Pregnancy Outcome of HIV-Infected Women on Anti-Retroviral Therapy in a Treatment Centre in Port Harcourt, Nigeria: a retrospective analysis

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ABSTRACT

Introduction
There are conflicting reports of adverse pregnancy outcomes following the administration of antiretroviral treatment (ARVs) to HIV-positive pregnant women. The aim of this study was to assess the magnitude of adverse effects of antiretroviral drugs and to underscore their importance in limiting adverse pregnancy outcomes in newborns.

Methods
The study was a retrospective analysis of medical records of HIV-infected pregnant women who received anti-retroviral treatment at the University of Port Harcourt Teaching Hospital between January 2010 and December 2013. Data was analyzed using Epi Info Version 7 Statistical Package. Proportions, measures of centrality/dispersion as well as measures of association between maternal predictors and birth outcomes were computed. The level of significance was set at p≤ 0.05.

Results
A total of 290 medical records of women who received anti-retroviral treatment were examined: 68.3% women commenced antiretroviral treatment before pregnancy, 3.8% started in 2nd trimester of pregnancy and 14.1% during labour. Pregnancy outcomes were as follows: 90.7% were live births; 92.4% neonates had Apgar scores ≥7 and 90.7% had birth weights of ≥ 2,500 grams. More than half, 55.9% had haemoglobin levels ≥ 10g/dl, while 84.8% of them were born full term. There were only 9.3% stillbirths and 9.3% low birth weights respectively, and also 15.2% preterm births.

Conclusion
The prevalence of adverse pregnancy outcomes in the study was minimal and stresses the value of antiretroviral treatment in the prevention of adverse pregnancy outcomes in newborns. We therefore recommend its intensified utilization for maximum impact in reducing adverse pregnancy outcomes.

Key words: *HAART, HIV, PMTCT, pregnancy, Port Harcourt, Nigeria*

INTRODUCTION

The human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) have remained a disease of public health concern in most developing countries of the world. Globally, there are approximately 1.4 million pregnant women living with HIV in low- and middle-income countries, [1] while most children infected with HIV acquire it from their mothers during pregnancy, labour and delivery and during breastfeeding. [2] For HIV positive mothers, the tendency to have poor birth outcomes have been reported to increase approximately 7 times compared to non HIV-infected mothers. [3] Meanwhile, untreated maternal HIV-infection has also been reported to be associated with higher frequency of low birth weight and 5-minutes Apgar score of less than 7. [4]

HIV prevalence among pregnant women in Nigeria is 3.6%, [5] while a vertical transmission rate of 3.9% was reported in the south-east geo-political zone of Nigeria.[6] Rivers State is one of the 36 states of the Federation of Nigeria with the highest prevalence of HIV/AIDS, posting a prevalence rate of 15.2% among women attending prenatal clinics.[5] The World Health Organization (WHO) in 2009 projected that there was a 15 to 45 percent chance of HIV-infected pregnant women transmitting the virus to their children in resource-constrained settings as a result of limited access to anti-retroviral drugs (ARVs).[7] The poor Prevention of Mother-to-Child Transmission of HIV programme (PMTCT) coverage in Nigeria readily comes into focus as only about 4.7% of the prenatal care facilities offer PMTCT services.[2] Anti-retroviral drugs given during pregnancy, labour or post-partum improve maternal health and survival, and reduce the risk of vertical transmission of the virus (HIV).[8] Unfortunately, only 27% of pregnant women living with HIV infection (PWLHIV) in Nigeria received ARVs in 2011.[9] The problem has been repeatedly attributed to long standing health systems issues, such as staffing, service accessibility, community-level factors, such as stigma, fear of disclosure and lack of partner support.[10] All the same, with an increasing number of pregnant women worldwide benefiting from an expanding access to antiretroviral treatment, the WHO has called for the "virtual elimination" of paediatric HIV infection by countries targeting a mother-to-child HIV transmission (MTCT) risk of less than 5%.[11]

