Published in final edited form as:
Sex Transm Infect. 2009 April ; 85(2): 82–87. doi:10.1136/sti.2008.032300.

Pregnancy Outcome in HIV-1-infected Women Receiving Combination Antiretroviral Therapy Prior versus After Conception

Elizabeth S. Machado[1,#], **Cristina B. Hofer**[1], **Tomaz T. Costa**[2], **Susie A. Nogueira**[3], **Ricardo H. Oliveira**[2], **Thalita F. Abreu**[2], **Lucia A. Evangelista**[2], **Iraína FA Farias**[2], **Regina TC Mercadante**[2], **Maria de Fátima L Garcia**[2], **Renata C Neves**[2], **Veronica M Costa**[2], and **John S. Lambert**[4]

[1]Serviço de Doenças Infecciosas e Parasitárias, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro (UFRJ), Brazil [2]Instituto de Puericultura e Pediatria Martagão Gesteira (IPPMG), UFRJ [3]Secretaria Municipal de Petrópolis, Faculdade de Medicina de Petrópolis, Rio de Janeiro [4]Mater University Hospital, Dublin, Ireland

Abstract

Objective—Results regarding potential adverse effects of antiretroviral drugs during pregnancy are discrepant and few studies, most from Europe, have provided information about pregnancy outcomes of those already on treatment at conception. The aim of this study was to investigate the impact of antiretrovirals on pregnancy outcome according to the timing of treatment initiation in relation to pregnancy in a cohort of Brazilian HIV infected pregnant women.

Methods—A prospective cohort of 696 pregnancies followed-up in one single center between 1996 and 2006 was studied. Patients in receipt of antiretrovirals before pregnancy were compared with those treated after the first trimester. The outcomes evaluated were preterm delivery (PTD): < 37 weeks; severe PTD (< 34 weeks); low birth weight (LBW): < 2500 g; very LBW: < 1500 g.

Results—Patients on pre-conception use of ARV had higher rates of LBW (33.3% vs. 16.5%; p = 0.0002), and a similar trend for PTD (26.3% % vs. 17.7%; p = 0.09). Stratification by type of therapy (dual vs. HAART) according to timing of initiation of ARV showed that patients in use of pre-conception HAART have a higher rate of PTD (20.2% vs. 10.2%, p = 0.03) and LBW (24.2% vs. 10.2%, p = 0.002). After adjusting for several factors, pre-conception HAART was associated with an increased risk for PTD (AOR: 5.0; 95% CI: 1.5 – 17.0, p = 0.009) and LBW (OR: 3.6; 95% CI: 1.7 – 7.7, p = 0.001).

Conclusions—We identified an increased risk for LBW and PTD in patients in receipt of HAART prior to pregnancy.

#**Corresponding author:** Serviço de Doenças Infecciosas e Parasitárias, Hospital Universitário Clementino Fraga Filho – HUCFF – UFRJ. Av. Professor Rodolpho Paulo Rocco, no 255, 5° andar. Cidade Universitária, Ilha do Fundão, RJ, Brasil. CEP 21941-913. Tel: (+55+21) 2562-2526, Fax: (+55+21) 2299-8250. emachado@infolink.com.br.

Competing interests: None declared.

Contributors:
ESM design the study and was the lead author of the paper. CBH contributed to the design of the study and performed the statistical analysis. ESM, CBH, TPC, SAN, RHO, TFA, IFAF, RTCM, MFLG, RCN, VMC contributed in the follow-up of the patients and children. JSL provided revision of the manuscript.

Keywords

pregnancy; outcome; HIV; antiretroviral

Introduction

Over the last decade, treatment for the prevention of MTCT has moved from AZT monotherapy, to the use of highly active antiretroviral therapy (HAART), resulting in transmission rates of 1–2%[1–7]. In Brazil, vertical transmission of HIV-1 has been responsible for almost 11,000 cases of aids in children younger than 13 years between 1996–2005, however, less than 350 cases were notified during the year of 2006 8.

