Birth outcome in HIV vertically-exposed children in two Romanian centers

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Abstract

Background The Romanian HIV epidemic is characterized by a high prevalence among children born in the late '80s, perinatally infected. The impact of long-term treatment on their offspring is unknown. We evaluated the influence of prenatal care on the rate of premature birth among the HIV-exposed children of heavily treated HIV-infected mothers in two Romanian centers.

Methods We retrospectively analyzed data on all patients born by HIV-infected mothers between 2006 and 2012 followed up in two main regional centers. We compared the rate of premature birth and the differences between the sites regarding children and maternal demographic characteristics and antiretroviral exposure in pregnant women.

Results A total of 358 children born to 315 women were enrolled between 2006-2012, 262 children from the National Institute for Infectious Diseases "Prof. Dr. Matei Balș" Bucharest (NIID) and 96 children from the Clinical Infectious Diseases Hospital Constanța (IDHC). Gender rate in newborns and mean age in mothers were similar. We recorded statistically significant differences between centers in the rate of HIV vertical transmission (16.8% vs. 6.2%, $p=0.002$) and prematurity (25.2 vs. 14.6%, $p=0.023$). The most used antiretroviral combination during pregnancy in IDHC was boosted lopinavir and fixed dose zidovudine-lamivudine (66% of cases), while in NIID a greater diversity of antiretrovirals were used. Women from IDHC were more frequently treated during pregnancy (83.3% vs. 68.6%, $p=0.004$). HCV coinfection and illegal drug use were associated with prematurity in the NIID cohort ($p=0.037$, $p=0.024$).

Conclusion We found a higher rate of premature birth and HIV infection in NIID. In IDHC we found a higher rate of low birth weight in children and a higher rate of heavily treated women. Prematurity was associated with hepatitis C infection and illegal drug use in the NIID cohort.

Keywords HIV exposure, antiretroviral drugs, prematurity

Background

Starting with 1990 Romania faced a particular HIV epidemic, characterized by a large number of

children born in the late '80s, perinatally-infected with HIV subtype F.^{1,2} Survivors of this cohort have experienced multiple antiretroviral

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combinations for at least 15 years, and they are now at fertile age, having their own children.^{3,4} There is little information on the impact of antiretroviral drugs exposure on children born to women infected with HIV from early childhood. In order to respond to this problem, the Romanian Registry on Mother to Child HIV Transmission was started in 2014.

The rate of HIV vertical transmission in Romania was 4.0% in 2014, in a steady trend from 2009 onward⁵, due to the implementation of a National Program for Prevention of Mother-to-Child HIV Transmission (PMTCT) started after 2000. The National PMTCT Guidelines comply with the European Guidelines and are 100% financially covered by the National Health Insurance House. Prevention of HIV vertical transmission is based on antiretroviral drugs administration in pregnant women and newborns. The children receive antiretroviral prophylaxis for 6 weeks after birth, usually zidovudine and lamivudine. In pregnant HIV-infected women antiretroviral treatment is started as soon as possible, or it is continued, if the therapy is efficient. The antiretroviral therapy consists of an association of two nucleoside reverse-transcriptase inhibitors (NRTI) and a boosted protease inhibitor (PI/r) or a non-nucleoside reverse-transcriptase inhibitor (NNRTI). The Romanian National Guideline recommends planned C section delivery and to avoid breastfeeding, as well.

Given the particular Romanian epidemiological data, it is important to evaluate the effect of antiretroviral drugs on children born to long-term multidrug treated women. The present study aims to compare the rate of premature birth in two Romanian cohorts from two regional centers and to assess the differences between the sites regarding children and maternal demographic characteristics and antiretroviral exposure in pregnant women, in

order to offer useful information to doctors involved in the medical care of HIV-infected pregnant women and HIV-exposed newborns.

Methods

Study Population

The studied population included HIV-exposed children and their mothers followed up in two large Romanian Regional Centers for AIDS: the National Institute for Infectious Diseases “Prof. Dr. Matei Balș” Bucharest (NIID) and the Clinical Infectious Diseases Hospital Constanța (IDHC). The eligible population consisted of all the children born between January 1st 2006 and December 31st 2012 and their mothers who accessed medical services in mentioned centers. There were no exclusion criteria.

