

ORIGINAL RESEARCH

Assessment of mother-to-child HIV prevention program in Albania

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Abstract

Aim: Mother-to-child transmission (MTCT) is one of the recognized routes of HIV transmission. This study aims to assess MCTC among HIV positive pregnant women in Albania.

Methods: This was a retrospective study that included a case series of 14 pregnant women in Albania diagnosed with HIV between 2014 and 2020 who were enrolled in HIV care ambulatory centre. The following variables were analysed: epidemiological characteristics (age, HIV diagnoses in regard to pregnancy), clinical characteristics such as use of antiretrovirals, adherence to treatment, CD4 cell count, viral loads, mode of delivery, gestational age at delivery) and the HIV status of the infant. Descriptive statistics were used to summarise the variables in the data sample.

Results: Eight women (57.2%) were aware of their HIV status prior to the pregnancy, while for the other 6 women (42.8%) an HIV diagnosis was done during the pregnancy as part of the antenatal testing. Only two women (14.28%) had a viral load of >1000 copies/ml before delivery. The mean time from diagnosis to initiation of antiretroviral therapy was 3.83 weeks \pm 2.4 SD (range 1-7 weeks). Adherence was calculated to be good, with 92.9% of women reporting taking the medication precisely as directed. No mother to child transmission cases were reported among the women in our cohort.

Conclusion: Gaps in prenatal screening for HIV and viral load measurements were identified in this study conducted in Albania. Thus, educating the providers, in this case the obstetricians, to offer first trimester HIV screening to all pregnant woman and to enhance testing, would reduce vertical transmission.

Keywords: Albania, HIV, mother-to-child transmission, prevention, screening.

Introduction

About 1.5 million women living with HIV become pregnant each year (1). Mother-to-child transmission (MTCT) is one of the routes of virus transmission and therefore protocols are constantly updated in this regard (2). Diminishing MTCT through treatment of pregnant women is key in achieving global health goals such as UNAIDS 90-90-90, as well as those that directly target the reduction of new paediatric infections (3,4).

Despite a steady rise of newly diagnosed HIV cases, Albania remains a low prevalence country (5). According to Institute of Public Health of Tirana, there were a cumulative total of 1402 HIV infections (23% female) reported until 2020. The main mode of reported transmission is heterosexual in more than 95% of the cases, with a cumulative total of 179 women diagnosed between 2014 till 2020 (out of 706 diagnosed in total) The National Institute of Health reports 37 documented cases of mother to child transmission since the beginning of epidemic in Albania.

The purpose of the study is to evaluate mother to child prevention (MTCP) effectiveness and pregnancy outcomes in Albania.

Methods

This is a retrospective, observational case-series study which aims to evaluate mother to child HIV prevention program in Albania. Fourteen HIV positive pregnant women, enrolled to care and followed at the HIV ambulatory center, University Hospital center of Tirana and University Obstetric Hospital in Tirana during the period 2014 to 2020 were included in the study. The HIV ambulatory center serves as the only specialized care center at a national level (5). During the same period, there were 7 newly diagnosed women following the HIV diagnoses of their new-borns, but these cases were considered as missed diagnosis during pregnancy and were not

included in the analysis. The following variables were analysed: epidemiological characteristics (age, parity, HIV diagnoses in regard to pregnancy), clinical characteristics such as use of antiretrovirals, adherence to treatment, CD4 cell count, viral loads, mode of delivery, gestational age at delivery) and new-born characteristics such as birth weight, neonatal morbidity and the use of postpartum prophylaxis.

New-borns exposed to HIV were managed accordingly by the paediatricians. In order to determine the HIV status of new-borns, HIV confirmatory antibody test was performed at 15-18 months of age.

Data was compiled in a secured database. The absolute numbers and their respective percentages were calculated to describe the category variables, while for continuous variables, the mean and standard deviation were calculated.

This study was approved by the Ethical Committee of the Medical University of Tirana.

Results

Between 2014 and 2020 there were a total of 14 HIV pregnant women which were followed at our center. The mean maternal age was 28.7 years \pm 5.8 SD (range 22-39 years) (Table1).

Table 2 shows that eight women (57.2%) were aware of their HIV status prior to the pregnancy, while for the other 6 women (42.8%) an HIV diagnosis was done during the pregnancy as part of the antenatal testing. Three patients (50%) were diagnosed during the first trimester. Two women (33.3%) were made aware of their HIV status during the second trimester and only one patient (16.7%) failed to know until the third trimester when she was diagnosed prior to delivery. The mean gestational age at diagnoses was 18.6 weeks \pm 9.4 SD (range 11-36 weeks).

