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Highly Active Antiretroviral Treatment (HAART) for the Prevention of HIV Mother to Child Transmission (PMTCT) at Roosevelt Hospital's Infectious Diseases Clinic in Guatemala: The Role of (LPV/r) Standard Dose

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ABSTRACT

Introduction: The transmission of HIV from mother to child is reported from 30% to 40% without any intervention [1]. When all the measures for prevention are implemented, including treatment with HAART (Highly Active Antiretroviral Treatment), the rate of infection can be reduced between 1% and 2% [2]. In Guatemala, the statistics demonstrated an estimated of 20,000 women living with HIV virus infection during the period of 2009. In this scenario, mother to child HIV transmission is an important public health fact. In preliminary reports, there is strong evidence of the impact of preventing mother to child transmission with Lopinavir/Ritonavir in Guatemala is showing a small incidence of new HIV infections and good tolerance [3,4]. **Objective:** To evaluate the effect of HAART with Lopinavir/Ritonavir on the prevention of mother to child transmission (PMCT) in HIV-positive pregnant women at Roosevelt Hospital in Guatemala City. **Methods:** A retrospective cohort analysis study. The detection of pregnant HIV positive women and the follow up period was from January 2003 to December 2009, and a total of 219 women completed the follow up time. The HIV diagnosis and follow up for the child was made with molecular testing and antibody testing up to 18 months of age or until testing was negative. Adherence was quantified by pill counts. The interventions where offered to all the women in the cohort. **Results:** Regarding the pregnancy outcome, the study cohort gave a rate of abortion of 2.3%; 10.6% of preterm births and 79.6% normal births. Of the 202/219 children born, there was a 1.4% rate of transmission (n = 3). The three infected children were born from mothers with high basal viral loads (50,000 C/mL or higher). There were no serious adverse events related to antiretroviral therapy with Lopinavir/Ritonavir, with a 6.1% of non serious adverse events, most of them of gastrointestinal type, and anemia. **Conclusions:** The rate of transmission of HIV from mother to child was low in this population (1.4%), comparable to findings from similar studies [4]. Lopinavir/Ritonavir was well tolerated in this cohort and no serious adverse events in this population were reported.

Keywords: HIV; Antiretroviral; Pregnancy; Lopinavir-Ritonavir

1. Introduction

The prevalence of HIV/AIDS in Guatemala proves to be the estimated of 0.9% in 2011 in the general population [1]. From January 1984 to December 2010, the national Guatemala STDs/HIV/AIDS program reported 22,647 cases of HIV/AIDS, of whom 38% (n = 8553) were women. An important note is that 5% of the cases relate to children under the age of 4 years. Mother to child transmission (MTCT) represents 5.1% of the infections. In pregnant women the prevalence is between 0.4 and 0.5%; in urban areas the range varies between 0.26 and 1.40%, at the rural areas between 0.13% and 0.16% [4,5].

Prevention of mother to child transmission (PMTCT) programs have been implemented since 2002 in the national hospitals in Guatemala, at that time also has been developing the first national guide for the management of pregnant HIV positive women. Starting in 2005, the services of PMTCT were expanded to cover also rural hospitals; specially in those areas where greater number of cases were reported, with the support of non-governmental organizations (NGOs), the Global AIDS Foundation UNICEF and other international organizations [6,7].

Highly active antiretroviral therapy (HAART) has been shown over the past decade to have a great impact in preventing MTCT in developed countries. The stan-

dard of care to prevent mother to child transmission has changed over the years, from single dose nevirapine (NVP) to HAART. There are several specific evaluations of large numbers of pregnant patients who have been taken different HAART schemes, but there is still discussion about potential side effects of some of the antiretroviral drugs during the pregnancy. The vertical transmission of HIV in children whose mothers were exposed to various schemes of HAART has been reduced to less than 1% - 2% [2,8,9], when using all of the associated preventive measures that are considered effective according to current scientific evidence. These measures include: active detection of HIV infection in antenatal care and at the time of delivery, timely initiation of HAART during pregnancy and/or labor, emergency cesarean section (ECS, clear efficacy in patients with viral loads higher than 1000 copies/ml), prophylactic use of antiretrovirals in the exposed children and avoidance of breastfeeding when possible [8-10].

In this study, a cohort with more than 500 patients who received HAART during the years of 2003-2010, including 219 pregnant women exposed to lopinavir/ritonavir (LPV/rtv), The results allowed the Guatemalan investigators to have a better understanding of the impact of this drug, both in pregnant women and in their children [9-11].

2. Methods

2.1. Study Design

Retrospective analysis of a Cohort of HIV positive pregnant women, from January 2003 to January 2010. All patients attended the Infectious Diseases Clinic from Roosevelt Hospital, located in Guatemala City, Guatemala.