Study Design

A retrospective observational study was conducted to evaluate and compare the rate of premature birth in children born to HIV-infected women in two Romanian Regional AIDS Centers. The characteristics of studied patients from the sites were compared, as well.

All women and children’s legal guardians signed the informed consent and the study was approved by the Ethical Committees from each hospital.

The children from both centers were followed up for 18 months in order to determine the final HIV status.

Medical care for studied patients was performed by individual case physicians based on the HIV Management National Guidelines.⁵

Definitions

Patient characteristics

The children’s HIV final status was determined after 18 months of follow-up using HIV RNA testing and serologic confirmation (ELISA and Western blot). Serum HIV RNA determinations were done using COBAS TaqMan HIV-1 Test Version 2.0, Roche Molecular Systems, Branchburg, NJ, USA (commercial kit with detection limit: 20 HIV RNA copies/mL). The HIV infection diagnosis was considered if, at any point in time during the

follow-up period, the serum viral load was detectable. If during the first 18 months of life the viral load was undetectable, and the serologic tests were negative at the end of the follow up, the infant was classified as HIV exposed, but not infected. If the follow-up was not complete, but the viral load was negative at all available determinations, we considered the child lost to follow-up.

Antiretroviral prophylaxis in newborns consisted in zidovudine and lamivudine for six weeks, as recommended in the Romanian HIV Management Guideline since 2000.⁵

Recorded data for studied newborns consist of: birth date, gender, weight at birth, gestational age at delivery and HIV final status. For pregnant women we recorded: age at delivery, type of delivery, age at HIV diagnosis, moment of antiretroviral treatment initiation, duration and type of antiretroviral treatment, type of antiretrovirals used during pregnancy, number of regimens used before pregnancy. For women in the NIID group, data regarding coinfection with syphilis and hepatitis B and C viruses, and illegal drug use were available, as well.

HIV infection in pregnant women was diagnosed using ELISA tests and confirmed with Western blot tests plus a detectable serum HIV RNA (viral load).

Planned C section delivery was defined as the type of birth indicated for PMTCT and unplanned C section delivery the one indicated for obstetrical complications during pregnancy.

Antiretroviral treatment in studied women consisted of a combination of at least three drugs, containing NRTI backbone plus an NNRTI or boosted PI. During the studied period, in Romania there were available three NNRTI drugs: efavirenz, nevirapine and from 2009 etravirine. The PIs used were nelfinavir until 2007, saquinavir, fosamprenavir, lopinavir, atazanavir and, from 2009, darunavir. Except for nelfinavir, all other PIs were used only boosted with ritonavir.

The number of antiretroviral regimens used before pregnancy in studied women was stratified as: none, one, two, three and more than three antiretroviral combinations (cART).

Outcome

The normal range for full term pregnancy was 37 to 40 weeks of gestation. In order to determine the gestational age at delivery we used the date of the last period or/ and fetal ultrasound data. In some cases with missing data about the last period and ultrasound determinations we used the Ballard score.^{6,7}

Babies' birth weight was classified as normal if it was greater than 2500 g, low if it was between 1500 g and 2500 g, very low between 1000 g and 1500 g and extremely low less than 1000 g.^{6,8}

Statistical analysis

Statistical significance ($p \leq 0.05$) was determined using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, NY, USA). Patients' characteristics were compared using the Chi-square test. To test for differences between two groups of categorical variables we used Fisher's exact test, and for three or more groups of categorical variables we used Pearson's Chi-square test. For non-parametric variables we used Mann-Whitney test.

Results

A total of 358 children born to 315 HIV positive women were enrolled, 262 children were monitored in NIID from January 1st 2006 until December 31st 2012 and 96 children in the IDHC from January 1st 2008 until December 31st 2012. Overall, 278 women had one delivery, 31 women had two deliveries and six had three deliveries. Three twin pregnancies were encountered: one reached full term and two led to premature birth. During the study period we did not register any deaths in children, but we lost to follow-up 41 infants. No women died at birth or in the first month after delivery.

