ARAŞTIRMA/ORIGINAL ARTICLE

Gülhane Tıp Derg 2015;57: 152-159

doi: 10.5455/gulhane.155305

Maternal immunologic and clinical response to antiretroviral therapy initiation before or during pregnancy in HIV-1 infected women and associated factors in Southwest Ethiopia

Girma Mamo Ijigu, Desta Hiko Gemeda, Mulugeta Tarekegn Angamo

SUMMARY

The aim of this study is to assess maternal treatment outcomes to antiretroviral therapy initiated before or during pregnancy in HIV-1 infected women and associated factors in southwest Ethiopia. Hospital based retrospective cohort study was conducted from January 1st 2008 to December 31st 2012.The data were processed using SPSS version 16 (Chicago: SPSS Inc., 2007). A p-value of < 0.05 was considered statistically significant. Among the 202 study participants, 169(83.6%) and 142(70.3%) had good immunological and clinical outcomes respectively. In adjusted logistic regression analysis, unknown HIV status prior to pregnancy (AOR=0.158, 95% CI=(0.041–0.602), P=0.007), Baseline CD4 count < 200 (AOR = 0.023, 95%CI= (0.003–0.190), P=0.000), baseline WHO clinical stage III (AOR=7.673, 95%CI=1.640–35.892, P=0.010), Highly Active Antiretroviral Therapy initiation during pregnancy (AOR=0.349,95% CI=0.157–0.776,P=0.010) were identified as independent predictors of maternal treatment outcomes. In conclusion, Women who started Highly Active Antiretroviral Therapy before pregnancy had good clinical outcome compared to those who started during pregnancy. The independent predictors of maternal outcomes were HIV status prior to pregnancy, baseline CD4 count before initiation of Highly Active Antiretroviral Therapy, time of Highly Active Antiretroviral Therapy initiation, world health organization clinical stage before initiation of Highly Active Antiretroviral Therapy and duration of treatment with Highly Active Antiretroviral Therapy.

Key words: *Treatment outcomes, Antiretroviral Therapy, Pregnancy, Southwest Ethiopia*

*Department of pharmacy, College of Public Health and Medical Sciences, Jimma University
**Department of Epidemiology, College of Public Health and Medical Sciences, Jimma University

Ayrı Basım İsteği: Mulugeta Tarekegn Angamo
Department of Pharmacy,
College of Public Health and Medical Sciences,
Jimma University, Ethiopia
e-mail: mulugeta.tarekegn@ju.edu.et

Makalenin Geliş Tarihi: Mar 20, 2014 • **Kabul Tarihi:** Apr 11, 2014 • **Çevrim İçi Basım Tarihi:** 30 Haziran 2015

Introduction

The emergence of the HIV epidemic is one of the biggest public health challenges the world has ever seen in recent history. In 2011, there were 34 million people living with HIV. Among these, Sub-Saharan Africa accounts for 69% of all people living with HIV. Women account for 58% of people living with HIV in sub-Saharan Africa. In the same year, 2.5 million people became newly infected with HIV; among these 330,000 were children and 1.7 million people died from AIDS-related causes worldwide (1).

In Ethiopia, among women aged 15-49years, HIV prevalence is 1.9 % (2). According to the 2012 world AIDS day report, 790, 000 Ethiopians were living with HIV/AIDS, 13,000 children were newly HIV infected and there were 53,831 HIV related deaths in Ethiopia [1]. During 2011, a total of 10,302 HIV positive pregnant women received ARV prophylaxis for prevention of mother to child transmission (PMTCT). However, overall coverage of PMTCT still remains as low as 24% of the expected eligible population. Mother to child transmission (MTCT) of HIV was 17% at six weeks and 30% including breast feeding (3).

Treatment outcome of HIV infected individuals can be evaluated using virological, immunological or clinical criteria. The earliest indicator is virological followed by immunological treatment success or failure; usually clinical treatment failure becomes apparent much later (4)

The immunological and clinical outcomes to HAART among HIV infected pregnant women vary according to timing of HAART initiation (5). Longer duration antenatal ARV prophylaxis is more effective than shorter duration ARV prophylaxis. In research done in 10 European countries, the risk of mother-to-child transmission was lower among those who initiated HAART before pregnancy than among women who initiated HAART during pregnancy, 0.25% (1 of 397) vs. 1.92% (10 of 52) respectively. The 11 women who have transmitted HIV to their children had relatively advanced HIV disease, with a median maternal CD4 cell count of 209 cells/ mm3 (64–468 cells/ mm3) (6). In the study done in Johannesburg, South Africa, MTCT in women who started HAART before pregnancy was 0.7% (1 of 143) and 5.7% (42 of 730) in those who started HAART during pregnancy (7).

Combination regimens are more effective than single-drug regimens in reducing perinatal transmission. A study done in Abidjan, Cote d'Ivoire, reported a significantly lower transmission rate among infants with maternal HAART (2.3%) compared to single-dose nevirapine (16.1%) (8). In Kesho Bora study, maternal median CD4 cell counts were higher in the triple antiretroviral group than the zidovudine and single-dose nevirapine group. At enrollment, the CD4 cell counts were 336 cells/mm3 versus 339cells/ mm3, at delivery 463 /cellsmm3

versus 416 cells/ mm3, and at 6 months 479 cells/ mm3 versus 374 cells/ mm3 and 12 months 401cells/ mm3 versus 378 cells/ mm3) in the triple antiretroviral group and the zidovudine and single-dose nevirapine group respectively. The cumulative rate of HIV transmission at 6 weeks was 3.3% in the triple antiretroviral group compared with 5.0% in the zidovudine and single-dose nevirapine group (9).