Discrepant results have been reported regarding the risk of adverse pregnancy outcomes in HIV-infected women treated with HAART. European studies have shown that exposure to any combination therapy increases the risk of premature delivery (PTD), being highest with the use of protease inhibitors (PI) 9–11, and also an increased risk for low birth weight (LBW) and stillbirths 12. Contrasting with these findings, several studies in USA and Latin America 13–16, failed to show a higher risk of adverse outcomes, although a report from one single site in USA showed a correlation between PTD and PI use 17.

Results describing the impact of antiretroviral drugs administered prior to conception have not been fully explored. The European Collaborative Study [10, 18] found a 2 times increased risk of premature delivery and a 4 times increased risk for severe prematurity in women who started combination therapy before conception. More recently, a 3.4 increase in the risk of PTD in patients treated with HAART was seen in a German/Austrian cohort where 52% of the patients were already being treated with HAART at conception[19].

There has been an increase in HIV-positive pregnant women receiving antenatal therapy. This might be an effect of the increasing age in the population of pregnant women with HIV, repeated pregnancies or changes in CD4 threshold for starting treatment in HIV-infected subjects. The aim of this study was to investigate the impact of ARV on preterm delivery and low birthweight according to the timing of initiation of therapy with respect to pregnancy.

Material and Methods

Study population

A prospective cohort of 899 pregnancies followed-up between 1996 – 2006 in a single HIV reference center in Rio de Janeiro (Program of Integral Assistance for HIV-Infected Pregnant Women of the Federal University of Rio de Janeiro, Brazil) was studied. Treatment of pregnant women has been performed utilizing a multidisciplinary team approach. ARV are offered free of charge. Mono and dual therapy were offered until 1998, when PI became available to the public healthcare system. All women are counseled not to breastfeed and formula, free of charge, is offered for a year. Elective C-section is usually performed at 38 weeks of gestation for those with a VL > 1000 copies/ml or an unknown VL and also in case of severe immunosupression (CD4+ T cell counts < 200 cells/ul). Patients who have a spontaneous loss of a pregnancy before 24 weeks were excluded. Data were collected during the follow-up and completed during the postpartum period. The constitution of an HIV-pregnant women databank was approved by UFRJ's Ethical Committee.

Study variables

The following pregnancy outcomes were evaluated: PTD: < 37 weeks of gestation; Severe PTD: < 34 weeks of gestation; LBW :< 2500 g at birth; 4. Very LBW: < 1500 g at birth.

Gestational age was estimated based on the date of the last menstrual period or the earliest ultrasound date available.

Co-variables studied were: age, use of tobacco, alcohol and illicit drugs. CD4+ T cell counts and viral load (VL) were evaluated at initiation of pre-natal care and before delivery. Symptomatic disease was defined as any clinical condition classified as category B or C (1993 revised CDC classification system) occurring during the current pregnancy or in the past. Antiretroviral therapy was categorized as monotherapy, dual therapy (2 NRTIs) or HAART (2 NRTIs + PI or NNRTI). Patients who were taking ARV before the estimated time of conception were included in the group of ARV prior to conception. Use of ARV was categorized as prophylaxis (if CD4 at entry ≥ 200 cell/ul) or treatment (CD4 at entry < 200 cells/ul or ARV pre-conception use).

Obstetric history included: multiparity (defined as women who have given birth at least once), mode of delivery (vaginal, emergency or elective C-section). Any previous history of miscarriage or PTD was considered as a single variable (previous adverse pregnancy) because information regarding the exact week of gestation in which the event occurred as well as LBW, fetal abnormalities, stillbirth or perinatal/neonatal mortality was not collected. Presence of hypertension was defined as any patient with chronic hypertension or development of hypertension, pre-eclampsia or eclampsia during the present pregnancy.

Sexually transmitted diseases (STD) were considered positive if patients had a diagnosis during the present pregnancy of trichomoniasis, HPV infection, syphilis, herpes infection or culture of vaginal swabs positive for *Gardnerella vaginalis*.

Patients with a HBSAg or HCV serology positive were considered as co-infected.

Statistical Analysis

Data analysis was performed using Stata version 9.0 statistical software (Stata Corp., College Station, TX). Univariate analyses were performed using independent ttests (for variables with a normal distribution) or Wilcoxon (Mann-Whitney) two sample tests (for variables that did not follow the normal distribution). The Chi-square test was used to evaluate associations for categorical variables (or Fisher Exact Test, if 20% or more cells on a table had an expected value of 5 or lower). Variables with a p value ≤0.15 were included in the multivariate analysis.

