ORIGINAL RESEARCH

EFFECT OF ANTIRETROVIRAL DRUGS ON MATERNAL CD$_4$ LYMPHOCYTE COUNTS, HIV-1 RNA LEVELS, AND ANTHROPOMETRIC PARAMETERS OF THEIR NEONATES

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PURPOSE: To study the effect of antiretroviral drugs administered during pregnancy on CD$_4$ lymphocyte counts and HIV-1 RNA levels of pregnant women and on the anthropometric parameters of their neonates.

METHODS: A prospective study was conducted on 57 pregnant women and their neonates divided into 3 groups: ZDV Group, HIV-infected mothers taking zidovudine (n = 20); triple therapy (TT) Group, mothers taking zidovudine + lamivudine + nelfinavir (n = 25), and Control Group, normal women (n = 12). CD$_4$ lymphocyte counts and HIV-1 RNA levels of pregnant women were analyzed during two periods of pregnancy. The perinatal prognosis took into account preterm rates, birth weight, intrauterine growth restriction, perinatal death, and vertical transmission of HIV-1. Data were analyzed statistically using the nonparametric chi-square, Mann-Whitney, Friedman, Kruskal-Wallis, and Wilcoxon matched pairs tests, with the level of significance set at $P < .05$.

RESULTS: The major maternal demographic and anthropometric data were homogeneous for the various groups. HIV-1 viral burden, which was initially elevated, median of 14,370 copies/mL, was significantly reduced in the TT group, reaching 40 copies/mL. With respect to T-CD$_4^+$ lymphocyte counts, there was a significant recovery in Group TT at the end of pregnancy, this value being significantly different from that for the ZDV group ($P = .0052$). There was no difference between groups regarding gestation length, Apgar scores, or neonatal anthropometric classification. There was no case of vertical HIV-1 transmission.

CONCLUSIONS: The results obtained for the present series demonstrate the efficiency and suggest safety of the use of antiretroviral drugs during pregnancy as revealed by anthropometric parameters of the neonate.

KEYWORDS: **Antiretroviral. HIV. Pregnancy. Neonate. Prognosis.**

Within the epidemiologic context of HIV-1 infection, women may be considered the main victims of the sexual dissemination of this viral disease and are currently presenting high seroconversion rates as recorded by the Ministry of Health of Brazil.[1] However, the improved quality of life and survival of HIV-1-infected patients, together with the significant reduction of vertical transmission obtained after a better understanding of the pathogenesis and risk factors for the disease and after the introduction of powerful antiretroviral (ARV) medications, has eliminated the condition of HIV-1 infection as an insurmountable obstacle regarding maternity.[2]

Antiretroviral compounds differ from most other new pharmaceutical agents in that they have become widely prescribed in pregnancy in the absence of proof of safety.[3] Combinations of 3 or more compounds are recommended when treatment of the mother is deemed necessary because of advanced HIV infection. Although many thousands of women

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have taken ARV drugs to reduce the risk of transmission, documented experience in human pregnancy remains sadly lacking, with the possible exception of zidovudine (ZDV), which has been prescribed in clinical trials to several hundred mother-infant pairs.[4]

In spite of the wealth of reports available regarding the adverse effects of ARV drugs in adults, there is a scarcity of national, prospective, or longitudinal studies emphasizing these results in pregnant women who use these drugs or of studies on the effects of ARV drugs on perinatal prognosis. In the present series, we evaluated the effects of two different intrauterine exposures, prophylactic use of ZDV or triple ARV treatment (zidovudine + lamivudine + nelfinavir) on CD$_4$ lymphocyte counts and HIV-1 RNA levels of pregnant women and on the anthropometric parameters of the neonate.

METHOD

The study was approved by the Research Ethics Committee of the Institution, and signed informed consent form to participate was obtained from each subject. The prospective study was conducted from September 2001 to March 2003 on 57 women aged 16 to 43 years with singleton gestations. Forty-five of these women were infected with HIV-1, and the remaining 12 were normal in both clinical and laboratory terms and were selected when they started prenatal care.

The women were considered infected with HIV-1 when two different serum samples were found to be positive for HIV-1 antibodies by ELISA and confirmed by the Western blot test. Only HIV-infected patients who had not been treated previously with ARV drugs were selected for the study.