The distribution of cases over the study period is shown in the Figure; an ascending trend in the number of cases accessing medical care was noticed. In NIID, the largest center for HIV care in Romania, the highest number of cases and of premature births was recorded in 2012. In IDHC the highest number of cases was in 2010, and the number of premature births remained stable during the last 3 years.

Figure. Distribution of cases over the study period in two Romanian centers

Table 1. Characteristics of newborns by center

Characteristics		NIID Center	IDHC Center	Total	p
Total number of children, n (%)		262 (73.2)	96 (26.8)	358 (100)	
Children's gender, n (%)	Male	145 (55.3)	47 (48.9)	192 (53.6)	0.340 ^a
	Female	117 (44.6)	49 (41.1)	166 (46.4)	
Final HIV status in children, n (%)	Negative	195 (74.4)	72 (75.0)	267 (74.6)	0.002 ^b
	Positive	44 (16.8)	6 (6.2)	50 (13.9)	
	Lost to follow-up	23 (8.8)	18 (18.8)	41 (11.5)	
Number of children born, n (%)	Full term	188 (71.7)	82 (85.4)	270 (75.4)	0.023 ^b
	Premature	66 (25.2)	14 (14.6)	80 (22.4)	
	Missing data about gestational age	8 (3.1)	0	8 (2.2)	
Number of patients, n (%)	Normal birth weight (>2500 g)	182 (69.5)	65 (67.7)	247 (68.9)	0.008 ^b
	Low birth weight (1500-2500 g)	50 (19.1)	30 (31.3)	80 (22.3)	
	Very low birth weight (1000-1500 g)	14 (5.3)	1 (1.0)	15 (4.2)	
	Extremely low birth weight (<1000 g)	2 (0.8)	0	2 (0.6)	
	Missing data	14 (5.3)	0	14 (3.9)	
Mean birth weight ± standard deviation, g		2728.7±581.9	2656.6±504.9	2708.9±562.9	
95% confidence interval		2758.3-2799.2	2505.6-2757.6	2648.2-2768.4	

^aFisher's exact test

^bPearson Chi-square test

^cStudent t test

The characteristics of newborns followed-up in the two regional Centers are summarized in Table 1. The newborns' male/female ratio was 1.2 (145/117) in NIID and 0.9 (47/49) in IDHC, but the difference was not statistically significant ($p=0.340$).

HIV vertical transmission was recorded in 50 out of 358 cases (13.9%), with significant differences between the two centers (16.8% vs. 6.2%, Pearson Chi-square=12.3, $p=0.002$, Table 1). Twenty three children (8.8%) in the NIID group and eighteen (18.8%) in IDHC group, ($p=0.013$, OR: 0.41, RR: 0.74) did not complete the 18 months follow-up after birth, but the viral load was undetectable at all available visits.

Table 2. Characteristics of HIV-positive women followed up in two regional centers (NIID and IDHC)