All pregnant women diagnosed with HIV infection from January 2003 to January 2010were included. The total number of LPV/rtv treated patients was 219.

Inclusion criteria: Any patient who received antiretroviral therapy during pregnancy by certain time, including combined HAART with LPV/rtv, standard dose, for at least 15 days prior to the resolution of the pregnancy.

Exclusion criteria: Patients who after the diagnosis did not continue the follow up and in whom the development of the newborn was unknown and/or patients who did not receive HAART during pregnancy.

Data sources: All data was obtained from the clinical records from the patients, at the Infectious Disease Clinic, from Roosevelt Hospital, in a retrospective time. Pharmacy information was collected during each visit to determine the level of adherence, and adverse events data were obtained from the clinical records and a specific database used for recording pharmacy events.

The evaluation of both acute and chronic adverse events was based on the classification of the US Division of Acquired Immunodeficiency Syndrome (DAIDS), at the National Institute of Allergy and Infectious Diseases (NIAD). All serious adverse events were reported within 24 hours of awareness, to Pharmacological vigilance authorities. The adherence was calculated by pill counts in each clinical visit by a pharmacist.

The research protocol was approved by the Committee for Teaching and Research of the Roosevelt Hospital and the Hospital authorities. The writing consent, was not required given the retrospective nature of the study. All data were tabulated and analyzed taking into account patient confidentiality.

Data Analysis: The data collected were analyzed according to the following scenarios that could have occurred during pregnancy: 1) initial diagnosis of HIV in pregnant women and initiation of antiretroviral therapy during this period; and 2) diagnosis of pregnancy in women who were already taking antiretroviral therapy.

All the pharmaceutical related information, including tolerance, adherence rates, and incidence of adverse events was obtained from the records of the patients. All the data were tabulated and analyzed using descriptive statistics. For assessment of risks, the relative risk ratio (RR) was determined; and the chi square test was calculated for categorical variables to assess statistical significance, with a 95% confidence. All analyses were done using the EpiInfo 3.5.1 software.

Laboratory Testing: The serological diagnosis of the patients, adults and children, was made according to the national protocols from Guatemala.

The CD4 cell count was determined using FACSCount, from Beckton Dickinson (San José, California). When available, viral load was determined using COBAS Ampliprep/COBAS Taqman from Roche Molecular Diagnostics (Alameda, California) version 1.0.

Definitions: Seroumreversion was considered in a child, born from an HIV positive mother, with a rapid test for HIV 1/2 positive, and with a follow up period of 9 to 18 months until the rapid test became negative. At this moment, a second test, in this case immune enzymatic, was done to confirm the negative result.

3. Results

Cohort Description: From January of 2003 to January of 2010, 219 HIV-positive pregnant women, were treated with LPV/rtv, of which 179/219 (81.7%) patients remain in the program with regular follow-ups, after the pregnancy resolution, at the end of the year 2010. 3.7% (8/219) were already HIV patients in HAART at the moment of the pregnancy detection. All the other patients were newly HIV diagnosed with the screening test in antenatal care. The average age of the cohort was 26 years (range 16 - 43). Regarding educational status, 12.8% of the cohort reported to be illiterate; and 87% had

less than 6 years of education.

Demographics: The average number of CD4+ cells/mL was 329 (range: 2 - 1034). 70% of the women had more than 200 CD4+ cells/mL. Viral load data was not available for the entire cohort. 187/219 had viral load (VL) results available for analysis. The mean VL was 4.84 $\log_{10}$ copies/mL (range: Undetectable-6.26). 66% of the patient had less than 50,000 copies/mL (4.68 $\log_{10}$). The data are summarized in **Table 1**.

Antiretroviral Treatment History

All the patients in the cohort took antiretroviral treatment, the main difference was the time of pregnancy in which therapy began. It was found that 105/219 (48.4%) of pregnant women began their follow-ups within the first trimester of gestation, 67/219 (30.9%), started during the second trimester and 45/219 (20.7%) in the third trimester. ARV treatment was started from week 14 in newly-diagnosed patients; treatment of the patients who were already in ARV treatment was not interrupted, patients taking AZT-3TC + Efavirenz (EFV) were switched to AZT-3TC of TDF-FTC + LVP/rtv.

The level of adherence (pills counts) was properly registered for 71.8% (n: 156) of women. The average level of adherence was 97.3%, based on compliance with scheduled appointments and pill counts in each visit. Women in whom the level of adherence could not be registered did not have records because they had been on therapy for less than a month.