Maternal plasma HIV RNA level is the best individual predictor of MTCT risk. Other risk factors include vaginal delivery, prolonged rupture of the membranes, prematurity, low CD4+ cell count, maternal symptomatic HIV disease, viral subtype, breastfeeding and host genetic factors (10).

Challenges and gaps against prevention of MTCT HIV infection include: drug resistance, drug safety, adverse effects associated with HAART, infant feeding of HIV-infected mothers, limited donor funding support, the fact that many women in resource limited settings deliver at home, many women may not seek antenatal services at health institutions, lack of male involvement in HIV testing, issues of disclosure by women of their HIV status that may prevent HIV-infected women from receiving appropriate antiretroviral interventions for both PMTCT and their own treatment and lack of comprehensive contraceptive services for HIV-infected women (11,12).

The CD4 cell count was significantly lower at delivery when HAART was initiated after week 14 of gestation than when it was initiated before week 14 (mean 420 cells/ mm3 vs. 484 cells/ mm3; P<0.05) in the study conducted in Denmark (13).

In the study done in Cape Town, South Africa, advanced immunodeficiency at presentation and duration of HAART before birth were significantly associated with transmission of HIV from infected pregnant mother to her infant. All of the mothers who gave birth to HIV-positive infants had less than 8 weeks' HAART prior to delivery. There were no HIV transmissions among women who received at least 8 weeks of therapy before delivery. The MTCT of HIV rate was 5.1% (11/217) for infants whose HIV status was known in mothers who had less than eight weeks HAART prior to delivery (14).

The risk of HIV transmission among persons with low CD4+ cell counts appears to be substantially higher than the risk among persons with higher CD4+ cell counts (15). In the study conducted in Cameroon, Yaoundé, duration of ARV regimens more than four weeks was very important for a better reduction of MTCT risk, through increase in CD4 counts. Mothers with CD4 counts below 350cells/ mm3 had a fourfold risk of MTCT of HIV (16).

In a pooled analysis of randomized trials from sub-Saharan Africa, children born to mothers in the advanced stages of HIV infection were at considerably higher risk of death when compared to those of mothers who were at a less advanced stage of the disease (irrespective of the child's HIV infection status), and this association was even stronger for uninfected children (17).

Mortality was estimated in sub-Saharan countries for HIV-infected children by timing of transmission; initial time was the estimated date of acquisition of HIV-infection. Overall, 12 months post-acquisition of infection, an estimated 52% of children with peripartum infection and 26% of those with postnatal infection died (18).

Advanced disease stage and low CD4 cell counts have been shown to be associated with a higher frequency of zidovudine resistance in the study done in Thailand (19). In research done in Tanzania, women carrying virus variants with zidovudine selected mutations at delivery displayed a 10 fold higher median viral load compared to women without zidovudine resistance mutation at delivery (p=0.021). Nevirapine resistance was 18% and lamivudine resistance was 8%. The overall HIV transmission rate in this study cohort of 50 mother infant pairs 4–6 weeks after delivery was 14.3% and thus unexpectedly high (20).

To enhance antiretroviral therapy initiation, antenatal care (ANC) and PMTCT have been integrated. HIV-infected women already receiving HAART are recommended to continue therapy. In addition, correction of risk factors (e.g. cigarette smoking),optimizing obstetric practice (e.g. limiting duration of membrane rupture, elective cesarean section), avoiding breast feeding and exclusive breast feeding are some among measures undertaken to improve immunological & clinical responses of HIV-infected mothers to prevent mother to child transmission (14,21,22)

In the study done in United kingdom and Ireland, among women on HAART, 24.1% started it before pregnancy, and the median gestational age at initiation for those starting in pregnancy was 25.9 weeks (interquartile range (IQR): 22.4–28.9 weeks)(23).

Thus, the main aim of this study was exploring the correlation of HAART initiation time and the treatment outcomes of mothers, and identifying factors affecting maternal treatment outcomes.

Method and Participants

The study was conducted at Jimma University specialized hospital (JUSH), which is one of the oldest public hospitals in the country. Geographically, it is located in Jimma city 352km southwest of Addis Ababa. It provides service for approximately 9000 inpatients and 80,000 outpatients a year coming to this hospital from the catchment population of about 15,000 million people (27).

In JUSH ART service was started in 2003 with fee. After two years, in 2005 antiretroviral therapy started to be dispensed freely. Now the enrolled number of HIV infected person in JUSH is 6841, among these 3828 are on HAART. PMTCT of HIV service was started in 2006. It was integrated with ANC in 2010. The study was conducted from March 3 /2012 to March 29/2012.

Hospital based general retrospective cohort was conducted among all HIV infected pregnant women who started HAART before and during pregnancy with regular follow up at JUSH from January 1st 2008 - December 31st 2012.

