Research Square

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A Cohort Study Of HIV Positive Pregnant Mothers On Antiretroviral Drugs (ARVs) In The Gambian Tertiary Hospital

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Abstract

Background

Aims: The use of HAART in pregnancy has shown remarkable improvement in immune status and have revolutionized the approach of care to people living with HIV. Some adverse pregnancy conditions have been reported which may depend on type of regimen, time and duration of use. The use of ARVs in pregnancy have been dynamic and transition from one regimen to the other have setting and country based variations. Therefore, knowing the impact of ARVs in pregnancy among PLHIV in our settings deserve evidence based information.

Methods

Pregnant women attending antenatal clinic at the hospital were prospectively recruited and followed up. HIV positive mothers were recruited irrespective of gestation age. At the time of delivery, obstetric and neonatal characteristics were entered into computer database. Mothers and their children were followed until 6 weeks postpartum. The data was analyzed with Epi-info version 7.1.5. Chi square at significant level of 0.05 and confidence level of 95% was used to determine significance.

Results

A total of 55 HIV positive mothers were in the study. The age range was between 18 to 45 years and parity was 0 to 8. The mean birth weight and gestation age at delivery was 2.92 kg (SD 0.556) and 36 weeks (SD 2.8 weeks) respectively. The absolute CD4 count of 350cells/mm3 and above (57.13%) was associated with low incidence of low birth weight. The mean glycaemic results were within normal range, 4.02–4.75 and 5.00-6.79 Mmol/l pre and post prandial respectively.

Conclusion

low birth weight was not associated with HAART in pregnancy and good immune condition was not associated any low birth weight. There was no association of protease inhibitors and gestational diabetes mellitus

Introduction

The use of HAART in pregnancy has shown remarkable improvement in immune status and reduction of MTCT of HIV infection [1] but some adverse pregnancy conditions have been seen in some studies [2, 3, 4]. These include preterm delivery, low birth weight and gestational diabetes. Although, some adverse effects on pregnancy outcome have been observed, the results from various studies are conflicting; which certainly depend on regimen, year at which the regimen was used, setting and country- hence their clinical significance is uncertain.

As the dynamic progressive changes in the use of ARVs and the evolution of HIV treatment regimen was not adapted at the same pace by various settings, country and practice. These variations in the literature and conflicts of research evidence may continue but a systematic robust evidence in the future may objectively resolve conflicts and issue statement on clinical significance.

However, in some studies the use of HAART may or may not have played a causative role. The European cohort studies had consistently demonstrated an increased risk of preterm delivery associated with HAART [3, 4, 5, 6] although this has been related to ARV regimen. In the study by Cotter et al [3] the preterm delivery was reported among those who had protease inhibitor (PI) in the ARV combination (HAART) and not in regimen without PI.

A South African study had inconclusive evidence regarding the association of preterm delivery and low birth weight to HAART [7]. A multicenter study conducted in Botswana [8] observed an increased risk of preterm delivery, small for gestation age (SGA) infants, Stillbirths, and neonatal deaths among pregnant women exposed to HAART.

Outside pregnancy, HAART regimens have been associated with a range of metabolic complications, including glucose intolerance, type-2 diabetes mellitus and dyslipidemia. However, in pregnancy, cohort studies investigating the association of HAART with gestational diabetes have yielded conflicting results [9].

The Gambia had transition from prophylactic use of ARV drug combination in 2011 where by the drugs were used from 14 weeks of gestation and discontinue after delivery which was named option A by WHO (10). But in 2015 during the time of this study ARVs was used for extended periods after delivery and during breastfeeding and subsequently for life. However, the transition of the ARV drugs regimen did not occur automatically as some patients continue in the older regimen and some in the new regimen of TDF/3TC/EFV- a single dose taking once a day.

Remarkably, those patients that had seropositivity for type 2 and dual infection (Type 1 and 2) continued in their primary regimen as evidence have shown (11) that sero status of HIV – 2 was insensitive to non-nucleotide reverse transcriptase inhibitors (e.g. EFV and NVP). Hence they continue on their ARV combination that has protease inhibitors (e.g LPVr). In view of these challenges since that time, scientific evidence and programmatic experience have accumulated on the use of dolutegravir (DTG) in both first- and second-line ART, including during pregnancy and tuberculosis co-treatment, and for children.