The HIV-1–infected women were divided into 2 groups: ZDV Group and triple treatment (TT) Group. The ZDV Group consisted of 20 pregnant women who fulfilled the requirements for the prophylactic use of ZDV (CD$_4$ >500 cells/mm^3 and viral load <1,000 copies/mL). The TT Group consisted of 25 pregnant women with a clinical and laboratory indication (CD$_4$ <500 cells/mm^3) for triple ARV treatment (zidovudine + lamivudine + nelfinavir) according to the criteria established by the Perinatal HIV Guidelines Working Group Members regarding ARV treatment of pregnant women.[5]

Antiretroviral agents recommended, from the 14th week, were zidovudine, 300 mg/dose, twice a day for the ZDV Group, and 300 mg zidovudine, 150 mg lamivudine, and 1250 mg nelfinavir in 2 daily doses for the TT Group.

Exclusion criteria were women with renal and hepatic insufficiency, women with a personal or first-degree relative with a history of diabetes mellitus, women with an initial body mass index (BMI) of more than 30 kg/m^2, pregnant women with predictors of recurrent gestational diabetes mellitus (GDM) such as the presence of spontaneous abortions, major congenital malformations, stillbirth, or macrosomia in their previous pregnancies, women who did not comply with the use of ARV drugs or used them irregularly, and women taking other medications of known diabetogenic effect. CD$_4$ lymphocyte counts were analyzed by flux cytometry, and HIV-1 RNA levels were determined by the ultrasensitive third-generation bDNA assay (Bayer Corporation, Diagnostics Division, Norwood, Mass.) conducted according to the manufacturer's instructions in HIV pregnant women. Additionally, BMI, weight gain during pregnancy, clinical and obstetrical interfering events, gestational age at delivery (determined by an obstetric ultrasonography at the moment of the enrollment for all pregnant women), Apgar score, neonatal anthropometric evaluation (birth weight, head circumference, crown-heel length, standards of fetal growth according to Lubchenco et al.[6]), and vertical transmission of HIV-1 were determined.

The variabilities of plasma CD$_4$ lymphocyte counts, HIV-1 RNA levels, and neonatal anthropometric evaluations were calculated on the basis of the median and interquartile variation (1st and 3rd quartile, respectively). The nonparametric chi-square, Mann-Whitney Kruskal-Wallis, and Wilcoxon matched pairs tests were used, with the level of significance set at P <.05. All analyses were performed using the SPSS 10.0 software.

RESULTS

Median maternal age was 22.5 years with an interquartile (IQ) variation of 6 years for the Control Group, 24 years (7 years) for the ZDV Group, and 27 years (6 years) for the TT group, with no statistical difference between groups (P = .13, Kruskal-Wallis test). Race distribution (white and non-white) was also uniform in the three groups (P = .14, chi-square test). Smoking habit data also did not differ significantly between groups (P = .10, chi-square test). Initial BMI, BMI at the end of pregnancy, and maternal weight gain from the beginning of prenatal care to delivery was, respectively, 21.95, 25.57, and 10.5 (median values) for the pregnant women in the Control Group. No differences were observed with respect to these variables among the three groups (P = .10, Kruskal-Wallis test).

As expected, HIV-1 viral burden, which was initially elevated (14,370 copies/mL), was significantly reduced in the TT group, reaching 40 copies/mL. The difference between the ZDV and TT groups was significant (P <.001, Mann-Whitney test). With respect to T-CD$_4^+$ lymphocyte counts,

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Table 1 - HIV-1 viral burden (VB) and T-CD$_4^+$ lymphocyte counts of HIV-infected pregnant women in two different periods during pregnancy.

Group	1st VB copies/mL	2nd VB copies/mL	P	1st TCD$_4$ cells/mm^3	2nd TCD$_4$ cells/mm^3	P
ZDV	860	278		692	660	
n=20	(600-3.400)	(40-2.923)	.03[b]	(502-895)	(574-862)	.50
TT	14.370	40		399	543	
n=25	(6.726-45.610)	(40-1.499)	<.001[b]	(297-494)	(377-689)	<.001[b]
P	<.001[a]	.38		<.001	.0052[a]	

[a] P <.05, ZDV Group X TT Group, Mann-Whitney test; [b] P <.05, First and second evaluation during pregnancy, Wilcoxon matched pairs test. Data are reported as medians and 1st and 3rd quartiles; 1st VB and 1st TCD4 = Performed between 14-20 weeks; 2nd VB and 2nd TCD4 = Performed between 33-38 weeks

there was a significant recovery in Group TT from an initial median value of 399 cells/mL to 543 cells/ml at the end of pregnancy, this value being significantly different from that for the ZDV group (P =.0052, Mann-Whitney test) (Table 1).