Pregnancy outcomes: Out of the 219 pregnant women in follow ups, n/219 (79.3 %) delivered at term infants, n/219 (10.6%) delivered live preterm infants, x/219 (4.6%) delivered stillbirths and 5/219 (2.35%) had spontaneous abortions (**Table 2**). Mean gestational age of live births was 36.8 weeks (range WX-40). All pregnancies ended in an average of 36.8 weeks (range week 10-week 40); 79.3% of the women did not report any adverse events during pregnancy. Registered adverse events were as follows: 5 abortions 5/219, for a probability of 2.35 × every 100 births; 7/219 (3.2%) of the mothers reporteda threat of premature birth. 2/179 (1.1%) of the children died in the perinatal period; the mean age for preterm infants was 31.3, (range w. 30 - 33) located between the 30 and 33 weeks of pregnancy (**Table 3**).

Table 4 describes pregnancy outcomes and calculated HR ratios according to BL CD4+ cells (or CD4 closest to delivery, which one?). A statistically significant relationship was found between CD4+ T cell count lower that 200 and abortion, HR 4.8 times higher compared to women with CD4+ T cell count > 200. In addition a statistically significant relationship was found between HIV RNA VL > 50,000 c/mL at the time of HAART initiation and the risk for stillbirth, and preterm deliveries, HR 3.08 when compared to women with HIV RNA VL < 50,000 c/ml. All other risk calculations were not statistically significant.

Infant Outcomes: From 219 pregnancies, 92.2% of the

Table 1. Cohort description.

Month of pregnancy in which started HAART	Basal CD4				Basal viral load			
	<200	>200	Total	%	<50,000	>50,000	Total	%
1 to 3 months	21	84	105	48.4	79	15	94	50.3
4 to 6 months	28	39	67	30.9	37	18	55	29.4
7 to 9 months	14	31	45	20.7	26	12	38	20.3
Total	63	154	217	100	142	45	187	100
Average	128 (SD: 191 cells/uL)	411 (SD: 193.7 cells/uL)	329 (SD: 194.3 cells/uL)	-	10,235 (SD: 14,441 cp/mL)	243,741 (SD: 377,289 cp/mL)	66,426 (SD: 209,403 cp/mL)	-
Range	2 - 199	201 - 1034	2 - 1034	-	Undetectable - 48400	50,021 - 1,840,000	Undetectable - 1,840,000	-

Table 2. General outcomes of pregnancy in HIV women with HAART.

Adverse events	Deaths	Alive	Total	%
Infected children	03/219		3	1.4%
Abortion	05/219		5	2.3%
Stillbirth	10/219		10	4.6
Premature birth	07/219	7	7	3.2%
Normal birth	2 after birth	170	172	79.3%
Lethality	17/219		17	

Table 3. Pregnancy outcomes and risk determination.

Adverse Outcome	<200 T CD4 cells	>200 T CD4 cells	%	RR	VL < 50,000 cp/mL	VL > 50,000 cp/mL	%	RR
Abortion	3	2	11.1	4.8 (CI 95%: 1.62 - 14.65)	2	1	10.7	1.85 (CI 95% 0.71 - 4.82)
APP	1	6	15.6	0.78 (CI 95%: 0.11 - 5.36)	1	3	14.3	0.6 (CI 95% 0.10 - 3.50)
Still birth		10	22.2	0	2	6	28.6	3 (CI 95% 1.27 - 7.08)
Premature birth	4	19	51.1	0.96 (CI 95%: 0.27 - 3.36)	8	5	46.4	3.08 (CI 95% 1.02 - 9.24)
Total	8	37	100	-	17	11	-	-

Table 4. Mother to child transmission rate in relation to diverse parameters.

Parameter	Outcome		
	Not infected	Infected	Total
Adherence of the mother			
More than 95%	134	1	135
Less than 95%	21	-	21
Not available	61	2	63
Maternal Viral load			
<1000	67	-	67
1001 to 10,000	26	-	26
10,000 to 50,000	48	1	49
50,001 and 100,000	15	-	15
>100,000	28	2	30
Time of HAART during pregnancy			
<4 weeks	21	-	21
4 to 12 weeks	43	-	43
>12 weeks	152	3	155
Gestational age at birth			
Abortion	5	-	5
Preterm birth	13	-	13
Normal birth	198	3	201
HIV infection determination using viral load			
<1 month	8	-	8
1 - 4 months	160	3	163
>4 months	15	-	15
Not available	33	-	33
Antibody seroumreversion			
6 - 12 months	64	-	64
12 - 18 months	46	-	46
>18 months	5	-	5
Not available	101	3	104

children were born alive. Of the 202 born children, 12% were born from mothers with baseline viral load > 100,000 c/mL and 33% from mothers with Bl VL between 50,000 and 100,000 c/mL. Regarding additional interventions for preventing transmission, 96% of children were delivered by caesarean section, 92.6% received zidovudine (AZT) during labor, 100% of children received oral suspension of AZT, and 99% were bottle fed (**Table 4**).

