



ANTIRETROVIRAL TREATMENT IN PREGNANT WOMEN: EFFECTS ON NEWBORNS

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Abstract. Antiretroviral drugs have been used routinely since 1994 to reduce the risk of mother-to-child transmission of HIV infection, following the AIDS Clinical Trials Group 076 trial, which demonstrated the efficacy of zidovudine in reducing the risk of in utero and intrapartum transmission. Some studies have detected associations between in utero antiretroviral therapy (ARV) exposure and birth defects but evidence is inconclusive. **Objective** To determine the immunologic status of the children, the number of cardiac abnormalities and other birth defects in a 150 children group of HIV positive mothers and comparing data of birth defects noted in a 73 children group from HIV non-infected mothers. **Methods.** 150 HIV exposed children were enrolled in the study. Fourteen (9%) were vertically infected with HIV. Birth defects were noted and cardiac anomalies were detected in 36 (24%) children and other congenital anomalies were noted in 28 (18.66%) children. These data were compared with the number of cardiac abnormalities and birth defects in a 73-second group of children born to HIV non-infected mothers. There were no statistical associations between cardiac anomalies in the two groups ($p=0.11$) but there was statistical association in other defects ($p<0, 01$). In **conclusion**, based on current knowledge, the immense benefits of antiretroviral prophylaxis in prevention of mother-to-child transmission outweigh the potential for adverse effects. However, these potential adverse effects require further and longer term monitoring. **Keywords:** HIV, congenital malformations, children

Introduction

HIV infection represents a global threat which targets both adults and children. If, in the

beginning this infection had a significant impact within the homosexual groups, today the most exposed to it are heterosexual women. In 2009, statistics at global level revealed that the share of HIV positive women remained relatively stable, accounting for 52% of the total number of PLWHA [1]. In 2009 HIV prevalence in Eastern Europe was 1.4 million people compared to 900,000 persons in 2001 [2]. In the same year, HIV mortality rate was 4

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times higher than the one in 2001 (76,000 deaths).

Children to HIV positive mothers are at higher risk of developing AIDS and of dying within the first two years of life. The effort to prevent HIV transmission from mother to child encompasses the administration of HAART treatments (Highly Active Antiretroviral Treatment) to both women during their pregnancy, at birth, as well as to newborns.

It is well known that besides the effects of disease deceleration and increase in the survival rate of HIV positive persons, ARV medication also has numerous side effects, which affect most organs and systems in the human body.

The moment of ARV administration is a crucial element for the onset of birth defects. It is suspected that if ARV medication was administered in the first pregnancy trimester, during organogenesis, it would produce more side effects than if it was given at the second or third trimester, but this has not yet been scientifically proved [3,4].

Several studies on small patient samples emphasised the presence of diverse birth defects in children to HIV positive mothers who were under ART. [5]. These anomalies were detected at all organs and systems [6,7] especially at the cardiovascular, kidney and nervous systems.

Objectives.

The study aims to analyse the impact of the ART the mother receives during pregnancy on the infectious status of a 150 children lot and on the occurrence rate of birth defects these children experience.

Material and methods

The present study comprised 150 children to HIV positive mothers, admitted for clinical investigations and treatment in National Institute of Infectious Diseases "Prof.Dr. Matei Balş" (INBI) in Bucharest (group A). The type of study is retrospective and case-control. For the A group the data was collected from the observation charts of children to HIV positive mothers, admitted in INBI „Prof.Dr. Matei Balş” in Bucharest during 2008-2010. In order to analyse the rate of birth defects in this group a second, witness B group was selected, made of 73

children to HIV non-infected mothers, admitted for different reasons in the Institute of Mother and Child Protection "Alfred Rusescu", Bucharest. The witness group was constituted of newborns, admitted at the Paediatric Clinic in the Institute of Mother and Child Protection "Alfred Rusescu" for two years (2009-2010). The inclusion criterion was the age proper to newborns, irrespective of the reason for the presentation at the emergency room. Children who had referrals or reasons to be admitted- cardiac malformations- were not included in the group. Due to their presentation at the emergency room of a hospital, the witness group does not stand for the general population. The legal guardians were asked to sign an informed consent.

Results

The A group of children to HIV positive mothers registered 80 boys (53%) and 70 girls (47%).

The B group of children to HIV non-infected mothers registered 41 boys (56%) and 32 girls (44%).

44% of the mothers in the A group were diagnosed with HIV prior to pregnancy, 26% during pregnancy, 25% during labour and 5% after birth. The mothers diagnosed intrapartum or postnatally and 16 women with HIV infection acquired prior to pregnancy (10.66%) did not receive ART during gestation, due to a low socio-economic level and other addictions (alcohol and drugs), which would cause poor adherence to treatment. This could also explain the presence of six HIV infected children to HIV positive mothers, diagnosed before pregnancy.

The analysis on the correlation between the moment of HIV diagnosis of the mothers and the immunologic status of the children (related to HIV) revealed that most seroreverters come from mothers diagnosed before pregnancy, who also received ART to prevent HIV materno-fetal transmission.