A main-effects logistic regression model was fitted. Interactions were assessed using the −2 log likelihood ratio test, comparing models with and without interactions. The Pearson's Chi-square goodness of fit test, as well as the Hosmer-Lemeshow test, was used to evaluate fitness of the model.

Results

We excluded 203 patients: 150 subsequent pregnancies, 13 because of missing data regarding weight of the newborn and 40 who started treatment ≤ 2 weeks before delivery (30 patients who received ≤ 1 week ARV, 10 patients who started ARV at 36 weeks of gestation). A total of 696 pregnancies were analyzed.

Women already on ARV treatment at the time of conception

130 patients (18.7%) conceived while on ARV. Thirty patients were on dual therapy (2 NRTIs), 47 (36.2%) on NNRTI-based HAART and 53 (40.7%) on PI-based HAART. Pre-conception ARV use was more frequent between 2001–2006 (82.3%). ARV treatment during pre-natal care for this group was: 2 NRTIs (22 pts- 16.9%), triple therapy with a protease inhibitor (73pts – 56.2%) or nevirapine (35 pts – 26.9%). Viral load at the beginning of pre-natal care was as

follow: in 32 patients it was undetectable, in 88 patients the median VL at entry was 4,900 copies/ml (19 patients with a VL ≤ 1,000 copies/ml) and in 10 patients it was unavailable. Pre-conceptual therapy was changed in 10 patients with an undetectable VL for substitution of unwanted combinations and in 58 patients with a detectable VL to increase viral suppression. At delivery, 47% (46/98) had an undetectable VL : 4 patients were treated with dual therapy, 18 patients treated with NNRTI-based HAART (nevirapine) and the rest with PI-based HAART). Median gestational age when the change of therapy occur was 15 weeks of gestation.

Women who started ARV after the 1st trimester of pregnancy

A total of 566 women started ARV after the first trimester of pregnancy (monotherapy with AZT: 179 (31.6%); 2 NRTIs: 182 (32.2%), HAART: 205 (36.2%). HAART with PI was used in 140 pts and nevirapine in 65 patients. Median gestational age at the beginning of ARV therapy was 24 weeks. VL at delivery was available for 336 patients and 44% achieved an undetectable VL of which 28 patients were treated with zidovudine, 41 with 2 NRTIs, 26 with NNRTI-based HAART 53 with a PI-based HAART.

The characteristics of both groups are described in Table 1. Patients already on ARV tended to be older, had a higher frequency of STDs, were more frequently multiparous, were commonly in receipt of HAART and had a higher frequency of VL ≥ 10,000 copies/ml at delivery. Although symptomatic disease was more prevalent in this group, most of the reported infections were related to a past event. The occurrence of opportunistic infections during the current pregnancy was similar in both groups studied: 5% (pre-conception ARV) and 3.3% (post conception ARV), and the difference was not statistically significant.

Most babies were delivered by C-section (69.7%). The mode of delivery was similar for both groups, as was the median gestation age at delivery (38.5 weeks). HIV status of 541 children was available (101 children born to ARV pre-conception mothers and 433 children from ARV post conception mothers). Seven children (1.3%) were infected of whom only one mother was already in receipt of ARV.

Adverse Outcomes—The overall frequency of PTD and LBW in our cohort was 80 (11.5%) and 90 (12.9%), respectively (Table 2). In univariate analyses both outcomes were associated with a VL ≥ 10000 copies/ml at delivery and pre-conception use of ARV. Hypertension was also a risk factor for LBW. Patients treated with monotherapy had a trend towards a lower rate of LBW (OR: 0.54; 95% CI: 0.29 < OR < 1.00).

Both outcomes were more frequent during the period of 2001–2006 when there was an increase in use of HAART pre and post conception. HAART use increased from 9% (19/207 - 8 before conception) to 60% (293/489 – 92 before conception) when comparing the two periods.