The median gestational age at delivery did not differ among groups: 39 weeks for the Control Group, 38.1 weeks for the ZDV Group, and 38.5 weeks for the TT Group (P = .57, Kruskal-Wallis test) (Table 1). Median neonatal weight also did not differ among groups: 3.250, 3.080 and 3.100 kg for the Control, ZDV, and TT groups, respectively (P = .45, Kruskal-Wallis test). Analysis of these variables, of the Apgar score, and of adequacy of anthropometric classification did not show any significant differences among the newborns of the various groups (P = .59, chi-square test).

There was no case of vertical transmission of HIV-1.

DISCUSSION

There is no doubt that prophylaxis with the exclusive use of ZDV has reduced the risk of perinatal transmission of HIV-1. However, when the mother is in an advanced phase of infection, the use of ZDV is considered to be insufficient both for maternal treatment and for the prevention of vertical HIV-1 transmission. In these cases, the use of schemes containing a combination of ARV drugs is the most appropriate option. This option has been consistently found to be associated with reduced HIV-1 RNA copies in plasma and with the objective improvement of immunologic markers, which reflect the undeniable and favorable clinical readaptation of these patients.[7] The ARV combination currently used involves two nucleoside analogues and a protease inhibitor. According to CDC data,[4] nelfinavir is preferred among protease inhibitors because of its reduced number of side effects for the mother and because of the B categorization assigned to it by the Food and Drug Administration (FDA).

Studies about determinants of viral load and CD$_4$

Table 2 - Gestational age (GA), weight, head circumference (HC), body lengths, and adequacy of anthropometric classification (AAC) from the newborn at the time of delivery.

Group	Control n = 12	ZDV n = 20	TT n = 25	P *
GA (weeks)	39.0 38.0-39.2	38.1 37.5-40.0	38.5 38.0-39.5	.57
Weight (kg)	3.250 2.920-3.408	3.080 2.795-3.260	3.100 2.778-3.300	.45
HC (cm)	35.2 34.5-36.0	35.0 34.0-35.7	35.0 34.2-35.5	.64
Length (cm)	49.7 48.5-51.2	48.2 47.2-50.5	49.0 48.0-51.0	.40
AAC	100%	95%	92%	.59**

* Kruskal-Wallis test; **chi-square test; Data are presented as median values and interquartile range.

lymphocyte counts in Brazilian HIV-infected pregnant women making use of ARV therapy are still relatively scarce. Two studies in Brazil have addressed these questions. One examined the safety and feasibility of the administration of AZT/3TC combination to infected pregnant women and their infants in Rio de Janeiro.[8] Another evaluated perinatal HIV-1 transmission among low-income women participants in a cohort study in Southern Brazil.[9] Several differences among these studies and the present series should be noted: the first study did not include an evaluation of a group taking combination ARV therapy with a protease inhibitor like nelfinavir; in the second study, HIV viral burden and immunologic parameters were analyzed during the inclusion period, but they were not re-evaluated near the delivery. Recent regulations regarding the management of HIV-1-infected pregnant women consider viral suppression in plasma during gestation and especially during the period immediately preceding delivery to be the primary objective in the care for these women.[4] In the series reported here, which was managed according to these guidelines, the use of ARV drugs, particularly in the group treated with a scheme in combination with a protease inhibitor, led to a significant improvement in CD$_4$ lymphocyte counts and a

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marked reduction of HIV-1 RNA copies in all pregnant women. Undetectable viral load levels were obtained for 64% of these women in a prospective evaluation from the 33rd to the 38th week of pregnancy. These results are in accordance with those of authors who have observed that the viral load decreases in HIV-positive adults receiving ARV therapy as the adherence level increases.[10] However, there are still persistent doubts about the use of combined ARV therapy during pregnancy, with emphasis on repercussions of protease inhibitors on the fetus.[4,11]

Despite the vast literature available about the adverse effects of protease inhibitors in adults, there is a scarcity of national, prospective, and longitudinal studies emphasizing these results during gestation.

