis. The Clinic is currently following close to 560 children exposed to HIV. All of the exposed but HIV negative children are followed on a less frequent basis. Longitudinal follow up is required for all infants born to women living with HIV even if they are uninfected because of two main reasons: they were “exposed” to the virus and to antiretroviral drugs while in-utero.

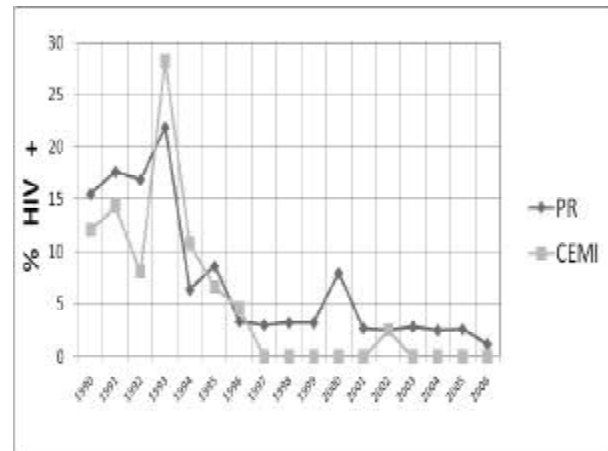
All of the services are available to these children. Medical care including laboratory assessments and management with HAART is provided by pediatricians with longstanding experience in the management of HIV infection in children.

In addition, the pediatric program became part of the Adolescent Trials Network (ATN, sponsored by the NIH) and has recruited more than 300 HIV infected or at-risk adolescents for participation in to studies. This adolescent unit will also provide evaluations and prevention opportunities to this special population.

## Results

Figure 1 shows the perinatal HIV transmission rates of the infants born to mothers cared at this comprehensive program, compared to the general HIV transmission rate reported by the PR Health Department for PR. Our transmission rate has been effectively zero during the past 10 years with one exception. This is the case of an infant girl born to a mother who was enrolled into a treatment

protocol and the drugs were suspended during the pregnancy for a period of five to seven days on two different occasions during the pregnancy. Even though she maintained an undetectable HIV RNA viral load during most of the pregnancy and had an elective C/S, the baby girl was found HIV infected at 18 months of age. Her prior testing was reported negative. We believe this was an unusual case which constituted the “exception to the rule”.



**Figure 1.** Perinatal HIV transmission rates (in percentage) of infants born to pregnant women cared at CEMI (line with squares) compared to the overall rates for PR (darker line with diamonds).

During the past 20 years we have evaluated more than 1,541 women living with HIV at the Maternal Infant Studies Center (CEMI-Spanish acronym). Of these, 612 are in active follow up. During the past 10 years we have evaluated and managed almost 400 pregnant women living with HIV, approximately 40 per year. Of those, only one infant was infected, and 399 infants were not infected. Without any interventions, at least 26% of these infants would have been infected (n=104). Therefore the interventions were successful in preventing 103 infections during the past 10 years. The impact of these accomplishments is profound and related not only to cost savings but also with quality of life, providing hope to families and allowing healthy children to grow and give back to the society and perhaps the world some of the gifts they received.

One important question we need to ask is: why do we continue to document pediatric HIV infections when treatment programs are so successful? One of the answers is that some women are not identified as HIV infected during the pregnancy because either: they are not tested, they are not in care, they do not get the results in time prior to the delivery or they do not accept therapy. The availability of rapid HIV tests that are designated as point-of-care (in the USA) and designed to be performed by staff (nurses, doctors, or counselors) and not necessarily

medical technologists should allow us to identify during labor every pregnant women that has not been tested. There are several FDA-approved tests that could provide results in less than 30 minutes. Even though Puerto Rico responded early and comprehensively to the early results and in the implementation of testing during prenatal care, we have not been as efficient implementing a second line of rapid HIV testing during labor and delivery to further decrease the few cases of pediatric infections that we consider preventable.

### **Economic Impact of the Programs**

An earlier (1997) cost study in another institution estimated the lifetime cost of caring for an infant with AIDS in the USA between \$172,217 and \$498,539 (15).