Babies born to pre-conception ARV women were lighter (2879 g) than those born to post conception ARV mothers (3077 g), $p = 0.001$. We noted a higher rate of LBW (30/130 (23%) vs. 60/566 (10.6%), $p = 0.0002$) in this group and also a trend for PTB (21/130 (16.1%) vs. 59/566 (10.4%); $p = 0.09$).

Very LBW was seen in 9 cases with no difference between groups (p=0.67). Severe prematurity was responsible for 23.7 % of the cases of PTD (19 cases). Despite the trend in relation to use of ARV pre-pregnancy ($p = 0.06$), no other risk factor was found, probably due to the small sample size.

In order to explore the impact of pre-conception use of dual therapy and HAART on both outcomes, we compared patients treated exclusively with dual therapy or HAART. We excluded 8 patients who were taking 2NRTIs at conception and changed to HAART after the

diagnosis of pregnancy and 1 patient with HAART pre-conception who changed to dual therapy. Only use of HAART prior to conception was significantly associated with PTD and LBW (table 3).

The HAART treated group was then split into 2 categories: those treated exclusively with NNRTI-based HAART or PI-based HAART (Pre and Post conception). We excluded 24 patients who were taking NNRTI-based HAART (19 patients) or PI-based HAART (5 patients) at conception and had their regimen switched to PI- and NNRTI-based HAART, respectively. In NNRTI-based HAART treated patients, PTD and LBW for those treated before or after conception were: 10/47 (17.8%) vs. 5/65 (7.7%); $p = 0.16$ and 5/28 (17.8%) vs. 8/65 (12.3%), $p = 0.52$, respectively. For the PI treated group, PTD and LBW were: 9/47 (19.1%) vs. 16/140 (11.4%); $p = 0.27$ and 12/47 (25.5%) vs. 13/140 (9.3%); $p = 0.009$, respectively.

Because splitting the HAART group yielded a low number of patients and outcomes, our multivariate analysis included the whole group who was treated with HAART (table 4). Prematurity was associated with pre-conception use of HAART (AOR: 5.06; 95% CI: 1.5 – 17.0) and a VL ≥ 10,000 copies/ml (AOR: 5.5; 95% CI: 1.0 – 30.8). A low birth weight was associated with HAART pre-conception (AOR: 3.6; 95% CI: 1.7–7.7) and hypertension (AOR: 3.8; 95% CI: 2.24–8.26).

Discussion

The analyses of our cohort of HIV-infected pregnant women followed-up in a single hospital with a uniform standard of care have shown rates of LBW and PTD of 12.9% and 11.5% respectively, among patients treated with antiretroviral therapy. This is higher than the average rate of LBW (9.1%) and PTD (7.8%) in public hospitals in Rio de Janeiro [20].

Our ratios are similar to a previous report in a Brazilian HIV-infected pregnant women cohort [15] where there was a slightly higher prevalence of LBW (14.3%) in comparison with PTD (10.6%). The lower rates of PTD and LBW in Latin American cohorts when compared to those in Europe and the US could be related to a lower prevalence of illicit drug use and to the absence of women who did not received ARV during pregnancy in the studies.

Stratification of our cohort by type and time of initiation of ARV revealed that HAART use prior to conception is associated with 3.6 times increased risk for LBW and a 5 times increased risk for PTD. LBW in this cohort was also associated with hypertension which is a well known risk for this outcome [21].

The higher frequency of PTD and LBW among women treated with ARV prior to conception, seen in our cohort, could be related to a more advanced stage of disease. However, inclusion of a present or past history of symptoms did not show a significant statistical association with any adverse outcome.

Stratification of our cohort by time of initiation of ARV and by type of therapy (dual therapy vs. HAART) revealed that HAART use prior to conception was associated with higher rates of LBW and PTD when compared with its exposure after conception. A VL ≥10,000 copies/ml at the time of delivery was found to be an independent risk factor for PTD. A study from one single center in UK [22] fail to show any increased risk for adverse outcomes in women treated with ARV before pregnancy. The low median VL of these patients (49 copies/ml) could explain this discrepancy. In our cohort, a high viral load was only marginally significant as a predictive factor for PTD and it should be carefully interpretated because VL at delivery was missing in 38% of the population studied.