Women who started HAART before or during pregnancy and whose baseline and current CD4+ cell counts were known, baseline and current WHO clinical stages were known, having legible and complete record card were included in the study. However, HIV infected women without complete CD4+ cell counts of their follow up period, who were on non–HAART or OIs prophylaxis were excluded from the study.

The independent variables or factors that could affect the outcome variables include age of the women, HIV status prior to pregnancy, HAART initiation time, duration on HAART, Baseline CD4+ lymphocyte count, baseline WHO clinical stage, history of AIDS defining events, mode of delivery, number of pregnancy, while the dependent variables is maternal treatment outcomes which was categorized as good and poor as defined below in the operational definition.

Data were collected using data collection tool adapted from similar literatures and commented by experts. The data collection tool includes socio-demographic characteristics and clinical characteristics of the pregnant women. Data collection

was done by three BSc degree holder nurses.

To ensure data quality, training was given by principal investigator for data collectors and supervisor to have common understanding of the objectives of the study and data collection tool. Pre-test was done on ten HIV infected pregnant women record cards before the actual data collection. The result was not included in the main study; however, modification was made on the data collection tool accordingly. Anything which was unclear or ambiguous was corrected on the next day. Before data analysis, data cleaning was also performed in order to ensure the quality.

Data were then checked, entered, coded, and analyzed using SPSS for windows version 16.0 statistical software package (Chicago: SPSS Inc., 2007). For descriptive statistics, results were expressed in terms of percentages in tables and figures. Binary logistic regression analysis was performed to see the association between each factor with maternal clinical and immunological outcomes. Independent predictors of maternal treatment outcome were identified by using backward multivariate logistic regression analysis. A p-value of <0.05 was considered statistically significant.

The research proposal was approved by the Jimma University IRB. A formal letter for permission and support was written to the respective hospital administration and subsequently official permission was obtained from the responsible hospital administration. Patients' names were not written on the data collection tool for keeping the confidentiality of the information obtained. The patient record cards were returned back to the record office.

The investigators operationally defined the following terms for the current study purpose as:

Good Immunological outcome: change in CD4+ lymphocyte count from start date of HAART to delivery. If there is an increase in CD4+ lymphocyte count; it is termed as good immunological outcome. But, if there is a decrease or constant in CD4+ lymphocyte count; it is termed as poor immunological outcome.

Good clinical outcome: is considered when the baseline WHO clinical stage is changed from higher stages to the lower stage (e.g. from WHO clinical stage III to WHO clinical stage I). Unless and otherwise, if it remains on the first recorded WHO clinical stage or if the WHO clinical stage declines, that means if the baseline WHO clinical stage is changed from lower stages to the higher stage (e.g. from WHO clinical stage II to IV) it is categorized as poor clinical outcome.

Study participants were classified according to timing of first HAART initiation. Women will be classified as initiating HAART before or during first pregnancy while in care if they started first HAART ≥30 days before estimated date of conception (DOC), <30 days before DOC respectively. The 30-day window before date of conception was used due to uncertainty of the estimated date of conception as determined by last menstrual period (28-31). Women who started HAART during pregnancy was presumed to start HAART for prevention of mother-to-child HIV transmission (PMTCT) and not for maternal health if they had no previous opportunistic infections, had nadir CD4+ lymphocyte count >350 cells/mm3.

HAART was defined as regimens of ≥7 day's duration that contained two nucleoside reverse-transcriptase inhibitors (NRTI) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI), or a third NRTI. Non-HAART antiretroviral therapy (ART) included mono- or dual-NRTI therapy.

Maternal treatment outcome: it is assessed using maternal clinical outcome and maternal immunological outcome. Both maternal clinical and immunological outcome were grouped as good or poor.

Results

1. Factors affecting maternal immunological outcome

Among 202 pregnant women, 33 (16.3 %) had poor immunological outcome (Fig 1). The immunological outcome was associated with unknown HIV status prior to pregnancy (COR = 0.196, 95% CI= 0.057 – 0.672, P = 0.009), baseline WHO clinical stage III (COR=0.253, 95%CI = 0.065–0.989, P=0.048) and baseline CD4 lymphocyte count < 200 cells/ mm3 (COR = 0.024, 95% CI = 0.003 – 0.178, P = 0.001) in binary logistic regression analysis (Table I).

In adjusted multivariable logistic regression, unknown HIV status prior to pregnancy was 0.15 times less likely to have good immunological outcome compared to known HIV status prior to pregnancy (AOR = 0.158, 95% CI = (0.041 – 0.602), P = 0.007). CD4 count before HAART initiation < 200 cells/mm3 was 0.023 times less likely to have good immunological outcome compared to CD4 count ≥ 200 cells/mm3 (AOR = 0.023, 95% CI = (0.003 – 0.190), P = 0.000) (Table II).