Characteristics		NIID Center	IDHC Center	Total	p
Total number of children, n (%)		262 (73.2)	96 (26.8)	358	
Maternal mean age at birth, years		23.2	23.2	23.2	
Standard deviation		4.7	2	4.4	0.965 ^c
95% confidence interval		22.6-23.7	22.8-23.6	22.7-23.7	
Number of women with HIV diagnosis, n (%)	Before pregnancy	158 (60.3)	68 (70.8)	226 (63.1)	0.090 ^b
	During pregnancy	47 (17.9)	18 (18.7)	65 (18.1)	
	After pregnancy	55 (20.9)	10 (10.4)	65 (18.1)	
	Missing data	2 (0.8)	0	2 (0.6)	
Number of women with cART initiation, n (%)	Before pregnancy	130 (49.6)	78 (81.2)	208 (58.1)	0.004 ^b
	During pregnancy	43 (16.4)	2 (2.1)	45 (12.6)	
	After pregnancy	82 (31.3)	16 (16.7)	98 (27.4)	
	Missing data	7 (2.7)	0	7 (1.9)	
Number of women with cART during pregnancy, n (%)	In the first trimester	182 (69.5)	65 (67.7)	247 (68.9)	<0.001 ^b
	Not from the first trimester	50 (19.1)	30 (31.3)	80 (22.3)	
	None	14 (5.3)	1 (1.0)	15 (4.2)	
	Missing data	2 (0.8)	0	2 (0.6)	
Antiretroviral drugs by class used during pregnancy, n (%)					0.010 ^b
3 rd drug PIs	Lopinavir/r	94 (35.9)	64 (66.7)	158 (44.1)	<0.001 ^b
	Saquinavir/r	23 (8.8)	7 (7.3)	30 (8.4)	
	Nelfinavir	12 (4.6)	0	12 (3.3)	
	Others	37 (14.1)	5 (5.2)	42 (11.7)	
	Total	166 (63.3)	64 (66.7)	158 (44.1)	
NNRTI	Efavirenz	2 (0.8)	0	2 (0.6)	
	Nevirapine	4 (1.5)	4 (4.1)	8 (2.2)	
	Etravirine	1 (0.4)	0	1 (0.3)	
	Total	7 (2.7)	4 (4.1)	11 (3.1)	
No treatment		82 (31.3)	16 (16.7)	98 (27.4)	
Missing data		7 (2.7)	0	7 (1.9)	
NRTI backbone, n (%)	Zidovudine+lamivudine	126 (48.1)	63 (65.6)	189 (52.8)	<0.001 ^b
	Abacavir+lamivudine	12 (4.6)	14 (14.6)	26 (7.3)	
	Others	26 (9.9)	3 (3.1)	29 (8.1)	
	None	91 (34.7)	16 (16.7)	107 (29.9)	
	Missing data	7 (2.7)	0	7 (1.9)	
Type of delivery, n (%)	Vaginal	97 (37.1)	18 (18.7)	115 (32.1)	<0.001
	Planned C section	121 (46.2)	74 (77.1)	195 (54.5)	
	Unplanned C section	16 (6.1)	3 (3.1)	19 (5.3)	
	Missing data	28 (10.6)	1 (1.1)	29 (8.1)	
Number of cART regimens before pregnancy, n (%)	0	127 (48.5)	9 (9.4)	136 (37.9)	<0.001 ^b
	1	35 (13.3)	32 (33.3)	67 (18.7)	
	2	40 (15.3)	20 (20.8)	60 (16.7)	
	3	28 (10.7)	17 (17.7)	45 (12.6)	
	More than 3	25 (9.5)	18 (18.7)	43 (12.1)	
	Missing data	7 (2.7)	0	7 (1.9)	

NRTI – non-nucleoside reverse-transcriptase inhibitors; NNRTI – non-nucleoside reverse-transcriptase inhibitors; PI – protease inhibitors; /r – ritonavir used to boost another protease inhibitor. ^aFisher's exact test. ^bPearson Chi-square test

^cStudent t test. cART = combination of at least 3 antiretroviral drugs

In order to identify the cause of vertical infection, we assessed the access to medical care during pregnancy for HIV-infected women in both centers. In the NIID group 40.5% (15/37) of the women who had HIV-positive children had been diagnosed before pregnancy, but only 3 had received cART. Another five women had been diagnosed in the last trimester of pregnancy, but they failed to access the PMTCT National Program. In IDHC none of the women who had HIV-positive children had received antiretroviral therapy during pregnancy.

The rate of premature birth in our studied patients was 22.4% cases (80/358), again with significant differences in the distribution of birth outcome between the two centers (Pearson Chi-square=5.1; $p=0.023$). Data about gestational age were missing in 8 (3.1%) cases from NIID.

The mean birth weight was similar in both centers, 2728 ± 581 g in NIID and 2656 ± 504 g in IDHC. In eight out of 358 cases (2.2%) the birth weight was over 3800 g, all in full term pregnancies.