The calculated mortality in the post neonatal period was 2.94%. Of the total of live births, 1.4% were identified as infected, 7.8 per cent were transferred to other clinics for their follow-ups as not infected, and 81.3% completed the follow-ups with serore version of antibodies. All children with negative results for HIV RNA during the first six months of life were confirmed as negative with antibodies, at the end of follow-up between 12 months and 18 months of life (**Tables 3** and **4**).

Tolerance to ARV therapy was good; only 6.1% of patients treated with LPV/rtv reported adverse events. All adverse events were not serious and predominantly of gastrointestinal type. There were no serious adverse events or adverse events affecting adherence or requiring changes to the scheme of treatment, with the exception of anemia related to zidovudine (AZT).As per published guidelines (Ref) EFV at the beginning of pregnancy was switched to Lopinavir/rtvfor its potential teratogenic effects.

4. Discussion

The results of our cohort of patients identified by a regular screening program in a resource limited country demonstrate that such programs are feasible and can provided access to high quality regular care to HIV-1 positive pregnant women. The patients in this cohort belonged to a Hispanic, mestizo population in Central America, and attended a tertiary referral hospital in Guatemala City. This model resulted in a successful program in which treatment with HAART including a PI (lopinavir/r) was implemented [12,13].

Antiretroviral therapy has proven to be a fundamental intervention in the prevention of the transmission of HIV-1 from mother to child. As demonstrated since the 1990s in the ACTG 076 study, the use of AZT administered both from pregnancy and during childbirth to the mother and in the postpartum to the baby, showed a reduction of 68% of the risk of transmission. The use of triple therapy, which includes drugs such as NPV, and subsequently protease inhibitors starting with nelfinavir and then followed by LPV/rtv, has become the standard of management. Such combination regimens have succeeded in decreasing the transmission rate to less than 1% - 2% in the majority of tertiary referral centers around the world [11,13-15].

In this study, has been demonstrated good maternal and pediatric outcomes with the use of triple therapy that included LPV/rtv in a low income country. Despite some challenges associated with educational and social aspects of the participating women, those were addressed with the use of a multidisciplinary team. This cohort represents a successful PMCTC program. The incidence of infected children was lower than 2%, and a high proportion of women (79%) had no adverse pregnancy outcomes.

There are few publications with large numbers of pregnant women who have been treated with LPV/rtv, standard dose, during pregnancy. That is an important contribution of this study, given that 219 pregnant women receiving ARV combination, involving LPV/rtv, without evidence of increase in the number of adverse reactions compared to published reports. Also, comparing to the national statistics, there was not an increase in the number of abortions, stillbirth or premature labor in this cohort. Also, it is important to note that the tolerability and safety of LPV/rtv was adequate in this cohort; no treatment failure due to intolerance or toxicity was been observed, and most adverse events were of gastro-intestinal type, were mild to moderate, were self limited or at most required use of antiemetics [16-18].

Regarding the two children that died after the neonatal period; both deaths were attributed to several gastrointestinal community acquired infections and were felt not to be related to the PMTCT program.

On the individual analysis of the three infected children, several aspects are important. It is important to note that two of the children were twins; therefore, HIV transmission occurred in only two mothers. In the three cases, the mothers had baseline CD4+ cell counts higher than 200 cells/uL, but the mother of the twins presented with a baseline viral load of 1,840,000 cp/mL (6.26 log) and the other one with 48,000 cp/mL (4.68 log). In the case of the twins, the viral load higher than 6 logs suggests a recent infection, and the mother also reported suboptimal adherence to the HAART. In the other case, the infection was unexpected because the mother reported good adherence and had a low baseline viral load. In the three cases, the same post delivery measures were provided: AZT after delivery and artificial feeding. No viral loads controls after beginning of ARV treatment were performed.

This study had several limitations: 1) although not all women had CD4+ cell counts measured at every visit, the available information was useful to classify the women in various risk groups, as shown in the **Table 4**. Not all the women had CD4 cell counts, not all the women had viral loads, although pill counts are a reason-

able measure of adherence, no other adeherence measures were used, and there was no control arm.

This is an important perspective for a low income country; it shows that triple combination therapy with a PI is feasible and better than alternative interventions such as single dose nevirapine, that can led to higher levels of infections and antiretroviral resistance. The favorable maternal and pediatric outcomes and the positive safety and tolerability of the regimens reported in this cohort in this setting should be replicated by other groups.

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