2. Factors affecting maternal clinical outcome

Of 202 HIV positive pregnant women, 60 (29.7 %) had poor clinical outcome (Figure 2). In unadjusted logistic regression analysis, unknown HIV status prior to pregnancy (COR=3.350,

Table I: Binary logistic regression analysis of factors affecting maternal Immunological outcome at Jimma University Specialized Hospital, January 1st 2008 – December 31st 2012

Variables	Maternal immunological outcome		COR (95% CI)	P – value
	Good n(%), N= 169	Poor N(%), N=33		
Age				
15 – 19	4 (2.4)	1 (3.0)	0.964 (0.093 – 10.047)	0.557
20 – 24	64 (37.9)	15 (45.5)	0.904 (0.331 – 2.466)	0.976
25 – 29	74 (43.8)	10 (30.3)	0.521 (0.180 – 0.180)	0.844
≥ 30	27 (16.0)	7 (21.2)	1	
Marital status				
Single	27 (16.0)	6 (18.2)	1.111 (0.192 – 6.440)	0.709
Married	109 (64.5)	23 (69.7)	1.055 (0.217 – 5.140)	0.906
Divorced	23 (13.6)	2 (6.1)	0.435 (0.053 – 3.536)	0.947
Widowed	10 (5.9)	2 (6.1)	1	
Religion				
Muslim	57(33.7)	13 (39.4)	1.901 (0.497 – 7.262)	0.642
Orthodox	87 (51.5)	17 (51.5)	1.628 (0.441 – 6.008)	0.348
Protestant	25 (14.8)	3 (9.1)	1	
Educational status				
Illiterate	41 (24.3)	9 (27.3)	0.768 (0.136 – 4.330)	0.314
Primary	62 (36.7)	16 (48.5)	0.903 (0.171 – 4.773)	0.765
Secondary	59 (34.9)	6 (18.2)	0.356 (0.060 – 2.114)	0.905
Tertiary	7 (4.1)	2 (6.1)	1	
Occupational status				
Employed	54 (32.0)	13 (39.4)	1	
Unemployed	115 (68.0)	20 (60.6)	0.722 (0.335 – 1.559)	0.408
HIV status prior to pregnancy				
Known	112 (66.3)	30 (90.9)	1	
Unknown	57 (33.7)	3 (9.1)	0.196 (0.057 – 0.672)	0.009
WHO clinical stage before HAART initiation				
I	25 (14.8)	7 (21.2)	1	
II	55 (32.5)	21 (63.6)	2.322 (0.943 – 5.719)	0.067
III	62 (36.7)	3 (9.1)	0.253 (0.065 – 0.989.)	0.048
IV	27 (16.0)	2 (6.1)	0.362 (0.073 – 1.803)	0.215

Table I: Binary logistic regression analysis of factors affecting maternal … cont'd

WHO clinical stage after HAART initiation				
I	113 (66.9)	19 (57.6)	1	
II & III	56 (33.1)	14 (42.4)	0.673 (0.314 – 1.440)	0.347
CD4 count before HAART initiation				
≥ 200	73 (43.2)	32 (97.0)	1	
< 200	96 (56.8)	1 (3.0)	0.024 (0.003 – 0.178)	0.001
CD4 count after HAART initiation				
≥ 200	161 (95.3)	31 (93.9)	1	
< 200	8 (4.7)	2 (6.1)	1.298 (0.263 – 6.408)	0.749
Time of ART initiation				
Before pregnancy	100 (59.2)	15 (45.5)	1	
During pregnancy	69 (40.8)	18 (54.5)	1.739 (0.821 – 3.684)	0.149
HAART regimen started				
d4t/3TC/NVP	93 (55.0)	15 (45.5)	1	
AZT/3TC/NVP	25 (14.8)	4 (12.1)	0.992 (0.302 – 3.254)	0.989
TDF/3TC/EFV	23 (13.6)	8 (24.2)	2.157 (0.816 - 5.700)	0.121
d4t/3TC/EFV	28 (16.6)	6 (18.2)	1.329 (0.471 – 3.747)	0.591
HAART regimen changed				
No	72 (42.6)	17 (51.5)	1	
d4t/3TC/NVP	5(3.0)	2 (6.1)	1.694 (0.302 – 9.488)	0.549
d4t/3TC/EFV	22 (13.0)	5 (15.2)	0.963 (0.319 – 2.908)	0.946
AZT/3TC/NVP	24 (14.2)	3 (9.1)	0.529 (0.143 – 1.965)	0.342
TDF/3TC/NVP	46 (27.2)	6 (18.2)	0.522 (0.203 – 1.504)	0.246
History of ADE				
No	139 (82.2)	30 (90.9)	1	
Yes	30 (17.8)	3 (9.1)	0.463 (0.133 – 1.618)	0.228
Total duration of treatment				
≤ 6 months	66 (39.1)	16 (48.5)	2.030 (0.814 – 5.065)	0.368
7 – 12 months	12 (7.1)	4 (12.1)	2.792 (0.725 – 10.751)	0.129
13 – 18 months	10 (5.9)	2 (6.1)	1.745 (0.520 – 5.855)	0.136
> 18 months	81 (47.9)	11 (33.3)	1	
Mode of delivery				
SVD	156 (92.3)	31 (93.9)	1	
CS	13 (7.7)	2 (6.1)	0.774 (0.166 – 3.603)	0.744
Number of pregnancy				
One	159 (94.1)	32(97.0)	1	
Two	10 (5.9)	1 (3.0)	0.497 (0.061 – 4.019)	0.512