Viral load testing was performed, at least once, for 13 out of 14 patients in our series (92.85%). Measurements, first at the time

of diagnoses and/or at the beginning of pregnancy, and then, repeated again before delivery were available for 8 patients (61.5%). These enabled the evaluation of antiretroviral treatment effects, by which

viral suppression was achieved in 7 out of 8 cases (87.5%). Two women (15.38%) reached delivery bearing a high viral burden. One of them was only diagnosed in the third trimester, prior to delivery.

Table 1. Baseline characteristics of cases

Baseline Characteristics	Descriptive statistics
Maternal age at HIV diagnoses (years)	28.7 ± 5.8*
Living in Tirana	
Yes	6 (42.8) †
No	8 (57.2)
Married	11 (78.6)
Not-married	3 (21.4)
Education level	
University or higher	2 (14.3)
High school or lower	5 (35.7)
Not declared	7 (50.0)
Working	
Yes	4 (28.6)
No	10 (71.4)
Serodiscordant couples	
Yes	5 (35.7)
No	7 (50.0)
Unknown	2 (14.3)
Reason for testing	
Pregnancy	6 (42.8)
Partner positive status	2 (14.3)
Symptomatic disease	3 (21.4)
Positive child from prior pregnancy	2 (14.3)
Other	1 (7.2)

* Mean and standard deviation.

† Absolute numbers and their respective column percentages.

The mean time from diagnoses to starting therapy was 3.83 weeks ± 2.4SD (range 1-7 weeks). Only 5 (62.5%) out of the 8 HIV+ women diagnosed prior to pregnancy were already receiving antiretroviral therapy. Of the 3 women who had not been receiving antiretroviral therapy, 2 manifested negative viral loads and the other had a CD4+ count of 889 cells. Nine patients (64.2%) started antiretroviral therapy during pregnancy (mean gestational age 21.6 ± 7.4 weeks, range 13-36 weeks of gestation), with the majority of

them (7 patients, 77.8%) only started taking the medication during the second trimester. By the moment of delivery, all the patients in our cohort were receiving antiretroviral therapy. Eight patients (57.1%) received a combination of two nucleoside reverse transcriptase inhibitors (NRTI) and one boosted protease inhibitor (PI) while 6 patients (42.9%) received a combination of two NRTI and one non-nucleoside reverse transcriptase inhibitor (NNRTI). Adherence was reported to be good, with 92.9% of women reporting that they took

the medication precisely as directed (Table 2).

Table 2. Clinical characteristics

Clinical Characteristics	N (%)*
Parity	
Nulliparous	4 (28.6)
Pluriparous	10 (71.4)
HIV status at entry into antenatal care	
Previously known HIV	8 (57.2)
Diagnosed during antenatal care	6 (42.8)
Gestational age at diagnoses	
1st trimester	3 (50.0)
2nd trimester	2 (33.3)
3rd trimester	1 (16.7)
On ART prior to pregnancy	
Yes	5 (35.7)
No	9 (64.3)
Gestational age at ART initiation	
1st trimester	1 (11.1)
2nd trimester	7 (77.8)
<20 weeks	2 (28.6)
20 - 28 weeks	5 (71.4)
3rd trimester	1 (11.1)
ART scheme used	
2 NRTI + PI	8 (57.1)
2 NRTI + NNRTI	6 (42.9)
Adherence to treatment	
Yes	13 (92.9)
No	1 (7.1)
Viral Load at beginning of pregnancy	
Undetectable	3 (21.4)
< 1000 copies	-
> 1000 copies	8 (57.1)
Undetermined	3 (21.4)
Viral Load during pregnancy/near delivery	
Undetectable	9 (64.3)
< 1000 copies	2 (14.3)
> 1000 copies	2 (14.3)
Undetermined	1 (7.1)
CD4+ counts during pregnancy	
> 500	8 (72.7)
500 - 350	-
200 - 350	3 (27.3)
< 200	-

*Absolute numbers and their respective percentages.

Delivery was mainly done by means of an elective caesarean section in 10 cases

(71.4%). Emergency caesarean section was performed on 2 patients (16.6%), indicated

by signs of foetal compromise (Table 3). 2 women (14.3%) delivered vaginally despite them being aware of their HIV status and the recommendation of c-section. One pluriparous patient showed at the maternity unit with advanced dilation, thus performing c-section was not possible, while the other case failed to attend the prenatal counselling and follow up sessions.

Premature delivery complicated only 14.2% (2 cases) of pregnancies of HIV positive women, though both were categorized as being late premature births. No other obstetrical complications were observed in our cohort. No mother to child transmission cases were reported among the women in our cohort (Table 3).