In 2018, these guidelines were reviewed to provide updated guidance on preferred option for these populations which now include dolutegravir (DTG) and raltegravir (RAL) (11). These new frontiers of ARVs were not in this study as country adaptation occur at varied pace, is a research interest of the future in our setting.

In view of the above explanation there was need to assess the impact of these diverge ARV combinations and regimen on different HIV strain sero- positivity among HIV positive pregnant mothers in our practice.

Methodology

Study location:

Edward Francis Small Teaching Hospital (EFSTH) is the only teaching hospital in the Gambia. It is located in Banjul and being the only teaching hospital in the country and serves as a referral center for divisional hospitals.

Study Design and population:

This was a prospective Cohort Study of HIV positive women, attending ANC at Edward Francis Small Teaching Hospital and the annexed clinic within greater Banjul.

Sample Size:

Prior data from a retrospective survey of pregnancy outcome among HIV Positive mothers in the Gambia between 2005 and 2011 suggests the rate of adverse outcomes of 0.1(10%) (12). Therefore, with p probability (power) 0.8 and Type I error probability associated with this test of null hypothesis placed at 0.05 using Power & Sample size (PS) calculation program 51 HIV positive subjects was needed for the study[13].

Inclusion and exclusion criteria: Pregnant mothers who tested HIV positive during pregnancy or before pregnancy that were currently pregnant and were receiving HAART either for their health or for PMTCT. Mothers who had pregnancy associated medical conditions or preexisting medical conditions such as Diabetes, Preeclampsia, Chronic hypertension and Sickle cell disease were excluded.

Procedure.

Awareness about this study was created among hospital staff at the antenatal clinic, labour ward, emergency obstetrics and gynaecology on call duty, outpatient clinics and infectious disease clinic at Edward Francis Small Teaching Hospital. Pregnant women attending antenatal clinic at the hospital between July to October 2015 were prospectively recruited and followed up. Recruitment continued until the sample size was achieved. This included those who had registered for antenatal care and those coming for the first time at any gestation age within the recruitment period. There was no upper limit of gestation age above which recruitment did not occur, however, the exclusion criteria were strictly applied.

Structured interviews were conducted at the first contact to collect information on demographic characteristics, clinical and obstetric history of each participant. The stage of HIV disease was classified in accordance with World Health Organization guidelines [14]. At recruitment, HIV positive mothers with preexisting diabetes mellitus or known risk factor for gestation diabetes mellitus (GDM) such as previous macrosomia, stillbirth at term or neonatal death, first degree family relatives with diabetes mellitus, obesity and previous structurally abnormal fetus were excluded from the cohort study. The screening modality was 75 g OGTT, a pre and post prandial glucose test was performed and documented. A

diagnosis of GDM was defined as a pre-prandial (fasting) glucose level of 7 mmol/l and above, and the 2hour result of 11.1 mmol/l and above [15].

Follow up

All participants were followed through pregnancy, delivery and up to six weeks postpartum. Their telephone numbers were confirmed at recruitment and they were called regularly for update and seen in case of any outcome of interest. Similarly, home address of the cohort was confirmed during the antenatal period and the consent covered phone calls and home visit when indicated. After delivery, HIV positive mothers were seen at the clinic on 2 occasions: at 2 weeks and at 6–8 weeks old. At 6–8 weeks of newborn life, dry blood sample (DBS) was collected for PCR-DNA tests.

Outcome measures: Adverse obstetric outcomes of interest were medically indicated and spontaneous preterm birth (defined as delivery before 37 weeks' gestation), gestational diabetes mellitus in relation to ARV regimen and maternal CD4 count in relation to birth weight. Adverse neonatal outcomes of interest includes low birth weight (birth weight < 2500 g) and MTCT rate.

Data analysis

Data tool for each mother was entered into a computer database. Consistent check was ensured to exclude data entering error. A univariate analysis was performed for factors indicated in the primary outcome measures, a test of significance was however, performed with Epi-info version 7.1.5.0. Chi square at significant level of 0.05 and confidence level of 95% was used to determine significance.