95% CI=1.759 – 6.379, P =0.000), WHO clinical stage III before HAART initiation (COR = 14.538, , 95% CI=3.293 – 64.192, P = 0.000), WHO clinical stage II & III after HAART initiation (COR=0.260, 95% CI = 0.138 – 0.490, P=0.001), WHO clinical stage III after HAART initiation (COR = 6.769, 95% CI = 1.173-39.066, P = 0.001), CD4 count < 200 cells/mm3 before HAART initiation (COR = 0.422, 95% CI= 0.225 – 0.793, P= 0.007), HAART initiation before pregnancy (COR = 6.331,

Table II: Multivariable logistic regression analysis of factors predicting maternal immunological outcome at Jimma University Specialized Hospital, January 1st 2008 – December 31st 2012

Variable	Maternal immunological outcome		AOR (95% CI)	P-value
	Good N(%), N=169	Poor N(%), N=33		
HIV status prior to pregnancy				
Known	112 (66.3)	30 (90.9)	1	
Unknown	57 (33.7)	3 (9.1)	0.158 (0.041 – 0.602)	0.007
CD4 count before HAART initiation				
≥ 200	73 (43.2)	32 (97.0)	1	
< 200	96 (56.8)	1 (3.0)	0.023 (0.003 – 0.190)	0.000

Table III: Binary logistic regression analysis of factors affecting maternal clinical outcome at Jimma University Specialized Hospital January 1st 2008 – December 31st 2012

Variables	Maternal clinical outcome: Good n (%), N=142	Poor N(%),N= 60	COR (95% CI)	P – value
Age				
15 – 19	4 (2.8)	1 (1.7)	0.523 (0.052 – 5.246)	0.875
20 – 24	54 (38.0)	25 (41.7)	0.968 (0.409 – 2.289)	0.581
25 – 29	61(43.0)	23 (38.3)	0.788 (0.332 – 1.870)	0.941
≥ 30	23 (16.2)	11 (18.3)	1	
Marital status				
Single	23 (16.2)	10 (16.7)	0.870 (0.212 – 3.566)	0.921
Married	92 (64.8)	40 (66.7)	0.870 (0.248 – 3.054)	0.846
Divorced	19 (13.4)	6 (10.0)	0.632 (0.139 – 2.862)	0.827
Widowed	8 (5.6)	4 (6.7)	1	
Religion				
Muslim	42 (29.6)	28 (46.7)	2.444 (.880 – 6.789)	0.065
Orthodox	78 (54.9)	26 (43.3)	1.222(0.447 – 3.342)	0.086
Protestant	22 (15.5)	6 (10.0)	1	
Educational status				
Illiterate	38 (26.8)	12 (20.0)	0.395 (0.091 – 1.710)	0.514
Primary	56 (39.4)	22 (36.7)	0.491 (0.121 – 2.000)	0.214
Secondary	43(30.3)	22 (36.7)	0.640 (0.156 – 2.624)	0.321
Tertiary	5 (3.5)	4 (6.7)	1	
Occupational status				
Employed	46 (32.4)	21 (35.0)	1	
Unemployed	96 (67.6)	39 (65.0)	0.890 (0.471 – 1.682)	0.719
HIV status prior to pregnancy				
Known	111 (78.2)	31 (51.7)	1	
Unknown	31 (21.8)	29 (48.3)	3.350 (1.759 – 6.379)	0.000
WHO clinical stage before HAART initiation				
I & II	52(36.6)	56 (93.3)	1	
III	63(44.4)	2 (3.3)	14.538 (3.293 – 64.192)	0.000
IV	27(19.0)	2 (3.3)	0.429 (0.005 – 0.101)	0.409

Table III: Binary logistic regression analysis of factors affecting maternal … cont'd

WHO clinical stage after HAART initiation				
I	106 (74.6)	26 (43.3)	1	
II & III	36 (23.9)	34(50.0)	0.260 (0.138 – 0.490)	0.001
CD4 count before HAART initiation				
≥ 200	65 (45.8)	40 (66.7)	1	
< 200	77 (54.2)	20 (33.3)	0.422 (0.225 – 0.793)	0.007
CD4 count after HAART initiation				
≥ 200	137 (96.5)	55 (91.7)	1	
< 200	5 (3.5)	5 (8.3)	2.491 (0.694 - 8.945)	0.162
Time of ART initiation				
Before pregnancy	99 (69.0)	16 (26.7)	1	
During pregnancy	43 (31.0)	44 (73.3)	6.331 (3.224 – 12.434)	0.000
HAART regimen started				
d4t/3TC/NVP	75 (52.8)	33 (55.0)	1	
AZT/3TC/NVP	21 (14.8)	8 (13.3)	0.816 (0.348 – 2.154)	0..757
TDF/3TC/EFV	24 (16.9)	7 (11.7)	0.663 (0.260 – 1.691)	0.389
d4t/3TC/EFV	22 (15.5)	12(20.0)	1.240 (0.549 – 2.797)	0.605
HAART regimen changed				
No	54 (38.0)	35 (58.3)	1	1
d4t/3TC/NVP	5 (3.5)	2 (3.3)	0.067 (0.113 – 3.358)	0.577
d4t/3TC/EFV	22(15.5)	5 (8.3)	0.351 (0.121 -1.012)	0.053
AZT/3TC/NVP	20 (14.1)	7 (11.7)	0.540 (0.207 – 1.410)	0.208
TDF/3TC/NVP	34 (23.9)	10 (16.7)	0.454 (0.199 – 1.034)	0.060
TDF/3TC/EFV	7 (4.9)	1 91.7)	0.220 (0.026 – 1.870)	0.166
History of ADE				
No	114 (80.3)	55 (91.7)	1	
Yes	28 (19.7)	5 (8.3)	0.370 (0.136 – 1.011)	0.052