Our study had some limitations such as absence of data regarding ethnicity, socioeconomic status, route of transmission (although more than 95% were due to heterosexual transmission), a detailed differentiation of previous adverse pregnancy outcomes and body mass index (BMI). A low BMI has been shown to increase two to three times the risk for both LBW and PTD [15, 23, 24]. Another limitation was the lack of data regarding the use of alcohol, tobacco and illicit drugs, which were missing for 35%of our cohort, but the prevalence of these behaviors were overall very low and would not have a great influence in our results. Finally, we were unable to evaluate the risk for individual ARV class.

As ARV use prior to conception cannot be stopped in women who are being treated for their own health, it will be important to continue monitoring adverse pregnancy outcomes in this population to assess if additional or different findings from cohorts with different geographies and demographics arise over time. As the number of patients who become pregnant while on ARV is increasing in Brazil and worldwide, detecting risk factors for adverse outcomes early in gestation will clearly be important to improve management for such women.

Key messages

Use of antiretroviral prior to conception was associated with an increased risk of premature delivery and low birth weight in a cohort of 696 Brazilian HIV-infected pregnant women during the period 1996–2006.

Stratification of our cohort by time of initiation of ARV and by type of therapy (dual therapy vs. HAART) revealed that HAART use prior to conception was associated with higher rates of PTD (AOR: 5.06; 95% CI: 1.5 – 17.0) and LBW (AOR: AOR: 3.6; 95% CI: 1.7–7.7) when compared with its exposure after conception. Hypertension was also an independent risk factor for LBW.

As ARV use prior to conception cannot be stopped in women who are being treated for their own health, it will be important to continue monitoring adverse pregnancy outcomes in this population to assess if additional or different findings from cohorts with different geographies and demographics arise over time. Detection of risk factors for adverse outcomes early in gestation in this population will clearly be important to improve management for such women.

Acknowledgments

We thank Andreia Fiorani for proofreading.

Financial support: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) – Research Grant for ESM. Ministério da Saúde do Brasil. Programa DST/AIDS (TC 238/07) for CBH.

References

1. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med 1994;331:1173–1180. [PubMed: 7935654]
2. Nogueira SA, Abreu T, Oliveria R, Araujo L, Costa R, Andrade M, et al. Successful prevention of HIV transmission from mother to infant in Brazil using a multidisciplinary team approach. Braz J Infect Dis 2001;5:78–86. [PubMed: 11493413]
3. Cooper ER, Charurat M, Mofenson L, Hanson IC, Pitt J, Diaz C, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. J Acquir Immune Defic Syndr 2002;29:484–494. [PubMed: 11981365]