Ethical Considerations

A participant information sheet was used to ensure the provision of adequate information about the study. Informed consent was documented on a consent form and the data collection tools did not capture the participant's name. Those who refused consent were not denied access to quality care. Participants were aware of no monetary incentive attached to their participation. The approval of the study was given by Joint Gambia government and Medical Research Council (MRC) ethics and scientific committee.

Results

There were 55 HIV positive mothers identified during the period of recruitment of this study.

Table 1; **shows demographic characteristics of the study population**:

Table 1
shows demographic characteristics of the study population:

	HIV POSITIVE n (%)
Age (years)	
< 20	5 (9.1)
20–24	10 (18.2)
25–34	28 (50.9)
> 35	8 (14.5)
Unknown	4 (7.3)
Total	55
Parity	
0–1	14 (25.5)
2–4	17 (30.9)
.>4	18 (32.7)
Unknown	2
Total	55 (100)
Level of education	
primary	6 (10.9)
Secondary	10 (18.2)
Tertiary	2 (3.6)
None	20 (36.4)
Unknown	17 (30.9)
Total	55 (100)

Majority of the women studied were in the age range of 25 to 34 years (50–53%) and predominantly multiparous (62–67%). A few of them were grandmultiparous (≧ Para 4) and many of them had no formal education (62.5%).

Table 2; **HIV Sero-status**

Table 2
HIV sero status

HIV SEROSTATUS	HIV POSITIVE (n)	HIV Positive (%)
Type 1	47	85.5%
Type 2	1	1.8%
Dual (1 and 2)	5	9.1%
Not seen	2	3.6%
Total	55	100

Human immunodeficiency virus type 1 was the most common strain (85.5%) driving the epidemic.

Table 3; **Pregnancy outcome measure of HIV positive mothers**:

Table 3
Pregnancy outcome of HIV positive mothers regarding birth weight and preterm delivery

Gestation age at delivery (weeks)		N	Mean	Std	Std Error
< 37	**>=37**			Deviation	Mean
14 (29.2%)	34 (70.8%)	48	36.00	2.815	.542
Birth Weight in kg					
< 2.5	>=2.5	50			
10	40		2.915	.5566	.0891

Low birth weight (LBW) was defined as birth weight below 2.5 kg.

The mean birth weight in the HIV positive cohort was 2.915 kg (SD .5566). Preterm delivery defined as delivery before 37 completed weeks of gestation. The mean gestation age of 36 weeks (SD 2.8) was recorded among the HIV positive cohort.

Table 4; **described the effect of different HAART regimen on blood glucose level during pregnancy**

Table 4
described the effect of different HAART regimen on blood glucose level during pregnancy

ARV Regimen	N = number tested	Mean glycaemic level Pre-prandial (Mmol/l)	Mean glycaemic level 2 hrs Postprandial (Mmol/l)
AZT/3TC/NVP	21	4.30	5.45
AZT/3TC/LPV/r	3	4.40	5.03
TDF/3TC/NVP	1	4.20	5.50
AZT/3TC/ABC	19	4.50	5.579

The mean value for pre and post prandial glycaemia was recorded for each ARV regimen and no glucose intolerance or gestational diabetes (GDM) was observed. The mean value was reported because all glycaemic results were within normal range, 4.02–4.75 mmol/l and 5.00-6.79 mmol/l pre and post prandial respectively.

CD4 count of HIV positive patient was inversely related to low birth weight. The absolute CD4 count of 350cells/mm^3 and above (57.13%) was associated with low incidence of low birth weight. Those with CD4 count above 500 form majority of the study group and none had birth weight less than 2.5 kg.

Discussion

Majority of the women studied were in the age range of 26 to 35 years (53%) and predominantly multiparous (68.6%). The age range is similar to other studies conducted elsewhere [16, 17, 18] which may explain strong sociocultural similarities and the importance of child birth despite increasing maternal age. However, high parity among HIV positive mothers was a remarkable finding in this study. This is contributing to the body of evidence that HIV infection do not adversely affect fertility. A systematic review of the literature and meta-analysis by French et al [19] on the effect of pregnancy on survival in women infected with HIV concluded that fertility rate was not affected by HIV infection.