Table 3. Obstetrical characteristics

Obstetrical Characteristics	N (%)*
Mode of Delivery	
Vaginal Delivery	2 (14.3)
Cesarean Section	12 (85.7)
Elective C-Section	10 (83.3)
Emergency C-Section	2 (16.7)
Gestational age at delivery	
<37 weeks	2 (14.3)
> 37 weeks	12 (85.7)
Neonatal HIV status	
Positive	-
Negative	14 (100)

*Absolute numbers and their respective percentages.

Infants born to these women received prophylaxis with oral zidovudine for 6 weeks. Formula milk was given to all newborns, as breastfeeding was not encouraged.

Discussion

This is the first study assessing the PMTCT program in Albania. Between 2014 and 2020, there were no registered mother to child transmission among HIV diagnosed women who were followed during their pregnancy. This demonstrates the importance of the implementation of prophylactic measures that incorporates and follows international guidelines in the matter of reducing vertical transmission of HIV.

Mother to child transmission remains an important contributing factor in the spread of HIV (2).

Introduction of better care sees the increase of women of reproductive age infected with

HIV and the increase of pregnancies among HIV positive patients. The average age of women in our study is 28.3 years \pm 5.4 SD. Factors to blame for increased risk of mother to child transmission are advanced disease, late diagnoses, elevated viral load, route of delivery and low CD4 counts among others (6-9). Most of the above mentioned would be preventable if access to care and initiation of antiretrovirals was done early in the course of pregnancy (10,11). This highlights the necessity to offer and sustain care access to women (3). In high income countries transmission is reduced to 1-2% since 2000 while in low-and middle-income countries rate as low as 5% have been achieved. WHO 2015 recommendation of lifelong ART despite the CD4 counts (option B+) was adopted by 83% of low-and middle-income countries (12) contributing to better neonatal outcomes (13-16). This strategy was also incorporated in our country, offering

therapy to all patients, regardless of their CD 4 count.

There are no recent robust data on implementation of antenatal screening program in Albania.

Late initiation of ART is another factor that may increase vertical transmission. Studies demonstrate that duration of less than 15 days correlates with higher risk of transmission. French Perinatal Cohort found a 2.2% transmission rate among women who start therapy late in pregnancy as opposed to 0.2% in the entire cohort (18,19). Only one woman in our cohort was diagnosed late at term, thus preventing her to be exposed to ART for an adequate time. A national guideline on HIV testing of pregnant women is approved since 2015. Although the establishment of an antenatal screening program is feasible since most women attend at least one gynaecological/obstetrician appointment during the course of their pregnancy, the data from Institute of Public Health (IPH) shows a low rate of HIV testing among pregnant women, with only 1430 HIV tests offered in 10 months (28561 live births are reported during 2019 in Albania) (20). Based on the Demographic and Health Survey 2017-2018, only 11% of women aged 15-49 years who gave birth in the 2 years before the survey received counselling on HIV during antenatal care (ANC), and 9% were tested and received results either during an antenatal visit or during labour (21). IPH reports that between 2014 and 2020, there were 7 cases of vertical transmission diagnosed after birth, which shows the existing gaps in the HIV screening program in Albania. Strengthening of HIV screening of pregnant women program should be accompanied by a training program of medical staff to certify that testing and associated counselling are performed professionally.

Another barrier to overcome is the non-adherence to treatment, defined as missing more than one dose of medication per

month. Despite a multidisciplinary approach to managing pregnancies in HIV positive women, some of them fail to adhere to treatment as for fear of possible medication side effects on the foetus (22,23). A cluster randomized controlled trial in Mozambique (24) noted a 23% adherence. Adherence is measured according to the women reporting that they have taken the medication as prescribed when they show to pick up the monthly therapy at the HIV ambulatory clinic in Tirana, thus leaving this measurement up to subjectivity with lack of a proper objective test to quantify the adherence. Measuring drug concentrations in plasma is not performed in our settings. Only one woman resulted to be non-adherent, but despite this, her viral load remained undetectable prior to delivery.

Viral load monitoring is the gold standard in monitoring treatments efficacy and predicting possible MTCT (25). Levels of maternal viremia are found to be directly proportional to the risk of transmission (26,27). Monitoring is recommended to continue postpartum, as half of MTCT occur during breastfeeding (28).

Viral load values, also dictate the decision regarding mode of delivery. In the presence of undetectable HIV-ARN vaginal delivery is encouraged despite theories postulating the presence of viral concentration in vaginal fluids (29). American College of Obstetrics and Gynaecology recommends a scheduled pre-labour caesarean section at 38th week of gestation, in the presence of HIV RNA > 1000 copies/ml near delivery (30). This threshold is largely based on findings of the Women and Infants Transmission Study cohort in 1999, where no cases of transmission were reported among 57 women viral loads lesser than 1000 copies/ml (31).