Table III: Binary logistic regression analysis of factors affecting maternal … cont'd

Duration of treatment with HAART				
≤ 6 months	40 (28.2)	42 (70.0)	7.700 (3.391 – 17.484)	0.000
7 – 12 months	13 (9.2)	3 (5.0)	1.692 (0.403 – 7.112)	0.000
13 – 18 months	23 (16.2)	6 (10.0)	1.913 (0.614 – 5.962)	0.473
> 18 months	66(46.5)	9(15.0)	1	
Mode of delivery				
SVD	131 (92.3)	56 (96.7)	1	
CS	11 (7.7)	4 (6.7)	0.851 (0.260 – 2.786)	0.789
Number of pregnancy				
One	135 (95.1)	56(93.3)	1	
Two	7 (4.9)	4 (6.7)	1.378 (0.388 – 4.892)	0.620

Table IV: Multivariable logistic regression analysis of factors predicting maternal clinical outcome at Jimma University Specialized Hospital, January 1st 2008 – December 31st 2012

Variables	Maternal clinical outcome		AOR (95% CI)	P-value
	Good n(%), N=142	Poor n(%), N=60		
WHO clinical stage before HAART initiation				
I & II	52(36.6)	56 (93.3)	1	
III	63(44.4)	2 (3.3)	7.673(1.640 – 35.892)	0.010
IV	27(19.0)	2 (3.3)	0.247 (0.031 – 1.953)	0.185
Time of ART initiation				
Before pregnancy	99 (69.0)	16 (26.7)	1	
During pregnancy	43 (31.0)	44 (73.3)	0.349 (0.157 – 0.776)	0.010
Duration of treatment with HAART				
≤ 6 months	40 (28.2)	42 (70.0)	0.321(0.061 -1.697	0.181
7 – 12 months	13 (9.2)	3 (5.0)	0.352(0.098 – 1.266)	0.110
13 – 18 months	23 (16.2)	6 (10.0)	0.193(0.056 – 0.669)	0.010
> 18 months	66(46.5)	9(15.0)	1	

95% CI =3.224 –12.434, P=0.000), duration of treatment ≤ 6 months (COR = 7.700, 95% CI = 3.391–17.484, P = 0.000) and duration of treatment 7–12 months (COR = 1.692, 955 CI=0.403–7.112, P = 0.000) showed association with maternal clinical outcome (Table III).

In adjusted logistic regression analysis, WHO clinical stage III before HAART initiation was 7.673 times more likely to have poor clinical outcome compared to WHO clinical stage I before HAART initiation (AOR = 7.673, 95 % CI = 1.640 – 35.892, P= 0.010). HAART initiated during pregnancy was 0.349 less likely to have good clinical outcome compared to HAART initiated before pregnancy (AOR = 0.349, 95% CI = 0.157 – 0.776, P= 0.010).Duration of treatment with HAART between 13-18 months was 0.193 less likely to have good clinical outcome compared to the duration of treatment >18 months (AOR=0.193, 95% CI =0.056 – 0.669, P= 0.010) (Table IV).

Discussions

In the current study, WHO clinical stages before HAART initiation accounts 108 (53.5%) for stage I & II, 65 (32.2%) for stage III and 29 (14.45%) for stage IV. This finding is comparable with the study done in Cape Town, South Africa in 2010 G.C., baseline WHO clinical stage III which accounts 78 (34%) but different with baseline WHO clinical stage I and II that account 179 (79%) and WHO clinical stage IV which accounts 8 (3%). The possible reason can be difference in time of visiting health institutions, which in turn is influenced by fear of stigma and discrimination (14).

The median CD4 count before HAART initiation in the current study, 210 cells/ mm3, was greater than the one reported from Johannesburg, South Africa, which was 160 cells/ mm3 and Cape Town, South Africa, which was 134 cells/ mm3. The possible reasons for these differences can be, in Johannes-

burg, most of the pregnant women had baseline CD4 count <200 (76 %) and in Cape Town, between the range of 84 and 168. But, in Cameroon, Yaoundé, the median baseline CD4 (368 cells/ mm3) was greater than the current study finding. The possible reason might be the IQR, which was between 310–450cells/mm3 that is greater than the IQR 111.75 – 324.75 of the current study (7, 14, 16).

Unknown HIV status prior to pregnancy which accounts 60 (29.7%) is less than the study done in Angola, 55 (52.9%) in 2012. The possible reason can be difference in the sample size. In this study, 87 (43.6%) pregnant women started HAART during pregnancy but majority of women (85.2%) started HAART during pregnancy in Johannesburg, South Africa. The possible reason for the difference can be most of the study participant in Johannesburg (76 %), South Africa had CD4 count less than 200 cells/mm3 before initiation of HAART. The time at which HAART initiated in Denmark was 77.4% and 22.6% before and during pregnancy respectively. The difference can be due to prior pregnancy HIV status screening behavior in Denmark. Pregnant women who delivered their birth through CS account 11(7.4%) which is comparable with the study done in Cameroon, Yaoundé, 36 (8.6%). The mean duration of treatment in those who initiated HAART during pregnancy was 4.07 months and 32.03 months for those who initiated HAART before pregnancy. This is greater than 10.7 weeks and 93.4 weeks of total HAART duration during and before pregnancy respectively, in Johannesburg, South Africa. The possible reason for this difference can be time of first visit of health institution, specifically ANC clinic (7, 16, 24).