Human immunodeficiency virus type 1 is the most common strain (85.5%) driving the epidemic. In the Gambia dual infection of HIV 1 and 2 is increasing and in the cohort 5(9%) were dually infected. The treatment regimen following the guidelines [20] would require a protease inhibitor (PI) (LPV/r) in the ARV regimen. A study by Hitti et al [21] on Protease inhibitor-based antiretroviral therapy and glucose tolerance in pregnancy demonstrated association with preterm delivery and gestational diabetes. However, this Gambia study did not show association with preterm delivery and gestational diabetes with HIV infection irrespective of ARV regimen.

HIV infection was found in some literatures to be associated with low birth weight when compared with HIV negative mothers. A Rwanda study [22] which was prospective similar to our study but case-control concluded that birth weight was significantly lower in singleton babies of HIV infected asymptomatic women than in babies born to uninfected women. Although the difference in mean birth weight between

the two groups (HIV positive and negative) was only 120 g. In this our cohort study we discovered that the mean birth weight among HIV positive was 2.92 kg with a SD .5556

The result did show a mean gestation age at birth of 36 weeks (SD 2.8) among HIV positive cohort which was in disagreement with the South African study [7] that had inconclusive evidence regarding the association of preterm delivery and HAART as not all HIV positive mothers were on triple ARV drugs. But in our cohort all HIV patients were on ARVs of varied duration and different regimen.

The use of HAART of different regimen such as AZT/3TC/NVP, TDF/3TC//NVP, AZT/3TC/ABC and AZT/3TC/LPV/r was analyzed in relation to glucose intolerance or gestation diabetes mellitus. There was no association of gestational diabetes mellitus or glucose intolerance in HIV positive pregnant women irrespective regimen or strain of HIV virus. Although the number of patients on PIs was small but may not get bigger in the near future following current dispensation of ARVs in the treatment of HIV.

In this study those with CD4 count above 500 did not experience low birth weight infant (Fig. 1). This could be a reflection of good health as there is overwhelming evidence [3, 18, 19] that a planned pregnancy achieved at the optimum health where the CD4 is high and viral load undetectable the transmissions rate (MTCT) is reduced to < 1% if appropriate infant feeding counseling is ensured. Similarly, neonatal and infant outcome is comparable with those without HIV infection [23, 24, 25].

Study limitation

Duration of data collection, sample size and limited cofounders' such as duration on ARV may have implication on the results of the study. The viral load machine was out of service during the study period.

Conclusion

Asymptomatic HIV infection was not associated with low mean birth weight and maternal CD4 of 500 cm3/ml was not associated with low birth weight. Majority of the patients were multigravida, little or no formal education and high parity. HAART in pregnancy was neither associated with preterm delivery, glucose intolerance nor gestational diabetes mellitus, although the study population was small.

Abbreviations

ABC	Abacavir
ART	Antiretroviral therapy
ARV	Antiretroviral
AZT	Zudovidine
CD4	T4 lymphocytes

DTG	Dolutegravir
EFSTH	Edward Francis Small Teaching
EFV	Effeverinze
HAART	Highly active antiretroviral therapy
HIV	Human Immunodeficiency virus
LVP/r	Lopinavir/retinovir
MTCT.	Mother to child transmission of HIV
OGTT	Oral glucose tolerance test
RAL.	Raltegravir
3TC	Lamivudine
TDF	Tenofovir disoproxil
UTG	University of the Gambia
WHO	World health organization

Declarations

Authors' contributions

AM conceived the idea of the study and participated in its design. AM developed the data collecting tool and piloted it. AM supervised data entry into a dedicated database. AS analysed data. AM wrote the first draft of the manuscript. OR and EB reviewed all drafts of the manuscript and made corrections.. All authors read and approved the final manuscript.

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Disclosure of interests

The authors declare no conflicts of interest.

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Ethical Clearance

The Joint Gambia Government/MRC Ethics and scientific committee granted approval of this study. Reference no L2015.E06; SCC1361V2; June 29 2015.