Access to viral load testing is one of the barriers to achieving a better HIV care, especially evident among lower-and middle-income countries (25). Alongside a gap in the screening programs, there is also

an evident gap in the access for viral burden testing not only for the pregnant subjects, but for all HIV positive patients (5). Thus, the inability to recognize the near delivery viral load in most cases has conditioned the decision of doctors to recommend and perform caesarean section for all HIV positive pregnant women. Similarly, breastfeeding is not encouraged.

On one hand, caesarean section rates, a preferred mode of delivery among obstetricians, are on the rise in Albania, with UNICEF reporting a nationwide rate of 31%. This number was as high as 40.35% at Obstetrical University hospital in 2017 (32). On the other hand, caesarean section is requested by women, who feel safer if the baby is delivered surgically. Only 2 women in our study group delivered vaginally. The presence of active progressed labour in the first case made performing a c-section impossible. It was the lack of adherence to proper antenatal care that prevented the second women to be informed of the need of having a caesarean section.

In such cases the use of parenteral zidovudine (ZDV) as evidence implies, especially in women with high viral loads of >1,000 copies/mL, would have been necessary to further reduce risk of transmission. It is also recommended in women primarily diagnosed with HIV during labour and with unknown viral load status. The national PMTC protocol should be revised according to the international guidelines.

The French Perinatal Cohort of >11,000 pregnant women with HIV on ART (72% receiving triple ARV regimens) evaluated the role of intravenous zidovudine use. 95% received intravenous ZDV. In woman bearing high viral loads, MTCT was significantly higher in women where IV zidovudine was not applied (10.2%) as opposed to women receiving ZDV (2.5%, $p<0.01$) (18, 19, 33).

This protocol is not embraced by our obstetrical institutions, where this drug is

not readily available. Once, based on PACTG 076 study, monotherapy with intrapartum zidovudine was the gold-standard of care reducing MTCT from 25.5% to 8%, now combination antiretroviral therapy, or HAART took over as the most effective mean of prevention further reducing transmission to the above-mentioned rates published by WHO (14). WHO guidelines in 2018 recommend fixed dose combination of tenofovir with either emtricitabine or lamivudine and efavirenz (34). 4 women were treated accordingly in our study. Efavirenz, taken by these patients, was initially blamed for neural tube defects. Such correlation was ruled out by recent studies, which found no increased risk of such defects in women exposed to efavirenz (35-37).

Updated recommendations list dolutegavir as the first line therapeutic agent, even in women of child bearing potential (38). Shahin Lockman et al report that dolutegavir containing regimens show better virologic efficacy compared to efavirenz, emtricitabine and tenofovir disoproxil fumerate regimens as of the data received from IMPAACT 2010/VESTED multicenter, randomised controlled phase 3 trial (39). In our country, this drug, although used as a first line in the general HIV-positive population, has not yet been implemented in the schemes offered to pregnant women.

Regardless of advances made in managing HIV positive pregnant women to further reduce MTCT, controversy still exists when it comes to pregnancy related side effect such as preterm birth, low birth weight and small for gestational age. A meta-analysis of 11 studies describes a significantly higher risk among women who conceive while receiving antiretrovirals as opposed to women initiating therapy during pregnancy (40). There were only two late preterm births among our cohort of women, both of whom had initiated therapy during the second trimester of pregnancy.

Despite the introduction of a range of antiretrovirals, zidovudine remains the prophylactic drug of choice for the newborn since the Paediatric AIDS Clinical Trials Group Protocol 076 (ACTG 076) (10). It should be administered every 6 hours for at least 6 weeks starting 8 hours after delivery. Earlier initiation of prophylaxis reduces the chance of a HIV positive infant.

When it comes to defining the HIV status of an infant, we should bear in mind that maternal IgG cross the placenta and may false positively show up on the new-born blood samples thus we can only definitely rule out infection with a negative assay at 18 months of age. On the other hand, virologic tests may be more useful for an earlier definite diagnosis of HIV. Three consequent negative virologic tests (at birth, at one month and four months),

translate into a 95% chance that the newborn is not HIV infected (41).

One limitation of this study is the impossibility of multivariate analysis due to the limited number of cases. Thus, the data can only be interpreted in a crude way.

However, we can draw conclusions about the efficiency of the prevention program. Issues such as gaps in prenatal screening for HIV, viral load measurement paucity and unavailability of intrapartum zidovudine were identified.

In the context of these discussions, where the importance of early recognition of disease status was emphasized several times, we conclude the necessity to make HIV screening tests more accessible, while simultaneously educating the providers, in this case the obstetricians, to request HIV evaluation in the first trimester screening.

Conflicts of interest: None.

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