In this study, unknown HIV status prior to pregnancy had association (P = 0.009) with maternal immunological outcome. It was also independent predictors of immunological outcome (AOR = 0.158, 95% CI = 0.041 – 0.546, P = 0.007). This finding was not similar with the study done in Nashville, Tennessee, in 2009(5). The possible reason can be, HIV status prior to pregnancy was not assessed in the study done in Nashville, Tennessee. Knowing HIV status can have an impact on effective HAART utilization, which results in increasing survival, better support for childbearing provided to HIV-infected women and early identification and testing, women at high risk of infection.

HIV status prior to pregnancy, WHO clinical stage before HAART initiation, CD4 lymphocyte count before HAART initiation, HAART initiation before pregnancy and duration of treatment with HAART were associated with maternal clinical outcome in binary logistic regression analysis ($p < 0.05$). However, from the above variables, independent predictors of clinical treatment outcome were time of HAART initiation, WHO clinical stage before HAART initiation and duration of treatment with HAART. From this we can understand that women who started HAART before pregnancy, those at lower WHO clinical stage (like I and II) and those who have been on HAART for longer period of time showed good clinical outcomes, which could be explained by absence of opportunistic infection or clinical improvement.

HAART initiation during pregnancy is 0.349 less likely to have good clinical outcome compared to HAART initiation before pregnancy (AOR = 0.349, 95% CI = (0.157 – 0.776), P= 0.010). Time of HAART initiation has impact in mother to child transmission of HIV. Different studies from South Africa, United Kingdom and Europe have showed similar reports as risk of MTCT of HIV increases markedly in those women who started HAART during pregnancy compared to those who started before pregnancy. Even though, it was not the objective of this study, there was MTCT of HIV in women who started HAART during pregnancy (2.3%) while no MTCT of HIV from those who initiated their HAART before pregnancy. The total treatment duration with HAART was one month in those women who transmitted HIV to their infants. The possible reason could be due to an increased risk of intra-uterus transmission before initiation of treatment. Of course, timing of HAART is not the only factor exhibiting MTCT of HIV (6, 7, 24).

WHO clinical stage III before HAART initiation was 7.673 times more likely to have poor clinical outcomes compared to WHO clinical stage I (AOR = 7.673, 95 % CI = 1.640 – 35.892, P= 0.010). Women who were with one or more opportunistic infection were less likely to achieve expected treatment outcome. The duration of treatment with HAART between 13-18 months was 0.193 less likely to have good clinical outcome compared to the duration of treatment with HAART >18 months (AOR = 0.193, 95% CI =0.056 – 0.669, P= 0.010). The longer the women on HAART, the better the clinical outcome. However, the independent predictors of maternal clinical outcome were different from the study done in Nashville, Tennessee (5). The possible reason can be difference in sample size, initial WHO stage during HAART initiation and treatment duration with HAART.

Even though effort has been made to achieve the objectives of this study, there were certain limitations like low sample size, lack of information about patients' adherence because of the nature of the study design, lack of maternal viral load result and lack of actual economic status of the women, poor documentations of the women follow up profile and being retrospective study.

In conclusion, Women who started HAART before pregnancy had good clinical outcome compared to those who started during pregnancy. The independent predictors of maternal immunological outcome were HIV status prior to pregnancy and CD4 count before initiation of HAART. The independent predictors of maternal clinical outcome were time of ART initiation, WHO clinical stage before initiation of HAART and duration of treatment with HAART. Women in the reproductive age group should be encouraged to know their HIV status before pregnancy and should be encouraged to start HAART early if they fulfill the eligibility criteria.

Competing interests: The authors declare that they have no competing interests.

Acknowledgments

Authors would like to extend appreciations to individuals who permitted their records for data collection without any reservation.

References

1. UNAIDS Report on the global AIDS epidemic | 2012. Available at:www.unaids.org (Accessed on: Nov 28/2012)
2. Central Statistical Agency Addis Ababa, Ethiopia, Ethiopia Demographic and Health Survey 2011, 2012: 234. Available at: www.csa.gov.et (Accessed on: Nov 28/2012)
3. FHAPCO. Country Progress Report on HIV/AIDS Response, Federal Democratic Republic of Ethiopia.2012: 30-31. Available at: www.unaids.org (Accessed on: Nov 28/2012)
4. Niehues T, Lyall H. Antiretroviral Therapy in Children. In: Hoffmann C., Rockstroh JK & Kamps BS. 15th eds. HIV Medicine, Paris, flying publisher, 2006; 369-86.
5. Melekhin VV, Shepherd BE, Stinnette SE, Rebeiro PF,

Barkanic G, Raffanti SP, et al.Antiretroviral therapy initiation before, during, or after pregnancy in HIV-1-infected women: maternal virologic, immunologic, and clinical response. PLoS ONE. 2009;4(9):e6961