A more recent lifetime estimate of the cost of care of adults living with HIV in the United States calculated the life expectancy of adults in 24.2 years and the discounted lifetime cost as \$385,200 and the undiscounted cost as \$618,900 for adults who initiate ART with CD4 cell count above 350/mL. Seventy-three percent of the cost is antiretroviral medications, 13% inpatient care, 9% outpatient care, and 5% other HIV-related medications and laboratory costs. For patients who initiate ART with a CD4 cell count of less than 200/mL, projected life expectancy is 22.5 years, discounted lifetime cost is \$354,100 and the undiscounted cost is \$567,000 (16). The cost of medications and laboratory assays is the same in the USA and in PR, while the cost for inpatient and outpatient care is lower in PR. Since the largest proportion of the cost is constituted by pharmacy and laboratories, we believe the numbers could be applicable with the previously mentioned caveat. Another limitation is that the calculations were made with adult data which might not apply to the pediatric population because medications might have different dosage and costs at least until adolescence. Nevertheless, we will use the published data as a general guide to estimate the cost-savings of the averted infections.

In their analysis, the average monthly cost is \$2000 when patients have a CD4 cell count over 300/mL. If we assume the same for the pediatric population, the cost estimate could increase by at least 30% assuming that the life expectancy could be more than 10 years beyond the calculated 22 years. Even without adding any more years into the formula, and assuming a discounted lifetime cost of \$354,100, the cost savings of 103 averted infections is \$36,472,300.00. Using the undiscounted figure, the savings are estimated in \$58,401,000.00.

So, a very rough estimate of the impact of this program in terms of cost savings would be between 34 and 58 million dollars. During times of budgetary constraints, the impact of these savings unquestionably justifies the investments

in the provision of comprehensive services to families living with HIV particularly pregnant women and their infants.

### **Conclusions**

One of the most dramatic successes in the fight against the AIDS epidemic has been the reduction in the perinatal HIV transmission. Puerto Rico has benefited by spectacularly successful programs particularly those at the UPR School of Medicine: CEMI and GAMMA. By coordinating maternal and pediatric care, prevention and longitudinal follow-up and integrating programs to provide comprehensive services these programs have served as a model for comprehensive successful interventions. The economic impact benefits of the programs clearly provide a justification for their implementation and expansion. The added uncalculated impact of the programs includes healthy infants and families and hope for our community.

### **Resumen**

La pandemia del SIDA ha tenido un impacto importante en Puerto Rico, en especial en las poblaciones heterosexuales y principalmente en las mujeres. Las mujeres constituyen uno de los grupos más vulnerables al VIH/SIDA y suman la mitad de los casos de SIDA en el mundo. Durante los últimos 10 años Puerto Rico ha estado entre las primeras 5 jurisdicciones en los Estados Unidos con las tasas más altas de casos de SIDA por población en hombres, mujeres y niños. En el 1987 se comenzó un programa de cernimiento prenatal para el VIH en la población cautiva del Hospital Universitario en el Centro Médico de PR correspondiente a 5,000 nacimientos por año. El acceso a investigación clínica, y a múltiples estrategias de cuidado integral, ha sido responsable de la reducción de la transmisión perinatal del VIH a cero desde el 1997, con la excepción de un caso en el 2002. Esto fue posible por la identificación temprana de mujeres embarazadas viviendo con el VIH, a consecuencia del programa de cernimiento universal. La disponibilidad y accesos a investigación en intervenciones tanto clínicas como de conducta han sido elementos claves del éxito de estos programas. Los programas responsables de estos resultados exitosos son: el Centro de Estudios Materno Infantiles (CEMI) y el proyecto GAMMA de la Escuela de Medicina de la Universidad de Puerto Rico. El impacto económico en la reducción de la transmisión perinatal del VIH se ha calculado entre \$34 y \$58 Millones de dólares en 10 años. El impacto más importante es el facilitar el nacimiento de niños saludables, el prolongar la sobrevivencia

y mejorar la calidad de vida de aquellos que viven con el VIH y el proveer esperanza a las familias afectadas por esta epidemia. Ese impacto es incalculable.

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