4. European Collaborative Study. Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. Clin Infect Dis 2005;40:458–465. [PubMed: 15668871]
5. Centers for Disease Control and Prevention (CDC). Achievements in public health. Reduction in perinatal transmission of HIV infection – United States, 1985–2005. MMWR Morb Mortal Wkly Rep 2006;55:592–597. [PubMed: 16741495]
6. Newell ML, Huang S, Fiore S, Thorne C, Mandelbrot L, Sullivan JL, et al. Characteristics and management of HIV-1-infected pregnant women enrolled in a randomised trial: differences between Europe and the USA. BMC Infect Dis 2007;20:7–60.
7. Warszawski J, Tubiana R, Le Chenadec J, Blanche S, Teglas JP, Dollfus C, et al. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. AIDS 2008;22:289–299. [PubMed: 18097232]
8. Boletim Epidemiológico AIDS e DST - ano III - no 1. Tabela VI, pg 35. Área técnica. Epidemiologia. Boletim epidemiológico. Janeiro a Junho de 2006. available at www.aids.gov.br
9. Lorenzi P, Spicher VM, Laubereau B, Hirschel B, Kind C, Rudin C, et al. Antiretroviral therapies in pregnancy: maternal, fetal and neonatal effects. AIDS 1998;12:F241–F247. [PubMed: 9875571]
10. European Collaborative Study and the Swiss Mother + Child HIV Cohort Study. Combination antiretroviral therapy and duration of pregnancy. AIDS 2000;14:2913–2920. [PubMed: 11398741]
11. European Collaborative Study. Exposure to antiretroviral in utero or early life: the health of uninfected children born to HIV-infected women. J Acquir Immune Defic Syndr 2003;32:380–387. [PubMed: 12640195]
12. Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland. AIDS 2007;21:1019–1026. [PubMed: 17457096]
13. Tuomala RE, Shapiro DE, Mofenson LM, Bryson Y, Culnane M, Hughes MD, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. New Engl J Med 2002;346:1863–1870. [PubMed: 12063370]
14. Tuomala RE, Watts DH, Li D, Vajaranant M, Pitt J, Hammill H, et al. Improved obstetric outcomes and few maternal toxicities are associated with antiretroviral therapy, including highly active antiretroviral therapy during pregnancy. J Acquir Immune Defic Syndr 2005;38:449–473. [PubMed: 15764963]
15. Szyld EG, Warley EM, Freimanis L, Gonin R, Cahn PE, Calvet GA, et al. Maternal antiretroviral drugs during pregnancy and infant low birth weight and preterm birth. AIDS 2006;20:2345–2353. [PubMed: 17117021]
16. Kourtis AP, Schmid CH, Jamieson DJ, Lau J. Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis. AIDS 2007;21:607–615. [PubMed: 17314523]
17. Cotter AM, Garcia AG, Duthely ML, Luke B, O'Sullivan MJ. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery low birth weight, or stillbirth? J Infect Dis 2006;193:1195–1201. [PubMed: 16586354]
18. Thorne C, Patel D, Newell ML. Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. AIDS 2004;18:2337–2339. [PubMed: 15577551]
19. Grosch-Woerner I, Puch K, Maier RF, Niehues T, Notheis G, Patel D, et al. Increased rate of prematurity associated with antenatal antiretroviral therapy in a German/Austrian cohort of HIV-1-infected women. HIV Medicine 2008;9:6–13. [PubMed: 18199167]
20. Soares MA, Lopes JM, Moreira ME, Gianini NO. Neonatal care and mortality in public hospitals in Rio de Janeiro, Brazil, 1994/2000. Cad. Saude Publica 2005;21:1269–1277. [PubMed: 16021265]
21. Gilbert WM, Young AL, Danielsen B. Pregnancy outcomes in women with chronic hypertension: a population-based study. J Reprod Med 2007;52:1046–1051. [PubMed: 18161404]
22. Martin F, Taylor GP. Increased rates of preterm delivery are associated with the initiation of highly active antiretroviral therapy during pregnancy: A single center cohort study. JID 2007;196:558–561. [PubMed: 17624841]

23. Villamor E, Dreyfuss ML, Baylín A, Msamanga G, Fawzi WW. Weight loss during pregnancy is associated with adverse pregnancy outcomes among HIV-1 infected women. J Nutr 2004;134:1424–1431. [PubMed: 15173407]

24. Castetbon K, Ladner J, Leroy V, Chauliac M, Karita E, De Clercq A, et al. Low birthweight in infants born to African HIV-infected women: relationship with maternal body weight during pregnancy: Pregnancy and HIV Study Group (EGE). J Trop Pediatr 1999;45:152–157. [PubMed: 10401193]