6. Thorne C., Patel D., Fiore S., Peckham C., and Newell ML Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. Clin Infect Dis. 2005 ;40(3):458-65.
7. Hoffman RM, Black V, Technau K, van der Merwe KJ, Currier J, Coovadia A, et al. Effects of highly active antiretroviral therapy duration and regimen on risk for mother-to-child transmission of HIV in Johannesburg, South Africa. J Acquir Immune Defic Syndr. 2010 ;54(1):35-41.
8. Ekouevi DK, Coffie PA, Becquet R, Tonwe-Gold B, Horo A, Thiebaut R, et al. Antiretroviral therapy in pregnant women with advanced HIV disease and pregnancy outcomes in Abidjan, Cote d'Ivoire. AIDS. 2008 ;22(14):1815-20.
9. De Vincenzi I. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. Lancet Infect Dis. 2011;11(3):171-80.
10. Thorne C, Newell ML. Hiv. Semin Fetal Neonatal Med. 2007;12(3):174-81.
11. Newell ML. Prevention of mother-to-child transmission of HIV: challenges for the current decade. Bull World Health Organ. 2001;79(12):1138-44.
12. Fowler MG, Lampe MA, Jamieson DJ, Kourtis AP, Rogers MF. Reducing the risk of mother-to-child human immunodeficiency virus transmission: past successes, current progress and challenges, and future directions. Am J Obstet Gynecol. 2007;197(3 Suppl):S3-9.
13. Von Linstow ML, Rosenfeldt V, Lebech AM, Storgaard M, Hornstrup T, Katzenstein TL, et al. Prevention of mother-to-child transmission of HIV in Denmark, 1994-2008. HIV Med. 2010;11(7):448-56.
14. Fitzgerald FC, Bekker LG, Kaplan R, Myer L, Lawn SD, Wood R. Mother-to-child transmission of HIV in a community-based antiretroviral clinic in South Africa. S Afr Med J. 2010;100(12):827-31.
15. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011 ;365(6):493-505.
16. Tchendjou P, Same-Ekobo C, Nga A, Tejiokem M, Kfutwah A, Nlend AN, et al. Effectiveness of multidrug antiretroviral regimens to prevent mother-to-child transmission of HIV-1 in routine public health services in Cameroon. PLoS ONE. 2010;5(4):e10411.
17. Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet. 2004;364(9441):1236-43.
18. Becquet R, Marston M, Dabis F, Moulton LH, Gray G, Coovadia HM, et al. Children who acquire HIV infection perinatally are at higher risk of early death than those acquiring infection through breastmilk: a meta-analysis. PLoS ONE. 2012;7(2):e28510.
19. Lallemant M, Jourdain G, Le Coeur S, Kim S, Koetsawang S, Comeau AM, et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand) Investigators. N Engl J Med. 2000;343(14):982-91.
20. Hauser A, Sewangi J, Mbezi P, Dugange F, Lau I, Ziske J, et al. Emergence of minor drug-resistant HIV-1 variants after triple antiretroviral prophylaxis for prevention of vertical HIV-1 transmission. PLoS ONE. 2012;7(2):e32055.
21. WHO.Antiretroviral drugs for treating pregnant women and preventing HIV infection in infant s: Recommendations for a public health approach. 2010:20-58
22. Kaizad DR, Parikshit TD.Prevention of mother to child transmission of HIV infection J Obstet Gynecol India, 2006;56(5): 390-395
23. Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. AIDS. 2008;22(8):973-81
24. Lussiana C, Clemente SVL, Ghelardi A, Lonardi M, Pulido Tarquino IA and Florida M. Effectiveness of a Prevention of Mother-to-Child HIV Transmission Programme in an Urban Hospital in Angola PLoS ONE. 2012; 7(4): e36381.
25. Hussain A, Moodley D, Naidoo S, Esterhuizen TM. Pregnant women's access to PMTCT and ART services in South Africa and implications for universal antiretroviral treatment. PLoS ONE. 2011;6(12):e27907.
26. Millenium development goals/UNDP.Available at: www.undp.org/mdg/(Accessed on: Nov 28/2012)
27. Jimma University specialized Hospital. Available at:www.ju.edu.et. (Accessed on: Feb 20/2012)
28. Alliegro MB, Dorrucci M, Phillips AN, Pezzotti P, Boros S, et al. (1997) Incidence and consequences of pregnancy in women with known duration of HIV infection. Italian Seroconversion Study Group. Arch Intern Med 157: 2585–2590.
29. Bessinger R, Clark R, Kissinger P, Rice J, Coughlin S (1998) Pregnancy is not associated with the progression of HIV disease in women attending an HIV outpatient program. Am J Epidemiol 147: 434–440.
30. 30. Weisser M, Rudin C, Battegay M, Pfluger D, Kully C, et al. (1998) Does pregnancy influence the course of HIV infection? Evidence from two large Swiss cohort studies. J Acquir Immune Defic Syndr Hum Retrovirol 17: 404–410.
31. Saada M, Le Chenadec J, Berrebi A, Bongain A, Delfraissy JF, et al. (2000) Pregnancy and progression to AIDS: results of the French prospective cohorts. SEROGEST and SEROCO Study Groups. AIDS 14: 2355–2360.