The distribution of the newborns in four weight categories: normal, low, very low and extremely low birth weight was significantly different between the two centers (Pearson Chi-square=13.6, $p=0.008$), mainly due to the presence of very low and extremely low birth weight among babies followed-up in the NIID center (Table 1). Although we found a higher proportion of children with low birth weight in the IDHC center than in the NIID center, 31.3% vs. 19.1%, the difference was not statistically significant ($p=0.065$, OR 0.5, RR 0.59).

The mean age of pregnant women (table 2) was 23.2 years in both centers, lower than the mean age at birth in the general population in Romania, which is 26.2 years old for the first delivery and 27.9 years old for the second delivery.⁹

Moreover, we did not find differences in the mean age and range of ages between women with full term or premature delivery ($p=0.802$, 95% CI: -1.4-1.1) (Table 3). The moment of HIV diagnosis in studied women was similar in both centers. (Pearson Chi-square=6.3, $p=0.090$).

The rate of planned C sections was higher in the IDHC center (Pearson Chi-square=28.8,

$p<0.001$), while more than one third of the women in the NIID center had vaginal delivery.

The number of cART regimens used before pregnancy in studied patients was significantly different between the two centers (Pearson Chi-square=31.6, $p<0.001$). More than half of the women had not received treatment before pregnancy in NIID, while in IDHC more than one third had received at least 3 regimens before pregnancy (Table 2).

The time of treatment initiation and the type of antiretrovirals used were different between the two centers. In the IDHC group more patients received antiretroviral drugs during pregnancy: 83.3% vs. 68.6% in NIID group. In the IDHC group most of the pregnant women were treated from the first trimester of pregnancy (Pearson Chi-square=31.6, $p<0.001$).

The most frequent combination used in both centers was based on protease inhibitors, mainly boosted lopinavir and a fixed-dose combination of NRTI – zidovudine plus lamivudine. In the NIID group a larger array of protease inhibitors were used: nelfinavir, boosted lopinavir, boosted saquinavir (Table 2). In 37 (14.1%) cases in the NIID group other boosted protease inhibitors were used: fosamprenavir (12 cases), darunavir (11 cases), atazanavir (8 cases) and indinavir (6 cases). Efavirenz was not used during pregnancy in the IDHC group and was used in only 2 cases in the NIID group.

In the NIID group there was a significant association between certain maternal comorbidities and preterm birth (Table 4). Preterm birth was significantly associated with HCV coinfection of the mother and drug use during pregnancy ($p=0.037$; OR 2.9, RR 2.0 and $p=0.024$; OR 3.0; RR 2.1).

Discussion

In our study the overall premature birth rate was 22.4%, higher than the European average level of 10%.¹⁰ Similarly high prematurity rates among HIV-exposed children were found in an Italian and an US cohort, 22.6% and 18.6% respectively.^{11,12}

The prematurity rate was significantly higher among NIID patients in comparison with IDHC patients. The rate of HIV vertical transmission

Table 3. Age at birth in studied women by center and by birth outcome

Center	NIID			IDHC		
	Premature birth	Full term birth	Total	Premature birth	Full term birth	Total
Birth outcome						
Mean age, years	23.3	23.1	23.2	23.7	23.1	23.2
Standard deviation, years	5.0	4.5	4.7	6.5	0.5	2.0
Range of ages, years	16-38	17-41	16-41	21-37	18-39	18-39

Table 4. Maternal health conditions associated with HIV infection during pregnancy in the NIID center

Maternal health conditions associated with HIV infection during pregnancy	Preterm birth, n (%)	Full term birth, n (%)	p
HBV chronic infection	15/57 (26.3%)	41/189 (21.7%)	0.332 ^a
HCV chronic Infection	8/57 (14.1%)	10/189 (5.3%)	0.037 ^a
Syphilis	2/57 (3.5%)	15/189 (7.9%)	0.183 ^a
Illegal drugs use	9/57 (15.8%)	11/189 (5.8%)	0.024 ^a
Obstetrical complications	3/57 (5.3%)	1/189 (0.5%)	NA*

^a Fisher's exact test

*Not applicable due to the low number of cases of obstetrical complications

was higher also in the NIID cohort, concordant with the significant differences in rate and time of treatment initiation of therapy use among studied women. The differences can be partially attributed to a concentration of difficult cases in the NIID site, which is the National Reference Center for HIV Management.