As the table above shows, in group A- 14 children remained HIV infected (9%), 72 were seroreverters (48%) and 65 were exposed (under evaluation) to HIV (43%). The 9% of vertically transmitted HIV infections is high compared to 1-2% of similar infections, reported by some authors in countries with an increased socioeconomic level where HAART therapy is administered in order to prevent materno-fetal transmission. Simultaneously,

Moment of HIV diagnosis for mothers	Immunologic status of the child		
	Seroreverter	Exposed (under evaluation)	Infected
Prior to pregnancy	34	27	6
During pregnancy	18	19	2
At birth	18	15	4
Postnatal	2	4	2

Table I. Immunologic status of children according to the mothers' HIV diagnosis moment

the percentage of infected children is low for our country, which in the past registered a rate of HIV materno-fetal transmission of 45%, this also being an indicator of the efficacy of ART administration to pregnant women and of their monitoring during the gestation period [8,19]. In this group, 52 HIV uninfected children and 2 infected children came from mothers who received antiretroviral treatment, while 38 uninfected children and 8 infected children came from mothers with no ART prior or during pregnancy. Statistically, the therapy applied to mothers in group A prior and during pregnancy offers anti-infectious protection to children after their birth ($p < 0, 01$).

Most children in this group received antiretroviral prophylactic therapy at birth, except for 20 who did not receive it (13.33%). 6 of them are boys (4%) and 14 are girls (9.33%), who come from HIV diagnosed mothers prior, during pregnancy or at birth.

HIV diagnosis in mothers	Children who did not receive ARV prophylaxis
Prior to pregnancy	6 (4%)
During pregnancy	4 (2.66%)
At birth	8 (5.33%)
Postnatal	2 (1.33%)

Table II. Distribution of children who did not receive ART prophylaxis, based on the detection of HIV infection in mothers

There is a statistical significance/difference between the prophylaxis given to children in this group at birth and the HIV status, with a $p < 0.01$ comparison value.

With respect to the analysis of malformations in children to HIV positive mothers with/without ART during pregnancy- 64 (42.66%) were detected in group A. They were diagnosed based on clinical evaluation, ultrasounds (transfontanellar ultrasound, cardiac ultrasound), some requiring comprehensive

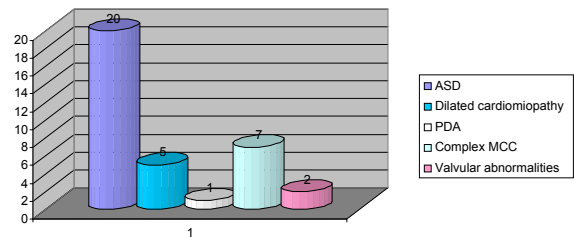
Malformations in the HIV group	Number of cases
Severe Psychomotor Retardation	10 (6.66%)
Psychomotor retardation	4 (2.66%)
Lenticulostriate vasculopathy	1 (0.66%)
Intracerebral hemorrhage	2 (1.33%)
Down Syndrome	1 (0.66%)
Thalamic Calcification	2 (1.33%)
Cheiloschisis	1 (0.66%)
Palatoschisis	1 (0.66%)
Ear pavilion malformation	1 (0.66%)
Renal malformations	4 (2.66%)
Mixed gonadal dysgenesis	1 (0.66%)
Cardiac malformations	36 (24%)

Table III. Malformations in the group of children from HIV positive mothers

investigation as karyotype and other genetic tests. Compared to the data in speciality literature, this number of malformations is larger; but there were children who presented one or more malformations.

As can be seen in group A, cardiac malformations predominate the panel (24%), but renal malformations, face malformations (cheiloschisis, palatoschisis, ear pavilion malformation) were also detected while a relatively large number of cases presented severe or moderate psychomotor retardation. Two congenital malformations were also discovered: one Down Syndrome entailing autosomes (trisomy 21, 47XX+21) and a syndrome with sexual chromosomes (mixed gonadal dysgenesis with karyotype 45,X/46,XY). Statistically, the presence of these malformations correlates with the ART medication that the mothers received ($p < 0.01$). They are more frequent in the male gender, our group having 37 (46.3%) boys diagnosed with congenital malformations.

The most frequently detected cardiac malformation was atrial septal defect (ASD) while other 5 cases were dilated cardiomyopathy, 7-complex cardiac malformations, one patent ductus arteriosus (PDA) and 2 valvular abnormalities.



Graphic 1. Heart malformations in the group of children of HIV positive mothers

In group B (the witness lot), out of 73 children to HIV negative mothers 14 presented malformations. Most of them were cardiac malformations (11 cases, representing 15%). Only 3 children (4%) had Turner syndrome malformations, polydactility and one case of true hermaphroditism. Cardiac malformations diagnosed in this group after echocardiography were ASD type for 4 cases, DSV for 2 cases, PDA for 2 cases and one complex heart malformation. In the witness group no diagnosis was made for cyanotic heart or valvular malformations or for dilated cardiomyopathy. Although from a strictly statistic point of view the incidence of heart malformations in the group of children of HIV positive mothers does not differ from the children in the witness lot ($p = 0.11$) their severity and complexity is greater. Between the two groups there is a statistically significant difference in the area of other malformations ($p < 0, 01$).