In recent years there has been widespread interest in perinatal biology. Accurate knowledge of fetal growth is imperative in clinical management, since growth retardation puts the fetus at increased risk of death and/or neurological damage.[12] There is a need for parameters of intrauterine growth that are reliable and applicable to each particular population. Since no study in Brazil regarding standards of fetal growth in HIV-infected women taking ARV drugs during pregnancy has addressed this question, the present series may be considered original. In this context, evaluation of neonatal weight and anthropometric classifications obtained for the present series supported previous reports demonstrating that ZDV therapy does not compromise fetal growth rates (weight, length and skull circumference) compared to control groups.[7,8] In addition, no difference was observed between the Control and TT groups. Whereas infection with HIV is associated with significant decrements across all standardized growth outcome parameters, HIV-uninfected infants usually do not show depressed results regarding anthropometric parameters. These important data may be viewed as an early indicator of HIV status.[13-17] Results reported here in uninfected infants exposed to ARV drugs during gestation are similar to those of another study that analyzed normal newborns in Brazil.[12]

In the present series, there was no difference in gestational age at delivery or in 1st and 5th minute Apgar scores among the neonates of the groups under study compared to the Control Group. These data agree with those obtained in the PACTG 076 study and in the meta-analysis of 2,123 pregnant women, 1,590 of whom were taking monoprophylaxis, 396 were taking combined therapy with no protease inhibitors, and 137 were taking combined therapy with protease inhibitors during the period from 1990 to 1998. When these women were compared to 1,143 pregnant women who did not receive ARV drugs, it was demonstrated that the gestational prognosis of mothers taking ZDV as monoprophylaxis during the prenatal period was

not compromised. There was no evidence that ARV drugs affected the incidence of preterm delivery or increased low birth weight rates, Apgar scores, or fetal mortality.[18,19]

In the present series, the resolution of pregnancy occurred after 38.5 weeks among the patients taking an ARV scheme containing a protease inhibitor, with no difference from the other groups, including the Control Group. These results are in accordance with those obtained in the PACTG 367, an observational study involving 1,472 HIV-1–infected pregnant women, 1,150 of them treated with a combined scheme, in which no association was observed between the use of these medications and preterm deliveries.[4]

The highest preterm delivery rates observed in the PACTG 367 involved women who had not received any ARV medications, in agreement with studies reporting higher rates of preterm deliveries among HIV-1–infected women who received no treatment.[20-24]

In the PACTG 185, 14% of the pregnant women underwent combined treatment with ARV drugs and presented gestational prognoses similar to those of HIV-1–infected women regardless of the use of ARV drugs or to those of uninfected women after controlling for smoking and drinking habits.[25] In 2000, the European Collaborative Study evaluated 3,920 mothers and their newborn infants and detected a 2.6-fold higher risk of preterm delivery among mothers who had used combined schemes before pregnancy compared to the group that started treatment with these schemes in the third trimester of gestation. Among the variables involved, CD4 lymphocyte counts and the use of injectable drugs were more prevalent in the group of women with preterm delivery.[26] In another study on 445 pregnant women treated with a scheme containing ZDV and 3TC, the rate of preterm deliveries was 6%, similar to the 9% value observed for women taking exclusively ZDV.[27] However, in the European Collaborative study,[28] even after potentially confounding variables regarding preterm delivery had been excluded, such as the use of drugs and the stage of maternal disease, a higher association was observed between the use of ARV medication (with or without protease inhibitors) and a higher rate of preterm deliveries.

Even though the results of the present series support the safety of the use of two schemes of ARV therapy during pregnancy—i.e., ZDV prophylaxis and combination of ARV agents (ZDV, lamivudine, and nelfinavir)—a limitation exists, based on the low power of the study reported here for detecting an effect of lower magnitude among groups.

An epidemiologic evaluation conducted in the US from January 1990 to June 2000 revealed maternal-fetal transmission of HIV-1 in 20% of the women who had not received ARV medication during pregnancy, in 10.4% of those who had taken ZDV only, in 3.8% of those who had re-

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ceived combined therapy without a protease inhibitor, and in 1.2% of those who had received combined schemes containing a protease inhibitor.[29] In the present series, no case of perinatal transmission was observed, perhaps owing to the care taken to support adherence to prophylactic measures or due to the limited number of cases studied.