In the NIID center the number of followed up cases is higher and the geographical area covered is larger in comparison with IDHC.

The lower rate of HIV vertical transmission and prematurity in IDHC suggests that patients attending this center can rapidly access the national PMTCT Program. This aspect points out the efficacy of a partnership established between the IDHC and a local non-governmental organization, the Baylor Black Sea Foundation, which provides continuous counseling and psychosocial support for HIV-infected women.¹³ Concurrently, the smaller size residential area coverage offers easier access to medical care centers and psychosocial support providers.¹⁴

There were significant differences between the two centers in terms of antiretroviral drugs used for PMTCT. In IDHC the most frequent PI used was lopinavir, and most of the therapy combinations contained PIs. Nevertheless, the

rate of premature birth was lower in this center. In NIID we found a higher variability in the antiretroviral combinations used. In this last group we found 2 cases of children exposed to efavirenz during pregnancy. Even though recent data shows that the incidence of neural tube defects is not as high as considered before, efavirenz should still be avoided, unless it was used in first trimester of pregnancy with good efficiency.¹⁵⁻¹⁷ While the Health and Human Services Guidelines¹⁸ allow the use of efavirenz, the European Guidelines recommend therapy switch in pregnant women using efavirenz.¹⁸

The higher number of regimens used in studied women before pregnancy in the IDHC group and the higher number of treated women in this group suggest that most of the patients from this center were part of the former Romanian pediatric cohort, while in the NIID center there were a higher number of women diagnosed during pregnancy, part of the new wave of HIV infection associated with intravenous drug use emerging in Romania in last five years.⁵

In the same time in the NIID cohort we found an association of premature birth and maternal illicit drug use and HCV coinfection. The association of prematurity with HCV

infection is supported by similar data reported in an Italian cohort,¹⁹ while the association of premature delivery and maternal opioids use has been reported by CDC in three Florida hospitals,²⁰ the main problem being the lack of maternal access to addiction counseling and treatment.

The upward trend in the number of cases registered during the study period suggests that a higher number of premature babies should be expected in the following years, as strategies to improve the medical care for HIV pregnant women and for their offspring have to be developed and implemented. It is worth mentioning that HIV testing in Romania is free of charge and mandatory in pregnant women.³

Birth outcome in HIV-exposed children is a multifactorial problem. Better prenatal care for HIV pregnant women could improve the birth outcome, lowering the rate of HIV vertical transmission and prematurity.

A prospective follow-up of HIV-exposed children through the Romanian HIV Pregnancy Registry will allow a better understanding of the risk factors for prematurity in children born to long-term multidrug treated HIV-positive women.

Our study's limitations included the design as a retrospective study, the lack of assessment of other risk factors associated with prematurity (tobacco and alcohol use, associated medication, social status in studied women), and the difference in sample size between the two sites.

Conclusion

In conclusion our study found a higher rate of premature birth and low birth weight in children born to HIV-infected women in comparison with the general population. Our assessment of differences between children and maternal characteristics in two Romanian AIDS Regional Centers showed differences in number of cases, moment of HIV treatment initiation and antiretroviral management in pregnant women.

Our findings support the need to improve medical care and psychosocial support for HIV pregnant women to ensure a better link to HIV care. More efficient strategies for early HIV

infection diagnosis in women, especially before pregnancy, will lower the risk of vertical and sexual HIV transmission.

Authors' contributions statement: AMT, MM, SR had substantial contribution to study conception and design, data collection, data analysis and interpretation. CP, RND, RU, SCC, DET, AMS had substantial contribution in patient monitoring, study design and data collection. CT contributed to analysis and interpretation of the data. DO contributed to laboratory diagnosis. AMT drafted the initial form of the manuscript. All authors read and approved the final manuscript.

Conflicts of interest: All authors – none to declare.

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