The adverse pregnancy outcomes reported in HIV-positive women include increased rates of spontaneous abortion, low birth weight babies, stillbirths, preterm delivery of less than 37 weeks gestation, low Apgar Score of less than 7 within 5 minutes, small-for-gestational age, neonatal deaths and birth defects.[12] HIV-positive pregnant women who received antiretroviral drugs were said to have had fewer of these adverse pregnancy outcomes when compared with HIV-positive pregnant women who did not.[4] While the beneficial effects of antiretroviral therapy on mother-to-child transmission are indisputable, monitoring antiretroviral therapy in pregnancy has remained a priority for achieving minimal adverse pregnancy outcomes. There are conflicting reports however, concerning adverse pregnancy outcomes following the administration of ARVs to HIV-positive pregnant women. Some studies have reported that the use of highly active anti-retroviral treatment (HAART) in itself might be associated with adverse pregnancy outcomes. For example, birth defects were reported to have occurred when *efavirenz*, a non-nucleoside reverse transcriptase inhibitor (NNRTI) was used as part of the regimen administered to HIV-positive pregnant women in early pregnancy. [13] Nevertheless, other researchers found no such relationships, but rather the opposite result that antiretroviral drugs reduced the risk of adverse birth outcomes. [4] Also, a more recent study also found no evidence of an increased risk of congenital abnormality of the central nervous system, such as neural tube defect with first trimester exposure to *efavirenz.* [14]

The aim of this study was therefore to assess the magnitude of adverse effects of antiretroviral drugs used for the prevention of mother-to-child transmission of HIV on birth outcomes at the University of Port Harcourt Teaching Hospital, and to determine the effects of some predictors which increase the risk of adverse birth outcomes. This is with a view to further underscore the public health importance of antiretroviral drugs in the prevention and control of the HIV epidemic in endemic resource-limited settings.

METHODS

Study Setting:

Rivers State is one of the 36 states of Nigeria with the highest prevalence rates of HIV/AIDS (15.2%) among women attending antenatal (ANC) clinics.[5] The University of Port Harcourt Teaching Hospital is an 840-bed capacity hospital that also serves as a treatment centre for HIV/AIDS patients in Rivers and other neighbouring states of Imo, Abia, Bayelsa, Akwa Ibom, and Delta states.

This study was conducted at the Maternity clinic of the Obstetrics and Gynaecology Department. The clinic runs a PMTCT Programme that first commenced in 2002. Before then, HIV-positive pregnant women were referred to the Anti-retroviral Clinic (ARV) clinic established in 1998 for antiretroviral treatment. The ARV and PMTCT clinics jointly monitor the patients for drug compliance and maternal/foetal welfare. At present, the hospital is being supported by an International non-governmental organization, Family Health International (FHI-360), under its SIDHAS Project (Strengthening integrated delivery of HIV/AIDS services).

Research Design and Population:

The study is a retrospective analysis of medical history and pregnancy outcome of HIV-infected pregnant women who received PMTCT services at the hospital between January 2010 and December 2013 and followed-up till delivery in the hospital.

Inclusion and Exclusion criteria:

All HIV-infected pregnant women who received PMTCT services from the hospital and who remained under care at the hospital until delivery were included, while all HIV-positive pregnant women who delivered without being registered for PMTCT services in the hospital were excluded.

Sample Size Determination:

A minimum sample size of the study (n) was determined using the formula: $n = z^2pq/d^2$. The computation was based on the study carried out at the University of Benin Teaching Hospital, Benin City, Nigeria, by Onakewhor, et al, [4] which compared the pregnancy outcome of HIV-positive pregnant women on antiretroviral treatment to that of HIV-positive pregnant women not on anti-retroviral therapy. In that study, preterm delivery of 25% was the highest birth outcome variable among women who did not receive anti-retroviral treatment, and thus informed the basis for the determination of the minimum sample size for the study.

n = required minimum sample size for the study; z = the z-score corresponding to 5% level of significance = 1.96; p = prevalence rate of preterm delivery at 0.25 (25%); q = 1 – p i.e. 1 – 0.25 = 0.75; d = 5% (precision); $n = 1.96^2 \times 0.25 \times 0.75 / (0.05)^2$ = Approx. 288 cases. Therefore a minimum of 288 cases was determined adequate for the validity of the study.

Sampling Technique:

A total of 16,493 pregnant women received care at the hospital during the period under review (between January 2010 and December 2013). Out of these, 492 were HIV-positive. Both the proportionate stratified and systematic sampling techniques were used to obtain the required sample for the study. Using the stratified sampling method proportionate to size, a breakdown of the number of records for each of the years under review was determined as shown in Table 1.