Availability of data and materials

The datasets generated and/or analyzed during this study are available from the corresponding author on reasonable request. No personal or individual data in this manuscript or database.

Consent to publish

Not applicable.

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Figures

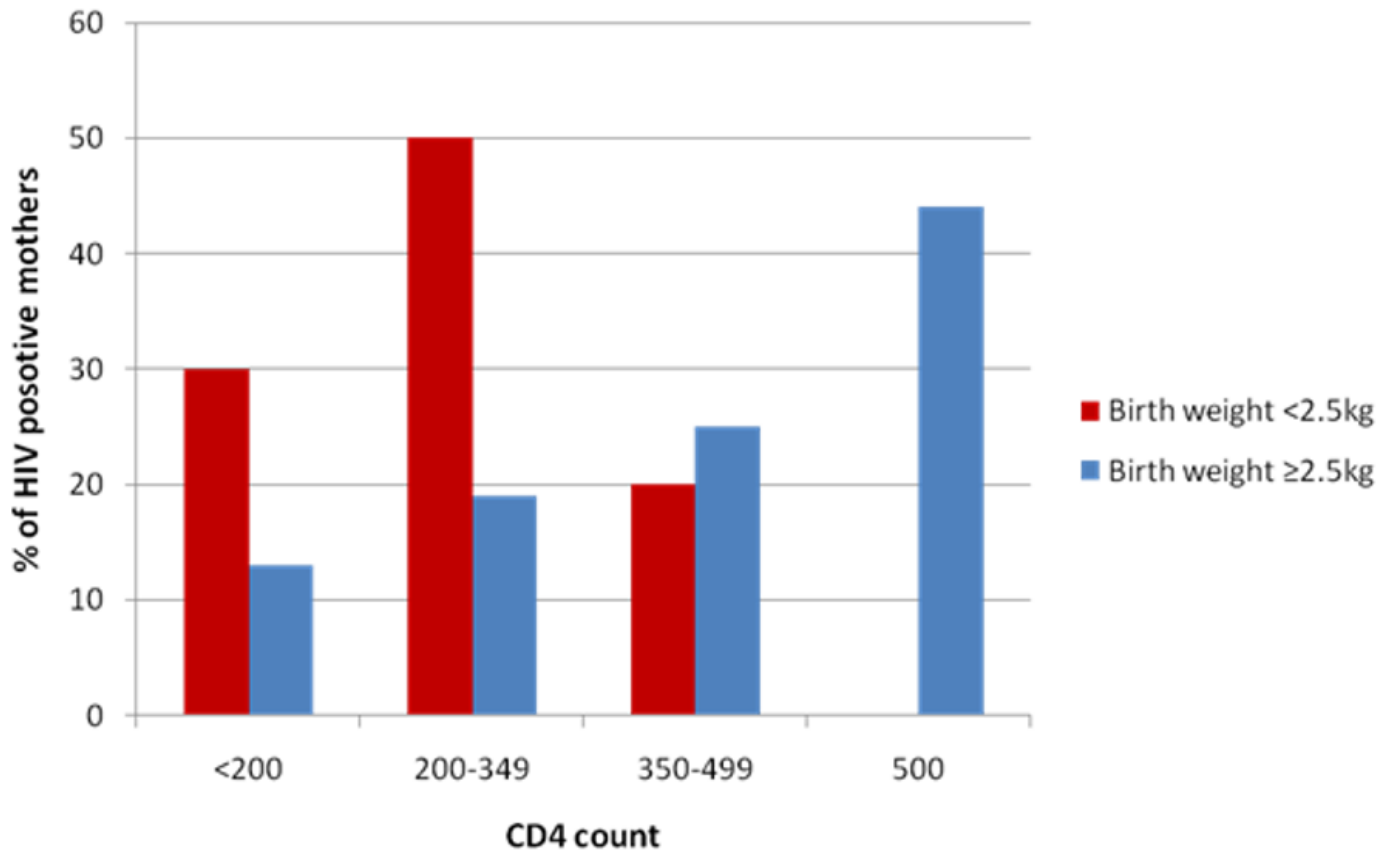


Figure 1

The relationship between CD4 count and low birth weight