The 150 children of HIV positive mothers in group A who presented at the "Prof.Dr. Matei Bals"

Institute were clinically and virologically assessed for HIV (CD4 count, CD3, CD8, viral load) and for other infections (antibodies for hepatitis B, hepatitis C, anti cytomegalovirus, antigenic determination for syphilis). The tests revealed no hepatic infections but detected one child with cytomegalovirus infection and 6 with congenital syphilis. In addition to that, two other children developed pulmonary TB, shortly after birth, one of them delivered by a mother who, despite her AIDS condition, did not receive ART during pregnancy or at delivery, passing the infection to him. Although there are no signs of cardiac malformations, the child has a renal malformation. In this case TB infection is one of the illnesses that trigger HIV and most importantly AIDS.

Other infectious diseases	Number of cases
Congenital syphilis	6 (4.0%)
CMV Infection	1 (0.66%)
TBC	2 (1.33%)

Table III. Other infectious diseases in children to HIV positive mothers

The mothers of children diagnosed with congenital syphilis were diagnosed with HIV in different stages: 3 were found HIV positive at birth, two during pregnancy and one prior to pregnancy. Although not all mothers received ART during gestation, all children with congenital syphilis got ART prophylaxis at birth. Nevertheless, two children with congenital syphilis remained with HIV infection. In specialty literature, many authors [9, 10, 11, 12] vastly described haematological and hepatic diseases in children to HIV positive mothers. Groups A presented one case of severe anaemia in a newborn, shortly after birth, another one month old infant with anaemia, as a side effect of HIV prophylaxis whose state required the immediate suspension of ART prophylactic medication and another case of hepatic cytolysis in an infant with no other viral or bacterial infection with hepatic tropism, probably ART related.

Discussions

On a global scale, the impact of antiretroviral treatment on conception continues to represent a largely debated topic, with many researchers offering contradictory results. Once these drugs were administered to pregnant women for the protection of the fetus and newborn against HIV, the issue of ART teratogenic effects was raised. Thus, a worldwide registry on possible teratogenic effects of ARV medication was set-up – APRegistry [13] (Antiretroviral Pregnancy Registry). The evidence in APRegistry

shows that the prevalence of congenital defects in newborns to HIV positive mothers, treated with antiretroviral medication during pregnancy does not differ significantly from malformation prevalence in the general population. Also, no significant difference was observed between prevalence of congenital defects if ART was administered during the first pregnancy term or during the following ones (2.8 at 100 alive newborns; ratio prevalence: 1.07, 95%; CI: 0.88-1.32) [12].

Another issue in determining the teratology of ARV medication is the combination between drugs. For example, a study raised questions concerning the combination between ARV medication and cotrimoxazole and their role in the development of congenital malformations [14].

Although APRegistry reports a link between different congenital malformations and the use of several antiretrovirals, there is also contradictory information. For instance, efavirenz [15] is the most frequently reported drug with side effects, but a series of studies did not confirm this [16], fact equally noted by the APRegistry [5].

Even though APRegistry tries to gather and corroborate world data [17], it has been observed that not all congenital defects have been reported: in USA only 15% of these cases are reported. In the same context, the detection of side effects is not standardized and it largely depends on the investigator's experience [18]. This could be a possible explanation for the presence of many malformations in the observed group.

It is also difficult to explain the reason why mothers known to be HIV positive prior or during pregnancy did not receive ART for the prevention of HIV materno-fetal transmission. This could be determined by a modest socio-economic level and especially by poor adherence to treatment on behalf of these women. It is equally hard to explain why children of mothers detected HIV positive prior or during pregnancy did not receive ARV prophylaxis at birth. This aspect proves a lack of addressability that HIV positive patients have towards other medical services, probably due to the concern not to be denied the right of investigation and treatment.

Once again, the statistical analysis of this group shows the importance that ART has for the prevention of HIV materno-fetal transmission and confirms the significance of ARV prophylaxis for newborns. Statistically, the presence of cardiac malformations was not significantly different between the two study groups (the group of children to HIV positive mothers and the witness group of children of HIV negative mothers) and this might be due to the fact that children in the witness group presented and admitted at the emergency room of other hospitals, in this case without being assimilated to the

general population. This limits our study.

Emphasis should also fall on a significantly large number of other materno-fetal infections (9 cases - 6%), the most common one being congenital syphilis which denotes a lack of sanitary education in mothers and deficiencies in the surveillance system of a pregnancy.

Conclusions: Despite the new generation of drugs and therapeutic schemes used in the effort to limit HIV infection, this continues to spread especially to women at fertile age and implicitly to their children. The large number of vertically transmitted HIV infections and diagnosed malformations in the described study is an alarm for doctors in our country (not only for infectionists who are directly involved in the treatment and care of these patients) who must strengthen the surveillance system of pregnant women. As for HIV positive women diagnosed a while ago, they must be informed by their doctors, especially on the risk of malformation for their children and encouraged to appeal to contraceptive methods.

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