Table 1

Characteristics of 696 pregnancies according to timing of antiretrovirals

Characteristic	Group 1 ARV prior conception (n=130)	Group 2 ARV after conception (n=566)	*P*
Median age (yrs)	28.7	26.7	0.001
Year of delivery			
1996–2000	23(17.7%)	184(32.5%)	
2001–2006	107(82.3%)	382(67.5%)	0.001
Duration of pregnancy			
<34 weeks	7(5.4%)	12(2.1%)	
≥34 and < 37 weeks	14(10.8%)	47(8.3%)	
≥37 weeks	109(83.8%)	507(89.6%)	0.07
Indication of ARV			
Prophylaxis of MTCT	0	473(86%)	
treatment	130(100%)	77(14%)	<0.001
CD4 at entry			
<200 cell/ul	22/129(17.1%)	77/550(14%)	0.46
Viral Load at entry			
≥10000copies/ml	34/120(28.3%)	219/494(44.3%)	0.002
CD4 at delivery			
<200 cell/ul	11/98(11.2%)	27/320(8.4%)	0.52
Viral Load at delivery(copies/ml)			
≥10000 copies/ml	15/98(15.3%)	23/336(6.9%)	0.02
Multiparity	96/104(92.3%)	353/422(83.6%)	0.02
Previous PTD or miscarriage			
≥1	25/96(26%)	103/353(29.2%)	0.51
Tobacco use	15/79(19%)	72/329(21.9%)	0.68
Alcohol use	1/79(1.3%)	21/325(6.5%)	0.09
Illicit drugs	8/79(10.1%)	28/320(8.7%)	0.87
Hypertension	6/130(4.6%)	38/566(6.7%)	0.49
STD	54/130(41.5%)	170/566(30%)	0.01
Mode of delivery			
vaginal	31(23.8%)	180(31.8%)	
emergency C-section	40(30.8%)	155(27.4%)	
elective C-section	59(45.4%)	231(40.8%)	0.20
Symptomatic disease	43/130(33.7%)	58/566(10.2%)	<0.001
HBV co-infection	2/108	3/414	0.27
HCV co-infection	2/108	10/381	1.00
ARV therapy during pregnancy			
Only AZT	0	179(31.6%)	

Characteristic	**Group 1 ARV prior conception (n=130)**	**Group 2 ARV after conception (n=566)**	***P***
2 NRTI	22(16.97%)	182(32.2%)	0.001
NNRTI-based HAART	35(26.9%)	65(11.5%)	<0.001
PI-based HAART	73(56.2%)	140(24.7%)	<0.001

Table 2

Univariate analysis for preterm delivery and low birth weight

	Gestational age < 37 weeks (n = 80)	**Gestational age ≥ 37 weeks (n = 616)**	***p***	**Birth weight < 2500g (t = 90)**	**Birth weight ≥ 2500g (t = 606)**	***p***
Age (years) ≤ 21	15 (18.8%)	119 (19.3%)	0.89	15 (16.7%)	122 (20.1%)	0.52
Year of delivery						
1996–2000	13 (16.2%)	194 (31.5%)		26 (28.9%)	181 (29.9%)	
2001–2006	67 (83.8%)	422 (68.5%)	0.007	64 (71.1%)	425 (70.1%)	0.94
Duration of pregnancy						
< 34 weeks				18 (20%)	1 (0.2%)	
≥ 34 and < 37 weeks				28 (31.1%)	33 (5.4%)	
≥ 37 weeks				44 (48.9%)	572 (94.4%)	< 0.001
Indication of ARV						
prophylaxis of MTCT (n = 473)[#]	49 (61.3%)	424 (77.1%)		48/88 (54.6%)	425 (89.9%)	
treatment (n = 207)	31 (38.7%)	176 (22.9%)	0.11	40/88 (45.4%)	167 (10.1%)	0.001
CD4 at entry						
CD4 ≤ 200 cell/ul	15/80 (18.8%)	84/599 (14%)	0.34	16/88 (18.2%)	83/591 (14%)	0.39
Viral load at entry						
≥ 10000 copies/ml	38/76 (50%)	212/538 (39.4%)	0.12	40/85 (47%)	213/529 (40.3%)	0.28
CD4 at delivery						
CD4 ≤ 200 cell/ul	4/42 (9.5%)	34/376 (9.0 %)	0.78	7/49 (14.3%)	31/369 (8.45)	0.18
Viral load at entry						
≥ 10000 copies/ml	6/29 (20.7%)	32/405 (7.9%)	0.03	9/43 (20.9%)	29/391 (7.4%)	0.007
Multiparity	61/65 (93.8%)	388/461 (84.2%)	0.06	60/68 (88.2%)	389/458 (84.9%)	0.59
Previous PTD or miscarriage	13/61 (21.3%)	115/338 (32.1%)	0.23	14/68 (20.6%)	114/458 (24.9%)	0.53
Tobacco use	16/52(30.8%)	71/356 (20.2%)	0.10	14/51 (27.4%)	73/357 (20.4%)	0.34
Alcohol	5/52 (9.6%)	17/352 (4.8%)	0.17	5/50 (10%)	17/254 (6.7%)	0.17
Use of drugs	7/53 (13.2%)	29/346 (8.4%)	0.29	5/51 (9.8%)	31/348 (8.9%)	0.80
Hypertension	9 (11.2%)	35 (5.7%)	0.09	11 (12.2%)	33 (5.4%)	0.02