Table 1: Sampling Proportionate to size of HIV Cases

Year	Total No. of Patients seen	HIV Positive cases (N)	Proportionate Sample Size/yr (n)
2010	4506	107	63
2011	4824	131	77
2012	3968	125	73
2013	3195	129	75
Total	16,493	492	288

The systematic random sampling technique was then used to select the stipulated number of patient records from the total number of HIV positive records in each year from a randomly selected starting point. A sampling frame (x) was constructed for each year and the sampling interval (k), approximately 2, was determined by dividing the study population (N) by the sample size (n) i.e. k=N/n (value of column D/ value of column C). The sequential order of: $x + k$, $x + 2k$, $x + 3k$ and so on, was then applied to select the desired sample size for each year. That translated to selecting every alternate case record for each year. However, eligible case notes without the relevant data were rejected and the next with required data was selected.

Data Collection:
A structured data tool, in line with the objectives of the research was developed and pre-tested to ensure that it could retrieve all relevant information from the patients' records. It contained sections on socio-demographic profile of the women, neonatal and maternal characteristics. Each folder was identified using the hospital number. Parameters assessed were based on WHO/UNAIDS definition of adverse outcome reported in HIV-positive women.[12] Some of those included: histories of miscarriages, Apgar score, preterm deliveries, stillbirth, maternal mortality and antiretroviral toxicities.

Data Analysis:
All collected data were analyzed using the Epi Info Version 7 Statistical Package. Statistical calculations for proportions, measures of centrality/dispersion and measures of association between maternal predictors and birth outcomes such as odds ratio, tests of significance were computed. Results were presented using frequency tables. A p-value of ≤0.05 was considered statistically significant.

Ethical Considerations:
Ethical approvals for the study were granted by the Ethics and Research Review Board of the University of Port Harcourt, Port Harcourt, while approval to conduct the study was obtained from the University of Port Harcourt Teaching Hospital. All information in the patients' folders, including patient identification was treated with utmost confidentiality and all folders were returned to the Medical Records Department after extraction of vital information.

RESULTS

Socioeconomic/Demographic Profile:
A total of 290 HIV- positive pregnant women were recruited into the study. Those in the age bracket of 25 – 29 years constituted the majority, 119 (41.0%), while those in the age bracket 15-19

years were only two (0.7%). Their mean age was 29.54 ± 4.65. Of these, 263(90.7%) were married, while the rest were single. The majority of the women had secondary level of education, 38 (13.1%) and 175 (60.3%) were statutorily employed. The rest were either housewives or students. (Table 2)

Table 2: Socio-economic/demographic characteristics of pregnant women

Characteristics (n=290)	**Freq (%)**
Age	
15-19	2 (0.7)
20-24	31(10.7)
25-29	119 (41.0)
30-34	92 (31.7)
35-39	36 (12.4)
40-49	6 (2.1)
Marital Status	
Single	27(9.3)
Married	263(90.7)
Education Status	
None	2 (0.7)
Primary Education	38 (13.1)
Secondary Education	162 (55.9)
Post-Secondary	88 (30.3)
Employment Status	
Unemployed	22 (27.6)
Self-employed	125 (43.1)
Government employed	50 (17.3)
Student	35 (12.1)
Religion (n=284)	
Christianity	280 (98.6)
Muslim	4 (1.4)

Characteristics of the mothers:

The majority of the women, 287 (99.0%) were positive for both HIV 1 & 2, while only 3 (1.0%) tested positive for HIV 1 only. All 290 women had their CD4 counts evaluated: 187 (64.5%) had CD4 values more than 350 cells/mm^3, while only 34 (11.7%) had CD4 counts less than 200 cells/mm^3. Most of the women, 258 (89.0%) had normal systolic blood pressure values of less than 140 mm Hg, and 237 (81.7%) had normal diastolic pressure values of less than 90mmHg. Nearly all the ARVs used by the patients were Nucleotide Reverse Transcriptase Inhibitors (NRTIs). Only one patient (0.3%) received *efaverenz*, a non-nucleotide Reverse Transcriptase Inhibitors (NNRTI). Also, none of the antiretroviral drugs contained any Protease Inhibitors. Overall, 198 (68.3%) of the pregnant women commenced ART before pregnancy, while only 11 (3.8%) started ART in 2nd trimester of the pregnancy. A total of 263 (90.7%) of the deliveries were live births, while 27 (9.3%) were stillbirths. There were no records of maternal deaths within the immediate postpartum period before discharge. Details of maternal characteristics are in Table 3.