Prophylaxis with ZDV has been implicated, although without proof, in changes in the neurologic and cognitive development of children exposed to HIV but not infected with the virus.[30] On the basis of data reported for children exposed to HIV but not infected followed up in the multicenter PACTG 076 study for a mean period of 4.2 years, (range: 3.2-5.6 years), no difference in neurologic, cognitive, or behavioral development was observed compared to the control group.[13] However, even more limited are the data regarding the potential toxicity to infants whose mothers had received combined schemes containing a protease inhibitor during pregnancy.[3,4,11,31] In a meta-analysis involving 7 clinical studies conducted on a total of 2,123 HIV-infected pregnant women who delivered between 1990 and 1998 and who had received ARV therapy during the prenatal period and on 1,143 women who did not receive ARV therapy during pregnancy (ZDV alone in 1590 cases, combined therapy without protease inhibitors in 396 cases, and combined therapy with protease inhibitors in 137 cases), the use of ARV medications was not associated with lower Apgar scores or increased fe-

tal death compared to untreated women or women taking ZDV alone.[18] These reports are similar to data demonstrated in the present series in which no difference was observed among treated and control groups.

The results obtained in the present series demonstrate the efficacy of ARV agents in terms improvement on CD$_4$ lymphocyte count, reduction in HIV viral load, and consequently on vertical transmission rates. The improvement of immunologic markers was higher for the TT Group. In addition, the present study suggests that the use of ZDV prophylaxis and ARV drugs, especially with the combined scheme containing nelfinavir as a protease inhibitor, is safe during pregnancy based on gestational age at delivery, Apgar score, and anthropometric parameters of the neonate. On the other hand, it is the gold standard to conduct follow-up of children with intrauterine ARV drug exposure into adulthood because of concerns regarding potential for adverse metabolic effect of combined scheme with protease inhibitors.[31]

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RESUMO

El Beitune P, Duarte G, Machado AA, Quintana SM, Figueiró-Filho EA, Abduch R. Efeito das drogas anti-retrovirais sobre os valores dos linfócitos TCD$_4$, RNA do HIV-1 e parâmetros antropométricos de neonatos de gestantes portadoras do HIV-1. Clinics. 2005;60(3):207-12.

OBJETIVOS: Estudar o efeito das drogas anti-retrovirais sobre a quantificação dos linfócitos TCD$_4$ e RNA do HIV-1 de gestantes portadoras do HIV-1 e parâmetros antropométricos de seus neonatos.

MÉTODOS: Estudo prospectivo avaliando 57 gestantes e seus neonatos em três grupos: Grupo AZT, gestantes portadoras do HIV utilizando zidovudina (n=20); Grupo TT, mães utilizando zidovudina+lamivudina+nelfinavir (n=25), e Grupo Controle, mulheres saudáveis (n=12). A quantificação dos linfócitos TCD$_4$ e RNA do HIV-1 de gestantes portadoras do HIV foi analisada em dois períodos durante a gestação. O prognóstico perinatal levou em consideração as taxas de pré-termos, restrição de crescimento intra-útero, mortalidade perinatal e transmissão vertical do HIV-1. Os dados foram analisados utilizando-se testes não paramétricos de qui-quadrado, Mann-Whitney, Friedman, Kruskal-

Wallys e Wilcoxon para amostras pareadas, considerando-se significativos valores associados a p<0,05.

RESULTADOS: Observou-se homogeneidade entre os dados demográficos e antropométricos de realce. A carga viral, inicialmente elevada (14.370 cópias/ml), reduziu-se significativamente no grupo com tratamento tríplice , chegando a 40 cópias/ml. Quanto à contagem de linfócitos CD$_4$, observou-se recuperação significativa nas pacientes do grupo TT, no final da gestação, sendo esse valor significativamente diferente em comparação ao grupo AZT (p = 0,0052). Não se observou diferença entre os grupos quanto à duração da gestação, aos índices de Apgar, e à classificação antropométrica neonatal. Não houve nenhum caso de transmissão vertical do HIV-1.

CONCLUSÕES: Os resultados obtidos na presente casuística demonstram eficiência e sugerem segurança no uso de anti-retrovirais na gestação sobre parâmetros antropométricos dos neonatos.

UNITERMOS: **Antiretroviral. HIV. Gestação. Neonato. Prognóstico.**

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