	Gestational age < 37 weeks (n = 80)	Gestational age ≥ 37 weeks (n = 616)	*p*	Birth weight < 2500g (t = 90)	Birth weight ≥ 2500g (t = 606)	*p*
STD	20 (25%)	204 (33.1%)	0.14	26 (28.9%)	198 (32.7%)	0.55
Mode of delivery						
vaginal	26 (32.5%)	185 (30%)		30 (33.3%)	181 (29.9%)	
emergency C-section	28 (35%)	167 (27.1%)		26 (28.9%)	169 (27.9%)	
elective C-section	26 (32.5%)	264 (42.9%)	0.17	34 (37.8%)	256 (42.2%)	0.70
Symptomatic disease	14 (17.5%)	87 (14.1%)	0.42	17 (18.9%)	84 (13.9%)	0.26
HBV co-infection	0/57	5/465	1.00	2/66	3/456	0.12
HCV co-infection	0/55	12/435	0.38	0/61	12/429	0.38
ARV during pregnancy						
only AZT	21 (26.3%)	158 (25.6%)	0.98	15 (16.7%)	164 (27.1%)	0.05
2 NRTI	18 (22.5%)	186 (30.2%)	0.20	29 (32.2%)	175 (28.9%)	0.60
HAART with NNRTI	11 (13.7%)	89 (14.5%)	0.99	13 (14.4%)	87 (14.3%)	0.89
HAART with PI	30 (37.5%)	183 (29.7%)	0.19	33(36.7%)	180 (29.7%)	0.22
Before pregnancy	21 (26.3%)	109 (177.7%)	0.09	30 (33.3%)	100 (16.5%)	0.0002

[#]16 patients excluded including 2 children with low birth weight

Table 3

Preterm delivery and low birth weight rates for dual therapy and HAART according to timing of initiation of ARV

Therapy*	Timing of ARV	Preterm delivery (<37 weeks)	*p*	Low Birth Weight (<2500g)	*p*
Dual therapy (n = 204)	Prior conception (n = 22)*	1 (4.8%)	0.70	5 (22.7%)	0.21
	After conception (n = 182)	17 (9.3%)		24 (13.2%)	
HAART * (n = 304)	Prior conception (n = 99)	20 (20.2%)	0.03	24 (24.2%)	0.002
	After conception (n = 205)	21 (10.2%)		21 (10.2%)	

*8 patients excluded whose conception occurred with 2 NRTIs (dual therapy) and have their therapy changed to HAART after the diagnosis of pregnancy and 1 patient whose conception occurred during HAART and was treated with dual therapy during pregnancy.

Table 4

Unadjusted and adjusted odds ratios for preterm delivery and low birthweight in patients treated exclusively with HAART

Outcome	OR (95%CI)	*p*	AOR (95%CI)	*p*
Preterm Delivery				
HAART before pregnancy	2.22 (1.08 – 4.54)	0.03	5.06 (1.5 – 17.06)	0.009
Multiparty	3.60 (1.00 – 15.40)	0.05	1.60 (0.19 – 13.70)	0.67
Hypertension	2.91 (0.84 – 9.60)	0.06	2.73 (0.25 – 30.30)	0.41
Viral load ≥ 10000 at delivery	3.93 (0.94 – 15.49)	0.04	5.52 (0.99 – 30.8)	0.05
Low Birth Weight				
HAART before pregnancy	2.80 (1.41 – 5.61)	0.002	3.60 (1.71 – 7.70)	0.001
Multiparty	3.88 (1.08 – 16.53)	0.03	2.07 (0.45 – 9.38)	0.34
Hypertension	4.59 (1.47 – 14.12)	0.006	3.78 (1.09 – 13.15)	0.03
STD	1.20 (0.60 – 2.40)	0.69	1.00 (0.46 – 2.12)	0.98