Table 3: Clinical Characteristics of Mothers

Characteristics	Freq (%)
Parity	
<3	248 (85.5)
≥3	42 (14.5)
HIV Type	
1	3 (1.0)
1&2	287 (99.0)
Systolic Blood Pressure level	
<140mmHg	258 (89.0)
≥140mmHg	32 (11.0)
Diastolic Blood Pressure level	
<90mmHg	237 (81.7)
≥90mmHg	53 (18.3)
CD4 count	
Less than200	34(11.7)
200-350	69 (23.8)
>350	187 (64.5)
Names of ART Used	
Efavirenz,tenofovir, lamivudine	1 (0.3)
Nevirapine, zidovudine, lamivudine	22 (7.6)
Zidovudine, Lamivudine, Nevirapine	267 (92.1)
Time of ART Commencement	
<14 weeks	35 (12.1)
≥14	11 (3.8)
At Labour	41(14.1)
During Lactation	4 (1.4)
Before Pregnancy	198 (68.3)
Type of Birth	
Singleton	283 (97.6)
Multiple	7 (2.4)
Mode of Delivery	
Elective Caeserean Section	84(30.0)
Emergency Caeserean Section	101 (34.9)
Spontaneous Vaginal Delivery	105 (36.2)
Delivery Outcome	
Live birth	263 (90.7)
Still birth	27 (9.3)
Survival status after delivery	
Alive	290 (100.0)
Dead	0 (0.0)

Characteristics of the newborns:

Regarding Apgar score ratings; 268 (92.4%) of the newborns had scores ≥7, while only 22 (7.6%) had Apgar scores less than 7 at 5 minutes after birth. On the prevalence of low birth weight (i.e. weight less than 2500grams): 263 (90.7%) had birth weights of ≥ 2,500 grams, while only 27 (9.3%) had low birth weights. Haemoglobin (Hb) levels of the neonates were as follows: 162 (55.9%) were above 10g/dl, while 128 (44.1%) had (Hb) levels less than 10g/dl. Preterm delivery (i.e. delivery in less than 37 weeks of pregnancy), occurred among 44 (15.2%) of the neonates, while the rest 246 (84.9%) were born full term (≥37 weeks), (Table 4).

Table 4: Birth Outcome of Neonates

Characteristics	Freq (%)
Apgar Score	
<7 at 5 min	22 (7.6)
≥7 at 5 min	268 (92.4)
Birth Weight	
<2500 grams	27 (9.3)
≥2500 grams	263 (90.7)
Haemoglobin Level	
<10g/dl	128 (44.2)
≥10g/dl	162 (55.9)
Preterm	
<37 weeks	44 (15.2)
≥ 37 weeks	246 (84.8)

The effects of some maternal predictors on birth outcomes:

There was no significant association between some maternal predictors which increase the risk of adverse birth outcomes and the actual result. The maternal CD4 cell count, haemoglobin level, HAART exposure and old age did not reveal any significant adverse association on the Apgar scores, birth weights, time of delivery and birth outcome *($p > 0.05$).* Similarly, there was no adverse association between the time of ART commencement and maternal CD4 cell count, Haemoglobin level of babies, and their birth weights. However, the timely commencement of ART, before pregnancy, improved the Apgar score of babies (Tables 5 & 6).

Table 5: The effects of maternal predictors on birth outcomes

Predictor	Birth outcomes		*Odds Ratio (OR)*	*P-value*	*95% Confidence Interval, (CI)*
Apgar Score	<7	>7			
CD4					
<350	1	34	0.41	0.389	0.02-4.20
≥350	4	56			
Haemoglobin Level					
<10g/dl	8	93	1.31	0.792	0.43-4.02
≥10g/dl	8	122			
HAART Exposure					
Before Pregnancy	7	133	0.596	0.596	0.16-6.73
During Pregnancy	2	35			
Old Age					
≥35 years	1	37	0.29	0.184	0.01-2.20
<35 years	17	184			
Birth Weight (gms)	<2500	≥2500			
CD4					
<350	1	36	0.41	0.386	0.02-4.16
≥350	4	59			
Haemoglobin Level					
<10g/dl	14	95	2.39	0.088	0.90-6.53
≥10g/dl	8	130			
HAART Exposure					
Before Pregnancy	16	134	0.103	0.103	0.58-9.20
During Pregnancy	1	37			
Old Age					
≥35 years	1	38	0.22	0.092	0.01-1.64
<35 years	23	196			

Table 6: The effects of maternal predictors on birth outcomes (cont.)

Predictor	Birth outcome		*Odds Ratio, (OR)*	*P-value*	*95% Confidence Interval, (CI)*
Pre-term de livery	<37 weeks	>37 weeks			
CD4:					
<350	3	29	0.72	0.473	0.14-3.48
≥350	7	49			
Haemoglobin Level:					
<10g/dl	16	76	1.61	0.312	0.69-3.74
≥10g/dl	14	107			
HAART Exposure					
Before pregnancy	18	118	2.21	0.237	0.45-14.64
During pregnancy	2	29			
Old Age:					
≥35 years	5	28	0.97	0.834	0.30-2.94
<35 years	29	158			
Still Birth	**Yes**	**No**			
CD4:					
<350	3	36	0.90	0.599	0.17-4.42
≥350	6	65			
Haemoglobin Level					
<10g/dl	9	108	1.05	0.889	0.38-2.84
≥10g/dl	11	138			
HAART Exposure					
≤14	0	25	0.00	0.242	0.00-5.67
≥14	25	7			
Old Age					
≥35 years	1	39	0.21	0.078	0.01-1.55
<35 years	26	217			

DISCUSSION

Pregnancy outcomes following antiretroviral treatment are commonly reported findings in scientific literature. This is because the HIV infection in pregnancy has become the most common complication of pregnancy in some developing countries and also a leading cause of maternal mortality in some populations in developing countries. [12] These adverse pregnancy outcomes include, but not limited to increased rates of spontaneous early abortion, low birth weight babies and stillbirths, preterm labour and preterm rupture of membranes. [12, 15, 16] However, the data from our study showed that the frequency of occurrence of these adverse birth outcomes was quite minimal. This might be attributed to the early commencement of treatment by most of the women and adequacy of monitoring during pregnancy as was postulated by Onakewhor and colleagues in

their study in Benin City[4]. There were neither recorded maternal deaths nor toxicities. The result was in conformity with those of Young et al, [17] in Uganda, which found no relationship between adverse pregnancy outcomes and HAART use. It also validates the findings of Onakewhor and colleagues in Benin City,[4] Nigeria, where untreated HIV mothers had more adverse obstetric and perinatal events than those who received HAART treatment. Our results thus support the argument that ART can be very useful in the prevention of adverse birth outcomes and the mother-to-child transmission of HIV, and hence stabilizing the epidemic in sub-Saharan Africa. However, we are conscious of the fact that ascertaining adverse outcomes based on the methodology of our study alone has some obvious limitations, since it was based on retrospective analysis of data. Other environmental and social factors might also have contributed to the observed results.

The maternal factors documented in our study included the maternal CD4 counts, maternal haemoglobin levels, HAART exposures, and old age. Chen et al, in 2012 had reported that maternal HIV was significantly associated with stillbirth (SB), preterm delivery (PTD), small-for-gestational age (SGA), and neonatal death (NND).[16] Similar adverse outcomes were also reported by Olagbuji and colleagues in Nigeria in 2010 in a case- control study.[18] However, none of these predictors showed any risk of relationship with pregnancy outcomes in our study. The noticeable decrease in adverse pregnancy outcome might be related to the early ART commencement and good adherence to treatment regimen by most of the HIV-positive women as was documented by by Onakewhor and colleagues[4]. This thus support the evidence that HIV-infected women who were initiated on antiretroviral therapy before their pregnancy, not only had significantly decreased risk of mortality, but also had better pregnancy outcomes compared with HIV-infected women who were not under any medication.[19, 4] Therefore, initiating HIV-positive women on antiretroviral therapy as early as possible should be considered a vital means of reducing the maternal mortality and other adverse maternal outcomes among them. To buttress this point further, a study by Baroncelli and colleagues in 2009 on trends in antiretroviral treatment in late pregnancy, observed an insignificant reduction in viral load and a reduction in HIV transmission rate of only below 2%, with no significant changes in preterm delivery, Apgar score, birth weight, and birth defects.[20]

The time of ART commencement against variables like CD4 count, Haemoglobin level, birth weight and Apgar score showed no significant negative association or outcomes; rather it showed that early commencement of ART was likely to improve the Apgar score of newborns at delivery. The finding supports the result obtained by von Linstow and colleagues in 2010 which showed that none of the women who received ART before week 22 of pregnancy in their study transmitted HIV to their children.[21]

Study Limitations:

The study was first, based on secondary data that were recorded without the objectives of the study in focus and therefore had some missing information. This was remedied by ensuring that only case notes with requisite data were included in the study. Second, the HIV status of children through early infant diagnosis (EID) could not be established because the facility was not available at the hospital during the period under review.

Conclusion:

The study underscores the significance of anti-retroviral treatment in the prevention of adverse pregnancy outcomes in newborns and recommends their intensified utilization for maximum impact in the reduction of adverse pregnancy outcomes in neonates.

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